



International Society
of Pharmacovigilance

Committed to safer use of medicines worldwide

**21st ISO P Annual Meeting “A New Era of Pharmacovigilance:
Challenges and Opportunities” 20–23 September 2022 Verona,
Italy**

ABSTRACTS

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Committed to safer use of medicines worldwide

The International Society of Pharmacovigilance (ISoP) aims to develop its activities on a worldwide basis towards supporting safer use of medicines in clinical practice.

ISoP encourages and supports the use of all types of information and methodologies in providing optimal drug treatment for patients. The Society is open to anyone interested in learning about better ways for patients to receive and use medicines safely, including academics, epidemiologists, medicines regulators, clinical pharmacologists, pharmaceutical industry representatives, practising clinicians, pharmacists, and other healthcare professionals.

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Dr Mira Harrison-Woolrych, President of the International Society of Pharmacovigilance

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International Society of Pharmacovigilance

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ORAL PRESENTATIONS

O-001

Oral presentation: Effectiveness and Tolerance of Biotherapy in the Treatment of Chronic Inflammatory Diseases and Rheumatism in Children

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Introduction: The use of biotherapy has vastly improved the treatment of patients with juvenile idiopathic arthritis and certain auto-inflammatory diseases by preventing long-term damage, and improving quality of life [1,2]

Objective: The main goal of our study was to evaluate the effectiveness and tolerance of biotherapy on the treatment of rheumatism and chronic inflammatory diseases in children in the pediatric ward IV at the Children's Hospital in Rabat.

Methods: We conducted a retrospective observational study in the pediatric ward IV at Ibn Sina Children's Hospital in Rabat (HER) with children treated for chronic rheumatic and inflammatory diseases for the period from February 2021 to June 2021. Data collection was carried using an excel datasheet from the pediatric department register, the record of pediatric rheumatology consultations and patient records. The data extracted concerned the socio-demographic data of patients, also the evolution of pathology, effectiveness of biotherapy used based on Giannini score. The second part of our study focused on the collection of adverse reactions reported of the biotherapy treatment and their classification.

Results: In the course of our study, the results showed that among (n = 100) patients were treated using Anti-Tumor necrosis factor, Anti-Interleukin 1, or Anti-interleukin 6. (n = 42) had a systemic form of arthritis, (n = 30) had polyarthritis, (n = 10) had oligoarthritis, (n = 14) with Spondyloarthritis, (n = 2) had BEH-ÇET'S disease, and one patient had familial Mediterranean fever, we found that (87%) of our patients had good progress under etanercept, infliximab and adalimumab with Giannini scores of (90%), (80%) and (70%), the effectiveness exceeded (70%) in patients on Anakinra and (90%) Tocilizumab. Our study also reported 15 adverse reactions in patients receiving Biotherapy with a single severe adverse reaction, which was severe hepatitis type A under Tocilizumab. The most common adverse reaction was the development of infections.

Conclusion: The children's short-term tolerance was overall good, the only biotherapy treatment that has caused a severe adverse reaction was Tocilizumab. prospective studies are required to assess long-term effectiveness and tolerance.

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O-002

Oral Presentation: European Pharmacovigilance Analysis of Cardiac Arrhythmias Events with Immune Checkpoint Inhibitors

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Introduction: Immune checkpoint inhibitors (ICIs) are novel biological agents with proven efficacy for several types of cancers. However, ICIs have also been associated with the onset of cardiac immune-related adverse events, which are rare but associated with high morbidity and mortality [1,2]. Moreover, these events are highly arrhythmogenic despite their related clinical manifestations are still poorly understood [3].

Objective: The objective of this study was to evaluate the occurrence of cardiac arrhythmias related to ICIs by analyzing European Pharmacovigilance data.

Methods: Individual case safety reports (ICSRs) on ICI-associated cardiac arrhythmias were retrieved from the website of suspected adverse drug reactions of the European pharmacovigilance database (Eudravigilance), available at www.adrreports.eu. Data were retrieved from the date of the marketing authorization of each ICI (pembrolizumab, nivolumab, atezolizumab, ipilimumab, durvalumab, avelumab, cemiplimab, and dostarlimab) to 30 April 2022. ICSR were classified based on the ICI. If more than one ICI was reported, the ICSR was classified as a combination of ICIs. To assess the reporting frequency of cardiac arrhythmias for each ICI/combination of ICIs compared to all other ICIs, the reporting odds ratio (ROR) and its 95% confidence interval (95% CI) were computed. The RORs and 95% CI were also computed for comparing ICIs' drug classes: anti-PD1 (nivolumab, pembrolizumab, cemiplimab, dostarlimab), anti-PDL1 (atezolizumab, durvalumab, avelumab), and anti-CTLA4 (ipilimumab). Finally, RORs and 95% CI were computed for the three most reported events of cardiac arrhythmias.

Results: A total of 1,262 ICSR related to an ICI and an event of cardiac arrhythmia were retrieved from Eudravigilance, of which 147 (11.6%) were related to combinations of ICIs. The most reported combination was nivolumab/ipilimumab (N = 140; 95.2%). The three most reported single ICIs were pembrolizumab (N = 456; 36.1%), nivolumab (N = 433; 34.3%), and atezolizumab (N = 74; 5.9%). A total of 1,426 events of cardiac arrhythmias were identified, of which 1,187 were serious (83.2%) and 429 had a fatal outcome (30.1%). The three most reported events were atrial fibrillation, tachycardia, and cardiac arrest. The ROR of ipilimumab was compared to all other ICIs was 0.71 (95% CI 0.55–0.92; p = 0.009). In the comparison between ICIs' drug classes, anti-PD1 were associated with a higher reporting frequency of cardiac arrhythmias compared to anti-CTLA4 (ROR 1.47, 95% CI 1.14–1.90; p = 0.003). In the analyses of the three most reported events, no statistically significant difference was observed for all comparisons.

Conclusion: The anti-CTLA4 ipilimumab was the only ICI associated with a reduced reporting frequency of cardiac arrhythmias. Further specific high-quality studies are needed on this topic.

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O-003

Oral Presentation: Potentially Inappropriate Medication in Older Adult's Adverse Drug Reactions Spontaneous Reports

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Introduction: A medicine is considered potentially inappropriate (PIM) when the potential risk of it in the older population exceeds the potential benefit, and for which there are safer alternatives [1]. This is highly prevalent in their medication therapy [1,2], enhancing adverse reactions. PIM are already identified from various tools developed, being the most common ones the explicit Beers criteria [3], the START/STOPP, which requires additional patient data [4] and in Europe the EU-7-PIM list [5].

Objective: The aim of this study was to identify suspected medicines classified as PIM in the Adverse Drug Reactions (ADR) reports received by the Portuguese Pharmacovigilance System of the National Authority of Medicines and Health Products (INFARMED, I.P.) in older adults, analysing in dept the reports including PIM as suspected medication.

Methods: A retrospective study was designed including all ADR reports received by INFARMED, IP., between January and December 2019 in 65 and more year-old patients. ADR were characterized according with MedDRA System Organs Classes (SOC), seriousness, and medication according with the Anatomical Therapeutic Classification. PIM were identified in the report's suspected medication applying the operationalization for the Portuguese reality of the EU (7) PIM list [5] as well as the Beers criteria from 2019 [3].

Results: Beers and EU (7) PIM criteria were applied in 2337 reports. PIM were found in 299 (12,8%). From the 3170 suspected medicines identified, 337 (10,6%) were classified as PIM. From the 299 reports including PIM as suspected medication, the population showed a mean age of 73.0 ± 6.6 years, being 56.5% (n = 169) female. 45.2% (n = 135) were reported by physicians. 71,4% (n = 215) of the reports were classified as serious, and hospitalization was the most common seriousness criteria identified (35,1%/n = 105). "Nervous System disorders" was the most common SOC criteria reported (49,1%/n = 147). Amiodarone (C01BD01) was the most frequent PIM identified by the criteria (n = 34/10.1%), followed by dabigatran

etexilat (B01AE07), (7.1%/n = 24) and Rivaroxaban (B01AF01) (6.2%/n = 21). Reports including PIM in suspected medicines had a significant higher number of ADR (p = 0.025) and number of suspected medicines per report (p < 0.001). Seriousness of the ADR report classification (p = 0.005) and hospitalization (p < 0.001) were more associated in reports including PIM.

Conclusion: These results reinforce the importance of improving medication appropriateness in older adults and promote the development and use of clinical decision support systems to avoid inappropriate prescriptions and, therefore, severe adverse reactions.

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O-004

Oral Presentation: Analysis of Medication Errors in Children and Adolescents Reported to HALMED

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Introduction: A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient [1]. Use of medicinal products in children is identified as a risk factor for occurrence of medication errors [2, 3].

Objective: Aim of this study is to describe medication errors and identify causes of medication errors in children and adolescents spontaneously reported to HALMED, in order to propose and implement appropriate risk minimisation measures.

Methods: We performed a search of HALMED's adverse drug reaction database using Standardised MedDRA Query (SMQ): *Medication errors (Broad)* with data lock point April 30th 2022. Cases in which medication errors occurred in patients up to 18 years of age were analysed according to the patient's age and gender, *Preferred Terms* (PTs) reported and root causes of medication errors.

Results: Out of 8603 cases in patients up to 18 years of age, 1684 cases included terms pertaining to SMQ: *Medication errors (Broad)*. Medication errors were most frequently reported for male patients (54%) and in the age group 2–11 years (67%). The most commonly reported PTs for medication errors were *Accidental exposure to product by child* (65%) and *Accidental overdose* (19%). Grouping of cases was observed for the following pharmaceutical formulations of the active substances: salbutamol nebuliser solution, paracetamol

solution for infusion, valproate oral solution and syrup and cholecalciferol oral drops, solution. Identified root causes for medication errors were the following: misinterpretation of prescribed dosage due to very small volume resulting in 10 times higher administered dose (e.g. 3 ml instead of 0.3 ml) for salbutamol; confusion between units millilitres and milligrams resulting in overdose for paracetamol; interchange between medicinal products due to primary package similarities resulting in overdose for cholecalciferol (e.g. swapping with simethicone, dimetindene, bromhexidine); interchange between oral solution and syrup resulting in overdose for valproate.

Conclusion: Medication errors were reported in 20% of all cases in patients up to 18 years of age, which highlights the importance of medication errors prevention in children and adolescents. Review of root causes for medication errors led to implementation of further risk minimisation measures, namely notifications for healthcare professionals (salbutamol and valproate), additional risk minimisation measures i.e. poster and dosage card (paracetamol) and workshops for healthcare professionals (salbutamol, valproate, paracetamol, cholecalciferol). Following implementation of risk minimisation measures, it is concluded there is a further need for evaluation or their effectiveness.

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O-005

Oral Presentation: Animated Explainer Videos as an Effective Way to Communicate Statistical Methods in Pharmacovigilance

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Introduction: Digital features such as videos and infographics are used to make scientific literature more understandable and accessible to a wider audience [1, 2]. Plain language summaries and graphical abstracts are fast becoming the norm in complementing scientific publications across disciplines, including pharmacovigilance. However, the use of video explainers is limited, and the usefulness of such features is not well known.

Objective: To evaluate the effectiveness of an animated explainer video in communicating a statistical method in pharmacovigilance.

Methods: An animated explainer video [3] previously created to complement an earlier scientific publication [4] and improve communication of UMC's novel clustering method vigiGroup was used as a digital feature in this study. Communication specialists and data scientists collaborated to create the video, focusing on identifying key elements of the method and how to best illustrate its application in a visual narrative. A survey of 10 multiple choice and rating scale questions was used to assess comprehension, perceived effectiveness

of communication, enjoyment, and desire to learn more. The survey was disseminated across 3 of UMC's social media channels (approx. 50,000 followers), including Twitter, Facebook, and LinkedIn, to an audience of predominantly pharmacovigilance professionals. Subsequently, responses were collected and analysed.

Results: Fifty-four individuals from 30 countries participated in the survey. Forty-four (81%) of the participants worked in a pharmacovigilance-related field and 30 (56%) had 5 or more years of professional experience. Over 80% of participants answered all comprehension questions correctly, demonstrating a good level of understanding. Additionally, most participants (see Table 1 for detailed results) found the video to be an enjoyable and helpful way to learn about vigiGroup; agreed that an animated explainer video could be a useful alternative to reading a scientific paper and an effective way to visualise scientific methods; and would like to see more scientific methods presented in this way.

Table 1 Rating scale questions and results

Question (1 = Strongly disagree, 10 = Strongly agree)	Median (Interquartile range)
The visualisations of the methodology helped me to understand how vigiGroup works.	8 (7-10)
I would like to learn more about vigiGroup after watching the animated explainer video.	10 (9-10)
The use of animation makes learning about the methodology enjoyable.	9.5 (8-10)
Animation is an effective way to visualise scientific methodologies.	10 (8.25-10)
When trying to understand a scientific method, watching an animated explainer video can be a useful alternative to reading a scientific paper.	9 (8-10)
I would like to see more scientific/statistical methods presented in this way.	10 (9-10)

Conclusion: The vigiGroup animated explainer video was effective in communicating cluster analysis of adverse event reports to an audience of both pharmacovigilance and non-pharmacovigilance professionals. Increasing the use of such videos, to complement scientific literature, could be an effective way of building knowledge of complex statistical methodology and scientific developments more broadly.

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O-006

Oral Presentation: Visual Communication of Safety Data in Ongoing Studies: The Adaptive Benefit-Risk Assessment tool for Clinical Trials (ABRA-CTV)

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Introduction: Data from ongoing open-label clinical studies are assessed for safety signals on a set cadence, complying with regulatory requirements. One challenge is the need to contextualize safety when individual subjects have different exposure times (rolling enrollment). Such issues resolve at the end of the study. However, during the study, visualizations add considerable value to the multi-disciplinary discussion of incoming safety data.

Objective: To develop an interactive dashboard (ABRA-CTV) to display patient safety data in a concise manner, identifying potential adverse event (AE) patterns across exposures (drug/dose) and time periods (exposure length).

Methods: The underlying data, used for various analytics and reporting purposes, were drawn from an Amazon Web Services (AWS) Redshift database and conformed to a standard data model via an extract, transform, and load (ETL) process using Enterprise Data Lake Services.

For a study, the user selects AEs of interest (filtered by intensity/grade, seriousness, and relatedness) and sets maximum exposure time of interest and risk period beyond last dose. The tool produces a column (x-axis) for each subject with a height (y-axis) corresponding to exposed time. Subjects are grouped by exposure (in open-label or completed studies), and AEs are displayed relative to start of exposure by symbols on each subject-column. The entire population can be displayed, or the display can be limited to the patients with the event(s) of interest. This allows viewing of AEs in the context of total study population (number of columns) and total exposed time (area of the graph as a whole), or to narrow the focus to affected patients.

Results: The pilot version of ABRA-CTV has been found most useful: (1) to display multiple events (overlap among subjects, relative timing), (2) to visually compare monotherapy and combination therapy (drug A, drug B, drug A+B), and (3) to compare results from ongoing and completed trials where the display of information from the completed trial is limited to an exposed time similar to the ongoing trial. Although the tool is capable of calculating AE incidence rates, its real value for the assessment of ongoing studies lies in the ability to display events and patient time in an adaptive and intuitive way that allows for meaningful discussion of safety data.

Conclusion: Interactive data visualizations can enhance internal risk communication and clinical decision-making during ongoing clinical trials.

References/Further Sources of Information

Not applicable.

O-007

Oral Presentation: Impact of the 2018 Pregnancy Prevention Program on the Use of Oral Retinoids in Childbearing Age Females in Europe

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Introduction: In 2018, European pregnancy prevention program for oral retinoids, i.e., isotretinoin (acne), acitretin (psoriasis) and alitretinoin (eczema) was updated as part of additional risk minimization measures (RMM) [1, 2] to prevent major congenital anomalies in new-borns whose mothers were exposed to these drugs [3, 4].

Objective: To measure the impact of the 2018 RMMs on utilization patterns of oral retinoids, alternative medications, contraceptives, and on rates of pregnancies occurring concurrently with retinoid prescriptions.

Methods: Retrospective cohort study between Jan-2010 and Dec-2020 in females of childbearing age (12–55 years) derived from six electronic healthcare record data sources in the Netherlands (PHARMO), Spain (BIFAP and VID-Valencia), Italy (Caserta and ARS-Tuscany), and Denmark (Danish National Registries-DNR). Information from data sources was transformed into the ConcePTION Common Data Model [5]. Common analysis scripts were implemented by study sites. Monthly utilization patterns of isotretinoin, alitretinoin and acitretin (incidence/1000 person-months, prevalence/1000 persons, and percentage of discontinuers) were estimated. An interrupted time series analysis was performed to assess immediate changes after the implementation (level change) and over time (trend change). Contraceptive use (percentage) and concurrent pregnancies during retinoid treatment episodes (rates/1000 users) were calculated as well.

Results: The study population comprised 11,570,047 females of childbearing age (12–55 years), 88,992 persons used an oral retinoid at any point during the study period. Monthly incidence and prevalence rates showed that retinoid prescriptions have a strong seasonal pattern with peaks of use in winter months. No significant ($p < 0.05$) level and trend changes were seen after the implementation of RMMs in August 2018 for incidence, prevalence, and discontinuation rates in any of the study sites. The low level of recording of pregnancy tests did not allow for trend analysis. Contraceptive use could not be measured in ARS and DNR, and was very low in Caserta; in PHARMO, recorded contraceptive use in retinoid users was far below 100%, in VID and BIFAP, recorded contraceptive use increased over time. In BIFAP, there was a significant trend increase after 2018 RMMs in the utilization of contraceptives before the initiation of an oral retinoid treatment, but still far below 100% (15% maximum). Pregnancy rates varied between 0.1 and 0.4 per 1000 retinoid users and occurred in all study sites pre- and post-intervention.

Conclusion: Based on the findings, there is very limited measurable impact of the 2018 RMMs among females of childbearing age in the included databases. Moreover, pregnancies still happen during oral retinoid treatment after the implementation.

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O-008

Oral Presentation: Performance of an Artificial Intelligence System Tool for the Detection of ADRs from Patients' Reports During the Covid-19 Vaccination Campaign

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Introduction: During the recent covid-19 vaccination campaign, the number of ICSRs reported by patients and professionals has dramatically increased, reaching up to almost 1 M declarations only in Europe (EMA numbers). To deal with such growing amount of data, Synapse Medicine®, in collaboration with The French National Agency for Medicines and Health Products Safety (ANSM), have developed an artificial intelligence (AI) tool, the Medication Shield, which, based on a natural language processing algorithm, is able to detect ADRs from patients' reports and to code them into an appropriate MedDRA preferred term (PT). Before the covid-19 pandemic, this system was successful in detecting ADRs from the patient reports declared through the French web national reporting system (1, 2). However, how it behaves in conditions of higher reporting flow rate is unknown at present.

Objective: To evaluate the performance of the Medication Shield in detecting vaccine-related ADRs from patients' ICSRs declared across the covid-19 vaccination campaign.

Methods: A machine learning (ML) pipeline composed by a light Gradient Boosting Machine ensemble model was employed to detect and code covid-19 vaccine-related ADRs from patients' ICSRs declared through the web reporting system during the vaccination campaign (Jan 2021–Apr 2022). The encoding of regional pharmacovigilance centers was employed as the reference ground truth to train the algorithm in a supervised manner. Moreover, a panel of three pharmacologists, with significant experience in ADRs encoding, was set-up to perform a case-by-case analysis of 200 hundreds reports for which the algorithm provided improper encoding.

Results: Overall, 65.191 ICSRs were extracted and used to train our ML algorithm. Of this, 54.987 were employed to validate the system. Importantly, almost 86% of the ICSRs were related to covid vaccines. Because the percentage of newly reported ADRs increased over time and was higher for vaccine than not-vaccine related reports, we split the training and validation sets in batches with similar ADRs distribution. Performance evaluation is currently under process. Initial feedbacks from the analysis performed by the experts are showing an uneven distribution of false positive and false negative across samples. Results from the other experts are needed to confirm this finding.

Conclusion: The core findings of this study will be gathered in the forthcoming weeks and be ready for the ISoP meeting in September. This work will provide new insights about the effectiveness of

deploying AI as a support to treat real world data in a context of sanitary crisis.

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O-009

Oral Presentation: Investigating Hidden Networks in Spontaneous Reporting Systems

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Introduction: The analysis of spontaneous reporting systems aims to identify potential adverse drug reactions in a timely and cost-effective manner. For their apparent simplicity, disproportionality analyses assessing the disproportionate presence of single drug-adverse event associations in spontaneous reports are rapidly expanding as a source of safety evidence complementary to clinical trials. However, the world (and spontaneous reports) is more complex than that: events occur in syndromes, drugs are taken in polytherapy, and patients are mosaics of multiple comorbidities. Network science is one of the most promising approaches to tackle such complexity.

Objective: To investigate the applications and promises of network science to spontaneous reporting data.

Methods: We identified four key examples to highlight the potentiality of network approaches to pharmacosurveillance: multiple drug intake in suicidal attempts, iatrogenic syndromes (i.e., adverse) in Covid-19 and immunotherapy, psychosocial adverse reactions to oxycodone. We used data collected by the FDA Adverse Event Reporting System. Entities (e.g., drugs, events, indications) were represented as nodes, and co-reporting relations as links. Depending on the aim, links' weights were estimated in two ways. We used co-reporting frequencies to describe cooccurrence patterns for example, polytherapy and iatrogenic syndromes. We used marginal and partial correlations to investigate the associations between entities and their direction: for example, to identify biases and secondary adverse events. We used multilevel algorithms to identify clusters of interest, and network measures to identify trends of co-reporting.

Results: The multiple drug intake network showed paracetamol at the center, as a drug of choice both alone and in combinations, and common combinations separated by therapeutic area, plausibly because of availability. The Covid-19 adverse identified a cluster of drug-induced hepatic injury and arrhythmia, and a disease-related cluster with Covid-19 infection and respiratory conditions (1). The immunotherapy adverse identified not only the known overlap syndrome (cooccurrence of myocarditis, myasthenia, and myositis), but also another cluster with hepatitis, colitis and thyroiditis. Finally, investigating reactions to oxycodone, we observed that the reporting of crime and psychosocial reactions was secondary to the reporting of drug dependence.

Conclusion: Networks allow to visualize and compare individual relations, identify clusters, and gather insights into the direction of

correlation (e.g., to investigate biases). Networks can complement traditional descriptive and disproportionality analyses characterizing the complexity of spontaneous reporting data.

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O-010

Oral Presentation: Search for Additional Cases in Electronic Health Records (EHRs) to Strengthen Potential Signals from Spontaneous Reporting

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Introduction: The spontaneous reporting system (SRS) has proven to be a cornerstone in the early and cost-effective detection of adverse drug reactions (ADRs) [1-3]. Electronic Health Records (EHRs) are relatively untapped sources of real-world information that can be used in order to facilitate signal detection in pharmacovigilance (PV).

EHRs are a rich source of information on (pharmaco)therapies, diagnoses, laboratory test results, and physicians' notes. However, utilizing the EHR for PV involves a number of critical challenges including the efficient extraction of valuable pieces of information from unstructured bulk of free-text.

Objective: To explore whether targeted searches in structured and unstructured fields in EHRs can be used as a method to detect possible cases in addition to spontaneous reports to strengthen a (potential) safety signal.

Methods: Searches were performed in the EHRs of the Leiden University Medical Centre (LUMC) in NL, to identify potential cases for two established and two suspected ADRs generated by signal detection of the SRS of Lareb. Suspected ADRs refer to potential signals based on the analysis of spontaneous reports with insufficient evidence insight into a possible relationship between the ADR and the drug.

The selected established ADRs:

- Hypokalemia caused by flucloxacillin.
- High anion gap acidosis (HAGMA) caused by the concurrent use of flucloxacillin and paracetamol.

The selected established ADRs:

- Atraumatic splenic rupture associated with direct oral anticoagulants (DOACs).
- Renal failure and acute tubular necrosis induced by ibrutinib.

Per (potential) signal, a search with a validated text-mining software tool (Ctcue) was performed via combined queries on both structured and unstructured data [4]. In order to perform the process of case detection systematically, a step-by step search plan was developed and applied to each signal based on:

1. Identify drug users.
2. ADR identification: based on reports of Lareb and literature.
3. Develop and apply the search strategy.

4. Identify and manually validate potential cases.
5. Case review by PV experts of Lareb

Results: The search retrieved 27 cases with flucloxacillin induced hypokalemia. For HAGMA after use flucloxacillin and paracetamol 21 potential cases were identified. After five confirmed cases via manual validation, no further validation was performed for the established ADRs. For each suspected ADR (potential signal), one validated case was detected.

Conclusion: A targeted search on structured and unstructured fields in EHRs using text-mining can be used as a method to detect additional cases next to spontaneous reports for a potential safety signal. It is recommend to implement this as a complementary method in the current pharmacovigilance system.

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O-011

Oral Presentation: Do Monitored Dosage Systems Increase Risk for Patients' Safe Discharge from Hospital? A Retrospective Analysis of Pharmacists' Interventions

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Introduction: Many patients who are admitted to hospital use Monitored Dosage Systems (MDS). Governing bodies such as NICE (1) recognise that for some patients, the use of MDS is essential. Research has proven that when patients are admitted to hospital, there are often changes to medication regimens (2, 3). Further research is necessary to establish if pharmacists' interventions on ensuring safety during patients' healthcare journey from hospital admission to discharge, differs between MDS using patients and non-MDS using patients.

Objective: The aim of this study was to analyse hospital pharmacists' interventions for patients' healthcare journeys for MDS using and non-MDS using patients.

Methods: The retrospective analysis was conducted at the Royal Victoria Hospital, a large general teaching hospital in the Belfast Health and Social Care Trust (BHSCT). The study took place over four months from 1st July to 31st October 2021. There were initially 487 admission episodes included in the study, and for each adult patient their healthcare journey from hospital admission to discharge was analysed for interventions and workforce input. Interventions were ranked using the validated Eadon Scale (4). The Royal Stoke

Pharmacy Workforce Calculator (RSPWC) (5) was used to evaluate the times associated with the various pharmacist activities between MDS and non-MDS using patients.

Results: A total of 387 patients' healthcare journeys were analysed. Patients whom did not have complete healthcare journeys from hospital admission to discharge were excluded. These patients had either died, had been transferred to another hospital, or were still inpatients when the study ended. There were 31.5% of patients using MDS and 68.5% of patients not using MDS. Of the total MDS using patient journeys, 99.2% needed hospital pharmacist interventions and were ranked by Eadon Scale; 3 (34.7%), 4 (32.2%) and 5 (33.1%). Of the total non-MDS using patient journeys, 50.9% needed hospital pharmacist interventions and were ranked by Eadon Scale; 3 (41.5%), 4 (52.2%) and 5 (5.9%). The median time in minutes for pharmacist workforce activity based on RSPWC was 160.9 minutes for MDS using patients, and 99.5 minutes for non-MDS using patients.

Conclusion: This study has identified that the use of MDS increase the burden to pharmacist workforce input. It is evident from the findings, that interventions may be needed for the majority of MDS using patients. It has highlighted that more significant interventions, Eadon Scale 5, are more prevalent for MDS using patients in comparison to non-MDS using patients

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O-012

Oral Presentation: Signal of Hypertension Associated with COVID-19 Vaccination: VigiBase® Data and Evidence from Real World

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Introduction: Hypertension is a serious disease that occurs when blood pressure is persistently elevated over time¹. During the COVID-19 vaccination campaign, several reports of hypertension occurred in plausible temporal relationship with immunization have been reported.

Objective: To explore a possible signal of risk of hypertension associated with COVID-19 immunization using VigiBase® the World

Health Organization (WHO) pharmacovigilance database and to review the evidence available from real world.

Methods: We performed a disproportionality analysis using data on spontaneous reports recorded in VigiBase®. Data have been extracted on May 8th, 2022. We calculated reporting odds ratio (ROR) as a measure of disproportionality for hypertension defined by the Standardized Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) narrow. ROR was estimated for all reports including the MedDRA preferred term (PT) “hypertension”, “blood pressure increased” and “hypertensive crisis” (cases). All other reports have been defined as non-cases. All reports in which the suspected causative agent was a COVID-19 vaccine were used as index reports and all other reports as reference. A signal was defined by at least three reports of the PT of interest and $ROR_{025} > 1$. We reviewed the medical literature using MEDLINE from January 2021 to May 2022 using “COVID-19 vaccines” AND “hypertension” as a search terms to check for evidence from observational studies.

Results: As of May 8th, 2022, VigiBase® included 3,746,090 reports of adverse events following immunization for COVID-19 vaccines and 87,653 de-duplicated reports of hypertension defined by the SMQ. We identified 34,955 reports of “hypertension” ($ROR:1.3$; $ROR_{025}:1.2$), 47,733 reports of “blood pressure increased” ($ROR:2.6$; $ROR_{025}:2.6$) and 3,741 reports of “hypertensive crisis” ($ROR:4.0$; $ROR_{025}:3.8$) in which a COVID-19 vaccine was indicated as suspected causative agent. Most frequently co-reported symptoms ($> 9\%$) included headache ($n = 16,817$; 19.2%), dizziness ($n = 12,892$; 14.7%), fatigue ($n = 8,406$; 9.6%). Overall, 75% of cases ($n = 65,761$) have been classified as not serious. A meta-analysis of observational studies that includes 357,387 individuals reported 13,444 events of blood pressure abnormal or increased². These events have been often described as short periods of hypertensive response and often observed in patients with risk factors.

Conclusion: Our results confirmed a signal of risk of events of elevated blood pressure following immunization with COVID-19 vaccines. However, there is no evidence that these episodes could result in serious complication typically associated with hypertension, such as stroke, aneurysms, heart failure, myocardial infarction and chronic kidney disease.

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O-013

Oral Presentation: Risk of Glaucoma Diagnosis in Patients Who Received Intravitreal Injections of VEGF Inhibitors: A Cohort Study

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Introduction: Intravitreal drugs such as bevacizumab, ranibizumab, and aflibercept are widely used to treat a wide range of retinal diseases. Several studies suggest that repeated injections of these drugs may lead to a sustained rising of intraocular pressure increasing risk for glaucoma. To date, a comparative safety study of these three drugs with respect to the incidence of glaucoma diagnosis has not been done.

Objective: The objective of this study was to evaluate the risk of glaucoma diagnosis compared among new users of bevacizumab, ranibizumab, and aflibercept in Tuscany.

Methods: A retrospective cohort study using the Tuscan regional administrative database was conducted. Subjects with a first intravitreal injection (index date) between January 2011–June 2020 were identified and followed to the first occurrence of glaucoma diagnosis. Patients with less than a five-year look-back period, those with less than one year of follow-up, and those with previous use of intravitreal dexamethasone, diagnosis of diabetes or glaucoma were excluded. We also excluded patients for whom we could not track the first injection to bevacizumab, ranibizumab or aflibercept. Glaucoma diagnosis was identified from exemptions, diagnosis in hospital discharge records or drug dispensations. An intention-to-treat analysis was conducted to analyze risk of glaucoma diagnosis between the three drugs. A Cox model was constructed to compute hazard ratios adjusting for age, sex comorbidities, corticosteroid use and binocularity. To control for retinal vein occlusion, a potential confounder for this question, a stratification by use of anticoagulants in the six months prior/after cohort entry was performed.

Results: A total of 6593 new users were included in the analysis (Aflibercept = 1749, Bevacizumab = 1115, Ranibizumab = 3729). Women made up 60% of the cohort with a mean age of 73 years ($\pm$ 12.3 years). Overall, the incidence of a glaucoma diagnosis was 2%, 5.3% and 5.9% in the aflibercept, ranibizumab, and bevacizumab group, respectively. The risk of incident glaucoma diagnosis compared to aflibercept was significantly higher among non-anticoagulant users who had received ranibizumab (HR 2.55; CI 95% 1.77–3.66) and bevacizumab (HR 3.07; CI 95% 2.03–4.66). Among anticoagulant users no statistically significant difference was observed.

Conclusion: Our study reported an incidence of glaucoma diagnosis of approximately 5% in patients treated with anti-VEGF drugs. Moreover, we found an increase in the risk of glaucoma with ranibizumab and bevacizumab compared to aflibercept among non-anticoagulant users. A time dependent exposure analysis is ongoing to confirm these results.

References/Further Sources of Information

Not applicable.

O-014

Oral Presentation: A Revised Time-to-Onset Signal Detection Algorithm in the Context of Mass Vaccination

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Introduction: A method of time-to-onset (TTO) signal detection for screening unexpected temporal patterns from vaccine spontaneous report data has been published in 2012 [1]. EMA listed TTO analysis as one of the methods to be considered for signal detection [2]. Due to the large number of spontaneous reports associated to covid-19

vaccines, highly significant TTO signals could be detected whereas there are no clinically relevant unexpected temporal patterns.

Objective: Objective was to revise the original method so that it is less sensitive to small differences and test it on two covid-19 vaccines (Pfizer/BioNTech and Moderna).

Methods: The revised method used only the most predictive measure [3] of the two Kolmogorov-Smirnov (KS) tests originally designed: the p-value of the KS test of the TTO distribution of a given event post a given vaccine against the TTO distribution of the same event post other vaccines. A threshold on the Kolmogorov-Smirnov distance, that can have values between 0 and 1-0 for no difference between time-to-onset distributions and 1 for extreme differences—was set at 0.2. A threshold on the p-value of the KS test was set at 0.05.

The Vaccine Adverse Event Reporting System was prospectively frozen every week of the first quarter 2021 and the revised TTO signal detection method was prospectively applied on the two covid-19 vaccines.

The performance in detecting events that were posteriori determined as causally related to the exposure of the covid-19 vaccines, namely Pericarditis and Myocarditis, was retrospectively assessed.

Results: Pericarditis post Pfizer/BioNTech covid-19 vaccine emerged as a significant TTO signal as early as 15JAN21 (N: 4, distance: 0.80, p-value: 0.012). Myocarditis post Pfizer/BioNTech covid-19 vaccine emerged as a significant TTO signal as early as 29JAN21 (N:5, distance: 0.59, p-value: 0.031).

Pericarditis post Moderna covid-19 vaccine emerged as a significant TTO signal as early as 12FEB21 (N: 13, distance: 0.55, p-value: 0.00093). Myocarditis post Moderna covid-19 vaccine emerged as a significant TTO signal as early as 05FEB2021 (N:7, distance: 0.73, p-value: 0.0014).

Conclusion: The revised TTO method allowed early detection of unexpected TTO patterns post exposure to covid-19 vaccines by controlling both the level of significance and the magnitude of difference between the TTO distributions in a context of mass vaccination where individual case review is challenging.

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O-015

Oral Presentation: Adverse Events to COVID-19 Vaccines and Policy Considerations that Inform the Funding of Safety Surveillance in Low- and Middle-Income Countries

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Introduction: As of April 3, 2022, 31 COVID-19 vaccines had received approval for use globally (1). With the fast-tracked development and concurrent introduction of vaccines in all countries, there is a need for equitable safety surveillance to monitor adverse events following immunization (AEFIs) in high-income and low- and middle-income countries (LMICs).

Objective: To profile the AEFIs to COVID-19 vaccines, explore the difference in reported AEs between Africa and the rest of the world (RoW), and understand the policy considerations that inform the decision by funding organizations to strengthen safety surveillance systems in LMICs.

Methods: We used a convergent mixed methods design involving secondary analysis of 14,671,586 AEFIs to COVID-19 vaccines reported to VigiBase[®] by countries in the WHO Africa Region and the RoW between December 2020 and March 2022. The qualitative component consisted of 12 in-depth interviews with key policymakers from some donor/funding organizations.

Results: With 87,351 out of 14,671,586 total reported AEFIs to COVID-19 vaccines (0.6%) Africa had the second-lowest crude AEFI reporting rate of 180 AEs per 1 million administered doses. Reports from females made up 73.6% of reports from African and RoW compared to 24.4% for males. The highest number of reports came from persons 18–44 years. 26.0% of the reports were serious, with death being the reason for seriousness in 5% of the reports. Statistically significant differences in AEFI reporting by gender, age group, and serious AEs were found between Africa and the RoW. AstraZeneca, PfizerBioNtech, and Janssen vaccines were the most frequently associated with AEFIs in terms of the absolute number of AEs for Africa and RoW. Sputnik V contributed the highest percentage of AEs per vaccine for Africa. Headache, pyrexia, injection site pain, dizziness, and chills were the top 5 reported AEs for Africa and RoW. Qualitative findings revealed decisions of many funding organizations to fund safety surveillance in LMICs were influenced by considerations about country priorities, the perceived utility of the evidence generated for local decision making, and the contributions to global health by safety surveillance systems.

Conclusion: Countries in Africa reported fewer AEFIs to COVID-19 vaccines in VigiBase relative to the RoW, with statistically significant differences in reporting of key parameters that warrant further investigation. Funding decisions by donor organizations were influenced by country priorities and the perceived value added by data generated from safety surveillance systems in LMICs to local and global decision making.

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O-016

Oral Presentation: Factors Associated with Hospital Death in Patients with Adverse Drug Events in Brazil, from 2011 to 2020

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Introduction: Therapeutic advances have reduced morbidity and mortality, but have led to an increase in adverse drug events (ADE). The study analyzed the factors associated with hospital death of patients admitted to UHS with ADE.

Objective: To describe patients with ADE identified in the SIH-SUS in Brazil over a ten-year period and to analyze the factors associated with in-hospital death in this study population.

Methods: This study is reported following the STROBE guideline. This is a case-control type study, with the original information from the administrative data from the hospital information system of the public health system in Brazil-SIH-SUS, in the period from 2011 to 2020.

Results: A total of 116,084,449 Authorization for Hospital Admissions (AHA) in SIH-SUS were evaluated, related to 112,882,404 hospitalizations paid by UHS in the period 2011–2020. After applying the exclusion criteria, 600,944 hospital admissions associated with at least one ADE were included in the study. 659,754 ADEs were reported, with an average of 1.1 ADE/inpatient and an ADE identification rate of 5.7 per 1,000 admissions. The proportion of patients with ADE in hospitalizations was 0.53%, and the risk of death among them was 1.8%. Among people with inpatient ADE, those with higher chances of in-hospital death were: women and older people; people living in more unequal and less developed municipalities—measured by the Gini index and HDI—; patients admitted to hospitals with larger size (number of beds) and medium complexity; patients who presented severity markers of the event that led to admission—shorter hospital stay (up to seven days), use of ICU and admission for urgent/emergency care. The main drugs involved were antineoplastics and immunomodulators (OR = 2.2; 95% CI = 1.6 to 2.9), causing mainly hepatobiliary (OR = 7.7; 95% CI = 6.8 to 8.7) or cardiac (OR = 3.7; 95% CI = 3.0 to 4.5) disorders. Drug intoxication (OR = 6.6; 95% CI = 3.5 to 12.4); and drug abuse were the EADs most associated with increased risk of death (OR = 3.9; 95% CI = 2.0 to 7.6).

Conclusion: Our findings indicate that patients with ADE who are female, older, of black/purple and yellow race/color, living in municipalities with lower human development and more unequal, who use antineoplastic and immunomodulatory drugs have a higher risk for in-hospital death. Drug poisoning and drug abuse are the adverse event classes most associated with increased risk of death. This study, confirm that the SIH-SUS is a robust source of data for the field of pharmacovigilance, enabling the identification of risk factors for death and facilitating the monitoring of ADEs in the hospital environment.

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O-017

Oral Presentation: Effectiveness and Safety of Maintenance Immunosuppressive Drug Therapies in Kidney Transplant: A Real-World Retrospective Cohort Study in Italy

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Introduction: Transplant recipients are chronically ill patients, who require lifelong drug therapies to prevent reject and graft loss. Maintenance therapy usually involves calcineurin inhibitors, tacrolimus (TAC) or cyclosporine (CsA), combined with mycophenolate (MMF) or mechanistic target of rapamycin (mTOR). To date, there is no consensus on the optimal immunosuppressive strategy [1-4].

Objective: The aim of the study was to assess the effectiveness and safety of maintenance immunosuppressive drug therapies in kidney transplant.

Methods: A retrospective multicentre observational study, involving 4 Italian regions, was conducted based on the national transplant Information system and regional healthcare claims data. Specifically, the regional analytical datasets regarding incident patients underwent to kidney transplant in the years 2009–19 were created using an open-source tool for distributed analysis. In the first step, patients in CsA and TAC-based therapy were matched by propensity score 1:1 considering donor/receipt demographical and clinical characteristics. The effectiveness (mortality or reject/graft failure) and safety (incidence of severe infections, cancer and diabetes) of treatments were estimated comparing outcomes between the two groups by a Cox proportional hazard model (HR; CI95%). Analyses were replicated comparing mTOR vs MMF treatment within patients in TAC therapy.

Results: Overall, 3,622 kidney recipients were considered, of which 21.7% treated with CsA-based therapy. Among patients in TAC-based therapy (N = 2,835), 69.8% and 19.7% were in combination with MMF and mTOR, respectively. During a median follow-up period of 4.0 years mortality and reject/graft failure incidence rates were equal to 1.9 and 2.1 per 100 patient-years (p-y), respectively. Among safety outcomes, serious infections had the highest incidence (9.4 per 100 p-y) followed by diabetes (3.6 per 100 p-y), and cancer (2.4 per 100 p-y). The first comparison showed that patients treated with CsA had higher risk of reject/graft loss (1.69; 1.16–2.46) and incidence of severe infections (1.25; 1.00–1.55) and a lower risk of diabetes (0.66; 0.47–0.91) respect those treated with TAC. While,

among TAC users, patients with mTOR had a lower risk of severe infections (0.81; 0.63–1.06) respect those with MMF.

Conclusion: In clinical practice, a significantly better benefit profile has been demonstrated for kidney recipients treated with TAC compared to CsA. In particular, the combination of TAC and mTOR appears to be the optimal strategy reducing the incidence of severe infections. Our findings on long term risk-benefit profile of immunosuppressive therapy may be helpful to define the optimal drug therapy in kidney recipients.

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O-018

Oral Presentation: Are COVID-19 Vaccines Safe in Children? Comparative Analysis of European Web-Based Prospective Monitoring vs. Pivotal Trials

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Introduction: To date, only two COVID-19 vaccines, Comirnaty and Spikevax, have received an extension of indication of use by European Medicines Agency (EMA) in 5–17 years old children/adolescents. Due to the small sample size of pivotal trials in pediatrics, real-world evidence on the safety of those vaccines in the pediatric population is urgently required.

Objective: (i) To investigate the safety of COVID-19 vaccines by measuring frequencies of solicited and serious adverse events following immunization (AEFIs) with the first and the second doses of

vaccines through active surveillance and, (ii) to compare the results with the published clinical trials in children and adolescents.

Methods: In 5–17 years old vaccinees, and up to April 21, 2022, we explored the COVID-19 vaccine safety using prospectively collected data from the “Covid Vaccine Monitor” (CVM) project [1]. CVM comprises several safety assessment approaches amongst which an active surveillance project of COVID-19 vaccines in Europe through web-based baseline + 6 follow-up questionnaires filled by vaccinees (or their parents). We measured the frequency of local/systemic solicited, and serious adverse reactions following COVID-19 vaccination (first and second doses). The results were compared with findings of pivotal trials in children/adolescents.

Results: Overall, 1,033 children/adolescents (5–11 years old: 32.9%; 12–17 years old: 67.1%) who received a first/second dose of vaccine (mostly Comirnaty: 98.2%) were enrolled in the study. Of them, only 658 (63.7 %) filled baseline and at least one follow-up questionnaire and were included in the CVM analysis. Overall, 293 (44.5%) reported at least one AEFI following first dose of COVID-19 vaccine, with injection site pain being the most frequently reported local solicited AEFI (N = 192; 29.2%) in both age groups. Fatigue was the most frequently reported systemic solicited AEFIs (N = 106; 16.1%) in both age groups, followed by myalgia (N = 90; 13.7%) and headache (N = 84; 12.8%). Similar trend was observed after administering the second dose of COVID-19 vaccine.

Conclusion: This study confirmed safety profile of COVID-19 vaccines in the pediatric population as already documented in the pivotal trials, with a high frequency of local solicited adverse events and an extremely low rate of serious adverse events.

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Not applicable.

O-019

Oral Presentation: The Risk of Oligospermia with Tyrosine Kinase Inhibitors: A Disproportionality Analysis from Vigibase and AERS Databases

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Introduction: Advances in the treatment of cancer in young patients have led to great improvements in life expectancy.

However, treatment with chemo or radiotherapy causes reduction of sperm counts often to azoospermic levels that may persist for several years or be permanent.

Oligospermia or azoospermia and long-lasting testicular atrophy are common adverse consequences of cancer treatment (1).

Objective: To quantify disproportionate reporting (Disp-Rep) (2-4) for the risk of drug-associated oligospermia/azoospermia for 29 tyrosine kinase inhibitors (TKIs) in 2 groups: (1) Anti-angiogenic (AA) TKIs; (2) Non-anti-angiogenic (NAA) TKIs.

Methods: We used the AERS and Vigibase databases, with data up to June 2021 and Oct 2021 respectively for analysis.

Cases of oligospermia and azoospermia were identified using MedDRA (v24.0) and the high-level-term (HLT) ‘Spermatogenesis and semen disorders’ (SSD).

Empirical Bayes Geometric Means (EBGM) with 90%CI were calculated to quantify Disp-Rep.

We considered Dis-Rep as confirmed if the lower bound, EB05, was > 2.

We studied 3 groups of drugs: (1) Positive control group (non-TKIs associated with oligospermia/azoospermia: sulfasalazine, colchicine and cisplatin) and two groups of TKIs: (2) AA TKIs (14 drugs) & (3) NAA TKIs (15 drugs).

Drugs were identified by non-proprietary name.

Results: We retrieved 101 SSD cases in AERS and 83 in Vigibase. In AERS, Disp-Rep with EBGM [90% CI, EB05–EB95] was confirmed for the positive control group: cisplatin 4.36 [3.31–5.70], and colchicine 3.53 [2.20–5.59] and in Vigibase for sulfasalazine 3.18 [2.07–4.72].

In AERS, Disp-Rep was confirmed for only 1 of 15 NAA TKIs: ibrutinib 3.37 [2.24–4.96].

No Dis-Rep (EB05 < 2) was found for the rest of NAA TKIs: afatinib, bosutinib, ceritinib, cobimetinib, crizotinib, dabrafenib, dasatinib, erlotinib, gefitinib, imatinib, lapatinib, nilotinib, osimertinib and vemurafenib.

No Dis-Rep was found for any of the 14 AA TKIs: acalabrutinib, axitinib, cabozantinib, dacomitinib, lenvatinib, neratinib, nintedanib, pazopanib, ponatinib, regorafenib, sorafenib, sunitinib, tivozanib and vandetanib. The analysis in Vigibase database yielded similar results. **Conclusion:** Ibrutinib (NAA TKI) was the only drug among the 29 different TKIs studied with Disp-Rep for oligospermia/azoospermia in both databases.

Our results however, should be interpreted with caution as disproportionality analyses are hypothesis generating rather than hypothesis testing.

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O-020

Oral Presentation: Perception and Utilization of Skin Lightening Agents Among Females of Asmara City: A Lesson for Strengthening Cosmetovigilance

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Introduction: Skin lightening agents (SLA) have been commonly self-used by African females to make their skin color lighter for cultural/social perception that equates beauty with fairer skin (1, 2). Skin lightening products contain high concentrations of harmful ingredients such as hydroquinone, mercurials, and corticosteroids, and are reported to cause serious complications such as hyperpigmentation, exogenous ochronosis, wound dehiscence, nephropathy, steroid addiction syndrome, predisposition to infections, and other endocrinologic complications. Despite all these public health risks, they have been used in many countries without regulation and consultation of healthcare professionals (3). Similarly, in Eritrea, there is uncontrolled marketing and use of SLAs even those with banned harmful ingredients.

Objective: This study was conducted to assess the perception and utilization of SLAs among females of Asmara, the capital city of Eritrea.

Methods: A cross-sectional descriptive study was conducted in representative samples of all beauty salons available in Asmara between May and July 2021. The study participants were selected using two-stage stratified cluster sampling technique. The data collected through face-to-face interview was entered and analyzed using CPro 7.3 and SPSS ver. 26, respectively.

Results: The study enrolled 721 females. The majority of the respondents agreed that SLAs can make someone white (84.4%), look beautiful (67.8%), trendy and fashionable (55.0%), and had the perception that white skin is more attractive than dark skin (58.8%). About two-third (64.2%) of the participants reported that they have ever used SLAs, mainly influenced by friends (60.6%). Of those who ever used SLAs, 46.4% were current users while 53.6% stopped it due to serious adverse effects, fear of adverse effects, and/or ineffectiveness of products. About half of the respondents (51.7%) used SLAs on a daily basis and the mean duration of use was 4 years (SD = 5.6; range = 0 to 38). With the use of SLAs, 43.7% experienced at least one adverse effect and 66.5% were satisfied with its use. Employed females (AOR: 1.68, CI 1.16, 2.43; $p = 0.006$) were more likely to be current users of SLAs compared to the unemployed and females who had favorable attitude against the use of SLAs were less likely to be current users (AOR: 0.96, CI 0.93–0.98; $p = 0.001$).

Conclusion: Utilization of SLAs among females was prevalent. They were satisfied with its use despite experiencing adverse effects which urges coordinated efforts in tightening the regulation of cosmetics in general and establishment of cosmetovigilance systems in particular.

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O-021

Oral Presentation: Drug-Related Hospital Admissions in Paediatrics—Is There Potential for Prevention?

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Introduction: Drug therapy in paediatrics is often associated with uncertainties due to lack of data from clinical trials. 42–90% of hospitalised children and adolescents are therefore treated with medication outside their product licence, in the outpatient setting 46–64% of patients are affected [1,2]. Due to this off-label use, missing paediatric dosage forms and complex dose calculations, medication errors (ME) occur up to three times more frequently compared to adults [3]. In addition, it can be assumed that 3–5% of admissions to paediatric hospitals are due to an adverse drug reaction (ADR) [4,5].

Objective: The aim of the study was to investigate the nature, characteristics and preventability of drug-related hospital admissions in paediatrics.

Methods: Within the study, all patients aged 0 to < 18 years, admitted non-electively to one of the 12 participating children's hospitals in Germany between 07/2018 and 06/2020, were screened for drug-related hospitalisations. A screening tool was used to systematically identify suspected ADRs and MEs. If parents had given consent for data transfer and further analysis, the suspected ADRs resp. MEs were subsequently validated by a blinded, independent expert team [6]. All ADRs and MEs were assessed with regard to their nature, preventability, severity and drug association.

Results: Of 41,829 patients admitted to these paediatric hospitals, 54.7% (22,875) had at least one drug administration before hospitalisation. Consent for further analysis was obtained for 9,732 (42.5%) of the patients with medication. Through the use of the screening tool, almost 40% (38.6%, 3,753) of these were suspected to be drug-related.

615 (16.4%) suspected cases were positively validated as drug(s) being the reason for hospital admission; the remaining cases in question were unlikely to be drug-related or suspected in error. 346 ADRs and 269 MEs were identified. Allergic conditions, seizures (incl. subtypes) and respiratory tract infections associated with the administration of immunosuppressants, viral vaccines and antiepileptic drugs were the main reasons for hospitalisation due to ADRs. Treatment noncompliance, accidental exposure to product and dosing problems (mainly underdosing) were primarily identified as MEs in connection with the use of antiepileptic drugs, insulins and analogues and other beta-lactam-antibacterials. 47.3% (291) of drug-related hospital admissions were preventable.

Conclusion: Drug-related hospital admissions play a significant role in paediatrics. Moreover, almost half of them are considered preventable and therefore result in unnecessary harm and treatment costs. Dosing databases, training, and systematic screening for ADRs and MEs have great potential to increase the safety of drug therapy in children.

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O-022

Oral Presentation: Development and Evaluation of a Blended Pharmacovigilance e-Learning Course in Africa

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Introduction: PhArmacoVigilance Africa is a project aiming at improving pharmacovigilance (PV) systems in Africa. The lack of staff trained in PV is one of the most serious limiting factors affecting the development of PV in resource-constrained settings. Previous experiences suggest that blending learning programmes can be implemented in resource-limited countries to train health care professionals (HCP) with remarkable gains in terms of knowledge acquisition.

Objective: To evaluate the effectiveness of our blended learning training programme

Methods: We developed the blended-courses integrated with a Train of Trainers scheme [1]. Two e-learning courses were made available on a web-based application, together with a manual on how to combine the e-learning courses together with face-to-face interactions. The blended course were given in Tanzania, Eswatini and Nigeria. We compared the participants pre- and post course test results (Students t-test evaluation), assessed the participants' satisfaction and changes in attitudes towards PV (questionnaires survey) and the total number of Individual Case Safety Reports (ICSRs) submitted to each National PV Agency twelve months before and after the training, although we did not match the reporters to the participants that took the courses.

Results: In the three countries 95 participants were trained (Table 1). All participants completed the two courses and the mean score of the post-test was significantly greater than on the pre-test (Table 1). In the second level, the participants from the first training were training others. The training was delivered to 360 and 283 HCPs respectively in Tanzania and Eswatini, out of which 48% and 39%, respectively, completed the two courses with a significant positive difference (Table 1). The majority of respondents to questionnaires have been satisfied, declared they felt more involved in PV and reported at least an ADR after the training both in the first and second level. The trends of reporting increased in the twelve months after the training if compared to the previous twelve months: 14523 vs 2369 and 1224 vs 729 ICSRs were reported to Vigibase for Tanzania and Eswatini National Agency respectively.

Table 1: Student's T-test score in the first and second level in Tanzania, Eswatini and Nigeria

COUNTRY (level)	Number of participants (% female, % profession**)	Student's T-test score in the first e-learning course	Student's T-test score in the second e-learning course
Tanzania (first)	36 (39%, 81% pharmacists)	13.32 (p<0.001)	11.59 (p<0.001)
Tanzania (second)	171 (60%, 43% pharmacists)	18.78 (p<0.001)	17.76 (p<0.001)
Eswatini (first)	34 (37%, 34% nurses)	7.91 (p<0.001)	10.77 (p<0.001)
Eswatini (second)	110 (76%, 61% nurses)	15.47 (p<0.001)	18.80 (p<0.001)
Nigeria (first)	25 (68%, 32% pharmacists)	5.03 (p<0.001)	9.02 (p<0.001)
Nigeria (second)	Working progress	Working progress	Working progress
** it is the % of the profession role profile more represented			

Conclusion: Our results demonstrated that a blended course can reach an important number of participants and improve their knowledge. The participants' satisfaction was high and a more positive attitude towards PV was observed. It is difficult to establish how much of the increase of reports was attributed to the blended learning training.

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O-023

Oral Presentation: Teaching Pharmacovigilance to French Medical Students During the Covid-19 Pandemic: Interest of Distance Learning Clinical Reasoning Sessions

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Introduction: Considering data from the literature in favor of active educational intervention to teach pharmacovigilance, we describe an

innovative model of distance learning clinical reasoning sessions (CRS) of pharmacovigilance with 3rd year medical French students.

Objective: The three main objectives were to identify the elements necessary for the diagnosis of an adverse drug reaction, report an adverse drug reaction and perform drug causality assessment.

Methods: The training was organized in 3 stages. First, students practiced clinical reasoning (CRS) by conducting fictive pharmacovigilance telehealth consultations. Second, students wrote a medical letter summarizing the telehealth consultation and analyzing the drug causality assessment. This letter was sent to the teacher for a graded evaluation. In the third stage was a debriefing course with all the students.

Results: Of the 293 third-year medical students enrolled in this course, 274 participated in the distance learning CRS. The evaluation received feedback from 195 students, with an average score of 8.85 out of 10. The qualitative evaluation had only positive feedback. The students appreciated the different format of the teaching, with the possibility to be active.

Conclusion: Through distance CRS of pharmacovigilance, medical students' competences to identify and report adverse drug reactions were tested. The students experienced the pharmacovigilance skills necessary to detect adverse drug reactions in a manner directly relevant to patient care. The overall evaluation of the students is in favor of this type of method.

References/Further Sources of Information

Not applicable.

O-024

Oral Presentation: Recommended Best Practices of Pharmacovigilance of Herbal Medicinal Products

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Introduction: Herbal medicinal products (HMP's) are commonly believed by consumers to be safe. In contrary to that believe, HMP's can cause adverse drug reactions (ADR's) and/or interactions with conventional medicines (CM). HMP's often do not have the same legal status as CM, but are often on the market as food supplements. To ensure the safety of the HMP's and to protect consumers, optimal pharmacovigilance (PV) practices must be in place.

Objective: To create an overview of the current state of herbal pharmacovigilance and to give recommendations about the best practices of PV of HMP's based on a study with interviews held with experts in herbal PV from different countries across the world.

Methods: This research used a qualitative inductive methodology through thematic analysis. The first step was to identify, through a literature review, current practices for herbal pharmacovigilance. Based on the findings a semi-structured interview guide was designed, and purposive sampling was used to recruit the interview participants. Through two different networks, the ISO-P-Herbal & Traditional Medicines Special Interest Group (SIG) and the Nutrivigilance network, 46 experts in herbal pharmacovigilance were invited via e-mail to participate in an interview. By using a snowballing technique more potential participants were reached. The interviews were originally performed face to face via Zoom[®] but to increase the number of participants, the possibility to hand in written answers to the questions

was added. Transcripts were analyzed with NVIVO[®]. This study was performed to adhere to the Consolidated criteria for reporting qualitative research (COREQ) [1].

Results: Sixteen people out of eleven countries (China, Ethiopia, Italy, Japan, Malawi, Morocco, New Zealand, Portugal, Saudi-Arabia, Thailand and The Netherlands) participated in the study in twelve interviews. Out of those twelve interviews, five general and two specific recommendations of best practices that are applicable to a certain country/region emerged.

- Improving and implementing legislation/creating new guidelines (general).
- Improving awareness (general).
- Improving and introducing education (general).
- Adapting ATC-coding system/causality assessment for HMP's (general).
- Improving underreporting (general).
- Funding (specific for region).
- Decentralization (specific for region).

Conclusion: This study identified barriers in the pharmacovigilance of HMP's and yielded recommendations of best practices of pharmacovigilance of HMP's. Most of these recommendations are applicable worldwide, while some are limited to certain regions.

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O-025

Oral Presentation: Safety of Medical Cannabis: A Descriptive Study Using the Quebec Cannabis Registry

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Introduction: Although medical cannabis (MC) has been available in Canada since 1999, lack of recognition of MC as a drug has restricted patient access. The Quebec College of Physicians, between 2015 and 2018, authorized MC use only within a research framework. This consisted of the Quebec Cannabis Registry (QCR), a clinical surveillance program.

Objective: To describe patterns of adverse events (AEs) reported over up to 3 years after MC initiation, within the QCR registry.

Methods: The QCR is a prospective registry of adults (≥ 18 years) who were enrolled through participating physicians when they initiated MC for any medical reason between May 2015 and October

2018, after which time recreational cannabis was legalized in Canada. Follow-up ended due to either MC discontinuation, loss to follow-up, 3 years follow-up, or end of data collection (May 2019, 6 months after the last patient in). Data were collected at inclusion and at follow-up visits every 3 months for the first 2 years, then at least once per year in the third year. MC mode of administration (ingestion, inhalation, other), and cannabinoid content ratio (tetrahydrocannabinol (THC)-dominant, cannabidiol (CBD)-dominant, or balanced) were documented. AEs occurring since the last follow-up visit were recorded and coded using MedDRA preferred terms (PTs).

Results: 2,991 patients were enrolled in the registry (mean age 50.9 years, 50.2% females) and the most frequent primary indications for MC were pain (77.5%), anxiety (9.7%), and insomnia (4.8%). Over follow-up, 108 (3.6%) patients experienced moderate or severe AEs, yielding 111 AE reports (3 patients had 2 reports), of which 9 were certainly/probably related to MC and met the regulatory criteria of seriousness (5 required intervention, 3 disability [transient according to case narratives], 1 hospitalization prolongation). Reports included a total of 214 AEs (average 1.9 AEs per report). The most common PTs were dizziness (12.9%), nausea (11.3%), somnolence (9.7%), and vomiting (8.1%) for ingested MC, and headache (13.0%) for inhaled MC. Dizziness and somnolence were the most frequent PTs associated with THC-dominant MC (12.0% each); for CBD-dominant products, vomiting (19.0%) was most common; and dizziness (17.5%), nausea (14.0%), somnolence (10.5%), and headache (8.8%) were the most frequent for balanced content.

Conclusion: There were no new safety concerns identified in the Registry, although notable differences in AE profile between modes of administration and cannabinoid content ratios should be considered by health professionals. Further work identifying and managing risk factors for AEs is warranted to maintain a favorable risk-benefit ratio for MC.

References/Further Sources of Information

Not applicable.

O-026

When Public Health and Politics Clash—Communicating about Dengvaxia Between Science and Emotions

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Introduction: Dengue is one of top ten global health threats and is a serious burden in the Philippines. Dengvaxia immunization program was launched on April 2016 for children 9–14-year-olds in three regions with high statistics of dengue, hospitalization, and deaths. This was coincidentally the campaign period for national elections. Use of vaccine, once available, was part of a strategy to control epidemic. Current measures were inadequate. On the 30 November 2017, Sanofi announced an advisory that vaccine should not be used in those who are dengue naïve otherwise they will have risk for severe dengue and additional hospitalization. What started as vaccine-vigilance information sparked a public outcry. This led to a series of parliamentary investigations, traditional and social media misinformation and disinformation vilifying the health decision makers and the company, and criminal charges filed against over 20 individuals by the state over alleged unproven vaccine caused deaths. Despite attempts to correct these narratives by a few health professionals, the damage to institution, the program, the product, and individuals have been done. The consequences of such actions of emotional approach without understanding the science have resulted

in creating general vaccine rejection, hesitancy, other outbreaks such as measles, lowered confidence even with recent COVID vaccines.

Objective: This abstract aim to describe the situation at that time in the Philippines and extract lessons that will inform better risk communications during crisis.

Methods: Literature analysis and environmental scans were undertaken.

Results: Some of the important lessons learned are in risk management and communications. Adverse health product information should be announced with circumspect considering the level of health literacy and risk appreciation in a country. Partisan politics interfered with poorly understood science, fueled by imprudent comments by officials and health professionals who spoke out of turn, amplified by the media and created chaos. The fear was so palpable that enlightened health professionals refused to provide countervailing facts. While the vaccine is listed as part of WHO EML and used in many countries, Philippines has imposed a ban on the product. Reinstating the vaccine would be perceived as the government had back-pedaled on a mistake. In the meantime, the drama contributed to vaccination hesitancy and outbreaks.

Conclusion: Public health decisions are policy and regulatory decisions anchored in ethical and utilitarian principles. Pharmacovigilance plays an important role in public health decisions but only if approached in a scientific and objective manner and in the context of a country's culture.

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O-027

Advancing the Science of Vaccine Safety: Introduction to the International Network of Special Immunisation Services

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Introduction: Vaccines are vital tools to control epidemic and pandemic diseases, such as COVID-19, demonstrating safety and effectiveness. However, rare adverse events of special interest (AESIs) following vaccination arise with every new emerging pathogen vaccine program. The mechanisms underlying AESIs such as myopericarditis following COVID-19 mRNA vaccines are not known. Adversomics, a set of technologies that measure the inventory of molecules (e.g., DNA, RNAs, proteins, inflammatory mediators) in a given sample collected during and after an adverse reaction, has potential to uncover the etiologies of AESIs. The International Network of Special Immunization Services (INSIS) brings together vaccine safety, public health, and systems biology experts in middle- and high-income countries to investigate the causes of, and identify strategies to mitigate AESIs following vaccination (insisvaccine.org).

Objective: INSIS aims apply an 'adversomics' approach to identify molecular signatures and biomarker risk factors associated with AESIs to inform vaccine development and risk-benefit of assessment of vaccines for pandemic and epidemic diseases, with scalability to respond to new safety signals anywhere in the world.

Methods: INSIS-led studies will employ a case-control design. Well-characterized cases with AESIs post-vaccination, starting with thrombosis with thrombocytopenia syndrome (TTS) following COVID-19 viral vector vaccines and myopericarditis following COVID-19 mRNA vaccines, will be matched to controls. Brighton Collaboration case definitions and harmonized protocols will be employed to collect detailed clinical data and serial blood samples suitable for adversomics (e.g., transcriptomics, proteomics, metabolomics, flow-based immunophenotyping) analysis. A central database and centralized sample processing at INSIS-affiliated multi-OMICS labs will ensure internal validity. Integration of clinical and biological data will enable comparisons of analyte levels and immune responses within groups over time and between cases and controls. Global collaboration across five continents will ensure adequate sample size.

Results: The INSIS approach and its reach as a global network will enable characterization of molecular signatures and biomarkers associated with post-vaccination AESIs.

Conclusion: INSIS-led studies will provide insight into pathways triggered in these AESIs and susceptible populations to inform vaccine development strategies to reduce the potential to trigger pathways involved in AESIs, risk-benefit assessment, and personalized vaccination strategies. Through global collaboration, INSIS aims to reduce the potential for AESIs in the COVID-19 pandemic and beyond.

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POSTERS

P001

Pharmacovigilance and Drug Safety Simulation Game: Innovative Approach for Training and Capacity Building

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Introduction: During the covid 19 period, several countries needed to set up or develop their pharmacovigilance systems, unfortunately containment and the closure of borders prevented the organisation of classic training sessions. the anti-poison centre of morocco, a WHO collaborating centre for the development of pharmacovigilance practices, set up several online training sessions and, in parallel, a pharmacovigilance simulation game was developed to allow for autonomous learning in this field Translated with www.DeepL.com/Translator (free version)

Objective: The objective of this work is to present the pharmacovigilance simulation game developed by CAPM, RCC and the results of its pilot use with 150 pharmacovigilants from 10 French-speaking African countries

Methods: Pharmacovigilance and drug safety simulation game was developed by the Rabat WHO collaborating centre (RCC) in collaboration with the IT company Nowedge. The game is based on good practices in Pharmacovigilance(PV), and inspired by the different WHO guidelines, the experience of the Moroccan PV center, and behaviors consensually considered as the norm in PV.

Results: The game allows the assessment of soft skills, and the evaluation of participants' ability to make decisions in real life situations. In fact, they are put in a real-life situation to choose actions and strategies for the development of a PV center and must be able to optimize the human and material resources at their disposal to make their center shine within their national health system but also at the level of the international PV network.

The main objectives are to:

- Better understand the challenges and outlooks linked to the creation and management of a PV center.
- Improve the participants capacity to analyze and make decisions.
- Encourage the participants to look for the right information.
- Put into practice the theoretical concepts in causality assessment, signal detection and risk minimization actions.
- Gain a 360° vision of pharmacovigilance above its scientific aspect.

During the game, within 10 levels, participants have to set up a PV center following WHO pharmacovigilance indicators: a practical manual for the assessment of pharmacovigilance systems as structural indicators, process indicators and outcome indicators, and following the pharmacovigilance process from collecting data, analyzing them, detecting signals, and setting up national technical pharmacovigilance committee to discuss about safety signals and risk minimization actions to put in place.

Conclusion: The use of the game by the 150 pharmacovigilantes during the pilot phase gave good feedback on the ease of use and the effectiveness of the game in capacity building in pharmacovigilance

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P002

Embedding Digital Health, AI/ML and RWD in Managing Safety Risks and Enhancing Pharmacovigilance

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Introduction: Pharmacovigilance has traditionally been a reactive science with a significant dependence on spontaneous adverse event reporting. The pandemic on the other hand has accelerated application of novel technologies and approaches to engaging with the patient, remote connected care at their home and dependence on technologies to supplement regular communication channels. Telemedicine is evolving rapidly and playing a key role in clinical interventions

Objective: Digital Health and novel technologies offer a significant opportunity to enhance pharmacovigilance thru proactive patient monitoring, risk communication, personalized care plans and access to real world data. Leveraging such approaches will not only lead to early detection of risks but also to personalized interventions and improved patient outcomes.

Methods: Digital devices can monitor vitals for the patient while AI/ML methods could identify patterns within the data which indicate clinical changes as well as personalize thresholds for individual patients. Educational material which is more interactive, visual and multi-dimensional can replace paper or text based risk communication material.

Results: Embedding digital health approaches as well as AI/ML technologies along with enhanced analytics with RWD help monitor the patients changing state and indicate clinically significant events. This could provide early signal detection in individual patients and enable proactive patient level pharmacovigilance. Educational and risk related material can be dynamically updated based on patient preferences, interactions and profiles. Machine learning approaches which link material with outcome can enhance impact of pharmacovigilance methods and tools.

Conclusion: Digital Health, AI/ML and RWD have created opportunities to enhance and personalize pharmacovigilance. In order to utilize the full potential of such options it is critical that the regulatory framework is updated to enable such approaches which complement traditional PV and can drive efficiencies and higher effectiveness in the risk communication process. Collaboration within the network of industry and regulators is essential to further such research and maximize the impact on value for patients, HCPs and sponsors.

References/Further Sources of Information

To be provided along with presentation material.

P003

Integration and Modeling of Translational Safety Data for Post-Marketing Surveillance

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Introduction: Large amounts of data associated with safety issues are generated along the entire lifetime of drugs, from its infancy as preclinical leads, through its adolescence as clinical candidates, all the way up to its adulthood as marketed drugs exposed to the human population. Across the different stages in the life of a drug, some of the data collected initially may be confirmed and consolidated with data at an advanced stage, whereas other data may not be translated, and in some cases may even contradict, those safety signals that are ultimately observed in the human population. Collecting and properly integrating such an heterogeneous pool of data is a complex and tedious task. But even if one manages to put all data together, the construction of useful models to anticipate and detect drug safety signals remains a challenge.

Objective: The presentation will cover our efforts to connect data from *in vitro* safety pharmacology, preclinical toxicology, clinical safety and post-marketing spontaneous reports for over 9,000 small molecule drugs, combination drugs, and biologics. A novel consensus approach using various statistical and machine learning methods to anticipate side effects of potential safety concern, detect adverse drug reaction signals and perform pharmacovigilance analyses will be introduced. Use case application examples to individual drugs and drug classes will be discussed.

Methods: Our consensus approach to post-marketing surveillance integrates four different methodologies based on detection of prior safety markers, identification of class reactions, statistical projection of disproportionalities based on reporting frequencies and velocities, and machine learning models of translational safety data.

Results: Results on the validation of our approach to anticipating adverse drug reactions of safety concern to the population at the postmarketing stage based on (i) *in vitro* safety pharmacology data, (ii) preclinical toxicology data, (iii) clinical safety data and (iv) the first sample of 25 postmarketing spontaneous reports will be presented. Based on data available in each case, the performance of the different methods varies for different drugs, drug classes, and side effects. A discussion on performances in selected use cases will be included. As an example, the analysis of long-term PARP inhibition on circadian patterns and its dependence on the reporting bias by consumers will be discussed.

Conclusion: Integration and modelling of the large amount of translational safety data currently available from all phases of drug discovery, development and post-marketing to anticipate and follow adverse drug reactions opens an avenue to a whole new perspective in pharmacovigilance.

References/Further Sources of Information

Not applicable.

P004

Online Interest in Cannabis and Psychedelics in Peri-Pandemic Europe for Robust Pharmacovigilance

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Introduction: Psychedelics are unique psychoactive chemicals that can change consciousness by acting on 5-HT_{2A} receptors [1-3]. There is limited knowledge concerning the online interest in psychedelics that we can extrapolate via trends websites.

Objective: We aim to examine the online information-seeking behavior concerning the most popular psychedelics, including cannabis—a quasi-psychedelic—in the European Union (EU) members of interest and the UK before and during the pandemic.

Methods: We designed a “dictionary” of terms to extract online search data from Google Trends concerning psychedelics and cannabis from 01-Jan-2017 to 1-Jan-2022. We conducted a triple (Holt–Winters) exponential smoothing—additive model—for time series analysis to infer seasonality [4, 5]. We utilized hierarchical clustering—an unsupervised machine learning method—to explore clusters of countries concerning the spatial (geographic) mapping of these chemicals. We also implemented—a t-test—for comparing the slope difference of two trends (before versus during the pandemic).

Results: There was an evident seasonal pattern for cannabis, NBOMe, and psilocybin in almost all nations of interest. In Italy, cannabis had a quarterly seasonality (p -value < 0.0177), while NBOMe and psilocybin exhibited a half-yearly and an annual seasonality, respectively ($p = 0.0007$ and $p = 0.0126$) (Table 1). Similar patterns existed in France and the UK, while those in Germany, Sweden, and Romania had relatively shorter periodicity. We could not infer seasonality concerning cannabis (Germany and UK) and psilocybin (Sweden and Romania). Analysis of slopes and hierarchical clustering conveyed differentiated patterns concerning the temporal and spatial mapping, respectively, while contrasting the two periods (before versus during the pandemic).

Table 1. Holt–Winters exponential smoothing for NBOMe.

Substance – Country	Seasonality	Seasonality	
	Period (weeks)	Estimate (+/-) SE	p-value
NBOMe – Italy	26	0.236 (+/-) 0.069	0.0007
NBOMe – France	52	0.790 (+/-) 0.075	<0.0001
NBOMe – Germany	13	0.188 (+/-) 0.065	0.0040
NBOMe – Sweden	13	0.329 (+/-) 0.055	<0.0001
NBOMe – Romania	26	0.356 (+/-) 0.078	<0.0001
NBOMe – UK	26	0.521 (+/-) 0.086	<0.0001

† SE: standard error; significant p -values are in bold font.

Conclusion: Cannabis and psychedelics follow somewhat a consistent pattern concerning seasonality across Europe; some correlate with the seasonal harvesting of mushrooms, and others with public holidays, including Christmas, the new year holiday, or school breaks. The pandemic influenced some significant changes concerning the online interest in the EU and the UK; nonetheless, we should rely on more rigorous longitudinal and experimental study designs—possessing a superior level of evidence—to confirm the causal relationship. However, these patterns might be insightful for decision-makers and regulatory authorities—like the EMCDDA—to prognosticate and prevent addiction catastrophes.

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P005

Challenges of Local Medical Literature Monitoring and Possible Automation

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Introduction: Continuous monitoring of the safety profile of drugs is one of the critical processes of pharmacovigilance. As medical literature might be valuable source of safety data, especially for rare, unlisted, serious cases, all MAHs are obliged to medical literature monitoring (MLM) in all marketing countries [1]. Current state of local MLM is manual reading “from cover to cover” without any automation. This approach can be changed through modern automation techniques.

Objective: To develop and test a tool for automated monitoring of local literature and enhance drug safety data identification.

Methods: Modern programming approaches were used to create PV platform, intended for automated literature screening. GAMP 5 recommendations were used to prove the validation status.

Results: We developed a tool—DrugCard PV platform which screens local medical sources for updates on a weekly basis. Till May 2022 we added around 150 local journals originated from 10 countries that cover different therapeutic areas. Our tool automatically searches for defined keywords (drug trade names, active substances) in published articles. Different file formats can be screened including text, pdfs, images etc. In case a new issue of a journal is published—a PV specialist will receive an email notification. The mandatory features of a validated computerized system, like audit trail, logs, reports are also present here. Instead of manual reading of the whole journal issue the user only should read a separate article, analyze whether there is a valuable safety data and label it depending on the content. PV specialists may work together inside the platform and provide a quality check for labeled articles.

Our pilot study of how a new tool may improve the efficiency revealed interesting results. We found out that around 12 times less time is needed for literature screening with automated approach vs traditional approach (average 24 hours/week vs 2 hours/week). This was calculated with the list of journals in Ukraine ($n = 100$) and portfolio of popular drugs ($k = 50$). Despite the dramatically decreased amount of time needed, the number of identified ICRs from literature increased. During the abovementioned pilot study of automated local literature monitoring lasting 2 months, 31 safety cases were identified (valid and non-valid ICRs). This is much more than usual rate of safety cases finding.

Conclusion: Automated local medical literature monitoring is current technological approach which should be widespread among PV departments of MAHs and CROs. It offers increasing efficiency in safety information identification with less time spent on routine activities.

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P006

Hyperacute Multisystem Toxicities with Immune Checkpoint Inhibitors in the FDA Adverse Event Reporting System: The Immune-Adversome

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Introduction: A plethora of pharmacovigilance studies have recently described the spectrum, kinetics and other features of immune-related adverse events (irAEs) with immune checkpoint inhibitors (ICIs) [1], including rare but potentially fatal irAEs such as overlap syndrome (myocarditis with myositis/myasthenia gravis) [2]. Hyperacute toxicity is a recent newly described entity, albeit incompletely characterized [3].

Objective: To describe pharmacological and clinical features of hyperacute toxicities reported to the Food and Drug Administration Adverse Event Reporting System (FAERS) through a network-based approach (the Immune-Adversome).

Methods: We collected adverse events to ICIs (including anti-CTLA4/PD-1/PD-L1 agents) recorded in FAERS up to December 2021. We selected reports with available information to calculate a plausible time-to-onset. Events of interest were classified into fulminant (within 7 days) and hyper-acute cases (within 21 days, i.e., during the first infusion cycle). Cases were described in terms of demographic and clinical features: age, gender, anticancer regimen (combination vs monotherapy), therapeutic indications, seriousness (hospitalization), case fatality rate (CFR, namely the proportion of cases where death was reported as outcome), co-reported symptoms, co-reported irAEs. The Immune-Adversome was estimated considering events as nodes and co-reporting as links. Analyses were performed using the “R” software (v. 4.1.2).

Results: Out of 11,798,098 FAERS reports, ICIs were recorded in 64,112 cases (59,022 had plausible time to onset). Hyperacute cases (18,691) represented 31.7% of total ICI reports, and were mainly reported in males (62.7%), from Asia (34.8%), by clinicians (46%). No significant differences emerged with regard to seriousness between hyperacute and other cases (onset >21 days), namely hospitalization (42.9% vs 49.8%), death (27.9% vs 23.21%) and CFR (15.6% vs 13%; 16% for fulminant cases). Monotherapy was reported in the majority of cases (88.6%), mainly pembrolizumab (5,687). Pyrexia, diarrhea, fatigue, dyspnea were the most frequently reported symptoms. Hyperacute myocarditis was reported in 34.7% of cases with specified time-to-onset (862 over 1,583 total cases), with a CFR of 46.5%. Among fulminant cases, most frequent irAEs were interstitial lung disease (624), colitis (450), hypothyroidism (369), and myocarditis (234). The Immune-Adversome identified different hyperacute multisystem irAEs, including overlap syndrome (median onset 10 days, CFR 37%). Other co-occurring irAEs were colitis-hepatitis-thyroiditis, and arthritis and psoriasis.

Conclusion: The spectrum of hyperacute multisystem irAEs with ICIs is heterogeneous. Our network approach may complement traditional disproportionality analyses in pharmacovigilance for a more effective signal detection technique, thus supporting regulatory and clinical monitoring, especially in complex scenario such as oncology.

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P007

Temporal Evolution of Disproportionality Parameters: Study of the Case of Opioids in Relation to QTc Interval Prolongation

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Introduction: The prolongation of the QT interval is a serious and potentially fatal adverse reaction that has led to the discontinuation of many drugs (including some opioids). Data mining on pharmacovigilance databases can detect signals that identify early the risk associated with some drugs.

Objective: To examine the association between opioids and risk of QT prolongation in reports submitted to the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) between 2004 and 2021.

Methods: Relevant reports in the FAERS were identified and analyzed. The reporting odds ratio (ROR ± IC95), Proportional ADR reporting ratio (PRR ± IC95), Chi square (Yates' correction), and Yule's Q (Q ± IC95) was used to detect spontaneous report signals, calculated using the case/non-case method. Cases were identified using Standard Medical Query (SMQ) for QT Prolongation defined by MedDRA 21.0 in which opioids (Meperidine, Tramadol, Dextropropoxyphene, Methadone, Fentanyl, Morphine, Hydromorphone, Oxycodone, Buprenorphine, and/or Nalbuphine) were the suspected drug.

Results: A total of 36239 drug-reaction pairs was found in 580261 opioid reports. Significant Signal (ROR, PRR, Chi2, Q) were found for whole opioid group: ROR 1.28 (1.26-1.29), PPR 1.27 (1.25-1.29), Yule's Q 0.14 (0.12-0.16) and Chi2 With Yates' Correction: < 0.00001. Analysis of individual opioids show significant signals for QT prolongation for each drug. The temporal evolution of the different signals according to the number of reports included from 2004 to 2021 shows early significant positization of signals in the first 6 to 12 months. Studying the parameters of disproportionality and

their evolution over time, the reduction of 10% of the confidence interval for two or three consecutive years was associated in most cases with the appearance of clinical reports in publications, incorporation of alerts and measures risk minimization.

Conclusion: Analysis of the FAERS database showed significant signals for QT prolongation with opioid treatments. Underlying mechanism is unknown, but it seems to be linked to hERG channel blocking. We propose the evaluation of the trend of change in the confidence intervals of the disproportionality parameters as a measure that can predict the occurrence of clinical events at the population level and a possible useful strategy to minimize adverse reactions.

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P008

Identifying Medications Underlying Communication Atypicalities: A Pharmacosurveillance Study Within the FDA Adverse Event Reporting System

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Introduction: Language and speech are increasingly debated as potential markers for diagnosing and monitoring patients with affective and psychotic disorders (1–3). However, many neglected factors may confound communicative atypicalities. A comprehensive list of potential confounding drugs will support the design of robust communicative marker studies.

Objective: We aim at identifying a list of drugs potentially associated with speech and language disorders, within psychotic and affective disorders.

Methods: We identified terms from the Medical Dictionary for Regulatory Activities (MedDRA) inherent to speech and language Adverse Drug Reactions (ADRs) and segregated them into clusters of overlapping terms to structure a search on the FDA Adverse Event Reporting System (FAERS, updated to June 2021). Within the FAERS, we considered separately 3 populations (psychotic, affective and non-neuropsychiatric disorders), to account for the confounding role of different underlying conditions. We calculated the Reporting Odds Ratio (ROR) for individual drugs with a Bonferroni correction. Associations which were not already reported in the SIDER database of labelled ADRs, were further stratified based on expected biases (using Directed Acyclic Graph). Robustness analyses were performed to account for the biases.

Results: We identified a list of 291 potential expected and 91 unexpected confounding medications for the identification of communication markers of affective and psychotic disorders (e.g.,

anticholinergic agents associated with dysphonia, sedatives with motor control impairment, antineoplastic medications and fluoroquinolones with aphasia and incoherence). We developed also a MedDRA query proposal for speech and language conditions, formalization of possible biases, and related analyses to account for them.

Conclusion: We provided a list of medications to be accounted for in future studies of communicative bio-behavioral markers in affective and psychotic disorders. The methodological procedure we developed does not simply facilitate future investigations of communicative biomarkers in other conditions, more crucially it provides a case-study in more rigorous procedures for digital phenotyping in general.

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P009

Competitive Intelligence in Pharmacovigilance—A Case Study on Two Covid-19 Vaccines

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Introduction: The comparison of safety profiles for products recently on the market is difficult. There is a lack of methodology for quantifying the potential differences between products that have the same indication.

Objective: Provide the tools to quantify the differences in spontaneous reporting between two products

Methods: Under the null assumption that two products have the same safety profile, the scatterplot of the Empirical Bayes Geometric Mean (EBGM) measured for the different MedDRA Preferred Terms (PTs) post Product A (axis x) and post Product B (axis y) should follow the diagonal line. An Euclidian distance from the EBGM to the diagonal line measures the deviation from what would have been expected under the null assumption of similar safety profiles. As the deviation does not capture the statistical uncertainty around the estimate, we propose as measure of the deviation the minimal distance of the four Euclidian distances calculated from each of the credibility intervals around the EBGM post Product A and Product B.

Results: We quantified the most significant differences in reporting between the two vaccines that were approved in the US against covid-19 using publicly available data from the Vaccine Adverse Event Reporting System (VAERS). A visualization capturing the global trend of the most substantial differences in reporting was generated.

Conclusion: This relatively simple method can provide quantification of the differences in reporting and could help prioritize one product over the other for some population subgroups.

P010

A Method for Identification of Renal Disease in Unstructured Clinical NarrativesH. Davies¹, P. Noble¹, I. Fins¹, G. Pinchbeck¹, D. Killick¹¹*University of Liverpool, Institute of Infection-Veterinary and Ecological Sciences, Liverpool, United Kingdom*

Introduction: The application of text mining approaches to identify adverse events (AEs) from electronic health records (EHRs) is a growing area of interest in pharmacovigilance research. In veterinary medicine, the majority of EHRs consist of unstructured clinical narratives, hence the development of appropriate methods for identifying AEs of interest is an important step in the research process. Identifying renal disease poses a specific challenge as the event may be described in narrative form or implied by reported test results or the use of renal disease specific medications. In this study we developed regular expressions (regexes) to identify relevant mentions of renal disease in veterinary free text clinical narratives.

Objective: To develop a method for identifying veterinary patients with renal disease in free text clinical narratives.

Methods: Using VeDDRA terminology as a starting point, we used an iterative approach to develop a series of regexes which were then applied to a random sample of 10,000 clinical narratives. In order to measure precision, clinical narratives containing a match to the regexes were reviewed against a case definition by two independent reviewers and disagreement was settled by consensus. Terms in the final regex were derived from three sources—VeDDRA, a word embedding model and expert opinion. To determine recall, the final regex was applied to a sample of consults where the main presenting complaint was deemed to be renal disease by a veterinary clinician.

Results: The regex containing only VeDDRA terms had a poor positive predictive value (PPV) (0.17). Expanding this terminology using a word embedding model improved the PPV to 0.27. Following changes suggested by a veterinary expert, the PPV of the final regex was improved to 0.43. When the regex was divided into three components, the PPV for these individual portions was mentions of renal disease (0.35), mentions of test results (0.44) and mentions of renal disease treatment (0.8). When compared against the veterinary clinician validated sample of renal disease consults recall was 0.07 for the VeDDRA regex, 0.52 for the word embedding model expanded regex and 0.68 for the final regex.

Conclusion: The developed regex can be used to identify animals with renal disease, with mentions of renal disease treatment being the most specific indicator of clinical disease. This method can be employed to filter potential cases of interest from large datasets for use in observational studies.

P011

Automated PV: What Are We Waiting for?J. Markey¹, M. H. Petersen²¹*Insife, Sales & Marketing, London, United Kingdom;* ²*Insife, Executive Management, Copenhagen, Denmark*

Introduction: We use AI in our everyday lives probably without even realising it. If we trust and have confidence in AI technology, why haven't we adopted it more in PV? There are many discussions about the use of AI in PV and the potential innovation that it could bring but given the conservative nature of our business and having to work in a

highly regulated environment, how can we build confidence to get us over that barrier. Will having the regulators use the same AI make us more comfortable or will legislation be necessary to drive us forward?

Objective: Explore why PV has lagged behind with AI technology that is commonplace in other parts of our lives and business. Aspects of AI, such as machine learning, are used in areas such as early disease prediction, clinical diagnosis, outcome prediction and prognosis evaluation, personalized treatments, drug discovery, manufacturing, clinical trial research, and more. In our personal lives, services like Amazon and Google use AI to understand and target their customers and we accept that as normal. The objective of this presentation is to explore the reluctance of accepting AI in PV and how we can move towards overcoming those obstacles.

Methods: This presentation is based on the presenters' experience of working in PV for 20+ years from an industry, consulting, technology vendor and regulatory authority perspective.

We will look at some real-life practical examples where AI in PV has worked and what it took to get there.

Results: N/A.

Conclusion: We will show that the practical application of AI is achievable and has been achieved in the high volume environment of a regulatory authority. Many of the AI features used by the RA, and the lessons learned from that project, can also be applied in industry, so why are we waiting?

References/Further Sources of Information

If accepted, we will invite a speaker from the regulator to join/replace one of the proposed speakers to discuss their experience of implementing AI solutions first hand.

P012

Automated De-Identification of Case Narratives Using Deep Neural Networks for the UK Yellow Card SystemE. L. Meldau¹, S. Bista¹, C. M. González², G. N. Norén¹¹*Uppsala Monitoring Centre, Research, Uppsala, Sweden;* ²*Uppsala Monitoring Centre, WHO Collaborating Centre-Signal Management, Uppsala, Sweden*

Introduction: Access to case narratives during signal assessment is crucial to provide a more complete picture of the cases [1], however patient confidentiality needs to be considered. Sharing of narratives while preserving privacy requires de-identification—the removal or replacement of personal identifiers. Automating this task can help with increasing data load. To ensure patient confidentiality throughout the full pharmacovigilance process, the narratives should be de-identified early in the process. Person names—one of the more common identifiers in case narratives—can lead to (in-)direct identification of patients but are challenging to recognise in free text.

Objective: To develop and evaluate a method for automated de-identification of names in case narratives.

Methods: We use an ensemble of BERT [2]—a state-of-the-art language model using deep-neural network—combined with hand-engineered rules for detecting names. Our model is trained on i2b2 2014 deidentification challenge data [3] combined with unprocessed data from the Yellow Card system [4] provided by the MHRA. Because names are rare in the Yellow Card data, the training dataset is prepared using active learning through an independent model. Model testing is done on a separate, manually annotated dataset.

Evaluation of the deidentification is guided by: (1) how often clinically relevant information is removed and (2) how identifiable the narratives that the model fails to completely de-identify are. We define three categories of identifiability: (a) Directly identifiable,

where subject identification is very likely with the leaked information (e.g., full names); (b) Indirectly identifiable, where identification is possible through combination with information from the narrative context (e.g., surname & occupation); and (c) Non-identifiable, where identification is highly unlikely (e.g. initials).

Results: Out of the 71 narratives with names and initials, only 12 contained occurrences missed by the system. Manual evaluation found only one directly and one indirectly identifiable narrative due to leaks. It should be noted that the leaked direct identifier was a foreign, non-English name. Automated de-identification only affected 7% of all narratives and only 1% were assessed as missing clinically relevant information after de-identification. A single narrative may contain multiple occurrences of names, the table presents results per occurrence.

Evaluation data	Recall	Precision	False positive rate
Names excluding initials (n = 120)	0.97	0.19*	0.002*
Names including initials (n = 179)	0.88	0.26	0.002

* This evaluation considers predicted initials as false positives, negatively impacting precision and false positive rate.

Conclusion: Automated de-identification of names is possible without compromising clinically relevant information. Our method can recognise and mask a vast majority of names and most initials while leaving most of the information untouched. Qualitative evaluation shows that the rare leaks that occur tend not to make cases identifiable.

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P013

Prescription Error: A Case of Metronidazole-Induced Pancreatitis

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Introduction: Metronidazole is a nitroimidazole antibacterial drug that is mostly used to treat anaerobic bacteria and protozoa infections. The adverse side effects of metronidazole include gastrointestinal upset, metallic taste, urticaria, headache, peripheral neuropathy. Metronidazole-induced pancreatitis has been rarely described in the literature so far.

Objective: We report a rare case of an acute pancreatitis associated with metronidazole which occurred as a result of a prescription error.

Methods: This case was reported in February 2022 to The National Centre of Pharmacovigilance and evaluated according to the updated French method of causality assessment.

Results: A 70-year-old male patient with a past medical history of chronic viral hepatitis B treated with entecavir since 2006, presented to the surgery department with an acute onset of a severe epigastric pain radiating through to the back associated with hepatic colic with nausea and vomiting. Symptoms started 7 days after initiation of metronidazole given by the patient's dentist for treatment of a periodontal abscess. Metronidazole was prescribed twice under two different trade names Birodogyl[®] (spiramycine, metronidazole) and Tamizol[®] (metronidazole) medications. On exam, he had severe epigastric tenderness. Biochemical analysis showed lipase 632 U/L (6N), and amylase 322 U/L (3N). The abdominal CT scan showed an aspect of acute oedemato-interstitial pancreatitis stage B (CSTI 1). Relative negatives in the history included, no lithiasis, no known drug allergies, and no alcohol consumption. Patient symptoms and lipase improved within 3 days after metronidazole withdrawal and initiation of supportive care.

Conclusion: The likelihood of metronidazole as the incriminating agent was likely in front of a suggestive delay and favorable outcome after the drug withdrawal. It was suggested a the possible dose-response mechanism between metronidazole use and occurrence of pancreatitis, and this case draw attention to the possible acute pancreatitis associated with metronidazole due to a prescription error.

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P014

IoT and the Future of Signal Reporting, Medication Management, Clinical Research and Drug Safety with New Tools and Process

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Introduction: The possibilities of using current scientific principles to create tools to help give efficiency and help to nurses thereby reducing stress and the potential for errors. Also enable patients to maintain independence and less outside contact as technology is used to expand the reach of telehealth. Solutions will be adaptable for independent use by the sight, hearing and mentally challenged. The 1st hurdle is to make it easier for patients and staff to accomplish what they have to do safely and consistently.

Objective: To simplify the taking of all drugs and supplements using IoT technology. This a paradigm shift from the many efforts to mitigate the challenges of the many aspects of drug delivery. Here medication is always kept in the labelled, legal safety of the original dispensed container until consumed. Safety concerns of pre-pouring will no longer exist. Authentic real-time medication usage data will be available. ISO P and other safety management organizations will be able to execute many tasks with precision.

Methods: The innovation is a multi-compartment device that holds a medication container in each compartment. The device has a display that resides in the lid or may be at the front of a drawer type or wall mounted unit. The concept of assigned location forms the basis for these innovations. Stored instructions for many aspects of care and follow-up resides in the device and will be communicated via the

display appropriately. It can be connected to a larger display, cell-phone or other mobile device.

Medicine containers are scanned to capture dosing instructions. The assigned location lights up. The container is placed within the compartment and receives an alert at dosing times. The compartment stays lit until the nurse picks up and replaces the container. Video may be activated. Biometric access ensures identity and pill count and time are automatically recorded.

Results: Feasibility indicates that the must touch to silent feature is a powerful feature that aids adherence. Also the timing methods that ensures safe dosing separation helps to ensure all doses are taken in a given day even if late taking a dose. Relative time rather than time of day dosing is used.

Conclusion: Believed to be unsolvable, these discoveries will open the door to the science of individual ingestion by effortlessly notifying and guiding individuals in the consumption and effects of medicines and other items for a safer and healthier life experience. Powerful data will be generated for use by ISO.

References/Further Sources of Information

www.ownumhealth.com.

P015

Litigation Following Adverse Drug Reactions: Impact of Regulator Oversight—A Case Scenario of a Ceftriaxone Medication Error

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Introduction: The Summary of Product Characteristics for Ceftriaxone states that as with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported [1]. However, the frequency is stated as unknown. Out of 46 reports to Ceftriaxone in the Uganda ADR database, 7 of these are of anaphylactic reactions, and one of them was fatal for the paediatric patient. It is not clear in cases of injurious or fatal drug effects who should bear the liability. However, it is important to describe the role and actions of the National Regulatory Agency to such an ADR report.

Objective: To present a case study of a successful legal resolution of a fatal medication error to Ceftriaxone with the involvement of the regulator.

Methods: This is a retrospective case report. Consent was sought from the patient's family and health care provider to share the case.

Results: A one-and-a-half-year-old male child was diagnosed with septicaemia with diarrhoea and admitted to a hospital. Day one treatment with Ceftriaxone was stopped due to a reaction of difficulty in breathing. A switch to Ciprofloxacin happened and the patient began to improve. Due to a weekend staff shift change, the change to ciprofloxacin was not noted resulting in re-administration of ceftriaxone and anaphylaxis that caused the death of the patient despite all efforts to resuscitate.

National Drug Authority performed a causality assessment of the serious adverse event and found that administration of Ceftriaxone was related to the outcome of death.

However, it was noted that this was a medication error with no malice afthought and therefore the health care provider was not liable.

Conclusion: Timely and objective causality assessment from the Medicines Regulatory Agency is invaluable in providing scientific evidence that can help patients receive compensation and/or protect health care practitioners from wrongful liability for drug effects that are inadvertent. Health care providers hesitate to report due to fear of

litigation but cases such as this one show that timely submission of quality reports is useful in establishing causality and therefore supporting compensation for the patient or protection from vicarious liability for the health care provider/manufacturer. Publication of these results can aid in encouraging reporting rates among patients and providers.

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P017

Clinical Impact of Pharmacotherapeutic Follow-up and Pharmaceutical Interventions in a Reference Hospital in Mexico City

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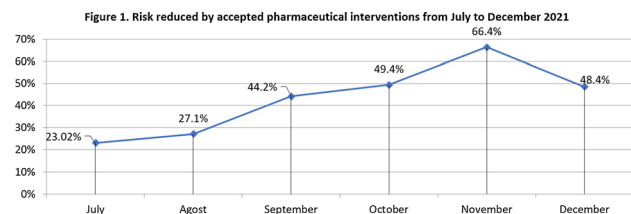
Introduction: Pharmacotherapeutic Follow-up is a professional practice focused on identification, prevention and resolution of Drug-Related Problems and the causes or errors that originate these problems in patients [1–4].

Objective: To assess the clinical impact of Pharmacotherapeutic Monitoring and pharmaceutical interventions performed in hospitalized patients at the Instituto Nacional de Cardiología Ignacio Chávez.

Methods: Clinical pharmacists perform Pharmacotherapeutic Follow-up of hospitalized patients through three evaluations: drug reconciliation, pharmacotherapeutic profile and drug prescription suitability, identifying Drug-Related Problems and medication errors and recording their activities in two databases: the first consists of the evaluation that is carried out weekly and the second corresponds to the pharmaceutical interventions; these bases are validated monthly with each other. For this study, data is taken from both databases in the period from June to December 2021 and the risk that was reduced by accepted pharmaceutical interventions is calculated.

Results: In the review of the database of activities carried out, a progressive increase in the number of evaluations done by clinical pharmacists was observed in drug reconciliation, pharmacotherapeutic profile and drug prescription suitability, identifying discrepancies, medication errors and Problems Related to Medications. In the database of pharmaceutical interventions, a significant increase in the risk that was reduced associated with the interventions carried out and

accepted was observed; as it can be identified in figure 1, which ranges from 23.02 to 66.4%, obtaining an average of 43.1% in the months of July to December.



Conclusion: The pharmaceutical interventions allowed to improve the prescriptions and with it, identify Problems Related to Medications and medication errors before causing harm to the patient, making the drugs safer

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P018

Management of the Anticholinergic Burden in a Nursing Home in Sardinia

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Introduction: Some side effects of anticholinergic drugs can be relatively harmless such as dry mouth or constipation, but in some cases, they can manifest themselves in the form of heart arrhythmias or as worsening of dementia or delirium. The elderly are more prone to show anticholinergic effects, due to a progressive decrease in acetylcholine levels, and are often also treated with drug polytherapy with additive effects which leads to an anticholinergic cognitive burden (ACB) [1–4].

Objective: Verify whether it is possible to identify patients who may experience an adverse reaction due to ACB in real clinical practice through a pharmacological investigation, identify which drugs are the possible cause and re-evaluate the therapy to prevent the onset of adverse reactions.

Methods: From October 2021 to May 2022, the drug therapy of 34 patients aged ≥ 65 years admitted to a nursing home in Sardinia was examined. The patients' drug therapy was analyzed using the INTERCheck WEB platform, which makes it possible to calculate the overall ACB value and that associated with each drug. The presence of clinical symptoms was verified for patients with $ACB \geq 5$. Clinical analysis was performed by assigning a score of 1 to each adverse

event attributable to ACB in the central nervous system, mouth, eyes, heart, gastrointestinal tract, bladder, and skin. Patients with a clinical symptom value (CS) $\geq 4/7$ were considered relevant.

Results: In 34 patients, the total number of drugs prescribed was 290 with an average of 8.5 drugs per patient. The main classes of ATC prescribed are N06 (psychoanaleptics) 8%, B03 (antiemetics) 12%, N05 (psycholeptics) 16%. Five patients with a critical ACB score ≥ 5 were identified. In these patients, the major drugs responsible for elevated ACB were quetiapine, chlorpromazine, and paroxetine, all three with a value of 3. The 5 patients also showed clinical signs of ACB. Three patients had CS $\geq 4/7$ and two of them experienced clinical improvement following therapy modification.

Conclusion: Computerized determination of CBA was helpful in preventing adverse reactions, identifying which drugs are responsible for adverse reactions and modifying therapy to avoid the occurrence of adverse events. Drug therapy analysis is useful in conjunction with clinical evaluation and can be a valuable tool used in conjunction with tools such as Mini Mental Status.

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P019

Measuring the Effectiveness of Electronic Prescription Systems in Reducing Medication Errors in Hospital Setting in Egypt

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Introduction: Presence of a strong medication safety system can prevent many potential medication errors (MEs) by enforcing safety monitoring on the ordering, prescription, preparation, and administration of medicines [1]. Furthermore, a well established medication safety system can solve many causes of communication problems which account for over half of all causes associated with medication

errors through its electronic based system. Unfortunately, many of the existing electronic health records (EHRs) were designed for purposes of medical billing rather than for medical care, resulting in challenges for using the recorded data for safety data capturing. Moreover, commercially available electronic prescribing and computerized physician order entry systems are cost-prohibitive for many health organization, especially non-profit ones. In a previous research project, Egypt Chapter of International Society of Pharmacovigilance (ISoP) was engaged in developing such system in the hospital of Palestine Red Crescent Society (PRCS) in Cairo to support identifying MEs that were experienced by refugees through remodeling and adding new features to the existing hospital management system. The developed system was used as the “intervention” in this research.

Objective: The objective of this study was to assess the effectiveness of introducing internally low-cost electronic prescription system in reducing the frequency of MEs of different types.

Methods: A pre- and post-intervention study was conducted to compare the frequency of MEs before and after replacing the traditionally used paper-based system with an internal electronic-based system in hospital setting. MEs were collected by reviewing randomized medical records at base line and after one year of introducing this electronic-based system. More focus was given to medical records of elderly patients and emergency ward. The prescribing errors, transcribing errors, dispensing errors, administration errors were investigated.

Results: We analyzed 314 paper-based prescriptions at baseline and 416 paper-based and electronic prescriptions at one year of follow-up. The total prescribing errors (before–after %) in elderly were (66–16%) while in the emergency wards they were (71–33%). The errors were (86.9–13.8%) due to a wrong or incomplete transfer of the information from the prescription. Regarding dispensing errors, it was shown that the content errors were (78–33%) and the labeling errors were (68–28%). There were (65–12%) dosing errors during administration.

Conclusion: The adoption of internal electronic prescription systems was effective in markedly reducing the frequency of MEs compared to the paper-based system in a low-resource setting where the expense on complex commercial electronic solutions are burden for institutions.

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P020

Paracetamol, a New Awareness on an Old Drug: A Survey Report on its Clinical Use in a Cancer Institute

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Introduction: In spite of its large use, a conspicuous number of paracetamol adverse reaction reports have been recently collected, due to overdosage or posologic mistakes. A recent metanalysis by BMC Med Inform Decis Mak [1] has inserted paracetamol in the list of the six drugs causing severe ototoxicity and a pharmacovigilance retrospective study [2] has highlighted that it induced 1.4% of all severe drug-induced adverse reactions. Another recent review on the

analgesic standard doses of paracetamol has demonstrated its grade of toxicity, at the maximum prescribed dose [3].

Objective: A knowledge assessment on paracetamol management among health professionals can rise new inputs for the risk/benefit ratio of this old molecule [4,5].

Methods: A survey of 7 questions on standard dosage, dose adjustment and antidotes to paracetamol overdose was submitted to 36 health professionals (nurses, pharmacists, oncologists, hematologists, surgeons) in the Cancer Institute of Bari. The answers were collected and charted in diagrams, in order to soon identify critical evidences.

Results: The correct answers to the 7 questions were distributed as follows: up to 30–33% to 4, 70% to 2 and 89% to 1 questions, respectively. The lowest value of correct answers (11%) was reported for the question on the minimum time interval among successive administrations, while the highest (89%) was related to the volume of drug solution per administration.

About 30–33% of correct responses were given to both questions on the maximum doses in patients with or without additional risks (kidney and/or liver comorbidity), respectively, highlighting the lack of knowledge on the need to personalize therapy. The 70% value of correct answers regards the maximum consented daily doses and the antidote N-acetylcysteine.

Conclusion: The collecting data have demonstrated the clinical need to manage accurately old and apparently well-known drugs to grant a controlled clinical risk in hospitals. The implementation of Recommendation n° 7 by Italian Ministry of Health and precise indications on medical reports of doses and timing in therapy are possible solutions to avoid bad interpretation on prescription and accidental paracetamol overdoses. Pharmacovigilance is a duty for health professionals and the awareness that also old drugs can be causes of toxicity is a substantial starting point for safety of care.

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P021

Assessment of the Quality of MedDRA Coding in a Sample of COVID-19 Vaccine Medication Error Data

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Introduction: High interest in the last two years was globally put by Health Authorities on the recording, coding, and reporting of medication errors to ensure the safety and effectiveness of the use of medicines and to provide reliable information to healthcare professionals and patients. Medical coding is a prerequisite for efficient, effective, and reproducible data outputs.

Objective: Not applicable.

Methods: A sample of medication error coding results was assessed for accuracy and consistency of MedDRA coding and identification of main types of coding errors. It included 1500 coded reported terms for COVID-19 vaccines medication errors, assigned to MedDRA codes by national regulatory authorities or pharmacovigilance centers and drawn from the Uppsala Monitoring Centre (UMC) Vigibase through August 25, 2021.

Results: One-third of the records could not be assessed due to incomplete or unclear verbatims. In one-third, code assignments were correct, but another third of the sample was not adequately coded. Most frequent coding errors corresponded to vague PT assignments, while more detailed information was available for a more precise coding. This observation is similar to the EudraVigilance database, where some of the most assigned MedDRA terms for medication errors also represent vague concepts.

Conclusion: These findings indicate that understanding of medication error documentation and assessment and of MedDRA content and coding guidelines need to be reinforced. The MedDRA Maintenance and Support Services Organization (MSSO) offers several MedDRA coding trainings, including coding of medication errors. The authors provide valuable references to the latter, to the applicable ICH-Endorsed Guides for MedDRA Users, and to relevant EMA guidance.

References/Further Sources of Information

Not applicable.

P022

Intoxications in a Pediatric Population: A Regional Retrospective Analysis

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Introduction: Pediatric intoxications represent one of the most common causes of harm to children under the age of six and the fourth leading cause of death in developing countries [1–2]. In Italy 56% of intoxications affect the age group between 0 and 19 years, 39% of which are consequent to drug exposure [3]. Data collection and systematic analysis of intoxication cases is of fundamental importance to gain a greater knowledge of toxic domestic, environmental and pharmacological agents [4–5].

Objective: To analyze pediatric intoxication cases managed by Liguria's major pediatric Hospital in the absence of a regional Poison Center.

Methods: We performed a retrospective observational study of the intoxication cases managed by the Emergency Department of the IRCCS G. Gaslini for the period from January 2017 to December 2019. All poisonings were retrieved from the Hospital Central Database using the International Classification of Disease (ICD 9)

classification code system, and subsequently entered into a local database for data management. Records from patients aged > 19 years old and from those whose ICD9 did not match a poisoning diagnosis were excluded. Included records were then categorized into four main types of intoxication: from drugs, alcohol, carbon monoxide (CO) and fumes, food/other substance. Descriptive statistics were undertaken.

Results: Over a 3 year-period 172 intoxication cases, of which 28 with no available data, were treated by the Emergency Department of the IRCCS G. Gaslini. Our analysis included therefore 144 poisoned patient cases, 70 were from females and 74 from males, with a median age of 3 years old. Out of the total of accesses, 38.9% of cases were attributed to drug intoxication in which the agents most involved were analgesics and sedative-hypnotic drugs, 29.9% to carbon monoxide (CO) and fumes poisoning, 24.3% to food/other substance intoxication and 6.9% to alcohol intoxication. Poisoning severity and the need for hospitalization have also been investigated.

Conclusion: Implementation of high-performance data collection systems in the Emergency Department could be decisive in guiding clinical choices. This study has gathered data on pediatric poisonings in a regional reality in the absence of a Poison Center. Although preliminary, these findings may guide for the improvement of the surveillance system of intoxications in pediatrics.

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P023

Identifying Adverse Drug Reactions from Free-Text Dutch EHR in Hospitalized Patients with the Development of an Algorithm (IADRESS)

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Introduction: While electronic health record (EHR) is a potentially valuable resource of adverse drug reactions (ADRs) [1,2], these ADRs are frequently not registered, registered in the wrong place or

only registered using free-text entry [3,4]. Free text data cannot be managed and analyzed with mainstream software tools, but this is possible with text mining (TM) tools.

Objective: To develop an algorithm to identify possible ADRs in free text of Dutch hospital EHR with a TM tool.

Methods: In phase I, the previous rule-based algorithm was translated to a R-algorithm and improved it with the help of previous mentioned issues. In phase II, the terms of MedDRA and SNOMED-CT were added to identify ADRs and in phase III R-scripts were used to improve the R-algorithm.

Results: In phase I, the R-algorithm identified 97% (n = 174) of the EHR notes containing possible ADRs identified by the rule-based algorithm. Five ADRs were missed compared to the rule-based algorithm, because of typo's and a EHR conversion. The last PDCA cycle compared to the golden standard achieved a sensitivity of 93%, a PPV of 11% and an F-measure of 0.2. For the potentially serious ADRs a sensitivity of 95% was achieved. There were 64 more EHR notes containing possible ADRs identified, by the R-algorithm. In phase II, there were 105 ADRs identified with the R-algorithm using MedDRA, SNOMED-CT and synonyms. In phase III, the R-algorithm improved the PPV, sensitivity and F-measure.

Conclusion: The developed R-algorithm identified ADRs, however further research is required to extrapolate the algorithm and to combine it with clinical decision support systems to bring the data back to the physician to increase ADR registration.

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P024

Are Monitored Dosage Systems Causing Drug Related Problems? A Retrospective Analysis of Hospital Admissions

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Introduction: Monitored Dosage Systems (MDS) are used by millions of patients in the UK. Also known as multicompartiment compliance aids, they are devices that allow for medicines to be dispensed into compartments which are separated by days of the week and times of the day. Published research has highlighted that between 5 and 15% (1) of hospital admissions are due to Drug Related Problems (DRPs). Studies which highlight the risks of MDS and DRPs appear to be limited (2), whereas research into MDS as the cause for hospital admission are scarce.

Objective: To analyse hospital admissions due to DRPs and association with MDS.

Methods: A retrospective analysis was conducted on four hundred and eighty-seven adult patients' hospital admission episodes. The retrospective analysis took place at the Royal Victoria Hospital, a large general teaching hospital in the Belfast Health and Social Care Trust (BHSCT), over a four month period from July 1st to October 31st, 2021. Each episode was analysed for DRPs and MDS causation using the Pharmaceutical Care Network Europe (PCNE)-DRP classification validation V 9.1 system (3) and the Anatomical Therapeutic Chemical code classification system (4).

Results: Of the four hundred and eighty-seven admissions included, 155 patients (32%) were using MDS, 43 admissions (9%) related to DRPs, out of these 43 admissions with DRPs; 26 patients (60.5%) were using MDS with DRPs, and three patients (7%) had an MDS related DRP. Medications most frequently implicated were antidepressants, ACE inhibitors, analgesics, and antipsychotics.

Conclusion: From this study, MDS have been identified as a cause of hospital admissions due to DRPs. The study highlights that inline with published evidence (5), the cohort of patients more at risk of DRPs are the older population. Older patients frequently use MDS and are already at risk of DRPs as they frequently have multi-morbidities and polypharmacy (6). This study has highlighted that ongoing measures should be considered to reduce DRPs such as deprescribing and regular medication reviews. It also highlights the importance of engaging with patients and carers to increase medication education and awareness.

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P027

Clinical Pharmacist Interventions in Critically Ill Patients with COVID-19

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Introduction: Amid the recent outbreak, the quality of medical care provided to COVID-19 (Coronavirus Disease 2019) patients has been deeply impacted as a result of organizational limitations and insufficient medical resources. This complex situation was amplified by additional factors that include the widespread use of experimental drugs, the lack of detailed guidelines and recommendations, and

workload increase. Consequently, COVID-19 patients became more vulnerable to medication errors and adverse drug events, especially in the intensive care units (ICUs) [1,2].

Objective: To describe the pharmaceutical interventions (PIs) carried out by a clinical pharmacist and to evaluate their clinical impact.

Methods: A prospective observational study was performed in a 16-bed, university-affiliated, COVID-19 ICU in Morocco. Drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification code system. PIs were registered by the pharmacist using the French Society of Clinical Pharmacy's PI sheet, and their clinical impact was assessed using Hatoum scale (0-to-3). Data of a two-month period, from October 2020 to December 2020, were analyzed using Excel.

Results: 201 PIs were generated by the clinical pharmacist and concerned 58 COVID-19 patients with respiratory failure. A median age of 64.5 years [IQR 58.25–69.75] was found and 83% of patients were male. The main drug-related problems were dosage error (37%), non-conformity to guidelines (24%), drug omission (18%), and drug interactions (7%). 58% of the interventions were performed after the medical prescription and consisted mainly of dosage adjustment (47%), followed by drug discontinuation (16%) and treatment reminder (13%). Drugs that belong to J, B, and P ATC groups accounted for 32%, 16% and 15% of PIs, respectively. Study results show an acceptance rate of 89%. 88% of the PIs had a clinical impact of 1 and 12% had a clinical impact of 2.

Conclusion: The active role of clinical pharmacists in the ICU is well established in the literature. Our study underlines the necessity of clinical pharmacy services in the COVID-19 ICU, which helps in preventing drug errors and providing optimal care to this sensitive population.

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P028

A Survey of Medication Errors Reported Due to Look-Alike Antiretroviral Therapy Amongst Adult Clients at Mbagathi Hospital in Nairobi, Kenya

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Introduction: Antiretroviral Therapy is recommended for all persons living with HIV to reduce morbidity and mortality and to prevent the transmission of the virus to others. Medications are offered by health services throughout the world, but their use comes with a substantial growing risk of harm [1]. This includes Medication Errors which is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer [2]. They are among the most common medical errors, harming at least 1.5 million people every year. The extra medical costs of treating drug-related injuries occurring in hospitals alone is at least \$3.5 billion a year in addition to lost wages, loss in productivity and additional health care costs [3].

Objective: To establish the number of medication errors reported due to look-alike Antiretroviral Therapy amongst adult clients over a 12month period at Mbagathi Hospital Comprehensive Care Center Pharmacy.

Methods: A survey was carried out over a 12month period between January 2021 and January 2022 to establish the number of medication errors reported due to look-alike Antiretroviral Therapy amongst Adult clients. The results of the study were captured in the medication error reporting forms at the Comprehensive Care Center Pharmacy and in a table indicating the error.

Results: Over the 12month period, 2 medication errors were reported due to look-alike Antiretroviral Therapy. The medication errors reported occurred after two adult clients were dispensed with the wrong medication due to look-alike medications that were stored next to each other on the dispensing shelf. The medications were Abacavir/Lamivudine (120/60 mg) instead of Tenofovir/Emtricitabine (300/200 mg) and Abacavir/Lamivudine (600/300 mg) instead of Zidovudine/Lamivudine (300/150 mg) respectively.

Conclusion: Medication errors were found to have occurred over the 12month survey period. The study was able to confirm that medication errors can occur when staff lack proper training on how to store and dispense look-alike medications. It is therefore important to continuously train staff on appropriate storage and dispensing practices to avoid these medication errors and to have standard operating procedures on how to store and dispense look-alike medications. After the medication error incident we proceeded to rearranged all the look-alike medications ensuring that they were not stored in close proximity to each other and we also printed bold labels for all the medications on the shelves.

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P029

Acute Liver Failure Following Therapeutic Doses of Paracetamol in Patients with Neuromuscular Diseases: A Preventable Medication Error

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Introduction: Neuromuscular diseases (NMDs) involve injury or dysfunction of peripheral nerves or muscles, with pain being a significant problem [1]. Paracetamol is used in patients with NMDs. The maximum recommended daily dose is 4 g or 60 mg/kg. In any 24-hour period: toxicity is very unlikely with daily doses consistently less than 75 mg/kg; toxicity rarely occurs with 75-150 mg/kg; and there is risk of serious toxicity with more than 150 mg/kg. Ingestion of a licensed dose is not considered an overdose [2]. However, this may not be true in some patients of NMDs with their different pharmacogenetics and phenotypes [3].

Objective: To collate evidence that in patients with NMDs, therapeutic dose of paracetamol might be an overdose leading to toxicity.

Methods: We performed a literature search on PubMed and EMBASE, from inception till May 2022, to identify cases of NMDs where paracetamol was associated with liver injury. Exclusion criteria were overdose, risk factors, and liver disease. Case reports were critically appraised [4]. Association was assessed using Bradford Hill criteria [5]. Case definition, severity grading and causality assessment were done using the RUCAM scale and criteria set by the Council for International Organizations of Medical Sciences [6].

Results: Eight case reports qualified: 6 males, 2 females; 6 had muscular dystrophies, 2 spinal muscular atrophies; median (Q_1 – Q_3) age 18.5 years (13–29); weight 47.5 kg (43–55). Paracetamol consumption was 3 g/day (2.1–3.5), or 50 mg/kg/day (42.9–72.5) for 4 days (4–5.8). Time to onset of clinical manifestations and abnormal liver function tests (LFT) was 4.5 days (4–5.8). LFT values, compared to upper limits or baseline, were: AST 161.7 times (66.6–243.5), ALT 49 times (30.3–167), total bilirubin 5 times (1.9–8) and INR 4.5 times (3.6–6). Paracetamol serum level was 273.3 $\mu\text{mol/L}$ (140.6–505.2). After stopping paracetamol 6 patients recovered (5 with N-acetylcysteine (NAC), 1 without). Two patients died, both had been treated with NAC. Liver injury in all cases was severe and direct (intrinsic). Association was causal and probable. Though we cannot exclude a possible role of concomitant drugs, the causality between paracetamol and liver injury appears probable.

Conclusion: Patients with NMDs are at increased risk of toxic serum levels and severe liver injury following therapeutic doses of paracetamol. Vigilance and personalised medicine based on pharmacogenomics can prevent this medication error. Therapeutic recommendations need to be revised.

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P030

Children Voluntary Intoxications: Cases of Attempted Suicide

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Introduction: Intoxications by ingestion is the second most common domestic accident in children after traumas. They constitute a serious problem in pediatrics, because of their frequency and difficulties of management.

Objective: The aim of our study is to determine the incidence of voluntary intoxications in children, as well as the different toxic agents involved and the morbidity and mortality related to these intoxications.

Methods: This is a descriptive cross-sectional study of voluntary intoxications (suicide attempts) admitted to the emergency department and managed at the Rabat Children's Hospital over a period of 5 months, from November 1, 2020 to April 1, 2021.

An operating sheet have been established and filled using the epidemiological data and the elements of management of these types of intoxications based on the diagnostic, therapeutic and prognostic levels, contained in the patient's files.

Results: During the study period, 79 children were admitted to the emergency department for ingestion of toxic products, 18.9% of recorded intoxications were voluntary (suicide attempts), while 81.1% were accidental.

A female predominance was noted with a percentage of 80% while 20% were male.

All patients belonged to the age group between 12 and 16 years.

73.3% of the children had no medical history, however, 26.7% had a depression.

Concerning the period between the accident and the admission, 40% came to the service within 2 hours, 20% came between 3 to 4 hours, 20% arrived over 18 hours while 20% of the cases the period was unknown.

The use of drugs was reported in 73.3% of the suicide attempts, pesticides represent 6.6% and finally 20% of the attempts whose cause was unknown.

The distribution according to the nature of the toxic agent used in the suicide attempt is as follows 13.3% concerned both anxiolytic drugs and oral antidiabetics with the same percentage, 6.6% by the following toxic agents: antidepressants, anti-inflammatories, antidiarrheals, anti-anemics, orexigenic drugs, hallucinogenic drugs and organophosphate pesticides and finally the nature of the toxic agent was unknown in 26.6% of cases.

In 13.3% of the cases the evolution was favorable, while the attempted suicides caused 13.3% of death with principally oral antidiabetic. 73.3% of patients files were not followed up in our study.

Conclusion: Pediatric toxicology is a particular entity because of the frequently accidental intoxication character and which can become voluntary in children between 12 and 15 years old by using commonly used drugs and other toxic agents. The best measure will be prevention, which has proved to be effective on a large level.

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P031

Is Preventability a Good Criterion for Medication Errors? A Proposal to Assess Continuous versus Binary Faultiness, Seriousness, Contribution to ADRs

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Introduction: Medication Errors (MEs) have been assessed by the criterion of whether they caused adverse drug reactions (ADR) which could have been prevented [1–5]. Typically, several questions are asked like “interaction involved?” and in case of any “yes”, the ADR is considered preventable, and an ME identified. There are problems with this approach. ADRs are assessed when many parameters of the preceding medication are known. In retrospect, it is always possible to conclude that the ADR could have been prevented had certain actions been different. Also, questions about “preventability” are used with a binary meaning, i.e., a “yes-” or “no-” answer is expected instead of a sensibly graded assessment.

Objective: To explore how the ME-criterion preventability could be replaced by a more appropriate criterion and which additional aspects of MEs should be assessed.

Methods: Literature review and proposal of a new approach with relevant examples of ADR cases.

Results: “Faulty” regarding the medication was considered as alternative to “preventable” with respect to an ADR, since it moves the assessor to the time of medication before the ADR occurred. Also, “faultiness” can be graded. Some more suggestions were made: First, to distinguish errors in deciding about a medication from errors in implementing the decision. Second, to distinguish between extent and seriousness of an ME: Aspects of ME-seriousness are how severe an ADR following the ME was, how much more severe or likely—compared to the typical severity or expected frequency—the ADR became, how far the medication deviated from established standards and which options were available to anticipate and minimise the risk. Third, to classify MEs according to whether their faultiness is continuous or binary. Fourth, if an ME preceded an ADR, to ask if—and to what extent—the ME caused or contributed to the ADR. A scheme to classify MEs and cases are presented.

Conclusion: In assessing possible MEs as causes of ADRs it is recommended a) to replace the binary hindsight-criterion “preventable” for ADRs by the term “faulty” for medications, b) to distinguish errors in deciding about a medication from errors in implementing the decision, c) to distinguish between the extent of a deviation from standard and the seriousness of the error, d) to distinguish between MEs by type of faultiness which is either binary or continuous, e) to grade the latter on a scale, and f) to assess the extent to which an ME actually caused the ADR.

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P032

COVID-19 Vaccination Errors During Tunisian Vaccination Campaign Collected from March 13, 2021 to September 29, 2021

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Introduction: Since March 13, 2021, Tunisia has started its vaccination campaign. In addition, the Ministry of Health has organized national mass vaccination days to accelerate the vaccination process. The National Centre of Pharmacovigilance, in collaboration with the Primary Health Care Direction, is charged with monitoring and managing adverse events following immunization (AEFI) that included vaccination errors.

Objective: Our work aims to describe the type and the frequency of these errors in order to prevent their occurrence.

Methods: We conducted an observational study from the onset of the vaccination campaign on March 13, 2021, to September 29, 2021. We collected vaccine errors through the different notification sources used by the National Centre of Pharmacovigilance in Tunisia. We have listed vaccine errors through Vigibase national reports. We categorized the error reports on the basis of the vaccine error type described by the Centres for Disease Control and Prevention (CDC).

Results: During this period, a total of 8.031297 doses were administered. We counted 153 COVID-19 vaccine errors out of 2609 AEFI (5.86%). Reports were related to wrong doses in 70% (Table 1).

Conclusion: Most vaccination misuses are related to technical errors. The enhanced pharmacovigilance reporting system is important for detecting and managing these errors to prevent recurrence during further vaccination campaigns [1]. Moreover, health care providers involved in the COVID-19 vaccine supply chain should anticipate and report COVID-19 vaccine-related errors to promote shared learning opportunities and make every dose of vaccine count.

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P034

Pre-Registration Evaluation of Proposed Invented Names for Human Medicinal Products: Saudi Food and Drug Authority Experience

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Introduction: Several medication error incidents are attributed to name-related issues.¹ Targeting this concern at an early stage through name appropriateness evaluation by regulatory authority as part of the registration process with the intention to prevent medication errors is

one of the core duties of Medication Errors Department at the Saudi Food and Drug Authority.²

Objective: To identify common safety concerns associated with proposed invented names rejection.

Methods: A retrospective observational study of the proposed invented names submitted to the Saudi Food and Drug Authority from January to December 2021 was performed. All received requests are entered into a Microsoft excel spreadsheet and classified accordingly: new request, variation request, and objection request. For the purpose of this study only new requests are being evaluated for proposed invented names' appropriateness.

Results: Submitted new requests throughout the study period counted for 739, while unique proposed invented names for evaluation made up 57% (n = 421 of 739) due to duplication in proposed intended names submission for medications available with various strengths and/or dosage forms. Among the proposed invented names, almost one-third (28.7%, n = 121) were rejected due to several reasons. Further analysis of the rejected proposed invented names revealed that name similarity is the most common reason (47.7% %, n = 73). Other rejection reasons included incorporation of International Nonproprietary Names (INN) stem in proposed names (15.7%, n = 24), followed by use of promotional and/or misleading names (9.8%, n = 15), inappropriate use of qualifiers, inappropriate use of company name, inclusion of dosage form, frequency, or strength, use of abbreviations, name discrepancies across submitted files, indication derived names, as well as use of ambiguous numbers as part of the proposed names.

Table 1. Classification of Proposed Invented Names Rejection Reason

Rejection Reason	Frequency n (%)
Name Similarity	73 (47.7%)
International Nonproprietary Names (INN) Stem	24 (15.7%)
Promotional/Misleading	15 (9.8%)
Inappropriate Use of Qualifiers	13 (8.5%)
Inappropriate Use of Company Name	8 (5.2%)
Dosage form/Frequency/Strength	6 (3.9%)
Abbreviations	5 (3.3%)
Name Discrepancies in Submitted File	4 (2.6%)
Indication Derived	3 (2.0%)
Ambiguous Numbers	2 (1.3%)

Conclusion: Pre-registration evaluation of proposed invented names is an essential process to prevent medication errors. Identifying the most common reasons for invented names rejection can be utilized by pharmaceutical companies to enhance the submission process efficiency. Pharmaceutical companies and regulatory authorities should join forces to promote medication safety and prevent medication errors.

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P035

Overview of Paediatric Opioid Overdose Cases in France

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Introduction: The use of opioids has increased in the general population by 150% from 2006 to 2017 in France. At the same time, an increasing number of intoxications and deaths related to opioid use have been documented [1]. In addition, cases of fatal paediatric accidental intoxication have recently been reported to the National Agency for the safety of Health Products (ANSM) [2].

Objective: In this study, we will analyse pharmacovigilance cases of opioid overdose in children.

Methods: A search for French cases of overdose in children aged 0-15 years with opioid drugs, of all galenic forms, was carried out on the European pharmacovigilance database "Eudravigilance", from 2001 to April 2022. The substances selected were: morphine, tramadol, fentanyl, methadone, codeine, oxycodone, loperamide, buprenorphine and hydromorphone. The preferred terms associated with the adverse drug reactions (ADRs) identified with the MedDRA 25.0 dictionary were: "accidental overdose", "extra dose administered", "incorrect dosage administered" and "incorrect dose administered".

Results: Over the 17-year period, 63 cases of paediatric overdose were collected. The average age of the children was 4 years (median: 3 years, range: 1; 15 years). 91% (n = 57) of the cases were medically confirmed and 65% are related to oral administration (60% capsules/tablets and 5% syrup).

97% (n = 61) of the cases were serious including 6% (n = 4) death, 38% (n = 24) life-threatening, 30% (n = 19) hospitalisation and 20% (n = 12) unspecified criteria.

Of the 63 cases 129 ADRs were reported with mainly neurological (32%, n = 41), respiratory (26%, n = 33), and gastrointestinal (12%, n = 15) ones.

In 46% of cases (n = 28), it was a medication error. Naloxone was administered in 57% of cases and the outcome, when indicated (n = 21), was favourable in 100% of cases.

Of the 63 cases, 22% (n = 14) were due to accidental exposure at home, of which 29% (n = 4) resulted in death. Naloxone was administered in only 29% (n = 4) with favourable outcome.

Conclusion: This analysis confirms the seriousness of opioid overdose in the paediatric population. ANSM raised awareness to the general public and the healthcare professionals about the rules of proper use, the need of the availability of the emergency therapy for opioid overdose, naloxone [3, 4] and moreover the absolute need to keep the treatment out of the reach and sight of children following the two recent cases of death while taking methadone [2].

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P036

Types and Frequency of Errors in the Preparation and Administration of Drugs in Pediatric Inpatient

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Introduction: Medication errors are defined as any avoidable happening that may result in improper use of medications or hazards for the patient for which the responsible person may be the health care professional, patient or consumer.

They can happen during different stages of the drug delivery process, which have been classified as prescribing, transcribing, dispensing and administering.

Objective: The aim of this study was to identify compatibility, types and frequency of errors in preparation and administration of drugs at 5 departments of children hospital of rabat Morocco.

Methods: This study was designed as prospective cross-sectional evaluations, extended over a period of 2 months from March 12, 2022 to May 12, 2022.

It was performed at five departments of *children hospital of rabat in Morocco*: Neonatal intensive care, General intensive care, Hemato-oncology, Respiratory and Infectious Diseases, endocrinology and metabolic diseases departments.

The sample consisted of 45 observations of the preparation and administration of 27 drugs by external pharmacists.

The following variables were collected: reconstitution and dilution errors, presence of physico-chemical incompatibility, administration errors and the conservation and stability anomalies.

Results: In this study 45 observations of 27 drugs were evaluated in the preparation and administration stages. 81.5% of drugs were injectable, 14.8% belonged to the oral route and 3.7% for respiratory route.

The most frequent drugs administrated were: ceftazidime 18.5%, 14.8% each for ceftriaxone and aciclovir and 11% each for vancomycin and metronidazole.

We observed 56 errors in the preparation and administration of drugs, 50% were associated to administration errors, 34% related to reconstitution and dilution errors and 16% had storage anomalies.

According to the Anatomical Therapeutic Chemical Classification System ATCCS, the class J (Anti-infective for systemic use) was the most common class involved in errors (50%).

In the preparation stage 42.3% of errors were using inappropriate diluents for solving while 57.7% were compliant.

During the administration of medications, the following errors were identified: 24.4% each for incorrect time of administration and physico-chemical incompatibility between the medications, 8.8% wrong route of administration, 4.4% underdosing drugs. 37.7% of administrations were compliant.

Conclusion: In the pediatric field, the administration of drugs involves a great responsibility, as it directly affects the safety and health of the assisted children.

Involvement of a clinical pharmacist can be a solution to reduce the rate of errors by training the health care professionals and establishing

a system of reporting medication errors to encourage documenting the information.

Acknowledgment: The authors would like to thank all pharmacists assigned to each department for their contribution to this study.

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P038

Need of Drugs and Supplements Recognition in Oncological Patients: Role of the Clinical Pharmacologist

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Introduction: Fluoropyrimidines (FP), including 5-FU and capecitabine, are antimetabolites commonly used to treat solid tumours. Several toxicities limit FPs treatments, including myelosuppression, Hand-Foot Syndrome (HFS) and diarrhoea. Drug-drug and supplement-drug interactions can cause or worsen FP-related toxicity but they are often overlooked.

Objective: To perform a systematic recognition of drugs and other compounds used in patients receiving FP-based therapy to identify potential adverse events associated to drug-drug and supplement-drug interactions.

Methods: Pharmacological anamnesis was recorded in 43 patients receiving FP-based therapy. This recognition was performed besides pharmacogenetic testing, routinely performed to identify congenital dihydropyrimidine dehydrogenase (DPD) deficit associated to severe FP-related toxicity. All drugs and supplements were recorded and several drug-interaction checkers were consulted (Drugs.com, Drugbank, Medscape, WEBMD and Lexicomp. Last access 23 05th, 2022).

Results: A careful recognition of oncological and non-oncological drugs and supplements was carried out by analyzing the records related to 43 patients submitted to clinical monitoring for at least 4 cycles of therapy. Of them, 35 were treated with 5-FU (4 were carriers of DPYD polymorphisms) and 8 with capecitabine. Patients carrying DPYD polymorphisms associated with DPD deficit were excluded from the analysis. Two out of 7 patients received a dosage of capecitabine of more than 2000 mg/m² per day, which represents the maximum tolerated dose in case of a concomitant folate-based supplementation. Both patients experienced severe HFS and diarrhoea. In one case, capecitabine dosage reduction was executed and statin/ezetimibe treatment was discontinued, while the folate supplementation was not suspended. In the other case, capecitabine and folate supplements were stopped and capecitabine was restarted after a month. Following these changes, severe toxicities were resolved. All the consulted drug interaction checkers could have foreseen the risk of worsening toxicity of capecitabine associated with capecitabine/folates co-administration.

Conclusion: To identify all factors involved in drug toxicity, a pharmacological analysis should be performed, without overlooking drug-supplement interactions. A systematic recognition of drugs and supplements used by oncological patients allows verifying prescription appropriateness and avoiding adverse events, including life-threatening ones. The role of the Clinical Pharmacologist in this field is crucial.

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P040

The Risk of Acute Kidney Injury in Bladder Cancer Patients Who Have Undergone Radical Cystectomy

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Introduction: Radical cystectomy (RC) is the standard of care for certain stages of bladder cancer (BC) [1]. Acute kidney injury (AKI), a complication of RC, is associated with increased mortality, largely due to chronic kidney disease and disease recurrence [2, 3]. In one study, 38.2% of BC patients developed AKI after RC [4]. Furthermore, AKI may preclude patients from anti-cancer therapy, potentially accelerating the rate of recurrence [5].

Objective: In this retrospective cohort analysis, two large US-based claims databases were used to assess the risk of AKI in BC patients who underwent RC.

Methods: IBM MarketScan and IQVIA PharMetrics Plus claims data from January 1, 2015 to December 31, 2020 were used to examine the occurrence of AKI in BC patients who had undergone RC. ICD-9-CM and ICD-10-CM codes were used to identify diagnoses and procedures. Patients were included if they: (1) had BC; (2) had a RC after their BC diagnosis; (3) were at least 18 years of age, and (4) had continuous enrollment (medical and pharmacy claims) of 12 months before the index date. The index date was defined as the date of RC. AKI occurrence after RC was identified from all inpatient claim records. Panalgo's Instant Health Data (IHD) healthcare analytics software was used to conduct the analysis.

Results: In the analysis using the PharMetrics Plus database, 1,988 patients were identified as being diagnosed with BC and who also underwent RC. Of those 1,988 patients, 950 were also diagnosed with

AKI (351 of these patients received their AKI diagnosis before the index date, i.e., before their RC). AKI prevalence was 47.8% and the incidence rate was 45.5 per 100 person years.

In the analysis using the MarketScan database, 1,263 patients were identified as being diagnosed with BC and who also underwent RC. Of those 1,263 patients, 574 were also diagnosed with AKI (214 of these patients received their AKI diagnosis before the index date). AKI prevalence was 45.4% and the incidence rate was 46.4 per 100 person years.

Conclusion: In this retrospective study, both incidence and prevalence rates generated from the two databases were similar. The risk of AKI among BC patients after RC treatment was higher than in the previously published study [4]. Further analyses are needed to identify possible risk factors associated with AKI and its potential impact on treatment options.

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P041

Safety Assessment of Biologics for Immune-Mediated Inflammatory Diseases Using Italian VALORE Healthcare Database Network and National Spontaneous Reporting System

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Introduction: Pre-marketing randomized clinical trials (RCTs) are designed to show efficacy but have limitations regarding safety [1]. Post-marketing surveillance plays a key role in exploring biologics safety issues, especially for long-term treatments of chronic diseases like immune-mediated inflammatory diseases (IMIDs) [2,3]. Several data sources are available to investigate the biologics safety in the

post-marketing setting, such as drug registries, spontaneous reporting system (SRS) or claims databases, including a larger and heterogeneous population than RCTs and integrating evidence from pre-marketing [4].

Objective: To assess the post-marketing safety profile of biological drugs approved in IMIDs using the Italian VALORE database network [5] and the national SRS database.

Methods: Suspected adverse drug reactions (ADRs) related to biologics approved in IMIDs from four Italian regions (Veneto, Lazio, Emilia-Romagna, Friuli-Venezia-Giulia) were retrieved from the SRS database between 2010–2020. Safety Outcomes of Interest (SOI) related to the same biologics and person-years (py) of exposure were identified from the VALORE database in the same period and regions. Suspected ADRs were analysed at High Level Term (HLT) of MedDRA® and stratified by drug class [TNF- α -inhibitors, interleukin (IL) inhibitors, and selective immunosuppressants]. ADR Spontaneous Reporting Rates (SRR) and SOI incidence rate (IR) were estimated using the total number of suspected ADRs and SOI as numerator and the exposure to biologics as denominator (among 100,000py).

Results: A total of 2,675 ADRs reports were identified in the SRS database: 2,042 involved TNF- α -inhibitors (76%), 478 IL-inhibitors (18%) and 155 immunosuppressants (6%). Biologics users from the VALORE database were 74,046: 176,039py for TNF- α -inhibitors (72%), 35,666py for IL-inhibitors (20%), 13,039py for immunosuppressants (8%).

The ADRs associated with the highest SRRs belonged to *Therapeutic and nontherapeutic responses* HLT category in TNF- α -inhibitors, IL-inhibitors and immunosuppressants (195, 53, and 752/100,000py, respectively); followed by skin disorders, included *Urticarias* (87/100,000py), *Erythema* (73), *Rashes, eruptions and exanthems* (70) and *Pruritus* (65) for TNF- α -inhibitors; *Lower respiratory tract and lung infections* (20) for IL-inhibitors; and *Neutropenia* (207) for immunosuppressants.

As regards to SOI, the highest IRs in the three cohorts were: *neoplasm* (567, 723, and 972/100,000py), *ischemic heart failure* (524, 745, and 810/100,000py), and *pneumonia* (522, 742, and 807/100,000py).

Conclusion: Among ADR reports, the highest rates were related to treatment inefficacy and immune system disorders while among healthcare data, were neoplasm, ischemic heart disease and pneumonia. These results showed the need of pooling data from healthcare databases and active surveillance as a comprehensive approach to detect different potential safety signals related to biologics.

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P042

An Overview of the Pharmacovigilance System in Ghana

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Introduction: The goals of Pharmacovigilance (PV) includes early detection of adverse events (AE) and interactions with other drugs/food, detection of frequency of a known adverse effect, Identification of risk factors and mechanisms behind adverse events, continuous monitoring for risk-benefit ratio of investigational product (IP) and distribution of information about discovered AEs and interactions(1) Ghana joined the WHO PV program as the 65th member in 2001 and as the first country in West-Africa. The use of pharmaceuticals preparations has become one of the fast growing components of global health care expenditure in Ghana (2).

Objective: To study the PV system in Ghana using World Health Organization (WHO) indicators

Methods: This study was directed towards the Ghana Food and Drugs Authority (FDA) which is the National Pharmacovigilance Coordination Center that also house the National Pharmacovigilance Centre in Ghana. A review of the government's National Policy on Pharmacovigilance and Implementation Framework was carried out using the WHO core and complimentary indicators as the basis. The Indicator-based Assessment Tool (IPAT), developed by WHO was used to assess Ghana's PV system

Results: Regulatory framework for PV activities was present in Ghana. Quality Control (QC) laboratory with a clear mandate and functioning, but the QC laboratory is yet to be prequalified by WHO. The budget for PV is available with a medicine safety advisory committee present and functioning. The system for co-ordination of PV data and adverse drugs reactions (ADR) reports collation is available but majorly online. Consumer reporting forms and suspected ADR reporting forms are available and being put to use but no product quality reporting form, medication error form and treatment failure form

Conclusion: Ghana FDA is mandated to regulate the development, manufacturing, importation and marketing of medicinal products in Ghana, with remarkable improvement since inception. The provision of national policy on PV and the recognition of Ghana FDA as WHO Global Benchmark Tool (GBT) performance maturity level 3 is a positive step in the right direction and with the continuous support from the government, the PV system in Ghana can only get better despite some shortcomings as identified by the WHO indicators

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P043

An Overview of the Pharmacovigilance System in Nigeria

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Introduction: The primary purpose of pharmaceutical regulation is to safeguard the public from unsafe medical products and the menace that may ensue from its administration. In many low and medium - income countries (LMIC), like Nigeria, Pharmacovigilance (PV) activities are fragmented, weak, and unable to protect the public adequately (1-3).

Objective: To study the PV system in Nigeria using World Health Organization (WHO) indicators

Methods: This study was directed towards the National Agency for Food, Drugs Administration and Control (NAFDAC), which is the National Pharmacovigilance Coordination Center in Nigeria. A review of the government's National Policy on Pharmacovigilance and Implementation Framework was carried out using the WHO core and complimentary indicators as the basis. The Indicator-based Assessment Tool (IPAT), developed by WHO was used to assess Nigeria's PV system.

Results: There is a presence of regulatory framework for PV in Nigeria. There is a Quality Control (QC) laboratory with a clear mandate, structure, and function, but the QC laboratory is not pre-qualified by WHO. The budget for PV is limited but a medicine safety advisory committee is present and functioning. There is a system for co-ordination and collation of PV data from all sources in the country, as well as a system for collation of adverse drugs reactions (ADR) reports. There is a presence of consumer reporting forms and suspected ADR reporting forms, but no product quality reporting form, medication error form and treatment failure form

Conclusion: The National Agency for Drugs Administration and control (NAFDAC) is mandated to regulate the development, manufacturing, importation and marketing of medicinal products and medical appliances in Nigeria, with considerable improvement since inception. The provision of national policy on PV is a positive step in the right direction and with the prompt and continuous support from the government, the PV system in Nigeria can only get better despite some weakness highlighted by the WHO indicators

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P044

Adverse Drug Effects Related to Biotherapy Used in the Treatment of Chronic Inflammatory Rheumatism at El Ayachi-Sale Hospital, Morocco

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Introduction: The biological treatment which is the most effective type of therapy for inflammatory rheumatic diseases, has become part of a standard clinical rheumatology practice in recent years. Thousands of patients with rheumatoid arthritis, different forms of spondyloarthritides and with psoriatic arthritis are now successfully treated in this way (1), however they may be associated with a new spectrum of adverse drug effects (ADEs).

Objective: identify the ADEs related to the use of biological drugs for inflammatory rheumatic diseases and also the impact of these ADEs on the treatment.

Methods: This was a prospective descriptive, monocentric study of patients suffering from chronic inflammatory rheumatism, receiving biotherapy treatment and collected in the rheumatology departments. The data collection included the socio-demographic characteristics, the pathological profile of the patients, the treatment of the biotherapy received and the study of the adverse effects that appeared during or after administration of the biotherapy.

Results: In total, 321 patients were identified between June 1 and August 31 2021, most of these received infliximab (27.4%), rituximab (17.4%), secukinumab (15.5%), golimumab (14.3%), adalimumab (12.4%), etanercept (7.1%), tocilizumab (3.4%). Of the 268 patients, 16 (4.3%) experienced one or more adverse effects related to biological agents. A total of 62.5% of the cases corresponded to women. Most of the adverse effects were classified as type B (58.2%) and A (18.7%), and 37.5% were serious cases. The most frequently reported ADEs were administration site reactions and skin effects (31.5%), nervous and gastro-intestinal system were also affected (25%), followed by cardiovascular disorders (12.5%). The drugs related to the significant number of ADEs were infliximab (37.5%) and rituximab (25%). Half of the patients who suffered from adverse effects switched to another biologic (50%), 43.75% of patients maintained the previous treatment, and 6.25% discontinued treatment.

Conclusion: The adverse effects observed in this study had no impact on the functional or vital prognosis of the patient. This type of study can support decision makers in ways that benefit patient safety and interaction with health systems (2).

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P045

Does Omalizumab Increase the Risk of Malignancy? A Retrospective Case-Control Study in a Single Tertiary Hospital

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Introduction: Omalizumab is a humanized anti-IgE monoclonal antibody indicated for the treatment of chronic idiopathic urticaria, IgE-mediated allergic asthma, and nasal polyps¹. Despite its overall safety, a disproportionate analysis (case/non-case study) within VigiBase indicated that omalizumab might be associated with a significantly higher risk of malignancies (3) from 1,380 reports of neoplasms associated with omalizumab.² The disproportionality signal was significant and positive, with a reporting odds ratio (ROR) of 1.65 which was particularly strong in breast and lung cancers.

Objective: Therefore, we aimed to analyze the frequency of primary malignancy in omalizumab-treated patients in a real-world clinical setting through propensity score matching (PSM).

Methods: We performed a retrospective case-control study in a single tertiary hospital to identify patients diagnosed with cancer after omalizumab treatment and a matching ratio of 1:4 was used to select omalizumab-untreated controls.

Results: A total of 2,340 patients (468 patients in the omalizumab group and 1,872 in the omalizumab-untreated control group) were included in our study. Baseline serum IgE before starting omalizumab treatment was significantly higher in the omalizumab group than in the control group (Table 1). The morbidity rates of malignancy did not differ between the omalizumab group and the control group (2.35% and 2.94%, respectively). This difference remained insignificant after dividing the number of patients with malignancy by observation time to calculate cases per 1,000 person-years. Omalizumab treatment did not show any association with any type of primary malignancy. The clinical characteristics of patients who were newly diagnosed as primary malignancy did not differ according to omalizumab treatment. The serum IgE levels did not differ between patients with and without malignancy as well.

Table 1. Baseline characteristics and incidence rate of primary malignancy in control vs. omalizumab

Parameter	Omalizumab (n = 468)	Control (n = 1,872)
Sex, no. (%)		
Male	204 (43.6)	816 (43.6)
Female	264 (56.4)	1056 (56.4)
Age, no. (%)		
<10	1 (0.2)	4 (0.2)
10-19	15 (3.2)	60 (3.2)
20-29	49 (10.5)	196 (10.5)
30-39	79 (16.9)	316 (16.9)
40-49	90 (19.2)	360 (19.2)
50-59	89 (19.0)	356 (19.0)
60-69	97 (20.7)	388 (20.7)
70-79	32 (6.8)	128 (6.8)
>80	16 (3.4)	64 (3.4)
Mean (SD)	49.0±16.5	49.2±17.0
IgE (IU/mL)*†	410.5 ± 47.0	260.0 ± 15.3
Diagnosis, no. (%)		
Asthma	127 (27.1)	508 (27.1)
Chronic urticaria	323 (69.0)	1292 (69.0)
Both	18 (3.8)	72 (3.8)
Patients with malignancy (n)	11	55
Observation time (y)	2875.0	14188.8
Incidence rate‡ [95% CI]	3.83 [1.57-6.09]	3.88 [2.85-4.90]

* $P < 0.05$

†available for 900 patients.

‡cases per 1,000 person-years

Abbreviations: SD, standard deviation; CI, confidence interval

Conclusion: Using real-world clinical data from a single tertiary hospital in Korea for the first time, we reported that omalizumab was not associated with a significantly higher risk of primary malignancy. The mean observation time per person was longer at 7.29 years (7.58 years in the omalizumab-untreated group and 6.14 years in the omalizumab-treated group) compared to the data from a previous clinical trial.³ This enabled us to observe slow-growing malignancies with long latency periods. Further studies with larger numbers of

patients and longer observation times are required to confirm the results of our study.

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P046

Safety Profile of PCSK9 Inhibitors in Clinical Practice: An Italian Prospective Pharmacovigilance Study

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Introduction: Primary hypercholesterolemia, which is not adequately controlled with the continued use of statins at the maximum allowed dose is a serious problem in patients at high risk of cardiovascular events¹. The new monoclonal antibodies alirocumb (Praluent ©) and evolocumab (Repatha ©) represent a further therapeutic option with demonstrated superiority over placebo and/or ezetimibe, in reducing LDL levels. Considering the potential chronicity of the treatment, dedicated pharmacovigilance studies are essential to define the long-term safety profile of these drugs.

Objective: The aim of the study was to collect safety data, track adherence to therapy and identify specific drug interactions by paying closer attention to adverse reactions (ADRs) detection.

Methods: The study included a 3-month enrollment phase, followed by a 6-month follow-up/monitoring period. Specifically, the Authorized Prescribing Centers identified the patients with prior informed consent, which were contacted by telephone within 15 days and then contacted again in the first month and at 3 and 6 months. All observed ADRs were included in the National Pharmacovigilance Network. In addition, the Morisky questionnaire was used to assess adherence to the therapy of the patients and the data were compared with the analysis of the therapeutic plans. The DIPS questionnaire was used to identify the interactions.

Results: Overall, 79 patients (48 males and 31 females, mean age of 65.4 years) with a diagnosis of familial mixed hyperlipidemia (3.8%, 3), familial hyperlipidemia (29.1%, 23) and pure or common hyperlipidemia (67%, 53) have been enrolled. In terms of comorbidities, most of the patients were affected by cardiac pathologies such as arterial hypertension (77.2%; 61) coronary heart disease (44.3%; 35), followed by diabetes (30.4%; 24); the 25.3% of patients had both diabetes and arterial hypertension. Moreover, the 40.5% of patients started the therapy with alirocumb while 59.5% with evolocumab. All patients have received previous statin therapy, in particular 73.4% atorvastatin, 15.2% rosuvastatin and 11.4% simvastatin. In the

majority of patients, statin therapy was suspended due to intolerance, while in a minority the switch occurred due to failure to reach target values. The most common ADRs described so far have been 2 cases of injection site pain (redness, itching) and 1 case of rhinorrhea by patients treated with alirocumab.

Conclusion: In conclusion, although few ADRs were detected, the awareness of health personnel led to greater consciousness of the importance of pharmacovigilance. Furthermore, the complete adherence to therapy by all enrolled patients confirms the tolerability and safety of these drugs.

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P047

Regorafenib-Related Myocardial Injury in Patient with HepatoCellular Carcinoma (HCC) Post Orthotopic Liver Transplant (OLT): Prevention and Management

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Introduction: The incidence of cardiac adverse events, specifically heart attack and myocardial ischaemia, related to the use of regorafenib is uncommon ($\geq 1/1.000$ to $< 1/100$).

Regorafenib is an oral tumor blocking agent that effectively blocks several protein kinases (PTKs) involved in tumour angiogenesis (VEGFR1, VEGFR2, VEGFR3, TIE2), oncogenesis (KIT, RET, RAF1, BRAF, BRAFV600E) and in the tumour microenvironment (PDGFR, FGFR) [1].

It is used as monotherapy for the treatment of adult patients with metastatic colorectal cancer, gastrointestinal stromal tumours, HCC after treatment with sorafenib.

Objective: To identify risk factors associated with using of regorafenib.

Methods: AS (56 years), weight 90 kg and height 170 cm, smoker for 30 years until 2015 (1 pack per day) diagnostic of moderately differentiated HCC not infiltrating the glissian cassock in the absence of neoplastic vascular infiltration, class C (advanced) [2], class Child-Pugh A [3], ECOG 1 [4], HCV and HBV infection, adequate renal function, subjected to OLT from a male donor organ (60 years) weighing 1.9 kg, steatosis in 0-20 %, staging 1 for the presence of fibrosis [5].

Immunosuppression therapy with FK506 (tacrolimus), basiliximab and steroid.

Regular perioperative course: no interventional radiological procedure, endoscopic, nor major infections or critical complications.

Subsequently emergence of post-transplant clinical problems: active relapse of HCC.

Initially on sorafenib therapy, discontinued due to disease progression, and subsequently with regorafenib.

In november 2020 the patient reported moderate chest pain that subsides with the rest for which echocardiography and stress testing were indicated.

After pharmacological stimulation, the diagnosis was of drug induced myocardial ischaemia.

The patient started cabozantinib and optimization of cardiac control therapy.

Drug-related Adverse Drug Reaction (ADR) Onset: cardiotoxicity (protocol n° 721581 in National Pharmacovigilance Network).

Results: The shift to a Tyrosine Kynase Inhibitor (TKI) with a lower cardiovascular impact (cabozantinib) and an optimization of cardiac therapy allowed a better control of the patient's clinical course, avoiding serious ADRs that could further compromise the antineoplastic therapy choice.

Conclusion: The joint work of multidisciplinary teams (in the specific case oncology and cardiology teams), the physical examination of the patient, the necessary instrumental and biochemical tests, the adequate training of health professionals on the management of ADRs reports and the therapeutic optimization, represent the key points, useful and effective, and the "unmet need" for the correct management of other patients, allowing to adopt of all the necessary precautions aimed at having a minimum impact on the patient's clinical condition.

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P048

Meeting the Need: A Training Course for Data Safety Monitoring Board (DSMB) Members in LMIC

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Introduction: Increasingly, vaccine clinical trials are being conducted in LMIC, especially for vaccines that target diseases that are endemic there. Having members of Data Safety Monitoring Boards for these trials who are from the geographic area where trials are conducted is critical to assure adequate safety assessment and to consider events observed in an appropriate context. However, the number of vaccine safety-experienced individuals to fulfill this role is currently limited.

Objective: To describe the next for trained DSMB members from low and middle income countries and a program developed to meet this need.

Methods: A DSMB training course combining online modules and facilitated live interactive sessions was developed with support from the Coalition for Epidemic Preparedness Innovations (CEPI). The initial two sessions targeted trainees in Africa while the third session includes individuals in Asia. The course runs over 8 weeks and contains eight modules which describe the role of the DSMB, rare events epidemiology, the phases and purposes of vaccine clinical trials, and regulatory issues. Pre-recorded lectures are provided by leaders in the field of vaccinology while the weekly one-hour virtual discussion sessions are led by a trained facilitator.

Results: Two sessions of the course have been successfully completed and a third is now in progress. Almost all enrollees have successfully completed the course with 29 graduates thus far and 15 enrolled in the current session. Surveys of participants have rated the course very highly in terms of content and relevance to their future work. Participants have also stated the course has provided them with increased confidence in becoming future DSMB members.

Conclusion: It is possible to develop and conduct a hybrid virtual and live interactive course to train future DSMB members for vaccine trials conducted in LMIC.

References/Further Sources of Information

Further information can be obtained at <https://brightoncollaboration.us/speac/>.

P050

Biological Medicines in Accidents with Poisonous Animals: Integrating Data from Various Sources

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Introduction: In Argentina, a public institute produces and distributes biological substances that include different antivenoms based on equine F(ab')₂ fragments for the treatment of accidents with snakes (bothrops, chrotalus, elapids) and arthropods (Loxosceles, Latrodectus, Phoneutria and Tityus). Currently, it has implemented a pharmacovigilance program that uses different sources of information and integrates them into a database to improve product safety analysis.

Objective: To describe the particular methodology of the integration of information sources in a public producer of biological medicines.

Methods: The institute integrates information from notifications of adverse reactions made directly to the institute (from patients, professionals, health coordinators and local health ministries), and forms of epidemiological report of accidents with poisonous animals. The different sources, available data fields and results of data integration are described.

Results: Through the use of relational tables, concordance can be found between the epidemiological reports and the adverse reactions reports (using geographical area, date and type of accident reported). The integration of the databases makes it possible to quantify the frequency of adverse reactions and their individual case analysis allows the classification of reactions by seriousness, preventability, and to compare these data between regions. The cases of adverse reactions show a prevalence of 7.05 ± 1.3 (6.1–8.3)% over the total of patients treated with antisera, with slight variations between years and geographical areas. The description of the type of event allows classifying them as early reactions in 85% (nausea, vomiting, local reactions), and late reactions in 15% (serum sickness). Non-serious

adverse reactions counted for 89%, being predictable in 87%, preventable in 94% and requiring medical treatment in 15% of cases. All of them evolved with ad-integrum restitution.

Conclusion: Joining data using relational databases can allow the collection of additional information that allows not only to quantify the frequency of adverse reactions more reliably, but also to describe other factors that may be associated with changes in effectiveness and/or safety. The correlation with geographic areas and times between the occurrence of the accident and the administration of the product could serve to optimize the distribution process. This strategy helps to generate new information that is superior to the mere sum of the individual data.

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P051

Use of Biological Drugs for Psoriasis: A Drug-utilization Study Using Tuscan Administrative Databanks

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Introduction: Psoriasis is an inflammatory skin disease that encompasses several clinical phenotypes and for which there has been much progress over the past 30 years in understanding the pathogenesis but for which there is currently no curative treatment [1]. Despite the frequency of switches in clinical practice, it is unclear which drugs are most frequently switched to and no clinical recommendations are available in this regard.

Objective: Our study aims at providing evidence on patterns of biologic drugs use for psoriasis in Tuscany, Italy.

Methods: We conducted a drug-utilization study based on administrative databanks of Tuscany (EUPAS45365). We selected new-users of etanercept, infliximab, adalimumab, ustekinumab, or secukinumab between January 1st, 2011 and December 31st, 2016. We considered subjects with psoriasis and followed subjects until end of study period (three years), or patient's death, whichever came first. We censored subjects for pregnancy or neoplasia. For each subject, we defined the state as the weekly coverage of one of biologic drugs of interest. We then defined the switch as the change from a state to another one.

Results: A total of 7062 subjects with a first dispensation of PSObio drug in the inclusion period was identified. We included 1839 psoriatic patients (52.9% females, 51.6 mean age), resident in Tuscany, with one year of observation before the first biologic dispensation, and three years of observation after the first biologic dispensation. Among new users of adalimumab (N = 770, 41.9%), one third showed a continuous behaviour, the others moved to etanercept and ustekinumab. New-users of etanercept (N = 758, 41.2%), had the highest proportion of switchers, with adalimumab most often being the second choice. New users of infliximab (N = 159, 8.6%)

experienced the highest proportion of treatment discontinuation, and of those who changed medication drug, most switched to adalimumab or, to a lesser extent, to etanercept. New users of ustekinumab ($N = 115$, 6.3%) had the highest percentage of subjects on continuous therapy, and a small percentage of switchers.

Conclusion: The present study suggests that the majority of patients treated with PSObio drugs do not switch from one active ingredient to another. However, patients who started biological therapy with etanercept had the highest frequency of switch to other PSObio drugs. Instead, patients with ustekinumab as index drug had the lowest frequency of switch to other PSObio drugs. Those who started treatment with infliximab had the highest discontinuation rate.

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P052

Local Experience on Adalimumab and Etanercept Biosimilar Drugs: Safety and Efficacy Confirmation Encourages Rheumatologist Biosimilar Prescription

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Introduction: Biosimilars are biological medicines of rigorous pharmaceutical standard quality, that can provide benefits for patients in terms of safety, efficacy and quality, for healthcare systems as well in increasing treatment alternatives, access and cost competitiveness [1].

Objective: To evaluate the safety reports of subcutaneous biosimilars of adalimumab (ADA) and etanercept (ETN), the two biological pillars of rheumatology, by considering the patients therapies and safety signals collected in the local center.

Methods: A three years period analysis was considered after the introduction of the first biosimilar of ADA (2019) and ETN (2017): the safety reports occurred in this period were analyzed after being reported in the AIFA National Pharmacovigilance Network (RNF) database [2]. Patients biological scheme assessments were defined by using an internal accounting system of provided drugs to outpatient and home regimen patients.

Results: Etanercept was the first biosimilar subcutaneous anti-TNF α introduced in the rheumatological center: the switching practice was embraced for the 23.1% of patients ($n = 93$) and the biosimilar prescription was adopted for the 26.2% naïve patients ($n = 105$). The safety signal rate of ETN biosimilar/originator (0.6) was in favor of the biosimilar; 25% of the events were considered serious, with no difference between biosimilar and originator. Drug ineffectiveness was recorded both for originator and biosimilar with different rate (60% and 41.7% respectively), proving that the poor control of the disease should be independent by the drug formulation itself. The second generation biosimilars of adalimumab were introduced into the clinical practice much more incisively, thanks to the raising physician confidence acquired with ETN. The 37.7% of patients ($n = 283$) in ADA originator were switched to biosimilar and the 47.7% ($n = 358$) received biosimilars as first-line therapy. Although in this case there was a 38.5% of reports for perceived ineffectiveness

of the biosimilars ($n = 13$), they were all classified as not serious and signaling rate was still favoring the biosimilars (0.76).

Conclusion: From what emerges from the quantitative and qualitative analysis of the adverse reactions reported in the RNF, there are no specific safety concerns or clinically meaningful differences in the use of biosimilars [3]. Indeed, doctors are increasingly supporting biosimilarity/interchangeability, combined with an appropriate level of communication with patients, that can enhance the biosimilars contribution to sustainability and patient therapy access [4].

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P053

Clinicians' and Patients' Involvement in Reporting Adverse Drug Reactions and Adherence to Treatment of Biological Drugs in Rheumatology, Dermatology, Gastroenterology

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Introduction: Biological/biotechnological drugs play a key role in the treatment of immune-mediated inflammatory diseases, such as rheumatoid arthritis, chronic inflammatory diseases of the intestines and psoriasis.

The involvement of clinicians and patients in the reporting of suspected adverse drug reactions (ADRs) is essential, and a more effective interaction aimed at the correct and safe use of medicines should be promoted. It is a regional Pharmacovigilance project funded by the Italian Medicines Agency.

Objective: To promote the collection of ADRs to biological drugs used in rheumatology/dermatology/gastroenterology, through an active interaction with clinicians, paying attention to the reports' quality, lack of efficacy and therapeutic switches; to produce information cards that improve adherence to therapy, promote proper methods of home intake and reporting of ADRs. To encourage the use of biosimilar drugs in clinical practice.

Methods: A multidisciplinary regional group composed by clinicians and pharmacists of Local Health Units and Hospital Trusts of Modena, Reggio-Emilia, Bologna, Ferrara, Romagna, Pharmacovigilance Regional Centre and Scientific secretary of the Regional Commission of the drug (CRF) was involved. They deepened the topic of the quality of ADRs' reports and shared methods of collection and analysis of ADRs. This collaboration led to definition of information

cards regarding each medicinal product and its medical devices, which were developed for patients and distributed for its use in health practice.

Results: During the period 02/01/2020–28/02/2022 a total of 232 reports were collected: 72.4% submitted online; 98.7% filled out by clinicians; 37.1% with at least one follow-up; 56.5% with outcome; 94.4% with de-rechallenge; 14.1% with lack of efficacy; 44% with therapeutic switches; > 90% use of biosimilars. The total of 51 patient information cards was produced, combining 25 cards related to active ingredients and 40 cards for medical devices. The contents included: methods of conservation; aspects to be addressed; expected behaviors in case of missed intake; side effects of clinical relevance.

Conclusion: The discussion among healthcare professionals has allowed a dialogue on pharmacovigilance, with insights on reports of ineffectiveness and therapeutic switches. A multidisciplinary approach has allowed patients to identify clinical relevance of ADRs and correct use of these drugs.

The collaboration between healthcare professionals is necessary to increase the quality of ADRs' reports aiming at the comprehension of potential risks of the medicines' use.

The development of information cards addressed to patients was a moment of sharing a collaborative multidisciplinary approach in creation of documents useful to promote a conscious and safe use of medicines.

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P054

A Rare Case of Polydactyly in a Newborn from Mother Affected by Multiple Sclerosis

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Introduction: Polydactyly is the most common congenital anomaly of hand and foot. It is characterized by extra fingers or toes and it can occur as part of a syndrome or as a separate event [1].

Objective: To report a case of congenital polydactyly in a baby born from a mother affected by multiple sclerosis (MS) in therapy with ocrelizumab.

Methods: We performed a prospective analysis of the relationship between the use of drugs modifying the course of MS, and the risk of serious adverse drug reactions (ADRs). The case was reported in the Italian National Pharmacovigilance Network (RNF) as serious event [2]. We performed an analysis of the number of ADRs occurred to pregnant women receiving ocrelizumab, through a comparison between the RNF and the Eudravigilance database [3].

Results: The mother is a 42-years-old Senegalese woman, affected by MS since 2014. She also suffers from bronchial asthma, atopic eczematous dermatitis, allergic rhinitis, obesity. On 2016 the woman delivered a healthy baby; during her first pregnancy she didn't receive any SM therapy. After 2 years of treatment with fingolimod, on January 2019 doctors switched to ocrelizumab (intravenous infusion, 600 mg every 6 months). The last infusion was in November 2020, and in January 2021 she got pregnant again. Therapy was discontinued and the baby was born in good health by vaginal birth on Oct. 2021 but had polydactyly in his hands and feet. Doctors are now considering amputation surgery. From the year of ocrelizumab authorization (2018) to date (30/04/2022), 5 other ADRs regarding "congenital, family and genetic diseases" and "pregnancy, puerperium and perinatal disorders" have been reported in the RNF [2] and 57 ADR in Eudravigilance [3]. According to an EMA Assessment report, 46 patients receiving ocrelizumab became pregnant during clinical study participation. Among these, 11 cases reported a spontaneous fetal loss and 9 cases reported premature delivery and/or an abnormal finding in a live born baby [4].

Conclusion: Pre-clinical studies do not indicate teratogenic effects of ocrelizumab, but there is some evidence of these effects in humans. Ocrelizumab Summary of Product Characteristics (SmPC) indicates to adopt a contraceptive method during the treatment and for 12 months after the end of therapy. Naranjo's algorithm did not exclude the causal relationship between the adverse event reported in this abstract and the therapy with ocrelizumab, defining it as "doubt".

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P056

Safety of Biologic Therapy for Crohn's Disease: An Active Pharmacovigilance Study

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Introduction: The rising incidence of Crohn's Disease (CD) led to a significant increase in biologics therapy. Due to their recent development, the long-term risk/benefit profile of these therapies is still not completely defined. Therefore, pharmacovigilance activities become essential to monitor their safety.

Objective: The purpose of this prospective pharmacovigilance study was to evaluate safety of biologics for the treatment of CD.

Methods: All patients treated with at least one biologic drug in gastroenterology centers located in Calabria between January 2019 to April 2021, were enrolled, including both bionative and previous biologics exposed patients. Demographic and clinical characteristics including age, sex, diagnosis, comorbidities, type of drugs used, discontinuation or switch/swap to another biologic and AEs were collected. Each patient was monitored for 6 months at least, since the date of enrollment (follow-up period). AEs were analyzed through mapping with the PT (Preferred Term) and SOC (System Organ Class) codes of MedDRA dictionary. The most common AEs were detected and reported.

Results: A total of 163 patients were enrolled, of which 116 (71.2%) were bionative: mean age ($\pm$ SD) was 39.7 ($\pm$ 13.6) years; 58.3% were males. At the index data, infliximab (IFX) was the most and widely used in study population (44.8% of patients), followed by: adalimumab (ADA) (38.7%), vedolizumab (VED) (11.0%), ustekinumab (UST) (5.5%). During the follow-up, the 15.3% of patients reported at least one AEs related to biologics administration (Total AEs reported: 35). The most common AEs were “general disorders and administration site conditions” (34.3% of total AEs); mainly, asthenia in patients treated with IFX (7 patients) and ADA (1). Injection site reaction (1), flushing (2), oedema (1) were also reported in patients treated with IFX. “Nervous system disorders” occurred in 17.1% of cases, which included: 3 reports of headache (2 IFX, 1 ADA), 2 of somnolence (1 IFX, 1 UST) and 1 of confusional state (IFX). We also detected 5 “musculoskeletal and connective tissue disorders”, such as arthralgia, in patients treated with IFX. In all cases, the most common AEs, belonging to three different SOC, occurred in the hours immediately after administration and resolved within 24/48 hours. Only one patient treated with IFX reported persistent headache that requires further neurological examination.

Conclusion: Results showed that the highest incidence of AEs was related to infusion reactions. Indeed, the majority of AEs resolved within a maximum of 2 days after administration of biologics. However, further studies are needed to address the questions about the long-term safety of biologics.

References/Further Sources of Information

Not applicable.

P057

Safety of Biological Drugs in Naïve Patients in Dermatological Field: Real Life Data from an Active Pharmacovigilance Project in Calabria Region

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Introduction: Biological drugs have made important advances in the treatment of many inflammatory diseases. With their increasing use in real life, post-marketing activities became crucial for evidence on their long-term safety.

Objective: Aim of this active pharmacovigilance study was to evaluate the safety of biologics in bio-naïve patients affected by psoriasis (Pso), psoriatic arthritis (PsA) and atopic dermatitis (AD).

Methods: A prospective analysis of patients with dermatological diseases, naïve to biologics, in the period 2019–2022 was carried out. All bio-naïve patients treated with at least one biologic drug in dermatology centers located in Calabria were enrolled. Demographic and clinical data have been collected for each enrolled patient: age, sex, diagnosis, disease duration, current biologic drugs, biosimilar drugs, other treatments, relevant comorbidities, switch/swap, potential failure, and adverse events (AEs) onset.

Results: The study sample consisted of 521 patients: 47% with PsA, 49.5% with Ps, and 3.5% with an AD. Mean age ($\pm$ SD) was 54.5 $\pm$ 13.4 years and 59.1% were male. Mean age at diagnosis was 45.6 $\pm$ 15.4 and the mean disease duration was 11.8 $\pm$ 9.1 years. The most prescribed drug was Adalimumab (ADA) 36.6% of which the 6% were biosimilar drugs, followed by etanercept (ETN) 22.3% which the 12.8% were biosimilar drugs, ustekinumab (UST) 15.9%, secukinumab (SEC) 10.7%, golimumab (GOL) 4%, dupilumab (DPL) 2.6%, infliximab (IFX) 2.5%, ixekizumab (IXE) 2.4%, tildrakizumab (TIL) 0.9%, guselkumab (GUS) 0.7%, risankizumab (RZE) 0.7%, brodalumab (BRO) 0.5%, tocilizumab (TCZ) 0.1%, and abatacept (ABT) 0.1%. Regarding safety, overall, 417 patients (80%) not reported AEs, whereas patients 20% experienced at least one AE, mostly due to ADA (39.4%). The most frequent identified AEs were general disorders, in particular: asthenia (26%), injection site reactions (14.4%), headache (13.4%), skin disorders and gastrointestinal disorders (6.7%); all the AEs observed were expected.

Conclusion: Considering the low rate of AEs reported, our data seems to confirm a good safety profile of biologics. The reported AEs have been generally mild to moderate and mostly related to general disorders and administration. Nevertheless, the acquisition of data from clinical practice should be endorsed to better define the safety and efficacy profile of new biologic agents.

References/Further Sources of Information

Not applicable.

P058

Venetoclax and Tumor Lysis Syndrome (TLS): Data Mining of the FDA Adverse Event Reporting System (FAERS) Database

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Introduction: Venetoclax is a BH3-mimetic compound that selectively antagonizes BCL-2 (B-cell lymphoma 2) and induces apoptosis of CLL (Chronic Lymphocytic Leukemia) cells [1].

This oral treatment has demonstrated significant clinical advantages, but rapid tumor debulking can lead to a treatment-related risk of the acute condition known as tumor lysis syndrome (TLS), caused by the abrupt release of cellular components into the bloodstream [2].

A warning has been issued by the European Medicine Agency (EMA) and Italian Medicine Agency (AIFA) regarding the risk of TLS in patients treated with venetoclax [3].

Objective: The objective of this study was to investigate whether a disproportionately elevated signal of developing TLS may be detected in patients treated with venetoclax as compared to those treated with other drugs.

Methods: A retrospective analysis of spontaneously reported cases of TLS contained in the free and publicly available FDA Adverse Event Reporting System (FAERS) database was conducted in the period January 2015–December 2020 [4].

We calculated, as a signal of disproportionality, the reporting odds ratio (ROR), and the relative 95% confidence interval (CI), of TLS in patients treated with venetoclax. The signal was considered significant when the ROR lower limit of the 95% CI was > 1 .

Results: A total of 11,800,647 FAERS reports were identified during the study period; 15,933 (0.13%) reports mentioned venetoclax. There were 2,978 (0.02%) reports of TLS of which 353 (11.8%) attributed to venetoclax treatment.

The majority of these reports referred to patients aged 65–85 years (41%) and male (61.18%) (OR = 87.89, 95% CI 78.53–98.14, $z = 78.72$ $P < 0.0001$) as compared to other drugs.

Conclusion: With this study we demonstrated that in patients treated with venetoclax exists a higher risk to develop TLS.

It would be of interest to further analyze reports of TLS associated with this drug, comparing signals deriving from FAERS and those deriving from the European pharmacovigilance database EudraVigilance [5].

EMA and AIFA has recommended a continuous and constant updating of information on venetoclax to reflect current knowledge on this issue and address it in the best possible way and in the shortest possible time.

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P060

Secondary Depression Associated to TNF- α Inhibitors

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Introduction: A number of adverse drug reactions are known to be associated with Anti TNF alpha drugs; they include infections, injection site reactions, liver function abnormalities, hematological, and solid organ malignancies. Potential psychiatric adverse events have been described only in few cases.

Objective: To investigate the relationship between the onset of neuropsychiatric symptoms and the use of anti-TNF alpha drugs.

Methods: We describe the case of a patient with no history of psychiatric disorders that experienced secondary depression on anti-TNF alpha with positive rechallenge.

Results: A 57-year-old woman was diagnosed with axial ankylosing spondylitis associated with psoriasis and started on etanercept, which was stopped for paradoxical uveitis and substituted with adalimumab, one injection every 15 days. She presented 15 days after the fourth adalimumab infusion, mood disorders with black ideas, negative thoughts, neglect of her appearance and insomnia. These symptoms resolved within 20 days of stopping treatment. She was put under infliximab, and had presented from the first day a recurrence of the depressive syndrome with auditory hallucinations that have disappeared 15 days after stopping this drug.

Conclusion: The results suggest that psychiatric disorders may be associated with TNF- α inhibitors. Thus, we draw the attention of clinicians to the possibility of this type of adverse event occurring with this therapeutic class

References/Further Sources of Information

Keywords: tumor necrosis factor alpha, depression.

P061

Safety Profile of Dupilumab Approved for Chronic Rhinosinusitis with Nasal Polyposis: Analysis from the European Spontaneous Adverse Event Reporting System

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Introduction: Chronic rhinosinusitis with nasal polyposis (CRSwNP) is characterized by a type 2 pattern of inflammation resulting in the production of some cytokines such as interleukin (IL)-4, IL5, and IL13. Options for treatment-resistant CRSwNP include aspirin desensitization, recurrent topic and systemic corticosteroid use, and functional endoscopic sinus surgery (FESS). However, frequent relapses after medical and surgical treatment have been observed. Thus, dupilumab, a human recombinant monoclonal IgG4 antibody, changes radically the treatment of CRSwNP because of its binding effects on major drivers of human type 2 inflammatory processes [1-

3]. Considering its recent approval, it may be useful to evaluate its safety profile.

Objective: The aim of this study was to describe better adverse drug reactions (ADRs) related to dupilumab in the treatment of CRSwNP analyzing all individual case safety reports (ICSRs) collected into the European Spontaneous Reporting System (SRS) database.

Methods: All ICSRs recorded starting from the drug approval up to 31 December 2021 with dupilumab reported as suspected and having the specific indication of CRSwNP were considered. A descriptive analysis was conducted to assess demographic characteristics and dupilumab-related variables.

Results: Out of 10,400 ICSRs related to dupilumab, only 481 (4.6%) had CRSwNP indication, of which 68.2% were related to adults and 54.3% to females. The 68.4% were serious; however, ICSRs mainly led to a completely or partial recovering (25.4%) and 8 cases were fatal (1.7%). The time to onset (TTO) of ADRs was 25 (1–84.75) days while the time to resolution (TTR) was 5 (1.75–15.75) days. Analyzing ADRs by System Organ Classes (SOCs), the most reported were general and administration site conditions (36.4%) followed by injuries (21.6%), infections (21.2%), respiratory (19.1%), skin (16.6%), and nervous system disorders (16.4%). Looking at Preferred Terms (PTs), arthralgia (7.3%), eosinophilia (6.9%), COVID-19 (6.0%), pyrexia (5.8%), asthenia (5.6%), rash (5.4%), and dyspnoea (5.2%) were the most reported. The 7.5% of ICSRs described an aggravated condition with persistent nasal polyps: in 4 cases (0.8%) a nasal polypectomy was required. Considering fatal ICSRs, two cases were related to progression of COVID-19, one to road traffic accident, one to accidental death and the others were not fully specified.

Conclusion: These results showed that dupilumab-related ICSRs are not commonly reported in CRSwNP. However, given the good treatment response and the minimal adverse effects observed, clinicians should consider treating CRSwNP with dupilumab. Moreover, additional analyses are necessary to better outline the safety profile of dupilumab in this particular setting.

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P062

Safety Profile of Tyrosine Kinase Inhibitors Approved for Gastrointestinal Stromal Tumors: Analysis from the European Spontaneous Adverse Event Reporting System

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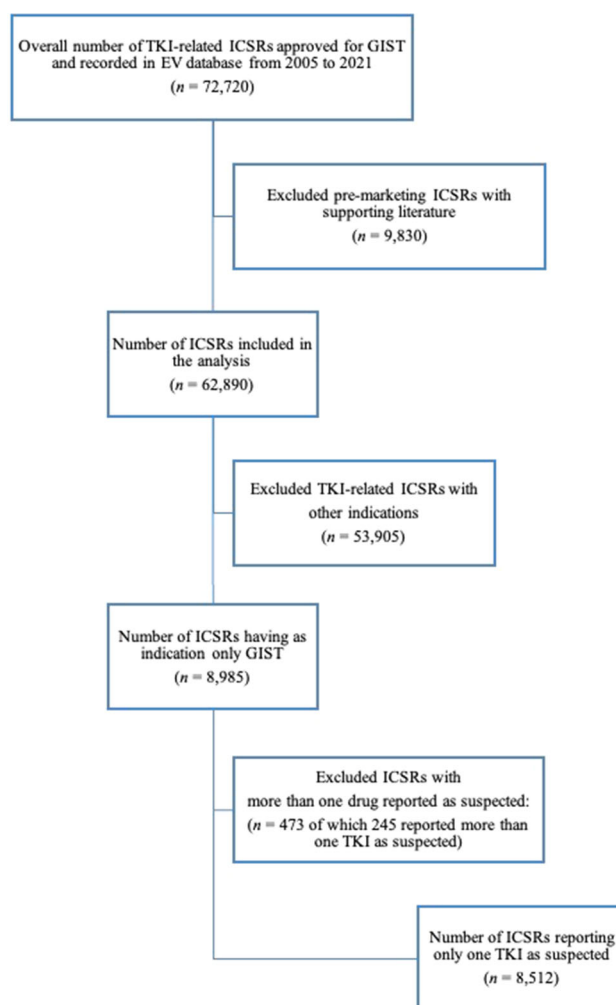
Introduction: Gastrointestinal stromal tumors (GISTs), soft tissue sarcomas of the digestive tract, are associated with oncogenic

mutations that led to the approval of tyrosine kinase inhibitors (TKIs) [1–2]. Considering the increased use of TKIs in clinical practice, it may be useful to identify unexpected adverse drug reactions (ADRs).

Objective: The aim of this study was to describe better ADRs and to identify unexpected potential safety signals through the analysis of individual case safety reports (ICSRs) among TKIs approved for GIST collected into the European Spontaneous Reporting System (SRS) database.

Methods: All ICSRs recorded starting from the drug approval up to 31 December 2021 with one of the following TKIs reported as suspected drug were included: imatinib (IM), sunitinib (SU), avapritinib (AVA), regorafenib (REG), and ripretinib (RIP). A descriptive analysis was conducted to assess all demographic characteristics. Moreover, a disproportionality analysis was performed using the Reporting Odds Ratio (ROR) with the corresponding 95% Confidence Interval (CI) to evaluate the frequency of ADRs for each TKI compared to all other TKIs.

Results



The number of analyzed ICSRs was 8,512 (Figure 1 Flowchart of ICSRs selection process): the 57.9% were related to IM, followed by SU (24.2%), AVA (13.1%), REG (2.7%), and RIP (2.1%). ICSRs were mainly serious (87.5%), related to males (51.7%), and to adults (44.7%); moreover, the 25.5% were fatal. The disproportionality analysis showed a higher reporting frequency of some unexpected ADRs for each TKI: gait disturbance (ROR 2.86; 95% CI 1.90–4.29), hyperhidrosis (2.57; 1.06–6.20), and hyperammonemia (3.92;

1.05–14.60) for SU; cerebrovascular accident (6.23; 2.18–17.84), hemoglobin decreased (2.23; 1.08–4.61), and internal haemorrhage (14.44; 3.94–52.92) for RIP; gastrointestinal ulcer (10.88; 2.98–39.81) for REG; hepatic and lung cancer for IM (12.79; 8.04–20.37 and 7.71; 3.33–17.84, respectively); hallucination (24.33; 9.02–65.68), mood swings (8.02; 2.44–26.33), and stress (6.68; 1.93–23.11), nephrolithiasis (6.69; 2.15–20.77), pollakiuria (3.08; 1.17–8.13), and dialysis (6.68; 1.67–26.73), sinusitis (3.34; 1.14–9.78), cellulitis (4.17; 1.36–12.78), and COVID-19 (7.25; 3.40–15.45), chills (2.36; 1.22–4.58), limb fracture (3.53; 1.63–7.60), hernia (9.23; 3.71–23.00), diabetes mellitus (5.02; 2.11–11.95), hyposideraemia (5.02; 2.11–11.95), tinnitus (3.64; 1.34–9.87), parosmia (5.00; 1.12–22.38), Raynaud's phenomenon (5.00; 1.12–22.38), and thyroid function test abnormal (8.90; 1.99–39.83) for AVA.

Conclusion: This study is largely consistent with results from literature but some unexpected ADRs were shown. Further studies are necessary to increase the awareness about the safety profiles of new TKIs approved for GISTs.

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P063

Safety Profile of Tyrosine Kinase Inhibitors Used in Non-Small-Cell Lung Cancer: An Analysis from The Italian Pharmacovigilance Database

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Introduction: Non-small cell lung cancer (NSCLC) is often caused by molecular alterations that led to the approval of new tyrosine kinase inhibitors (TKIs) [1-2]. Given the clinical relevance of some TKI-related adverse drug reactions (ADRs) not yet fully characterized it may be useful to evaluate the safety profile of TKIs in NSCLC.

Objective: The aim was to highlight all Italian open data-related ADRs associated with TKIs approved for NSCLC and, consequently, to focus on all regional Sicilian reports.

Methods: All national publicly-available aggregated ADR reports recorded from 2002 to 2021 into the Reports of Adverse Reactions of Medicines (RAM) system and all complete Sicilian data reported into the Italian spontaneous reporting system (SRS) database having as suspected drugs the following TKIs approved for NSCLC were consulted: afatinib, alectinib, brigatinib, ceritinib, crizotinib, erlotinib, gefitinib, lorlatinib, nintedanib, and osimertinib. Descriptive analyses of national publicly-available aggregated data and full-access regional data were performed to assess demographic and drug-related variables followed by a more in-depth analysis of all Sicilian ADRs.

Results: Out of 3,048 collected reports, the 47.5% were related to erlotinib, followed by afatinib, gefitinib, and crizotinib. ADRs were mainly not serious (n = 2,192; 71.9%), related to females (n = 1,592; 52.2%) and to the age group > 65 years (n = 1,617; 53.1%). The most reported ADRs were skin and gastrointestinal disorders (n = 1,766; 57.9% and n = 1,024; 33.6%, respectively) followed by general disorders and infections (n = 536; 17.6% and n = 483; 15.8%, respectively). The case-by-case assessment of Sicilian reports showed 68 serious ADRs (28.8%) with a median time-to-onset of 45 (21-134) days that mainly involved rash (n = 13; 19.1%), diarrhea (n = 10; 14.7%), respiratory failure (n = 7; 10.3%), hypertransaminasemia and dermatitis (both with n = 6; 8.8%), asthenia, folliculitis and nail conditions (n = 4; 5.9%). Four cases of death related to erlotinib were associated with the onset of epilepsy and cerebral ischemia, the occurrence of pneumonia with neutropenia and leukopenia, the onset of respiratory failure and cardiogenic shock, and the occurrence of intestinal lung disease; two cases of death, associated with osimertinib, concerned a case of neoplasm progression and a case of sudden death.

Conclusion: The reporting of drugs-related ADRs in NSCLC were mostly reported in the literature and not unexpected ADRs were shown. However, further studies are necessary to increase the awareness about the safety profiles of new TKIs onto the market.

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P064

Focus on the Management of Reporting for Drug Ineffectiveness

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Introduction: About "MANAGEMENT OF REPORTS OF LACK OF EFFECTIVENESS IN THE NATIONAL PHARMACOVIGILANCE NETWORK", the AIFA Post-Marketing Supervision Area highlighted that, for therapeutic ineffectiveness reports, it's important to establish if there is a drug therapeutic ineffectiveness or a disease progression, not attributable to the drug itself, but related to the natural course of the disease. AIFA ha sottolineato che, per una corretta valutazione clinica, i quattro requisiti minimi (un segnalatore identificabile, un paziente, una reazione avversa e un farmaco sospetto) non sono sempre sufficienti per considerare valida una segnalazione. Pertanto, per le segnalazioni di inefficacia del farmaco biologico, particolare attenzione deve essere pagato per ottenere informazioni relative a: anamnesi, durata della terapia, lotto, azioni intraprese, test di laboratorio, obiettività, indici di valutazione della malattia pre e post trattamento.

Objective: È stata effettuata un'analisi comparativa delle segnalazioni di mancata efficacia terapeutica pervenute prima e dopo il 10 maggio 2021 (data di pubblicazione nota AIFA). L'obiettivo dello studio era verificare l'efficacia delle informazioni aggiuntive richieste.

Methods: The data relating to drug ineffectiveness reports about the most populous ASL (1.221.857, ¼ regional population) were

extrapolated from the National Pharmacovigilance Network (NPN), filtered by ASL of interest, from 01/01/2017 to 04/30/2022.

Results: In the analyzed period, 39/2046 (1.9%) reports were received for ineffectiveness. In 2017, 2/269 (5% of 39), records were related to therapeutic ineffectiveness (1 originator Adalimumab; 1 equivalent Formoterol). In 2018, 2/217 (5% of 39), related to biosimilar Eritropoietin. In 2019, 1/249 (3%), related to measles, mumps, rubella vaccine. In 2020, of 13/288 (33%), 6 related to Adalimumab (2 originators, 4 biosimilars); 2 Etanercept (1 originator, 1 biosimilar); 1 Certolizumab; 1 Tofacitinib; 1 Secukinumab; 1 Dimethyl Fumarate. In 2021, of 19/793 (46%), 11 were received before the AIF Anote (5 biosimilar Adalimumab; 1 biosimilar Infliximab; 1 cyclosporine; 1 Tocilizumab; 1 Methotrexate; 1 Fingolimod; 1 Carbomer), while 8 after the AIF Anote (3 biosimilar Adalimumab; 1 Sarilumab; 1 Vedolizumab; 1 Secukinumab; 1 Certolizumab; 1 Apremilast). As suggested by AIFA, for the last 8 reports, additional information was requested. In 5/8 cases, through additional information, 4/5 reports were evaluated like disease progression attributable to the drug itself. For Apremilast, by the clinical information, the progression of the disease was not attributable to the drug, rather to its physiological progression. Therefore, the report was sent to the AIC Holder, and not recorded in the RNF, like AIFA document. In 2022, up to 30 April, 3 reports were received for ineffectiveness (2 biosimilar Adalimumab; 1 Guselkumab), supported by the reporters information.

Conclusion: The analysis of the therapeutic ineffectiveness reports has shown an increase over time. After the AIFA note publication, however, was recorded a reports decrease, from which it is possible to deduce a different approach by the reporters.

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P065

Real-World Pharmacovigilance Analysis of Lenvatinib Use in Qatar

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Introduction: Lenvatinib is a Tyrosine Kinase Inhibitor (TKI) that has been approved for different solid tumors including hepatocellular carcinoma (HCC), renal cell carcinoma, endometrial and thyroid cancer (1–4).

Objective: A Medication use evaluation (MUE) was performed for Lenvatinib. MUE is a systematic and interdisciplinary performance improvement method with an overarching goal of optimizing patient outcomes via ongoing evaluation and improvement of medication utilization (5).

Methods: The electronic health record identified of patients who received Lenvatinib between January 2020 and November 2021 were reviewed.

Results: A total of 28 patients were identified. Most of the patients used the Lenvatinib as a first or second line. Lenvatinib was used as monotherapy in 10 cases while as combination therapy in 18 cases: with pembrolizumab, everolimus or nivolumab. Lenvatinib was used as first line in 9 cases, second line in 8 cases, third line in 6 cases,

fourth line in 3 cases and as fifth line in 2 cases. Three patients received Lenvatinib for non-FDA/non-EMA approved indications, including cholangiocarcinoma and metastatic melanoma (in combination with Nivolumab). Oncologists chose to start with lower doses than approved ones in 57 % of patients. Despite that, nearly 90 % of patients had multiple-dose reductions due to adverse drug reactions (ADRs) development. 60% of the patients were still alive during the review period; 82 % of them (14 out of 17) still receiving Lenvatinib while 18 % (3 out of 17) progressed. Unfortunately, 22% (6 out of 28) deceased while 18 % lost follow-up. Mortality was within less than or equal to 30 days post Lenvatinib initiation in one patient with HCC. A total number of 26 ADRs were identified. All ADRs were documented by Clinical pharmacists. The most-reported ADRs were cardiovascular and dermatological followed by endocrine ADRs. A list of reported ADRs is summarized in table 1. In more than 50 % of cases; monitoring parameters were not done as baseline or follow up (especially ECG, ECHO, dental clearance, and protein urine dipstick), which in some cases leads to toxicities and ADRs development.

Table 1 : Summary of Lenvatinib induced ADRs

System	Number of ADRs	ADR description
Cardiovascular	6	- Lenvatinib induced cardiomyopathy (reduced EF, HTN & tachycardia) - Hypertensive crisis with Lenvatinib - Lenvatinib induced uncontrolled (grade 3) HTN (4 cases)
Dermatologic	6	- Lenvatinib induced Hand foot syndrome (4 cases) - Chemotherapy induced Lichenified eczema (pembrolizumab + Lenvatinib) - Grade 1-2 acneiform rash
Endocrine	4	- Drug induced thyroiditis (pembrolizumab + Lenvatinib) - Drug induced hypothyroidism (pembrolizumab + Lenvatinib) (3 cases)
Nervous system	3	- Lenvatinib related fatigue, asthenia and insomnia (3 cases)
Neuromuscular & skeletal	3	- Grade 1 myalgias and joints pain - Generalized body aches and tiredness - Recurrent Gingivitis V5? Osteonecrosis of the jaw
Genitourinary	2	- Recurrent urinary tract infection (2 cases)
Gastrointestinal	1	- Severe mucositis, decreased oral intake, weight loss
Hepatic	1	- Suspected Lenvatinib induced transaminitis

Conclusion: Lenvatinib is a vital oncology medication but it has been badly tolerated in our center. Utilizing this medication as indicated with performing the appropriate monitoring parameters as recommended can benefit patients. Encouraging all health care providers to document ADRs will lead to a better patient experience. A monitoring plan sheet will be implemented in our center.

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P066

Psoriasis Associated with Interferon Bêta-1b in a Multiple Sclerosis Patient with Positive Rechallenge

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Introduction: Several drugs such as lithium, beta-blockers, adrenergic antagonists, and interferons can aggravate pre-existing psoriasis or cause de novo psoriasis. Few cases of psoriasis were described with interferon bêta-1b.

Objective: Herein we report a rare case of interferon bêta-1b induced nummular psoriasis that occurred in a multiple sclerosis patient with positive rechallenge.

Methods: This case was reported in August 2020 and evaluated according to the French imputation method of causality assessment.

Results: A 39-year-old woman with no medical history of skin diseases has started interferon bêta-1b for her multiple sclerosis. After one month of daily use, she presented a generalized erythroderma and secondary diffuse erythematous-squamous coin-sized lesions evocative of nummular psoriasis. The patient denied any recent infection or stress. The evolution was favorable 20 days after drug withdrawal with corticosteroids treatment. After full recovery the rechallenge was attempted and the same symptomatology recurred one month later after the onset.

Conclusion: We suspected that interferon was the causative agent in the induction of psoriasis. The imputation score was likely due to the evocative delay of psoriasis occurrence, the favorable outcome after drug withdrawal, and the positive rechallenge.

Activation of psoriasis is an uncommon side effect of drugs and could mimic other cutaneous diseases in its rare features [1]. Physicians taking care of sclerosis patients should be aware of this affection which need careful evaluation of an added morbidity.

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P067

Optic Neuritis: A Serious Adverse Effect of Etanercept

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Introduction: Etanercept is a TNF-alpha inhibitor with proven efficacy in both rheumatic diseases and psoriasis. In contrast to uveitis and scleritis, which are the most reported ocular adverse reactions with etanercept, optic neuritis has been rarely described.

Objective: We hereby report a rare case of optic neuritis secondary to etanercept treatment.

Methods: This case was notified to the department of collection and analysis of adverse reactions of the Chalbi BELKAHIA national centre of pharmacovigilance of Tunis, and analysed according to the updated French method of imputability [1]

Results: A 34-year-old female patient with type 1 diabetes is followed for 18 years for pustular psoriasis with psoriatic arthritis. She was initially put on ciclosporin and methotrexate without improvement. Treatment with etanercept at a dose of 50 mg/week was then initiated with good cutaneous and articular evolution. After 15 months of treatment, the patient presented an amputation of the left temporal visual field with, on ophthalmological examination, a visual acuity of 8/10, a fundus examination without abnormality with no signs of papillary edema on angiography and a present and symmetrical photomotor reflex. The visual evoked potential, cerebral-medullary MRI, lumbar puncture and the immunological and infectious work-up were without abnormalities.

The diagnosis of optic neuritis was retained, etanercept was stopped and evolution was marked by the recurrence of the cutaneous and articular symptomatology with resolution of the visual disorders (visual acuity at 10/10). Later reintroduction of etanercept was marked by reappearance of visual disorders.

Conclusion: Optic neuritis remains a serious visual complication. Therefore, a visual field test before and during etanercept treatment is recommended.

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P068

Safety of Biologic Therapies for Severe Asthma: An Analysis of Adverse Reactions Reported in the WHO Pharmacovigilance Database

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Introduction: Biologics for severe asthma, targeting specific steps of the TH2 immune inflammation, represent a revolutionary treatment option for asthma therapy. Five biologics are approved for type 2 asthma phenotype: anti-IgE (omalizumab), anti-IL5 (mepolizumab, reslizumab, benralizumab), and anti-IL4 (dupilumab) [1]. These drugs are generally well tolerated, though information on long-term safety is limited and some adverse effects have not yet been fully characterized [2]. Spontaneous reporting systems represent the cornerstone for the detection of potential signals and exploration of the safety profile of all marketed drugs.

Objective: To provide an overview of safety data regarding biologics for severe asthma using VigiBase, the WHO global pharmacovigilance database.

Methods: We selected all Individual Case Safety Reports (ICSRs) attributed to biologics for severe asthma in VigiBase, up to May 8th, 2022. Study drugs included omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab. Descriptive frequency analyses of

ICSRs as a whole class, as well as by individual products have been conducted. Reporting odds ratio (ROR) and the Information Component (IC) with 95% confidence intervals (CIs) were used as measures of disproportionality for adverse drug reactions (ADRs) associated with the study drugs compared with all other suspected drugs (reference group).

Results: Out of a total of 30,620,801 ICSRs collected in VigiBase up to May 8th, 2022, 147,467 (0.5%) were related to all biologics for severe asthma. Dupilumab was indicated as a suspected drug in 58.3% reports, followed by omalizumab (27.9%), mepolizumab (8.8%), benralizumab (4.8%), and reslizumab (0.3%). Most ICSRs concerned adult patients (39.4%) and mainly involved women (54.8%). Biologics for asthma were associated with a lower frequency of serious ADR reporting than for the reference group (24.5% vs 32%; $p < 0.001$). The most reported ADRs included in the important medical events (IME) list were pneumonia ($n = 2,706$), anaphylactic reaction ($n = 2,102$) and angioedema ($n = 794$). The frequencies of ocular, general, immune, cutaneous and respiratory disorders, injury, poisoning and procedural complications and infections were significantly higher for study drugs than for reference group ($p < 0.001$). Focusing on serious ADRs of IME list, selected biologics were disproportionately associated with unexpected adverse reactions, such as malignancies, pulmonary embolism, sarcoidosis, and acquired haemophilia A, in particular with omalizumab, herpes infections with dupilumab and mepolizumab, and eosinophilic granulomatosis with polyangiitis related to benralizumab.

Conclusion: The analysis of ADR reports related to biologics for severe asthma showed that the most frequently reported events concerned general, cutaneous and respiratory disorders. Potential safety signals, including malignancies, herpes infections, pulmonary embolism were detected, requiring further investigation.

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VigiBase, the WHO global database of individual case safety reports (ICSRs) is the source of the information; the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases; the information does not represent the opinion of the UMC or the World Health Organization.

P069

Tofacitinib-Induced Acute Pancreatitis

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Introduction: Tofacitinib is an oral active immunosuppressant drug mainly indicated in rheumatoid arthritis (RA), inflammatory bowel disease¹. It is generally well tolerated. However, some adverse reactions (ADR) were reported. The most common ADR are severe infection, malign and benign tumors and thrombotic events. Pancreatitis has never been reported.

Objective: We report an exceptional case of pancreatitis associated with tofacitinib.

Methods: A 57-year-old female was treated since 2017 with captopril 50mg/day for hypertension and by several immunosuppressive treatment for rheumatoid arthritis (RA). On February, 14th 2022, for RA therapeutic failure, the patient started a new treatment based on tofacitinib 10mg daily. On February 20th, the patient presented acute abdominal pain with vomiting. Abdominal CT scan was performed in spite of a sub-normal biological tests (including the serum amylase and lipase level) showing a grade C pancreatitis. Etiologic investigations were normal including metabolic and lithiasic origin. The newly introduced drug (tofacitinib) was withdrawn. The patient presented a rapid clinical improvement with no recurrence of pancreatitis episode after 3 months of follow-up.

Results: The responsibility of tofacitinib was retained with an imputation score of I4 (C2, S2)³ mainly because of a compatible delay, the favorable outcome following its withdrawal (tofacitinib was the only drug stopped), and the negative investigations. Pancreatitis is reported with immunosuppressive drugs. However, this ADR is not associated with the new anti-JAK, especially tofacitinib.

The mechanism is generally either toxic or immunologic. In this case, the mechanism seems to be toxic since the short delay of occurrence and the absence of immunologic symptoms.

Conclusion: This observation reported an exceptional case of pancreatitis induced by tofacitinib. The probable mechanism is toxic.

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P070

Collection of Data for Detecting Adverse Drug Events in Smart Hospitals via Electronic Health Records, the GTT, Sensors and IoMT

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Introduction: There is a need for a more comprehensive adverse drug event (ADE) surveillance system that would be capable of handling all of more extensive information sources [1]. This goal can be advanced by positioning hospitals in the centre of research work, and by exploiting the growing role of the secondary use of healthcare data laws such as a recent Finnish legislation fostering a broader and easier collection and exploitation of healthcare data for secondary use [2].

Objective: An improved detection of ADEs requires smart solutions for the collection of data, which has to occur in a more effective and comprehensive way at the hospital level [3].

Methods: Based on previous literature and experiences, we suggest a more efficacious integration of electronic health records with the employment of the Global Trigger Tool (GTT, developed by the Institute for Healthcare Improvement) [4] as the main backbone of a data collection system to be deployed in combination with monitoring technology [5] and Internet of Things for healthcare purposes, known as Internet of Medical Things (IoMT) [6].

Results: This ensemble of methods can help building a secondary surveillance network for adverse drug events. This network is an important step in improved detection of ADEs and development of traditional pharmacovigilance networks.

Conclusion: Enabling legislation with smart hospital concept can facilitate development of pharmacovigilance towards more precise direction and service individual patient [1].

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P071

Voriconazole-Induced Junctional Tachycardia: A Case Report

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Introduction: The antifungal voriconazole is effective for the treatment of invasive fungal infections in immunocompromised patients. A serious adverse reaction to other triazoles is QT interval prolongation, which may precede life-threatening arrhythmias, such as twisted tips. Although ventricular arrhythmias are mentioned as a possible adverse effect of treatment with voriconazole (1).

Objective: We report a case report of Voriconazole-induced junctional tachycardia notified in the Regional Pharmacovigilance Service of Sfax.

Methods: The imputability study was performed according to the French Bégaud method.

Results: A 15-year-old patient with acute lymphoblastic leukemia and candidiasis infection was treated with Voriconazole. He developed 15 days later junctional tachycardia. Laboratory examinations showed a white blood cell count of 8140/mm³, absolute neutrophil

count of 300/mm³, hemoglobin level of 4.4 g/dL, platelet count of 54,000/mm³, sodium level of 133/mm³ and potassium level of 3.5/mm³. Voriconazole was continued and the patient was treated with Flecainide with slight improvement.

The imputability score of voriconazole for junctional tachycardia was rated as doubtful C1S2I1B2

Conclusion: Voriconazole can induce QT prolongation and ventricular arrhythmia in the absence of other arrhythmogenic factors. It is recommended, as a precautionary measure, to monitor the heart rate and QT interval in patients receiving long-term treatment with voriconazole and, possibly, in patients receiving treatment with other antifungal azoles (1). The mechanism may be dependent or independent of dose and concentration

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P072

Safety of Linagliptin in Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis

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Introduction: Linagliptin is an oral dipeptidyl peptidase (DPP) -4 inhibitor, which is indicated for the treatment of Type 2 diabetes mellitus (T2DM) as monotherapy or add-on therapy with other hypoglycemic drugs.¹

Objective: We aimed to summarize the evidence from randomized controlled trials (RCTs) to assess the safety of linagliptin focusing on cardiovascular risks among subjects with type 2 diabetes mellitus.

Methods: We performed a systematic search in the following databases: Medline, Embase, Cochrane Central, and Register of Controlled Trials from inception to November 2021. Randomized controlled trials (RCTs) of linagliptin compared to placebo in patients with Type 2 diabetes were included. The primary safety points were: cardiovascular (CV) adverse events including nonfatal stroke, non-fatal myocardial infarction (MI), CV death, MI, stroke, and hospitalization for unstable angina. While, secondary safety points were included 17 reported adverse events such as infections, hypoglycemia, and abdominal pain. Three reviewers independently screened and reviewed each study to extract relevant information. Any discrepancies were resolved by consensus. We performed meta-analyses using the random-effects model. Pooled risk ratios (RRs) of targeted adverse events with linagliptin compared to placebo were estimated using Mantel Haenszel.

Results: 24 studies with 19,981 adults patients were included. There was no difference in the incidence of all CV adverse events or individual CV adverse events between linagliptin and placebo arms. The pooled estimate of the risk of upper respiratory tract infection was reported in twelve trials, and a 32% risk reduction was shown among patients treated with the linagliptin group compared to the placebo group (RR = 0.68, 95% CI 0.51–0.90, and I² = 0%), while no difference was found in other infections. For gastrointestinal disorders, only the risk of abdominal pain showed a 5% risk reduction among patients treated with the linagliptin group compared to the placebo group (RR = 0.35, 95% CI 0.16–0.77, and I² = 0%).

Conclusion: Our meta-analysis study shows that there is no difference in CV. risks between linagliptin and placebo groups. Moreover, our study shows that there is a 32% risk reduction of upper respiratory tract infection and a 5% risk reduction for abdominal pain when using linagliptin compared to placebo.

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P075

Drug Related-Problems in Hospitalised Patients with Chronic Kidney Disease

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Introduction: A drug-related problem (DRP) is defined as “an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes”.^[1] Patients with chronic kidney disease (CKD) are more susceptible to DRPs due to comorbidities and polypharmacy.^[2,3]

Objective: This study aimed to investigate the types, characteristics, severity, causes, most common involved drug classes, and risk factors for DRPs in hospitalised patients with CKD.

Methods: A prospective follow up study was conducted in one of the largest teaching hospital trusts in England examining adults ≥ 18 years with a diagnosis of CKD (stage 1–4) hospitalised in medical and renal wards from November 2021 to April 2022. This study reviewed patients’ records, prescriptions, laboratory tests’ results to identify DRPs. Identified DRPs were classified according to Pharmaceutical Care Network Europe (PCNE) v 9.0 classification system and assessed by an expert panel for severity and preventability. Potential risk factors of DRPs were tested using logistic regression statistical analysis.

Results: Three hundred and seventy-eight patients were included in this study with a mean age of 74.1 and a median of 78 (IQR 67–87). Females represented 54% of the sample, with polypharmacy present in 86% of patients. A total of 375 DRPs were identified in 240 patients (64%) with an average prevalence of 1.56 per patient. Prevalence of DRPs was 0.4% in stage-1 CKD, 1.7% in stage-2 CKD, 55% in stage-3 CKD, and 42.9% in stage-4 CKD. Number of DRPs per patients ranged from 1 to 4 (IQR 1–2). Treatment effectiveness was the most frequent DRP type (215–57.3%), followed by treatment safety (157–41.9%), and other (3–0.8%). The severity of DRPs was

minor (n = 56, 14.9%), moderate (n = 315, 84%), and severe (n = 4, 1.1%). Most DRPs were definitely preventable (n = 268–71.5%). Common drugs groups involved were: Blood and blood forming organs (n = 88, 19.8%), Alimentary tract and metabolism with (n = 78, 17.6%), and Cardiovascular system with (n = 61, 13.7%). Hospital stays over 5 days and using ≥ 6 drugs were independent factors for DRPs in CKD hospitalised patients with (OR 6.5, 95% CI 3.2–13.2; P = < 0.001) and (OR 6.3, 95% CI 2.9–13.5; P = < 0.001), respectively.

Conclusion: The majority of hospitalised CKD patients experienced a DRP, with polypharmacy and co-morbidities as significant risk factors. Awareness of this increased risk should inform prescribing decisions. Future work should focus on interventions to reduce DRPs in patients with CKD.

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P076

Factors Associated with Patient-Experienced Burden of Adverse Drug Reactions of Non-Vitamin K Oral Anticoagulants

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Introduction: Experiencing adverse drug reactions (ADRs) may impact the patient’s well-being and attitude towards their therapy with medicines. It has been demonstrated that the majority of patients who discontinued drugs reported a very high burden of ADRs [1]. How patients experience the burden of ADRs may be explained by several factors. Insight in these factors can help healthcare professionals (HCPs) to optimize the guidance of patients through their drug therapy.

Objective: To explore factors that are associated with a high, or low to moderate patient-experienced burden of ADRs.

Methods: A web-based prospective cohort design was used to collect information on patient characteristics and their experienced ADRs on non-vitamin K oral anticoagulants (NOACs) through four questionnaires. The experienced burden of ADRs was asked using a 5-point Likert scale ranging from 1 (not burdensome) to 5 (extremely burdensome). Burden scores 1 to 3 were considered as low to moderate burden, and burden scores 4 and 5 as high burden. To identify associated factors for the burden of ADRs, we performed backward stepwise selection to create a logistic regression model. Factors included in the analysis were: gender, age (< 70 or ≥ 70 years), type of NOAC, previous vitamin K antagonist use, self-managing NOAC use, consulting a HCP, (considering) withdrawing the NOAC, hospitalisation, haemorrhagic ADRs, the amount of ADRs (< 4 or ≥ 4), and outcome of the ADR. RStudio with R version 4.1.3 was used for the statistical analysis, with a significance level of < 0.05.

Results: A total of 1076 ADRs reported by 627 participants were included. Factors associated with a high burden are demonstrated in

Table 1. Hospitalisation (OR 6.07), (considering) withdrawing the NOAC (ORs 6.10 and 6.34 respectively), and worsening of the ADR (OR 6.17) had the strongest association with a high burden. Consulting a HCP and experiencing four or more ADRs increased the odds by respectively 4.18 and 2.57. Furthermore, women had a 1.55 increased odds for a high burden compared to men.

Table 1. Multivariable logistic regression model.

Associated factors	Odds ratio (95% confidence interval)	P-value
Gender (female)	1.55 (1.05 - 2.30)	0.029
Hospitalisation	6.07 (1.26 - 34.33)	0.028
Considering NOAC withdrawal	6.10 (3.78 - 9.85)	<0.001
NOAC withdrawal	6.34 (2.29 - 20.99)	0.001
Consulting HCP	4.18 (2.77 - 6.31)	<0.001
≥ 4 ADRs	2.57 (1.70 - 3.87)	<0.001
Outcome of the ADR		
Recovering	1.17 (0.60 - 2.32)	0.646
No improvement	1.51 (0.85 - 2.78)	0.169
Worsening	6.17 (3.09 - 12.65)	<0.001

Conclusion: This study demonstrates that multiple factors are associated with the patient-experienced burden of ADRs of NOACs. Worsening of the ADR, hospitalisation and (considering) NOAC withdrawal were mostly associated with a high burden of ADRs. Other factors associated with a high burden were female gender, consulting a HCP, and experiencing ≥ 4 ADRs. More studies are needed to explore how these factors influence drug therapy.

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P077

Factors Affecting Clopidogrel Safety in the Montenegrin Population

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Introduction: Clopidogrel is an antiplatelet drug that inhibits platelet activation and aggregation by blocking adenosine diphosphate (ADP) P2Y₁₂ receptor [1]. Along with aspirin, it represents the mainstay in the management of patients suffering from myocardial infarction, ischemic stroke, acute coronary syndrome, and atrial fibrillation [2]. However, clopidogrel therapy is not always efficient or safe since the possible outcomes range from complete resistance to treatment to major bleeding events [3].

Objective: The aim of this study was to provide the analysis of genetic and non-genetic factors that influence clopidogrel efficacy and safety in cardiology patients.

Methods: We have conducted a prospective study in 200 hospitalized patients. *CYP2C19* genetic testing was conducted, and the PREDICT score was calculated in 102 out of 200 patients treated with clopidogrel in order to determine the influence of genetic and non-genetic factors on outcomes of interest. Adverse cardiovascular events and adverse reactions to clopidogrel were assessed during 12 months follow up period.

Results: In univariate logistic regression model, statistically significant predictors of the outcome of interest are: the PREDICT score ($p < 0.001$), enzymatic activity [slow metabolizers ($p < 0.001$) compared to the rapid, extensive and intermediate metabolizers as a reference category] and concomitant use of other drugs that are also metabolized through *CYP2C19* ($p = 0.030$). In multivariate logistic regression model, predictors from the model of univariate logistic regression which were statistically significant at the significance level of 0.05 were included. The model contains three predictors—PREDICT score, enzymatic activity and concomitant administration of other drugs that are metabolized via the same CYP enzyme. The whole model was statistically significant ($p < 0.001$). There is no significant multicollinearity or interaction between the predictors ($p = 0.002$ and 0.009 , respectively).

Conclusion: In assessing the clopidogrel resistance in cardiology patients the stepwise approach could be used, combining the PREDICT score, platelet aggregation test, and genetic testing for *CYP2C19* polymorphism [4].

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P078

Urinary MicroRNAs as Possible Biomarkers of Cisplatin-Induced Nephrotoxicity in Patients with Head and Neck Cancer

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Introduction: The treatment of head and neck cancer (HNC) currently recommended consists of chemotherapy with cisplatin concomitant with radiotherapy. However, cisplatin treatment is frequently associated with renal adverse drug reactions (ADRs) (1), impacting patients' quality of life; besides, as traditional biomarkers have low sensitivity and specificity (2,3), there is currently a search for new ones.

Objective: This study aimed to evaluate miRNAs as possible biomarkers of cisplatin-induced renal ADRs in HNC patients.

Methods: Massive sequencing was performed using urinary miRNAs from HNC patients, collected 5 days after cisplatin chemotherapy. To assess the expression of miRNAs, a comparison was made between the case and control groups (6 patients with nephrotoxicity and 6 without nephrotoxicity, respectively); differential expression was analyzed by GeneGlobe (Qiagen) and normalized by DESeq2. Based on the results of sequencing and analysis of the current literature, 6 miRNAs were selected (hsa-miR-6729-5p, hsa-miR-1238-5p, hsa-miR-4706, hsa-miR-6805-5p, hsa-miR-4322 and hsa-miR-21-5p) to

have their expression evaluated by qPCR, before and 5 days after chemotherapy (D5), also in urine samples. In this validation stage, the expression profile of these miRNAs was compared between the case and control groups (composed, respectively, of 24 participants with renal ADRs and 25 participants without); the relative expressions were evaluated by the $2^{-\Delta\text{CT}}$ method.

Results: The results obtained in the validation stage showed that, except hsa-miR-6729-5p, all other miRNAs showed a tendency to be upregulated in the control group before and after chemotherapy when compared to the case group. Some miRNAs resulted in remarkably high fold regulation (FR) values (1. hsa-miR-6729-5p—baseline: FR = 11.8, $p = 0.5958$; D5: FR = 4.1, $p = 0.6306$; 2. hsa-miR-4706—baseline: FR = -1.3, $p = 0.4843$; D5: FR = -26.7, $p = 0.8623$) and others were smaller but still relevant (3. hsa-miR-1238-5p—baseline: FR = -2.4, $p = 0.1170$). However, although a difference in expression was found between the groups for all miRNAs, this difference was not significant.

Conclusion: Renal ADRs are still an obstacle to the effective therapy and quality of life of patients treated with cisplatin. The preliminary results of this work show that some miRNAs tend to be elevated in patients without ADRs, therefore they could be protecting against the induction of renal injury; however, in order to possibly help the clinician in the evaluation/choice of chemotherapy treatment for these patients, further studies are still needed and in a larger number of patients.

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P079

ABCC2 Gene Polymorphism and Adverse Reactions to Carboplatin and Paclitaxel Treatment in Non-small Cell Carcinoma Patients

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Introduction: The estimate for each year of the triennium 2020–2022 that will occur 30 thousand lung cancer new cases in Brazil¹, which can be classified as: small cell lung cancer (SCLC) and non-small cell lung cancer cells (NSCLC), that corresponds the 85% of the cases². The main NSCLC treatments are platinum-derived chemotherapeutics, highlighting carboplatin and paclitaxel³, adverse drug reaction (ADRs) may compromise the treatment. *ABCC2 gene is involved in*

molecules of transport, polymorphs in this gene may be related with ADRs and response compromising the effectiveness of treatment⁴.

Objective: Investigate the prevalence the main ADRs after the first cycle of chemotherapy with Carboplatin and Paclitaxel in patients with NSCLC. Analyze the frequency of polymorphism in the gene *ABCC2* (rs717620) in those who had hematological and renal ADRs.

Methods: Hematological and biochemical tests were performed before and after 21 days of the first chemotherapy session. Hematological, renal, hepatic and gastrointestinal ADRs was determined using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, criteria. Genomic DNA was extracted and purified from peripheral blood using a Wizard® Genomic DNA Purification Kit (Promega, USA) according to the manufacturer's protocol. The *ABCC2* (rs717620) the polymorphisms were studied with Taqman® (Applied Biosystems, CA, USA), determined by rt-PCR.

Results: A total of 85 patients with NSCLC, treated at Clinics of Hospital Unicamp, the most with an average age of 63 years, men (55%), Caucasians (85%), accentuated smokers (35%), abstainer (35%), with *performance status* (KPS) at 100% (88%) and with adenocarcinoma (63%). Observed that 72% of patients had a hematological ADRs, grade 1 anemia was the most prevalent. 61% had a grade 1 gastrointestinal ADRs: nausea (25%), vomit (8%) and diarrhea (18%). Hepatic ADRs (59%) grade 1 hepatic ADRs was observed in 59%. Renal ADRs grade 1 was observed in 74%, the most prevalent were: reduced creatinine clearance (28%), Hyponatremia (24%), and Hypocalcemia (18%). In the gene *ABCC2*, was observed heterozygosity (CT) in 56%, 28% homozygous CC and 15% homozygous TT in the population studied, those with genotype CC had more hematological (54%) and renal (44%) ADRs when compared to the others genotypes, the polymorphism were in the *Hardy-Weinberg equilibrium*.

Conclusion: Patients in this study has a high prevalence of hematological and renal ADRs. The finding suggests that patients who are homozygous (CC) for the gene *ABCC2* (rs717620) are at increased risk for hematologic and renal ADRs if compared to the other genotypes (CT + TT).

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P080

Development of a Clinical Focus Pharmacovigilance System

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Introduction: Now more than ever the pharmacovigilance has demonstrated great relevance in making medication safer by evaluating the benefit-risk ratio in the treatment used in COVID-19 patients [1]; nevertheless, pharmacovigilance has always aimed to help clinicians and patients make wiser therapeutic decisions as Dra. Marie Lindquist's once said. Therefore, we have developed at the Instituto Nacional de Cardiología Ignacio Chávez the Pharmacovigilance Institutional Center, establishing as our goals to manage a pharmacovigilance's system that aims to take the World Health Organization Challenge Medication Without Harm by promoting the rational use of medication, and identifying risks related to drugs before they impact the patients.

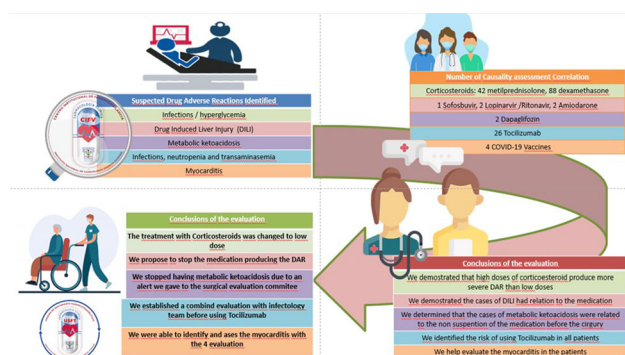
Objective: Exemplify the impact that a clinical focus pharmacovigilance system has had in the patients at the Instituto Nacional de Cardiología Ignacio Chávez.

Methods: With the Pharmacovigilance Institutional Center databases of Drug Adverse Reactions (DAR) and Event Supposedly Attributed to Vaccination or Immunization (ESAVI) identify the most important cases in which a clinical decision has been made and exemplify the process of the decision making.

Results: From the opening of the Institutional Center in 2020 at the start of the COVID-19 pandemic, we have identified and reported 292 DAR in VigiFlow and 421 ESAVI to the General Direction of Epidemiology. From these reports we can identify several different pharmaceutical interventions related to the pharmacovigilance evaluations, that have given as a result the modification of the clinical approach:

- Corticosteroids used in COVID-19 patients: we modified the dosage given to patients reducing the severity of the DAR.
- Drug Induced Liver Injury: we alerted in early moment the elevation of hepatic markers making changes in the prescriptions.
- Dapagliflozin use in heart failure patients that produced ketoacidosis: after alerting the surgical team there was no more patients presenting this DAR.
- Tocilizumab used in COVID-19 patients, there was a concern to use this monoclonal medication: with this intervention we established the safety parameters to use this medication.
- RNA COVID-19 vaccines producing myocarditis: with this intervention we have been able to establish a fast identification of these cases.

Exemplifying the process in the next table.



Conclusion: Pharmacovigilance now a day require to explore a more patient focus and clinical approach in where there are

pharmacovigilants working hand by hand next to the clinicians and understanding the needs of the patients. For that we require assemble teams that can identify, evaluate and give feedback on the best way to treat DAR.

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P081

Falling for Amiodarone—A Safety Analysis in Patients 60 Years and Older

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Introduction: Older patients, representing a frail population, are at a high risk of falling because of age-related changes in multiple physiological systems. Falls are the leading cause of injury-related deaths in elderly individuals [1]. Cardiac arrhythmias affect a large proportion of the world's population and are frequent within the older population [2]. Amiodarone is one of the most effective and commonly prescribed antiarrhythmic drugs. It has a very long plasma half-life and undergoes extensive hepatic metabolism via several CYP enzymes [3]. Its toxicity profile is broad, potentially affecting various organs. Amiodarone may interact with other clinically important drugs. The mechanisms of its drug interactions could be the change of pharmacokinetics (mainly by inhibition of hepatic metabolism), or pharmacodynamics of co-administered drugs [4].

Objective: To review the risk of falling with amiodarone in older patients.

Methods: A quantitative analysis of data in VigiBase, the WHO global database of suspected adverse reactions of medicinal products.

Results: As of 3 May 2022, VigiBase included 378 cases reporting the MedDRA preferred term “Fall” and the substance amiodarone as suspected or interacting agent. After de-duplication and removal of irrelevant reports, 279 reports remained for analysis. Most reports (n = 270; 97%) concerned patients aged 60 years or older. The patients' median age was 81 years, ranging from 60 to 96. In 108 cases (39%), amiodarone was reported as the only suspected drug. Most patients received more than one drug with a median of two drugs being administered concomitantly, ranging from one to fifteen medicinal products.

The event “Fall” was reported to occur in median six months after start with amiodarone treatment, with a wide range between days to years. However, information about the time-to-onset was reported only in a limited number of cases. A subgroup analysis comparing patients with and without polypharmacy was performed (see Table 1). Median time-to-onset was remarkably shorter and fatality was higher in patients receiving more than five drugs.

In 20 cases (38%), a drug-drug-interaction between amiodarone and one or more other substances was identified and flagged by the reporter.

Table 1. Comparison of cases based on the number of administered drugs

		All cases n = 279 (100%)	Patients receiving ≤ 5 drugs n = 237 (85%)	Patients receiving > 5 drugs n = 41 (15%) **
Patients' sex	Female	133 (48)	109 (46)	23 (56)
	Male	144 (52)	127 (54)	17 (41)
	Unknown	2 (0.7)	1 (0.4)	1 (2.4)
Patients' age	Median (range)	81 (60–96)	80 (60–96)	82 (60–94)
	Number of drugs*	2 (1–15)	2 (1–5)	7 (6–14)
Seriousness	Yes	221 (79)	184 (78)	36 (88)
	Fatal	30 (11)	22 (9.3)	8 (20)
Time-to-onset	Median (range)	6 months (0 days – 15 years)	7 months (0 days – 15 years)	2 months (4 days – 1 year)

*only suspected/interacting drugs

**one case was excluded from the subgroup analysis due to an unreasonable high number of concomitant drugs

Conclusion: Prescribers should be aware that adding drugs—especially drugs able to cause extensive toxicity and drug-drug-interactions, such as amiodarone—to a pre-established multi-drug therapy regime in an older patient population, may significantly increase the risk for experiencing falling and potentially severe adverse outcomes.

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P082

Pharmacogenomics (PGx) as a New Special Interest Group (SIG) at ISOP

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Introduction: The risk of certain adverse drug reactions (ADRs) is known to be associated with variation in so called pharmacogenes [1]. Pharmacogenomic information has been included in the labels of a number of medicines to provide guidance on appropriate dose or to advise patients carrying risk alleles to carefully monitor for ADR symptoms or to not take the medicine [2].

Pharmacogenomic information in the product label takes into consideration the overall benefit-risk balance, magnitude of the genomic biomarker effect, strength of evidence as well as other aspects such as seriousness of the ADRs, underlying diseases, therapeutic alternatives, and interactions with other medicines. The label regarding pharmacogenomic testing may be classified into three categories as mandatory, recommended, or for information [3].

Objective: A global Special Interest Group (SIG) has been established in 2020 within the International Society of Pharmacovigilance (ISoP) to provide an opportunity for members interested in pharmacogenomics to expand knowledge of how medicines cause ADRs in genomic subpopulations; and to support Pharmacovigilance relevant to medicines with pharmacogenomic associations.

Methods: The SIG is open to all ISoP members and is made up of clinical and academic members from medicines regulatory bodies, non-governmental organizations and the pharmaceutical industry. SIG members regularly share news amongst the members and exchange experiences to support the coordination, evaluation and training on pharmacogenomics in pharmacovigilance, this with the purpose of improving knowledge and contributing to the safety of those patients who must use medications.

Results: Examples of the activities of the SIG will be shared.

Conclusion: The pharmacogenomics SIG at ISoP will contribute to the goal of identifying patients at risk and to improve the benefit/risk balance of drug treatment in genomic subpopulations.

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P085

Influence of the CYP450 Genetic Variation in Lipid Abnormalities with Clozapine Treatment: A Pilot Study in Patients with Psychiatric Disorder

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Introduction: Clozapine (CLZ) is one of the antipsychotics considered the gold standard for treatment-resistant schizophrenia (ERT); despite its effectiveness, it is related to adverse drug reactions (ADRs), which can be caused by several factors, including genetic variability [1–3]. Despite the significant benefits involved in the treatment of CLZ, its use may be associated with an increased prevalence of metabolic disorders such as diabetes, obesity, metabolic syndrome, and dyslipidemia [4–5].

Objective: This study aimed to verify whether *CYP450 Genetic Variation* related to Clozapine metabolism can influence the presence of ADRs related to lipids metabolism in patients with psychiatric disorders

Methods: This prospective and observational study was conducted at the Psychiatry Outpatient Clinic of HC/UNICAMP. Lipids ADRs was determined using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Genomic DNA was extracted and purified from peripheral blood using a Wizard® Genomic DNA Purification Kit (Promega, USA) according to the manufacturer's protocol. The CYP genetic variation were studied with Taqman® (Applied Biosystems, CA, USA), determined by rt-PCR. The project was approved by the Research Ethics Committee (83192918.9.0000.5404).

Results: Thirty-nine patients aged 29.7 ± 10.0 years were enrolled in the study, mostly men (64.1%), Caucasians (82.1%), and single (64.0%). Observing the ADRs for hypertriglyceridemia, 29.7% had grade 1 severity, 8.1% had grade 2, 2.3% had grade 3, and 2.3% had grade 4. No patient had hypercholesterolemia. For the *CYP2D6* Gene (rs1065852), *CYP3A4* (rs2740574) and *CYP1A2* (rs762551) we observed a prevalence of 62.0% for the homozygote GG, 79.0% homozygote TT and 89.2% for the heterozygote (CA), respectively. The allelic variant rs762551 (*CYP1A2*) can be related to the

occurrence of hypertriglyceridemia, where patients with homozygous CC had more probability in this ADR (75.0%) than in the group of heterozygous (CA) (39.4%).

Conclusion: Most of the patients in the study are young male adults and singles. Hypertriglyceridemia was observed in 43.2% of patients to some degree. This increase in triglycerides is related to increased body weight, a necessary ADR of clozapine can lead to other metabolic disorders such as diabetes and hypertension. Preliminary data also suggest that patients homozygous (GG) for the CYP1A2 gene (rs762551) have a higher risk of having hypertriglyceridemia when compared to the other genotypes.

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P086

Clinical Pharmacokinetics and Pharmacodynamics of Moxifloxacin in Human Tuberculosis

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Introduction: Clinicians treating patients with tuberculosis have recommended that the current regimen requires improvement and/or a less cumbersome and easy to adhere to therapeutic medicine/regimen. In the current therapeutic treatment, the duration of the treatment is overly long and patients unable to tolerate the combination. The current 6 months regimen was introduced in early 80's and there is a growing threat of multidrug resistant (MDR) and extremely drug-resistant (XDR0-TB). One of the best approaches to TB drug development that can yield results rapidly is to repurpose drugs that also have activity against TB. Moxifloxacin is an example of this drug. Moxifloxacin has been reported to play an important role in the management of patients who are unable to tolerate multidrug resistance TB regimen

Objective: To assess the pharmacokinetic and Pharmacodynamics of Moxifloxacin in human tuberculosis.

Methods: A narrative review of Moxifloxacin pharmacokinetics and pharmacodynamics in adults with TB was carried out across a range

of doses and various variables that influence its pharmacokinetics/pharmacodynamics. Several factors including malnutrition, fasting, HIV infection, diabetes mellitus, dose size, pharmacogenetic polymorphisms, hepatic cirrhosis, and substandard medicinal products alter Moxifloxacin exposure and/or efficacy

Results: Renal impairment has no significant influence on Moxifloxacin pharmacokinetics when dosed at 800 mg/day. The mean maximum concentration of drug in serum and the area under the concentration–time curve from 0 to 24 h (AUC_{0-24h}) is $3.2 \text{ mg} \cdot \text{L}^{-1}$ and $29.2 \text{ mg} \cdot \text{h} \cdot \text{L}^{-1}$ maximum (peak) concentration is an independent predictor of sterilizing activity and therapeutic drug monitoring at 6, 12, and 18 h post-dose may aid in optimizing dosing to achieve the recommended moxifloxacin concentration of $\geq 29 \text{ mg/L}$. A higher Moxifloxacin C_{max} is required for severe forms TB such as TB meningitis, with $C_{max} \geq 35 \text{ mg/L}$ and area under the concentration–time curve (AUC) from time zero to 6 h (AUC_6) $\geq 7 \text{ mg} \cdot \text{h/L}$ associated with reduced mortality.

Conclusion: Further studies are needed to confirm whether doses achieving exposures higher than the current standard dosage could translate into faster sputum conversion, higher cure rates, lower relapse rates, and less mortality. It is interesting to discover that daily Moxifloxacin dose of up to 800 mg/ 70kg were found to be safe and well-tolerated over a period of 3 months. Higher -dose Moxifloxacin may be considered in future studies when examining potentially and shorter regimens and markers of efficacy like AUC/MIC (Minimum inhibitory Concentration) and AUC/MIC should equally be examined.

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P087

Evaluation of Circulating MicroRNAs as Biomarkers of Hematological Adverse Reactions in Lung Cancer Patients Treated with Carboplatin and Paclitaxel

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Introduction: Lung cancer is the leading cause of cancer-related morbidity and mortality worldwide [1]. The treatment of lung cancer initially depend on the definition of the type of tumor and its staging [2]. The most common treatment is chemotherapy and the first line of treatment is the combination of carboplatin and paclitaxel. The effectiveness of this treatment is low and presents a high prevalence of adverse reactions, especially hematological [3]. Studies of new biomarkers, such as circulating miRNAs, related to these adverse reactions are very important to optimize the quality of life of patients.

Objective: To verify a relation between circulating miRNAs and hematologic adverse reactions caused by treatment with carboplatin and paclitaxel in lung cancer patients.

Methods: This study was approved by the ethics committee no. 83196318.8.0000.5404. Blood was collected from patients before and 15 days after chemotherapy, for hematological adverse reactions analysis, for MicroArray and for qPCR validation. Adverse reactions were classified according to the Common Terminology Criteria for Adverse Events v4.0 [4]. The MicroArray was performed with plasma from 6 patients without and 6 patients with hematological adverse reactions. Three miRNAs identified by MicroArray were validated via qPCR using 20 patients without and 26 with hematological adverse reactions. Bioinformatics analyses were performed by miRwalk, DAVID and GeneMani.

Results: Patients with lung cancer treated with carboplatin and paclitaxel are mostly white, with a mean age of 63.50 years, retired, with low schooling, heavy smokers, not eligible for surgical resection, with histopathological diagnosis of adenocarcinoma and stage 4. We observed a high prevalence of grades above 0 for anemia (44%). The MicroArray of patients with and without hematological toxicity verified 9 differently expressed plasma miRNAs among these patients. Of these 3 were chosen for validation being miR-1273g-3p, miR-3613-5p and miR-455-3p. Only miR-455-3p showed a significant expression reduction ($p = 0.04$) between the groups, before chemotherapy with carboplatin and paclitaxel. The bioinformatics analysis of hsa-miR-455-3p showed an important relationship of this miRNA with the hematopoiesis pathway, especially with action on the RUNX1 and TAL1 genes.

Conclusion: The most prevalent adverse reactions in lung cancer patients treated with carboplatin and paclitaxel were hematological, especially anemia. This adverse reaction, caused by a dysfunction of the hematopoietic system, can be explained by a possible relation between important genes in this system, RUNX1 and TAL1, and hsa-miR-455-3p.

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P088

ABCB1 Transporter Allelic Variants and Dermatologic Adverse Reactions Related to Gefitinib Therapy in Lung Cancer Patients: A Pilot Study

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Introduction: Lung cancer is the leading cause of cancer related death worldwide [1]. Gefitinib is a first-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) that has consistent clinical benefit in non-small cell lung cancer (NSCLC) patients with the activating mutations of the *EGFR* gene. However, dermatological adverse drug reactions (ADRs) are common in patients receiving gefitinib [2,3]. *ABCB1* gene variants may be associated with skin rashes [3,4].

Objective: To investigate associations between *ABCB1* transporter allelic variants with dermatological ADRs in patients treated with gefitinib.

Methods: This is a cohort study that included patients with NSCLC receiving oral gefitinib (250 mg/day). DNA was isolated from whole blood samples. Genotyping was performed by TaqMan[®] using real-time PCR. For the *ABCB1* gene, dbSNP-ID rs1045642 (C3435T) and rs1128503 (1236T>C) were studied. Dermatological ADRs (cutaneous rash, maculopapular rash, and hyperpigmentation) were evaluated after 8 weeks of TKI use and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Results: Eighteen patients were included with a mean age of 63.0 ± 11.0 years, mostly women (55.5%), Caucasian (83.2%), and non-smokers (66.6%). Stage IVA (50.0%) was the most observed. Moreover, 72.2% had *EGFR* exon 19 deletion and 27.7% had *EGFR* exon 21 mutation. The two *ABCB1* variants studied were in Hardy-Weinberg equilibrium. For rs1045642, AG heterozygous was observed in most patients (41.1%); 29.4% of patients showed GG and AA homozygous genotypes. For rs1128503, AG alleles were also predominant (64.7%); AA and GG homozygous genotypes were observed in 17.6% of patients. The most observed ADR was hyperpigmentation (grade 1: 44.4%; grade 2: 11.1%). Also, 33.3% and 11.1% of patients showed grade 1 and grade 2 cutaneous rash, respectively. For rs1045642, AA homozygous individuals showed a higher prevalence of cutaneous rash (80%) when compared to AG + GG genotypes (25%), similar to that observed for rs1128503. For rs1045642, maculopapular rash was more frequent in AA homozygous individuals (60%) than in AG + GG group (33.3%), similar to that observed for rs1128503. Only for rs1128503, it was possible to observe a higher prevalence of hyperpigmentation in the AG + GG group (57.1%) when compared to the AA homozygous patients (33.33%).

Conclusion: This study suggests the possibility of a association between AA genotype and the presence of rashes, for both dbSNP-ID in *ABCB1* gene.

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P089

Prescribing Patterns in Hospitalised Chronic Kidney Disease Patients: An Observational Study

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Introduction: Multiple comorbidities and altered pharmacokinetics are common in patients with CKD, which can have long-lasting consequences on quality of life.^[1,2] Understanding the nature of medication prescribed for co-morbidities, and the monitoring they require, is essential for safe prescribing practice and to avoid drug-related problems (DRPs) in CKD.

Objective: This study aims to describe the drug utilisation patterns of in-hospital CKD patients, with reference to the World Health Organisation (WHO) drug use indicators.^[3]

Methods: An observational follow up study on the drug utilisation pattern was conducted in hospitalised CKD patients over five months (November 2021 to April 2022) in a large teaching hospital in England. The study included hospitalised patients ≥ 18 years with CKD and followed them until discharge. WHO core drug use indicators were evaluated. Prescribed drugs for each patient were recorded on a data collection tool prepared for the purpose of this study and all drugs were classified according to the Anatomical Therapeutic Chemical (ATC) Classification System. Polypharmacy (≥ 6 drugs) risk factors were assessed with univariable and multivariable logistic regression using STATA 17 Software.

Results: During the study period, 387 patients were included in this study, with mean (SD) age of 75 (± 15.5). Over half were female ($n = 208$ 54%). The mean (SD) number of drugs per patient was 11 (± 4.9), the percentage of patients requiring a prescription of an antibiotic was 61.8%, the percentage of patients requiring a prescription of an injection was 93.5%, the percentage of drugs prescribed by generic name was 90.2%, and the percentage of drugs prescribed from essential drugs list or formulary was 88.9%. The most frequent drug groups prescribed were: Alimentary tract and metabolism (22%), Cardiovascular system (18.7%), and Blood and blood forming organs (17%). Longer hospital stay ($P < 0.001$), admission to a renal ward ($P = 0.02$) and number of comorbidities ($P < 0.001$) were independently associated with polypharmacy.

Table 2: World Health Organisation prescribing indicators

Indicator	WHO recommendation	Result
1. Average number of drugs per encounter	1.6 - 1.8	11 $\pm$ 4.9
2. Percentage of encounters resulting in prescription of an antibiotic	20 - 26.8 %	61.8%
3. Percentage of drugs prescribed by generic name	100 %	90.2%
4. Percentage of encounters resulting in prescription of an injection	13.4 - 24.1 %	93.5%
5. Percentage of drugs prescribed from essential drugs list or formulary	100 %	88.9%

Conclusion: In this cohort of CKD patients, we found mixed compliance with the WHO drug use indicators. There was relatively good compliance with drug formulary use and with generic prescribing, but a high number of drugs prescribed. As might be expected more complex patients with longer stays, and multiple co-morbidities had a higher chance of polypharmacy with the potential for increased DRPs. Further work should investigate prescribers' views on prescribing in CKD patients.

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P090

Associations of Genetic Polymorphisms of the Transporters with Cisplatin-Induced Renal Adverse Reactions in Patients with Head and Neck Cancer

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Introduction: Head and neck cancer (HNC) is the set of malignant tumors located in the upper aerodigestive tract [1]. Treatment of locally advanced HNC is based on radiotherapy concomitant with high-dose cisplatin chemotherapy, which is limited by the occurrence of severe toxicities [1,2]. Regarding cisplatin-induced adverse reactions, mainly in the kidney, there are considerable interindividual differences. Several aspects are considered to explain the different grades of adverse reactions and outcomes of the same treatment, and in this scenario, pharmacogenetics stands out. Genetic factors may include polymorphisms that affect the pharmacokinetics of cisplatin [3,4].

Objective: To evaluate the association of genetic polymorphisms of the transporter genes (*ABCB1*, *ABCC2*, *OCT2*, and *MATE1*) with cisplatin-induced renal adverse reactions in patients with HNC.

Methods: This is a prospective cohort study with consecutive sampling. Blood samples were collected from patients with HNC treated at the Clinical Oncology Outpatient Clinic of a tertiary teaching hospital in Brazil, before (baseline) and after cisplatin administration (80–100 mg/m²). Ten single-nucleotide polymorphisms (SNPs) in four transporter genes *ABCB1* (rs1045642, rs1128503, rs2032582 C>A, and rs2032582 C>T), *ABCC2* (rs717620, rs2273697, and rs3740066), *OCT2* (rs316003 and rs316019), and *MATE1* (rs2289669) were selected to investigate their associations with renal adverse reactions. Genotyping was conducted by quantitative PCR using TaqMan probes. Renal adverse reactions were graded according to Common Terminology Criteria for Adverse Events v4.0. Multivariate Logistic Regression analyses were performed with SPSS v.27 and a P value less than 0.05 was considered statistically significant. This study was approved by the Research Ethics Committee (number 69402017.1.0000.5404).

Results: Ninety-five patients were enrolled in this study, with a mean age of 58.00 ± 7.71 years; most patients were male (90.5%). A low creatinine clearance was observed after the first cycle of cisplatin, affecting 40.0% of patients in grades ≥ 2 (4.44% with grades 3 and 4), accompanied by ionic imbalances, even after prophylactic intravenous hydration. Associations were observed between the SNPs of the *ABCB1* (rs2032582 C>A) and *ABCC2* (rs3740066) genes with cisplatin-mediated renal adverse reactions. *ABCB1* rs2032582 C>A wild type allele was significantly associated with hyponatremia in grades > 1 (P = 0.045, OR = 3.398). *ABCC2* rs3740066 wild type allele was significantly associated with increase in serum creatinine in grades > 1 (P = 0.010, OR = 31.18). The other SNPs were not associated with renal adverse drug events.

Conclusion: *ABCB1* rs2032582 C>A and *ABCC2* rs3740066 might be potential clinical markers for predicting cisplatin-induced renal adverse reactions.

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P099

COVID-19 Vaccine Safety Surveillance and Causality Assessment of Adverse Events Following Immunisation: Lessons from South Africa

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Introduction: The South African Health Products Regulatory Authority (SAHPRA) utilises various AEFI reporting tools to monitor vaccine safety in the country. In 2020, SAHPRA in collaboration with the National Department of Health's (NDoH) Expanded Programme on Immunisation (EPI), joined the African Union Smart Safety Surveillance programme, as one of four pilot countries, to introduce an electronic adverse event following immunisation (AEFI) reporting system (Med Safety App) for healthcare professionals and consumers [1]. On 17/05/2021, the NDoH introduced its national COVID-19 vaccination programme. SAHPRA launched a microsite during 2021, to provide feedback to the public on AEFI with the COVID-19 vaccines.

Objective: To provide an overview of COVID-19 vaccine safety surveillance and describe causality assessment outcomes for serious AEFI reported during the first year of COVID-19 vaccine administration.

Methods: All severe and/or serious AEFI are investigated by provincial EPI surveillance teams, followed by causality assessment conducted by the National Immunisation Safety Expert Committee (NISEC), using the World Health Organization (WHO) methodology [2]. Causality assessment outcomes are classified based on the final diagnoses determined during the assessment by NISEC according to WHO categories, seriousness, Medical Dictionary for Regulatory Activities (MedDRA) system organ class and patient demographics. Data were collected retrospectively from the SAHPRA COVID-19 AEFI microsite and the EPI national AEFI database.

Results: By 01/04/2022, 33,063,221 COVID-19 vaccine doses had been administered, with 5 815 spontaneous AEFI reports (0.0173%) submitted. Of these, 2,571 (0.008%) were reported as serious. Spontaneous reporting of AEFI increased significantly compared to pre-COVID-19 vaccine introduction. The most frequently reported AEFIs were side effects already listed in the product information. No safety concerns were raised based on causality assessment outcomes for 273 serious cases analysed by 01/04/2022. Over two thirds of these cases were classified as coincidental (70.7%) as cardiac,

respiratory- or vascular disorders (MedDRA system organ class), with 12.1% classified as vaccine product related (see table below).

WHO Causality Assessment Category	COVID-19 vaccine (17 May 2021 to 1 April 2022)		
	Comirnaty® (Pfizer)	COVID-19 Vaccine Janssen® (J&J)	Total
No of AEFI reported/ No doses administered (%)	4,385/ 25,557,272 (0.0172%)	1,274/ 7,505,949 (0.0170%)	5,815/ 33,063,221 (0.0173%)
A1. Vaccine product-related	26 (11.0%)	7 (19.4%)	33 (12.1%)
A4. Immunisation anxiety-related	6 (2.5%)	2 (5.6%)	8 (2.9%)
B1. Temporal; insufficient evidence	9 (3.8%)	2 (5.6%)	11 (4.0%)
B2. Conflicting trends with causal association	2 (0.8%)	0	2 (0.7%)
C1. Coincidental; underlying/emerging	168 (70.9%)	25 (69.4%)	193 (70.7%)
UC. Unclassifiable; inadequate information	26 (11.0%)	0	26 (9.5%)
Total	237	36	273

The presentation will include all causality assessments conducted up to 31/08/2022, and more detailed information about causality assessed cases will be available in the public domain at the time of the conference and will be included in the presentation.

Conclusion: Vaccine safety surveillance and monitoring trends of reported AEFI are vital measures to ensure that the benefits of immunisation are maintained in the interest of public health and efficient vaccination programmes. Transparent communication with the public is important to maintain public confidence in vaccines and prevent all AEFI being misinterpreted as caused by the vaccine.

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P100

mRNA COVID-19 Vaccines Induced-Sudden Sensorineural Hearing Loss (SSNHL): Descriptive Analysis of French Pharmacovigilance Database (FPDB)

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Introduction: Several case reports and pharmacoepidemiological studies suggested a potential association between the mRNA COVID-19 vaccine, tozinameran (Comirnaty) and elasomeran (Spikevax) and SSNHL. However, data remain controversial because of scarcity of this adverse effect (1,2).

Objective: To assess a descriptive analysis of all spontaneous reporting of mRNA COVID-19 vaccines induced-Sudden Sensorineural Hearing Loss (SSNHL) to the French Pharmacovigilance system and to estimate the incidence of SSNHL reported cases.

Methods: All cases of mRNA COVID-19 vaccines induced-SSNHL recorded in the FPDB from the beginning of the campaign of COVID-19 vaccination in France until 2 February 2022 were included. Following data were collected: demographic data (age, gender), risk factors, history of immunologic disease, other factors leading to

SSNHL (trauma, infections,...), the range and the month of vaccination, the delay of onset of SSNHL, associated symptoms (dizziness and tinnitus), the degree of hearing loss and the outcome. Audiogram and/or medical reports were requested in order to guarantee a better informativeness of data. All cases were reviewed by a staff including two pharmacologists and two otorhinolaryngologists. All cases with a delay onset >30 days were excluded. Cases were split in “well completed” and (non completed) based on the availability of audiogram and medical reports.

Results: A total of 250 cases were recorded during this period for the 2 vaccines (60 Spikevax/190) (23 cases excluded because of other reasons or missed data). 226 cases were analyzed and will be described according to over mentioned criteria, corresponding to 151 cases classed as “well completed” (31 Spikevax/120 Comirnaty). The estimated incidence of SSNHL was estimated as 0.18/100000 for serious cases for Comirnaty and 0.27/100000 for both serious and non serious cases for Spikevax. For Spikevax, the median age was 50 years with a sex ratio of 0.9, the half of cases occurred after D1, 5 cases of positive rechallenge and hearing loss was associated with tinnitus in 50% and dizziness in 21.6%. For Comirnaty, the median age was 56 years with a sex ratio of 0.8, 76% of cases occurred after D1, 1 case of positive rechallenge, associated with tinnitus in 84% and dizziness in 39% of cases.

Conclusion: In our knowledge, it is the first study analysing all cases of mRNA vaccines-induced SSNHL supporting by audiogram analysis. This adverse effect remains rare but should be considered in patients with audio-vestibular risk factors. Other studies would be necessary in order to understand the mechanism which remains unclear.

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P102

Upgrade of Croatian ADR e-Reporting System for COVID-19 Prospective Cohort Event Monitoring (ACCESS Project)

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Introduction: Building on the lessons learnt from 2009 H1N1 pandemic, in order to prepare EU network for monitoring of COVID-19 vaccines, ACCESS project (vACcine Covid-19 monitoring readiness, VAC4eu.org) was funded in May 2020 by the European Medicines Agency (EMA). It was designed to ensure infrastructure for effective monitoring of COVID-19 vaccines. The Croatian Agency for Medicinal Products and Medical Devices (HALMED) saw this as an opportunity to upgrade existing ADR e-reporting system (OPeN) and set up post-marketing active surveillance of adverse drug reactions (ADRs).

Objective: To upgrade existing OPeN system to prospectively collect data about Adverse Events Following Immunisation (AEFIs) against COVID-19 in near real-time.

Methods: For the purpose of data collection defined by the ACCESS protocol, OPeN system has been upgraded to incorporate an informed consent, survey tool, survey data report, direct reporting of AEFI reports, when applicable, and their transmission to EudraVigilance. To participate in the study an user account needs to be created and consent given. Study participants access the system via the appropriate link. The system is protected by a firewall and Secure Sockets Layer (SSL) protocol. Data protection has been established for both internal and external users.

Results: The first phase of the OPeN upgrade started in November 2020 and finished in February 2021. The inclusion of participants in the Croatian study began on 12 February 2021. In the first phase, only healthcare professionals could participate, but the variation in protocol allowed that from April 2021 all vaccinated people could be included. With second phase of upgrade, we were able to include additional questions on relevant medical history, pregnancy, 3rd and booster vaccine dose. 374 vaccinees were recruited in the period from start until the end of April 2022. Almost all vaccinees were adults. Majority were female (77%), and average age was 38 years-old (SD 10, CI $\pm$ 1). Total of 303 AEFI reports were collected, of which 97% were non-serious.

Conclusion: The OPeN system has shown a wide upgradeability and HALMED was able to establish a system of post-marketing active surveillance in very short time frame as addition to our routine pharmacovigilance activities. However, throughout this process we have identified several issues: time consuming multi-step registration process, not enough user friendly interface and insufficient promotion of the OPeN system. Nevertheless, since this was the first time HALMED performed prospective safety monitoring by using a web-based tool we find results encouraging for future activities.

References/Further Sources of Information

Not applicable.

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Psoriasis Induced by COVID 19 Vaccine

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Introduction: Psoriasis is a chronic, immunologically mediated, inflammatory skin condition. It is characterized by well-defined, erythematous, indurated scaly plaques, with predilection of extensor surfaces, the scalp and the nails. It may be caused by drug, infection, stress, physical trauma, and vaccination. COVID 19 vaccines have recently been linked to worsening of pre-existing psoriasis.

Objective: We report an exceptional case of new onset of psoriasis following COVID-19 vaccine.

Methods: This case was reported in February 2022 to The National Centre of Pharmacovigilance and evaluated according to the updated French method of causality assessment.

Results: A 58-year-old female patient with a past medical history of hypothyroidism treated by sodiclevothyroxin received on 07 August 2021 her first dose of VAXZEVERIA COVID-19 vaccine. On 17 August 2021, she presented to the emergency department because of an erythematous and febrile eruption on her limbs. Dermatological

examination, revealed, erythematous skin with yellow crusts on the limbs and desquamation over the upper and lower limbs. No mucosal membrane or palmo-plantar involvement was noted. The bacterial skin swab was negative. Histological findings confirmed the Psoriasis. Based on the history and clinical findings, she was diagnosed with psoriasis onset with the vaccine. The patient was started on betametasone an calcipotriol resulting in a significant resolution of the skin eruption one month later.

Conclusion: In this case, the responsibility of the COVID-19 vaccine in inducing Psoriasis was evaluated as I4 (C2S2) according to the updated French method of imputation in front of: a suggestive delay (10 days after starting the treatment), mainly the favorable outcome after the vaccination and the finding of skin biopsy. The responsibility of sodic levothyroxin was non retained because of the favorable outcome despite his pursuit. Psoriasis associated with COVID-19 vaccine is a rare condition.

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Incidence of ischaemic Stroke Following Comirnaty™

Administration: Comparison of Data from ASST GOM Niguarda and FAERS

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Introduction: Although the mechanism of neurological complications after COVID-19 vaccination has not been precisely explained, it could be attributed to the inflammatory state triggered by COVID-19 vaccine as in the course of COVID-19 viral infection. This condition induces disseminated intravascular coagulation (DIC) in combination with vascular endothelial dysfunction, leading to stroke of the large vessels. This hypothesis may be the main cause of DIC, especially in mRNA-based vaccines, whose mechanism involves delivery of the mRNA code of the spike protein to human cells. Cellular synthesis of the spike protein stimulates the immune system to recognize and store it for future attack. Based on this hypothesis, the inflammatory state triggered by the vaccine can be considered the main pathway for neurological complications of COVID-19 vaccine.

Objective: The aim of this work is to analyse the incidence of ischaemic stroke risk following administration of the Comirnaty™ vaccine in ASST GOM Niguarda, an Italian hospital based in Milan, and to compare it with data from FAERS database.

Methods: The Reporting Odds Ratio (ROR) was calculated in order to evaluate a possible correlation between the risk of ischaemic stroke and Comirnaty™ vaccine administration in the period of January–December 2021. For this purpose, we consulted FAERS public domain database that allows you to search information relating to adverse events reported to the FDA.

Results: From reports of adverse events of Comirnaty™ vaccinated patients at ASST GOM Niguarda hospital, it was observed that after administration of this vaccine there is a correlation with the risk of developing ischaemic stroke mainly in over 65 years old patients (OR = 1.26; 95% CI 0.17–9.13; z = 0.230; p value = 0.8182) when comparing the data with other vaccines. These data match the data

obtained from FAERS (OR: 1.29; 95% CI 0.85–1.96; $z = 1.205$; p value = 0.228), confirming the data collected in ASST GOM Niguarda.

Conclusion: The data extrapolated from this analysis conducted at ASST GOM Niguarda mirror those obtained from the FAERS database with a comparable significance index (p value).

In conclusion, the possible correlation between ComirnatyTM vaccine administration and the development of ischaemic stroke as an adverse event was confirmed.

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COVID Vaccines AEFI Monitoring in Tunisia: March 2021 to May 2022

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Introduction: As part of vaccines surveillance, a reinforced surveillance strategy for Covid-19 vaccines adverse events following immunization (AEFI) was set up in Tunisia. This strategy was conducted since the Covid-19 vaccination campaign has been started in March 2021. The safety profile of available vaccines was monitored in real time to ensure security of the population and to be able to anticipate coincidental events that might be attributed to the vaccine.

Objective: to analyze the reported AEFI associated with different types of COVID-19 vaccines.

Methods: A descriptive study on AEFI from Covid-19 vaccines collected at the National Chalbi Belkahia Center for Pharmacovigilance (CNPV) from March 13th 2021 to May 22, 2022. During this period, vaccines used were Pfizer BioNTech[®], Vaxzevria[®], Spikevax[®], Janssen[®], Sputnik V[®], Coronavac[®], and Sinopharm[®].

Results: We collected 3116 AEFI on 13 173 137 COVID-19 vaccines administered doses (0.02%).

The mean age was 48.8 years [13–98]. The sex ratio M/F was 0.59. The vaccines mainly used were the Pfizer BioNTech[®] vaccine in 51.6%, Vaxzevria[®] in 16.1%, Spikevax[®] in 10.9% and Janssen[®] in 7.6% of cases.

AEFI SOC were general manifestations and injection site reactions (44%), nervous system disorders (27.4%), musculoskeletal and connective tissue disorders (16.4%), Skin and subcutaneous tissue disorders (16.2%), gastrointestinal disorders (12.1%), respiratory, thoracic and mediastinal disorders (6.7%), immune system disorders (5.9%), vascular disorders (5.8%), infections and infestations (5.7%), Injury, poisoning and procedural complications (5.5%), Ear and labyrinth disorders (4.9%), cardiac disorders (4.6%), and others (9.2%).

The most reported MedDRA terms were fever (20.2%), asthenia (16.9%), headache (13.8%), injection site pain (9.4%), and muscle pain (8.9%).

Serious AEFI were noted in 7% of AEFI. SOC were Nervous system disorders (38.7%), Cardiac disorders (17.5%), General disorders and administration site conditions (15.2%), vascular disorders (12.9%), Infections and infestations (12.4%), Respiratory, thoracic and mediastinal disorders (7.8%), Skin and subcutaneous tissue disorders (6.5%), and others (21.2%).

The most used vaccines in serious AEFI Pfizer BioNTech[®] in 47%, Vaxzevria[®] in 21.2% and Coronavac[®] in 11.1%.

Conclusion: This study confirms clinical trials data in which the most frequent AEFIs were general and injection site disorders. Serious adverse event were rare. These results show that the benefit of vaccination outweighs the risk and encourage vaccination

References/Further Sources of Information

Not applicable.

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Maternal, Fetal, and Neonatal Outcomes among Pregnant Women Receiving COVID-19 Vaccination: the Preg-Co-Vax Study

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Introduction: Although the International and National Regulatory Authorities encourage COVID-19 vaccination in pregnant women [1–2], the scientific evidence supporting maternal exposure to COVID-19 vaccines during pregnancy is still limited and further studies are needed to monitor their safety profile in order to evaluate the potential consequences in both mother and child.

Objective: We aimed to investigate Adverse Events Following Immunization (AEFI) with COVID-19 vaccines that occurred after maternal exposure during pregnancy.

Methods: We retrieved Individual Case Safety Reports (ICSRs) following maternal exposure to COVID-19 vaccines during pregnancy from the EudraVigilance database of the European Medicines Agency during the year 2021. We investigated outcomes related to the mother and child age groups (defined as fetus, infant, and neonate). The Reporting Odds Ratio (ROR) was computed to compare the reporting probability of spontaneous abortion between each COVID-19 vaccine and all other COVID-19 vaccines.

Results: During the study period (1 January 2021–31 December 2021), among 1,315,315 ICSRs related to COVID-19 vaccines, we retrieved 3,252 (0.25%) reports of AEFI that occurred after maternal exposure during pregnancy. More than half (58.24%) of ICSRs were submitted by non-healthcare professionals. The majority (87.82%) of ICSRs concerned serious AEFI. More cases of AEFI occurred in pregnant women ($n = 2,764$; 85.0%) than in child age groups ($n = 258$; 7.9%). Moreover, 55.16% ICSRs related to pregnant women exposed to COVID-19 vaccines involved non pregnancy-specific adverse events, mostly headache, pyrexia, fatigue, myalgia, and pain in extremities. The 17.92% were pregnancy-, neonatal-, or

fetal-specific adverse events. Moderna and Oxford-AstraZeneca vaccines had a higher reporting probability of spontaneous abortion (ROR 1.2, 95% CI 1.05–1.38, $P = 0.009$; and ROR 1.26, 95% CI 1.08–1.47, respectively), while a lower reporting probability was found for Pfizer-BioNTech vaccine compared with all other Covid-19 vaccines (ROR 0.73, 95% CI 0.64–0.84). We also observed that 5.8% ($n = 188$) of cases reported a fatal outcome, 17 of them were clearly associated with the mother, while 171 with the child.

Conclusion: We did not observe any strong insight into any unknown adverse events associated with COVID-19 vaccination. However, we analyzed data related to only one year of the vaccination program. Therefore, our experience also highlights the need for continuing to monitor the safety profile of COVID-19 vaccines and to identify long-term adverse events following immunization. In conclusion, in the European context, the analysis of real-world evidence suggests that the benefits of COVID-19 vaccines during pregnancy outweigh the possible risks for pregnant women and children.

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COVID-19 Vaccines and Reproductive Disorders: An Analysis of the European Database EudraVigilance

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Introduction: Rare or serious Adverse Events (AEs) in the reproductive sphere have been reported following the administration of the COVID-19 vaccine, especially mRNA vaccines. Although several fertility Societies have announced that COVID-19 mRNA vaccines are unlikely to affect fertility, pregnancy, or breastfeeding, there is no denying that the current evidence is very limited [1].

Objective: Aim of this study was a post-marketing assessment of the safety profile of COVID-19 vaccines, through the analysis of the Individual Case Safety Reports (ICSRs) collected in EudraVigilance in 2021 year, by focusing on reproductive disorders.

Methods: We analyzed all ICSRs that contained at least one COVID-19 vaccine as suspected and at least one AE belonging to the Standardized MedDRA Query (SMQ) level 1 “Fertility disorders” or “Pregnancy and neonatal conditions”. We performed a descriptive analysis and all AEs have been coded as Preferred Term (PT) according to MedDRA. Finally, we used the Reporting Odds Ratio (ROR) with a 95% of Confidence Interval (95% CI) to investigate disproportional reporting of AEs belonging to the SMQs of interest among the vaccines included in the analysis.

Results: During the study period, 27,089 ICSR were collected and the total number of AEs was found to be 31,337; of these, 62.8% were referred to Comirnaty[®], 20.8% to Spikevax[®], 12.7% to Vaxzevria[®],

and 3.7% to Janssen[®]. For each of the four COVID-19 vaccines, 96.4% were related to female patients, aged between 18–64 years (88.1%), 71.5% were not serious, 46.0% were not resolved yet and 82.3% were reported by non-healthcare professionals. Regardless of the type of vaccine, the most reported PTs were amenorrhea, irregular menstruation, and delayed menstruation. The ROR showed that the probability to report an AE belonging to the SMQ “Fertility disorders” is greater for Comirnaty[®] (ROR: 4.20, 95% CI 4.08–4.32) while no statistically significant difference was observed to the SMQ “Pregnancy and neonatal conditions”.

Conclusion: In this study, no potential signs of reproductive system safety were found regarding fertility, pregnancy or breastfeeding. Most of the reported events were related to changes in the menstrual cycle, although these disorders are temporary and normally common in the female population. At the time, the EMA’s PRAC concluded that the evidence did not support a causal link between these vaccines and menstrual disorders, however, it decided to further studies collecting data from real life contexts are strongly needed to assess their safety profile in relation to reproductive function.

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Pharmacovigilance Regulatory Actions by National Pharmacovigilance Centres in Fourteen Middle Eastern Countries Following COVID-19 Pandemic

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Introduction: Pharmacovigilance (PV) activities were affected by COVID-19. Therefore, several health authorities around the world have issued guidelines and practices to ensure that PV activities are maintained and continued during the pandemic [1].

Objective: This study aimed to assess the impact of COVID-19 on the preparedness and performance of national PV systems in 14 Arab Countries in the Middle East.

Methods: This was a cross-sectional study that was conducted between July and October 2020. National PV centres in 18 in the Middle East were invited to participate in this study. Descriptive analysis was used to summarize and present the results of this study.

Results: Responses were obtained from 14 (77.8%) countries. Adverse events reporting was the main PV activity that was covered by PV guidelines and practices. National guidelines and practices covered other PV activities in 8 (57.14%) of the participating countries. Performance and practices of national PV centres vary considerably among participating countries during the pandemic.

Conclusion: The findings highlight the differences in preparedness and performance of different national PV centres in participating

Middle Eastern countries. Improving digital infrastructure among participating countries could serve as a useful tool to minimize the impact of the pandemic on PV activities.

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P109

The Impact of SARS-CoV-2 on Mental Health. Focus on depression, Antidepressants Consumption and ADRs Signal Detection

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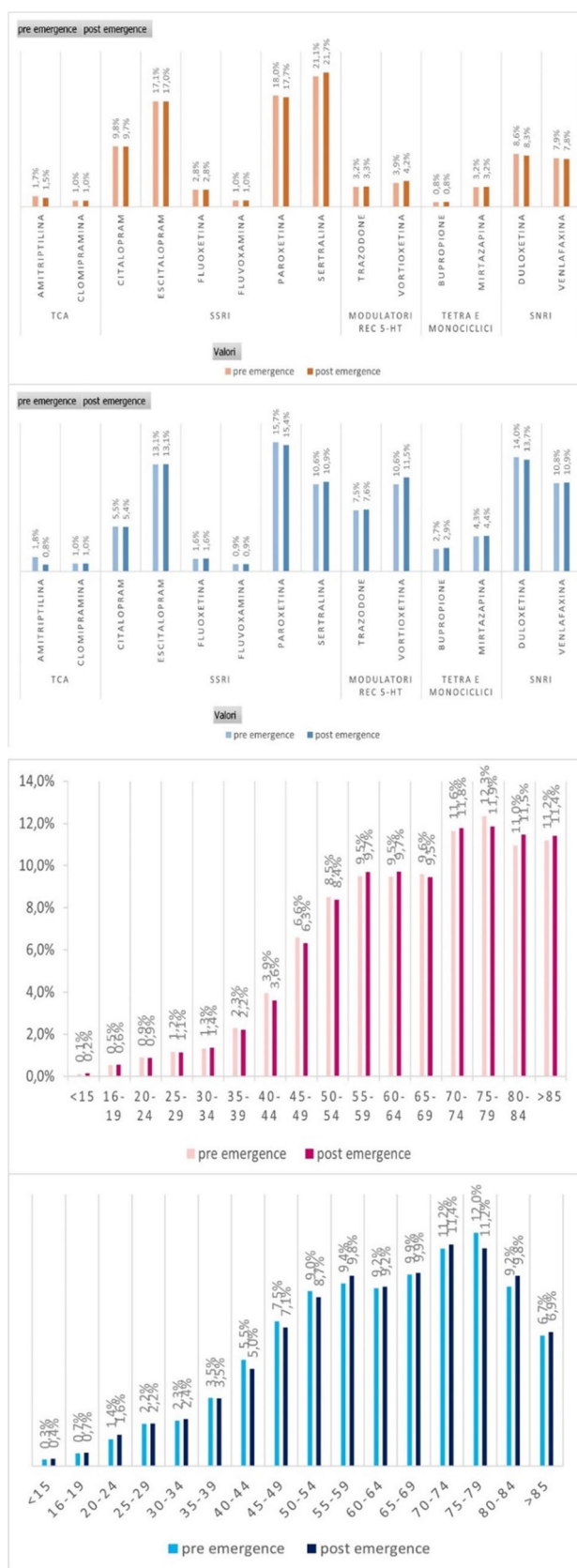
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Introduction: The SARS-CoV-2 public health emergency is leading to challenges for healthcare professionals, students, patients with COVID-19 and vulnerable persons, blocking the economic development and mental wellbeing. The pandemic containment measures and the fear of infection have caused psychological distress and inflamed underlying diseases

Objective: To analyse the impact of the SARS-CoV-2 on the Mental Health in Friuli-Venezia Giulia Region, Italy, focusing on depression disorder and Antidepressants consumption. Furthermore, to assess the state of adverse event reports, from spontaneous signalling method, in patients taking Antidepressants

Methods: For consumption data extraction I utilized the Regional Social and Health Information System. About reports of ADRs based on the National Pharmacovigilance Network I used the VigiSegn app. I accessed on INTERCheck System to balancing the risks and benefits of therapies. I compared two periods from 11.03.2019 to 10.03.2020 and from 11.03.2020 to 11.03.2021 separated by 11 March 2020, when the Director General of the WHO described the situation as a pandemic [1]. Antidepressants were classified using the ATC code system. Anonymous drug utilization was expressed in DDDs

Results: Since 11 March 2020 I observed a marginal increase in consumption of sertraline, trazodone and vortioxetine. Regarding pharmaceutical spending there has been an increase of sertraline, trazodone, vortioxetine, bupropion, mirtazapine and venlafaxine. In the feminine gender, I observed an increase in AD consumption in the age ranges < 15 yrs, 16–19, 30–34, 55–59, 60–64, 70–74, 80–84, over 85; in the male gender in the ranges < 15 yrs, 20–24, 30–34, 55–59, 70–74, 80–84, over 85 (Picture 1). Concerning ADRs I analysed one tab about AD out of a total of 2146 medicines and vaccines reports in which the “hyponatremia” is reported on the warning label and caused by significant drug interactions



Conclusion: Although the SARS-CoV-2 public health emergency is a rapidly evolving situation, the knowledge about the impact on the Mental Health is still limited. It is likely that the psychosocial demand will increase in the coming months. In the regional context, the thesis has highlighted a very slight rise in AD consumptions and a significant decrease of spontaneous signalling method compared to the previous year. These scenarios also depend on the new balance of health services and the lack of access to care (10% of citizens has given up on care) [13, 14]. The healthcare systems will have to face important challenges and the success of the creation of high-quality healthcare reality will depend on the alliance between healthcare specialists

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Ivermectin-Induced Liver Injury when Used as Self-Medication in SARS-CoV-2 Infection

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Introduction: In the context of the global health emergency due to SARS-CoV-2 pandemic, ivermectin has been repurposed in some Latin American countries to treat COVID-19; in these countries its use as self-medication has been frequent (1). Ivermectin-induced liver injury, though extremely rare(2,3), had been previously described even before the COVID-19 pandemic

Objective: To characterize clinical features of liver injury associated with ivermectin when used as self-medication for treating COVID-19.

Methods: Clinical records of those patients diagnosed with severe COVID-19 at the Emergency Room in Rebagliati Hospital in Lima, Peru, during March 2021, were carefully revised. To establish diagnosis of drug-induced liver injury (DILI) and causality assessment, the criteria of DILI-Expert Working Group and the Council for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM), respectively, were used

Results: Out of 327 patients identified, 38 took ivermectin as self-medication (11%); of those 38, five were diagnosed with liver injury presumably related to that medication (13.2%). The mean age of those patients who developed the condition was 49.3 (12.3) [men, 4; woman, 1]. The mean (standard deviation) of Tomographic Severity Score (TSS), C-reactive protein, ferritin levels, Lymphocyte count and D-dimer were 52.2% (22.6), 13.8 (12.2) mg/dl, 1325.375 (239.7072) ng/ml, 2.0 (2.0) K/μl and 0.9 (0.7) μg/ml. The patients had no identified risk factors, but two; one patient had type I diabetes mellitus, and other, obesity. Mean daily ivermectin dose, duration, and total ivermectin dose were 32.9 (21.8) mg/day, 2.6 (0.6) days, and 89.6 (71.4) mg, respectively. As an average, liver injury occurred 11 (3.8) days after the start of treatment, none developed jaundice. Mean levels of alanine aminotransferase, alkaline phosphatase, gamma-

glutamyltransferase were increased 8 (4.4), 1.66 (0.9), 10.9 (5.0) times above the upper limit of normal. Two patients presented a hepatocellular pattern, 2 mixed and 1 cholestatic. All cases were mild and recovered. As for causality assessment, 4 cases were considered as “possible”, and one, as “highly probable”.

Conclusion: Given its widespread use in some countries, ivermectin-induced liver injury requires further pharmacovigilance studies when used for treating COVID-19.

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COVID-19 Vaccine Pharmacovigilance Spontaneous Reporting in a Pandemic—Notes from a Small Country

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Introduction: Medsafe, the New Zealand Pharmacovigilance Centre (NZPhVC) and the Covid Vaccine Immunisation Programme (CVIP) created a vaccine pharmacovigilance strategy. We report pros and cons of the strategy.

Objective: We aimed to use existing systems and expertise but leverage new technologies to manage an expected increase in reporting to support signal detection activities and requests for data. [1]

Methods: A new reporting form was included in the new Covid Immunisation Register (CIR) so events occurring at the vaccination centre could then be easily reported into a database.

A new on-line COVID-19 vaccine reporting form was constructed which populated the database. This form incorporated a list of common vaccine side effects and AESIs that could be selected by the reporter [2].

A new COVID-19 vaccine database for storing reports was built in the same electronic environment as the CIR. This facilitated data linkage, report triaging, dedicated access and analysis. Importantly this database was accessible remotely through secure VPN.

Qlik Sense data visualisation and analytics were used to report on data incorporating daily data transfers to allow tracking of reporting and daily updates to support policy and communications.

Results: From start to 29 April 2022, 62,427 cases of adverse events were received in New Zealand, more than 12 times the normally expected number. The average reporting rate was 5.7 reports per 1000 vaccinations.

The CIR reporting option was used over 15,000 times and the online form was used more than 28,000 times by consumers.

The CIR linkage to the AEFI database allowed duplicate and fake reports to be quickly detected and ensured vaccine administration data was high quality. Rapid processing of the massive increase in reports was possible, but there were issues due to limitations of the database and the volume of reports received.

Event tick boxes in the reporting form had advantages for reporters but impacted the granularity of the data. The AESI event tick boxes were undesirable. These were often selected by vaccinees based on self diagnosis, in error and not supplemented by supporting evidence. This resulted in an increase in work to follow up these reports.

The Qlik app facilitated rapidly identifying trends in the data and AEFI report updates.

Conclusion: The system enabled close to real time data for signal analysis, public reassurance and communication. Data-linkage supported accurate determination of data.

However, an increase in staff was still required and it was impossible to review all reported cases for accuracy or need for further information.

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Factors Influencing Patient Reporting of Adverse Reactions to Covid-19 Vaccines

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Introduction: The Covid-19 pandemic and the resultant vaccination programme has seen greatly increased discussion of adverse drug reactions (ADR) and how to report them, and non-healthcare professions have submitted many more ADR reports. Various barriers have been proposed to influence the reporting by patients [1, 2] and patients' motives to report have also been discussed [3]. We investigated differences in COVID-19 vaccine ADR reporting rates within this region to identify factors that may influence the number of reports received from patients.

Objective: To identify factors which may influence the number of reports received from patients

Methods: The West Midlands Centre for ADRs receives data from Yellow Card reports that are generated in the Midlands NHS region (population 6.6 million) in the UK. We compared the rates of ADR reporting by patients with COVID-19 vaccination rates and indices of deprivation [4] in the 12 clinical commissioning groups (CCGs)—areas with populations ranging from 0.13 to 1.38 million. We ranked CCGs by number of patient reports to COVID-19 vaccines and

compared these with the rankings of the number of vaccines received and each of the domains of deprivation using Spearman's rank correlation.

Results: In the period 9/12/20 to 31/12/21 there were 30,874 patient reports from the region (83% of all COVID-19 vaccine reports). Reporting rates per CCG ranged from 167 to 307 (mean 240) per 100,000 vaccinations administered, with a mean of 2.00 (range 1.69 to 2.14) vaccines per person—the UK at this stage was part way through the booster campaign with only adults routinely vaccinated. Table 1 shows the correlation between ADR reporting and the listed factors

	p	p
Rank vaccines per person (where 1 is lowest)	0.916	0.00003
Index of Multiple Deprivation (IMD) Rank (where 1 is most deprived)	-0.727	0.007
Income Rank (where 1 is most deprived)	-0.721	0.008
Employment Rank (where 1 is most deprived)	-0.699	0.011
Education, Skills and Training Rank (where 1 is most deprived)	-0.762	0.004
Health Deprivation and Disability Rank (where 1 is most deprived)	-0.804	0.002
Crime Rank (where 1 is most deprived)	-0.637	0.026
Barriers to Housing and Services Rank (where 1 is most deprived)	0.112	0.729
Living Environment Rank (where 1 is most deprived)	-0.65	0.022

Table 1. Univariate correlation between Rate of ADR reporting and other factors. Spearman's ρ and unadjusted p value are shown.

Conclusion: ADR reporting rates had, perhaps unsurprisingly, a strong correlation with high vaccination rates. However, higher deprivation, lower education levels, and more unemployment were all negatively correlated with patient ADR reporting to COVID-19 vaccinations, echoing similar findings in professionals ADR reports from deprived areas. [5] The experiences of adverse effects that patients from lower socio-economic groups have are likely to have been less well recorded than those of more wealthy and educated groups. This may have implications for the design and availability of ADR reporting forms and for the assessment of ADRs more generally.

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Digital Media and Pharmacovigilance: The SIMeF Pharmacovigilance Working Group Perspective

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Introduction: Digital media are integrated in our daily routine, play a critical role in the dissemination of health information and disease prevention guidelines and are becoming more impacting in pharmaceutical companies activities, with an increasing trend after the pandemic period. They pose pharmacovigilance challenges for application of PV rules. A structured approach is needed for pharmacovigilance departments in the new digital scenario.

Objective: The SIMEF pharmacovigilance working group worked on digital topic since two years, addressing it in a structured way: from a specific survey (1), to proposals for addressing the needs underlined, to seminars and events for capability building and discussions among experts. SIMEF group also worked on a proposal guideline for supporting PV departments (6), suggesting a framework for managing sponsored digital activities with potential collection of adverse events, to provide useful operative suggestions on PV requirements management.

Methods: A research on the regulation in force and the current status of digital media was conducted, with a focus on pharmacovigilance, privacy and quality aspects. The guideline was written considering the expertise of the authors in the management of pharmacovigilance activities. Seminars were done to favour discussions among experts.

Results: All healthcare sectors are impacted by digital media: scientific societies, academic institutions, patients' associations, hospitals and healthcare institutions are increasing their online presence ^{2,3}. Social media are used by patients to compare health data, collect treatment information and discuss with physicians, with an increasing active role. Digital media should be considered as a potential source of AEs by pharmaceutical companies, when managing sponsored activities. PV aspects of digital activities are currently described, although not in details, in different regulations by EMA, FDA and MHRA.

Management digital projects by pharmaceutical companies is complex and require a structured multifunctional process, to guarantee a holistic approach to regulatory and legal requirements. Many aspects should be considered for compliance and efficiency. SIMEF work pose considerations on the importance of crossfunctional work, early pharmacovigilance advice, tracking system, execution of risk-based assessment, escalation to quality, SOPs presence, personnel trainings (including vendors) and a Quality System covering PV. New skills and capability will be crucial for PV departments in future.

Conclusion: Digital media are powerful instrument to increase patients and physicians involvement and to support disease knowledge. The rising amount of safety data generated through digital opens a challenge for pharmaceutical companies. This work is a starting point to trigger broader discussions around PV quality system for digital activities.

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Previous Use of Proton Pump Inhibitors (PPI) in Hospitalized Patients and COVID-19 Mortality in Peru

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Introduction: One of the known adverse reactions among long-term proton pump inhibitor (PPI) users, especially the elderly, is that it increases the risk of community-acquired pneumonia [1]. The probable mechanism is that the increase in gastric pH produces a decrease in elimination or an increase in colonization of bacteria; PPIs promote the proliferation of bacteria in the mouth and oropharynx and would increase in this manner the risk of pneumonia [2]. In COVID-19, lungs are particularly at risk. Currently, there is a great interest in establishing the relationship between the severity and mortality of SARS-CoV-2 infection in patients using PPIs [3].

Objective: To explore the relationship between the previous use of PPIs and mortality due to COVID-19

Methods: A retrospective observational study was carried out in a tertiary care hospital in Lima, Peru. Patients hospitalized in March 2021 for severe SARS-CoV-2 infection, confirmed by molecular tests (reverse transcription polymerase chain reaction), were included. Severe COVID-19 disease was defined as peripheral oxygen

saturation on admission less than 93% (without supplemental oxygen) or pulmonary involvement greater than 30% (on the total severity score or TSS) in the lung tomography

Results: A total of 327 patients entered the study (mean age, 61.36 $\pm$ 16.0 years; male, 59.95%). PPIs users and non-users were 10 (3.06%) and 317 (96.94%), respectively. The mean age, Charlson score and total severity score (TSS) between PPIs users and non-users were 68.8 $\pm$ 17.11 vs. 61.12 $\pm$ 15.93 ($p = 0.134$), 3.6 $\pm$ 2.32 vs. 2.25 $\pm$ 1.715 ($p = 0.019$) and 55 $\pm$ 25.28 vs. 48.44 $\pm$ 24.30 ($P = 0.399$), respectively. Mortality in those using and not using PPIs were 80.0% (8 out of 10) and 38.49% (122 out of 317), respectively (Crude odds ratio, 6.39; 95% confidence interval 1.34–30.61; $p = 0.008$). No significant difference was observed in the leukocyte count, mean lactate dehydrogenase concentration, Ferritin, D-dimer and fibrinogen and serum levels of C-Reactive Protein, in those users of PPIs compared to non-users.

Conclusion: Among hospitalized patients for severe SARS-CoV-2 infection, prior use of PPIs was associated with a higher mortality risk. This association does not necessarily imply causality. Further research would be required to clarify potential mechanisms.

Keywords: COVID-19, SARS-COV-2, proton pump inhibitor, mortality (Source: DeCS-BIREME).

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Utilization WHO Vaccine Hesitancy Tool to Assess the Refusal Rate of Routine Immunization Among Parents in Egypt

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Introduction: Vaccine hesitancy is defined as intentional delay or refusal to vaccinate children despite vaccine availability and it has been considered by the World Health Organization (WHO) as one of the ten major risks to public health globally. In fact, Egypt has achieved several successes in controlling vaccine preventable diseases, including strong national vaccination coverage of over 90%, through an increase of vaccine coverage and continuous surveillance leading to reduced illness, disability and death from diseases such as diphtheria, tetanus, whooping cough, measles and polio [1].

If we want to maintain this vaccine coverage ratio, we must verify whether parents agree to vaccinate their children because they are convinced of the efficacy and safety of vaccines, or because it is mandatory?

Objective: To determine the prevalence of hesitancy among Egyptian parents towards routine immunization for their children by using the WHO Strategic Advisory Group of Experts (SAGE) on Vaccine Hesitancy Survey Tool [2].

Methods: A cross-sectional study was conducted among 410 of parents between December 2021 and April 2022 in Cairo, Egypt. A WHO validated questionnaire was used consists of 13 questions designed to measure parents' hesitation towards vaccinations.

Results: Of 410 families screened, No parent had ever refused a vaccination, and only 4 parents (0.97%) had been reluctant or hesitated to get a vaccination for their children. Parents either with higher or moderate educational levels were strongly agree that childhood vaccination is important for child health ($p < 0.001$). No doubts or concerns related to vaccine safety have been reported and this has been mainly due to the presidential national immunization initiatives to increase Expanded Program on Immunization (EPI) coverage. Its worth to mention, Egypt announced that it was completely free of polio in 2006, and this was due to these presidential campaigns, which gave greater confidence in the safety and effectiveness of vaccines.

Conclusion: To maintain high levels of immunization, healthcare professionals should be kept on the same level of awareness with vaccine safety and vaccine risk communication to keep the trust of the population with the safety and effectiveness of vaccines. Because when high immunization rates are reached and sustained in the population they generate herd immunity to protect communities. In addition, the mass media played an active role as it has covered the results of these presidential campaigns, which has increased parents' confidence in these vaccinations. Finally, Egypt must continue with this successful approach of encouraging the vaccination.

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Active Monitoring of Adverse Events in a Closed Population: Contributions from Colombia to COVID-19 Vaccines Safety

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Introduction: Information on the effectiveness and safety of vaccines for COVID-19 is limited as clinical trials did not provide enough evidence about long-term effects and all possible adverse events [1]. Moreover, marketing authorization for these vaccines was conditioned on providing more information about adverse events and effects on populations not included in clinical trials, like pregnant and pediatric population [2,3].

Objective: To evaluate the clinical performance and Adverse Events Following Immunization (AEFIs) of the vaccines against COVID-19 in a closed cohort from a Colombian university.

Methods: This is an observational study of a prospective cohort, with members of the *Universidad Nacional de Colombia* (UNAL, by its Spanish acronym) followed from June 2021 to April 2022. Data was collected via a telephonic survey and additional clinical information was provided by the health institution Unisalud. Description of the AEFIs in the population and the characteristics of the people with adverse events was analyzed.

Results: A total of 3,764 persons were included, 35.73% reported AEFIs from which around 8.55% (115/1,345) experienced them 5 days after immunization. AEFIs tended to have low or medium intensity (70% on a 5 Likert scale, from very low to very high) and a duration between 1 and 3 days (65.1%). The vaccine with fewer AEFIs was Sinovac and was statistically different from Pfizer and AstraZeneca (using Tukey HSD and 95% confidence).

Conclusion: The percentage of AEFIs is consistent with findings in active monitoring programs. Risk factors coincide with other studies. This study demonstrates high rates of AEFIs in the population differing by brand. Serious events were rare. This study contributes to the knowledge of AEFIs for vaccines only used in middle and low-income countries. The active monitoring program of UNAL gives very relevant and reliable information. Models to study risk factors for AEFIs are needed and are currently in development by the authors.

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COVID-19 Pandemic: A Surge in Counterfeit Medicines

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Introduction: Falsified medical products may contain no active ingredient, the wrong active ingredient, or the wrong amount of the correct active ingredient [1]. The prevalence of falsified medicines spans from 1% in developed settings to 10% in the Global South [2]. Due to broken supply chains, strong demand for medicines and limited capacities of law enforcement, the COVID-19 pandemic created the optimal conditions for the falsified medicines' market to expand.

Objective: Aim of this abstract is to present evidence about the surge in counterfeit medicines amid the COVID-19 crisis.

Methods: This review examines the existing published scientific literature and peer-to-peer networks, grey literature as well as briefs and policy reports on counterfeit medicines amid COVID-19 pandemic.

Results: According to EOCED, People's Republic of China and India are the primary producers of counterfeit medicines, with the United Arab Emirates, Singapore and Hong Kong (China) serving as transit economies [3].

The review has identified three areas of impact for counterfeit medicines amid COVID-19. These are: (i) the increased demand for

COVID-19-related medicines, due to the medical supply restrictions related to the pandemic. These restrictions have been introduced by local authorities (e.g. supply restriction for Chloroquine and Azithromycin) or occurred because of air traffic reduction. Over 60 countries have implemented export restrictions and 25% of restricted products were medicines [4]; (ii) E-commerce as a relevant platform for substandard medicines. For instance, advertisements of illicit COVID-19-related medical products have been reported on social media platforms, such as Instagram. According to the industry, online distribution becomes predominant and about 50% of purchases of illicit medicines are done on-line [5]; (iii) weak regulatory frameworks, including insufficient technical capacity, constrained access and ineffective over-sight to address substandard and falsified medical products. WHO reports that 30 per cent of national regulatory authorities do not have full effective capacity to perform their functions [6].

Conclusion: COVID-19 pandemic has increased the vulnerability to counterfeit medicines, leading to serious damage to the health of individuals or failure to treat their medical needs adequately. The abstract identifies three relevant governance gaps (increased demand, E-commerce and weak regulatory frameworks) to be further addressed in dedicated fora.

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Pharmacovigilance in Healthcare Emergency: Lessons Learned from COVID-19: Uganda

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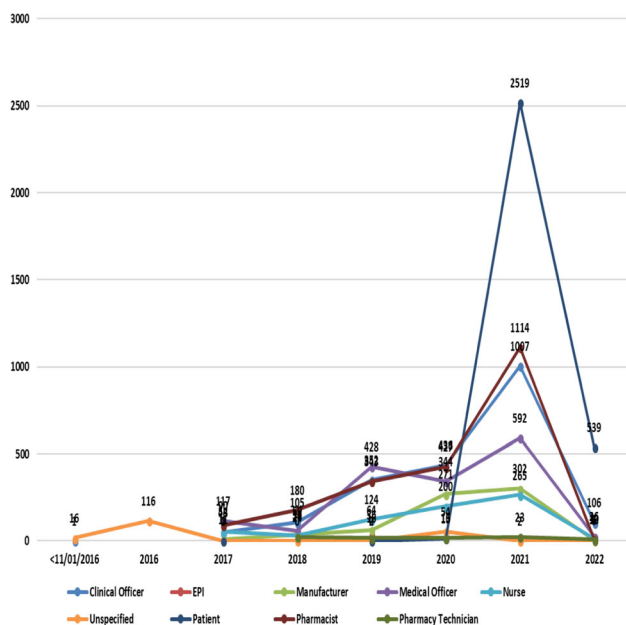
Introduction: Before the pandemic, reporting of Adverse Drug Reactions had been the preserve of health care professionals and they

were the main beneficiaries of sensitizations and trainings. However, with the outbreak of the Covid pandemic, it became necessary to expand pharmacovigilance to the lay person as they were likely to receive the vaccine in a non-hospital setting, making it difficult to monitor them.

Objective: To describe the actions taken to foster pharmacovigilance during the pandemic and the lessons learned.

Methods: Retrospective primary data analysis of reporter details in the individual case safety reports submitted to the National Pharmacovigilance Centre of the Uganda National Drug Authority.

Results: Before the pandemic, patient reports numbered below 10 over the years. After the pandemic, WHO supported the NPC to develop a patient reporting platform using the USSD code which led to a leap in reports up to over 2000, and ultimately enabling the NPC to pass the 10,000 reports mark in Vigiflow since 2004. Trends of Reporters Showing Patients Overtaking Other Reporter Categories During the Pandemic



Conclusion: Patients had been a long neglected reporting segment. The Covid pandemic showed that given the right tools and knowledge, they are able to report and provide important data components that may be missed when health care providers report on their behalf. The Centre is now including patient engagements among the routine activities to reach out to patients.

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Impact of the Inclusion of Covid-19 Vaccines in the National Pharmacovigilance Database on the Measurement of Disproportionality

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Introduction: During the strengthened Covid-19 vaccine safety surveillance, the Moroccan pharmacovigilance center has collected a higher number of adverse events following immunization (AEFI) reports. More than half of the Individual Case Safety Reports (ICSRs) collected in the National pharmacovigilance database since its creation are linked to Covid-19 vaccines [1].

Objective: To assess the impact of the inclusion of the AEFI related to Covid-19 vaccines on the measures of disproportionality in the national pharmacovigilance database.

Methods: Measurement of disproportionality by the calculation of the Reporting odds ratio (ROR) [2] for the “Drug-Effect” pairs collected at the National pharmacovigilance database (data from March 16, 2022) with and without inclusion of Covid-19 vaccines. Using “VigiLyze” (Uppsala Monitoring Center) we calculated the RORs and exported to “Excel” the list of “Drug-Effect” pairs for which the lower limit of the 95% confidence interval of the ROR is greater than 1. Then, on the list obtained, we recalculated by Excel the RORs after excluding the Covid-19 vaccines from the database.

Results: Among the 69,814 cases of adverse effects recorded in the National pharmacovigilance database from March 16, 2022, 36,541 cases (52.6%) concerned Covid-19 vaccines (Table 1). The measurement of the disproportionality showed that 88% of the RORs increased and 5% decreased after inclusion of Covid-19 vaccines in database. The median of the ROR change factor following this inclusion ($ROR_{Covid\ vaccines\ included} / ROR_{Covid\ vaccines\ excluded}$) was 2.1 (1.8–2.1); this can be explained by the higher proportion of Covid-19 vaccines cases (half of the database). Also, the degree of this influence depends on the frequency of AEFI to Covid-19 vaccines. Thus, the ROR had decreased with inclusion of cases of covid-19 vaccines for most common reactions and had been multiplied by a factor more than 2 for the low-reported reactions with Covid-19 vaccines.

Table 1. Epidemiological characteristics of ICSRs with covid-19 vaccines and with other vaccines and drugs, Moroccan pharmacovigilance database, data of March 16, 2022.

	Covid-19 vaccines	Other vaccines and drugs	Global
Date of first case	February 2021	September 1992	September 1992
Total cases	36 561	32 908	69 469
Sex ratio M/F	1.03	0.70	0.87
Age of patient :			
- [0 – 17 years]	1.8%	19,7%	10,3%
- [18 – 64 years]	84,9%	51,4%	69,0%
- ≥ 65 years	8,8%	8,2%	8,5%
- Unknown	4,6%	20,7%	12,2%
Primary source			
- Health professional	17,8%	81,5%	48,0%
- Consumer/Non health professional	82,1%	13,1%	49,4%

Conclusion: The inclusion of Covid-19 vaccines in the National pharmacovigilance database has influenced the measures of disproportionality, which would influence signal detection. This bias must

be taken into account when a type of drug or vaccine is very represented in a database. The proposed solution is to specify database for these types of products or to improve Vigilyze to be able to perform disproportionality measurements from parts of the national database.

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Evaluation of Suspected Adverse Reactions to COVID-19 Vaccines in Patients with Autism Spectrum Disorder: Analysis of VAERS Database

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Introduction: Several neurobiological mechanisms have been proposed to support the hypothesis of a higher COVID-19 risk in individuals with Autism Spectrum Disorder (ASD) [1]. Since the end of 2020 EMA and FDA, among others Agencies, issued Emergency Use Authorization for COVID-19 vaccines, approved for prevention of COVID-19 disease [2]. Safety of these vaccines are monitored in all countries. In USA, spontaneous reports are collected in the Vaccine Adverse Event Reporting System (VAERS), that is freely accessible [3]. This continuous and intense safety monitoring is needed to enable a timely evaluation of the benefit/risk profile of COVID-19 vaccines to ensure the benefit of vaccination continues to outweigh risks.

Objective: To evaluate suspected adverse reactions following vaccination with COVID-19 vaccines in persons with ASD reported to VAERS.

Methods: This study analyzed VAERS reports of suspected adverse reactions following vaccination with Pfizer-BioNTech, Moderna and Janssen COVID-19 vaccines until 04/Mar/2022 in children, adolescents and adults with ASD. Reports were analysed by age, sex, seriousness, type of vaccine (manufacturer), dose, onset interval, length of hospitalisation and outcome.

Results: Eighty-seven reports have been retrieved from VAERS. The most affected age group is between 18–29 years with a higher percentage distribution in males than in females. Seventy-six (76%) reports were related to non-serious events, thus, the most frequent reactions reported were expected: fever, pain at the injection site and headache. Other adverse reactions are rare and unexpected including febrile seizure and eye rolling. Two cases of amonorrhea were also observed. Among the 11 serious cases, 6 (6.90%) were hospitalized; 2 (2.30%) were reported as life-threatening and 2 (2.30%) caused permanent disability. Death was reported in one case, occurring few hours after the vaccination. At the time of the reporting, the patients presented concomitant medical conditions, treated with various product medications, who contributed, therefore, to the onset of events.

Conclusion: The number of cases reported to VAERS and related to suspected adverse reactions in individuals with ASD does not suggest a safety concern attributable to authorized COVID-19 vaccines at this time in this special population.

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Safety and Pharmacokinetic Profile of an Immunobiological Drug (anti SARS-Cov-2) in the Treatment of CoViD-19

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Introduction: Equine hyperimmune serum (F(ab')₂ fragments) has been widely used in Argentina in the last 100 years with satisfactory results and an acceptable safety profile in the treatment of accidents with poisonous animals such as snakes (bothrops, chrotalus, elapids) and arthropods (Loxosceles, Latrodectus, Phoneutria and Tityus). These antisera were developed by the National Institute for the production of Biologicals (ANLIS-Malbrán) and distributed free of charge in public hospitals in the country.

Objective: The aims of this study (NCT04913779) is to analyze the efficacy and safety of a passive immunotherapy strategy using hyperimmune equine serum known as Anti-SARS-CoV-2 elaborated by the National Institute for the Production of Biologicals (ANLIS-Malbrán) as an addition to the standard therapeutic approach for hospitalized patients with COVID-19, in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Methods: A randomized, double-blind controlled clinical study is carried out in 200 patients with COVID-19 requiring oxygen therapy in which the safety and efficacy of early use (72 hours from the onset of symptoms) of the research product is evaluated. The present work corresponds to a preliminary result of the safety and pharmacokinetic analysis in the first 20 patients included.

Results: 20 initial patients (1:1 treatment: control ratio) were studied. The post-administration follow-up time was 28 days. The pharmacokinetic analysis shows that the research product presents an

extracellular volume of distribution, with a median half-life of distribution was 6.3h (10–90% percentiles: 3.4–8.1 h) and half-life of elimination, 121h (10th–90th percentiles: 83–171 h). Neutralizing activity in plasma was correlated with drug concentration. Daily controls were carried out including physical examination, questioning in relation to symptoms presented, and blood extraction for routine laboratory control. No patient reported symptoms consistent with adverse reactions. Although some patients presented mild laboratory alterations (hepatogram, urea, creatinine), in all cases they were alterations that existed prior to the administration of the research product and that improved after treatment.

Conclusion: Despite the small number of patients studied initially, and the possible masking of an adverse event due to the underlying disease (COVID-19), no significant adverse reactions were evidenced during treatment with the research product. There were no serious reactions and the pharmacokinetic characteristics appear to show a long-acting profile correlated with neutralizing activity *in vitro*.

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Self-Medication Among Romanian Patients in General and in the Context of the COVID-19 Pandemic

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Introduction: Self-medication is important for public healthcare as it allows patients to make their own decisions about how to maintain their health and well-being. In the context of COVID-19 healthcare emergency, self-medication is likely to have been increased for prevention or treatment of perceived infection.

Objective: To assess self-medication in general and in the context of COVID-19.

Methods: We conducted a cross-sectional survey among Romanian patients during December 2020–March 2021. Participants were recruited through patients' associations (email, Facebook groups). Those who agreed to participate to the study were directed to an online questionnaire. The in-house developed questionnaire was anonymous, consisting of 42 questions assessing knowledge, attitudes (using Likert scale) and practice regarding self-medication and it was pretested for adjustments in a community pharmacy in 14 patients.

Results: A total of 398 participants (77.1% female), with most (64.8%) in the age category of 35–64, responded to the survey. The majority were urban residents (84.9%), having under and postgraduate studies (63.1%). More than half (57.3%) reported having chronic disease. *In general*, 89.7% reported practicing self-medication, with 70.4% of participants taking an average of 1–2 OTC drugs over the course of a month. Among those self-medicated, 12.9% reported using doses higher than recommended in the leaflet. Of those who experienced adverse reactions (15.4%) when self-medicated, 30.9% reported exceeding the doses. Only 25.4% agreed that self-medicated OTC drugs are safe and 42% of respondents disagreed/strongly disagreed. A considerable percentage of participants (71.3%) agreed that it is a good idea to consult a specialist before using OTC drugs. When

asked which drugs are OTC, respondents gave mainly correct answers, however, 24.9% considered antivirals being OTC and therefore suitable for self-medication. *In the context of COVID-19*, only 17.8% reported going to the pharmacy more often than they usually did, with 42.7% and 29.9% taking medicines for preventive and treatment purposes. Medicines/ supplements mostly purchased from the pharmacy during COVID-19 pandemic were vitamin C (61.8%) and D (44.7%), paracetamol (56.0%), zinc (29.4%), ibuprofen (20.1%), and in lower percentages azithromycin (6.0%), oseltamivir (3.3%) and hydroxychloroquine (3.0%). 76.4% respondents stated that they were not influenced by media reports about medicines used to prevent SARS-CoV-2 virus infection and only 6.8% bought medicines online in the context of the COVID-19 pandemic.

Conclusion: Self-medication was commonly reported among our study population; however, it seems that it was not greatly influenced by the COVID-19 pandemic and by media information on drugs to be used for COVID-19 prevention.

References/Further Sources of Information

Not applicable.

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Systemic COVID-19 vaccines Adverse Events Following Immunizations and Their Associated Factors: A Comparative Study Using Iraqi Consumers' Self-Reported Data

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Introduction: Three types of COVID-19 vaccines were deployed in Iraq; PfizerBioNTech, AstraZeneca, and Sinopharm. Spontaneous self-reported safety data received directly from consumers was an important source of COVID-19 vaccine reporting sources for the first time in Iraq.

Objective: To study the common systemic AEFIs and factors influencing them, using self-reported data by Iraqi consumers vaccinated with different COVID-19 vaccine types.

Methods: As a part of the national plan for COVID-19 vaccines safety surveillance, an online self-assessment form was designed by the national pharmacovigilance center for the public consumers across the country. The form was quadrilingual and captures the necessary information for a valid AEFI report. Demographic data, contact details, vaccination details, adverse event information, and medical history were collected. To facilitate the filling process and standardize the answers, a list of predefined common short-term AEFIs were included as a checklist, in addition to a free text for other unlisted AEFIs.

A retrospective cross-sectional study using the collected responses from April, 2021 until April, 2022 was performed. Data was validated and cleaned. Analyses was performed using SPSS software version 26. Selected common short-term AEFIs were analysed. The incidence of these AEFIs were compared between vaccine types using chi-square test. Moreover, predictors of reporting these AEFIs were explored using binary logistic regression for each vaccine type.

Results: A total of 2843 report were included, 62.0% of them were male. The age mean was 36.33 (SD $\pm$ 12.2). The participants were more likely to report after the 1st dose (79.4%). AstraZeneca vaccine was found to produce the highest number of AEFIs per report, 4.31 (SD $\pm$ 2.4). AstraZeneca and PfizerBioNTech were significantly associated with a higher incidence of multiple AEFIs as compared with Sinopharm (fatigue, joint pain, headache, fever, and chills).

PfizerBioNTech vaccine was associated with 71 out of the 76 reported lymph nodes AEFIs.

Factors that were significant predictors of higher reporting of systemic AEFIs were; for PfizerBioNTech (female gender, increased dose number, and increased likelihood of previous COVID-19 infection); AstraZeneca (younger age, female gender, and increased likelihood of previous COVID-19 infection); and in case of Sinopharm (younger age, and female gender)

Table: Types of common AEFIs according to vaccine type

		Vaccine Type								P-Value
		AstraZeneca		Cominarty		Sinopharm		Total		
		Count	Layer column N %	Count	Layer column N %	Count	Layer column N %	Count	Layer column N %	
Fever	No	248	30.9%	843	50.2%	229	63.4%	1320	46.4%	0.000
	Yes	555	69.1%	836	49.8%	132	36.6%	1523	53.6%	
Chills	No	473	58.9%	1151	68.6%	290	80.3%	1914	67.3%	0.000
	Yes	330	41.1%	528	31.4%	71	19.7%	929	32.7%	
Headache	No	282	35.1%	706	42.0%	205	56.8%	1193	42.0%	0.000
	Yes	521	64.9%	973	58.0%	156	43.2%	1650	58.0%	
Joint Pain	No	232	28.9%	613	36.5%	196	54.3%	1041	36.6%	0.000
	Yes	571	71.1%	1066	63.5%	165	45.7%	1802	63.4%	
Fatigue	No	210	26.2%	565	33.7%	173	47.9%	948	33.3%	0.000
	Yes	593	73.8%	1114	66.3%	188	52.1%	1895	66.7%	
Nausea	No	602	75.0%	1212	72.2%	285	78.9%	2099	73.8%	0.020
	Yes	201	25.0%	467	27.8%	76	21.1%	744	26.2%	
Vomiting	No	747	93.0%	1553	92.5%	343	95.0%	2643	93.0%	0.236
	Yes	56	7.0%	126	7.5%	18	5.0%	200	7.0%	
Diarrhea	No	720	89.7%	1501	89.4%	334	87.0%	2535	89.2%	0.353
	Yes	83	10.3%	178	10.6%	47	13.0%	308	10.8%	
Chest Pain	No	682	84.9%	1334	79.5%	302	83.7%	2318	81.5%	0.002
	Yes	121	15.1%	345	20.5%	59	16.3%	525	18.5%	
Body Rash	No	756	94.1%	1551	92.4%	330	91.4%	2637	92.8%	0.162
	Yes	47	5.9%	128	7.6%	31	8.6%	206	7.2%	
Lymph nodes pain/ enlargement	No	798	99.4%	1608	95.8%	361	100.0%	2767	97.3%	0.000
	Yes	5	0.6%	71	4.2%	0	0.0%	76	2.7%	

Chi-Square test was performed. P-value was calculated with a significance level of 0.05
Layer column N% shows the percentage of reports containing the AEFI for each vaccine type

Conclusion: The results showed that AstraZeneca and PfizerBioNTech vaccines were associated with more AEFIs than Sinopharm. Predictor factors of AEFIs include; female gender in all vaccines; the presence of previous COVID-19 infection in both PfizerBioNTech and AstraZeneca vaccines; second dose in PfizerBioNTech; and younger age for both AstraZeneca and Sinopharm.

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How Covid-19 Pandemic Affected the National Pharmacovigilance System in the Czech Republic

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Introduction: Covid-19 pandemic has impacted all areas of human society worldwide, including drug regulatory authorities. Enormous public interest and seriousness of the disease resulted in boom of new medicines for treatment and prevention of Covid-19. Patients and healthcare professionals (HCP) concerns on safety of these new medicines resulted in the highest increase in the reporting rate of adverse drug reactions (ADRs) in the history of the Czech Republic (CZ).

Objective: To present how the PV processes were affected by Covid-19 pandemic. To present the impact of increased reporting rate and related workload on the national PV system in Czech regulatory authority (SUKL) and the influence on awareness of ADRs reporting in the Czech public.

Methods: In 2020, the total number of ADRs (n = 2904) reported to SUKL was the lowest in the past 5 years (2016-2020). The probable cause may be the Covid-19 pandemic, including the lack of time for HCP to report ADRs.

Results: On the contrary, in 2021 (1) with the entry of the treatment and prevention of Covid-19 into the clinical practice, there was a massive increase in reported ADRs in CZ. Of the total number of reported cases (n = 13 759), 81.10 % (n = 11 159) were vaccine-related (all types of vaccines). Of these vaccine-related ADRs 95.27 % (n = 10 631) were reported for Covid-19 vaccines only. Considerable interest in vaccine safety in CZ is evident, resulting in high number of suspected ADRs reported following vaccine administration.

Conclusion: Due to the significant increase in the ADRs reported, the national PV system had to be adapted. A system of triage of case reports was set including pre-assessment of seriousness by PV assessors. More staff had to be hired and trained to assist with the case processing, including receipt of the report, HCP confirmation of patient reports, follow-up and hospital records requests. To satisfy an extensive media attention and to increase transparency of vaccine safety, SUKL published an overview of reported ADRs on weekly basis (2) and communicated the most serious concerns online, together with EMA recommendations. Czech PV assessors were deeply involved in all European procedures related to Covid-19 treatment (e.g., remdesivir) and prevention (vaccines). The Czech public became more aware of the possibility of reporting ADRs, the number of reports will be presented. Based on reporters' suggestions the online reporting form for ADRs was re-designed. This experience has been challenging and brought new approaches and improvements to the national PV system.

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Active Surveillance for Safety Monitoring of COVID-19 Vaccines in Saudi Arabia

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Introduction: At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, China [1, 2]. It is generally accepted that the world will not return to the pre-pandemic normal situation until safe and effective vaccines become available. However, the rare and unknown adverse events following immunization (AEFIs) are not usually detected in the clinical trials. Thus, monitoring the safety of COVID-19 vaccines in real-world population is essential.

Objective: To perform a post-marketing safety surveillance of AEFIs of COVID-19 vaccines.

Methods: A prospective cohort study conducted and followed subjects who received COVID-19 vaccines from the first day of vaccination for seven days after the first and second doses, then biweekly for three months. All vaccinee demographic information, vaccine type, co-morbidities, concomitant medications and AEFIs were collected by phone through a standardized online questionnaire. Baseline characteristics and AEFIs were analyzed descriptively by SPSS software. AEFIs were classified according to medical Dictionary for Regulatory Activities (MedDRA).

Results: 544 subjects of 8867 agreed to be part of the study. Among them 218 subjects completed the study, of them 110 individual were male (50.5%) and 108 (49.5%) were female; the median age was 33 year. Out of 218, 87 (39.91%) individual received Pfizer-BioNTech vaccine, 45(20.64%) individual received Oxford/AstraZeneca vaccine, 5(2.3%) individual received Moderna vaccine, and 81 (37.2%) received two different COVID-19 vaccines. The reported events were categorized to system organ class (SOC) according to MedDRA. The most reported SOC were respiratory, thoracic and mediastinal disorders (n = 8 with Pfizer-BioNTech vaccine, n = 4 with Oxford/AstraZeneca vaccine, n = 1 with Moderna vaccine), Injection site reactions (n = 66 with Pfizer-BioNTech vaccine, n = 34 with Oxford/AstraZeneca vaccine, n = 5 with Moderna vaccine), nervous system disorder (n = 20 with Pfizer-BioNTech vaccine, n = 18 with Oxford/AstraZeneca vaccine, n = 3 with Moderna vaccine), infections and infestations (n = 23 with Pfizer-BioNTech vaccine, n = 33 with Oxford/AstraZeneca vaccine, n = 4 with Moderna vaccine), musculoskeletal disorders (n = 53 with Pfizer-BioNTech vaccine, n = 46 with Oxford/AstraZeneca vaccine, n = 7 with Moderna vaccine). Only 10 (4.6%) cases were serious and required medical intervention to overcome the harm.

Conclusion: The preliminary results of the study shows the short-term safety profiles of included COVID-19 vaccines are acceptable in Saudi Arabia.

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RESPIR'Nantes Study: What About the Safety ?

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Introduction: Remdesivir, has been evaluated in the treatment of SARS-CoV-2 pneumonia in several clinical trials, then it has been used in routine care since the European approval in this indication.

Objective: The main objective of the RESPIR'Nantes study was to describe the clinical outcome and safety of patients treated with remdesivir in real life. We chose here to focus on safety outcomes.

Methods: To describe the safety, we considered adverse events (AEs), based on those reported to date in the Summary of Product Characteristics and potential post-marketing signals from the international pharmacovigilance database Vigilyze®. AEs were classified according to the System Organ Class (SOC) of the Medical Dictionary of Adverse Events terminology. The AEs of SOC “hepatobiliary disorders” and “renal and urinary disorders” being the most reported to date, a detailed analysis was performed

Results: A total of 76 patients were included in the study from March 13 to December 31, 2020. The most common AEs were metabolism and nutrition disorders, hepatobiliary disorders, gastrointestinal disorders and renal and urinary disorders.

Patients with hepatobiliary disorders had mainly include transaminases increases and 60% had pre-existing hepatobiliary disease that worsened during treatment. The median time to onset or worsening of hepatobiliary disease was one day [1-2]. It led to discontinuation of treatment in one case. Among patients with renal and urinary disorders, 50% had increased blood creatinine levels prior therapy initiation. The median time to onset or worsening of renal and urinary disorders was one day [0–16]. It led to discontinuation of treatment in two cases.

Conclusion: A potential signal of pharmacovigilance has been identified for liver and renal disorders in Vigilyze® and we have reported the expected remdesivir AEs. However, it is difficult to suspect remdesivir only without considering the pathology itself, but remdesivir appears to have favorable safety profile in patients who require minimal supplemental oxygen.

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Not applicable.

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Covid-19 Vaccines: Is the Seriousness Criterion “Medically Important” Applied Correctly in Reports and Are There Differences between HCPs and Non-HCPs?

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Introduction: During the Covid-19 vaccination campaign, Swissmedic received approximately 50% of the spontaneous reports from health care professionals (HCP) and 50% directly from

patients/consumers. The rate of adverse drug reactions (ADRs) following Covid-19 vaccination categorized as “serious” by the reporters is approximately 35% in Switzerland and thus significantly higher than e.g. in the US (6.6%), while rates of reports with fatal outcome are comparable (1.4% vs. 1.3%) (1).

A high proportion of the cases labelled as “serious” in Switzerland was classified based on the category “medically important”. Since this criterion is used very commonly but is less distinct than the other seriousness criteria, we aimed to analyze whether it is used correctly by the reporters and whether differences between healthcare professionals and patients/consumer can be identified.

Objective: To evaluate the appropriate usage of the seriousness criterion “medically important” in spontaneous ADR reports submitted by health care professionals compared to non-health care professionals following immunization with a Covid-19 vaccine.

Methods: All serious ADR reports received between the 1st of January 2021 and 31st of December 2021 following immunization with a Covid-19 vaccine were extracted from the Swiss database. Cases categorized as “medically important” were further analyzed. We extracted the preferred terms (PT) according to the medical dictionary for regulatory activities (MedDRA) (2) of the reported ADRs and matched them with the important medical event terms list (IME list) (3).

Results: From a total of 11,115 ADR reports, 4,125 (37.1%) were classified as “serious”. 2,773 (67.2%) of the serious cases were reported by HCPs and 1,352 (32.8%) by non-HCPs. In 2,260 (55%) reports, the seriousness was based solely on the criterion “medically important”. 755 (33.4%) of these reports would also be classified as “serious” according to the IME List. 498 (39%) reports by HCP and 257 (26%) by non-HCP match with the IME list. The proportion of correctly categorized ADRs is significantly higher ($p < 0.0001$) in reports from HCPs compared to non-HCPs.

Conclusion: Only approximately one third of the cases, which were classified as “medically important” and thus reported as “serious”, would also be classified as such according to the IME list. The proportion of correctly categorized ADRs is significantly higher in reports from HCPs. Additional information and training for HCPs appears necessary to achieve a higher rate of appropriate seriousness categorization in ADR reports. The usage of the category “medically important” in reports by patients/consumers requires general revision.

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Hepatic Disorders in Adults Associated with the Use of Ivermectin for SARS-CoV-2 Infection: A Pharmacovigilance Study in VigiBase

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Introduction: In the face of the global health emergency due to SARS-CoV-2, Ivermectin has been, among other drugs, repurposed in some Latin American countries to treat COVID-19 [1]. Studies are needed on the safety of Ivermectin for this new indication. VigiBase is the WHO pharmacovigilance database that registers all Individual Case Safety Reports (ICSRs) from more than 130 countries.

Objective: To review in VigiBase the reports of serious hepatic disorders in adults associated with the use of Ivermectin for COVID-19.

Methods: We extracted, in men or women aged ≥ 18 years between 1 January 2020 and 7 March 2021, all ICSR registered as “serious” associated with the use of ivermectin, and established the prevalence of serious hepatic disorders when Ivermectin was indicated for COVID-19

Results: During the study period, there were 1,393 ICSR in VigiBase associated with Ivermectin, of which 60 (4.3%) were registered as “serious”; in 25 of those, Ivermectin had been used for COVID-19. Out of those 25, five reported serious cases of hepatic disorders (hepatitis, hepatocellular injury, cholestasis, increased alanine aminotransferase and aspartate aminotransferase, abnormal liver function test). Three patients were male and overall mean age was 59.2 ± 9.7 years. Ivermectin was administered during a mean of 2.5 ± 2.4 days, and the mean daily dose was 14.3 ± 2.9 mg. Two patients simultaneously received other drugs (Remdesivir, Hydroxychloroquine, Azithromycin). Two patients had concurrent conditions (strongyloidiasis, diabetes mellitus). Only in 2 patients liver enzyme data were reported. In all patients the evolution was favorable after stopping the drug (de-challenge), and no patient was re-exposed (re-challenge). Causality analysis was reported in 3 cases, qualifying as possible or probable.

Conclusion: The safety of the use of Ivermectin should be studied more exhaustively, especially as regards the probability of hepatic disorders when used for COVID-19

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Strengthened Pharmacovigilance in France for Monitoring COVID-19 Vaccines and Therapeutics Toward a New Surveillance Era?

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Introduction: Following the emergence of SARS-CoV-2, a range of measures have been put in place in France: strengthened surveillance

of COVID-19 therapeutics and vaccines, using tools and methods developed to detect promptly any safety issues in order to take appropriate risk minimisation measures [1].

For COVID-19 therapeutics, ANSM has mobilized the French Network of regional pharmacovigilance centers (CRPV) to ensure continuous monitoring and assessment of adverse reaction reports through a specific survey. The results were discussed at an experts' monitoring committee which involves several scientific experts. The members assess collegially the potential safety signals. Then, a specific communication associated with the investigation reports are published on the ANSM website.

For COVID-19 vaccines, a similar organization was put in place with additional components.

Artificial intelligence and an information system have been used to optimize reports processing and improve specific data collection. Information sheets on adverse events have been made available to patients and healthcare professionals.

Finally, pharmaco-epidemiological studies have been conducted in case of a potential signal for confirmation or to quantify the risk.

Objective: To evaluate the implementation of strengthened monitoring of vaccines and therapeutics used in COVID-19.

Methods: Potential signals detected on vaccines and drugs used in COVID-19 following the implementation of new pharmacovigilance tools and methods were analysed.

Results: As of March 31th, 2022, more than 140 million doses of COVID-19 vaccines administered with more than 150,000 adverse reactions reports, 45 monitoring committees held and 43 potential signals of COVID-19 vaccines have been transmitted by ANSM to European authorities to reinforce or initiate a signal.

As of January 26, 2022, more than 2 300 adverse reactions reports collected for treatment used for patients with COVID-19, 21 monitoring committees held and 3 signals were identified.

Conclusion: The use of tools and methods in COVID-19 vaccines and medicines monitoring have allowed for early detection of signals and implementation of appropriate risk minimisation measures. This has been made possible thanks to the whole organization of strengthened surveillance which remains agile along the pandemic crisis. Furthermore, facilitation was given to accelerate evaluation, methods to prioritize a large volume of spontaneous reports, and different channels to communicate transparently in order to build trust among stakeholders.

There are still challenges to build a new era of surveillance concerning the management of a large number of adverse drug reports, expertise and communication in a daily routine.

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Background Incidence in Spontaneous Reporting: Observed/Expected analysis of Myocarditis and Pericarditis with COVID-19 Vaccines in the Netherlands

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Introduction: Pericarditis and myocarditis have been recognized as rare adverse drug reactions of the mRNA COVID-19 vaccines of Pfizer and Moderna [1,2]. Most cases are observed in young males within 5 days following the 2nd dose and the course is often mild. The estimated excess risk is about 1-3 per 100,000 vaccinated persons, whereas the risk ratios following Sars-CoV-2 infection are 5-18 for myocarditis and pericarditis respectively [3]. Few studies indicate an increased risk of myocarditis with the 1st dose of the vector vaccine of AstraZeneca [4]. General incidence of myocarditis is 10-20 per 100,000 person-years and young men are at increased risk. Incidence-rates of pericarditis are not exactly known, since the condition is often self-limiting and underdiagnosed [5].

Objective: We evaluated the use of Standardised Morbidity Rates (SMR) to compare spontaneously reported cases of myocarditis and pericarditis with COVID-19 vaccines with stratified Dutch background incidence rates from 2019 in the vaccine exposed population.

Methods: SMRs are calculated by dividing the reported as observed (O) cases by the expected (E) number within risk windows of 5/14 days following each dose and vaccine. SMR > 1 indicates that more cases were reported than expected [6].

Results: Until January 2022, 373 reports of myocarditis and pericarditis were received. The majority of the cases was reported following an mRNA vaccination (85%), mostly following the second dose (47%). The mean age for men and women was 34.7–45.1 years for myocarditis and 45.2–46.6 years for pericarditis. The mean times to onset (TTO) for myocarditis and pericarditis with the 1st and 2nd doses are about three weeks, with a wide range. Median TTO show a latency of 5 days for myocarditis and 9–14 days for pericarditis. Six patients died following myocarditis or pericarditis. In the table, SMRs for myocarditis within 5 days are summarized, stratified for vaccine, dose, sex and age. For pericarditis, SMRs show a similar pattern, and more reports were received than expected in men and women < 40 years with all doses of Pfizer, in men < 40 with Moderna, in men < 40 and women > 40 with the first dose of AstraZeneca and in men who received the Janssen vaccine.

	Myocarditis (men)	Myocarditis (women)
PFI_1_<40	5.35 (1.96-11.64)	3.74 (0.77-10.93)
PFI_1_>40	2.04 (0.42-5.96)	0
PFI_2_<40	12.05 (6.10-20.01)	0
PFI_2_>40	2.89 (0.79-7.39)	4.77 (0.57-17.21)
MOD_1_<40	30.96 (8.44-79.26)	11.01 (0.28-61.35)
MOD_2_<40	25.81 (5.33-75.46)	12.13 (0.30-67.57)
JAN_1_<40	11.59 (1.39-41.84)	0
AZ_1_<40	42.37 (1.06-244.46)	0
AZ_1_>40	0	24.38 (0.61-140.67)

Table 1: SMRs (95% CI) of myocarditis with COVID-19 vaccines in a 5-day risk window. Limitations of this method: first, media attention may have influenced awareness and diagnosis of both conditions compared to the reference period (2019) and its incidence rates; second, the risk cannot be quantified since the rate of underreporting is unknown.

Conclusion: Myocarditis and pericarditis were reported more frequently than expected in various patient groups with both mRNA and vector vaccines. However, spontaneous reporting is signal generating and epidemiological studies are needed to confirm the potential signal with vector vaccines.

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Role of the Hospital Pharmacist in the Evaluation of the Anti-COVID-19 Vaccine Safety Profile in the Post-Marketing Phase

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Introduction: The European Medicines Agency, following positive evaluation regarding the safety, quality, and efficacy of anti-COVID-19 vaccines, granted conditional marketing authorization (CMA) for these drugs on the condition that the developers would continuously provide additional data on their safety and efficacy even after marketing authorization in order to confirm the risk-benefit ratio. Following the start of the vaccination campaign in December 2020, special attention was paid to the occurrence of possible adverse reactions (ADRs). The pharmacist staff of Pugliese-Ciaccio Hospital, in order to monitor the safety of the new vaccine and to promptly report suspected vaccine ADRs, prepared a short questionnaire to be administered to the employees of the hospital at the time of administration of the second dose of vaccine.

Objective: Monitoring vaccine safety & promptly reporting side effects.

Methods: The survey was conducted between January and April 2021. All employees were administered mRNA vaccine and, at the time of the administration of the second dose, were asked to answer the above questionnaire specifying the following information: biographical data, gender, date of administration of the two doses of vaccine, occurrence of any ADRs resulting from the first dose of vaccine, type of resolution, presence of concomitant diseases and related medication intake in the days before/after the vaccination.

Results: The questionnaire was administered to 1,656 health care workers and all of them answered the questions comprehensively. Among them, 51.6 percent experienced adverse reactions after administration of the first dose of vaccine, and the predominantly noted symptoms included systemic diseases and conditions related to

the site of administration, musculoskeletal and connective tissue disorders, nervous system disorders and gastrointestinal disorders. The frequency of reporting was higher among the young than the elderly population (58% vs. 38.67%). ADRs occurred approximately 1.7 times more frequently among women than men.

Conclusion: The intense pharmacovigilance activity carried out by the Hospital Pharmacist was a pivotal moment during the pandemic emergency, as it allowed the safety profile of anti-COVID-19 vaccines to be readily confirmed with real-life data. Infact, it was found that the main symptoms detected were in line with what was reported in the safety data from the pre-registration studies [1], from which it was also found that the frequency of ADRs was higher among the young than the elderly, a finding that was also confirmed by our study. So, the questionnaire survey was able to substantiate the safety of vaccines, confirming that the benefits of vaccination outweigh the risks.

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Sotrovimab—Flashes of Safety in COVID-19 Patients

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Introduction: Sotrovimab is a monoclonal therapy authorized for emergency use (EUA) on May 26, 2021, by the US (FDA) for treatment of mild-to-moderate coronavirus disease (COVID-19) in adults and children ≥ 12 years old). The drug showed positive viral testing in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and, reduced risk for progressing to severe COVID-19, including hospitalization or death¹.

Objective: This paper reviewed published data on safety of Sotrovimab 500mg in COVID-19 patients.

Methods: The study based on reviewing published literature. Pubmed and FDA web was searched for data on Safety of Sotrovimab use in COVID-19 patients (May2021-May2022).

Results: Gupta A et al² reported among (n = 291 Sotrovimab group, n = 292 placebo group) mild diarrhea occurred in 5 cases (1%) in Sotrovimab group, compared to 1 case of moderate diarrhea, while diarrhea occurred in 3 patients in placebo group. One patient who received Sotrovimab had moderate dyspnea, an infusion-related reaction that was related to Sotrovimab. Hospitalization adverse events occurred in 2% of Sotrovimab group and in 6% in placebo group. No death or serious adverse events e.g., hematological disorders or liver damage were related to Sotrovimab. Further study by Gupta A et al³ for Sotrovimab (n = 528) or placebo (n = 529) reported that adverse events were infrequent and are similar between two groups (22% for Sotrovimab vs 23% for placebo); the most common events were diarrhea with Sotrovimab (n = 8; 2%) and COVID-19 pneumonia with placebo (n = 22; 4%).

Kreuzberger N et al⁴ reported treatment with Sotrovimab may reduce the number of participants with oxygen requirement weaned in 3 days and risk of all-cause hospitalization or death without exhibiting significant adverse reaction.

Fernandes G et al⁵ observed that following administration of Sotrovimab to kidney transplant recipients infected with Omicron variant, two patients required hospitalization for oxygen therapy. None were admitted to the intensive care unit or died.

Conclusion: This review found limited number of safety studies of Sotrovimab in COVID-19, which reflects low numbers of publications. This is probably because of the Emergency utilization of drug and limitation of use in many countries. Lately, FDA US announced Sotrovimab is no longer authorized to treat COVID-19 in US due to increases in the proportion of COVID-19 cases caused by the Omicron variants⁶. Further data is needed to evaluate Sotrovimab safety in COVID-19 patients and examine risk-benefit, adverse events, and risk correlation to disease severity in patients with various risk factors.

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Characteristics of Spontaneous Reports of Thrombosis with Thrombocytopenia Syndrome after COVID-19 Vaccines in the Netherlands

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Introduction: In March 2021 first cases of thrombosis with thrombocytopenia syndrome (TTS), also called vaccine induced thrombosis with thrombocytopenia (VITT), were published and reported, raising a concern with the adenovector vaccine of AstraZeneca [1, 2]. One month later, TTS was also associated with the Janssen vaccine [3]. No conclusive evidence of VITT with mRNA vaccines is found [4]. In Europe, vaccination programmes were put on hold and the indications for use restricted. The role of pharmacovigilance was to monitor the events closely and estimate its frequency of occurrence. While mass vaccination campaigns were ongoing, information on case criteria and definitions was limited. In the Netherlands, internists wrote

guidelines, organised centralised diagnostics for PF4 ELISA and HIPA tests and encouraged expert physicians to report suspected cases to The Netherlands Pharmacovigilance Centre Lareb [5]. Lareb managed to monitor TTS cases closely by a fast triage of relevant reports and strong collaboration with external specialists.

Objective: Spontaneously reported cases of TTS in The Netherlands are described.

Methods: We used CDC classification criteria combined with Dutch guidelines to determine confirmed and strongly suspected cases. CDC classification recognizes 'tier 1' with thrombosis at unusual sites not requiring tests and 'tier 2' with common types of thrombosis and requiring confirmatory tests [6].

Results: In total, 75 cases of thrombocytopenia with any kind of thrombosis were reported. Only 26 reports met criteria of TTS, concerning 19 AstraZeneca, 5 Janssen and 2 mRNA vaccines. The majority (23; 89%) of the cases was reported following the first dose. Reporting rates for AstraZeneca and Janssen were 7.7 and 5.7 per million vaccinations in total, respectively, and 13.4 per million vaccinations of the first dose with AstraZeneca. Patient and report characteristics are described in table 1. 'Tier 1' criteria were met in 15 cases. 'Tier 2' criteria were met in 6 cases and in 5 cases TTS was strongly suspected based on the Dutch guidelines. A functional HIPA test was performed in 20 cases of which 17 were positive and 3 negative. Also, two reports were received with mRNA vaccines, one well documented with positive PF4-ELISA and HIPA-tests (Moderna, 3rd dose) and the other poorly documented but meeting 'tier 1' criteria (Pfizer, 1st dose).

	AstraZeneca	Janssen	mRNA vaccines
Reports per dose (n)	17 (dose 1), 2 (dose 2)	5 (dose 1)	2 (Pfi_1, Mod_3)
Sex (Male, Female)	6 M, 13 F	2 M, 3 F	2 F
Age (mean)	54.7	30.6	79.0
Time to onset, mean (range)	13.5 (4-41 days)	14.4 (1-35 days)	18.5 (15-22 days)
Platelet count, mean (range)	56 (9-156 /nl)	59 (40-62 /nl)	20 /nl (unk.)
Sites of thrombosis (n)	PE (6), Abd. (5), CVST (3), ATE (3), ATE cereb. (3), DVT (1), DIC (1)	CVST (2), DVT (1), DIC (1), no thrombosis (1)	Abd. (1), PE (1)
Tier 1, 2, Dutch guidelines (n)	11, 5, 3	2, 1, 2	2, 0, 0
Outcome fatal (n)	3	0	0

Table1: Summary of reported TTS characteristics. Pfi_1= 1st dose Pfizer, Mod_3=3rd dose Moderna. PE=pulmonary embolism, Abd.= abdominal vein thrombosis, CVST=cerebral venous sinus thrombosis, ATE=arterial thrombosis, ATE cereb.=cerebral arterial thrombosis, DVT=deep vein thrombosis, DIC=diffuse intravascular coagulation.

Conclusion: In The Netherlands, TTS was predominantly reported after the first dose of the AstraZeneca vaccine, similar to other countries [1]. Intensive collaboration between clinical practice and pharmacovigilance resulted in good monitoring of TTS cases with spontaneous reporting.

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How a Community Approach Can Drive Pharmacovigilance Activities in Low-Resource Settings during a Public Health Emergency: Lessons from COVID-19

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Introduction: Undertaking effective drug safety monitoring can be particularly challenging in low-resource settings due to a lack of infrastructure, weak regulatory systems and poor access to training and education [1]. Given the continued impact the COVID-19 pandemic is having upon health systems globally, it is essential to ensure that pharmacovigilance systems in these vulnerable settings have the capacity to address both the exacerbated pre-existing and novel challenges that they now face [2]. This project seeks to harness the membership of an online pharmacovigilance platform, globalpharmacovigilance.org (GPV) to work together in a ‘community of practice’ (CoP) on specific challenges facing pharmacovigilance during the pandemic [3, 4].

Objective: To gather consensus on pharmacovigilance priorities in low-resource settings during the COVID-19 pandemic and provide resources to address them using a CoP model.

Methods: This project has built on a consensus-gathering methodology developed by The Global Health Network that has been implemented successfully during the pandemic to address wider COVID-19 research priorities. An online survey of GPV members was used to identify highly-ranked areas for pharmacovigilance improvement in low-resource settings during the pandemic. A virtual workshop was then hosted to invite further discussion on the survey results and reach consensus on the highest priorities. Members of the CoP were next invited to form virtual working groups, each focussing on one of the top 3 priorities identified. These groups are being supported by GPV to work together and facilitate the development (or provision, if pre-existing) of pharmacovigilance resources to address the priorities identified.

Results: Of the 43 pharmacovigilance ‘themes’ that were presented to the CoP membership in the initial survey, 3 topics were identified as the highest priorities at that point in the COVID-19 pandemic, where support, training and guidance are needed; ‘The safety of COVID-19 vaccination in pregnancy’, ‘The safety of COVID-19 vaccination in children/adolescents’ and ‘Analysis of COVID-19 vaccine safety data’. As of May 2022, the number of GPV members interested in

involvement in working groups addressing these themes are 207, 206, and 284 respectively. Initial group meetings took place in April 2022 and discussions are ongoing as to how to take group activities forward and address the priorities identified.

Conclusion: A CoP model represents an effective method of consensus gathering amongst pharmacovigilance stakeholders at a global level, and allows rapid identification of healthcare priorities during public health emergencies. It is anticipated that working groups outputs will include the provision of resources designed to address the priorities identified.

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Pharmacists’ Engagement in the Adverse Drug Reactions Reporting Process During the COVID-19 Pandemic

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Introduction: The COVID-19 pandemic put a burden on healthcare systems worldwide [1]. Pharmacists have shown their significant role as a part of the frontline workers in many countries [2–3]. Pharmacists have a suitable position in the process of adverse drug reactions (ADRs) reporting of COVID-19 treatments and vaccines.

Objective: To assess the engagement of pharmacists in the pharmacovigilance process related to the treatment of COVID-19.

Methods: A systematic search of the electronic databases PubMed, Scopus, ScienceDirect and Google Scholar was carried out for relevant articles published between December 2020– April 2022, reporting the engagement of community, clinical and hospital pharmacists in the ADRs reporting process during the COVID-19 pandemic. In this systematic review the following keywords were used: “COVID-19”, “pharmacists”, “drug safety”, “pharmacovigilance” “ADRs”. The inclusion criteria were full text articles.

Results: A total of 18 articles matched our inclusion criteria. In the beginning of the COVID-19 pandemic drug-repurposing was used as a treatment strategy. Chinese clinical pharmacists were involved in close monitoring, documentation and reporting of ADRs. Some European countries (Italy, Belgium, Switzerland and Serbia) actively involved hospital pharmacists in the safety monitoring of COVID-19 vaccines. In Australia a national vaccine safety surveillance program (AusVaxSafety) was launched with the active engagement of community pharmacists. The goal of this new pharmacists-led pharmacovigilance system is to provide critically significant safety data regarding potential ADRs following vaccination.

Conclusion: Pharmacists may play a key role in maintaining the rational and safe use of medicines. Effective reporting of ADRs by the pharmacists is an essential aspect of the pharmacovigilance system

during COVID-19 pandemic. Enhanced collaboration, and availability of resources, tools and methods will add to the lessons learned from previous experiences.

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How to Handle a Sudden Tenfold Increase in ICSRs—Lessons Learned During the SARS-Cov-2 Pandemic

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Introduction: The unprecedented vaccination efforts related to COVID-19 have strained PV systems and resources of stakeholders globally.

Objective: The Norwegian Medicines Agency (NoMA) wishes to present lessons learned from changes implemented nationally before and during the vaccination campaign.

Methods: Anticipating a large increase in spontaneous reporting, improved tools and procedures simplifying reporting, case processing, and analysis were implemented. Resources for hiring additional temporary staff was made available. The overall aim was that of an agile preparedness with ability to replan and reprioritize activities to fulfil pharmacovigilance obligations of a national competent authority, while continuing NoMAs tradition of transparency towards the public.

Results: NoMA experienced a tenfold increase in ICSRs from healthcare professionals and consumers during COVID-19 vaccination. Compared to normal vaccine reporting the increase was even higher. Case processing, signal detection and signal management procedures were stretched thin. Still, several international signals were detected and managed early. Despite additional resources supplied, a backlog in handling of non-serious reports accumulated while serious reporting was unaffected. Communication to the public was radically increased.

Among measures put in place by NoMA before and during the vaccination campaign, the following were useful:

- Electronic reporting forms.
- Collection of unique patient identification number.
- Daily status meetings, both internally and externally (i.e. Norwegian Institute of Public Health).
- Daily triage of incoming ICSRs.
- A clear order of priority for case processing.
- Simplified processing of non-serious ICSRs.
- Automated report generation to monitor special groups, events or outcomes, e.g. children, Adverse Events of Special Interest, fatal cases.

- Weekly overviews of suspected adverse reactions associated with COVID-19 vaccination in Norway was made available to the public, both in Norwegian and English.

Conclusion: By implementing various measures NOMA managed to prioritise processing of the ICSRs that added most value to detecting signals of possible new safety issues.

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Nocebo Responses in Relation to COVID-19 Vaccine Safety

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Introduction: Nocebo effect is the negative counterpart of the placebo phenomenon.¹ It refers to the adverse effects that occur in clinical or laboratory medical contexts, respectively, after administration of an inert treatment or as part of active treatments, due to mechanisms such as expectancies of the patient.² The nocebo responses are extremely common in medical practice and multiple factors contribute to it including risk communication strategies.³

Objective: To summarize the existing literature on nocebo responses reported in relation to COVID-19 safety, factors which might contribute to the same and its implications.

Methods: Concerns on the safety of the COVID-19 vaccines contributed by various sources including social and mass media, and other members in the public have contributed to the significant minority of people who were hesitant to receive the vaccine.^{3,4} Here lies the importance of appropriate modes and process of risk communication. Nocebo responses observed by COVID-19 vaccine recipients by virtue of expectations on the potential adverse effects might have had an impact of public's decision on receiving the vaccine. In a systematic review carried out by Amazio et al, rates of solicited adverse events in the active and placebo groups of SARS-CoV-2 vaccines were compared.⁵ It was reported that a substantial proportion of solicited AEs are not a result of the vaccine per se but are, in fact, nocebo effects. A meta-analysis was performed to evaluate the frequency and magnitude of nocebo responses in COVID-19 vaccine trials based on the data from four RCTs with a total of 119,110 participants. The frequency and magnitude of nocebo responses were 16.4% and 0.3%, respectively.⁶

Results: It is important to understand the factors which contribute to the nocebo responses noticed by the recipients of the COVID-19 vaccines. Methods to prevent or tackle these responses should be identified and discussed to reduce the vaccine hesitancy. For the present and future vaccination campaigns, there should be prevention strategies for nocebo effects to promote a possible greater adherence to the vaccination campaign. Raising awareness of nocebo effects by media and health care professionals and positive framing of the side effect information can help to reduce nocebo effects.⁵

Conclusion: The role and responsibilities of various stake holders including patients, patient organisations, health professionals, media, pharmaceutical companies and regulatory agencies in this regard should be identified and delineated. Risk communication strategies should be tailored to the need of the situation and focused on avoiding any negative impact.

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PharmaCovigilance: Role of the Pharmacist During COVID-19 Vaccination Campaign

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Introduction: COVID-19 vaccination campaign at Pederzoli Hospital (Veneto, Italy) started in January 2021 using the two approved mRNA vaccines. The vaccination schedule included 2 doses and one booster.

Objective: The Pharmacy unit created a digital form in order to collect information on the incidence of the adverse events after the anti-covid vaccination.

Methods: The Pharmacy Unit created a simplified digital form including a set of questions about the occurrence of adverse events. To improve the adherence to this pharmacovigilance program, the digital form was uploaded on the hospital website and all the employees received a remainder about this vaccine adverse event reporting system via e-mail regularly. The data collected from the electronic spreadsheet were analyzed by the Health Department in order to produce a report in the dedicated national website (Vigifarmaco).

Results: From January 2021 to April 2022 1076 employees received the first dose, 965 received the second dose, and 1019 received the third dose. 323 adverse events reporting forms have been collected after the first dose (30% of those who received it). 291 forms (30%) were collected after the second dose. 12 forms (1.2%) were collected after the third dose. The most reported adverse events after the first dose were: local pain (38% of reported adverse events), muscle pain 15%; asthenia 12%, headache 11%. Moreover, 6 employees reported fever above 38.5 °C and 19 employees reported fever between 37.5 °C and 38.5 °C. The most reported adverse events after the second dose were: local pain 19%, muscle pain 18%; asthenia 15%, headache 13%. An employee reported a syncope. In addition, 35 reported fever above 38.5 °C and in 70 fever between 37.5 °C and 38.5 °C. After the third dose, 10 reported headache, 9 local pain, and 8 asthenia and muscle aches. Only 2 employees reported fever above 38.5 °C and 5 fever between 37.5 °C and 38.5 °C.

Conclusion: The active role of the Hospital Pharmacy Unit during the vaccination campaign of the health care workers of our hospital permitted to collect data regarding the side effects of these new vaccines and nonetheless made the health care workers about more aware about the importance of vaccine adverse event reporting system. The use of this digital form supported the pharmacovigilance program creating a useful and “user friendly” tool which may be tailored to new future projects.

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Covid-19 Vaccines and Menstrual Disorders: Reports from Sardinian Regional Centre of Pharmacovigilance

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Introduction: The anti-Covid vaccines approved in Italy are: Comirnaty, Spikevax, Vaxzevria, Janssen, Nuvaxovid. As of March 26th, 2022, 134,361 adverse events following immunization have been collected in the National Pharmacovigilance Database, 69% of them concern women [1]. Regarding the Sardinian region, as of May 12th, 2022, there are 3043 total reports, 63.4% involve women. In July 2021, the French Drug Agency issued an alert about reports concerning menstrual alterations [2]. PRAC, since new studies have been published, recently decided to further investigate [3]. A cohort study conducted in the US comparing cycle length in a vaccinated cohort vs. an unvaccinated cohort, showed a statistically significant difference [4]. A British case-control study found that 20% of the population included reported menstrual changes, with a higher incidence in individuals with a history of Covid infection [5]. A Norwegian study showed similar results [6].

Objective: To describe the adverse events regarding menstrual disorders in the Sardinian population vaccinated against Covid-19.

Methods: We analyzed reports of suspected adverse reactions in the National Pharmacovigilance Database regarding the region of Sardinia, from December 27th, 2020 to April 30th, 2022, we extracted those concerning menstrual cycle alterations after Covid-19 vaccine administration.

Results: A total of 78 reports referring to all three scheduled administrations were collected. The majority concerned Comirnaty, with 56 reports: 51 were non-serious, concerning abnormal menstrual cycles in length and flow, amenorrhea, dysmenorrhea; five cases were considered serious, but there were other adverse events associated (hypersensitivity reactions, autoimmune disorders, myocarditis in one case). Six reports were related to Vaxzevria, with similar manifestations as for Comirnaty; in one case the patient was treated with Tamoxifen. Sixteen cases were reported for Spikevax, with one reporting an episode of bleeding in a three-year menopausal patient. In one case, the patient (IUD carrier) reported menstrual disturbances following all three vaccine administrations (two Comirnaty, one Spikevax).

Conclusion: The different distribution of reports among the vaccines can be explained by the increased administration of Comirnaty in the general population and the phasing out of Vaxzevria. Menstrual

disorders are common and can be related to several conditions, although a link with Covid vaccines is plausible, as highlighted by recent studies [4–6] and as already observed for other vaccines. In particular, the strong immune system response created by mRNA vaccines may affect the hypothalamic-pituitary-ovarian axis, which regulate the menstrual cycle.

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Lessons Learned from COVID19: Enhancing the Discipline of Communications in Pharmacovigilance

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Introduction: Pharmacovigilance (PV) organizations are traditionally structured to address and comply with global regulations. However, PV organizations are well poised to contribute beyond legislation, by sharing insights across communities in a digestible, accessible way.

Examining communication needs following the height of the COVID-19 pandemic may elucidate opportunities for PV to play a more central role in public health, particularly in generating and disseminating timely, credible and accurate communications.

The need for safety to play a larger role in combating vaccine hesitancy is well documented and is fundamental to building trust in patient populations.¹ While previous initiatives have focused on meeting the needs of legislation, research has indicated new approaches that incorporate a listening mechanism for public feedback are needed to provide tailored communications.^{1–2}

PV organizations carry a responsibility to communicate directly to patients, due to their central positioning as a ‘source of truth’ for emerging safety information. The challenge is the level of uncertainty as a product’s benefit/risk profile is characterized over time.

Objective: We aim to identify safety-related communication needs across the healthcare ecosystem and propose an enhanced safety communication framework.

Methods: A three-part approach was taken to design a safety communications framework, addressing internal and external information needs. We performed a literature search to identify trends in PV innovation (2009–2022). Interviews were conducted with the BeiGene Global Patient Safety (GPS) organization to evaluate needs and

communication opportunities within PV. Results were compared with lessons learned from the COVID-19 crisis.

Results: Literature results demonstrated that PV innovation publications increased over the past decade, with a peak in 2015 and marked rise in 2021–2022, spanning numerous concepts. Publications relating to safety communications increased yearly since 2010, with over 300 articles published this year to date.

Results from BeiGene interviews (N = 5) demonstrated the following opportunities: (1) Building awareness and understanding of PV externally, (2) Building networks of relevant stakeholders, (3) Demonstrating transparency with the public, (4) Generating accessible safety communications for patient populations by drawing on the discipline of communications in other industries.

Qualitative research across 19 EU countries demonstrated critical gaps in addressing information needs throughout the pandemic relating to under-resourced public health services and lack of inter-operative health IT systems.³

Conclusion: GPS has implemented a safety communications framework focused on internal and external communications, research and publications and ongoing intelligence monitoring. Its focus is to increase transparency, visibility and understanding of PV, with the aim to establish trust and credibility in healthcare communities.

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Cross-Reactivity between Pfizer/BioNTech and Johnson Vaccines: A Case Report

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Introduction: Polyethylene glycol (PEG) is one of the ingredients in the Pfizer/BioNTech COVID 19 vaccine (mRNA vaccine) and has been known to cause hypersensitivity [1–3]. Polysorbate is an ingredient in the Johnson vaccine (adenovirus vaccine) which may cross-react with PEG.

Objective: We report a case of cross-reactivity between Pfizer/BioNTech and Johnson vaccines.

Methods: This observation was notified in the pharmacovigilance center of Sfax, Tunisia (faculty of medicine of Sfax). The study of drug imputability was carried out according to the WHO method.

Results: We report the case of a 32-year-old Tunisian woman with a history of atopy and intolerance to non-steroidal anti-inflammatory drugs (NSAIDs) but no history of SARS-CoV-2 infection.

On August 15, 2021 (at 08:30), she developed sweating, vomiting and dizziness immediately after receiving the initial dose of Johnson COVID-19 vaccine. Her blood pressure became lower (less than 90/60 mmHg). She had to stay at the vaccination centre for one hour, and the clinical signs improved spontaneously after one hour. In the evening of the same day, the patient presented a febrile maculopapular eruption in the abdomen, trunk, and face. The rash resolved spontaneously over a week. The patient was referred to the pharmacovigilance center of Sfax (Tunisia). The messenger RNA vaccine was advocated for the second vaccine.

On December 2021, she was received the second dose of the Pfizer/BioNTech COVID 19 vaccine (mRNA vaccine). Six hours later, she experienced a pruritic maculopapular rash on the abdomen, trunk, neck, and face. These clinical signs improved spontaneously after two days. the diagnosis of cross-allergy between these two vaccines was retained for this patient

Conclusion: To our knowledge, this is the first cross-allergy between mRNA and adenovirus COVID-19 vaccines notified in Tunisian population. Healthcare professionals should be aware that hypersensitivity can occur with COVID-19 vaccines containing macrogols/PEGs and those containing polysorbates. Its recognition may be challenging and often require skin testing. Per CDC guidance, consultation with an allergist-pharmacologist should be considered to help determine if the patient can safely receive vaccination [4].

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Cerebro-Vascular Accident after Covid-19 Vaccination

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Introduction: Stroke is the second cause of death and a major cause of disability worldwide. Its incidence is increasing related to the increase in the age of the population [1]. Younger people can be affected especially when they have risk factors (hypertension, diabetes, dyslipidemia, smoking or obesity) [2].

Objective: The aim of this study was to describe all the cases of Cerebral Vascular accident that occurred after Covid-19 immunization.

Methods: We conducted a retrospective study involving all cases of cerebral vascular accident that occurred after Covid-19 vaccination, from the beginning of the campaign of immunization in March 2021 to May 2022. These cases were notified to the National Center of Pharmacovigilance, Tunisia.

Results: There were 36 cases of Cerebral Vascular accident over 12 million doses of vaccine. These cases represented 1.2% of all the Adverse Effects following Immunization (AEFI) notified to the pharmacovigilance center.

These cases were notified by attending physicians in 45.6% of cases. The sex ratio M/F was 3.2. The mean age was 73.4 years [51–87 years].

The onset of neurological symptoms ranged between 1 and 34 days with an average of 6,18 days following immunization.

The cerebral vascular accident occurred after the 1st shot in 19 patients and after the 2nd shot for 7 patients. This data was not available for 10 patients.

The involved vaccines were Pfizer/BioNTech (mRNA vaccine) in 63.8% cases, an adenovirus viral vector in 22.2% (AstraZeneca COVID-19 vaccine in 19.4% and Sputnik V in 2.8%), an inactivated Covid 19 vaccine in 11.1% cases (Coronavac 8.3% and Sinopharm 2.7%)

Investigations revealed that 25 patients (69.4%) had at least one cardiovascular risk factors, 11 patients had at least 2 and 6 patients had 3 or more factors.

Four patients had a cerebral vascular accident history. Hypertension was noticed in 15 patients, diabetes in 12 patients, dyslipidemia in 3 patients, cardiac rhythm disorders in 4 patients and a concomitant Covid-19 infection in 2 patients. For the other 11 patients, this data was not provided.

There were no cases of Thrombosis with Thrombocytopenia Syndrome in our survey.

Conclusion: Despite a temporal relationship, the vaccine responsibility cannot be retained given the patient's medical histories and the existence of several risk factors.

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Myocarditis Related to SARS-CoV-2 Vaccines: Comparing Spontaneous Adverse Drug Reaction Reports with Intensive Monitoring of Nationwide Health-Registers in Sweden

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Introduction: In spontaneous reporting, it is normal is to presuppose a more or less pronounced under-reporting to Adverse Drug Reaction (ADR) databases. During 2021, the Swedish Medical Products Agency (MPA) received a record total of more than 100.000 ICSRs on SARS-CoV-2 vaccines. At the same time, MPA implemented a record-linkage study using data from several nation-wide health registers to monitor the safety of said vaccinations [1].

Objective: To estimate the degree of under-reporting of myocarditis to the MPA ADR-database in 2021 through January 2022.

Methods: We compared the number of ICSRs on suspected myocarditis submitted to the MPA with the number of cases of the same condition identified in the Swedish National Patient Register (SNPR).

Dates of vaccination(s) were collected from the National Vaccination Register. A main diagnosis in SNPR within 28 days of any SARS-CoV-2 vaccination was considered an exposed case. This association has been thoroughly studied and established in another study [2].

Cases of myocarditis in the SNPR were incident since 2017; such status in the ICSRs was however unknown.

Results: Until September 2021, the number of submitted ICSRs was less than the number of patients identified in the SNPR. However, the accumulated number of ICSRs surpassed the number of cases in the SNPR in October 2021 and remained higher thereafter.

By the end of follow-up, a suspected myocarditis had been reported in 322 ICSRs, while 254 such cases had been identified in the SNPR.

However, if only ICSRs from health care professionals are considered, the apparent under-reporting prevailed throughout the period: 220 ICSRs v 254 SNPR cases.

Conclusion: This is a special observation where the number of submitted ICSRs exceeds the number of cases in an intensive monitoring of health-care registers.

This can be explained by (1) the case-definition in the SNPR where only admissions within 28 days after a vaccination was considered; this limitation was not applied to the ICSRs; and (2) ICSR of misdiagnosed or only suspected myocarditis.

On October 5, the month during which ICSR reporting surpassed register cases, the Public Health Agency of Sweden declared that individuals under the age of 30 would not be given the Moderna mRNA-1273 vaccine due to the risk for myocarditis.

This was probably a strong motivation for the increased reporting that followed, especially from consumers.

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Bell's Palsy and Covid-19 Vaccination

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Introduction: Bell's palsy incidence varies from 15 to 30 cases/ 100,000 persons/year in general population. Various etiologies are identified such as viral infection, neoplastic or traumatic causes. Otherwise, Bell's palsy has been also reported after vaccines such as influenza vaccine, anti-diphtheria, anti-viral B hepatitis and others. Several cases of Bell's palsy were reported since phase 3 of clinical trials of Covid-19 vaccines.

Objective: The aim of this study was to describe all the cases of Bell's palsy that occurred after Covid-19 immunization.

Methods: We conducted a retrospective study involving all cases of Bell's Palsy that occurred after Covid-19 vaccination, from the beginning of the campaign of immunization in March 2021 to May 2022. These cases were notified to the National Center of Pharmacovigilance of Tunisia.

Results: We collected 13 cases of Bell's palsy over 12 million doses of vaccine. These cases represented 0.4 % of all the Adverse Event following Immunization (AEFI) notified to the National Pharmacovigilance Centre.

The sex ratio M/F was 1.6. The mean age was 49.7 years [29–77 years].

The onset of symptoms following immunization ranged between 1 and 13 days with an average of 6 days. Evolution was favorable in 5 cases and unknown in the other cases.

Bell's palsy occurred after the 1st shot in six patients and after the 2nd shot in 5 patients. This data was not available for 2 patients.

The involved vaccines were mRNA vaccines in 84.6% cases (Pfizer/BioNTech vaccine in 76.9% cases and Spikevax Covid-19 vaccine-Moderna in 7.6%), an adenovirus viral vector in 7.6% (AstraZeneca COVID-19 vaccine), and an inactivated Covid 19 vaccine in 7.6% cases (Corona-vac).

Conclusion: Bell's palsy following Covid-19 vaccination are rare, benign and generally resolve in few days.

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Rates of ADR Reports by Number of Administered SARS-CoV-2 Vaccination Doses in Sweden: Large Temporal Variations Especially in Consumer Reporting

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Introduction: During the SARS-CoV-2 vaccinations in 2021, a record number of Individual Case Safety Reports (ICSR) were submitted to the Swedish Medical Products Agency (MPA).

MPA further initiated a record-linkage study [1] by which vaccination data from the National Vaccination Register (NVR) was made accessible.

Objective: We aimed at identifying temporal variations in reporting rates of ICSRs by number of administered vaccine doses, and if found, seek plausible explanations to them.

Methods: The weekly number of ICSRs submitted to the MPA was divided by the weekly number of administered doses between December 27, 2001, and May 1st, 2022, resulting in the reporting rate per 1,000 doses and week.

Results: A total of 102,798 submitted ICSRs and 21.9 million administered doses resulted in an overall reporting rate of 4.7 ICSRs per 1000 doses, range: 0.9/1000 (April 2022) to 21.3/1000 (March 2021). Eighty-two percent of the reports were submitted by consumers.

A four-fold increase in reporting rate was observed between weeks 5 and 11, 2021. This coincided with the start of vaccination of prioritized health-care personnel and ensuing mass media activity on e.g. whole hospital wards having to close due to the personnel's flu-like symptoms (fever, headache, fatigue, chills, etc.) following vaccination.

On March 16, the Public Health Agency of Sweden decided that only individuals aged 65 or older would receive the Astra Zeneca AZD1222 vaccine. This was followed by a steep seven-fold decline in reporting in three weeks.

Reporting rates from both health-care professionals and consumers increased and decreased in a similar fashion.

During the summer of 2021, additional peaks in reporting rates were observed. At the same time, menstruation disorders following vaccination were debated in both social and traditional media.

The most recent decline in reporting rates, which has yet to turn to an increase, occurred after the Russian invasion of Ukraine in the end of February 2022.

The fluctuating reporting rates observed since April 2021 and onwards were almost exclusively seen in consumer reports.

Conclusion: Rates of submitted spontaneous reports per 1,000 vaccinations in Sweden varied markedly during the studied period, the most pronounced of which originated from changes in consumer reporting.

Many peaks in reporting rates can be—at least temporally—associated to various media or world events, even if a causal relationship can't be proven.

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Fixed Drug Eruption after ChAdOx1 nCoV-19 Vaccine

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Introduction: ChAdOx1 nCoV-19 vaccine is an adenoviral-vectored COVID-19 vaccine. The most common side effects are headache, muscle pain, redness, swelling, and tenderness at the injection site. Cutaneous reactions have been rarely reported.

Objective: To discuss the association between a fixed drug eruption (FDE) and ChAdOx1 nCoV-19 vaccine.

Methods: We report one case of (FDE) following administration of the ChAdOx1 nCoV-19.

Results: A 60-year-old man with no medical history and no regular medication presented with a rash that had appeared 24 hours after he had received his first dose of the ChAdOx1 nCoV-19 vaccine (Oxford–AstraZeneca). The lesions had appeared abruptly without any accompanying symptoms. Physical examination revealed three, well-defined, round to oval, erythematous to violaceous plaques in the face. A punch biopsy was taken, and histopathology findings were consistent with fixed drug eruption.

Conclusion: This case shows that the fixed drug eruption can be a result of receiving the ChAdOx1 nCoV-19 vaccine (Oxford–AstraZeneca).

References/Further Sources of Information

Keywords: fixed drug eruption, COVID-19 vaccine, ChAdOx1 nCoV-19 vaccine (Oxford–AstraZeneca).

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Adverse Reactions Associated with Comirnaty® Among Healthcare Professionals: A Cohort Event Monitoring Study in a Portuguese Hospital

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Introduction: The Portuguese government put into practice a vaccination plan soon after the approval of the first COVID-19 vaccine, prioritizing healthcare professionals (HCPs) and other population groups at risk.

Objective: To characterize the case reports of adverse drug reactions (ADRs) associated with the administration of Comirnaty® to HCPs in a Portuguese oncology hospital (IPO Coimbra).

Methods: This study was a nine-month prospective, observational study following a cohort event monitoring approach focused on signalling ADRs associated with the administration of Comirnaty® to HCP in IPO Coimbra. The case reports of ADRs were sent to the Pharmacovigilance Unit of Coimbra (UFC) between 14/01/2021 and 13/10/2021. The population of HCP was characterized according to gender and age distribution. The seriousness of ADRs was assessed for each individual case in accordance with WHO criteria [1]. ADRs were coded with MedDRA® version 24.0 (System Organ Classification [SOC] and Preferred Term [PT]). ADRs were classified as “expected” or “unexpected” according to their description in the Summary of Product Characteristics (SmPC) of Comirnaty® [2].

Results: A total of 816 HCPs were inoculated with at least one dose of Comirnaty®. The case reports of ADRs concerned 469 (57.5%) HCPs: 386 (82.3%) females; 642 (78.7%) aged 30-59 years old. Of the 469 case reports, 24 (5%) were assessed as serious, 44 (9.4%) as unexpected, and 11 (2.3%) as both serious and unexpected. The 469

case reports contained a total of 1,955 ADRs. “General disorders and administration site condition” (n = 1,075; 54.9%), such as vaccination site pain, chills and vaccination site swelling; “Musculoskeletal and connective tissue disorders” (n = 373; 19.1%), including myalgia and arthralgia; and “Nervous system disorders” (n = 250; 12.8%), including headache, were the most frequently reported ADRs, which is in line with the SmPC of Comirnaty®. The 11 case reports classified as both serious and unexpected contained a total of 17 ADRs, including hyperhidrosis and paraesthesia.

Conclusion: The results of this study bring value to the characterization of the safety profile of Comirnaty® since the use of a cohort of individuals allows to estimate frequencies of ADRs in the real-world. Further, serious, and unexpected ADRs were identified. Importantly, this type of safety data was further included in the SmPC of the vaccine. In conclusion, the results are in favour of the positive benefit-risk ratio of Comirnaty®, and reinforce the importance of post-marketing pharmacovigilance to increase knowledge on drug safety.

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The Impact of the COVID-19 Pandemic on Spontaneous Reporting of Adverse Drug Reactions in the Central Region of Portugal

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Introduction: The COVID-19 pandemic has had an impact on several sectors of the society. Whether it has disrupted drug safety monitoring is yet to be determined.

Objective: To investigate whether the COVID-19 pandemic has had an impact on the proportions of spontaneous reports (SRs) of serious and unexpected adverse drug reactions (ADRs).

Methods: SRs received by the Coimbra Pharmacovigilance Unit (UFC) between January 2017 and December 2021 were included, except for those containing COVID-19 vaccines as suspected medicines. The SRs were categorized into two groups: pre-pandemic (2017–2019); and post-pandemic (2020–2021). The SRs were classified as serious or non-serious, and expected or unexpected, depending on the seriousness and expectedness of the suspected ADRs, according to the WHO criteria and the Summary of Product Characteristics [SmPC] of each suspected medicine, respectively [1,2]. To study the impact of the COVID-19 pandemic on the patterns of spontaneous reporting of suspected ADRs, two null hypotheses were proposed to test whether (i) the seriousness, and (ii) the expectedness were independent of the pandemic (i.e., if the pandemic has had no impact, then the proportions of SRs containing (i) serious and (ii) unexpected ADRs were expected to be the same in both periods). The qui-square test was used to test the hypotheses; p-values < 0.001 were considered statistically significant. Microsoft Excel® was used for the statistical analyses.

Results: A total of 1,311 and 657 SRs were received in the pre-pandemic and post-pandemic periods, respectively. Of the 1,311 SRs received in the three pre-pandemic years, 1,012 (77%) were serious and 657 (13%) contained unexpected ADRs; of the 657 SR received during the two post-pandemic years, 434 (66%) were serious and 133 (20%) contained unexpected ADRs. The changes from pre- to post-pandemic on both proportions of SRs containing serious (an absolute decrease of 11%; p = 0.01) or unexpected ADRs (an absolute increase of 7%; p = 0.01) were not statistically significant.

Conclusion: The COVID-19 pandemic has had not a significant impact on the proportions of SRs of serious or unexpected ADRs in the Central Region of Portugal. Further research should be carried out in other pharmacovigilance databases to understand if the present conclusions are applicable to other geographic regions.

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Acute Angle Closure Glaucoma Following COVID-19 Vaccination

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Introduction: Although vaccines against COVID-19 are strongly recommended as safe and effective at alleviating the morbidity and mortality, different types of ocular complications have been reported after COVID-19 vaccination, including oculomotor nerve palsy, episcleritis, anterior uveitis, multifocal choroiditis, reactivation of Vogt-Koyanagi-Harada disease, acute macular neuroretinopathy and central serous retinopathy(1).Acute angle closure glaucoma (AACG) is an ophthalmic emergency that can be drug induced. If not promptly identified and treated, it can cause irreversible blindness.

Objective: To describe an exceptional case of bilateral AACG that occurred within 4 hours following COVID-19 vaccination.

Methods: This case was notified to the pharmacovigilance department in February 2022.

Results: A 38-year-old woman with a history of high myopia experienced stabbing pain in her left eye 4 hours after she received the second recombinant mRNA vaccine (Pfizer)injection. Few hours later, periorbital headache appeared in left side and the eye pain became much more severe. She took paracetamol by self-medication and stayed in the darkness. The following morning, she complained of sudden loss of vision in both eyes. She consulted an ophthalmologist, where elevated intraocular pressure (IOP) was noted in her left eye (60mm of mercury). Visual acuity examination showed results of 0.5 and 0.3 for right and left eyes, respectively. Goldman visual field test revealed a nasal field defect in her left eye. The angles of both eyes were closed on optical coherence tomography. Anterior segment examination demonstrated areflexic mydriasis. The patient was diagnosed with bilateral AACG. Topical instillation of pilocarpine was provided and the IOP decreased to 45 mm Hg in left eye. Then, the patient was prescribed systemic acetazolamide, and a fixed combination of bimatoprost-timolol. On follow-up after 24 hours,

IOP improved to 19, 5 mm Hg in left eye and 11 mm Hg in right eye, however, the decreased vision persisted. Bilateral peripheral iridotomy was performed 10 days later. Two months after onset, the visual acuity was completely restored but the areflexic mydriasis was permanent. There was no recurrence of her glaucoma during a 3-month follow-up period.

Conclusion: To the best of our knowledge, this is the first case to describe AACG following COVID-19 vaccination. The onset of ocular symptoms suggests a possible correlation between this complication and COVID-19 vaccination. However, the presence of other risk factors mainly high myopia puts this cause and effect relationship into question.

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Do Patients with SARS-CoV-2 Vaccine-Induced Chronic Urticaria Can Have Their Second Dose?

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Introduction: Adverse skin reactions, either immediate or delayed, were reported following COVID-19 vaccines [1]. Chronic spontaneous urticaria (CSU), a persisting urticaria beyond six weeks, has been rarely reported. These skin conditions present the challenge of the possibility of taking or not of the second dose and also its nature.

Objective: To report cases of CSU after receiving vaccination against SARS-CoV-2 and the outcome after taking their second dose.

Methods: We performed a research on the database of the pharmacovigilance center from March 2021 to March 2022 using the keywords: urticaria, covid vaccine. The inclusion criteria were

- persisting urticaria beyond six weeks after immunization
- no urticaria prior the immunization during at least one month
- second dose taken

Non inclusion criteria were:

- CSU not related to the vaccine

Results: We retained three cases of CSU following COVID19 vaccine with second dose. There were two women and one man. Their age varied from 24 to 48 years. Two patients had chronic disease: one presented dysthyroidism, and the other presented asthma. The delay of occurrence of CSU varied from few hours to five days. The CSU in the three cases was not associated with other symptoms such as angioedema or dyspnea. In the three cases, the use of antihistamine drugs was only effective in reducing pruritus without complete release of urticaria. Follow up of the patients showed that they had their second dose after a period that varied between one and six months. They took their second dose while they continue to present urticaria. In the three patients, there was no exacerbation or specific complications.

Conclusion: Our study showed that the administration of the second dose in patients that developed CSU after the previous vaccine can be

considered safe and is advisable. Most of cases of exacerbation or worsening of CSU reported in the literature appear to be transient and can be managed by antihistamine therapies [2].

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Establishing Patient Safety Monitoring in the Benefit-Risk Paradigm for Off-Label and Emergency Use of Medications for COVID-19: A Pharmacovigilance Perspective

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Introduction: With the massive widespread impact of COVID-19 [1, 2], before the accelerated development timelines for vaccines, one of the options to help mitigate disease impact was in repurposing already approved drugs [3–6]. In the race to discover/implement an already approved agent, which may also be effective in treating COVID-19, we have learned lessons to form a pharmacovigilance perspective that is central to the conscientious approach one is required to employ to ensure patient safety and continued assessment. This work was written under the umbrella of NASoP and represents learnings/recommendations for safety monitoring relating to off-label use in future pandemics or other emergency scenarios after an appropriate benefit-risk assessment, it does not represent an official view of our respective companies/institutions.

Objective: Within the lens of optimizing pharmacovigilance through both the planning and the implementation phases of drug repurposing, we outline a strategy and provide suggestions to ensure optimal drug rollout and patient safety.

Methods: An international, multi-institutional expert panel provides a review of lessons learned through a descriptive narrative.

Results: All drug repurposing should be pursued through a systems approach insuring institutional/regional collaboration, innovation, and data-driven decision making. The roll-out of any repurposed drug should occur in two phases: the planning and implementation. Institutional responses in drug repurposing requires identification of key stakeholders, establishment of local expert working groups tasked with continuous assessment and critical review of emerging literature. The off-label use is at the discretion of the healthcare provider, in collaboration with institutional/regional authorities after an appropriate benefit-risk assessment, and we are not recommending or promoting off-label use. A shared decision making strategy is central to ensure patient involvement and understanding of not just the available evidence, but the rationale and acceptance of the repurposed drug. Pharmacovigilance plays a crucial role in the expedient evaluation of new uses for existing therapies and can rely on already established institutional monitoring modalities. A close institutional partnership with regional/national drug regulatory agencies, healthcare professionals, and pharmaceutical companies allows for a wider breadth of information and experience dissemination for the purposes of patient safety and continuation of a drug's repurposed indication.

Conclusion: As more data emerges during the COVID-19 pandemic, one can presume other medications for off-label use in COVID-19 will have been identified. Therefore, it is important that increased attention and awareness is created regarding drug safety and the potential harm these medications may have on an individual and reaffirm the critical role of pharmacovigilance expertise.

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Active Pharmacovigilance in COVID-19 Patients: The Role of a Clinical Pharmacist in the Reporting of Adverse Drug Events

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Introduction: Like many countries in the world, the first wave of the COVID-19 (Coronavirus Disease 2019) pandemic in Morocco was marked by an overload of infected patients and unprecedented challenges. This, combined with the unknown nature of the disease, has compelled clinicians to prescribe a wide range of medicines, including experimental drugs as well as symptomatic therapies. These practices were associated with an increase in the incidence of adverse drug events (ADEs), which were reported to be higher in the COVID-19 population [1]. Among front-line health workers, pharmacists were assigned various roles such as active and passive pharmacovigilance in order to ensure the safe use of drugs [2]. This was the case of our hospital, where some pharmacists participate in medical rounds to provide pharmaceutical care near patients.

Objective: To demonstrate the importance of a clinical pharmacist in the reporting of ADEs in hospitalized COVID-19 patients.

Methods: An observational study was conducted between September 2020 and January 2021 at a university hospital in Rabat. Only one of

five COVID-19 units had a pharmacist as a full time member of the medical team. The notification of ADEs are made on a sheet designed by the National Pharmacovigilance Center. After assessing the collected ADE's, the pharmacist compared them to all ADE's that were reported from other COVID-19 units during the study period. Data were subsequently analyzed using Excel.

Results: A total of 42 ADEs in 35 patients were notified by the pharmacist (population size = 120). Experimental drugs used for the viral treatment (hydroxychloroquine and azithromycin) were the most commonly recorded medications with ADEs (30%), 27% were anti-coagulants and 13,5% were corticosteroids. Regarding ADEs, 26% consisted of QT interval prolongation, followed by hyperkalemia (26%), hyperglycemia (19%), bleeding (7%), and hepatic cytolysis (5%). In comparison, only 3 ADEs were notified from other COVID-19 units of the hospital.

Conclusion: Results of our study suggests that the presence of a pharmacist in a multidisciplinary team is crucial to enhance patient care and safety, particularly in these times of crisis. Our study has also shed light on the poor reporting rate of ADEs in the hospitalized patients, which was previously mentioned to be common in the developing world [3]. Strategies to improve the pharmacovigilance system in Morocco are needed to better prepare healthcare structures for future epidemics.

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Urticaria Reactions after COVID-19 Vaccination: A Case Series

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Introduction: COVID 19 vaccines are considered as an important medical advance in healthcare. It is the most promising approach for curbing the COVID-19 pandemic. However, as the number of people receiving vaccination rises, we are inevitably faced with increasing adverse drug reactions. The most common adverse reactions to vaccines are non-allergic, as flu like-symptoms and injection site reactions. Immediate hypersensitivity reactions are fortunately rare [1,2].

Objective: The aim of our work was to study clinical characteristics of acute urticaria following COVID-19 vaccines reported to the Tunisian National Center of Pharmacovigilance.

Methods: We conducted a retrospective study involving all cases of acute urticaria related to COVID-19 vaccines since the onset of the vaccine campaign in March 2021 to May 2022.

Results: This study included 70 patients. Age ranged from 15 to 77 years old with a median age of 26 years. There were 51 women, and the sex ratio M/F was 0.37.

The onset of urticaria varied from few hours to 17 days following vaccine injection with an average delay of 4 days.

In 56 cases, urticaria occurred following 1st shot, in 10 cases following the 2nd dose and one case was reported following the 3rd dose of vaccine. This data was not mentioned in 3 cases.

Outcome was favorable in 57 cases and unknown in 13 cases.

Involved vaccines were Pfizer/BioNTech (47.14%), SPIKEVAX COVID-19 Vaccine Moderna (20%), AstraZeneca COVID-19 vaccine (15.71%), COVID-19 Vaccine Janssen (11.42%), CORONAVAC SINOVAR COVID-19 VACCINE (2.85%) and Sputnik V (2.85%).

Urticaria was isolated in 58 cases, was associated with angioedema in 7 cases, and with fever in 5 cases.

Conclusion: Our work showed a very low number of cases of acute urticaria following Covid-19 immunization. The Center for Disease Control and Prevention recommend, in patients who had even within 4 hours of getting vaccinated a non-severe allergic reaction to COVID-19 Vaccine to receive another dose of the same vaccine under medical surveillance. This is suggesting a non-specific mechanism.

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Dermatomyositis Following Pfizer BioNTech Covid-19 Vaccination

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Introduction: Dermatomyositis is an idiopathic autoimmune connective tissue disease. It is typically characterized by proximal muscle weakness and skin rashes. Dermatomyositis is associated with a higher risk of malignancy compared to the general population (1). One case in literature has reported a dermatomyositis post COVID-19 vaccination (2).

Objective: Case report.

Methods: We report a case of dermatomyositis following Covid-19 immunization, notified to the National Centre of Pharmacovigilance of Tunis in May 2021.

Results: A 33 year old woman, with no significant past medical history. She developed in March 2021, two days after 1st dose Pfizer BioNTech Covid-19 vaccination, a mild facial erythema and ipsilateral auxiliary adenopathy. The evolution was marked by a persistence of the erythema and a regression of the adenopathy.

In April 2021, 2 days following the 2nd dose, she presented an accentuation of the symptomatology: skin erythema and edema in the photo-exposed areas: face, neck and upper limbs. As well as a diffuse

myalgia in upper and lower limbs. She was afebrile and didn't present itchiness.

The patient received intravenous methylprednisolone 1 injection per day for 5 days, followed by 1 mg/kg prednisolone and anti histaminic drugs without amelioration.

The diagnosis of dermatomyositis was suspected in view of the persistence of the symptoms 1 month after vaccination and the installation of a proximal muscular deficit.

Laboratory studies revealed a high level of creatine phosphokinase (CPK) at 3800 UI/l (< 140) and Lactate dehydrogenase (LDH) at 628 UI/l (< 248).

The skin biopsy showed an aspect consistent with a moderate inflammatory myopathy.

Autoimmune serology revealed the presence of anti-nuclear antibodies (ANA) (1/100) and a positive anti-Mi-2 antibodies.

The patient underwent thorough malignancy screening. Findings of cervico-thoraco-abdomen pelvic scan didn't reveal any evidence for solid organ malignancies or interstitial lung disease. However, the mammogram and ultrasound-guided biopsy has identified an invasive carcinoma.

Conclusion: This case showed a dermatomyositis case suspected initially to be associated to mRNA COVID vaccination which was finally related to a breast cancer.

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Investigating a Signal of Acquired Haemophilia Associated with COVID-19 Vaccination: A Systematic Case Review

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Introduction: Acquired haemophilia A (AHA) is a rare, haematological disorder characterized by the development of autoantibodies to Anti-Factor VIII (FVIII), which can cause spontaneous hemorrhage¹. During 2021, some authors reported an unusual and unexpected number of AHA diagnoses that were temporally related to COVID-19 vaccination^{2,3}.

Objective: To explore a possible signal of risk of AHA associated with COVID-19 immunization.

Methods: We performed a disproportionality analysis on the World Health Organization (WHO) database (VigiBase[®]) to investigate the presence of a signal of risk for AHA associated with COVID-19

vaccines. We calculated the information component (IC) for all the COVID-19 vaccines and for single COVID-19 vaccine product using the entire database as reference. Reports of AHA have been systematically reviewed all the selected cases to check for clinical plausibility

Results: In Vigibase, we identified 150 cases of suspected AHA associated with COVID-19 vaccines (146 included the PT “acquired haemophilia”). Only three vaccine products have been reported as suspected causative agents for AHA. The disproportionality analysis showed a significant IC for the Preferred term “Acquired haemophilia” associated with all COVID-19 vaccines (IC: 1.3; IC025: 1.1) and with the vaccine product BNT162b2 (IC: 1.9; IC025: 1.6). After the integration with data available on VAERS and on the medical literature, and after the elimination of duplicates, 96 unique cases of AHA following COVID-19 vaccines (mostly mRNA vaccines) have been reviewed. Overall, about 22% of cases occurred in patients ≤ 65 and no case associated with pregnancy was reported. Patients with at least one pre-existing condition that can be considered a risk factor for AHA (history of AHA, cancer, autoimmune disorder) were 20 (21%). A pre-existing condition predisposing to AHA was excluded in 57 (59%) of cases and not reported in 19 (20%) cases. The outcome was death in 10 (11%) patients and complete resolution or recovering in 39 (41%) patients with a single resolution without specific AHA treatment. Median time from last vaccine dose to diagnosis was 18 days and 40% of cases documented the occurrence after the second dose.

Conclusion: Our disproportionality analysis confirmed a reporting risk for AHA associated with COVID-19 vaccines. The case review analysis identified several good-quality reports of AHA for which no alternative causes other than COVID-19 immunization can be considered. Although detection bias should be considered to explain the unexpected frequency of AHA in the population, the signal identified is robust and deserves further investigation.

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COVID-19 Vaccines and Thromboembolic Events with Thrombocytopenia: Data from Italian Pharmacovigilance Public Database

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Introduction: During large-scale vaccination campaign against COVID-19, the Italian Medicines Agency (AIFA) in collaboration with the Regional Centres of Pharmacovigilance have carried out a closely monitoring of Individual Case Safety Reports (ICSRs) about Adverse Event Following Immunisation (AEFIs) related to COVID-19 vaccines and have assured a constant communication through public monthly reports¹. During the first months of the vaccination campaign, a signal of rare events of thrombosis associated with thrombocytopenia², particularly in young women, was detected by health authorities associated with the viral vector vaccines ChAdOx1-S and Ad26.COV2-S.

Objective: To present a comprehensive assessment of thrombotic and thromboembolic events associated with thrombocytopenia following COVID-19 immunisation with viral vector vaccines recorded in the Italian National Pharmacovigilance Network database

Methods: We selected all ICSR reported from 27 December 2020 to 26 December 2021 containing Preferred Terms (PT) related to platelet count reduction associated with PT related to thrombotic and thromboembolic events (clinical symptoms and/or diagnostic tests). All cases of thrombotic and thromboembolic events reporting thrombocytopenia in the narrative description of the report were also reviewed. The selected ICSR were submitted to the independent evaluation of three pharmacovigilance experts who blindly classified into 5 levels of diagnostic certainty, according to the definition provided by the Brighton Collaboration Group (BCG)³. Disagreement were resolved by plenary discussion.

Results: 12,166,236 doses of ChAdOx1-S and 1,500,746 of Ad26.COV2-S have been administered in Italy during the considered interval with overall 23,358/117,947 ICSR related to ChAdOx1-S (19.8 %) and 1,580/117,947 related to Ad26.COV2-S (1.3 %). A total of 134 reports after vaccination with adenoviral vaccines were identified according to the inclusion criteria, of which 107 cases were defined as thrombotic thrombocytopenia (95 following ChAdOx1-S and 12 after Ad26.COV2-S). 27 reports were defined as “not case” (level 5, Brighton) on the basis of clinical examination or investigation, or because of the presence of heparin as a concomitant drug. Furthermore, 3 reports were excluded because of a hereditary thrombophilia or a previous history of other thrombotic episodes. Seventy-seven cases were classifiable as BCG levels 1, 2, and 3 (definite, probable and possible cases, respectively) with an overall reporting rate at about 1 case per approximately 200,000 doses administered. Women aged 30 to 49 years showed the highest reporting rates.

Conclusion: In Italy, the rates of thrombotic thrombocytopenia following COVID-19 immunisation with viral vector vaccines are in line with those reported in other Countries.

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Leveraging Free-Text Information to Detect Duplicates in COVID-19 Vaccine Adverse Event Reports

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Introduction: Uppsala Monitoring Centre (UMC) manage VigiBase; the largest global database of reports of suspected adverse events (side effects) to medicines, on behalf of the World Health Organisation (WHO). Following the emergency rollout of the vaccines against COVID-19, combined with a global focus on monitoring their safety, UMC saw a sharp increase in the volume of reports of suspected side effects of the vaccines.

UMC sometimes receives multiple reports corresponding to the same suspected adverse event. This can have undesirable effects when it comes to both statistical signal detection and manual review of cases. Duplicate detection of vaccines has historically been especially challenging, due to homogeneity of patients. However, the extreme quantity of COVID-19 vaccine reports has highlighted the necessity for automated duplicate detection to be performant for them.

Detecting duplicate reports is a non-trivial problem. Since reports do not always contain the same level of detail, and data errors can lead to different values in corresponding fields for duplicate reports, reports cannot simply be compared field by field. Several methods have been proposed for detecting duplicates based on information provided in structured form (sex, age, date of onset etc) (1,2). In our study we additionally incorporate free text information into a duplicate detection model.

Objective: To leverage the free text information in suspected adverse event reports to identify duplicate reports which are referring to the same adverse event.

Methods: Our method ensembles state-of-the-art machine learning methods. Narratives are placed in a space where a smaller distance between two narratives conveys higher semantic similarity. This is done with vector embeddings using the SapBERT model, fine-tuned on a set of known duplicate reports (3). Two reports are then compared using the cosine similarity between the vector embeddings for the two narratives. This similarity is combined with representations of the structured information used in other methods in a gradient boosted decision tree model, calibrated by a logistic regression model to fine tune the probability output (4).

These methods are evaluated on a set of curated datasets of COVID-19 vaccine reports comprising 1239 pairs of known duplicates. We use random pairs of COVID-19 vaccine reports as examples of non-duplicates.

Results: Our model successfully identifies 78.9% of known duplicate pairs. It achieved a false positive rate (the number of non-duplicates erroneously marked as duplicates) of 0.001%. The full results can be seen in table 1.

	All Data (including random reports)	
Duplicate	977	262
Non-Duplicate	3	366015
	Predicted Duplicate	Predicted Non-Duplicate

Conclusion: Not Applicable.

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Enhanced Surveillance of Italian Vaccinovigilance Group During COVID-19 Pandemic

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Introduction: The vaccinovigilance Italian group was established since 2014 (1), with members from AIFA, Italian National Institute of Health (ISS), Ministry of Health (MH), Pharmacovigilance Regional Centers (PVRC) and Regional Prevention (RP). Signal detection of vaccines, annual reports on vaccine surveillance and supporting documents for pharmacovigilance activity are the main core of the group activities (2). During pandemic, enhanced surveillance was conducted to better characterize safety profile of the new anti-COVID-19 vaccines.

Objective: We reported the enhanced surveillance for anti-COVID-19 vaccines, managed by the AIFA in collaboration with ISS, MH, PVRC and RP.

Methods: Actions implemented for the enhanced surveillance: daily control of the RNF and follow-up requests, periodic publication of reports, interactive graphs on web site updated monthly, meetings of signal detection for anti-COVID-19 vaccines on a monthly basis.

Results: From the first month of the vaccination campaign (27/12/2020-26/01/2021) a report on the course of safety surveillance was made publicly available (3). Until 26/09/2022 the report was published on a monthly basis, then, considering the downward trend in report submission and the greater knowledge of the vaccine safety profile, we moved to a quarterly frequency. The 10th report is referred to an observation period of one year from the start of the vaccination campaign with 117.920 reports submitted to RNF and 108.530.987 administered doses. In this annual report, there are specific focuses

developed with the contribution of the regions, tailored on reproductive health, pediatric population and adverse events of special interest such as anaphylaxis, Guillain Barré syndrome, myocarditis/pericarditis, Bell paralysis and thrombosis with thrombocytopenia syndrome. The report was presented in live streaming on the AIFA YouTube channel. Regarding the signal detection within the group, it was performed monthly since September 2021; the work was distributed among regions on the basis of vaccines and MedDRA System Organ Class (SOC). As a result of the analysis two signals were validated by AIFA. The signal CLS-Elasomeran was confirmed by the lead member state and determined the update of the Product Information (4).

Conclusion: Despite the high number of reports, coordination with the territory and continuous and enhanced surveillance, supported by an integrated group with different expertise (epidemiologist, pharmacist, medical doctors), have proved to be effective in safety monitoring of COVID vaccines.

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Pharmacovigilance Contribution During National Mass Immunization Days

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Introduction: Rapid vaccination rollout against COVID-19 is the current main solution to overcome the pandemic morbidity and mortality but also to restart economies [1]. In Tunisia, 8 mass vaccination days have reinforced the national strategy. During these days, pharmacovigilance provided a real time monitoring regarding therapeutic advices and Adverse Events Following Immunizations (AEFIs).

Objective: The objective of this study is to describe pharmacovigilance activities during these days.

Methods: This is a descriptive study. The reporting system was a combination of both passive and active surveillance. Notifications concerned therapeutic advices and adverse events following immunization (AEFI).

Results: We collected 855 reports among 3,423,884 vaccinated people during these 08-mass vaccination days, corresponding to an average of 25 reports per 100,000 administrated doses. Reports of 720 AEFI's were collected: 268 (37.2%) were collected from the passive monitoring and 313 (43.4%) from the active surveillance.

The passive surveillance reported 80% of vasovagal reaction, 19,3% vaccine errors and others notifications concerned cutaneous eruption, face swelling...

Vaccine errors (139) which occurred in 63.1% of cases during the 3rd National immunization day, concerned dilution errors, a double dose administration or errors in the vaccination pattern.

AEFIs active monitoring revealed vasovagal reactions in 96.8% of cases, an elevated blood pressure, cutaneous eruption...

The Pharmacovigilance team managed 135 therapeutic advices concerning history of drug reaction, previous vaccine reaction, comorbidities...

Conclusion: The specificity of these immunization days was the increase of vasovagal cases and vaccination errors. Therefore, health authorities should deploy necessary means to prevent avoidable AEFIs during mass vaccination days.

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The Italian Approach to Improve Standard Quality of ICSRs for COVID 19 Vaccines: From Patient Data to Causality Assessment

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Introduction: The COVID-19 pandemic determined a necessary reorganization of pharmacovigilance resources and strategies, particularly after vaccines authorization. Enhanced monitoring and quality of ICSRs is crucial for the causality assessment of the adverse events following immunization (AEFI) occurred in the COVID-19 vaccinated population [1].

Objective: To evaluate the effectiveness of enhanced Italian Pharmacovigilance activities during the first year of COVID-19 vaccination campaign on the quality of the ICSRs.

Methods: The Italian Pharmacovigilance System is a network connecting the Italian Medicine Agency (AIFA) to local health authorities [2]. The collected ICSRs were prioritized by seriousness, special interest and disproportionality and harmonized for coding and key information requirements. Further follow up information were requested to reporters from Local/Regional PhV Representatives or AIFA. Targeted templates tailored on Brighton Collaboration Group case definitions were implemented for adverse events of special interest (AESI) [3]. The percentage of completed ICSRs by fields and the rate of evaluable causality assessments by WHO causality assessment tool for AEFI [4] were used as indicators for descriptive analysis of effectiveness. Completeness of ICSRs was evaluated for the following AESI: anaphylaxis, Guillain-Barré syndrome, peripheral facial palsy, vaccine-induced thrombotic thrombocytopenia, myocarditis and pericarditis.

Results: Between 26 December 2020 and 26 December 2021, 117,920 ICSRs were reported (98,717 not serious and 19,055 serious). Overall, patients' demographic field were updated in 35% of ICSRs,

with a total of 97,6% of cases with valid age and sex data. Suspected medicinal products section was modified in 11% of ICSRs with 91% of cases reporting batch number and administration date. Follow up was obtained in 26% of ICSRs (7% after AIFA request). Available information on seriousness and outcome was reported in 97,6% of cases. Time-to-onset was assessable in 95,2% of cases. Overall, causality assessment was applicable in 15.731/19055 (83%) of serious reports, only 751/15.731 (4,8%) of which was unclassifiable. Follow up information was not obtained in 831/3887 cases related to selected AESI (21%). Complete clinical data were available in the remaining 3056/3887 ICSRs (79%) and were used for BCG classification as cases (38%) or not cases (62%).

Conclusion: A harmonized approach to ICSR enhanced surveillance and management through a structured Pharmacovigilance network was effective in improving the quality of AEFI reports related to COVID-19 vaccines, resulting in a high percentage of cases with complete information.

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COVID-19 Vaccination and Herpes Zoster/ Herpes Simplex Reactivation in Tthe Elderly Population: A Pharmacovigilance Analysis

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Introduction: After the primary infection, the reactivation of both Herpes Simplex viruses (HSV) and Varicella Zoster virus (VZV) is mainly triggered by a secondary immunodeficiency state, either age-related or iatrogenic, or due to concomitant diseases (e.g., HIV, cancer), especially in the elderly population [1–3]. Indeed, Herpes reactivation has not been commonly associated with immunization and only few cases are described in literature [4]. To date, HSV/VZV reactivation is listed in the Summary of Product Characteristics (SPC) of only one COVID-19 mRNA vaccine [5]. However, even if limited, evidence on a potential correlation between vaccines expressing the SARS-CoV-2 spike (S) glycoprotein and Herpes reactivation is increasing [6]. In Italy, elderly patients represent a population of particular interest for this specific adverse event (AE) since they are currently involved in the 4th booster campaign (which may not be the last one).

Objective: To investigate the occurrence of Herpes reactivation following COVID-19 vaccination of elderly patients (≥ 65 years old) who are going to be frequently vaccinated with this type of vaccines.

Methods: We present Individual Case Safety Reports (ICSRs) concerning COVID-19 vaccination and Herpes reactivation that were collected at our Pharmacovigilance Unit (Milan, Italy) from January 2021.

Results: So far, 21 ICSRs have been collected, 16 (76%) from ordinary citizens, mainly men (62%) and non-serious. Median age was 74 years (min-max: 65–89). Further analyses are ongoing.

Conclusion: Cases of interest were of non-serious nature and the estimated incidence of pharmacovigilance reports concerning Herpes reactivation was non-significant compared to the total number of Italian citizens who usually suffer from these conditions and to those who have been vaccinated. The vaccination remains strongly recommended. However, it is crucial that clinicians continue to monitor and report all suspected AEs in order to better characterize the safety profile of vaccines.

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Menstrual Changes Following COVID-19 Vaccination: A Pharmacovigilance Study Based on Spontaneous Reports of Adverse Events Following Immunization (AEFI)

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Introduction: Vaccination remains the best option for the prevention and control of SARS-CoV2 infection, and a key topic of interest is its safety. Although many studies reported vaccine-related side effects, ranging from mild symptoms such as injection site pain, fever, headache, and fatigue to rare and serious side effects like anaphylaxis and thrombosis, their safety profile is overall acceptable [1;2].

Recently, given the increase of spontaneous reports of menstrual disorders with mRNA COVID-19 vaccines and sporadic observational studies from the scientific literature, the European Medicine Agency's Pharmacovigilance Risk Assessment Committee (PRAC) has decided to assess the causal link between these vaccines and menstrual changes [3].

Objective: To describe the occurrence of menstrual changes following the COVID-19 vaccination.

Methods: We collected Adverse Events Following Immunization (AEFI) related to menstrual changes after the COVID-19 vaccination received up until April 30th, 2022, at the Pharmacovigilance Unit of the Fatebenefratelli-Sacco Hospital and have performed a descriptive analysis.

Results: A total of 14 AEFI reporting menstrual changes following COVID-19 vaccines were analyzed. All patients were female, with a mean age of 26.5 years. Most cases were referred to the Comirnaty vaccine (85.7%), whereas 14.3% of cases were attributed to Spikevax. The most commonly reported events were amenorrhea and menstrual cycle abnormal, and 78.6% of cases were defined as nonserious.

Conclusion: The relationship between the occurrence of menstrual changes and COVID-19 vaccines has not been fully characterized yet. Our analysis provides additional evidence to the issue. Continuous monitoring of these events plays a key role in better characterizing the safety profile of COVID-19 vaccines.

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Risk Management Strategy to Promote the Uptake of COVID-19 Vaccination at a Tertiary Care Facility in Kenya

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Introduction: An essential component of risk management strategy is effective risk communication, which includes range of communication capacities required to manage serious public health events from preparedness, response to recovery phase. Risk communication became even more vital in COVID 19 global health crisis and utilized in European countries in roll out of COVID vaccines, especially since vaccinations are not mandatory therefore public willingness must be high to achieve herd immunity in the population (1). Taking note of the unique authorization of pandemic vaccines, it implies that only

limited safety and immunogenicity data is available when post marketing phase commences (2).

Objective: To describe a hospital initiative to promote COVID 19 vaccine uptake through safety monitoring and educational campaigns

Methods: We reviewed all Adverse Events Following Immunization (AEFI) reports from healthcare workers after administration of the COVID 19 vaccine reported to the Kenyatta National Hospital Pharmacovigilance system from 7th March 2021 to 30th September 2022. All reports were classified by age group, by system organ class and Preferred Term according to Medical Dictionary for Regulatory Activities Terminology and degree of seriousness. We identified the educational sessions held where: possible adverse events were described, channels of support and reporting were shared and, monitored the trend in reporting of AEFIs over the period of roll out of the first dose of vaccine.

Results: From the 11,773 vaccinations administered to healthcare workers during the period, 328 AEFI reports were received all but 1 were categorized as non-serious AEFI events. The trend in AEFI events reported reduced markedly from 236 reported in first 2 weeks of campaign to 5 reports after 8 weeks of campaign. The weekly education sessions on COVID vaccines and vaccine vigilance reported attendance of 800 healthcare workers on average. The uptake of vaccines was reported to be high among healthcare workers as misinformation and concerns with regards to AEFIs was addressed.

Conclusion: Institutional initiatives for vaccine pharmaco-vigilance coupled with educational sessions, in a season where vaccine hesitancy was high, enable risk management for early COVID vaccine rollout in Kenya.

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Cases of Guillain Barré Syndrome Following COVID-19 Vaccination

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Introduction: Guillain-Barré Syndrome (GBS) is a rare immune system disorder that results in muscle weakness, pain or numbness, and, in severe cases, paralysis. GBS is usually due to infections, and occurs more frequently in males and persons over 50 years old [1]. Some cases were described following vaccination among them COVID-19 vaccines.

Objective: To describe features of COVID-19 vaccine-associated GBS.

Methods: We carried out a retrospective, descriptive study of GBS patients following COVID-19 vaccine, submitted to the World Health Organization (WHO) global adverse drug reaction database

(VigiBase[®]) from Tunisia during the period between march 2021 and May 2022. We extracted the data using VigiLyze[®] software with the English version 25 of MedDRA to identify features of COVID-19 vaccine-associated GBS. In addition, we evaluated vaccine causality using the updated French causality assessment method [2].

Results: Overall, we retrieved 8 patients with GBS post COVID-19 vaccination: Men were representing 62.5% (5/3) of cases. The median age of affected patients was 59 (range: 41; 80) years. The most frequently reported vaccine type was followed in order by Comirnaty[®] Pfizer-BioNTech vaccine ($n = 3$ reports [37.5%]), Vaxzevria[®] AstraZeneca vaccine ($n = 3$ [37.5%]) and Janssen[®] vaccine ($n = 2$ [25%]). The mean time interval from vaccination to symptom onset was 15.3 days (range 7–30 days). Four patients developed GBS after receiving the first dose of a COVID-19 vaccine, three after the second dose and one after the third dose. Clinical manifestations were different with varying severity: classical GBS [1] (progressive ascending limb weakness associated with reduced or absent reflexes) in 5 cases, and GBS with unilateral facial palsy in 3. In all cases, electromyography (EMG) studies were consistent with the demyelinating pathology of GBS. Cerebrospinal fluid (CSF) examination showed albuminocytologic dissociation in 3 cases, was normal in 3 and not done in 2. Five patients were treated with a course of intravenous immune globulin (IVIg) for five days and one patient received a total of 2 sessions of plasma exchange. In 2 patients the nature of the treatment was unknown. Six patients reported clinical improvement within 7–10 days while two showed treatment-related fluctuations (TRF).

Conclusion: Our observations suggest that COVID-19 vaccines may be associated with GBS. Continuous surveillance and further studies are warranted to assess the significance of the association.

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Notoriety Bias in the Reporting of Adverse Events Following Immunization with COVID-19 Vaccines in the United States and Canada

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Introduction: The large-scale immunization with COVID-19 vaccines has brought safety surveillance to unprecedented levels. This context provides a unique opportunity to study the impact of communication on the reporting of adverse events following immunization (AEFIs), also known as notoriety bias.

Objective: To describe trends over time in the reporting of AEFIs with COVID-19 vaccines in the US and Canada following regulatory and major media communications, without implying causality.

Methods: Data sources were US VAERS and Canada Vigilance. Weekly reporting rates were estimated by vaccine type (mRNA vs. non-replicating viral vectors) using the number of doses administered

in each country, and time trends were derived. Study period started on the date of availability of vaccines in each country until 24 December 2021 (VAERS) and 31 August 2021 (Canada Vigilance), last available updates. A rapid review was conducted to identify major communications on COVID-19 vaccine safety. The dates and contents of communications were compared to time trends in reporting rates, without making causal inferences.

Results: In the US, the risk of thrombosis associated with viral vector vaccines was covered by 5 major communications [13 April 2021, 2 warnings, 20 April 2021, 30 April 2021, 16 December 2021], which was followed by an increase in reporting rate of thrombotic events of 529.6% within 1 week after the first communication. There were 2 communications on thrombosis in Canada (16 March 2021, 13 May 2021) as well as 1 warning on capillary leak syndrome (29 June 2021). In Canada Vigilance, an increase in reporting rate of 452.5% was found almost 3 weeks prior to the publication of the first communication, which coincides with the date of release of the communication in the US. There was 1 major communication on the risk of pericarditis and myocarditis associated with mRNA vaccines in the US (24 June 2021) where an increase in reporting rate of 33.6% was observed less than 1 week before the warning. There were 2 communications in Canada (both on 30 June 2021) where the reporting rate of pericarditis and myocarditis for mRNA vaccines increased by 47.8% within 1 week following the communications. Changes in reporting rates were not observed for AEFIs not covered in communications. Observed trends were the same for reports submitted by health care providers and consumers.

Conclusion: The dramatic increase in reporting rate immediately after, or sometimes just before, the release of communications was likely due to notoriety bias. There was no spillover effect to other AEFIs.

References/Further Sources of Information

Not applicable.

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Thromboembolic Events and COVID-19 Vaccine

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Introduction: Thromboembolic events (TE) are a major source of morbidity and mortality. Several risk factors have been associated to this condition such as age over 65 years, obesity, history of venous thromboembolism and hereditary thrombophilias [1]. Otherwise, TE have been associated with SARS-CoV-2 infection. Following the introduction of COVID-19 vaccines, these events were expected to decrease significantly [2]. However, some TE cases appeared after COVID-19 vaccination.

Objective: The aim of this study was to summarize all the cases of TE that occurred after COVID-19 immunization in Tunisia.

Methods: We conducted a retrospective study involving all cases of TE that occurred after COVID-19 vaccination, from the beginning of the campaign of immunization in March 2021 to May 2022. These cases were notified to the National Center of Pharmacovigilance, Tunisia.

Results: There were 25 cases of thrombotic events over about 12 million doses of vaccine. The mean age was 51.2±15.8 years. The sex ratio (M/F) was 1,27. Symptom onset occurred within 1 to 60 days.

Both arterial and venous thrombotic events were reported. Venous thromboembolism was observed in 21 cases (84%). Deep vein thrombosis in 9 cases (36%), superficial vein thrombosis in 3 cases (12%), pulmonary embolism in 3 cases (12%) and the site of venous thrombosis was not specified in 6 cases (24%). Arterial thromboembolism was reported in 4 patients: splenic infarction (1 case), thrombosis of the renal artery (1 case), thrombosis of the brachial artery (1 case) and femoral artery embolism (1 case). The TE were reported after the first shot in 72% of cases, after the second shot in 24% and after the third shot in one case (4%). The involved vaccines are summarized in table 1.

Table 1 : COVID-19 vaccines and thromboembolic events

COVID-19 vaccine		Number of cases	Percentage (%)
mRNA vaccines	Pfizer/BioNTech	13	52
	Spikevax (Moderna)	4	16
Adenovirus viral vector	AstraZeneca	5	20
	Janssen	2	8
Inactivated COVID-19 vaccine	Sinopharm	1	4
Total		25	100

Investigations revealed risk factors for TE in 12 patients. There were: age over 65 years in 25% of cases, thrombophilia in 25%, thromboembolic events histories in 25%, varicose vein thrombosis in 16.7% and immobilization in 8.3% of cases. This data was not provided for the 13 other patients. The outcome was favorable in 19 patients, one patient died and 5 patients were lost to follow up. There were no cases of Thrombotic Thrombocytopenia syndrome.

Conclusion: Despite a temporal relationship, the vaccine responsibility cannot be retained given the patient's medical histories.

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Adverse Effects of Hydroxychloroquine in COVID-19 Patients—A Review of Eudravigilance Database

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Introduction: Hydroxychloroquine is an antimalarial drug that belongs to the 4-aminoquinolone group [1]. Despite of this properties presents several immunomodulatory and anti-inflammatory characteristics [1,2]. In 2020, with the emergence of the COVID-19 pandemic, researchers used existing drugs with potential for the treatment of COVID-19, including hydroxychloroquine, which ended up being used *off-label* [3,4]. From the clinical trials hydroxychloroquine has many adverse effects that can increase risk for the SARS-COV-2 patients health. Common adverse effects are related to gastrointestinal and cardiovascular systems, neurotoxicity and retinopathy [2,5].

Objective: The objective of this research was to describe the adverse effects profile of hydroxychloroquine in COVID-19 patients and to characterize the risks associated with off-label use of hydroxychloroquine.

Methods: An observational, retrospective and descriptive study was conducted. Information collected from the “Eudravigilance” database was analyzed using descriptive statistics with R Studio® software. Information about the source of reporting, patient sex, serious adverse reactions, deaths and *off-label* cases and their outcome, were evaluated and compared in the pre- and post-pandemic period.

Results: The number of reports of adverse reactions to hydroxychloroquine increased significantly during the pandemic period (increase of 310.3%), with health professionals (92.0%) and woman (2020: 64%; 2021: 81%) reporting the most. The analysis of age groups allowed us to conclude that the 18-64 age group has the highest number of reported patients (2020: 49%; 2021: 53%). The off-label use of hydroxychloroquine was also an important aspect to consider in this study: in the period of 2020-2021, a total of 29.8% of suspected ADR have been caused by hydroxychloroquine in off-label use, with an important percentage of those being associated with COVID utilization (20.0%). Finally, deaths associated with the use of hydroxychloroquine were also evaluated, of which 67.0% are described in off-label use.

Conclusion: The number of reports of adverse reactions to hydroxychloroquine increased significantly during the pandemic. The potential for harm increased as off-label administration of hydroxychloroquine was associated with an increased incidence and severity of adverse reactions. However, associated with other drugs, this drug may potentiate certain adverse reactions, such as QT interval prolongation, nausea, dizziness, hypoglycaemia, heart failure, among others. Regarding outcomes, there seems to be an increase in the number of deaths associated with hydroxychloroquine, however causality has not been established for the observed data. Hydroxychloroquine presented varied adverse reactions in the observed data, and its off-label use during the pandemic showed an increase in its incidence.

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Guillan-Barré Syndrome Following COVID-19 Vaccines: Analysis of the Vaccine Adverse Event Reporting System (VAERS) Database

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Introduction: As part of post-authorization safety surveillance, the European Medicines Agency (EMA) has identified a potential safety concern for Guillain-Barré syndrome (GBS) following CORonaVirusDisease 2019 (COVID-19) vaccines [1,2].

Objective: To assess reports of GBS reported in the Vaccine Adverse Event Reporting System (VAERS) following COVID-19 vaccination and to evaluate if a COVID-19 vaccine has a lower/higher probability of reporting Individual Case Safety Reports (ICSRs) with GBS in a direct comparison with all other COVID-19 vaccines.

Methods: After selecting all ICSRs of GBS following vaccination reported in VAERS from 1 January 2021 to 31 December 2021, we assessed them through the case definition and classification of the Brighton Collaboration (BC). We performed a descriptive analysis. Finally, we used the Reporting Odds Ratio with a 95% of Confidence Interval to investigate disproportional reporting of GBS among the vaccines included in the analysis.

Results: 774 ICSRs of GBS have been reported in VAERS, and 279 of them met the BC Case Definition: 30 (10.7%) have been evaluated as Definitive, 56 (20.0%) as Probable, and 193 (69.3%) as Possible. COVID-19 Vaccine Pfizer-BioNTech was the most commonly vaccine reported (N = 118; 42.3%) followed by COVID-19 Vaccine Moderna (N = 82; 29.4%) and COVID-19 Vaccine Janssen (N = 79; 28.3%). GBS was more commonly reported for male subjects (N = 143; 51.3%) aged between 12 and 20 years (N = 59; 21.1%). GBS mainly occurred between the 1st and 12th day following the first dose administration of mRNA vaccines and between the 4th and the 15th day following COVID-19 Vaccine Janssen. COVID-19 Vaccine Janssen was significantly associated with increased risks for Guillain-Barré syndrome (ROR 3.47, CI 95% = 2.58–4.65) compared to COVID-19 Vaccine Pfizer-BioNTech and COVID-19 Vaccine Moderna.

Conclusion: GBS is an adverse event of special interest for all COVID-19 vaccines requiring specific safety monitoring. GBS is very rare, and the benefit-risk balance of the vaccine remains unchanged.

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Capillary Leak Syndrome and COVID-19 Vaccines: An Analysis of the European Spontaneous Reporting System EudraVigilance

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Introduction: Recently, capillary leak syndrome (CLS) emerged as new suspected adverse event after immunization (AEFI) associated to

COVID-19 vaccination. This condition is rare, but serious and potentially fatal [1].

Objective: Our pharmacovigilance study aims to evaluate the onset of CLS as AEFI with COVID-19 mRNA vaccines (Spikevax and Comirnaty) compared to viral vector vaccines (Janssen and Vaxzevria).

Methods: We carried out descriptive and disproportionality analyses of all Individual Case Safety Reports (ICSRs) reporting a vaccine COVID-19 as suspected drug and the CLS as AEFI, which were collected in the pharmacovigilance database EudraVigilance from January 1st, 2021, to January 14th, 2022. For the disproportionality analysis we applied the Reporting Odds Ratio (ROR) 95% CI.

Results: During study period, CLS was described as AEFI in 84 out of 1,357,962 ICRs reporting a vaccine COVID-19 as suspected drug and collected in the EV database.

Overall, the ICSR reported by CLS were mainly related to the viral vector COVID-19, Vaxzevria[®], (N = 36) and Janssen[®], (N = 9), while the ICSR reported to vaccines COVID-19 mRNA were 39 (Comirnaty[®], N = 33; Spikevax[®], N = 6). Majority of ICSRs were reported by healthcare professionals (N = 60; 71.4%). The non-healthcare professional represented the primary source in the 41.7% of Vaxzevria[®] related ICSRs.

Majority of the patients were adult (N = 49; 58.3%). The female gender accounted in more than 65% of ICSRs referred both to mRNA and viral vector vaccines.

The CLS outcome was more frequently favorable in mRNA ICSRs (N = 13; 33.3%). On the other hand, among the ICSRs reporting CLS with unfavorable outcome (N = 25; 29.8%) we found 9 ICSRs describing fatal CLS (Comirnaty[®] N = 1; Vaxzevria[®] N = 4; Janssen[®] N = 4).

From disproportionality analysis emerged a lower CLS reporting probability after COVID-19 vaccination with mRNA vaccines compared to viral vector-based ones.

Conclusion: According to our results, few ICSRs describing CLS have been collected in EV in front of billion administered doses. This could underline the rarity of this AEFI or the limit of underreporting of spontaneous reporting and therefore also our study. Since the significant clinical relevance of CLS, this AEFI requires a careful monitoring.

Healthcare professionals as well as patients should be aware of the signs and symptoms of CLS. Patients with a history of CLS require particular attention because of a possible risk of flare-up of disease. Since a precise mechanism is still not identified, further studies are necessary to confirm the causal relationship between CLS and COVID-19 vaccination.

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European Safety Analysis of mRNA and Viral Vector COVID-19 Vaccines on Glucose Metabolism Events

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Introduction: COVID-19 is a complex disease with several clinical phases of progression, affecting many organs apart from the respiratory tract that has shown a worst prognosis in both patients with type 1 and type 2 diabetes mellitus [1]. Based on these considerations, the vaccination for COVID-19 is a priority for this subpopulation [2]. However, few data have been published on the effects of impaired glucose metabolism induced by COVID-19 vaccines.

Objective: We decided to perform a study to describe Individual Case Safety Reports (ICSRs) of impaired glucose metabolism events reported in the European database (Eudravigilance, EV).

Methods: ICSR were retrieved for the period from January 1st, 2021 to December 11th, 2021. An ICSR related to events of impaired glucose metabolism was identified by using selected preferred terms (PTs) from Standardized MedDRA Queries “Hyperglycaemia/new onset diabetes mellitus” and “Hypoglycaemia”. Impaired glucose metabolism events were described and analyzed based on the Diabetologists’ classification into nine groups: “diabetes in pregnancy”, “acute complications of diabetes”, “pre-diabetes”, “type 1 diabetes mellitus”, “type 2 diabetes mellitus”, “high glucose levels”, “diabetes mellitus inadequate control”, “diabetes mellitus not specified”, and “hypoglycaemia”. The reporting odds ratios were computed to assess the reporting frequency for COVID-19 mRNA vaccines compared to COVID-19 viral vector-based vaccines.

Results: During the study period, 3,917 ICSR with a COVID-19 vaccine as suspected and at least an event of impaired glucose metabolism were retrieved from the EV, of which 2,027 (51.75%) referred to Pfizer-BioNTech vaccine, 586 (14.96%) to Moderna vaccine, 1,163 (29.70%) to Oxford-AstraZeneca vaccine, and 141 (3.59%) to Janssen vaccine. From 3,917 ICSR, we observed 4,275 impaired glucose metabolism events (1.09 adverse events per ICSR). Most adverse events were classified as serious (2,694; 63.02%), and the most reported events were related to “high glucose levels” (2,012; 47.06%). The mRNA vaccines were associated with an increased reporting frequency of “type 1 diabetes mellitus” (ROR 1.86; 95% CI 1.33–2.60), “type 2 diabetes mellitus” (ROR 1.58; 95% CI 1.03–2.42), “high glucose levels” (ROR 1.16; 95% CI 1.06–1.27), “diabetes mellitus inadequate control” (ROR 1.63; 95% CI 1.25–2.11), and “hypoglycemia” (ROR 1.62; 95% CI 1.41–1.86) compared to viral vector-based vaccines. The highest reporting rate per 100,000 was observed for Oxford-AstraZeneca vaccine (1.87; 95% CI 1.77–1.97).

Conclusion: In conclusion, mRNA COVID-19 vaccines were associated with an increased reporting frequency of alterations of glucose homeostasis compared to viral-vector COVID-19 vaccines. Clinicians should be aware of these events to better manage glycaemic perturbations. Larger nationwide studies are warranted to verify these findings.

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Safety of mRNA-Platform based Covid-19 Vaccines in Pediatric Population: An Analysis of the European Pharmacovigilance Database Eudravigilance

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Introduction: Recently mRNA-based COVID-19 vaccines have been approved also for use in pediatric population. Vaccines safety require particular attention in this population. Analysis of pharmacovigilance database allows to extrapolate important information to identify possible safety signals.

Objective: Our pharmacovigilance study aims to describe and evaluate the onset of adverse events following immunization (AEFIs) with COVID-19 mRNA vaccines in the pediatric population.

Methods: We retrieved all pediatric Individual Case Safety Reports (ICSRs) collected in the European pharmacovigilance database, Eudravigilance from the 01/01/2021 to 4/03/2022 related to Spikevax and Comirnaty. We carried out a disproportionality analysis (Reporting Odds Ratio-95% CI) to compare the reporting probability of some AEFIs of interest (seizure, pericarditis, myocarditis, multi-system inflammatory syndrome (MIS), menstrual disorders, failure and anaphylactic shock) between Comirnaty and Spikevax.

Results: We retrieved in Eudravigilance 25,019 ICSR related to Comirnaty describing a total of 75,040 AEFIs and 1,862 ICSR referred to Spikevax reporting overall 5,361 AEFIs occurred in pediatric population. Majority of ICSR reported well-known general disorders (headache, pyrexia, fatigue and nausea) for both mRNA vaccines. ICSR were more frequently referred the adolescent patients (Comirnaty, 86.2%; Spikevax, 86.4%). We found a slight prevalence of female gender for both mRNA vaccine (Spikevax, 52.6 %; Comirnaty 53.9%). Reproductive system disorders were more frequently referred to females. In particular, these events included menstrual disorders (N = 609, Comirnaty; N = 23, Spikevax), amenorrhoea (N = 408, Comirnaty; N = 16, Spikevax) or intermenstrual bleeding (N = 169, Comirnaty; N = 10, Spikevax), polymenorrhoea (N = 172, Comirnaty; N = 10, Spikevax). Few cases described reproductive system disorders in males, mainly related to Comirnaty. These AEFIs included testicular pain (N = 14, Comirnaty; N = 1, Spikevax), erectile dysfunction (N = 5, Comirnaty), testicular torsion (N = 4, Comirnaty) or swelling (N = 4, Comirnaty), scrotal pain (N = 3, Comirnaty) or oedema (N = 1, Comirnaty). Outcome of AEFIs was unknown in 14.8% and 21.1% cases for Spikevax and Comirnaty, respectively. AEFIs had a favorable outcome in more than 50% of cases for both mRNA vaccines, including a complete resolution (30%) or an ongoing resolution (20%). From disproportionality analysis emerged a statistically significant ROR for menstrual disorders (ROR 1.72, 95% CI 1.43–2.10; p < 0.05), failure (ROR 8.11, 95% CI 5.05–13.97; p < 0.05) and seizure (ROR 1.54, 95% CI 1.03–2.41; p = 0.037) when compared Comirnaty versus Spikevax.

Conclusion: Majority of pediatric AEFIs are mild and with a positive outcome, supporting the role of ongoing COVID-19 vaccination campaign in this population as a critical public health tool for disease prevention and control of pandemic. Further investigations are needed in this population.

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Pharmacovigilance Among Patients from the Perspective of Pharmacists: A Survey Study in Morocco

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Introduction: Patient reporting of adverse drug reactions (ADRs) could supplement the existing reporting system of the Moroccan Pharmacovigilance Poison Control Center (CAPM) and contribute to the early detection of ADRs, which are important causes of morbidity and mortality worldwide.

Objective: This study is considered the first study in the region it was conducted to assess the knowledge, attitude, notification, and practice of pharmacovigilance among patients during the COVID-19 period, through pharmacists of the DRAA-TAFILALET region in Morocco. In order to model the impact of Good Pharmacovigilance Practices over the COVID-19 period on pharmacist's reactivity to pharmacovigilance.

Methods: It was a questionnaire-based cross-sectional study devoted to 120 pharmacists in the DRAA-TAFILALET region. Using latent variable structural modeling by the partial least squares (PLS) method via the XLSTAT software (version 2017).

Results: A total of 120 pharmacists completed and returned the questionnaire. The reliability of the measurement was > 0.7, which allows us to test the internal and external validity of our conceptual model. Nine hypotheses were validated, against two invalid derivative hypotheses. The results obtained allow us to propose areas for improvement and action plans to be taken into account by the Moroccan strategy of pharmacovigilance.

Conclusion: Spontaneous ADRs reporting is the cornerstone of any pharmacovigilance system to maintain patient safety. Indeed, it is necessary first to initiate all healthcare professionals to report through training and secondly to inform the general public of the availability of a national pharmacovigilance center where they can report an ADR, in order to keep the culture of ADR reporting perennial.

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Vogt-Koyanagi-Harada Uveitis Following Covid-19 Vaccine

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Introduction: Vogt-Koyanagi-Harada (VKH) syndrome is a multi-system condition with chronic, bilateral, non-necrotizing, granulomatous panuveitis and exudative retinal detachment (1). It is a very rare adverse event of vaccination, and cases of VKH disease following Covid-19 vaccine have rarely been reported so far [1-3].

Objective: Herein, we report a case of VKH disease following mRNA-1273 (SpikeVax[®]) COVID-19 vaccination.

Methods: This case was notified in November 2021 to the National Centre of Pharmacovigilance and evaluated according to the updated French method of causality assessment.

Results: A 33-year-old female patient with a medical history of renal failure and without any history of ophthalmic disease, received her second dose of SpikeVax[®] on August 20, 2021. Four days later, she experienced headache and fatigue and subsequently developed bilateral blurred vision seven days following the vaccination. The evolution was marked by the persistence of symptoms and a decreased bilateral visual acuity a week later. Ophthalmologic examination showed an aqueous flare, keratic precipitates, iris nodules and cells in the anterior vitreous in both eyes work up ruled out systemic infection or autoimmune disease. ANCA were negative. ACE levels were normal. Serology test for HBV, HIV, syphilis and mycobacterium tuberculosis were also negative. A VKH syndrome was diagnosed. One month after treatment with oral prednisolone and mycophenolate mofetil, the evolution was favorable without any sequels.

Conclusion: Although there is a chronological relation between the onset of VKH and the SpikeVax[®], the role of vaccination couldn't be certainly assessed.

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Pattern of Adverse Effects of COVID-19 Vaccine Among the People of Bangladesh

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Introduction: Since the WHO classified COVID-19 a pandemic, vaccines have been developed to minimize the SARS-CoV-2 virus's incidence around the world. [1] For better understanding of the safety and effectiveness of the vaccines the identification of the localized and systemic side-effects after vaccination is important because the side effects between in a real-world community setting than reported in phase 3 trials, mostly minor in severity, and self-limiting. [2-5]

Distribution of the patients according to sociodemographic and adverse effects pattern among the vaccinated people			
Variables	Frequency	Percentage	No. of Participants
Sex			n= 2345
Male	1565	66.7	
Female	780	33.3	
Age			
<40	1473	62.8	
40–60	699	29.8	
>60	173	7.4	
Occupation			
Physician	306	13.0	
Nurse	222	9.5	
Others	1817	77.5	
Co-morbidity			n= 511
DM	311	14.9	
HTN	137	6.5	
IHD	11	0.5	
Asthma	39	1.9	
Obesity	13	0.6	
History of contact with COVID-19 positive after vaccination			n= 2227
Yes	77	3.5	
No	2150	96.5	
Pattern of side-effects			n= 2345
Local side-effects	403	17.1	
Systemic side effects	278	11.8	
Pattern of local side-effects			n= 403
Pain	351	87.1	
Swelling	9	2.2	
Tenderness	20	5.0	
Swollen ampit	2	0.5	
Redness	10	2.5	
Warmth	6	1.5	
Allergic Reactions	5	1.2	
Pattern of systematic side-effects			n= 277
Headache	49	17.6	
Fatigue	44	15.8	
Chills and Shiver	154	55.5	
Arthralgia	2	0.7	
Myalgia	28	10.1	
Nausea	1(0)	0.3	

Objective: To identify pattern of adverse effects of covid-19 vaccine among the people of Bangladesh.

Methods: This follow up study was conducted among 2345 vaccinated people at Bangabandhu Sheikh Mujib Medical University from June 2021 to December 2021. Data was collected by face to face and telephone interviewing through a structured questionnaire for 7 days daily for local effect and upto 28 days for systemic side effects after vaccination and SPSS software version 25.0 was used for statistical analysis

Results: Among the total participants 2345, Most of the people were male 1565 (66.7%). 17.1% of people had local side effects. About 33.1% participants were experienced systemic side effects. Among the local side effects pain was more common and chill and shiver in systemic effects respectively 14.3% and 2%. About 89.1% participants were with co morbidity. Male were predominant and middle aged were more than older people.

Conclusion: This study portrayed a precise scenario about the adverse effects of vaccine. The adverse effects of vaccine should be evidence based. Further education and research needed to encourage on evidenced based vaccination among the people. This was generated information for the clinical care providers to take necessary steps as a precaution in treating the adverse effects of any patients and the policy makers to take necessary steps in related to vaccine to handle this pandemic.

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Ecchymotic Plaques Induced by Spikevax: About 2 Cases

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Introduction: Several post-vaccination adverse events (AEFI) have been reported after anti-COVID 19 vaccine SPIKEVAX[®] administration. By the way, we can mention cutaneous manifestations (1).

Objective: We report 2 cases of women who presented ecchymotic skin plaques after vaccination with SPIKEVAX[®] notified in the Regional Pharmacovigilance Service of Sfax.

Methods: The assessment of the causal link was made according to the method of the World Health Organization.

Results: Two women, with no previous medical history, presented ecchymotic skin patches after SPIKEVAX[®] (Moderna) vaccination. Platelet and D-dimer levels were normal in both cases. But an

immunological assessment was not requested. The first woman was 33 years old. She presented 2 days after the first dose of the vaccine generalized ecchymotic plaques which measured 7 cm of diameter and was located on the right flank. These plaques persisted for one month before disappearing. The second woman was 26 years old, she presented 20 days after the second dose of the vaccine, 3 ecchymotic plaques on one thigh followed. Two days later, another plaque was appeared on the other thigh. These lesions were associated with myalgias in the lower limbs and headaches and disappears after 2 months. A probable causal link was established in these patients.

Conclusion: The ecchymotic plaques in our patients may suggest vascular involvement particularly a vasculitis. Few cases have been reported with anti-COVID 19 vaccination (1).

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Pharmacovigilance Before and After COVID-19 Pandemic: A 3-Years Analysis of Adverse Drug Reactions Reporting at the University Hospital of Catania

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Introduction: COVID-19 pandemic has dramatically affected healthcare systems, as well as everyday life worldwide [1,2]. Pharmacovigilance has definitely had a central role in this context of emergency, for both new and old molecules being investigated as potential treatments for COVID-19, but above all for the monitoring of COVID-19 vaccines [3].

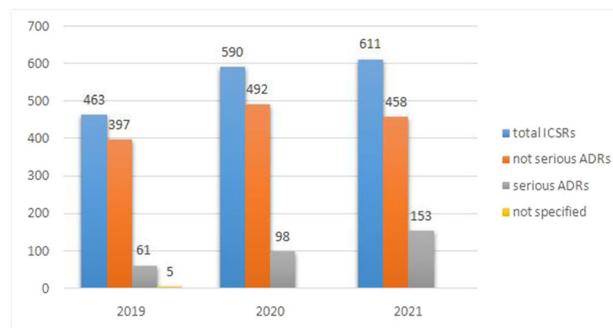
Objective: The aim of this study was to investigate how COVID-19 pandemic has changed the adverse drug reactions (ADRs) reporting at the University Hospital of Catania.

Methods: We performed a descriptive analysis of individual case safety reports (ICSRs) collected in the Italian National Pharmacovigilance Network by the University Hospital of Catania from January 2019 to December 2021. Data were compared in terms of number of reports per year, patient characteristics, treatments, severity of reactions, and type of reporter.

Results: Overall, the number of ICSR collected was 1,664, 463 in 2019, 590 in 2020 and 611 in 2021 (Figure 1). In the majority of cases, ADRs have involved female subjects in the 18–65 years age group (mean age 49 years). Most cases were classified as not serious (81%); nevertheless, reports of serious ADRs progressively raised from 13.2% in 2019 to 16.6% in 2020 and 25% in 2021. In 2019 and 2020 almost all ICSR were spontaneously sent by physicians, while in 2021 a greater reporting by citizens (13.9%), pharmacists (11.1%) and other health care professionals (3.8%) has been observed. Adalimumab represented the most frequently reported suspected drug in 2019 and 2020, with the highest number of ICSR concerning lack of therapeutic response (77% and 92.5%, respectively). In 2021 the number of ADRs caused by vaccines has dramatically risen, from zero in 2019–2020 to 251 in 2021, as a consequence of COVID-19 vaccination campaign (tozinameran 32.6%). Most of ICSR

concerned general and administration site conditions (68.8%), with fever being the most frequently reported ADR (29.1%). Tozinameran was also associated with the highest number of serious ADRs (n = 34) in 2021.

Figure 1: Total number of individual case safety reports (ICSRs) per year and seriousness of reported adverse drug reactions (ADRs)



Conclusion: This study showed that COVID-19 outbreak did not have a significant impact on ADRs reporting until the introduction of COVID-19 vaccines. It is noteworthy that treatments for COVID-19 were not listed among the suspected drugs, although the high number of patients treated in our institution during 2020 and 2021. It will be useful to investigate the possible underlying reasons (lack of ADR? difficulty in distinguishing ADR from the disease? lack of time in an emergency situation?) with healthcare professionals directly involved in the treatment of COVID-19.

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Adverse Drug Reactions Associated with Anti-Infective Agents Reported to the National Pharmacovigilance Centre in Saudi Arabia: A Descriptive Study

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Introduction: Adverse Drug Reactions (ADRs) are among the leading causes of mortality and morbidity worldwide [1]. International organisations such as the World Health Organisation (WHO) [2] has recognised the need for detecting, assessing and understanding ADRs in order to ensure safe drug use. In Saudi Arabia (SA), the National Pharmacovigilance Center (NPC) within the Saudi Food and Drug Authority (SFDA) has been responsible for collecting, analysing and learning from ADRs reported in SA, allowing it to contribute to the global effort to minimise ADRs [3]. A recent study has analysed around 17,730 ADRs reported to NPC in the period between 2015 and 2017 which found that anti-infective agents were most commonly involved with ADRs (22.27%) [4]. Whilst informative, these reports were not analysed extensively in terms of their composition, seriousness, and patient group commonly involved in these ADRs. The

present study, however, presents an updated and a more extensive review of anti-infective agents involved with ADRs over the period between 2018 and 2020.

Objective: The aim of this study is to analyse and characterise ADRs associated with anti-infective agents reported to the NPC within the SFDA between the years 2018 and 2020.

Methods: A retrospective review was carried out of all ADRs involved with anti-infective agents submitted to the NPC between 2018 and 2020. A descriptive analysis was undertaken to determine the number of ADRs, and then to characterise them according to their Medical Dictionary for Regulatory Activities (MedDRA) classification, age and gender of patients involved, as well as seriousness and type of anti-infective class(es) involved. The SFDA's Ethics Committee has exempted this study from formal ethical approval.

Results: A total of 12,567 ADRs were included, of which 53.78% occurred in males. Among all age groups, adults between the age of 45 and 64 were the ones most reported (10.89%). The most reported ADRs were classified according to the MedDRA in terms of investigations (26.76%), gastrointestinal disorders (22.76%), as well as skin and subcutaneous tissue disorders (14.88%). The level of seriousness was not specified in 91.47% of the reports. Almost two percent of ADRs were reported to require intervention to prevent permanent damage followed by ADRs that resulted in prolonged hospitalisation (1%). Antibacterials were commonly reported (83.5%), followed by antiviral (10.9%), and antifungal medications (3.8%).

Conclusion: This is the first study to characterise ADRs associated with anti-infective agents. Our study showed that these anti-infective agents pose a threat to patient safety in our health care system.

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Post-marketing Safety of Onasemnogene Apeparovvec and Nusinersen in Pediatric Population: Analysis of FAERS Database

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Introduction: Spinal muscular atrophy (SMA) is a degenerative neuromuscular disorder recognized as the most common genetic cause of infantile mortality described so far [1]. Food and Drug Administration (FDA) approved two new treatments in SMA: nusinersen, the first new oligonucleotide-based drug targeting the central nervous system, and onasemnogene apearovvec, the first

gene therapy approved to treat children less than two years of age [2,3].

Objective: A post-marketing evaluation of the safety of onasemnogene apearovvec and nusinersen through the analysis of the FDA Adverse Event Reporting System (FAERS) database with a focus on the pediatric population (0–17 years).

Methods: Data on Individual Case Safety Reports (ICSRs) reported in children (0–17 years) were retrieved from the FAERS database for the period January 2017–December 2021. A descriptive analysis was performed, and characteristics of all ICSR, including the reported drugs and events, were described and stratified by drugs and age groups. Moreover, cases with fatal outcomes were investigated as a sub-analysis. All data manipulation and statistical analysis were performed using R Statistical Software.

Results: We included 2,263 pediatric ICSR (48.0% females and 68.1% from United States). The median age was 3.0 years. 59.8% was submitted through expedited (15-days) (65%) or periodic reporting (39.4%) and 0.8% by non-manufacturers. A total of 63.2% of all ICSR were serious and 10.2% had a fatal outcome. The most frequent reported System Organ Classes (SOCs) were "Infections and Infestations" (N = 572), "General disorders" (N = 542), and "Investigations" (N = 511). The most commonly Preferred Terms (PT) were pyrexia (N = 214), vomiting (N = 169), and headache (N = 132). In sub-analysis, a fatal outcome was reported in 121 male (52.9%) and infants (59.9%) with a median age of 1.0 years. The adverse events more frequently reported as cause of death was cardio-respiratory arrest (3.7%), respiratory failure (3.6%), cardiac arrest (3.3%) and pneumonia (3.0%).

Conclusion: Onasemnogene apearovvec and nusinersen demonstrated a favorable long-term benefit-risk profile in real-world context. Since only a few years of marketing is available, further followed-up studies need to be performed to investigate the longer-term safety of onasemnogene apearovvec and nusinersen.

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Risk Communication: Ethionamide Mediated Gynecomastia

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Introduction: Gynecomastia is defined as enlargement of male breast due to benign enlargement of the duct tissue and periductal stroma in the male breast. It can be bilateral and symmetrical or unilateral or asymmetrical. For reasons unknown, unilateral gynecomastia seems to be more common on the left side (1). But for the cases in Uganda, the breast tissue swelling was bilateral. Unlike headache, dizziness, asthenia, and paraesthesia that are labelled common side effects, gynecomastia is mentioned in the product summary characteristics of

Ethionamide as a 'Not Known' undesirable effect. This is because it is an ADE that was identified post approval use of the drug.

Objective: To characterize a rare reaction to a commonly used drug for MDR-TB.

Methods: This is a case series presentation of retrospective data from the Ugandan pharmacovigilance database.

Results: There are 8 cases of gynaecomastia, experienced by male clients of mean age 43.625 years taking Ethionamide for treatment of multidrug resistant TB that have been reported to the National Drug Authority.

Results:

There are 8 cases of gynaecomastia, experienced by male clients of mean age 43.625 years taking Ethionamide for treatment of multidrug resistant TB that have been reported to the National Drug Authority.

Table 1: Case Series of Reported Gynaecomastia (PT) Suspected to be due to Ethionamide

ID	Age	Time to Onset	Concomitant Drugs	Action Taken	Outcome
1	45		Capreomycin, Moxifloxacin, Isoniazid, Pyridoxine, Cycloserine, Levofloxacin, Bedaquiline and pyrazinamide, Ethionamide, cycloserine, levofloxacin and Bedaquiline	Dose not changed	Not recovered
2	49		Pyrazinamide, Cycloserine, Levofloxacin, Bedaquiline and pyridoxine, kanamycin, Ethionamide, cycloserine, levofloxacin and Bedaquiline	Dose not changed	Recovering
3	unk	6 months	pyrazinamide, cycloserine, levofloxacin and Bedaquiline	Dose not changed	Not recovered
4	62		Pyrazinamide, cycloserine, levofloxacin and Bedaquiline	Dechallenge, Rechallenge.	Subsided on dose reduction
5	28		kanamycin, pyrazinamide, levofloxacin, Ethionamide and cycloserine	Unknown	Recovering
6	unk		Isoniazid, moxifloxacin, ethambutol and pyridoxine	Dose not changed	Not recovered
7	44		Levofloxacin, Cycloserine and Pyrazinamide	Dose not changed	Not recovered
8	36	2 months		Unknown	Not recovered

Key: Unk = Unknown

CS Scanned with CamScanner

Conclusion: Usually there is no requirement for treatment of gynaecomastia. However, with the known information, early detection of gynaecomastia and withdrawal of the medication is critical among patients using Ethionamide as the condition usually causes discomfort and embarrassment to some clients thus affecting their quality of life (7). We also recommend that endocrinological and biochemical investigations including LFTs and TFTs should be carried out in order to rule out systemic causes.

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Signal of Congestive Cardiomyopathy in Association with Olanzapine—Evidence Review from Pharmacovigilance Data

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Introduction: Olanzapine is atypical antipsychotic. The drug's mechanism of action is not fully understood. It mainly mediates its antipsychotic action via dopamine and serotonin type 2 (5HT₂) antagonism [1]. Congestive Cardiomyopathy (a.k.a. Dilated Cardiomyopathy) is a type of cardiomyopathy characterized by structural modifications of myocardium. Due to these modifications, abnormal stretching and dilation of heart chambers results in reduced pumping activity of heart muscle. Patients with Congestive Cardiomyopathy may remain symptom-free for unspecified period of time and then experience sharp deterioration in cardiac functions suddenly [2].

Objective: The aim of this review is to evaluate the risk of Congestive Cardiomyopathy associated with the use of Olanzapine and to suggest regulatory recommendations if required.

Methods: Signal Detection team at SFDA performed a signal review using National Pharmacovigilance Center (NPC) database, and World Health Organization (WHO) database, VigiBase, with literature screening to retrieve all related information to assess the causality between congestive cardiomyopathy and olanzapine use. The search conducted on August 26th, 2021.

Results: Case Review: Signal detection team at SFDA have searched Saudi national database and WHO database to find individual case safety reports (ICSRs) of congestive cardiomyopathy associated with olanzapine. While the search resulted in zero reported local cases, the search in the WHO database resulted in 20 global case-reports. The authors used signal detection tool (Vigilyze) to retrieve all reported cases [3]. Authors also applied WHO-UMC causality assessment criteria on ICSR with completeness score (0.5) and above (n = 9). Among them, 6 cases of congestive cardiomyopathy were possibly linked to olanzapine.

Literature: A scientific literature search was performed for olanzapine and risk of congestive cardiomyopathy. We found a case of 28-year-old male patient with bipolar disorder suffered congestive cardiomyopathy after taking olanzapine for 10 years was published in 2016 [4].

Datamining: The disproportionality of the observed and the expected reporting rate for drug/adverse drug reaction pair is estimated using information component (IC), a tool developed by WHO-UMC to measure the reporting ratio. Positive IC reflects higher statistical association while negative values indicates less statistical association, considering the null value equal to zero. The results of (IC = 1.4) revealed a positive statistical association for the drug/ADR combination.

Conclusion: The weighted cumulative evidence identified from local and global cases is sufficient to suggest causal association between olanzapine and congestive cardiomyopathy. Despite the need for a more thorough review of safety data to confirm the risk, health care professionals should be aware of the potential risk in drug recipients.

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Isotretinoin Associated Risk of Blood Growth Hormone Decrease-Signal Review

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Introduction: Isotretinoin is a form of vitamin A used to treat acne. It is the only therapy that has an impact on all of the major etiological factors implicated in acne [1]. Adults with growth hormone deficiency (which may result from problems with the pituitary gland or hypothalamus) may have symptoms including: poor bone density and osteoporosis, reduced muscle mass, fatigue, depression, and poor memory [2].

Objective: To assess the risk of blood growth hormone decrease associated with isotretinoin and, if necessary, make regulatory recommendations

Methods: The Signal Detection team at SFDA performed a signal review using the National Pharmacovigilance Center (NPC) database and the WHO database, Vigibase, with literature screening to retrieve all related information to assess the causality between blood growth hormone decrease and isotretinoin use. The search was conducted on November 11th, 2021. The disproportionality of the observed and the expected reporting rates for drug/adverse drug reaction pair was estimated using an information component (IC), a tool developed by WHO-UMC to measure the reporting ratio. Positive IC reflects higher statistical association, while negative values indicate less statistical association.

Results: Case Review: A search in the NPC database and WHO database (Vigibase) was conducted to retrieve all reported cases. There were five global ICSRs found, but no local ICSRs. The Signal Detection team applied the WHO-UMC causality assessment tool to all cases. 1 case was found supportive of the association, and 4 cases lacked the necessary information to assess causality.

Datamining: The results of (IC = 2.7) revealed a positive statistical association for the drug/ADR combination.

Literature: In 2015, a pre-and post-exposure study was published. The effects of various isotretinoin dosing regimens on pituitary hormones in drug recipients were studied. Blood samples were taken before the start of treatment and three months later. Growth hormone levels were found to be significantly lower ($p = 0.002$) [3].

Conclusion: The weighted cumulative evidence identified from global cases, literature and datamining is sufficient to suggest a causal association between isotretinoin and a decrease in blood growth hormone. Despite the need for a more thorough review of safety data to confirm the risk, health care professionals should be aware of the potential risk in drug recipients and monitor signs of blood growth hormone decrease.

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Pfizer-BioNTech COVID-19 Vaccine Associated Risk of Olfactory Hallucinations-Signal Review

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Introduction: Pfizer-BioNTech Covid-19 vaccine is highly purified single-stranded messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates indicated for preventing coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Olfactory hallucination is a condition in which a person perceives odors that aren't present. Some might notice the odor in just one nostril, while others have it in both [2].

Objective: The purpose of this review is to assess the risk of olfactory hallucinations from the Pfizer-BioNTech Covid-19 vaccine and, if necessary, make regulatory recommendations.

Methods: The Signal Detection (SD) team at SFDA performed a signal review using the National Pharmacovigilance Center (NPC) database and World WHO database, Vigibase, with literature screening to retrieve all related information to assess the causality between olfactory hallucinations and Pfizer-BioNTech Covid-19 vaccine use. The search was conducted on January 4th, 2022.

The disproportionality of the observed and the expected reporting rates for drug/adverse drug reaction pair was estimated using an information component (IC), a tool developed by WHO-UMC to measure the reporting ratio. Positive IC reflects higher statistical association, while negative values indicate less statistical association.

Results: Local Cases: The SD team at SFDA has searched the NPC database for individual case safety reports (ICSR) reporting olfactory hallucinations in association with the Pfizer-BioNTech COVID-19 vaccine. The search resulted in one ICSR and, on the basis of WHO-UMC causality assessment criteria, olfactory hallucinations were considered probably associated with the vaccine.

Global Cases: A search was conducted in the WHO database (Vigibase) to retrieve all reported cases using a signal detection tool (Vigilyze) [3]. The search yielded 59 ICSRs. The signal detection team applied the WHO-UMC causality assessment tool on cases with a completeness score of (0.8) and above ($n = 13$). 11 cases were found supportive of the association, with 10 being probable and one being possible.

Literature: Late November 2021, a case report of a 57-year-old woman seeking medical care after complaining of “smelling smoke” after receiving her second dose of the vaccine was published [4].

Datamining: The results of (IC = 1.9) revealed a positive statistical association for the vaccine/ADR combination.

Conclusion: The weighted cumulative evidence identified from local and global cases is sufficient to suggest a causal association between the Pfizer-BioNTech COVID-19 vaccine and olfactory hallucinations. While a more thorough review of safety data is needed to confirm the risk, health care professionals should be aware of the risk that could happen after vaccination.

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Effect of Direct Healthcare Professional Communication on Citalopram and Escitalopram

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Introduction: In 2011, the US Food and Drug administration informed on the dose dependent QTc-prolonging effect of citalopram¹. In Germany, direct healthcare professional communication letters (DHPC) were sent out to inform on the cardiac risk associated with citalopram and escitalopram administration. As regulatory measures the maximum daily dose of citalopram and escitalopram was restricted, in the summary of product characteristics QTc-prolonging co-medication was stated as contraindicated^{2,3}.

Objective: To analyze the effect of the DHPC in inpatients with the diagnosis of an anxiety disorder by using data from the project “Arzneimittelsicherheit in der Psychiatrie e.V.” (AMSP).

Methods: AMSP is a multicenter pharmacovigilance project in which adverse drug reactions of psychotropic drugs are documented. Data on drug utilization is recorded in participating psychiatric hospitals on two days per year (reference dates)⁴. Data from 2004-2010 (pre-DHPC) and 2013-2017 (post-DHPC) were used to examine whether both (1) the proportion of patients treated with a higher than the newly recommended maximum daily dose of citalopram or escitalopram and (2) the proportion of patients with QTc-prolonging co-medication (according to the German SPC) declined post-DHPC. Adult inpatients with anxiety disorders treated with citalopram or escitalopram were included in this analysis. Dose levels and co-medication were screened. Citalopram and escitalopram were evaluated together.

Results: From 1993 to 2017, data of 67.000 patients in total were recorded on reference dates. In this analysis, 364 patients with anxiety disorders treated with citalopram or escitalopram were identified pre-DHPC, 262 post-DHPC. Demographic data pre- and post-DHPC did not differ. The proportion of patients exceeding the recommended daily dose decreased from 10.7 to 5.4 % (p = 0.019). The proportion of patients with QTc-prolonging co-medication remained unchanged (54.7 vs. 51.5 %, p = 0.437).

Conclusion: As in previous studies on different patient populations, the proportion of patients with anxiety disorders exceeding the newly recommended maximum daily dose declined significantly while the proportion of patients with QTc-prolonging co-medication remained unchanged. Precise instructions such as recommendations regarding the reduced maximum daily dose are obviously easier to implement than the introduction of a contraindication with regard to the simultaneous administration of any, but not specified, QTc-prolonging drug.

In conclusion, information on drug risks should be precise and formulated clearly. As far as possible, advice for specific clinical situations should be given. This could facilitate the appropriate implementation of regulatory guidance on drug use in clinical practice.

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Regulatory Action Following Dextromethorphan Misuse in Adolescents in the Czech Republic

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Introduction: In 2017, Czech regulatory authority (SUKL) was contacted by non-healthcare professionals (non-HCP) who reported concerns about adolescents abusing dextromethorphan (DXM) tablets to achieve psychogenic effects. Therefore, SUKL sought for HCP confirmation. Co-operation with psychiatrists and toxicology centre (TIS) revealed the extent of the problem and misuse of DXM tablets was confirmed as serious concern.

The recommended therapeutic DXM dosage is 15–30 mg every 4 hours. The four dose-dependent levels of abuse are described: feelings of stimulation (100–200 mg), hallucinations, euphoria (200–400 mg), impaired motoric functions (400–600 mg) and strong dissociative effects (over 600 mg). (1,2)

Objective: To describe the national regulatory action in 2017 based on reported cases of DXM misuse and its update.

Methods: Due to active pharmacovigilance and intensive co-operation in field, a total of 113 serious reports of misuse were captured within few months (May–July 2017). Reports identified two risk groups—adolescents and young adults (mainly 12–24 years) and psychiatric patients.

To decrease the risk of DXM abuse, urgent action was required. After thorough assessment, switch of solid forms of monocomponent DXM products from OTC to Rx mode (prescription only) was considered the most appropriate regulatory action. DXM monocomponent syrups and polycomponent tablets and syrups for cough treatment remained OTC available with request for periodic safety reports from MAHs (6-monthly, annually, with 3-years period). Following Rx switch in August 2017, intensive communication was initiated including: DHPC (3), web announcement (4), ADR bulletin (5), scientific publication (6), participation at local psychiatrists' conferences.

Results: Update in 2022: Rx switch led to withdrawal of both solid monocomponent DXM products authorised in CZ. Moreover, 2 polycomponent syrups were withdrawn, out of 12 DXM products authorised in 2017. The analysis of reports in Q2 2017–Q1 2022 ($n = 47$) showed listed ADRs in therapeutic doses of DXM ($n = 11$), unintended exposure to children ($n = 4$), historical literature cases ($n = 6$) and cases of misuse reported retrospectively from TIS ($n = 26$). Few comments from DXM abusers of syrup followed by gastrointestinal ADRs with no or little psychogenic effect were identified in non-scientific discussions (2). The public exposure to DXM has been successfully limited and no new reports of misuse were identified in SUKL database.

Conclusion: This topic shows the importance of spontaneous reporting to the authority which enables strict regulatory action and thus provided useful feedback to HCP to enhance the reporting of ADRs. Rx switch led to desired effect on significant decrease in DXM misuse.

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Survey on Pharmacovigilance Knowledge and Activities in Sardinia

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Introduction: In the Sardinia region, over the years, several awareness-raising programs have been launched to promote reports of adverse reactions (ADRs). Despite this, there are low numbers of spontaneous reports of adverse reactions annually [1–3].

Objective: A survey was developed and administered to all health professionals (e.g. doctors, pharmacists, nurses and socio-health workers) with the aim of evaluating their knowledge on pharmacovigilance and identifying targeted intervention actions to compensate for any lack of information and lead to an implementation of the number and quality of reports.

Methods: The survey, consisting of 11 questions, was sent electronically to healthcare professionals in Sardinia. The answers were recorded from 02/25/2022 to 05/10/2022. In the first part, general information on the profession and workplace was collected, in the second part questions on pharmacovigilance were asked.

Results: 113 people responded to the survey, 51% doctors, 25% pharmacists, 13% nurses and 11% other health workers. 77% of the participants said they observed at least 1 adverse reaction, but of these 40% said they never reported ADRs. The main reasons for not reporting include: the adverse reaction was already known, i.e. present in the summary of product characteristics (SmPC) (34%), the adverse reaction was not serious (29%), it was not sure that the adverse reaction was caused by the medicine, the reporting methods take too long (12%). The 57% of the participants said they were unaware of the existence of drugs subjected to additional monitoring and the 30% after seeing the additional monitoring symbol and its explanation said they did not understand its meaning.

Conclusion: In order to promote pharmacovigilance activity, a poster will be distributed to clarify to healthcare professionals that they must report all adverse reactions of which they become aware, both those already known and present in the SmPC and those that are not serious. It will be clarified that each report sent constitutes suspicion of an adverse reaction and that only thanks to the large collection of specific reports for a particular drug is it possible to trace the causal link between the drug administered and the observed ADR. Therefore, they are all encouraged to report to increase data flow. The significance and importance of additional drug monitoring will also be explained.

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Patch Tests and Cross-Reactivity Among Antiepileptic Drugs

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Introduction: Cross-reactivity (CR) has been reported among anti-convulsant drugs, known to cause cutaneous adverse drug reactions (cADR). However, inconsistent results among studies evaluating patch-testing usefulness for cross-reactivity are frequently reported.

Objective: To investigate the risk of cross-reactions documented through patch test (PT) among antiepileptic drugs (AED) based on a review of the literature.

Methods: Research was carried out to find data on PT performance in patients who had presented cADR after AED exposition. Articles matching keyword search “cross-reactivity” AND “antiepileptics” and “Patch-Test” AND “antiepileptics” were retrieved. From 609 references matching keyword search, 84 articles were included for preliminary analysis; of these, 31 were excluded for absence of individual data for a total of 51 articles (n = 340 patients): 37 publications included only PT results for the initial suspect (IS) of cADR and 14 publications included patch testing for the IS and other AED.

Results: Carbamazepine (CBZ) was the IS in 88% (n = 301) of patients. For publications that tested only patients for the IS, 52% of the PT were positive; for publications testing other drugs than the IS, the patch tests were 50% positive (n = 63) for the IS.

Data on cross reactivity explored by patch tests included 113 patients; among them, CBZ PT, which was the IS, was positive for 57% of them. Other PT included: 26 for lamotrigine, with 12% PT positive; 11 for phenobarbital (PB) all negative; 41 for phenytoin with 27% positive; 10 for valproic acid all negative and 95 for oxcarbazepine with 19% positive.

Among patients with PB cADR (n = 10), only 7 patients were included. Six had a positive PT. Results for other PT included: 7 patients for CBZ with 1 patient positive, 6 patients for valproate sodium, none positive and 1 patient to oxcarbazepine, negative.

Among patients with lamotrigine cADR (n = 2), PT to the IS was positive; 1 patient was tested to CBZ, negative and 1 to phenytoin, PB and gabapentin, all negative.

One patient with cADR to oxcarbazepine was tested negative to all PT, the IS, CBZ and phenytoin; finally one patient with cADR to phenytoin was positive to the IS, but for negative to CBZ.

Conclusion: Literature data on PT doesn't allow concluding on CR risk assessment between AED. For the IS, PT was negative in half of them. For other drugs, the numbers of positive PT remain low, including drugs with similar structures as CBZ and oxcarbazepine. A case-by-case evaluation on potential AED cross-reactions should be privileged.

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Stevens-Johnson Syndrome Induced by Lidocaine at the University Hospital of Libreville in Gabon: A Case Report

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Introduction: Stevens Johnson syndrome (SJS) is an acute toxidermia characterized by abrupt destruction of the superficial skin layer and mucous membranes [1]. With the exception of some idiopathic cases, Stevens-Johnson syndrome is usually triggered by drugs or associated with infections [2]. In this report, we present a first case notified at the University Hospital of Libreville as a serious adverse reaction during a prospective study on the monitoring of serious adverse reactions at the University Hospital of Libreville. This is the first study of its kind on Pharmacovigilance in Gabon. It reports the case of a patient who developed SJS after taking lidocaine hydrochloride.

Objective: To study the occurrence of SJS as an adverse event and to identify the cost of its treatment/management.

Methods: The patient is a 28-year-old man who was hospitalized after the development of cheilitis and non-pruritic erythematous papules on the plantar surface of the feet and on the palm of the hands compatible with SJS. His case was monitored for a period of 8 days at the Dermatology Department of the University Hospital of Libreville, Gabon. Medication management consisted of dextchlorpheniramine, pantoprazole, tramadol, demiconazole, fusidic acid and lidocaine.

Results: Complete blood count (CBC), red blood cells (RBC) = 8130/mm³ (Norm = 4500 to 11,000 per microliter and therefore normal); Hemoglobin (HB) in men = 17.1 g/dl (Standard = 14 to 17 g) and therefore normal; Platelet = 108,000/mm³ (Norm = 140,000 to 250,000 μ l explaining the bleeding disorder without anemia or leukopenia; CRP = 100 mg (norm, lower than 6) and therefore an inflammation instead of an infection and that it is an SJS. We note that the reaction was acute and severe, with the appearance of the first signs of pain and redness a few hours after taking the Lidocaine. The global direct medical cost during his hospitalization was 341,22 Euro.

Conclusion: Stevens-Johnson syndrome may also be a Type B adverse effect caused by lidocaine.

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inflammatoires cutanées/syndrome de Stevens-Johnson et/ou érythème multiforme exanthématique aiguë. Le syndrome de Stevens-Johnson, les causes et les plus fréquents.

P203

Experience in Communicating Vaccine Side Effects in a Covid-19 Population Vaccination Centre in North-East Italy

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Introduction: Our hospital operated a population vaccination centre (CVP) in Verona between March and August 2021, administering an average of 2000-2500 anti-SARS-CoV-2 vaccinations per day. Risk communication offers a methodology for assessing the risk perception of vaccines; managing high volumes of activity may need to consider the ways and processes of communicating the risk of adverse events [1-2].

Objective: What to improve for better risk communication in CVP during a mass-vaccination campaign; compare the differences between reports detected by hospital, regional, and national pharmacovigilance.

Methods: A fact sheet was produced based on the guidance of the ministry of health and the drug agency. It was possible to look up information regarding vaccine adverse events during online booking. Multiple videowall were installed before the medical check. Healthcare workers were trained on adverse event risk communication and reporting methods: an online dataset was collected and shared online to physicians involved in the vaccination campaign. Moreover through a surveillance conducted between March and August 2021, we asked users about their level of satisfaction with the information they received regarding clarity, completeness of information received, and informed consent form. We collected adverse event reports from the Verona hospital through 2021; we collected data from regional reports and from AIFA reports. We compared the hospital data with regional and national data.

Results: Survey collected 3871 answers; about information area 71.10% were “extremely satisfied”. Who were dissatisfied requested more information materials at each stage of vaccination: before (information about vaccines), during (information about procedures and side effects) and after the vaccination session (more complete information on how to report adverse events). Staff area (medical and nurse) collected 88.40% “extremely satisfied”. AOVR collected 392 reports of adverse events (356 [99.82%] non serious and 36 [9.18%] serious); Veneto collected 15,982 (14,513 [90.82%] non serious and 1,468 [9.18%] serious); National data were 97,846 (83,967 [85.93%] non serious and 13,741 [14.06%] serious) [3-5].

Conclusion: The management of risk communication during the operation of a population centre (CVP) was perceived with satisfaction by the users. The values of adverse event reports received by AOVR’s pharmacovigilance system are comparable with regional data and serious events are lower than national data. Integrations in

risk communication may be useful at different points in the vaccination process.

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P205

Impact of Risk Communication on the Number of Pharmacovigilance ICSRs in Brazil

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Introduction: Since December 2018 the Brazilian Health Regulatory Agency (Anvisa) adopted the system VigiMed (Brazilian name given to VigiFlow), to receive the Individual Cases Safety Reports (ICSRs). Since March 2021, it has intensified the implementation of risk communication strategies like the publication of alerts and notices, the promotion of online events open to the general public.

Objective: Check whether the greater interest in pharmacovigilance topics on the internet and Anvisa’s risk communication had an impact on the increase in ICSRs.

Methods: This study where were compared the interest on the internet for searching the terms like “VigiMed”, “report of adverse event”, “how to report” and “adverse reaction” (terms in Portuguese) and the impact on the number ICSRs forwarded to the Agency, collected through Google Trends (terms), VigiMed (notifications) and Anvisa’s website (risk communication actions). The study period was from 1st March to 15 June 2021. It was considered as an impact the increase of ICSRs above the average after up to 72 hours of the risk communication actions or interest in the terms related above.

Results: After the 19 risk communication actions in the period evaluated, there were an increase in ICSRs in 15 (79%). In 13 actions, categorized as alerts and communications, an increase in reports from health professionals and pharmaceutical companies was identified. In the other two actions, consumers were the main reporters and seem to have been impacted by online open events and in interviews with mass media—the two actions that had the greatest impact. Looking at terms, 11 of the 12 peaks of interest for “VigiMed” coincided with 6

communication actions and resulted in an increase in notifications in 5 moments. Interest in the term “report of adverse event”, improved after the publication of 3 alerts, but it did not affect the number of reports received. The term “how to report” was the most interesting in the period evaluated, with 25 peaks, which coincided with 18 risk communication actions and with 11 peaks of increased ICSRs.

Conclusion: Despite being a preliminary study and with the possibility of bias from other actions such as the dissemination of objects related by the media, there is a coincidence between the interest of internet users in topics related to pharmacovigilance and the increase in ICSRs sent to the Anvisa. Another importance of the study is knowing the terms of interest can support the language to be used in risk communication.

References/Further Sources of Information

Not applicable.

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Digital Risk Minimization Measures: Qualitative Feedback from Healthcare Professionals in Egypt

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Introduction: Routine risk minimization measures (rRMM) are implemented for all pharmaceutical products, aiming to provide Healthcare Professionals (HCPs) and patients with information on a product’s risks and benefits [1, 2]. However, some products may also require additional risk minimization measures (aRMM), which cover major risks and describe actions that should be taken upon risk occurrence [1, 2]. Such aRMM are usually distributed in a paper-based form to HCPs, which has its limitations. Therefore, digital versions of these aRMM have been under discussion in many pharmaceutical companies. An exploratory study by Da Silva-Tillmann et al [3] showed that HCPs and patients in 6 countries were open to the idea of digital tools for aRMM, and we sought to gain an initial impression of whether this would apply to HCPs in Egypt.

Objective: This study aims to understand reactions of Egyptian HCPs to the idea of using digital tools for aRMMs along with or instead of paper tools.

Methods: A digital aRMM tool was presented to Egyptian physicians, through a short video and tool demonstration. A questionnaire, distributed through social media platforms, was then used to gather HCP feedback.

Results: The majority of responders were physicians from a variety of specialties (88%) and 12% were pharmacists. 90.9% of the HCPs who took the questionnaire thought that they would benefit from digital aRMM. Regarding the usefulness of the proposed features, 94% of respondents felt that information on safety concerns was useful, with 84% supporting inclusion of a prescribing guide, 79% finding emergency treatment information useful and 64% seeing benefit from a section on “information to discuss with your patients”. In terms of whether a digital tool would be used instead of or alongside paper, 48.5% of respondents preferred a combined approach, with 51.5% supporting the use of digital alone. Nearly two-thirds of the HCPs surveyed would prefer to access a digital tool through a website and a mobile application, with only 3% preferring a website alone and 33% favoring an app-led approach. Sixty-six percent of respondents

believed that a digital aRMM tool for patients would be useful for those in their care.

Conclusion: Digital tools are widely used in healthcare and beyond, and may offer opportunities to improve HCP and patient engagement with key safety information. The responses of the HCPs sampled in this study suggests that the use of digital aRMM in Egypt may be an area worthy of further research.

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P207

Risk Communication about Medicines: Initiatives for improving in Saudi Arabia

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Introduction: Pharmacovigilance risk management is composed of four main tasks; risk identification, risk assessment, risk medication and risk communication. Risk communication largely depends on active human interaction to be effective.¹ The purpose of communicating drug safety information for healthcare providers (HCP) and the patient is to ensure the safe and effective use of medications post-marketing, which is one of duties of the Saudi Food and Drug Authority (SFDA).

Objective: To share the Drug Safety and Risk Management Department (DSRM) initiatives for improving risk communication about medicines targeting healthcare providers (HCP) and the patients.

Methods: We included all initiatives targeted HCPs and patients that were performed in 2021 to improve risk communication about medicines such as; scientific activities, short messages, training programs, publishing articles, animated videos as well as short videos.

Results: DSRM at SFDA performed in 2021 many scientific activities directed to HCP such as; 36 educational lectures about pharmacovigilance and risk communication, 4 workshops conducted by local and international speakers in topics about vaccine safety, additional risk minimization measures (aRMMs) and risk communication, safe use of medications during pregnancy and drug interactions). In addition, DSRM conducted two training programs directed to Health Educators and Medication Safety Officers in different hospitals at Saudi Arabia to improve the application of aRMMs. Furthermore, in cooperated with pharmaceutical companies, DSRM performed 97

animated videos about approved aRMM directed to HCPs that will be published on the SFDA aRMM e-learning platform. Moreover, DSRM prepared over than 30 risk communication short messages that published on SFDA application “Tammini”. DSRM made efforts to improve safe and effective use of medications directed to the public e.g. Published 20 articles in Arabic in SFDA websites and 13 short videos in media of the SFDA about medication safety.

Conclusion: The DSRM at SFDA use different tools to improve risk communication about medicines in Saudi Arabia. A constant exchange of information and communication between regulatory authorities and its stakeholders such as pharmaceutical companies, healthcare professionals, patients and health sectors should be maintained and improved to ensure proper delivery of risk communication about medicines to the target audience.

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P208

Risk Communication: Ensuring an Appropriate Benefit Risk Ratio in the Safety Profile of a Medicinal Products in Ghana

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Introduction: Risk communication can be defined as the open, two-way exchange of information and opinion about the harm and benefits. In the pharmaceutical industry in Ghana, one major way of communicating risks and benefits associated with a drug product to patients is through the patient information leaflet. This patient information leaflet (PIL) seeks to address the actual risk, the perceived risk as well as to explain why it matters to the patient or individual taking the drug product. However, several factors tend to interfere with the effectiveness of this approach. Notable among these factors are literacy, age, poverty. In view of this, effective communication supports the optimal use of medicinal products

Objective: To develop principles to guide consistent and easily understood patient information leaflets to patients.

Methods: Questionnaires were administered to randomly selected patients. A total number of 100 patients were involved in the study. The questionnaire sought to identify: 1. Patients who read the Patient Information leaflet 2. Patients who read and understand the Patient Information Leaflet 3. Patients who read and understand the Patient Information Leaflet and adhere to the details provided in them.

Results: The results showed that, out of the 100 patients who participated in the study, 56 of the patients could not read and understand the Patient Information Leaflet, 44 of the patients could read the Patient Information Leaflet. Out of the 44 patients, 16 of the patients could easily understand whereas 28 did not understand Out of the 16 patients, 12 patients adhered strictly to the instructions and 4 did not.

Conclusion: The study has been identify that, several patients could not read the Patient Information Leaflet and that it will recommended that Healthcare professionals, Pharmacists, Medical Counter Assistants (MCA's) should educate patients who purchase drug products from their respective outlets on all the vital instructions recommended for the Patient to adhere to. Also, for those who are able to read but do

not understand, a user friendly Patient Information Leaflet in plain language should be used.

References/Further Sources of Information

Upsulla Monitoring Center.

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Decision Tree to Distinguish Important Urgent Safety Concern Types and Other Safety Concerns to Fulfill Reporting Requirements

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Introduction: In the European Union (EU), a new Regulation for clinical trials of medicinal products came into effect 1st February 2022 specifying new requirements and timelines for important and urgent safety concerns (IUSCs) [1]. Also, globally, the requirements and guidance on IUSCs continue to evolve for clinical trials (CTs) and the post marketing (PM) setting, requiring a global and standardized approach.

Objective: A decision tree was developed to improve harmonisation of safety concern assessment and classification, thus reducing the possibility of inconsistent global submissions to Health Authorities (HAs).

Methods: The decision tree distinguishes between CT and PM scenarios. As active substances can have a marketing authorization while still being used in clinical trials, both paths may need to be followed. In the CT setting, if the safety signal has a potential impact on the benefit-risk balance or the overall conduct of a CT, it is important to decide if prompt notification and/or action is required. If it is, the IUSC can be classified as follows: (1) Urgent safety measure (reportable within 72 hours, EU within 7 days), (2) Unexpected event (reportable within 15 days), or (3) Temporary halt/early termination (reportable within 15 days). If the safety signal does not require prompt notification or action, an “other concerns” classification is followed: (1) Temporary halt in accordance with the protocol (reportable prior to restart), (2) Early termination (e.g., due to low recruitment/end of development; reportable within 15 days), or (3) Change in conduct of CT (e.g., increased monitoring measures; reportable as a substantial amendment in accordance with internal timelines). In the PM setting, IUSCs are classified as follows: (1) Emergent safety issue/significant safety issue (reportable within 72 hours, EU 3 business days), (2) Dear Health Care Professional Letter (as agreed with HA), or (3) Urgent safety restriction triggered by the marketing authorization holder (notification within 24 hours followed by a variation submission within 15 days). Other safety concerns are classified as follows: (1) Important risk (submitted within 3 months) or (2) Non-important risk (submitted within 6 months).

Results: The IUSC decision tree streamlined and harmonized the implementation of global regulatory requirements, allowing the marketing authorization holder to provide a consistent classification of safety concerns and timely information to all impacted HAs.

Conclusion: The enhanced tool supported teams in decision making regarding the classification of safety concerns and minimized inter-country variability in interpretation.

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Evolving Global Requirements for Signal Notification to Health Authorities: How to Standardize and Harmonize Signal Communication

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Introduction: Globally, the requirements and guidance on signal communication provided to marketing authorisation holders (MAHs) have evolved, requiring a global and harmonised approach with the aim to provide all Health Authorities (HAs) with the same information on signals, ideally at the same time.

Objective: Define a global end-to-end process to streamline the signal information provided to HAs of International Reference for authorized medicinal products for human use respecting all global HA requirements while maintaining high scientific standards of signal communication.

Methods: The oversight role of the Qualified Person for Pharmacovigilance (QPPV) in European Union (EU) was expanded to play an active role in the harmonized signal communication to HAs. Upon receipt of an MAH- or HA-identified signal or a HA-imposed safety action in the scope of the process (Day 0), a “QPPV Notification” is drafted by the QPPV Office. This draft is subsequently reviewed by subject matter experts, who are the MAH’s pharmacovigilance (PV) and regulatory professionals (Day 1). The decision to disseminate is made by the EU QPPV and is communicated to the MAH affiliates on Day 2. Country PV and regulatory personnel determine the appropriateness of notification to the country HA. This notification is performed in accordance with local regulatory requirements using the standard scientific wording provided in the QPPV Notification, ensuring that HAs worldwide receive the same information (Day 3). In the case of country-specific requirements, such as additional data (information, documents, etc.), these are provided to the HA as appropriate. The HA notification decision is independent of any subsequent regulatory activities. All HA notifications worldwide are internally tracked using the same unique identifier/code, provided by the QPPV Office to enable end-to-end oversight, from receipt (input) until notification (output) at the country level.

Results: The implementation of the streamlined process ensures global regulatory requirements (e.g., EU [1], UK [2], Switzerland [3], Saudi Arabia, [4], and Australia [5]), are met and the MAH provides consistent and concise signal information to all HAs.

Conclusion: The active role of the QPPV Office and the re-defined global process has been demonstrated to be effective in providing timely and consistent safety information to HAs around the world.

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Riluzole Prescribing Beyond Therapeutic Indications in Clinical Practice

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Introduction: Riluzole is a drug indicated to improve survival and time free from invasive mechanical ventilation (or tracheostomy) in individuals with amyotrophic lateral sclerosis (ALS). Riluzole is contraindicated in the presence of renal and/or hepatic impairment, after tracheostomy, or in patients with an ALS history of more than 5 years, and during pregnancy and breastfeeding [1-2].

Objective: This brief analysis aims to describe the use of riluzole in ALS individuals with contraindications and the off-label use for subjects with other motor neuron diseases (o-MND) in three Italian regions.

Methods: A cohort of adults diagnosed with ALS and incident users of riluzole during the years 2016-2019 was enrolled from administrative databases of Latium, Tuscany and Umbria, excluding subjects with o-MND in the preceding 5 years. Being affected by ALS for more than 5 years, presence of tracheostomy, renal or hepatic failure were considered as contraindications to riluzole use. A cohort of adults affected by o-MND was enrolled in 2016–2019, for whom off-label use of riluzole was retrieved, analysing over the time differences related to sex and Italian region.

Results: Among 206 ALS individuals prescribed with riluzole in Latium, 336 in Tuscany and 60 in Umbria, less than 1% were diagnosed with ALS for more than 5 years. Less than 2% had undergone tracheostomy or were affected by hepatic failure. Renal failure was documented for 1.9%, 2.7%, and 5.0% of ALS individuals in Latium, Tuscany and Umbria. The o-MND cohort comprised 264 subjects in Latium, 222 in Tuscany, and 66 in Umbria. Non-negligible off-label riluzole use was observed: 8.5%, 33.0%, and 4.2% in females, and 19.9%, 26.5% and 2.4% in males in Latium, Tuscany and Umbria.

Conclusion: These preliminary findings highlight that riluzole use in ALS in the presence of contraindications was rare, and its off-label use in o-MND was found to be non-negligible.

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A Safety Profile Analysis of Adverse Events After Measles-Mumps-Rubella and Varicella Immunization Based on Italian Pharmacovigilance Network in Veneto Region

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Introduction: Immunisation against measles, mumps, rubella and varicella can be achieved with two different strategies: the combination of measles-mumps-rubella (MMR) vaccine (available in Italy since the early 1990s) at the same time with the varicella vaccine (V) since 2005, or the use of the combined measles-mumps-rubella-varicella vaccine (MMRV) available in the Veneto region since 2007. Several studies have compared the immunogenicity, reactogenicity and side effects of the two strategies since the introduction of MMRV [1-3]. There is evidence that shows a potential increased risk of febrile convulsions with the first dose of MMRV vaccine: several post-marketing surveillance studies have shown an approximately 2-fold increase for MMRV [4-5]

Objective: To compare the safety profile of MMR + V and MMRV by analysing data from the Italian spontaneous reporting system in Veneto region.

Methods: All reports coming from the Veneto Region related to MMRV or MMR+V vaccines and sent to the national pharmacovigilance database up to the end of March 2022 were included. Among each vaccine group the proportion of reporting AEFI and the proportion of serious events were compared. Adverse events were grouped according to the Medical Dictionary for Regulatory Activities (MedDRA).

Results: A total of 5662 reports related to MMRV and 3848 reports related to MMR + V were retrieved and analysed. A high number of these reports was collected within an active surveillance project on the safety profile of the first doses of both schedules. Most of the reports referred to infants (1 month to < 2 years 94.5% of total reports for MMRV versus 99% for MMR + V) and children (2–11 years 5.3% for MMRV versus 0.6% for MMR + V). Proportion of serious reports was 19.7% (1116/5662) for MMRV and 9.7% (375/3848) for MMR + V. Preferred terms (PT) most frequently reported were pyrexia (45.5% for MMRV versus 29.5% for MMR + V), morbilliform rash (10.3% vs 12%) and post-vaccinal irritability (7.8% vs 14%). Among serious events the most frequent was hyperpyrexia (9% vs 3.7%, on the total PT reported). Febrile convulsions were 157 for MMRV (2.8%) and 43 for MMR + V (1.1%) 140 febrile convulsions were reported in 1% of MMRV reports and 0.4% of MMR+V.

Reports of thrombocytopenia were 15 associated to MMRV (0.1%) and 1 to MMR+V (0.01%).

Conclusion: Data from spontaneous reporting show some differences in the risk profile of MMRV in comparison to MMR + V, in line with data from the literature.

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The Case Review Vignette

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Introduction: Review of case data is a significant activity for the preparation of aggregate reports, signal detection, safety topic reviews, and health authority queries

Objective: The Case Review Vignette is aimed at reducing overall review time by accessing the needed information outside of the corporate safety database (CSD).

Methods: The experiment involved identification of data fields needed for review beyond the OOB CIOMS attributes, creation of an extensible framework in the semantic layer, portability of the solution to various visualization interfaces, and multi-lingual capability. After discussions with user communities in the internal safety organization, over 100 fields corresponding to case data were identified for display in the vignette. A user interface comprising the identified data elements was created in the enterprise reporting tool. The interface can be connected to various ecosystems using HTTP and can produce data output in multiple formats, including Microsoft Excel and PDF. The interface can be generated for a single case, a single patient, or in bulk (for a study, site, or asset).

Results: On average, the vignette was generated in 4 seconds, whereas opening the case in the CSD required 56 seconds. Also, the report allowed review of multiple cases simultaneously, versus only one case at a time for the CSD. The interactive option enabled data output to be embedded as a hyperlink in the parent report as well as the exported versions.

Conclusion: Case Review Vignettes have been incorporated as an interactive option in various aggregate and ad hoc reports. Over the past year, 44 Safety Topic Review Reports were generated with an average of 100 cases for review, 41 DSURs were generated with an average of 100 cases for review, 12 PBRERs were generated with an average of 200 cases for review, 8 PADERs were generated with an average of 10 cases for review, 3 Secondary Primary Malignancy Reports were generated with an average of 200 cases for review, 2000 cases were reviewed for health authority re-examination purposes, and other ad-hoc reports were generated with an average of 200 cases for review. The data output interface saved approximately 200 work hours for the user community in a year. This framework significantly improved the response time for health authority requests and inter-departmental interactions

References/Further Sources of Information

Not applicable.

P220

Expansion of VigiFlow® Network to a Third Level for Post-Marketing Surveillance of COVID-19 Vaccines in Iraq

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Introduction: During the COVID-19 vaccines' deployment into health institutions (hospitals, primary public health centers (PPHCs)); there was a great need to establish a robust pharmacovigilance system to follow the COVID-19 vaccines' safety. Integrating both EPI and Iraqi pharmacovigilance center (IPC) systems at different levels to enforce the documentation, share COVID-19 adverse events following immunization (AEFIs), and effectively communicate safety information was crucial.

Objective: Describe the steps taken to introduce a third level of the VigiFlow® network at the level of hospitals and public health districts (PHDs).

Methods: The VigiFlow® network was expanded to include not only the 18 regional centers, but also the hospitals where the COVID-19 vaccines were deployed and the PHDs that are connected to the PPHCs. In order to integrate the proposed system for monitoring AEFIs of COVID-19 vaccines; the EPI manager at each Directorate of Health, granted access to the regional center database (VigiFlow®). Likewise, national EPI representatives would also have access to the national database at the ministry level (IPC). At the IPC level, the pool of data from all over the country will be available for analysis, signal detection, and decision-making.

Induction training program was performed in collaboration with the WHO and EPI. An Arabic manual for using VigiFlow® for AEFIs was distributed to users. UMC educational videos on how to use the VigiFlow® were translated into Arabic and shared with all participants to facilitate the use of the VigiFlow®. A special guideline document was created with simple and comprehensive explanations of the AEFI reporting form(s) and how to transfer the information from the paper form to the VigiFlow® system. pharmacovigilance officer at the national center was assigned the mission of supporting all the VigiFlow® users across the country.

Results: The results showed that 56% of the total COVID-19 vaccine VigiFlow® AEFI reports were received through 3rd level VigiFlow® organization users. Around 30% were active and sent more than 10 reports per year, representing 33.3% of hospitals and 29% of PHDs. Only 12% of these organizations shared more than 100 reports. The highest number of reports shared in one month was 905 AEFIs reports during August 2021. During December 2021, the highest number of

3rd level VigiFlow® organizations sharing AEFIs reports in a single month was 35.

Conclusion: The VigiFlow® system was successfully used as a national COVID-19 vaccine AEFIs database, with hospitals and public health districts serving as third level.

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Genital Itching and Other Genital Discomforts Associated with the Parenteral and Oral Clindamycin in VigiBase

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Introduction: Parenteral and oral clindamycin can cause cases of pruritus and vaginitis[1,2,]. However, genital itching can be a characteristic of vaginitis, but it is not the only one since it has other factors that can be use by antibiotics [3,4]. These clinical manifestations are not described in Summary Characteristics Product (SmPC).

Some antibiotics (cephalosporins) describe genital pruritus as a rare adverse reaction [5,6,].

Objective: Evaluate the possible causal relationship between the use of clindamycin and genital itching and other genital discomforts in VigiBase™.

Methods: We performed a retrospective observational study in VigiBase™, with the distance tutoring of the Uppsala Monitoring Center (UMC), selecting only individual case safety reports (ICSR) associated with Clindamycin (oral and parenteral) and genital itching and genital discomfort (vulvovaginal discomfort, pelvic discomfort, vulvovaginal pruritus, genital burning sensation, vulvovaginal burning sensation, vulvovaginal itching sensation)

Results: To December 2020 a total of 157 ICSR in VigiBase™ were identified for association Clindamycin and genital itching and other genital discomfort, 112 ICSR were excluded. The expected value of reports to association was 64 (including those from Peru) with an IC: 1.3 (IC_{0.25} = 1.1). In Peru all cases (12) were reported by healthcare professionals. Globally, were identified 15 ICSR from consumer.

45 ICSR (female) included 47 adverse reactions and genital itching (20) and vulvovaginal itching (15) were the most reported. The time to onset was 2 days (median). The age in the reported cases ranged from 8 to 76 years (median: 42 years). Co-reported reactions related to the genitourinary area describe: anal itching, genital tract inflammation, genital infection, vulvovaginal swelling, genital swelling and vulvovaginal rash.

53% (24) reported the use of clindamycin with other suspected drugs, while 47% (21) did not report drugs other than clindamycin. The time of onset of the adverse reaction was mostly (64%, n = 29) reported in the first 5 days of treatment. It was observed that, in 25 (29%) reports the withdrawal of the drug presented a disappearance of the adverse reaction (24) ICSR describe other indications: animal bite, osteomyelitis, sinusitis, prophylaxis, pneumonia and mammary infection, bronchiectasis, acute tonsillitis, wound, herpes zoster and other lung disorders, as well as related with dental procedures.

Conclusion: In this study, has found mostly non-serious reports of genital itching and other genital discomfort in female. Despite limited information in ICSR, these discomforts could lead to unexpected treatment withdrawal and generate bacterial resistance, so health care

professionals are advised to take this information into account and perform additional follow-up.

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Monoclonal Antibodies Diseases Modifying Agents: A Drug Safety Surveillance Study in Patients with Multiple Sclerosis

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Introduction: The prevalence of multiple sclerosis (MS) has significantly increased worldwide and in Saudi Arabia over time, with estimated prevalence of (40.40/100,000 Saudi-nationals). Although there is still no cure available of MS, monoclonal antibodies diseases modifying agents (MABs) are one of the preferred treatments for MS due to their efficacy, however, their side effects remain a concern. Therefore, a post-marketing surveillance program was implemented to monitor the safety of MABs in real-world setting by the Saudi Food and Drug Authority (SFDA). The objective of this study is to evaluate the safety profile of MABs (ocrelizumab, natalizumab, rituximab, and alemtuzumab) in MS patients.

Methods: A retrospective cohort study using real-world data from a tertiary hospital in Riyadh, Saudi Arabia was performed to detect safety profile of MAB in patients with MS. The Study included newly-treated patients with one of the MABs during the period from January 2015 to December 2021. The objectives were to identify adverse drug events (ADEs) associated with the use of MABs. The medical dictionary for drug regulatory affairs (MedDRA) was used to classify ADEs according to the System Organ Classification (SOC) and the Preferred Term (PT). Moreover, ADEs were classified based on the seriousness, and expectedness, according to SFDA guidelines on Good pharmacovigilance Practices.

Descriptive analyses were performed, including frequency/percentages for categorical variables and mean with standard deviation or median with range for continuous variables. All ADEs were

crosschecked listing with local summary product characteristics (SPC), United States Food and Drug Administration (FDA) drug label, and European SPC to identify new safety signals using the scheme illustrated in Figure 1.

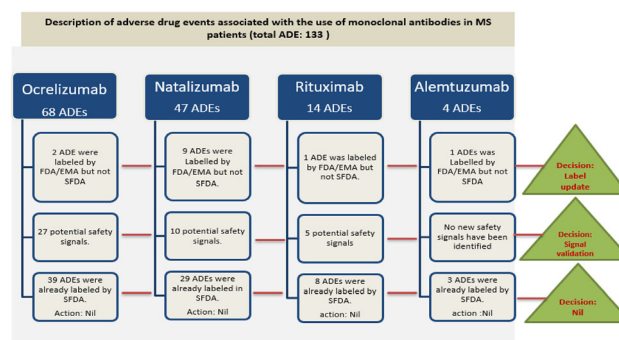
Results: Two hundred-fourteen patient's records met the eligibility criteria. There were 144 patients on ocrelizumab, 46 on natalizumab, 19 on rituximab, and 4 on alemtuzumab. Their socio-demographic characteristics are summarized in Table 1.

Table 1: Demographic characteristics of the study population (n = 214)

No. of cases/patients	Total N=214
Demographics	
Male	73 (33.6%)
Female	142 (66.3%)
Age, years [Mean (SD)]	33.33: 8.77 yr. (14-65)
Patient with ADR	87 (35.95%)
Disease Duration in Years (Median)	6, 5.51 years (1-34)
DMAs	
Ocrelizumab	144 (67.3%)
Natalizumab	47 (22 %)
Rituximab	19 (8.8%)
Alemtuzumab	4 (1.9%)
Line of treatment	
First	67 (32 %)
Second	88 (41 %)
Later	58 (27 %)

A total of 133 ADEs were reported with the use of MABs including 55 serious ADEs. Based on the local and international product information assessment, there were 42 unexpected ADE (potential signals), 79 known and labeled ADEs, and 13 ADEs not labeled in the local product information label but included in the product information label approved by the FDA or European Medicines Agency, no fatal ADEs have been reported. Fig 1

Figure 1: Decision tree for categorization of reported ADEs during assessment



Conclusion: This study shows an acceptable safety profile of MABs in MS patients. Besides, it reports data that identified new safety signals not previously addressed in the local and international product information label, which need further investigation. Thus, there are strong motives for implementing similar programs to provide data for updated risk-benefit analyses.

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Adverse Events Related to Lutetium (177Lu) Oxodotreotide (Lutathera): “Real-Life” Data from the Eudra-Vigilance Database

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Introduction: Gastroenteropancreatic neuroendocrine tumours are a heterogeneous group of neoplasms that originate in endocrine tissues throughout the body characterized by an overexpression of somatostatin subtype 2 receptor, with an increasing incidence [1]. On September 2017 the European Medicines Agency (EMA) approved lutetium (177Lu) oxodotreotide (Lutathera) through the centralized procedure based on the pivotal study Netter-1 [2]. This medicine was designated as an orphan drug and an additional monitoring was decided [3]. Lutathera was launched on the Italian market on October 2018 (class C non-negotiated) and on May 2019, the Italian Medicines Agency (AIFA) classified it in reimbursement's class “H” and its therapeutic innovation was recognized [4,5]. Related to the increased use of Lutathera in the real-world setting, important safety signals have emerged that require further investigations.

Objective: This study aims to analyse adverse events (AEs) associated with Lutathera using real life data stored in the Eudra-Vigilance (EV) database over the last 12 months (up to 30/04/2022) and to compare them with data reported in the pivotal study [6].

Methods: AEs for Lutathera from April 2021 to April 2022 were extracted from EV database and processed with Microsoft Excel®, statistical tests were performed using Graphpad Prism®. Data are expressed in number and percentage (referred to all AEs on Lutathera reported in the EV database and in the Netter-1 trial, respectively) and classified per System Organ Class category. Real-world data and those of the pivotal trial were compared using chi-squared test (χ^2 ; CI 95%; p-value < 0.05).

Results: Data are reported considering the most clinically relevant categories based on the EPAR's Risk Management Plan (RMP). Real-life data confirmed that the most frequent AEs in patients treated with Lutathera were blood and lymphatic system, general, hepatobiliary, renal and urinary disorders and neoplasm as already stated in the RMP. Particularly, data from EV database show that patients treated with Lutathera have statistically significant higher risk of blood and lymphatic system ($\chi^2 = 14.62$; $P = 0.0001$), general ($\chi^2 = 26.94$; $P < 0.0001$), hepatobiliary ($\chi^2 = 17.04$; $P < 0.0001$), renal and urinary disorders ($\chi^2 = 5.195$; $P < 0.0226$) and neoplasm ($\chi^2 = 47.22$; $P < 0.0001$), when compared to patients included in Netter-1 trial (Table 1).

Table 1. AEs reported in EV database and Netter-1 study.

Adverse Events	Lutathera ¹ n (N)	Pivotal study (Netter-1) n (N)	P
Blood and lymphatic system disorders	208 (17,34%)	57 (17,23%)	<0.0001
General disorders	385 (31,67%)	90 (21,44%)	<0.0001
Hepatobiliary disorders	54 (3,37%)	4 (8,16%)	<0.0001
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	148 (8,84%)	13 (13,57%)	<0.0001
Renal and urinary disorders	13 (0,80%)	13 (13,57%)	<0.0001

Conclusion: The analysis confirms the Lutathera's AEs emerged during the pivotal trial and also the need to monitor its safety profile as committed in the EPAR RMP [3]. Waiting for the results of its long-term use, clinicians should be aware of these updated data on Lutathera when treating patients in the daily practice.

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A Retrospective Analysis of Adverse Drug Events Leading to Hospitalization or Prolonged Hospitalization in Saudi Arabia

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Introduction: Adverse Drug Events (ADEs) are a well-known cause of hospital admission and prolonged hospitalization. To our knowledge, no data regarding the rate and frequency of ADE-related hospitalization in Saudi Arabia has been published. With the majority of ADEs being preventable, we seek to identify the frequency and characteristics of these events.

Objective: To measure the rate and percentage of ADEs leading to hospitalization or prolonged hospitalization in Saudi Arabia using the spontaneous reporting system.

Methods: A retrospective analysis of the Saudi Food and Drug Authority (SFDA) spontaneous reporting system for 12 months. All cases reported by health care providers that led to hospitalization or prolonged hospitalization from January 2020 until December 2020 were included. All cases that did not cause hospitalization or prolonged hospitalization were excluded. Reports that were received from the public or pharmaceutical companies and ADEs that were not

reported during the study period were also excluded. The outcomes include the rate and percentage of events associated with hospitalization/prolonged hospitalization, the age group and gender of patients in these reports, and the five most frequently reported events and medications related to hospitalization/prolonged hospitalization. All the findings were summarized using descriptive statistics.

Results: A total of 44719 ADR were reviewed, of which 1649 (3.68%) met the inclusion criteria, in which 547 (1.23%) caused hospitalization, and 1102 (2.45%) prolonged it. Amongst these reports, the majority concerned males with 932 (56.52%), and the rest were females. Regarding age groups, 590 (35.77%) reports were adults and 92 concerned the pediatric population (5.60%), and the rest were not specified. The most frequently reported medications associated with hospitalization/prolonged hospitalization were; Heparin (6.36%), Lopinavir; Ritonavir (5.21%), warfarin (4.7%), Vancomycin (4.18%), and Favipiravir (2.66%). The most frequently reported events associated with hospitalization/prolonged hospitalization were; hepatotoxicity (136, 8.25%), allergic reaction (103, 6.2%), Prolonged Partial Thromboplastin Time (PTT) (72, 4.36%), increased International Normalized Ratio (INR) (65, 3.94%), and acute kidney injury (48, 2.91%).

Conclusion: Although the percentage of ADEs associated with hospitalization remains relatively low, recommendations to achieve absolute medication safety should be placed. Future plans include increased efforts to promote awareness regarding medications frequently related to hospitalization and the implementation of future studies analyzing specific medications and events related to hospitalization.

References/Further Sources of Information

The Saudi Food And Drug Authority (SFDA) Spontaneous Reporting System.

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The Effect of the COVID-19 Vaccine on Menstruation and Hair loss Amongst the Saudi Population Using the National Reporting System

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Introduction: During the current pandemic, Covid-19 vaccination has become an indispensable solution for what used to be a normal life. Several side effects commonly reported with Covid-19 vaccination are injection site reactions, fatigue, and fever. Although not common, there have been some reports of hormonal disturbances such as menstrual irregularities and hair loss. A reasonable explanation of menstrual changes includes the effect of immune response activation on menstrual cycle driving hormones. Similarly, hair loss could be explained by the interrelation of the immune response with vaccination (1,2).

Objective: To determine the rate and seriousness of menstrual disturbance and hair loss events following COVID-19 vaccine administration in Saudi Arabia using the Saudi Food and Drug Authority's (SFDA) spontaneous reporting system.

Methods: a cross-sectional retrospective study measured the rate of spontaneous reports of hormonal change, including menstrual disorder and hormonal hair loss events, after the COVID-19 vaccine was received on SFDA electronic system from January 2021 to December 2021. All reports associated with hormonal change other than menstrual disturbance and hair loss were excluded. The SFDA manages

the Vigilance reporting System, which receives spontaneous reports from healthcare providers and the public. The study examines the rate and seriousness of the hormonal changes post-vaccination, specifically menstrual irregularities & hair loss (AEFI), for all covid-19 reports received from any stakeholders during 2021 and for all types of COVID-19 registered vaccines in Saudi Arabia including Pfizer (BNT162 vaccine), AstraZeneca (ChAdOx1-S) and Moderna (mRNA embedded in SM-102 lipid nanoparticles) vaccines.

Results: During the study period, a total of 280,000 Adverse events Following Immunization (AEFI) reports with COVID-19 vaccines were received. Of all reports, 58 reports concerning menstrual disturbance and 20 reports concerning hair loss were identified. The majority of reported hair loss cases were female (95%). By vaccines, BioNTech BNT162 (14), AstraZeneca (5), Moderna (1). On the other hand, (76%) of menstrual disturbance cases occurred after administering BioNTech BNT162, followed by (17%) AstraZeneca, and a minor percentage was with Moderna at (7%). Regarding seriousness, from the total number of cases reported, 97% were non-serious.

Conclusion: The association between hormonal disturbances and COVID-19 vaccines remains uncertain. Hence, further studies are warranted to investigate our observation. In conclusion, the key recommendation generated from the study is the implementation of awareness campaigns to promote an ADR reporting culture to correlate rare events occurrences with the use of COVID-19 vaccines.

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Assessing the Post-Marketing Experience of Drug Ineffectiveness Reports Received by the Saudi Vigilance System

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Introduction: Therapeutic ineffectiveness is a frequent drug-related problem that involves therapeutic failure, inefficacy or resistance, that includes both unintended and potentially harmful responses. Therapeutic ineffectiveness reports can also contribute to identifying pharmaceutical defects of drugs. Many problems with medicinal products may not arise during the initial, pre-marketing testing phases, and may become apparent only after they are released into the market. The goal of many regulatory bodies is to monitor drugs through rigorous testing and post-marking reports.

Objective: To evaluate the drug ineffectiveness reports received by the Saudi Vigilance System by:

v Determining trends associated with time, gender, age, and the Anatomical Therapeutic Chemical (ATC) classification system in the therapeutic ineffectiveness reports.

v Identify factors contributing to the reported therapeutic ineffectiveness.

Methods: Design: Cross-sectional study was conducted to assess the post marketing experience of Drug Ineffectiveness (DI) reports received by the Saudi Vigilance System (SFDA spontaneous reporting system) from January 2018 to December 2021.

Setting: The SFDA manages the Vigilance reporting System, which receives spontaneous reports from healthcare providers, Marketing Authorization Holders (MAHs), and patients directly.

Outcomes: The study will be focus on which drugs are reported as being therapeutic ineffectiveness, what age group and gender chiefly report therapeutic ineffectiveness, and who is primarily reporting the therapeutic ineffectiveness (HCPs, MAHs, or patients).

Results: A total of 2716 DI reports were included, in which the majority of them were reported from Health Care Providers (HCPs). Of all reports, 92% of the DI reports were classified as non-serious events and 8% of the DI reports were classified as serious events. Additionally, the study was found the percentage of males who experienced DI was higher than females.

Conclusion: Reports of unexpected ineffectiveness can provide important information about Drug Ineffectiveness (DI). As such, unexpected or unexplained ineffectiveness can be potentially vital reportable event in pharmacovigilance. Additionally, Drug Ineffectiveness can occur as a result of different situations and can be contributed to different mechanisms. Therefore, an extensive research should be conducted to address inappropriate use, interactions or metabolic abnormalities and other factors that might contribute to Drug Ineffectiveness.

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The Impact of Mobile Apps for Spontaneous Reporting: Experience from COVID-19 Vaccines Safety Surveillance

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Introduction: Web reporting is mandatory in Europe, but in the surveillance of COVID-19 vaccines specific web forms or apps were developed in several EU member states [1]. In UK for example, a native app for reporting was introduced in 2015. In Germany, a specific native app (SafeVac) was introduced in 2021, associated to an active surveillance project. In both countries a modified web form for covid-19 vaccines is present. In Italy no different web form or app for covid-19 vaccines-AEFI reporting were developed. In the Italian Veneto region, a progressive web app (Vigicovid) was developed and added to the Italian web form (Vigifarmaco) from February 2021.

Objective: To investigate the impact of Apps on spontaneous reporting for COVID-19 vaccines in these three countries in 2021.

Methods: The reports from UK and Germany in the period January–December 2021 were analyzed in VigiBase, the WHO global database of reported potential side effects of medicinal products, developed and maintained by Uppsala Monitoring Centre. Reports from the Apps were identified through the national country code. Reports in Veneto Region were analyzed in the regional database in the period February–December 2021. Reports sent from the Veneto vaccination registry through a direct link to spontaneous reporting database were excluded.

Results: In 2021 UK submitted 450,819 AEFIs (56% serious, 85% from patients) to VigiBase, out of which 13,834 (3%) via the App (56% serious). In the same period Germany submitted 176,063 AEFIs (18% serious, 94% from patients) to VigiBase, 13,043 (7%) of which were sent via SafeVac (6% serious). Patients also contributed to App-reporting (86% in the UK vs 85% on the global level and 100% vs 94% on the global level) in UK and Germany, respectively. During the study period February 2021–December 2021 VigiBase received 10,885 (15% serious, 48% from patients) AEFI reports from the Veneto region, 4,568 (42%) of which submitted by App Vigicovid (10% serious) with 2,634 (58%) reports submitted by citizens.

Conclusion: The Apps developed in UK and Germany had a limited impact on spontaneous reporting in comparison to the usual reporting (with specific web forms). The progressive web app Vigicovid had a more relevant impact, particularly among citizens.

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Adverse Drug Reactions in Older People Reported to the Portuguese Pharmacovigilance System during 2019

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Introduction: Chronic diseases have become prevalent in older patients with the rise of the average life expectancy [1]. The ageing process modifies the pharmacokinetic and pharmacodynamic processes [2], aggravated the risk of possible adverse drug reactions (ADR) in older adults [3]. ADR cause significant morbidity, mortality and healthcare costs having a significant prevalence in older adults [4].

Objective: The aim of this study was to characterize the ADR reports received by the Portuguese Pharmacovigilance System of the National Authority of Medicines and Health Products (INFARMED, I.P.) during 2019 in patients with 65 and more years old.

Methods: A retrospective study was designed including all ADR reports received by INFARMED, I.P., between January and December 2019 occurred in 65 and more year-old patients. Patients were characterized by age, gender, and notifier of the ADR. ADR were characterized according to MedDRA System Organs Classes (SOC), and seriousness, and medication according with the Anatomical Therapeutic Classification.

Results: 2337 valid ADR reports occurred in older adults were considered. The population had a mean age of 74.6 ± 6.8 years old, up to a maximum of 97 years, with females representing 54.3% ($n = 1189$). Almost half of the reports were sent by physician ($n = 1137/48.7\%$), and users and non-health professionals participated in 14.4% ($n = 337$) of the reports. 64.7% ($n = 1512$) of the ADR reports were classified as serious. 600 older adults were hospitalized (25.7%) and 114 died (4.9%). It was possible to identify 6617 ADR, each report having an average of 2.83 ± 2.89 (min. 1; max 36) ADR. “General Disorders and administration site conditions” was the most frequent SOC, identified in 28.7% ($n = 671$) of reports, followed by “Skin and subcutaneous tissue disorders”, in 21.9% ($n = 512$). 3170 suspected medicines were identified, representing an average of 1.36 ± 1.07 drugs identified per report. The ATC subgroups most often identified were group A10B—Oral Antidiabetics ($n = 160/5.0\%$), B01-A—antithrombotic agents ($n = 193/6.1\%$) and L01X—Other antineoplastic agents ($n = 275/8.7\%$) as the most frequent.

Conclusion: Most of the suspected ADRs were classified as serious, being antineoplastic and antithrombotic agents the suspected drugs most frequently identified. Pharmacovigilance databases and spontaneous reports are fundamental to target specific drugs with an increased risk for ADRs in older adults. Clinical medication review in older patients should be continuously performed, enhancing quality of prescriptions in this age group.

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Immune Checkpoint Inhibitors and Pregnancy:

A Pharmacovigilance Analysis in VigiBase®

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Introduction: In pregnancy, immune checkpoint pathways play a physiological role in maintaining maternal immune tolerance to the developing foetus [1]. Although preclinical studies showed that immune checkpoint inhibitors (ICIs) increased the risk of spontaneous abortion [2], whereby their use in pregnant women as well as in women of childbearing potential not using effective contraception is not recommended [3], clinical cases of maternal exposure to ICIs reported in the literature to date showed successful pregnancy outcomes [4–6].

Objective: To provide further insight into ICI safety in pregnancy by querying VigiBase®, the World Health Organization’s global pharmacovigilance database of safety reports of suspected adverse drug reactions.

Methods: Pharmacovigilance study in VigiBase® with disproportionality analysis using the reporting odds ratio (ROR). Safety reports concerning pregnancy-related outcomes reported in association with ICIs and gathered in VigiBase from its inception through August 17th 2020 were retrieved. Disproportionality analyses were performed for pregnancy-related outcomes reported in at least five safety reports associated with ICIs and compared to either the full database, other antineoplastic drugs (analysis by therapeutic area), or other antineoplastic drugs starting from 2011 (when the first-in-class ICI, ipilimumab, received marketing authorization).

Results: Of 80 safety reports included in the study, median age was 32 years (interquartile range 28–35 years, $n = 35$), and 77 (96.3%) were in females. Reporting of safety reports with ICIs in relation to pregnancy peaked in 2019 (25, 31.2%), and was mostly from health professionals (68, 85.0%). Exposure to ICIs occurred during pregnancy in 68 (85.0%) safety reports, more often to treat malignant melanoma (23, 28.8%). 41 (51.3%) safety reports reported only ICI exposure, 39 (48.7%) reported ICI exposure and additional adverse events related to pregnancy. The most frequently reported adverse events related to pregnancy were spontaneous abortion, foetal growth restriction, and premature delivery (in 5, 6, and 18 safety reports respectively), for which no signals of disproportionate reporting with ICIs emerged.

Conclusion: This pharmacovigilance study showed that spontaneous abortion, foetal growth restriction, and premature delivery were not disproportionately more frequently reported with ICIs in VigiBase®. However, as signal detection depends on the number of safety reports, a signal of disproportionate reporting might be detected on larger samples, thus disproportionality analysis should be reassessed at regular intervals for confirmation or rejection.

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Follow-up of Covid-19 Vaccinated Pregnant and/or Breastfeeding Women in Tunisia

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Introduction: Initially, vaccination against Covid-19 was not recommended during pregnancy due to the lack of data. With the benefit of hindsight, it has become recommended. This decision followed the reassuring results from pregnant women who voluntarily or inadvertently received Covid-19 vaccines, especially with mRNA vaccines [1].

In Tunisia, from May 2021, pregnant women have been prioritized in the national vaccination program with the recommendation of the messenger RNA platform.

Objective: To follow-up Covid-19 vaccinated pregnant and/or breastfeeding women in Tunisia.

Methods: We have started a pilot study (from September 2021 to April 2022) for monitoring pregnant and/or breastfeeding women. Data collection was carried out via telephone calls. We excluded women who were unreachable after two phone calls. The data collected concerned the course as well as the outcome of the pregnancy and the health status of newborns. In addition, women were asked about the possible occurrence of adverse effects following immunization.

Results: Our study included 1253 women. Seventeen percent of them were previously infected with Covid-19. The vaccination schedule was complete (two doses) in 83% of cases. Pfizer-BioNTech vaccine (PBV) was used in 73% of cases (11% of cases in the first trimester, 42% in the second trimester and 19% in the third trimester) and Moderna vaccine in 26%. Coronavac vaccine was used in 1% of cases. Vaccination was performed during pregnancy in 74 % of cases and breastfeeding in 11% of cases. Fifteen percent of women received the first dose during pregnancy and the second dose after childbirth. Reported adverse events following vaccination were: pain at the injection site in 47%, fever in 23%, soreness in 15%, asthenia in 6%, headache in 5%, hot flashes in 3% and chills in 1% of cases.

Pregnancy and breastfeeding outcomes were favourable in 1246 women (99.4% of cases). Forty-seven percent of women delivered at term without incident and newborns were apparently in good health.

One case of spontaneous miscarriage was reported in a woman with a history of spontaneous abortion and Covid-19 infection two weeks after receiving the first dose of PBV. Six cases of neonatal jaundice were also reported with PBV with good evolution with phototherapy.

Conclusion: Our study confirms the data in the literature concerning the safety of Covid-19 vaccines on pregnant and/or breastfeeding women.

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Cutaneous Adverse Reactions Reported with Antiepileptic Drugs in Tunisian Pediatric Population

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Introduction: Antiepileptic drugs (AED) are widely used in pediatric population (PP). They are mainly indicated in the treatment of epilepsy and some psychiatric pathologies and behavioral disorders. AED are among the drugs most frequently associated with cutaneous adverse reactions (CAR) in children. These CAR are usually mild and disappear spontaneously after the AED withdrawal. However, severe life-threatening reactions can sometimes occur [1].

Objective: To study the epidemiological and clinical features of CAR occurring in PP and to identify the most implicated AED.

Methods: We conducted a descriptive retrospective study over a period of seven years from January 2014 to December 2020 about CAR of AED in PP (aged under or equal to 16 years-old) notified to The Tunisian National Center of Pharmacovigilance. All cases were analyzed according to the updated French method of imputability [2].

Results: We collected 41 cases of CAR associated to AED.

The age varied from 2 to 16 years old (mean = 9.5 years old) with a sex ratio (H/F) = 0.5.

AED were indicated for neurological pathology (epilepsy) in 98% of cases and for psychiatric disorder (attention deficit hyperactivity disorder) in 2% of cases. Notified CAR in our study are summarized in table 1.

Incriminated AED were lamotrigine (LMG) (41%), carbamazepin (27%), valproic acid (22%), phenobarbital (7%), phenytoin (2%) and levetiracetam (2%). These AED was prescribed in monotherapy in 56% of cases and in polytherapy in 44% of cases.

Severe cutaneous adverse reactions (SCARs) accounted for 24% of all CAR. There was no statistically significant difference in occurrence of SCARs according to the number of prescribed AED ($p = 0.72$) or their aromatic nature ($p = 0.1$).

LMG dose-escalation guidelines was not respected in one case. It was a patient who developed a maculopapular exanthema 3 days after initiating LMG treatment with 150mg/day.

Therapeutic drug monitoring was performed in three cases of hair loss with VPA. The VPA plasma concentration was supra-therapeutic in two cases and within the therapeutic range in one case.

Table 1: Notified cutaneous adverse reactions

Cutaneous adverse reaction	Number of cases	Percentage (%)
Maculopapular exanthema	16	39
Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)	8	20
Hair loss	6	16
Erythematous rash	4	10
Acneiform rash	2	5
Acute urticaria/Angioedema	2	5
Erythema multiform	1	2
Stevens-Johnson syndrome	1	2
Gingival hypertrophy	1	2

Conclusion: Thus, according to this retrospective study, maculopapular exanthema was the most frequently reported CAR with AED in PP. Also, LMG was the most incriminated AED. However, a comparative study could be considered in order to specify the risk factors for the occurrence of AED-induced CAR.

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A Survey on the Adverse Drug Reactions of Covid-19 Vaccines Administered within the Local Health Authority of Verona

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Introduction: European pharmacovigilance legislation requires healthcare professionals and citizens to report any suspected adverse drug reaction (SADR). SADRs are uploaded into the National Pharmacovigilance Network (RNF) database by the local responsible of pharmacovigilance. This information feeds Eudravigilance, the European database appointed to collect spontaneous reports of adverse reactions [1]. In the Veneto Region the quality of data entered in the RNF database by the Local Health Authority (LHA) is monitored by the Regional Centre of Pharmacovigilance [2]. Given the central role of vaccines in tackling the pandemic, we focused our attention on SADRs reported for the Covid-19 vaccines.

Objective: This analysis aims to evaluate the SADRs related to Covid-19 vaccines entered by the LHA of Verona into the RNF database. Number and type of SADRs for the different vaccines administered to people assisted in the LHA were analyzed.

Methods: The doses of Comirnaty-Pfizer/BioNTech, Vaxzevria-AstraZeneca, Spikevax-Moderna and Janssen-Janssen Cilag vaccines administered in the period 01.01.2021–31.12.2021 were considered suitable for the analysis and the SADRs were classified using MedDRA terminology. Data related to the vaccines were analyzed using Microsoft Excel[®] and were expressed in number and percentage.

Results: The LHA recorded 3,595 signaling forms corresponding to 10,657 SADRs. 74.8% of the SADRs referred to females, mostly aged 40–59. 53.4% of the cases showed a complete symptom resolution; 22.4% experienced an improvement or resolution of the symptoms with persisting side effects. 19.4% of the SADRs were not completely resolved at the reporting time. Death was reported in 0.3% of the cases, while in 4.5% the outcome was not available. Table 1 shows the number of administered doses for each vaccine and the related reporting rates (RRs) for all the SADRs. RR for Spikevax was the highest, regardless of the SADR seriousness. Regarding the SADRs specifically investigated by the regulatory agencies, our analysis highlighted the following figures: risk of pericarditis/myocarditis (5 vs. 2 vs. 1 reports with Spikevax, Comirnaty and Vaxzevria, respectively), vaccine-induced immune thrombotic thrombocytopenia (one report with Vaxzevria) and menstrual disorders (six reports with Comirnaty vs. one with Vaxzevria).

Vaccine	Administered doses	Reporting rate (%)	Serious/total (%)
Comirnaty	1,147,654	0.22%	10.8%
Vaxzevria	298,531	0.18%	15.3%
Spikevax	156,507	0.32%	14.9%
Janssen	16,009	0.14%	17.4%
Total	1,618,701	0.22%	12.1%

Conclusion: The number of signaling forms received by the LHA of Verona highlights an increasing awareness on the importance of reporting to provide useful data for public safety. Our analysis confirms current available data regarding the most frequently SADRs experienced with Covid-19 vaccines [3–6]. However, our data are important to underline that SADRs of clinical interest related to each type of vaccine have a low incidence.

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Spontaneous Reports of Delayed Urticaria Following Booster Vaccination with Spikevax® in Switzerland

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Introduction: The post-marketing surveillance of COVID-19 mRNA vaccines revealed that urticarial reactions could occur with a delayed time course following both primary vaccinations [1-4] and the booster vaccinations [5,6]. While delayed urticarial reactions following COVID-19 primary vaccinations resolve in general with a median of 2-4 days, delayed urticaria after booster vaccination can show a prolonged and intermittent clinical course requiring treatment for several weeks [5,6]. Shortly after the booster vaccination campaign began in Switzerland in December 2021, an increasing number of delayed urticarial reactions in association with Spikevax® was reported to Swissmedic, whereby a safety signal was opened.

Objective: To characterize cases of delayed urticarial reactions reported in Switzerland following booster vaccination with Spikevax®.

Methods: Case-by-case assessment of spontaneously reported delayed urticarial reactions following booster vaccination with Spikevax® recorded in the Swiss national pharmacovigilance database up to February 8th, 2022.

Results: There were 107 cases of delayed urticaria following booster vaccination with Spikevax®. Of these, 79 (73.8%) were reported by consumers/non-health professionals. Women were more frequently affected (55, 51.4%) and median age was 38 years (interquartile range, IQR, 34–44 years). Urticaria developed a median of 10 days after booster vaccination (IQR 9–11.5 days). In 55 (51.4%) cases, urticaria was the solely reported adverse event, whilst 52 (48.6%) cases reported urticaria with additional adverse events, including pruritus (n = 27) and angioedema (n = 7). In 81 (75.7%) cases, delayed urticaria had not serious consequences (i.e. did not require/prolonged hospitalisation, was not disabling/incapacitating, did not determine other clinically relevant conditions). In 69 (64.5%) cases the outcome of urticaria was not recovered at the time of reporting, which occurred a median of 14 days after booster administration (IQR 6–21 days).

Conclusion: To our knowledge, this is the first case series to date of delayed urticaria following booster vaccination with Spikevax®, showing that these reactions were more frequently not self-limiting and with a prolonged course in contrast to delayed urticaria developed after COVID-19 mRNA primary vaccinations. Although these reactions should not discourage from subsequent COVID-19 mRNA vaccinations, further investigations with regard to additional booster vaccinations seem necessary.

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Signal Detection by Disproportionality Analysis in the Monitoring of COVID-19 Vaccine Safety in Switzerland

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Introduction: Initial knowledge on the COVID-19 vaccines' safety from randomised clinical trials was limited and concerned mostly common adverse events related to vaccine immunogenicity occurring rapidly after vaccination [1,2]. Since these vaccines have been approved and used in large scale, the Swiss Agency for Therapeutic Products Swissmedic has been conducting an intensive surveillance activity on their safety, based on the collection and analysis of spontaneous reports from healthcare professionals and patients.

Objective: Signal detection in spontaneous reports associated with COVID-19 vaccines first relies on a case-by-case analysis by clinically qualified assessors who take into account detailed information provided by reporters. However, with the number of reports increasing, the clinical review could benefit from the use of statistical methods for signal detection, such as disproportionality analysis [3].

Methods: In light of this, the Institute of Pharmacological Sciences of Southern Switzerland, in close collaboration with Swissmedic, set up and routinely perform a signal detection activity by disproportionality analysis in VigiBase®, the global database of the World Health Organization (WHO) Programme for International Drug Monitoring, using spontaneous reports originating from Switzerland and concerning adverse events following immunization (AEFIs) associated with the Moderna (Spikevax®) and Pfizer/BioNTech (Comirnaty®) COVID-19 vaccines. These included the measurement of the reporting odds ratios (RORs) for COVID-19 vaccine/AEFI combinations meeting two predefined statistical signal detection criteria, namely a minimum of 5 reports concerning a COVID-19 vaccine/AEFI combination and a ROR lower limit of the 95% confidence interval > 1. Excluding AEFIs either already labelled in the Swiss information for healthcare professionals, or already debated internationally, a panel of pharmacovigilance and clinical pharmacology experts are examining and discussing findings on novel and unexpected COVID-19 vaccine/

AEFI combinations, in order to promptly detect potential safety signals that could warrant further investigation.

Results: Since the start of the signal detection activity in August 2021, an early signal of disproportionate reporting in VigiBase® for *paraesthesia* with the Moderna (Spikevax®) vaccine was detected in Switzerland. This occurred a few months before the same signal was assessed and validated by the European Medicines Agency, which ultimately added *paraesthesia* to the European summary of product characteristics for the Moderna (Spikevax®) vaccine [4].

Conclusion: Disproportionality analysis has some limitations such as lack of information about incidence rate of the adverse event in the population, and the existence of reporting biases. Nevertheless, continued research on newly identified safety signals can provide valuable information to support public health, guide regulatory decisions and design specific follow-up confirmatory studies.

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Vitamin D-Induced Cardiovascular Toxicity: Preliminary Evidence from the FDA Adverse Event Reporting System (FAERS)

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Introduction: The role of vitamin D on cardiovascular toxicity is a long-debated issue and some recent studies have associated its supplementation with adverse cardiovascular outcomes [1]. Its underlying mechanism probably involves an increased secretion of fibroblast growth factor 23 (FGF23) induced by calcitriol [2]. Indeed, FGF23 is a relevant biomarker of cardiovascular risk: while it physiologically inhibits phosphate renal tubular reabsorption, it seems to have a direct role in the development of cardiac hypertrophy,

fibrosis and dysfunction [3]. This issue is particularly relevant in patients affected by chronic kidney disease (CKD), who have a higher cardiac failure risk compared to the general population, caused by a systemic inflammatory state that contributes to vascular and myocardial remodelling, calcification and senescence [4]. Furthermore, CKD patients typically develop hyperparathyroidism, have increased FGF23 concentrations and require vitamin D supplementation, which is due to the inability to activate 25-OH-calciferol into calcitriol and to the reduction of calcitriol concentrations induced by FGF23 [5]. All these factors concur in further increasing the risk of cardiovascular mortality in CKD, supporting the need for a thorough investigation of the toxic effects of vitamin D.

Objective: To estimate the risk of reporting cardiovascular adverse events (AEs) triggered by the administration of vitamin D in a real-life context through the investigation of a comprehensive spontaneous reporting system database.

Methods: We retrieved all Individual Case Safety Reports (ICSR) submitted to the FDA Adverse Event Reporting System (FAERS) between 2010 and 2021 reporting vitamin D or its analogues as suspected in the AE occurrence. After a systematic process of data cleaning, we carried out a case-level clinical review of all ICSRs reporting CKD as indication of vitamin D use by analysing patient characteristics and the details concerning the AEs, coded by the Medical Dictionary for Regulatory Activities (MedDRA).

Results: We identified 10,840 ICSRs reporting vitamin D as suspect drug, among which CKD was reported as its indication of use in 575 cases, which were retrieved and analysed: details on administered dose and frequency were provided in 192 cases, patients had a mean age of 61 ± 15 years and a 47% female prevalence. Cardiovascular disorders were reported in 203 cases and, based on their clinical outcome, over 90% AEs resulted of serious nature. Complete results are underway.

Conclusion: Patients requiring vitamin D supplementation should be closely monitored and a careful benefit/risk ratio should be implemented in clinical practice.

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Symptoms Potentially Related to Small Fiber Neuropathy (SFN) and Anticovid Vaccines

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Introduction: SFN is a relatively rare condition related to finer fibers of peripheral nervous system. A specific diagnostic procedure is necessary to reach a correct diagnosis. The most frequently reported symptoms are: pain (described as burning or a sensation of intense heat, as “aching cold”, “pinpricks”, “electric shocks”), paraesthesia (spontaneous sensations of tingling, numbness, itching), dysesthesia and allodynia. Some published papers hypothesized a correlation between SFN and anticovid vaccine.

Objective: Study target was to analyze the adverse events following immunization (AEFI) reported in our ASL (resident population 1,221,857, ¼ regional population) potentially linked to the SFN symptoms.

Methods: Data relating to AEFI were extrapolated from the National Pharmacovigilance Network (NPN), while data referring to administered doses were extracted from the ASL QlinkView platform.

Results: From 27 December 2020 to 26 April 2022, 624 reports, relating to vaccines anticovid AEFI, were received and recorded in the NPN. 2.109 AEFI were described in these reports. Administered vaccines: **Comirnaty** (346/624 sheets; 1.164/2.109 AEFI; 2.092.042/3.028.781 total administered doses), the most reported AEFI were related to general pathologies: pain, wheal or erythema at the injection site, headache, fever, asthenia, nausea, malaise, tachycardia, muscle pain, fatigue, joint pain (25% of 1.164 AEFI). Other described symptoms: other pains, burning, itching, paraesthesia, tingling, numbness, allodynia, potentially linked to SFN (17.3% of 1.164 AEFI); **Spikevax** (112/624 sheets; 392/2.109 AEFI; 607.626/3.028.781 doses), the most reported AEFI, like Comirnaty, were related to the injection site (26% of 392 AEFI), while the potentially symptoms related to SFN were the 20.2% of 392 AEFI; **Vaxzevria** (146/624 sheets; 512/2.109 AEFI; 298.188/3.028.781 doses), the most reported AEFI, related to general pathologies, were the 33% of 512 AEFI, while potentially symptoms related to SFN were the 18.8%. Finally, as regards the Janssen vaccine (10/624 sheets; 32/2.109 AEFI; 30.702/3.028.781 doses), the most described events, related to general pathologies, are the 47% of the 32 AEFI, while 31% are potentially linked to the of SFN symptoms. No AEFI was reported related to the 223 doses about Novavax vaccine. The causality assessment was defined correlatable about 37 records (6% of 624 records). 12/37 records describe potentially linked to SFN symptoms (6 Vaxzevria (1%), 3 Comirnaty (0.5%) and 3 Spikevax (0.5%)).

Conclusion: The analysis about AEFI reported in our ASL related to anticovid vaccines underlined the existence of symptoms potentially linked to SFN, although only in a few cases it was evaluated a causality assessment to vaccination. Just a specific diagnostic procedure can confirm the diagnosis and the correlation. Therefore, the correlation between SFN and vaccine needs larger-scale studies and insights for a correct evaluation.

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Safety Profile of Antiviral Therapies for the Early Treatment/Prevention of COVID-19: Analysis of the International Pharmacovigilance Database VigiBase

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Introduction: After many months from the COVID-19 pandemic beginning, several anti-spike monoclonal antibodies (mAbs) and, more recently, other antiviral drugs for COVID-19 treatment in non-hospitalized patients have been marketed. Specifically, those drugs are indicated for SARS-CoV-2 infection early treatment in outpatient adults at high risk of developing severe COVID-19 [1].

Objective: To evaluate the post-marketing safety profile of antiviral drugs used for early COVID-19 treatment, using the World Health Organization global spontaneous reporting database (VigiBase).

Methods: From VigiBase we identified all the individual case safety reports (ICSRs) of marketed mAbs (regdanvimab, sotrovimab, casirivimab/imdevimab, bamlanivimab/etesevimab and, specifically for COVID-19 prevention in immunocompromised patients, tixagevimab/cilgavimab) and other antiviral therapies for COVID-19 early treatment (remdesivir, nirmatrelvir/ritonavir, molnupiravir). We performed a descriptive analysis of ICSR recorded in VigiBase of patients’ demographics (age, sex, continent of origin) type of reporter, adverse drug reactions (ADRs) (Preferred Term level) and the Important Medical Events (IMEs), from their marketing date to May 4, 2022. In addition, we conducted a disproportional analysis using Reporting Odds Ratio (ROR), along with 95% confidence intervals (CIs), by comparing the frequency of ADRs (System Organ Class level) for each drug of interest with distribution of all ADRs from the whole database, excluding vaccines, reported in the same period.

Results: Overall, up to 4th May 2022, 15,437 ICSR of anti-spike mAbs (casirivimab/imdevimab: 27.2%; bamlanivimab/etesevimab: 7.3%; sotrovimab 3.3%; tixagevimab/cilgavimab 2.7% regdanvimab: 0.2%) and other antivirals (remdesivir: 54.5%; nirmatrelvir/ritonavir: 4.3%; molnupiravir 0.5%) from VigiBase were retrieved. ICSR mainly involved females and 45–64 years old. The percentage of ICSR that included IMEs was 32.4%. Overall, the most frequently reported ADRs were infusion-related reaction for both casirivimab/imdevimab (20.1%) and bamlanivimab/etesevimab (19.3%), pyrexia for regdanvimab (30.0%) and sotrovimab (8.1%), increased alanine aminotransferase for remdesivir (13.3%), dysgeusia for nirmatrelvir/ritonavir (39.5%), and diarrhoea for molnupiravir (18.8%). Overall, statistically significant RORs were observed for “Investigations” with remdesivir (N = 3163; ROR: 5.56; 95% CI 5.32–5.81), “Gastrointestinal disorders” for molnupiravir (N = 178; ROR: 3.43; 95% CI 2.82–4.17) and “Vascular disorders” for sotrovimab (N = 51; ROR: 2.07; 95% CI 1.55–2.76).

Conclusion: This study shows that the safety profile of anti-spike mAbs and other newly marketed antiviral therapies for the early treatment of COVID-19 is overall favourable. The most frequently reported ADRs in VigiBase are in line with those reported in the pivotal trials and Summary of Product Characteristics for all investigated antiviral drugs. The disproportional analysis identified some potential signals requiring further investigation.

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Real-World Patterns and Trends of Idarucizumab Use in an Italian Region: A Probabilistic Record-Linkage Approach in the Period 2015-2020

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Introduction: Idarucizumab is a specific reversal agent for dabigatran that was approved in 2015 to restore coagulation. The drug is administered only during inpatient or emergency care: in such settings, its use is poorly captured by most *real-world* databases.

Objective: To retrieve individual level information on idarucizumab use from an Italian record-linkage claims database to describe main characteristics of users.

Methods: All person-years (PYs) exposed to dabigatran from January 2015 to December 2020 were calculated from record-linkage claims database, using defined daily doses to estimate the duration of each dispensation. Idarucizumab use was identified from inpatients and/or emergency care, and incidence rate was calculated over PYs of dabigatran use. To identify patients treated with idarucizumab, emergency visits and hospital discharge records were probabilistically linked to dabigatran users, matching date and ward of admission. A further selection was made by a manual assessment of diagnoses and indications of idarucizumab use. The hierarchical criteria used to match each idarucizumab record to a single patient were: (a) date of dabigatran initiation; (b) clinical outcome; (c) diagnosis. Subsequently, each association between idarucizumab administration and hospitalization/emergency visit was ranked as (1) probable, (2) possible, (3) incompatible, (4) non assessable. Linked users were described in terms of indication and followed-up for 30 days to assess mortality.

Results: During the study period, 49,134 PYs of dabigatran use were observed, and 249 administrations of idarucizumab were recorded, corresponding to 5.1 (95% CI 4.5–5.7) per 1,000 PYs. At the end of the manual assessment 158 (69.0%) administrations were defined as probable (N = 103) or possible (N = 55). Overall, 230 idarucizumab administrations (92.4%) were linked to at least one patient. Each administration was associated with a median number of 8 hospitalization/emergency visits (interquartile range: 3–14). Hospitalizations/emergency visits referred to 126 patients: 109 (86.5%) with one administration of idarucizumab, 11 (8.7%) with two administrations, 5 (4.0%) with three administrations, and 1 (0.8%) with four. Most of them were men (62.7%), with a median age of 79.1 years. Indications were emergency surgical procedures and life-threatening bleeding in 43 (34.1%) and in 83 (65.9%) patients, respectively. Overall, 30-days mortality was 23.0% (N = 29).

Conclusion: This drug utilization study highlights the potential of the Tuscany administrative database in retrieving patient-level information on idarucizumab use and sets the stage for post-marketing surveillance on its safety profile in a *real-world* setting.

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Antipsychotic Drugs Use in the Territory of the Central Tuscany Healthcare Authority—Preliminary Results of the ANTIGONE Project

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Introduction: In 2004, the European Medicines Agency issued a first warning on the increased risk of stroke and all-cause mortality associated with the use of olanzapine and risperidone, extending this warning in 2009 to all antipsychotics (APs) employed in individuals with dementia. In addition, the use of APs appears to be associated also with an increased risk of pneumonia.

Objective: As part of ANTIGONE (ANTIpsychotics General pOpulationN safEty study), a regional project financed by AIFA, the Italian Medicines Agency, a study with the aim to evaluate the use of APs in the population resident in the territory of the Central Tuscany Healthcare Authority (Tuscany, Italy) was conducted.

Methods: A descriptive analysis using information contained in the dataset of drug dispensing records, which are coded using the Anatomical Therapeutic Chemical drug classification system adopted by the World Health Organization, was carried out in order to estimate prevalent users. A record-linkage was done deterministically by means of the universal anonymous identifier, which is adopted within all the electronic health records of the Regional Health System of Tuscany, between drug dispensing records, the dataset of hospital discharge records, with one main and five secondary diagnoses coded using the International Classification of Diseases, the emergency department dataset and mortality data.

Results: From 2014 to 2018 prevalent users in the territory ranged among 23,828 in 2016 (1.5 per 100 residents) and 20,539 in 2018 (1.3 per 100 residents), while the median age ranged from 65 in 2014 to 61

in 2018. The majority of APs users were women: in 2018 they were 54.0% of the study population, corresponding to 1.3 APs users per 100 female residents vs 1.2 per 100 male residents. APs use among patients > 64 years was 55% among women and 34.2% among men in 2018. Among AP users, 0.7% had a diagnosis of dementia. Around 1/3 of prevalent cases each year was admitted to the emergency department and/or hospitalised for any cause. Each year 2.5% of prevalent users were hospitalised with a diagnosis of a cerebro- or cardiovascular disease, and 2% were hospitalised with a primary diagnosis of pneumonia.

Conclusion: Considering these preliminary findings, the risks associated with APs use will be assessed among incidence users one year after the start of therapy. Particular attention will be paid to the risk of emergency department admission or hospitalisation for cerebro- and cardiovascular diseases and pneumonia, and a specific analysis on patients suffering from dementia will be conducted.

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Herpes-Zoster Reactivation Following SARS-CoV-2 Vaccines

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Introduction: Recently, due to the massive administration of SARS-CoV-2 vaccines to a large population, a series of adverse events have been observed after its commercialization [1]. Post-marketing, sporadic case reports and series of Herpes Zoster reactivation were reported [2,3]. These cases constitute a potential signal.

Objective: In this study, we aim to present a series of patients with Herpes-Zoster (HZ) reactivation following SARS-CoV-2 vaccination.

Methods: This is a retrospective study of HZ cases, reported to the National Centre of pharmacovigilance (CNPV) following SARS-CoV-2 vaccination from March 2021 to May 2022.

Results: We included 20 patients; 19 patients presented shingle and one patient had varicella. The sex ratio (M/F) was 0.8. The median age was 68.5 years. Nine patients were aged 70 years or older. The administered vaccine was an mRNA vaccine in 15/20 cases. The mean onset delay was 4.5 days. There was no concomitant use of immunosuppressants. All patients have recovered within a few days and no severe cases were reported. Two patients received the second dose, without recurrence of the symptomatology in one case. In the second case, there was an aggravation of the symptomatology and occurrence of facial paralysis; noting that the initial symptomatology was not entirely disappeared when the patient received the second dose.

Conclusion: Our study does not establish causality but draws attention to a chronological association between the SARS-CoV-2 vaccine and HZ reactivation, which have to be investigated.

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Cytolytic Hepatitis Following mRNA Vaccination

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Introduction: A few months after the commercialization of the COVID-19 mRNA vaccine, published case reports started to open-eyed concerns about patients who presented autoimmune hepatitis (AIH) after receiving a COVID-19 vaccine [1-3].

Objective: We aim to describe cytolytic hepatitis following administration of the COVID-19 mRNA vaccine.

Methods: We report a case of cytolytic hepatitis following administration of the COVID-19 mRNA vaccine notified to the National Center of Pharmacovigilance.

Results: A 37-year-old man with no notable medical history was incidentally diagnosed with cytolytic hepatitis during his preoperative lab tests for acute appendicitis. Liver transaminases were thrice the upper limit. He had received his two doses of mRNA vaccine Moderna® two months before getting his lab tests. His serum immunoglobulins G, A, and M levels were within the normal range, and his immune lab tests were normal. Hepatitis serologies were negative. The abdominal ultrasound didn't demonstrate any abnormalities. The liver biopsy has revealed chronic active hepatitis lesions classified as F1A2. The patient had recovered spontaneously and had a normal liver transaminase level within 10 days. This case was scored I3 according to the french imputability updated method.

Conclusion: Hepatitis following COVID-19 vaccination is an uncommon condition. Even if causality is still not proven clinicians must be vigilant for liver injuries in patients who have received COVID-19 vaccination.

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Myocarditis Following SARS-CoV-2 Vaccines: A Series of Six Cases

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Introduction: Myocarditis was observed after the commercialization of mRNA vaccines and was not initially described in the safety data of these vaccines [1,2]. Lately, it was considered an adverse effect of mRNA vaccines and mentioned in the summary of product characteristics.

Objective: In this work, we aim to present the cases of myocarditis after SARS-CoV-2 vaccination reported during the vaccination campaign.

Methods: We present the cases of myocarditis reported to the pharmacovigilance national center after the SARS-CoV-2 vaccination. Data were collected retrospectively. All cases were defined according to Brighton's case definition of myocarditis. The vaccine causality assessment was estimated by the French imputability updated method of Bégaud et al. [3].

Results: A total of six patients were included in this study. The sex ratio (M/F) was 0.5. The mean age was 31 years ranging from 18 to 41 years. All patients had no notable cardiovascular history and did not report any significant past medical history. The mean onset delay was 10 days post-vaccination. The predominant reported symptoms are chest pain and dyspnea in the six cases. Five patients have received an mRNA vaccine and one patient a viral vector vaccine. Cardiac magnetic resonance imaging confirmed the myocarditis diagnosis in five patients (not performed for one patient). All patients presented a troponin serum level elevation. The ejection fraction was reduced for five patients and conserved for one patient.

All cases were classified as definitive cases according to the Brighton case definition of myocarditis. One patient required hospitalization in a cardiac intensive care unit. All the patients have recovered from acute myocarditis within a few days. Five cases were scored I2 and one case I1 according to the French updated imputability method.

Conclusion: Reported cases of myocarditis post-SARS-CoV-2 vaccination are rare, generally not severe, and have a quick favorable outcome. Currently, causal relationships have been demonstrated with mRNA vaccines only.

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Demonstration of TreeScan Techniques on a Federated Real-World Data Network

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Introduction: TreeScan and associated techniques have been successfully applied to Real-World Data (RWD) such as administrative claims and electronic health records (EHR) to identify associations within large datasets [1,2,3]. FDA is commonly implementing TreeScan for signal detection and the use of RWD in support of pharmacovigilance (PV) is increasing [4,5]. TreeScan can be employed using an exposure-based approach or an outcome-based approach [6]. Gaining access to curated and harmonized global RWD, let alone federated data, remains challenging and additional research must be performed with these data so that the PV community may leverage them in the future.

Objective: To investigate using TreeScan on a federated EHR network by implementing an exposure-based and an outcome-based analysis focusing on previously identified associations: COX-2 inhibitors and increased CV events and increased risk of suicide to Benzodiazepine [7,8,9,10].

Methods: Using the TriNetX Network, we created two cohorts for exposure-based comparison (COX-2/NSAIDs) and 2 for outcome-based comparison (suicide/non-suicide). The NSAIDs cohort included patients exposed to ibuprofen and the COX-2 cohort included patients exposed to valdecoxib, celecoxib, or rofecoxib. Both cohorts included patients exposed from 1999–2004 to reflect prior investigations and ensure COX-2 exposures. Suicide was defined using ICD-10-CM codes T14.91, R45.851 and X71-X83. These cohorts included patients from 2014–2019. Data from 26 healthcare organizations were curated to a common terminology. We focused on executing these methods across a federated network of EHR data and limited signal assessment to several known associations. The federated TriNetX Platform was used to calculate diagnosis and medication hierarchies for the exposure and outcome analyses respectively. TreeScan v1.4 was used to calculate statistics.

Results: 27,579 NSAIDs and 16,285 COX-2 patients were identified. CV disease signaled at the top of the hierarchy along with arterial disease, myocardial infarction, stroke, and pulmonary heart disease. The relative risk of myocardial infarction was 1.63 [Unspecified: 1.97; NSTEMI: 1.70; STEMI: 1.56] p-value 0.001 in the COX-2 cohort as compared to the NSAIDs cohort. 10,636 first suicide and 382,277 non-suicide patients were identified. As expected, Benzodiazepine derivatives were associated to the first suicide cohort with a relative risk of 2.17 [Clonazepam: 2.56; Lorazepam: 3.34] p-value 0.001.

Table 1:	Selected	Signals	and	Relative	Risks
Exposure-Based Analysis		Outcome-Based Analysis			
NSAIDs cohort	27,579	First suicide cohort		10,636	
COX-2 inhibitors cohort	16,285	No suicide cohort		382,277	
	RR (p-value)			RR (p-value)	
Myocardial infarction	1.63 (0.001)	Anticonvulsants		1.79 (0.001)	
Unspecified	1.97 (0.003)	Gabapentin		2.53 (0.001)	
NSTEMI	1.70 (0.001)	Sedatives/hypnotics		2.07 (0.001)	
STEMI	1.56 (0.001)	Benzodiazepine derivative		2.17 (0.001)	
Stroke	1.70 (0.001)	Clonazepam		2.56 (0.001)	
Cerebral Infarction	1.83 (0.001)	Lorazepam		3.34 (0.001)	

Conclusion: TreeScan was successfully applied to hierarchical counts generated from a federated EHR research network. Previously identified associations were replicated. TreeScan and similar methods can

be applied to a federated network providing the pharmacovigilance community another tool for active surveillance and research.

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VAC4EU: A Pan-European Research Network for Collaborative Post-authorization Vaccine Safety and Benefit Monitoring

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Introduction: VAC4EU (Vaccine monitoring Collaboration for Europe) is a not-for profit international association with 24 member organizations specialised in the collaborative generation of real-world evidence on coverage, safety, and efficacy of vaccines in Europe. VAC4EU was established as a result of the IMI-ADVANCE project with the aim to enable, coordinate and accelerate the creation of the best evidence at European level on vaccine effects. In the past two years, VAC4EU has proven preparedness and efficiency in designing post-authorization monitoring for COVID-19 vaccines responding to the requests of both the European Medicines Agency (EMA) and vaccine manufacturers

Objective: To describe the VAC4EU organization, data, tools and the accomplishments made towards the generation of real-world evidence on vaccine benefit-risk evaluation.

Methods: Not applicable.

Results: Since its creation in October 2019, VAC4EU has established a large research network composed of 24 institutions from 9 European countries (BE, DE, DK, FR, IT, NL, NO, ES, UK) providing access to different health care data sources covering more than 150 million European citizens. VAC4EU has implemented a research infrastructure including a catalogue, a codemapper tool, a sharepoint, Github, digital research environment (DRE), a phenotype library of more than 100 variables with definitions and a Zenodo community to facilitate collaboration, transparency, and federated data analysis. VAC4EU has adopted the ConcePTION common data model as a basis for the structural harmonization of electronic health data, but it also allows for primary data collection. VAC4EU has consolidated its governance structure for implementation of pharmacovigilance studies on vaccines and successfully participated in four public tenders regarding vaccines safety and effectiveness launched by the European Medicines Agency (EMA) [1–3] as well as four required post-authorization safety studies on COVID-19 vaccines sponsored by vaccine manufacturers [4–8], and other studies promoted by the Global Vaccine Data Network. All protocols developed within VAC4EU are registered in the EU PAS register, and results are published in the open science VAC4EU Zenodo community.

Conclusion: We know already from the H1N1 pandemic that collaboration is needed to study vaccine effects. This collaboration was designed and tested in the IMI-ADVANCE project and implemented in VAC4EU. VAC4EU has demonstrated readiness of its research framework making a key difference in COVID-19 vaccine monitoring in Europe. Research and public health organizations can join the initiative.

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Adverse Events Following HPV Vaccination in the Veneto Region: Data from Spontaneous Reporting

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Introduction: According to WHO, the path towards cervical cancer elimination includes to fully vaccinate 90% of all girls by the age of 15 by 2030. Moreover, in order to eradicate worldwide even others HPV related cancers (i.e. head and neck region, anal and genital cancers) efforts need to be implemented to extend vaccination also in male population [1-2]. In Veneto Region HPV vaccine is actively offered to 12 years old females since 2008, and to 12 years old males since 2015. Since 2018, the Veneto Region started offering the 9vHPV vaccine, which is currently administered for routine immunization.

Objective: To describe and compare the safety profile of 4vHPV and 9vHPV in the Veneto Region, according to spontaneous reporting

Methods: All AEFIs referred to HPV, collected in the Veneto Region and inserted in the Italian Spontaneous reporting database up to March 31th 2022, were analysed. Adverse events are classified according to MedDRA terminology.

Results: In the study period, 638 cases and 1320 reactions associated to HPV vaccination were received: 470 cases referred to 4vHPV (74%) and 168 to 9vHPV (26%). Serious reactions were 49 (10.4%) for 4vHPV and 22 (13.1%) for 9vHPV. Reports in female subjects were 89% in 4vHPV (9.3% serious) and 67% in 9vHPV (11.6% serious). Reports in male subjects were 11% in 4vHPV (20.8% serious) and 33% in 9vHPV (16.7% serious). The most reported systemic reactions were headache (114 reports, 18% of 4vHPV and 17% of 9vHPV reports), hyperpyrexia (65 reports, 9% of 4vHPV and 13% of 9vHPV reports), fever (64 reports, 11% of 4vHPV and 8% of 9vHPV reports) and urticaria (56 reports, 10% of 4vHPV and 6% of 9vHPV reports). Hyperpyrexia was present in almost half of serious reports. Adverse events of special interest according to the Standardized Meddra Queries include 11 seizures (8 for 4vHPV and 3 for 9vHPV) and only one anaphylactic reaction (associated to 4vHPV).

Conclusion: Data from spontaneous reporting in the Veneto region confirm the good safety profile of HPV vaccination both in male and female subjects.

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Medicinal Cannabis and Related Products—Analyses of Quality Defects and Adverse Drug Reactions Reported by German Community Pharmacists

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Introduction: In Germany, the prescription of medicinal cannabis flowers at the expense of statutory health insurance is allowed since May 2017 [1]. Since then, community pharmacists dispense medicinal cannabis to patients, alongside related finished medicinal products or cannabis extracts. In terms of suspected quality and safety issues, German pharmacists are obliged to report adverse drug reactions (ADR) and quality defects (QD) to the Drug Commission of German Pharmacists (AMK).

Objective: Analyses of spontaneously reported ADR and QD of medicinal cannabis (formulations).

Methods: The AMK database was analyzed between January 1, 2014 and March 31, 2022 for reports of QD and ADR related to cannabis flowers, cannabinoid-containing finished medicinal products, and other cannabis extracts. Various cannabis medicines were clustered: (i) finished products (Sativex[®], Canemes[®], Epidyolex[®]); (ii) cannabidiol formulations; (iii) dronabinol formulations; (iv) cannabis flowers, and (v) cannabis extract. These clusters were examined for number of reports received, frequency and types of QD and ADR, as well as patient characteristics.

Results: The total number of spontaneous reports was 211 [n = 38 ADR, n = 137 QD and n = 36 QD/ADR combined]: Sativex[®], n = 17, Canemes[®] n = 1, no reports for Epidyolex[®] [8.5%]; cannabidiol formulations, n = 4 [1.9%]; dronabinol formulations, n = 99 [46.9%]; cannabis flowers, n = 63 [29.9%], and cannabis extract, n = 27 [12.8%]. ADR and QD for Sativex[®] were reported equally. Most QD were reported for dronabinol formulations [n = 80; 58%] and comprised invalid THC rapid tests or deviations in galenics. About 20% of QD reports accounted for cannabis flowers. Here, pharmacists frequently reported high proportions of seeds/stalks or mold. Most ADR reports were associated with dronabinol formulations [n = 14, 36.8%]. Side effects comprised pain, sensory disturbances/dizziness, numbness, tachycardia, and circulatory problems. 49% of all ADR and QD/ADR reports were recorded for male and 41% for female patients. The remaining reports stated no gender. Pharmacists suspected ADR in male patients primarily in the context of cannabis flowers [35%]. In fact, 78% of reports where QD referred to ADR accounted for cannabis flowers. The reported QD related to

wrong cannabis odor, taste or color, excessive seed/microseed content or mold contamination. The associated ADR comprised cough, headache, dizziness, nausea, irritated mucous membrane, and abdominal pain.

Conclusion: Cannabis flowers and dronabinol formulations are associated with relatively high numbers of QD reports. Moreover, QD of cannabis flowers were often associated with ADR, especially in male patients. Thus, future surveillance of potential risks associated with the use of cannabis (as a medicine) should focus on both, drug safety and quality.

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Gemcitabine-Induced Leukocytoclastic Vasculitis

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Introduction: Leukocytoclastic vasculitis (LCV), can be induced by drugs such as nonsteroidal anti-inflammatory drugs, β -lactams, sulfonamides and diuretics.

Gemcitabine, a nucleoside analogue used as chemotherapy, was exceptionally associated with LCV [1].

Objective: We report a new case of gemcitabine-induced CVL.

Methods: This case was analyzed according to the Naranjo causality scale method [2].

Results: A 73-year-old man with a history of high blood pressure and coronary artery disease, on aspirin, atorvastatin, bisoprolol, amlodipine and valsartan, has been followed for squamous cell carcinoma of the lung since 2012.

He received two chemotherapy protocols (gemcitabine and cisplatin in 2013, carboplatin and paclitaxel in 2016) without incident.

During the third protocol, started on May 22, 2019, he presented, five days after the first infusion of gemcitabine, with generalized pruritus and erythema of the upper chest.

On May 29, 2019, the patient received a second gemcitabine infusion associated with premedication. Few hours later, rash generalized.

The diagnosis of vasculitis was suspected. The skin biopsy, performed on the arm, confirmed the diagnosis of CVL. Symptoms resolved in 18 days.

Conclusion: Gemcitabine vasculitis, although rare, is important to diagnose in order to discontinue the causative drug and thus avoid potentially serious systemic complications.

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A Dashboard to Visualize Adverse Events Data from the United States National Library of Medicine ClinicalTrials.gov Database

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Introduction: Draft Guidance from the United States (US) Food and Drug Administration (FDA) was published in 2021 concerning safety reporting and assessment for IND studies. The goal of the guidance is for all parties to focus on reporting of suspected adverse reactions that are serious and unexpected. A wealth of adverse event data are available in the ClinicalTrials.gov website. These data are not standardized and require processing but once available in a standard format and dashboard can be used effectively as part of a safety surveillance plan.

Objective: The objective of this project was to collect, standardize and visualize adverse event data from ClinicalTrials.gov website in a dashboard. The dashboard will enable safety teams to more effectively identify potential anticipated events in clinical research.

Methods: A direct connection to the clinicaltrials.gov database was established to extract all relevant data. Preliminary processing steps were necessary to ingest the data in a standard process. Due to the volume of data available a limited number of cancer indications were selected by filters included in the clinicaltrials.gov database, manually reviewed and standardized. All Adverse event terms were extracted and will be reviewed and standardized. A dashboard was created utilizing Tableau (version 2021.3.6) in order to visualize the data.

Results: The dashboard allows for the easy filtering and selection by several parameters. The user can select the condition, study ID, study arm, therapy, trial phase, age group, gender, AE term or event seriousness. The results of all trials describing the number of studies and subjects included is displayed along with the count and frequency of all adverse event reported across studies if no filter is applied for adverse events. Additional features including statistical measures that will summarize the cohorts under study will be included as future enhancements.

Conclusion: Visualization of adverse event data from the clinicaltrials.gov database will provide a useful way to establish background rates of adverse events in various patient populations that will assist in interpretation and contextualization of events that are observed in clinical studies. Using these data will improve a sponsor's ability to focus on reporting of suspected adverse reactions that are serious and unexpected.

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Not applicable.

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Comparison of the Pathologic Complete Response of Pseudopolumorphic Forms of Docetaxel 80 mg in an Oncology Outpatient Clinic in Brazil

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Introduction: Docetaxel is a chemotherapeutic medication used to treat several types of neoplasms, such as lung, breast, prostate, bladder, head, neck and gastroesophageal cancer. It is available on the pharmaceutical market in the trihydrate (reference medicine) and anhydrous forms (generic). Few studies has compared pathological responses among oncology outpatients who used different pseudopolymorphic forms of this medication [1–5].

Objective: To compare the pathological response of trihydrate and anhydrous forms of docetaxel 80 mg among patients assisted in an oncology outpatient clinic in Brazil.

Methods: A cross-sectional study was performed in an oncology outpatient clinic located in São Paulo, Brazil. Patients aged over 18 years old assisted in the clinic from 2018 to 2020, whose chemotherapy regimens included docetaxel as monotherapy or in combination with other cytotoxic drugs were included. Chart review was carried out to collected data related to demographic characteristics, clinical history and pathological response of participants. Pathologic complete response (pCR) was defined as no invasive and no in situ residuals in tissue samples after chemotherapy [6].

Results: Of the 503 patients who met the inclusion criteria, most were female (78.7%). The mean age of patients was 56.7 years old (SD 12.4). Breast cancer (74.3%), II (34.6%) and III (37.2%) clinical stages of cancer, and neoadjuvant chemotherapy (42.1%) were the most common characteristics observed. Trihydrate docetaxel was used by 55.1% patients, anhydrous form by 23.1%; both forms by 21.8%. pCR were observed, respectively, in 62.9%; 25.7% and 11.4%.

Conclusion: Most patients used the trihydrate form of docetaxel, the pseudopolymorphic that presented the best result for pathologic complete response. However, to ensure that the reference drug is more effective, more studies need to be carried out evaluating not only the effectiveness, but also the safety of the drug.

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Strong Signs of Increased Number of Intoxications Following Rise in Prescription of Promethazine

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Introduction: Promethazine, a first-generation antihistamine, was initially developed for allergies. However, promethazine is today primarily used as a sedative and hypnotic. Promethazine has been approved in Sweden since the 1950s in children over 2 years of age and restricted to prescription only. In recent years, the prescribing of promethazine has increased considerably in Sweden. Promethazine is a phenothiazine derivate and overdose can result in severe intoxication potentially leading to CNS depression, respiratory depression, and even fatalities (1).

Objective: We aimed to investigate if the increased use of promethazine was related to increased number of intoxications.

Methods: We compared the number of patients per year that were prescribed promethazine with the number of calls to the poison centre concerning promethazine, and with deaths where promethazine was assessed during forensic autopsy as a direct contributor to the death. Prescription data were collected from the Swedish Prescribed Drug Register (SPDR), number of consultative calls about acute poisonings were collected from the Swedish Poison Information Centre (SPIC), and number of deaths were collected from the Swedish National Board of Forensic Medicine. Data were collected between 2016 and 2021.

Results: Statistics from the SPDR show that the total prescribing of promethazine increased from 88,568 patients in 2016 to 185,419 in 2021 (109 % increase). This increase can be seen in all age groups except the youngest (0–4 years) and the oldest (85+ years). In 2021, 68 % of those filling prescriptions for promethazine were women. The number of calls to the SPIC increased from 1,133 calls in 2016 to 2,073 calls in 2021 (83 % increase). Most calls concerned intentional overdose. Between 2016 and 2021, promethazine was assessed during forensic autopsy as directly contributing to the death in about 20 cases per year (16, 14, 18, 27, 22, and 22, respectively). Most of the cases (58 %) were considered suicides and 68 % of the deaths occurred in women.

Conclusion: The increased number of intoxications as measured by calls to the poison centre seems to be related to the increased prescribing of promethazine. Similarly, deaths confirmed by forensic autopsy show a slight increase during the study period. Calls to the poison centre as well as deaths mainly involved intentional overdose/suicide. When prescribing promethazine it is important to consider the risks of severe intoxication in case of overdose and to prescribe the minimal possible amount.

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What Is the Safety Profile of Cannabis-Based Medications? Analysis of the Post-Marketing Signals from the FDA Adverse Event Reporting System

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Introduction: The prevalence of cannabis preparations utilization has increased worldwide (1,2). The evidence on their risk-benefit profile remains unclear (3). Post-marketing surveillance plays a crucial role in generating evidence on the safety of these formulations.

Objective: This study aimed to characterize post-marketing adverse drug events (ADEs) related to the use of cannabidiol (CBD), tetrahydrocannabinol (THC), and nabilone reported to the FDA Adverse Event Reporting System (FAERS).

Methods: We used the FAERS quarterly data from January 2004 to December 2021 to identify cannabis products (CBD, THC, and nabilone). Sociodemographic characteristics of the patients reporting cannabis-related ADEs were described. The reporting odds ratios (ROR) with 95% confidence intervals (CI) were calculated for important medical events to detect signals of disproportionate reporting for the three different products. Product labels were used to highlight unexpected signals.

Results: We retrieved 27,868 cases of cannabis-related ADEs, of which 40.1% involved CBD, 24.0 % THC, and 3.2% nabilone. Patients with CBD-related ADEs were younger (median: 46 years; IQR: 23–61) than those with THC (56; 42–67) and nabilone (51; 37–61). Reports involved more often women (60.5% of CBD, 48.8% of THC, and 67.1% of nabilone ADEs). For CBD, the ADE outcomes were more often non-serious (54.6%), with life-threatening or death events reported, respectively, in 1.1% and 4.6% of ADEs. Nevertheless, CBD was considered as primary suspect of the ADE in 72.1% of reports. THC and nabilone were more often recorded as concomitant therapy and not as the real cause of ADE (84.0% and 83.0%, respectively) and associated with more serious outcomes (death: 19.2% for THC and 8.5% for nabilone; hospitalization: 32.2% for THC and 31.4% for nabilone). The analysis of important medical events revealed mostly known events such as drug abuse for CHT (ROR = 3.84; 95% CI 3.11–4.70), or events possibly related to indication bias, such as seizure for CBD (31.89; 30.53–33.35), failure to thrive for THC (25.11; 18.95–32.64), and rheumatoid arthritis for nabilone (14.26; 10.85–18.43). New signals emerged for THC, such as febrile neutropenia (4.81; 3.92–5.84), pancytopenia (3.56; 2.8–4.5), thrombocytopenia (2.54; 2.07–3.09), renal failure (2.21, 1.83–2.65), chronic kidney disease (3.66, 3.01–4.41), and deep vein thrombosis (2.62, 2.05–3.30). For CBD, new signals were pneumonia (1.29, 1.14–1.46) and pneumonia aspiration (4.10, 3.16–5.24).

Conclusion: Cannabis preparations seem to have, in general, a safe profile. Nevertheless, cytopenia, kidney-related conditions, and thrombosis were reported with THC and pneumonia with CBD. These ADEs, not reported in the summary of product characteristics of the corresponding formulations, deserve further investigation.

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Risk of Psychotic Disorders Among Patients with Medical Cannabis Authorization: A Longitudinal Cohort Study

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Introduction: The use of cannabis for recreational purposes is associated with an increased risk of psychotic disorders (1,2). However, the risk of psychosis is not well characterized for patients using cannabis for medical purposes.

Objective: Thus, this study assessed the risk of emergency department (ED) visits or hospitalization for psychotic disorders among adult patients authorised by their healthcare providers to use cannabis to treat a health condition in Ontario, Canada, from 2014 to 2020.

Methods: This was a longitudinal retrospective cohort study of patients who received medical cannabis authorization and followed-up in cannabis clinics, matched by high dimensional propensity scores to population-based controls (with a ratio of patients in cannabis clinics to controls of 1:3). Clinical and health administrative data were used. The primary outcome was an ED visit or hospitalization with a primary diagnosis reason (ICD-10 codes) related to psychotic disorder. Conditional Cox proportional hazards regressions accounting for the matching were used to assess the risk.

Results: A total of 60,414 cannabis patients were matched to 180,397 controls. Less than half of the patients (42%) were aged ≤ 50 years, and 54% were female. Incidence rates for psychotic disorders were 2.25/1000 person-years (95% CI 2.02–2.51) in the cannabis group and 1.56/1000 person-years (95% CI 1.45–1.68) in the control group. The hazard ratio (HR) based on the conditional Cox model further adjusted for age, sex, and history of psychotic disorders was 1.25 (95% CI 1.05–1.36). Among patients without a history of psychotic disorders, the HR was 1.25 (95% CI 1.07–1.46).

Conclusion: Medical cannabis authorization was associated with an increased risk of ED visits or hospitalization for psychotic disorders. Careful benefit-risk assessment is needed before medical cannabis authorization.

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Assessing the Brighton Collaboration Case Definition of Sensorineural Hearing Loss in Ghana

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Introduction: Lassa fever (LF) is endemic over most of West Africa and a third of LF survivors develop sensorineural hearing loss (SNHL). Multiple LF vaccine candidates are in the development pipeline. In February 2020, the Brighton Collaboration Safety Platform for Emergency vAccines (SPEAC) project has developed a case definition to assess SNHL as an adverse event of special interest for LF vaccines [1,2].

Objective: To assess the applicability of this SNHL case definition to data collected in routine clinical care settings at a tertiary hospital in Ghana.

Methods: The study subjects were patients aged 18–59 years who attended the Eye, Ear, Nose and Throat Department at the Komfo Anokye Teaching Hospital between 1 January 2007 and 30 June 2020. We used the keywords “hearing loss”, “sensorineural hearing loss”, or “SNHL” to retrospectively identify eligible patients from electronic (EMR) and paper medical records. We applied the Brighton Collaboration criteria for level of diagnostic certainty (LOC) ascertainment to up to 300 potential SNHL cases, by date from the most recent patient backwards. The following parameters were assessed: (1) completeness to obtain information on each criterion of the case definition; (2) ability to assign LOC up to level 3, and what LOC was ascertainable; (3) ability to achieve the same LOC for the same case by different assessors; and (4) reasons for being unable to classify cases.

Results: Overall, 860 eligible cases were identified; data from 42 EMR and 258 paper case records were abstracted (median age 43 years, 55% male). Most SNHL cases were assessable (85.0%) and assigned level 1 LOC (84.3%); missing information on otoscopy (86.7%) was the main reason for being unable to classify cases. Consistency of LOC classification between assessors was 99.3%. Completeness on the recorded evidence of otoscopy (38.1% vs 93.7%, $p < 0.001$), tympanometry (38.1% vs 93.4%, $p < 0.001$), and audiometry (30.9% vs 93.0%, $p < 0.001$) was lower in EMRs than in paper records. Other diagnostic tools, including Tuning fork exam, auditory brainstem response test, otoacoustic emissions test, behavioral or neurodevelopmental assessment, and remote screening were rarely documented.

Conclusion: The Brighton Collaboration SNHL case definition would be applicable to retrospectively ascertain and classify cases in resource-limited settings. Developing an EMR template to document otoscopy results may improve the feasibility at this hospital to ascertain SNHL in the context of an LF vaccine trial or post-introduction.

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Safety and Tolerability of Dimethylfumarate, an Analysis of Pharmacovigilance Data Within the Region of Sardinia

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Introduction: The first description of a medical use of DMF dates back to 1959, when biochemist Schreckendiek highlighted the benefits on psoriasis [1]. In 1994, DMF was approved in Germany under the trade name Fumaderm® for the treatment of psoriasis [2]. Subsequently, several new therapeutic uses were proposed, like the treatment of multiple sclerosis [3]. Currently in Europe, DMF is available as Tecfidera®, approved by the European Medicines Agency (EMA) in 2013 for the treatment of multiple sclerosis [4] and Skilaren®, approved in 2017 for the treatment of psoriasis [5]. The side effects most frequently associated with DMF are those of flushing and gastrointestinal complaints. Less frequent side effects include a reduction in the number of lymphocytes and liver disorders [6].

Objective: To evaluate the trend of reports of adverse reactions from DMF in the region of Sardinia.

Methods: An analysis on the National Pharmacovigilance Network database has been conducted up to May 4th, 2022 and for the Region of Sardinia alone, including both approved medicinal products. Various percentage frequencies were calculated on the reports found.

Results: There were found 26 reports, of which, 22 were from health professionals, 4 from patients/citizens, 22 reports were non-serious, and 4 reports were serious. In 16 out of 26 (61%) reports, the time-to-onset (TTO) was less than one month. 8 out of 26 (31%) patients were younger than 35 years old, 7 out of 26 patients (27%) were older than 50, 19 patients were female (73%) and 7 male (27%). 9 out of 26 (34%) reactions were characterized by hypersensitivity reactions, 7 out of 26 (27%) were gastrointestinal reactions, one reaction (4%) of lymphocytopenia, one reaction with increased transaminases (4%), one reaction of alopecia (4%). 10 of the reports (38%) were submitted by November 2018, 16 reports (62%) were submitted from August 2020 through May 4th, 2022.

Conclusion: The reported adverse reactions are divided into 3 main subgroups, in line with literature data, and cases of liver damage and alopecia were also reported. Adverse reactions predominantly affect the female sex, and most reactions did not require hospitalization. The time gap of reporting between the end of year 2018 and mid 2020 could get further investigation to clarify whether it's related to the Pharmacovigilance signals that led the European regulatory authority to re-establish the risk-benefit ratio for this drug in the year 2018.

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Post-Marketing Safety of Anti-Calcitonin Gene Related Peptide Antibodies: A Disproportionality Analysis of the FDA Adverse Event Reporting System

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Introduction: Monoclonal antibodies (mAbs) blocking the calcitonin gene related peptide (CGRP) have been recently approved for migraine prophylaxis. Adverse events reported by pivotal trials and post-marketing studies were mild to moderate and tended to decrease over-time. However, to date, studies evaluating the long-term safety and rare adverse events are still scarce.

Objective: To investigate adverse events potentially associated with the use of the four anti-CGRP mAbs (erenumab, galcanezumab, fremanezumab, eptinezumab) captured in the real-world setting by using the Food and Drug Administration Adverse Event Reporting System (FAERS).

Methods: We performed a case/non-case pharmacovigilance study with disproportionality analysis on FAERS reports submitted over the 2004–2021 period. Reports with any suspect anti-CGRP mAb were selected as cases and compared with all the reports not recording anti-CGRPs. Descriptive analyses were performed to investigate the demographic and reporting characteristics associated with cases relative to non-cases, testing for significant differences. Both raw and adjusted (on sex and age) Reporting Odds Ratios (RORs) were calculated as a measure of disproportionate reporting across medical dictionary for regulatory activity (MedDRA) hierarchy, namely from system organ class (SOC) to preferred term (PT) level. Results were prioritized using Bonferroni and focusing on Important Medical Events.

Results: FAERS database contains 39,878 reports with an anti-CGRP listed among suspect drugs. The majority recorded erenumab (N = 25,882) and fewer eptinezumab (770). Comparing cases with non-cases, women were more represented (85% vs 61%, $p < 0.001$), together with adults aged 30–65 years (73% vs 52%, $p = 0.003$). Among retrieved reports, non-serious adverse events were 82% vs 39% in non-cases ($p = 0.003$). All the anti-CGRP mAbs were associated with nervous system disorders, general disorders, and administration site conditions at the SOC level. Concerning Important

Medical Events, erenumab was exclusively associated with colitis ischemic (N = 31; ROR = 3.0 95% CI [2.1–4.3]), impaired gastric emptying (N = 40; 3.5 [2.5–4.8]), faecaloma (N = 26; 3.4 [2.2–4.9]), sternal fracture (N = 12; 6.6 [3.4–11.5]), thyroid gland injury (N = 6; 187.8 [59.2–518.4]), reversible cerebral vasoconstriction syndrome (N = 11; 6.9 [3.4–12.4]).

Conclusion: Overall, demographic characteristics of cases appeared consistent with migraine epidemiology and anti-CGRP utilization patterns in clinical practice. New signals potentially linked to the blockage of the vasodilating effect of CGRP (ischemic conditions), of its protecting role against osteopenia (sternal fracture), and of its interactions with TSH (thyroid gland injury) deserve further investigations.

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Not applicable.

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A Case Report of Possible Pembrolizumab-Induced Myasthenia Gravis from an Italian University Hospital: A Fatal Case Report

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Introduction: Pembrolizumab is a monoclonal antibody, Programmed death-1 (PD-1) inhibitor, currently approved for the treatment of a wide range of malignancies. This immunotherapy has a favorable efficacy/safety profile even though it could be related to very serious and sometimes fatal adverse events [1]. In particular, pembrolizumab use has been associated with several life-threatening immune-related adverse events. Among them, Myasthenia Gravis (MG) induced by pembrolizumab was rarely reported previously in the medical literature [2].

Objective: To present a clinical case report concerning a patient with possible pembrolizumab-induced MG treated at our university hospital.

Methods: Starting from a report of an adverse drug reaction (ADR) received by our Local Responsible for Pharmacovigilance (LRPV) and included in the National Pharmacovigilance Network, we retrospectively collected information about the drug therapy taken by the patient and his clinical history.

Results: A 74-years-old Caucasian man with a diagnosis of clear cell renal cell carcinoma (ccRCC) since 2012, with more recent finding of additional pancreatic and pulmonary localizations, entered the emergency room in September 2021 with a suspected MG and deep bulbar involvement. Since July 2021, the patient has been treated according to the standard of care (SoC) with intravenous pembrolizumab and axitinib. Just a month later, he complained of general malaise, fatigue and a sense of heaviness in the neck with drooping of the head. The symptoms have worsened in dysphagia associated with marked dysarthria, hypophonia, difficulty in raising the upper limbs and walking. Episodes of diplopia were also reported.

The clinical scenario suggests the indication for urgent hospitalization for appropriate clinical investigations. From the first results, a picture compatible with MG emerged. Immediately, the patient underwent appropriate treatment (such as intravenous immunoglobulins and high-dose corticosteroid therapy) followed by five consecutive plasmapheresis sessions. Nevertheless, the general conditions have worsened and the patient expired after 12-day hospitalization.

Conclusion: Pembrolizumab, as many other PD-1 inhibitors, can provide great benefit to patients but can also be associated with rare but serious adverse events. Although rare, cases of pembrolizumab-associated MG are increasing. Early recognition of symptoms and possible discontinuation of pembrolizumab are necessary to improve prognosis. Finally, any adverse effects reported by patients should be closely monitored and evaluated.

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The Approaches to Assess Robustness of Disproportionality Findings in Pharmacovigilance. A Meta-Epidemiological Research

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Introduction: Disproportionality analyses aim to identify potential adverse drug reactions from spontaneous reporting systems in a timely and cost-effective manner. For their apparent simplicity, their use is rapidly expanding as a source of safety evidence complementary to clinical trials. In fact, most disproportions in reporting are not robust enough to identify a safety signal, and strategies used to assess robustness are heterogeneous and inconsistently used (1-4). Documenting these strategies would move forward harmonization in pharmacovigilance studies and simplify signals prioritization for regulatory interventions.

Objective: To describe the approaches used in the last two decades to assess the robustness of disproportions.

Methods: One hundred studies were randomly selected through a systematic literature search performed on Medline to identify all published disproportionality analyses since inception up to January 1, 2020 (search terms: “case-non case”, “disproportionality analysis”, “pharmacovigilance analysis”, “pharmacovigilance study”). We designed an extraction table to gather, for each article, general information, disproportionality techniques, other new clinical data, integration with other sources, and literature support (see Picture 1). A pilot analysis was performed to train 3 operators (MF, MI, ER). Disagreements were solved through discussion and consensus.

Picture 1 – Approaches to assess robustness of disproportionality findings in Pharmacovigilance.

Disproportionality Techniques	Disproportionality Index (PRR [20%], ROR [86%; 29% adjusted], EBGM [9%], IC [20%]) Strength/Prioritization (correction [0%], Designated Medical Event [3%]) Consistency (on subpopulations [17%], multiple databases [20%], or time [14%]) Coherence (SMQ [17%], MedDRA hierarchy [11%], ad hoc query [34%]) Specificity (positive [26%] and negative [20%] controls) Temporal and Biological plausibility (time to onset [34%] and dose [31%]) Reversibility (dechallenge and rechallenge [11%]) Differential Diagnosis (case by case causality assessment [14%]) Exclusion of bias [14%]
Integration with Other Sources	Drug-utilization [3%] Patient-susceptibility (genetic data) [3%] Pharmacological basis (pharmacokinetics [11%], pharmacodynamics [6%])
Other New Clinical Data	Case-report/series [0%] Observational [0%] Systematic Review [3%]
Literature	Study rationale (preclinical [11%], case-reports [43%], clinical trials [12%], observational [40%], other case-non case studies [20%], methodological [3%], regulatory [51%], other [40%]) or literature support (preclinical [20%], case-reports [14%], clinical trials [34%], observational [23%], other case-non case studies [17%], regulatory [11%], systematic review [11%], other [23%])

Results: This pilot study was based on 35 articles, of which 20% used more than 1 database, 26% employed a Bayesian method, and 54% used standardized or ad hoc queries for a more sensitive case retrieval. Techniques used to increase the robustness of the disproportionality were adjustment (29%), consistency on subpopulations (17%), positive and negative controls (26 and 20%), disproportionality time-trend (14%). Clinical elements of the reporting systems were investigated in a minority of studies: time to onset (34%), dose (14%), dechallenge/rechallenge (11%). Only 14% performed a causality assessment and 31% of the studies accounted for at least one bias (11% indication, 9% comedication, and 9% notoriety bias). Drug utilization data and systematic reviews were used to support robustness only in 1 study each. Most studies stemmed from regulatory reasons (51%) or case series (43%) as rationale. The main literature support presented in the discussion came from clinical trials (34%). Biological plausibility was discussed by 60% of the studies, but only 11% employed a dedicated pharmacokinetic-pharmacovigilance approach.

Conclusion: We found a wide heterogeneity in the use of approaches to assess the robustness of disproportions. We call for consensus to harmonize the reporting of pharmacovigilance studies, including minimum robustness criteria.

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Paliperidone and Potential Risk of Hyponatremia

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Introduction: Paliperidone is atypical antipsychotic drug. The Saudi Food and Drug Authority (SFDA) approved paliperidone for the treatment of schizophrenia in patients ≥ 12 years of age and schizoaffective disorder in patients ≥ 18 years old.

Objective: The aim of this report is to examine the association between paliperidone use and the potential risk of hyponatremia as part of the proactive drug safety monitoring program at the at SFDA.

Methods: A systematic literature search was conducted using the following databases: Medline using PubMed interface, Google scholar, and Clinicaltrial.gov from inception to April 23, 2022. Inclusion criteria were English publications and studies on humans that reported adverse events interest with the use of paliperidone. The search included the following key words: [paliperidone OR Invega OR Xeplion OR Trevicta] AND [hyponatremia OR low sodium level OR sodium deficiency OR blood sodium decreased]. In addition to that, a search in the local adverse drug reactions database and World Health Organization (WHO) database was performed on April, 2022 via signal detection tool (Vigilyze) using the terms paliperidone (substance [WHO Drug] [AND] "Blood sodium decreased or Hyponatraemia" (reaction preferred term (PT) (MedDRA)).

Results: We identified one observational study, and six published case reports. The observational study found that the adjusted reporting odds ratios for the association between paliperidone and hyponatremia was 1.34 (95% confidence interval (CI) 1.09–1.51).¹ Furthermore, six published cases of hyponatremia following the use of paliperidone were summarized in table 1.^{1,2,3,4,5,6} Most of the patients developed hyponatremia secondary to syndrome of inappropriate antidiuretic hormone (SIADH) which is a known risk of paliperidone.⁷

	Gender	Age (years)	Time to onset	Assessment*	De-challenge (Yes/No)
1	Male	40	2 months	probable	Yes
2	Male	35	2 days	Possible	NA
3	Male	41	3 days	probable	Yes
4	Male	62	1 year	Probable	Yes
5	Female	39	2 months	Possible	NA
6	Female	60	3 months	Possible	NA

Table 1 *Using the WHO-UMC causality assessment system NA: Not available

The search on the WHO database yielded 101 reported cases.⁸ There were 58 males (57.4%), 41 females (40.6%) and two cases with unreported gender. The patients' age range in most cases was between 18 and 64 years old. An assessment of cases with completeness score identified 20 cases including three cases reported positive de-challenge. WHO-UMC causality assessment system was applied resulting one case with probable association due to reasonable temporality and positive de-challenge, eight cases had a possible association with reasonable temporality, ten cases were unlikely due to confounding by medical history or concomitant medications and there was one un-

assessable case due to limited information provided. No local cases found.

Conclusion: The Available evidence suggests a potential association between the use of paliperidone and hyponatremia. Further epidemiological studies are needed to support this potential association.

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Drug-Induced Acute Pancreatitis Cases Notified to the CNPV

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Introduction: The incidence of acute pancreatitis (AP) varies between 15 to 40 cases/ 100,000/year [1]. Drugs are responsible for 2% of acute pancreatitis cases [2]. In Tunisia, few studies have been carried out on drug induced pancreatitis [3].

Objective: To analyze the clinical characteristics of DIAP cases notified to the Chalbi Belkahia National Center for Pharmacovigilance (CNPV) and identify incriminated drugs.

Methods: Retrospective study carried out in the department of collection and analysis of adverse reactions over 22 years from 1997 to 2018 collating the cases of DIAP notified to the CNPV. We included

cases meeting the diagnostic criteria of AP [4] and whose drug imputation was retained by the pharmacovigilance investigation evaluated according to the French method of Bégaud et al [5].

Results: We collected 41 cases in which 48 drugs (33 active ingredients) were incriminated. The median age of the patients was 42.3 years (15 to 78 years). The sex ratio F/H was 1.05. The notifying physicians were gastrologists in 34% and surgeons in 27% of cases. Chronic pathologies were present in 37/41 patients where IBD represents 27% of cases. Scannographic stage was B in 27% of cases. Stages D and E were found in 27% of cases. The onset delay varied from one day to 12 years. In 46% of the cases, it was more than one month. Immunosuppressants, antihypertensive, and intestinal anti-inflammatory drugs were incriminated in 12% of cases each, followed by glucocorticoids and antibiotics (10% of cases each). Among the immunosuppressants, azathioprine was found in 12% of cases. Among antihypertensive drugs, captopril was incriminated in 7% of cases. The drug-induced pancreatitis cases were mostly moderate with a favorable outcome after discontinuation of the drug in 98% of cases. Positive re-challenge occurred in one case with captopril. The imputation score was plausible (I2) in 51% of cases.

Conclusion: Our study showed a predominance of DIAP in young adults with a slight female predominance. The delay of onset is essentially more than 1 month with a favorable evolution in almost all cases. The incriminated drugs belonged essentially to the classes of immunosuppressants, antihypertensives, and intestinal anti-inflammatories. Up-to-date knowledge of drugs that can cause PA can help clinicians be aware of this infrequent etiology and facilitate rapid discontinuation of the causative agent, thus reducing complications.

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Personalized Approach to the Diagnosis and Treatment of Acute Psychoactive Substance Poisoning in Adolescents

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Introduction: Acute psychoactive substance poisoning is one of the main reasons for admission of adolescents to the emergency and intensive care hospital department [1]. Recently there has been a change in the structure of poisoning such as the exponential growth of new synthetic psychoactive substances [2, 3]. It is necessary to

conduct analytical screening and develop personalized diagnostic and treatment algorithms for emergency medical care.

Objective: To develop individual algorithms for the diagnosis and treatment of acute psychoactive substance poisoning in adolescents.

Methods: A retrospective study of adolescents with acute poisoning in 2016–2019 period hospitalized in the Regional Children's Clinical Hospital. The exclusion criterion was the presence of concomitant pathology. Statistical processing included evaluation of descriptive statistics parameters.

Results: Use of various substances was widespread among the adolescents (n = 57): psychoactive substances (61.4%), drug combinations (8.8%), antipsychotic (5.3%) and anxiolytic (5.3%) drugs, and other drugs (19.2%). For patients with acute poisoning with psychoactive substances the main syndromes were: impaired consciousness (96%), tachycardia (78%), psychomotor agitation and ataxia (70%), depression of consciousness (56%), miosis (45%), arterial hypertension (42%), mydriasis (30%), visual and auditory hallucinations, disorientation (25%). In 70% of cases it was not possible to determine the exact name of the substance that caused acute poisoning, the diagnosis was made according to the main clinical syndrome (toxidrome). The identification of the main syndromes: cholinergic, opioid, sympathomimic and anticholinergic allows to assume the toxic substance and choose an individual therapy scheme.

Conclusion: The study revealed the need to develop a personalized approach for acute poisoning with psychoactive substances based on the main toxidrome to ensure prompt diagnosis and effective therapy.

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Adverse Drug Events in an Intensive Care Unit: A Pilot Study Using the Global Trigger Tool

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Introduction: Patients admitted to an intensive care unit (ICU) are more susceptible to adverse drug events (ADE) due to the severity of their illnesses, which often require administration of drugs with a high potential to cause harm [1,2]. The Global Trigger Tool (GTT) [3] is an efficient easy-to-use method to identify ADE and to measure their prevalence rates, and its implementation does not require high levels of technological or financial resources [4].

Objective: To estimate the prevalence of ADE in adult patients admitted to an ICU and assess the efficiency of defined triggers in detecting ADE.

Methods: We performed a retrospective descriptive study based on the analysis of medical records of adult patients admitted to an ICU at Sumaré State Hospital—Brazil, for the period from January to December 2020. The GTT was adapted considering the reality of the study setting. Twenty-nine triggers were used, 15 of them were medication, 10 were abnormal laboratory results, and 4 related to care. The efficiency of the triggers was defined as the ability to identify an ADE, and its positive predictive value (PPV) calculated by the ratio between the number of ADE identified by a trigger and the number of trigger per medical record. The data will be presented under descriptive analysis of the absolute and percentage frequencies of the variables.

Results: Of the 60 medical records reviewed, 37 had at least one ADE (62%). Fifty-seven ADE were identified, 43 of them (75%) due to established triggers. Only 5 ADE were detected using spontaneous reporting in the same period. A total of 447 triggers were identified. The most found triggers were: glucose < 50 mg/dl (90.0/100 medical records), abrupt medication stop (70.0/100 medical records), and hydrocortisone (68.3/100 medical records). The most efficient triggers for ADE detection were INR > 3 (PPV 70.9), abrupt medication stop (PPV 47.6), and platelets < 50,000 (PPV 33.3).

Conclusion: With the data collected so far, we were able to identify a number of ADE almost 10 times greater than the number reported in the same period via spontaneous notification. The results found show the efficiency of using GTT in the detection of ADE, which can contribute to optimizing the pharmacovigilance actions performed at the Sumaré State Hospital

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A Cross-Sectional Investigation for Verification of Falsified Medicinal Product in Egypt, Indicated by vials of Ampicillin/Sulbactam

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Introduction: The trafficking of falsified and substandard medicinal products is a global socio-economic problem, which poses a serious threat to economy and health of populations of most countries [1]. World Health Organization (WHO) press department issued a press release with the bold headline: “1 in 10 medical products in developing countries is substandard or falsified” [2].

Objective: Detection of the unusual appearance of monitored ADRs.

Methods: A cluster of 8 reports for Adverse Drug Reactions (ADRs) have been received by the pharmacovigilance department at the Medical Union Pharmaceuticals co (MUP) regarding its products, Unictam[®] 1500 mg (Ampicillin/Sulbactam). Shortly after, more 3 similar cases have been received. The reported ADRs were uncommonly to be related to Ampicillin/Sulbactam, not to mention the sudden trending in their reporting. At this stage, an underlying counterfeit had been suspected by the company's pharmacovigilance department. In a timely manner, serious cases were notified to the regulatory authority with a highlight of potential counterfeit. Meanwhile, a multidisciplinary investigation has been initiated within the company including: analysis of product's collected samples from the cases' reporters, in-depth literature review about the suspected product in relation to the reported ADRs, more active social media screening to capture any similar posted cases, establishing published electronic-based product questionnaire for healthcare professionals and the public to support data collection.

Results: Visual inspection of the samples showed differences compared to the original pack of Unictam[®] 1500 mg in the outer pack, powder color, flowability and quantity. Samples analysis has confirmed a product counterfeit. During the period February to April 2022, a total of 48 cases were collected for this product compared to 0 and 3 reports in 2021 and 2020 respectively. Which represent a noted trend attributed to the product counterfeit. 59% of the reported cases for this counterfeit product were serious. The reported ADRs which were characterized as important and cannot be explained by the product pharmacology included; Blood pressure increased, Syncope, Mydriasis, Vomiting blood, ECG signs of Myocardial infarction and Myocardial infarction. Other reported expected ADRs included Anaphylaxis, Vomiting and hypotension.

Conclusion: Counterfeit products can be detected from cases initially reported as ADRs. An effective Pharmacovigilance system at pharmaceutical companies can play an important role in detecting and investigating such counterfeit, in particular, those associated with ADRs. Companies seeking such responsibilities attain public trust in the company as a whole.

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Erythema Multiforme Reactions Following Pfizer/BioNTech (BNT162b2) and Oxford/AstraZeneca (chAdOx1-S) COVID-19 Vaccination: A Case Series

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Introduction: Pfizer/BioNTech (BNT162b2) and Oxford/AstraZeneca (chAdOx1-S) COVID-19 vaccines were approved for emergency use. Clinical trials of both vaccines reported no safety concerns other than a few local and systemic reactions that resolved in few days for both vaccines. Cutaneous reactions to COVID-19 vaccination are generally minor and self-limited. The most common cutaneous reaction reported was a local injection-site reaction.

Objective: Here we present 3 cases of erythema multiform following COVID-19 vaccination with positive rechallenge in 2 cases.

Methods: Not applicable.

Results: Case 1: A 51 year old woman with no past medical history presented with a macular, erythematous, round-shaped itchy rash on the hands, knees and soles. She denied having a neither recent illness nor sick contact. However, she received the first dose of the mRNA Pfizer/BioNTech (BNT162b2), 3 days earlier. Lesions disappeared in 7 days with local corticosteroid treatment.

One month later and two days after receiving the second shot of the same vaccine, lesions reappeared and extended to upper members. Skin biopsy was compatible with erythema polymorph.

Case 2: A 55 year old man with a past medical history of hypertension, presented 6 days following the 2nd shot of the mRNA Pfizer/BioNTech (BNT162b2), vesicular eruptions on the upper and lower members. The outcome was favorable within 2 weeks under local corticosteroid. The patient reported that he had the same skin lesions in ankles and soles few days following the 1st shot of the same vaccine. Histological findings revealed an erythema polymorph.

Case 3: A 57 year old woman with a medical history of hypertension and anxiety disorder presented with a worsening rash and fever for 6 days. The patient reported that she experienced fever, polyarthralgia and that she had received the second shot of Oxford/AstraZeneca (chAdOx1-S), the day before these symptoms appeared. On the physical examination, she had targetoid skin lesions over the trunk, on the ear, upper and lower members. Otherwise she had oral and genital mucosal ulcerations.

A thoracic CT scan was performed because of the persistent fever and showed multiple enlarged lymph nodes, a layer of pericardial and plural effusion.

A favorable outcome was observed in 3 weeks.

Conclusion: Erythema multiform remains an exceptional COVID 19 vaccine adverse effect. Health care workers must be aware of this potential adverse effect or its recurrence and advise patients accordingly. Benefits of receiving a COVID 19 vaccine remains more important.

References/Further Sources of Information

Not applicable.

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The Risk of Posterior Reversible Encephalopathy Syndrome with Tyrosine Kinase Inhibitors: A Disproportionality Analysis from Vigibase and AERS Databases

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Introduction: Posterior Reversible Encephalopathy Syndrome (PRES) is a clinical radiologic syndrome characterized by symptoms such as headache, seizure, altered consciousness and visual disturbances(1).

PRES has been associated with sepsis, malignant hypertension, transplants, and the use of chemotherapeutic agents, immunosuppressants, or cytotoxic treatments for malignant neoplasms, but its pathogenesis remains poorly understood (2-3).

Objective: To quantify disproportionate reporting (Disp-Rep) (4-6) for the risk of PRES for 41 different tyrosine kinase inhibitors (TKIs) in 2 groups: (1) Anti-angiogenic (AA) TKIs; (2) Non-anti-angiogenic (NAA) TKIs and (3) Control group of 3 drugs associated to PRES.

Methods: For analysis we used the Vigibase and AERS databases, with data up to March 2022 and December 2021 respectively.

Cases were identified using MedDRA (v24.1) and the Preferred Term (PT) "Posterior reversible encephalopathy syndrome". Empirical Bayes Geometric Means (EBGM) were calculated to quantify Disp-Rep.

We considered Dis-Rep as confirmed if the lower bound of the 90% confidence intervals, EB05, was > 2.

We studied 3 groups of drugs: (1) a positive control group (non-TKIs associated with PRES: cyclosporine, tacrolimus and bevacizumab) and groups of TKIs: (2) AA TKIs (16 drugs) & (3) NAA TKIs (25 drugs). Drugs were identified by non-proprietary name.

Results: We retrieved 1,991 cases of PRES in Vigibase and 2,551 in AERS.

In Vigibase; Disp-Rep with EBGM [90% CI, EB05–EB95] was confirmed for the positive control group: tacrolimus 34.54 [32.43–36.76] cyclosporine 32.48 [30.21–34.88], and bevacizumab 22.94 [21.0–25.02].

Disp-Rep for 10 of 16 AA TKIs: axitinib 41.12 [33.77–49.68], lenvatinib 41.24 [32.62–51.56], pazopanib 14.22 [11.07–17.87], sunitinib 8.63 [6.98–10.61], cabozantinib 7.6 [5.28–10.8], regorafenib 5.98 [4.07–8.56], ponatinib 5.55 [3.42–8.65], sorafenib 4.06 [2.9–5.55], vandetanib 5.7 [2.72–14.2] and tivozanib 23.56 [2.7–128.78].

Few AA with no Disp-Rep (EB05 < 2) were found: acalabrutinib, dacomitinib, neratinib, nintedanib, ripretinib and seliprecatinib.

No Dis-Rep (EB05 < 2) was found for any of the NAA compounds: afatinib, alectinib, avapritinib, bosutinib, brigatinib, ceritinib, crizotinib, dabrafenib, dasatinib, entrectinib, erlotinib, fostamatinib, gefitinib, gilteritinib, ibrutinib, imatinib, lapatinib, lorlatinib, nilotinib, osimertinib, pemigatinib, pexidartinib, pralsetinib, tucatinib and zanubrutinib.

The analysis in AERS yielded similar results with the exception that vandetanib and tivozanib did not show Dis-Rep.

Conclusion: All TKIs with confirmed Disp-Rep were from the AA group. This finding suggests a potential class effect for the event of PRES for AA TKIs.

Our results however, should be interpreted with caution as disproportionality analyses are hypothesis generating rather than hypothesis testing. Further analysis are planned to better understand this potential class effect.

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Evaluation of Deprescribing Services in Frail Patients: A Systematic Review

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Introduction: Frailty is a geriatric syndrome associated with decreased physiological systems, increased vulnerability to adverse drug effects, and unfavorable clinical outcomes (1). Medication management in patients with frailty remains an understudied challenge (2). Existing clinical guidelines rarely provide interventions specific to frail people with multiple co-morbidities and treatments (3). Deprescribing, a process of dose reduction or withdrawal of inappropriate medication that no longer has benefit, is a proposed intervention in the care of older adults living with frailty (4,5).

Objective: To evaluate safety, clinical impact, and long-term outcomes of deprescribing services in frail patients, including the barriers and enablers of deprescribing services in such settings.

Methods: A systematic review was performed in Scopus, CINAHL PLUS (EBSCO), MEDLINE (OVID and EMBASE) and Cochrane library. Interventional studies with any design about deprescribing services in frail patients were included. Search terms included deprescribing, frailty, safety, and efficacy. The Mixed Methods Appraisal tool (MMAT) was used for appraising the methodological quality of the included papers (6). Studies were selected after title, abstract, and full text screening, with independent review. Data

extraction for the selected studies included study aims, setting, location, study design, duration, participants, sample size, methods of frailty assessment, method of analysis, results, description of deprescribing services, and gaps of deprescribing interventions. Thematic analysis was used for analysing data from the selected articles.

Results: 590 unique titles were identified, with 9 (6 trials, 1 interview, 1 survey, and 1 designed-delay study) meeting inclusion and exclusion criteria. Five main descriptive themes have been identified: barriers, enablers, deprescribing services in frailty, safety management and deprescribing outcomes.

Conclusion: This systematic review provides limited evidence that deprescribing services in frail patients are effective in reducing the number of potentially inappropriate medications and medication costs. A full understanding of frailty, barriers, enablers, and deprescribing long-term outcomes are critical to improve medication safety. To further improve deprescribing in frailty, clinicians should consider a customised safety plan and benefit/risk assessment for each patient. High-quality clinical trials with larger sample size and longer duration are needed to demonstrate the safety and long-term effectiveness of deprescribing in frail people.

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Using Real-World Data for Rapid Safety Investigations: Value of Near-Real-Time Clinical Data Querying

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Introduction: Real-World Data (RWD), such as electronic health records (EHR), has enormous potential to support pharmacovigilance (PV) activities across the drug development and post-approval lifecycle. RWD is used to generate evidence of product effectiveness to support approval of new indications for approved drugs or to meet post-approval study requirements [1]. Although RWD has excellent potential supporting PV activities, limitations such as PV departments' lack of direct data access to RWD, the complexity of query generation to create matching populations, and delay in obtaining

results with PV workflow timeline (e.g., regulatory reporting timeline) create barriers to more effective use of RWD in PV.

Objective: To investigate whether an EHR-based data network can be used in PV investigations to calculate background rates of anemia in NSCLC patients.

Methods: Using the TriNetX Dataworks USA EHR Network, the rate of anemia was assessed among patients with NSCLC between 2018 and 2020 using ICD-10-CM diagnosis codes and laboratory values for hemoglobin (Hgb). Any occurrence of anemia within one year after NSCLC diagnosis was included. NSCLC was defined using ICD-10-CM diagnosis code C34 (Malignant neoplasm of bronchus and lung) and North American Association of Central Cancer Registries ICD-O morphology code 8046 for non-small cell carcinoma [2]. Anemia was assessed based on laboratory results by severity grade using definitions from CTCAE version 5.0, as follows: Grade (G)1, < LLN to 10.0 g/dL; G2, < 10.0 to ≤ 8.0 g/dL; G3, < 8.0 g/dL [3]. The Hgb lower limit of normal (LLN) was set as 13.8 g/dL for males and 11.3 g/dL for females [4]. G3 was also evaluated by assessing patients that received packed red cells or whole blood transfusion procedures.

Results: 15,727 newly diagnosed NSCLC patients were identified between 2018 and 2020. Of those patients, 3,238 (20.6%) experienced anemia in the year following diagnosis based on anemia diagnosis codes and 8,689 (55.2%) experienced anemia based on CTCAE G1-G3 [G1: 7,545 patients (48.0%); G2: 4,804 (30.5%); G3: 2,528 (16.1%)].

Conclusion: Real-World background rates of anemia in NSCLC, including G1, 2, and 3, based on laboratory findings and transfusion data, were calculated using the TriNetX EHR querying platform. This type of real-time interactive querying tool combined with deep clinical data can be effectively utilized by pharmacovigilance teams to quickly assess background rates to compare to observed potential signals seen with drug-event pairs in the clinical trial or post-market reporting.

Table: Rate of anemia in the year after NSCLC diagnosis among 15,727 NSCLC patients (Male: 8,126, Female: 7,601)

	Patients	Background Rate
NSCLC (2018-2020) and Anemia (ICD10)	3,238	20.6%
NSCLC (2018-2020) and Anemia (Lab Results):	8,689	55.2%
Grade 1 (Hgb <LLN – 10.0 g/dL)	7,545	48.0%
Grade 1: Male (Hgb <LLN – 10.0 g/dL)	4,484	55.2%
Grade 1: Female (Hgb <LLN – 10.0 g/dL)	3,061	40.3%
Grade 2 (Hgb <10.0 – 8.0 g/dL)	4,804	30.5%
Grade 3 (Hgb <8.0 g/dL or Transfusion)	2,528	16.1%
Grade 3 (Hgb <8.0 g/dL)	2,496	15.9%
Grade 3 (Transfusion)	540	3.4%

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Localized Edema Occurring During Treatment with Risperidone

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Introduction: Atypical antipsychotics are increasingly prescribed because their relative reduced extrapyramidal adverse effects (AE). Risperidone (RSP) is an atypical antipsychotic that has a strong affinity to serotonin type-2 (5-HT_{2A}), dopamine D₂, α₁- and α₂-adrenergic, and histamine H₁ receptors causing antagonism at these receptors [1]. It has proven to be effective in several psychiatric disorders such as schizophrenia, schizoaffective disorders and childhood and adolescence behavioural disorders [2]. Weight gain and sedation are among the most commonly reported AE with this drug [3]. However localised edema is uncommon with RSP.

Objective: To report a rarely AE with RSP.

Methods: These cases were notified in the Tunisian National Centre of Pharmacovigilance and were evaluated according to the updated French method of imputability [4].

Results: Case reports: Case 1: A 14-year-old teenager started a treatment with RSP (2 mg/day) and lorazepam (2 mg/day) for behavioral disorders since March 2019. Two months later, she developed an edema in the lower limbs which has been gradually progressive since then. Physical examination excluded any other pathology and laboratory tests were normal. RSP treatment was stopped and the edema gradually regressed.

Case 2: A 23-year-old woman, with past medical history of schizophrenia, was initiated on RSP (2 mg/day) and lorazepam (1.25 mg/day) since January 2022. After 45 days' follow-up, she presented a facial edema that led her to voluntarily interrupt her treatment. The swelling resolved completely 5 days after the drug withdrawal.

In both cases, the role of lorazepam in inducing the edema was ruled out since its resumption without incident.

Conclusion: Edema associated with RSP, is a rare but increasingly reported AE. Many theories have been suggested to explain the mechanism by which RSP lead to edema. Also available data suggest that this AE may be dose-dependent and can occur at any time during therapy [5].

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The Risk of Myasthenia Gravis with Tyrosine Kinase Inhibitors: A Disproportionality Analysis from Vigibase and AERS Databases

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Introduction: Myasthenic syndromes are typically characterized by muscle weakness and increased fatigability due to an impaired transmission at the neuromuscular junction (NMJ); most cases are caused by acquired autoimmune conditions such as myasthenia gravis (MG), typically with antibodies against the acetylcholine receptor (AChR).

Different drugs are among the major factors that may complicate pre-existing autoimmune myasthenic conditions by further impairing transmission at the NMJ (1).

Objective: To quantify disproportionate reporting (Disp-Rep) (2-4) for the risk of drug-associated MG for 29 clinically approved tyrosine kinase inhibitors (TKIs) in 2 groups: (1) Anti-angiogenic (AA) TKIs (14 drugs); (2) Non-anti-angiogenic (NAA) TKIs (15 drugs).

Methods: We used the AERS and Vigibase databases, with data up to Dec 2020 and Mar 2021 for analysis respectively. Cases of MG were identified using MedDRA (v23.1) and the preferred-term (PT) 'myasthenia gravis' (MG).

Empirical Bayes Geometric Means (EBGM) with 90%CI were calculated to quantify Disp-Rep.

We considered the lower bound of the 90% CI, EB05 > 2 as the threshold for claiming an observation of Disp-Rep.

We studied 3 groups of drugs: (1) Positive control group (non-TKIs associated with MG: penicillamine, prednisone and ciprofloxacin) and two groups of TKIs: (2) AA TKIs & (3) NAA TKIs.

Drugs were identified by non-proprietary name.

Results: We retrieved 366 MG cases in AERS and 271 in Vigibase. In AERS, Disp-Rep with EBGM [90%CI, EB05-EB95] was confirmed for the positive control group: prednisone 3.10 [2.76–3.38] and in Vigibase for penicillamine 7.69 [2.57–44.53] and prednisone 5.74 [5.10–6.44].

In AERS, no Disp-Rep was confirmed for any of the 15 NAA TKIs: afatinib, bosutinib, ceritinib, cobimetinib, crizotinib, dabrafenib, dasatinib, erlotinib, gefitinib, ibrutinib, imatinib, lapatinib, nilotinib, osimertinib and vemurafenib.

No Dis-Rep was found for any of the 14 AA TKIs: acalabrutinib, axitinib, cabozantinib, dacomitinib, lenvatinib, neratinib, nintedanib, pazopanib, ponatinib, regorafenib, sorafenib, sunitinib, tivozanib and vandetanib. The analysis in Vigibase database yielded similar results.

Conclusion: No Disp-Rep was found for any of the 29 TKIs (15 NAA TKIs and 14 AA TKIs) evaluated and the risk of MG.

Our results however, should be interpreted with caution as disproportionality analyses are hypothesis generating rather than hypothesis testing.

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Osteomalacia Following Rifampicin-Induced Hypovitaminosis D

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Introduction: Tuberculosis disease remains a major public health issue in Tunisia. A therapeutic strategy with four antibiotics has been standardised. These drugs are generally well-tolerated but may have side effects such as cutaneous, hepatic and neurological effects. Rifampin among these four antibiotics is a hepatic enzyme inducer and can be responsible of drug interaction.

Objective: We report a case of osteomalacia following rifampicin-induced hypovitaminosis D.

Methods: This case was analysed according to the French method of imputability [1].

Results: A 54-year-old woman presented on august 2019 with one year history of progressive generalized bone pain, muscle weakness and gait disturbance.

Twenty months previously she had been diagnosed with disseminated tuberculosis and she was prescribed an association of isoniazid₇₅, rifampicin₃₀₀, ethambutol and pyrazinamide (4 pills a day) for 2 months then an association of isoniazid, rifampicin (4 pills a day) for 18 months.

Medical questionnaire revealed that the symptoms began 6 months after the initiation of the anti-tuberculosis drug.

The diagnosis of osteomalacia was suspected.

Investigations revealed hypocalcemia and hypophosphatemia. The level of 25-Hydroxyvitamin D was 6.11 ng/ml [normal range 30–100 ng/ml].

Radiological findings showed diffuse demineralization.

Treatment was initiated with oral 25-Hydroxyvitamin D and anti-tuberculosis drug was ended.

Symptoms disappeared, calcium, phosphate and 25-Hydroxyvitamin D levels returned to normal levels within few days.

Other etiologies of Hypovitaminosis D were ruled out

Conclusion: The responsibility of rifampicin in inducing osteomalacia was evaluated as II(C2S1) because of the compatible delay and

mainly the favorable outcome after the medication withdrawal. In literature, rifampicin was associated in few cases of osteomalacia with decreased serum vitamin D levels. Rifampicin is an enzyme induced especially CYP3A4, thereby increasing the catabolism of active vitamin D and lowering their levels.

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P274

Obinutuzumab and Non-Overt Disseminated Intravascular Coagulation: A Case Study of Signal Detection and Management in Italy

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Introduction: Disseminated intravascular coagulation (DIC) is a rare disorder of coagulation with different etiologies, including treatments with drug [1]. On December 2020, during a scheduled periodic assessment meeting, the Agenzia Italiana del Farmaco (AIFA) evaluated four individual case safety reports (ICSRs) reporting obinutuzumab and non-overt DIC [2] as new possible signal.

Objective: We reported the process of signal detection for obinutuzumab-associated non-overt DIC.

Methods: Periodic assessments of signal detection for drugs are conducted by AIFA in collaboration with the Italian Regional Centers of Pharmacovigilance. Reporting odds ratio (ROR) is calculated for each drug-event pair as measure of disproportionality. A signal is generated when the number of ICSRs is ≥ 3 and the lower limit of the 95% confidence interval of ROR is ≥ 1 . Priority is given to unexpected and important medical events. Possible signals are presented and discussed in the light of information reported in medical literature. Eudravigilance is also checked for similar ICSRs. When a signal is considered enough robust, an assessment report is submitted to the rapporteur country for a possible evaluation by the Pharmacovigilance Risk Assessment Committee (PRAC) at the European Medicine Agency.

Results: During routine signal evaluation meetings in December 2020, 4 cases of obinutuzumab-associated non-overt DIC meet the criteria for signal definition (ROR 213.6 and IC025 77). At that time, the Italian database of ICSRs, contained about 150.000 ICSRs. The patients (2 men and 2 women, age 67-77) received obinutuzumab for chronic lymphocytic leukemia. Patients received drug for the treatment of age-related diseases. A subclinical DIC was detected within 48 hours from obinutuzumab administration. After the exclusion of alternative causes, the hematologists decided to report all the 4 cases as suspected adverse drug reactions to obinutuzumab. The DIC spontaneously resolved in all cases. Three more ICSRs were reported in Eudravigilance database. Medical literature reported only one case-

report on a woman who developed a DIC following obinutuzumab administration was published [3]. Other authors showed that the administration of the drug induced a pro-inflammatory response with the increase of interleukins and tumor necrosis factor [4, 5]. The DIC is a rare adverse reaction also for rituximab, another anti-CD20 and a rare class effect cannot be excluded [3]. The evidence was robust enough to present the signal to the PRAC.

Conclusion: The PRAC identified non-overt DIC as an uncommon adverse reaction to obinutuzumab, and recommended to update the summary of product characteristics (SPC) of obinutuzumab.

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Pharmacovigilance of Cytotoxic Drugs in Childhood Cancer: A Retrospective Study

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Introduction: Pediatric cancer is one of the leading causes of death in children and its incidence is constantly increasing worldwide. cancer therapy, especially chemotherapy, still has significant toxicities compared to other classes of drugs. The detection and evaluation of adverse drug reactions (ADRs) related to drug treatments allows better management of the risks associated with their use.

Objective: The aim of this study is to determine the incidence and frequency of adverse drug reactions (ADRs) induced by cancer chemotherapy in pediatric patients.

Methods: It is a retrospective study at hemato-oncology department of the children's hospital of Rabat which lasted 2 months from October 2021 to December 2021. It took into account adverse drug reactions (ADRs) manifested by children with 8 different types of cancer who all received cisplatin in their chemotherapy protocols. We collect demographic, clinical, cancer treatment and ADR-related data from 62 patient's medical records.

Results: During the period of study, 47 patients including 24 (51%) boys, received chemotherapy spread over 9 cures. 15 patient's medical records were not available.

The median age was 5 years. The majority of patients were in the 2–5 year age group (26%).

The most common types of cancer were Neuroblastoma (51%), Malignant Germ Cell Tumor (13%), Medulloblastoma (11%), Osteosarcoma (9%), Nasopharyngeal Undifferentiated Carcinoma (7%), Hepatoblastoma (5%) and 2% each for Metastatic Rhabdomyosarcoma and Sacrococcygeal Teratoma.

A total of 175 adverse drug reactions were reported, all patients developed at least one adverse event.

The types of adverse drug reactions according to the CTCAE classification by class of organ affected were: blood and lymphatic system (55%), gastrointestinal (12%), infections and fevers (8%), skin (8%), hepatic (7%), kidney and urinary system (4%), and eye disorders (2%), respiratory (2%), nervous system (2%).

The most frequent adverse events were neutropenia (26%), anemia (14%), leukopenia (10%) and fever (8%).

The most frequently administered agents were etoposide (28%) followed by cisplatin (26%) and ifosofamid and doxorubicin with same percentage (9%).

To manage these adverse events 88% of cases medicines were administrated, 5.5% the cures were shifted, 4.7% the cures were stopped and in 1.8% the dosages of cytotoxic drugs were reduced.

Conclusion: Through this study, we determined a high incidence of chemotherapy-induced adverse drug reactions ADRs in pediatric cancer patients.

This study therefore emphasizes on the importance of adverse reaction reporting in hospital, especially in pediatric settings. Awareness-raising among healthcare professionals but also among patients and parents is required.

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Photoallergic Eczema Induced by Fenofibrate

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Introduction: Fenofibrate may cause adverse skin reactions, such as photosensitivity. Sun protection measures are generally sufficient to reduce it, especially if it is a phototoxicity reaction. However, in certain situations, the only way to reduce symptoms, is to stop the causative drug.

Objective: We report a case of photoallergic eczema caused by fenofibrate with regression only upon treatment withdrawal.

Methods: This case was notified to the National Center of Pharmacovigilance and was analyzed according to the Naranjo causality scale method [1].

Results: A 66-year-old woman was put on glicazide for type 2 diabetes, ibesartan-hydrochlorothiazide for arterial hypertension and fenofibrate 160 mg for hypertriglyceridemia. Two months after the start of this last, she presented with edematous erythema of the forehead and the back of the hands, concomitant with prolonged sun exposure. Despite several cutaneous topicals and physical sun protection measures, there was an exacerbation of the edema and appearance of vesicular elements. The diagnosis of photoallergic eczema was made and discontinuation of fenofibrate was recommended. The symptoms regressed then, in 10 days.

Conclusion: Drug photosensitivity, a trivialized and under-reported drug event, can be serious and even life-threatening. This risk is all the more important in sunny areas, such as African continent, where physical sun protection measures, seem ineffective and only stopping the causative drug improves the symptomatology. Hence the importance of making practitioners aware of this adverse event induced by fenofibrate.

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Recurrent Erythema Multiforme with Paracetamol

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Introduction: Erythema multiforme (EM) is an acute eruptive dermatosis induced by various agents, the most common being herpes virus simplex [1]. Certain drugs may be implicated, in particular nonsteroidal anti-inflammatory drugs, sulfonamides and penicillins. Cases of EM attributed to paracetamol are relatively rare [2].

Objective: We report a case of recurrent erythema multiforme minor induced by paracetamol.

Methods: This case was notified in June 2019 and was analyzed according to the Naranjo causality scale method [3].

Results: A 25-year-old woman with a history of atopy, namely dust mite, pollen allergic rhinitis and allergic asthma, regularly takes paracetamol for dysmenorrhea. She consulted us for a predominant rash on the palmar side of the hands, which appeared 2 days after taking paracetamol. These lesions would be recurrent for 6 years, and

coincide with taking paracetamol. The diagnosis of EM caused by paracetamol was suspected. A biopsy was performed and confirmed the diagnosis of EM. Paracetamol was stopped. The evolution was spontaneously favorable after 9 days with regression of symptoms and persistence of residual pigmentation. There has been no recurrence since paracetamol withdrawal.

Conclusion: EM is an acute pathology that can be recurrent and even disabling without the triggering factor being highlighted. It is therefore important to draw attention to the possible EM induced by paracetamol, a drug widely prescribed but rarely incriminated.

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Assessment of Adverse Drug Reactions to Off-Label Drug Use in an Oncological Population Treated in a Northern Italian Hospital

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Introduction: Off-label drugs can be an alternative clinical tool to authorised therapies that have failed. However, their use raises several concerns about efficacy and patients' safety due to the lack of high-level clinical evidence [1]. More information is therefore needed to assess if such treatments are related to an increased risk for patients to develop adverse drug reactions (ADRs).

Objective: To analyse the frequency of ADRs after off-label drugs use in a cancer patients' cohort and to compare it to ADRs reported in the Summary of Product Characteristics (SmPC) of the administered medicines.

Methods: performed a retrospective observational study of the ADRs reported by clinicians in the electronic health records of adult patients undergoing an off-label treatment at the Istituto Oncologico Veneto in Padua, Italy. The study period was from January 1st, 2014 to August 31st, 2021. After having collected ADRs, we evaluated their severity according to the CTCAE [2]. In the end, a comparison between these results and the ADRs reported in the SmPC was carried out.

Results: 310 Patients (183 M) were considered, with 37 different off-label treatments. The median age was 60 years and ECOG/status 0-1 were mostly registered. In 165 patients were reported 423 ADRs, of which 43 (10.2%) were classified G3 and only 3 (0.7%) were classified G4. Moreover, 98 (23%) of them were classified as Important Medical Events, mainly thrombocytopenia (n = 28), neutropenia (n = 23) and hyperbilirubinemia (n = 14). The comparison between the obtained ADRs and those reported in the SmPC proved that only 17 (4.0%) of them were absent and 387 (91.5%) were classified as very common or common ADRs. Considering the most used drug regorafenib (a Tyrosine Kinase Inhibitor or TKI), a comparative analysis between the type and frequency of ADRs found in this study and similar ADRs reported in the SmPC was also performed. A minor percentage of ADRs in the patients of this observational study was reported.

Conclusion: As in previous studies [3], results demonstrate a similar risk of ADRs between off-label treatments and authorised ones.

Almost all of the few ADRs detected had been already reported with the on-label use. Hence, we conclude that the use of off-label drugs does not increase treatment toxicity in cancer patients.

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Interferon-β Induced Psoriasis in a Multiple Sclerosis Patient with Positive Rechallenge

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Introduction: Psoriasis is an erythematous dermatosis with unclear etiology. Several drugs such as lithium, beta-blockers, adrenergic antagonists, and interferons can aggravate pre-existing psoriasis or cause de novo psoriasis. Few cases of psoriasis were described with interferon-β.

Objective: Herein we report a case of interferon-β induced nummular psoriasis occurring in a multiple sclerosis patient with positive rechallenge.

Methods: This case was reported in August 2020 and evaluated according to the French imputation method of causality assessment.

Results: A 39-year-female patient with no medical history of psoriasis has started interferon beta 1b for her multiple sclerosis. After one month, she presented general erythroderma and secondary diffuse erythematous-squamous coin-sized lesions evocative of nummular psoriasis. The evolution was favorable 20 days after drug withdrawal and with symptomatic treatment. This same symptomatology recurred one month after the rechallenge. We suspected that interferon was the causative agent in the induction of psoriasis.

Conclusion: The imputation score was likely (I3) due to the evocative delay (30 days) of psoriasis occurrence, the favorable outcome after drug withdrawal, and the positive rechallenge. Activation of psoriasis is an uncommon side effect of drugs and could mimic other cutaneous diseases in its rare features that need careful evaluation of an added morbidity.

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Oxybutynin Induced Blindness in a Child

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Introduction: Oxybutynin is an anticholinergic and a spasmolytic drug used as a therapeutic option in patients with overactive detrusor function—either idiopathic detrusor instability or detrusor hyper-reflexia. The most common ocular side effects of oxybutynin include reduced lacrimation and cycloplegia. Blindness has exceptionally been reported with this drug (1).

Objective: Herein, we report an exceptional case of sudden onset of bilateral blindness in a child following oxybutynin prescription.

Methods: This case was notified in April 2022 to the National Centre of Pharmacovigilance and evaluated according to the updated French method of causality assessment.

Results: A 5-year-old female child with a past medical history of Asthma since the age of 8 months treated with cortis and aerol and of a recurrent urinary tract infection since the age of 4 years, started oxybutynin for an overactive detrusor function. One month later, she complained of blurry vision. The evolution was marked by the rapidly progressive aggravation of the symptomatology leading the parents to consult. An examination revealed decrease in visual acuity limited to seeing the hand move with anormal fundus and a normal ocular tone. The brain CT scan and the magnetic resonance revealed no abnormalities and the EPI showed an axonal left optic neuropathy. Serology test for EBV, HIV, CMV, HBV, HCV, mump virus, adenovirus and measles virus were also negative. The evolution was marked by the persistence of the ocular symptoms one month after drug withdrawal. We suspected that oxybutynin was the causative agent in induction of blindness with an imputation score of 12 mainly because of the negative investigations and the compatible delay of occurrence after the drug intake.

Conclusion: The mechanism involved would be an inhibition of the M3 receptor which is located on the ciliary body, the iris sphincter muscles and the lacrimal gland. When this receptor is blocked, a cascade of blurred vision occurs due to mild mydriasis, cycloplegia and/or dryness of the ocular surface. This effect tends to occur for high initial doses of oxybutynin (≥ 10 mg) (1).

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GRESIF: A Project for the Management of Severe Adverse Drug Reactions (SCARs). The Experience of Lombardy and Piedmont

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Introduction: In Lombardy and Piedmont (Northern Italy, about 14 million people) the GRESIF pharmacovigilance network project, aimed to collect, assess, treat and prevent severe systemic drug reactions was activated in 2021, supported by the Italian Medicines Agency (AIFA). GRESIF involves regional and hospital pharmacovigilance centers, and several hospital wards: burn, dermatology, allergology, internal medicine, infectiology and intensive care departments. The registry collects in the National Pharmacovigilance Network all reports of suspected adverse drug reactions (ADRs) concerning Toxic Epidermal Necrolysis (TEN), Stevens-Johnson Syndrome (SJS), Drug reaction with eosinophilia and systemic symptoms (DRESS) and Acute Generalized Exanthematous Pustulosis (AGEP).

Objective: The specific objectives of the study are to early detect severe systemic ADRs, evaluate their incidence, morbidity and mortality rates, focus on new generation drugs such as RNA antivirals and oncological drugs, implement and optimize guidelines, manage long-term sequelae by follow-up and create a consultable web-based database.

Methods: We have drawn up the guidelines [1,2], through a multi-disciplinary approach in order to improve the management of very complex patients even in facilities that are not habitually involved in the treatment of these pathologies. This document aims to support professionals in standardizing diagnostic criteria and methods of therapeutic approach. It's useful to inform the general practitioner about responsible drugs and give some information about risk/benefit on the re-exposure.

Results: In 2021, 27 cases of SJS/TEN, 18 cases of DRESS and no cases of AGEP were collected. There is a female prevalence (25 cases out 44); the age range is from 20 to 93 years. The median age of patients in Lombardy and in Piedmont is respectively 55 and 66 for females, 47 and 63 for males. The total mortality for cases of SJS/TEN is about 19% and for DRESS we have no deaths. More frequent suspected drugs are antibiotics, followed by allopurinol and anti-convulsants. Noteworthy is the presence of 4 cases of severe ADR related to anti Covid19 RNA vaccines. In all cases, according to the guidelines, the timely discontinuation of the responsible drug was fundamental as the general management. Furthermore we started a study for the HLA typing of these patients. We enrolled 18 cases and the results showed that 6 patients who received allopurinol were all positive to HLA B 58:01.

Conclusion: Despite being extremely rare but serious reactions, the absolute need to implement shared diagnostic and therapeutic protocols to be applied promptly is highlighted, in order to reduce both patient mortality and long-term sequelae.

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Adverse Events of Imatinib

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Introduction: Imatinib is a tyrosine kinase inhibitor used in cancer treatment mainly indicated in chronic myeloid leukemia (CML) and gastrointestinal stromal tumors [1]. Despite its effectiveness, it exposes to frequent adverse events (AE).

Objective: Study clinical and epidemiological characteristics of imatinib AEs notified to the Tunisian National Centre of Pharmacovigilance.

Methods: Retrospective study of AEs attributed to imatinib, notified to the National Centre of Pharmacovigilance between January 2010 and December 2018. Imputability was studied using the method of Bégaud et al. [2]. Plasma concentration was determined by high performance liquid phase chromatography.

Results: This study included 32 patients. The age ranged from 13 to 88 years old (median = 59 years). The F/M sex ratio was 1.28. Imatinib was indicated for the treatment of CML in 17 patients, GIST in 14 patients and desmoid tumor in one patient.

Daily dose was 400 mg/day in 71.9% of cases. Plasma concentration was measured in seven patients. It was infratherapeutic in 3 cases (including one case of neutropenia) and superior to 1000 ng/ml in 4 cases.

The most common AEs were: skin damage (47.4%), edema (21%), gastrointestinal damage (15.8%) of which 30% were nausea and vomiting, haematological damage (15.8%) such as neutropenia (50%) and thrombocytopenia (33.3%).

The onset delay varied from few days to 3 years. Outcome was favorable in 77.5% of cases. The responsibility of imatinib was assessed as I1 (40.6%) and I2 (37.5%).

Conclusion: This work highlights the characteristics of imatinib AEs. Cutaneous damage are the most common AE.

Adverse events are usually of toxic mechanism and can be controlled either by a reduction of the dose or by a temporary interruption of the treatment [3].

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Carbamazepine-Acetazolamide Interaction Leading to an Hepatocellular Liver Injury: A Relevant Case Report

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Introduction: Carbamazepine is the drug of choice for the treatment of focal epilepsy. Despite its widely proven efficacy, its use can be complicated with severe and life-threatening adverse drug reactions up to 10% (1). Besides, carbamazepine is also subject to interactions changing its serum concentration and exposing the patient to the risk of toxicity or inefficacy

Objective: To describe a case of concomitant use of carbamazepine and acetazolamide, with a highly relevant interaction that requires attention.

Methods: This is a 27-year-old male with a past history of facial traumatism, complicated with osteomeaningal breach for which he was treated with acetazolamide. He was hospitalized for a five-day history of vomiting, rhinorrhea, and neck pain. On admission, physical findings were limited to positive Kernig or Brudzinski signs. The patient's Laboratory data indicated a biological inflammatory syndrome. A lumbar puncture revealed a colourless cerebrospinal fluid with a normal cell. With a diagnosis of aseptic cerebral meningitis, and taking into consideration the high risk of contracting Streptococcus pneumonia with his prior head injury, cefotaxime (2g × 6/day) was initiated as a prophylactic treatment. Unfortunately, the patient developed a focal seizure. Laboratory investigation ruled out any metabolic disorder and neuroimaging were normal. Carbamazepine, then, was started at 200 mg twice a day in addition to ongoing cefotaxime and acetazolamide. Routine check-up analysis objected, 5 days later, severe hepatic cytolysis (ASAT = 11 ULN and ALAT = 22ULN), was associated with a normal prothrombin index. Systemic research of classical causes of acute hepatitis was performed: The patient denied any use of alcohol and Viral serologies for hepatitis A, B, C, E, CMV, and EBV were negative, serology for Epstein-Barr virus revealed signs of past infection, autoimmune serological antibodies and liver biopsy were not performed. An abdominal ultrasound examination showed an intact liver and a normal-sized spleen. Carbamazepine was immediately discontinued. ASAT and ALAT levels decrease 3 days after the discontinuation of carbamazepine achieving 3ULN and 7ULN, respectively and total recovery of perturbed hepatic enzymes was obtained 20 days later.

Results: With a score of 6, this interaction is 'probably' the cause of this liver injury (2). Acetazolamide, a carbonic anhydrase inhibitor may increase the serum concentration and the risk of toxicity of carbamazepine. Hepatotoxicity related to carbamazepine, ranging from a benign increase of liver enzymes to rare cases of hepatic failure has been reported and is usually reversible with stopping treatment.

Conclusion: We hypothesize that concomitant use of acetazolamide increases carbamazepine serum level.

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Chronic Effects of Non-steroidal Anti-inflammatory Drugs (NSAIDs) and Hormones on the Animal Model Danio Rerio

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Introduction: The dispersion of chemicals in water ecosystems nowadays is a serious threat to wildlife animals, plants and can cause damage also to humans. Studies confirmed the presence of pharmaceuticals, namely NSAIDs and hormones, per- and polyfluoroalkyl substances (PFAS), and pesticides in small amounts in a wide variety of ecosystems, including rivers, lakes, and seas. As regards the pharmaceuticals class, NSAIDs and hormones have been detected in concentrations ranging from ng/L to µg/L [1]. Exposure to these compounds could damage the central nervous system, altering behavior and cognitive capacities. Among NSAIDs, ibuprofen and diclofenac were proven to be the most harmful for freshwater fish, also acting in a concerted fashion [2]. As for the hormones, 17-α-ethinylestradiol and 17-β-estradiol are the ones most present in the environment and contributed > 97% to the total potential estrogenicity of the waters of Venice lagoon [3]. Many studies investigated the occurrence of human pharmaceuticals in the environment [4], although very limited knowledge is available on the effects of those drugs on non-target organisms (polychaetes, crustaceans, mollusks, fish, and others) in the aquatic environment [5].

Objective: Evaluate the neurodegenerative effects that the chronic exposure of adult zebrafish to diclofenac, ibuprofen, 17-α-ethinylestradiol, and 17-β-estradiol at levels encountered in the environment.

Methods: Animals are exposed for four weeks to 4 ascending concentrations of each pharmaceutical. Behavioral trials are carried out before and after the treatment. Novel tank test is performed to evaluate anxiety-like, stress and locomotion parameters, T-maze for assessing damages in spatial memory and olfactory preference test for the recognition of the insurgence of anosmia—i.e. the impairment of the sense of smell. Immediately after these trials, fishes are euthanized and included in paraffin. Immunohistochemistry studies are focused on the detection of tyrosine hydroxylase (TH) and choline acetyltransferase (ChAT), markers of dopaminergic and cholinergic neurons. TH+ and ChAT+ neurons are expected to be reduced by the treatment.

Results: Ongoing studies prove that chronic exposure to diclofenac, ibuprofen, 17-α-ethinylestradiol, and 17-β-estradiol alter cognitive and motor performance in line with neuroanatomical rearrangement.

Conclusion: Our study provides a useful model for understanding the effects of pharmaceuticals in concentrations found in environmental waters [6], on behavioral and neuroanatomical substrates in the central and peripheral nervous systems.

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The Value of International Pharmacovigilance Databases to Help Contain Antibiotic Resistance from a ‘One Health’ Perspective

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Introduction: An inter-disciplinary ‘one health’ effort is required to contain antibiotic resistance. Surveillance is a key tool in containing ABR [1], and there has been considerable progress, but gaps remain [2]. International pharmacovigilance databases may be a useful tool in antibiotic resistance surveillance, particularly where laboratory capacity is limited [3].

Objective: This project aims to explore the current use and possible areas of improvement of pharmacovigilance systems as a source of surveillance of antibiotic resistance from a ‘one-health’ perspective.

Methods: The project comprises of three sub-studies, all of which will focus on the ‘one health’ aspect of ABR through describing human, animal, and environmental health. The first sub-study will describe international pharmacovigilance databases and how antibiotic resistance is reported within in these databases. Thus far, the planned databases for inclusion are VigiBase, the WHO global database of reported potential side effects of medicinal products, and Veterinary EudraVigilance, which is maintained by the European Medicines Agency. While no suitable international eco-pharmacovigilance database has been identified so far, efforts will be made to highlight the relevant reports within the other databases. The primary outcome will be the case characteristics of reports identified using “ATC:J01-Antibacterials for systemic use” and an adapted MedDRA SMQ “Lack of efficacy/effect” and the VeDDRA equivalent. The second sub-study will use similar methodology and databases but compare this reporting to that of specialised antibiotic resistance databases, with a focus on geographic distribution. The third sub-

study will be a mixed-methods follow-up cross-sectional survey that follows focus group discussions of pharmacovigilance experts to establish attitudes to the reporting of ABR in pharmacovigilance and to explore the possibilities to improve reporting.

Results: As of 03/05/22 there are 22,853 reports in VigiBase for “ATC:J01—Antibacterials for systemic use”, in combination with the SMQ “Lack of efficacy/effect”. The number of reports and other baseline characteristics are not yet available for the other databases.

Conclusion: This project has the potential to increase the knowledge of how international pharmacovigilance systems can be beneficial to ABR surveillance. There is potential for the project to highlight areas of benefit from expanding or improving current pharmacovigilance practices in general, but it can also highlight the valuable information within pre-existing databases and how utilisation of the current systems can benefit those working within containment of global AMR.

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Medications Use While Breastfeeding—Prevalence and Attitude of Women

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Introduction: Human milk is considered the ideal nutrition for infants. Despite the increased attention for breastfeeding, information about drug use by breastfeeding women is scarce [1–2].

Objective: to evaluate the prevalence of medications use while breastfeeding and the associated factors.

Methods: Women who gave birth at the study hospital and stayed with their newborns were asked to participate in a structured interview. The questions included social status, health problems, breastfeeding status, prescribed medications, personal attitude to medications use during breastfeeding and related informational sources.

Results: By the time of the analysis 50 questionnaires were evaluated. Forty eight women had babies younger than 1 month. Mean age was 32±5 years (17 to 44). 37 (74%) had higher education. Three women were not breastfeeding due to the medications: cyclosporine, antithymocyte globulin; amitriptyline, chlorprothixene, sulpiride; ciprofloxacin. Among those breastfeeding the prevalence of medications use was 76%; 15 women (30%) received 1 medication; 23 (46%)—2 to 7 medications. These were: oxytocin (11 (22%)); heparins (9 (18%)); ferrous preparations (8 (16%)); vaginal anti-infectives (8 (16%)); methyl dopa (7 (14%)); antibiotics (6 (12%)); warfarin, ketoprofen, nifedipine, perindopril, torasemide, spironolactone, herbal urinary antiseptic, sotalol and metoprolol were used by 1 woman each.

Thirty-six (72%) women considered breastfeeding necessary for the baby; seven (14%) believed it can easily be stopped. All women agreed that there are safe medications during breastfeeding while three of them believed the medications shouldn't be used; 31 women (62%) stated that even doctors don't know if it is safe to take medications while breastfeeding. The respondents told they would receive information from doctors (23–46%); Internet (11–22%); other women (10–20%); pharmacist (2–4%); family members (2–4%); professional associations (2–4%); 43 (86%) women reported that they can't get information about medications safety in breastfeeding.

Conclusion: During the early postpartum period, almost all women in our cohort were breastfeeding. No unnecessary interruption due to the medications was noted. 14% of the women were negative towards breastfeeding in general, but not due to possible need for medications. Despite general readiness to use medications while breastfeeding, most women noted lack of information about their safety, and less than half of them showed trust in doctor's advice. Although our cohort may not represent the general population, the results highlight high prevalence of medications use during breastfeeding and the clear lack of safety information.

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Comparative Safety of Metformin and Insulin in Gestational Diabetes—a Retrospective, Case-Control Study

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Introduction: The incidence of gestational diabetes mellitus (GDM) is increasing worldwide [1]. Untreated or insufficiently treated GDM is associated with adverse maternal and neonatal outcomes and a predisposition to obesity and type 2 diabetes in the offspring in later life [2, 3]. If appropriate glycemic control is not achieved by diet and lifestyle changes, pharmacological therapy should be started. Although Insulin is considered first-line therapy, the current evidence shows that metformin could be a promising and safe option for managing GDM [4].

Objective: To compare and assess the maternal and neonatal outcomes in women with GDM treated with metformin or insulin.

Methods: A retrospective, case-control study was carried out using the electronic database of OB/GYN Hospital “Dr. Shterev”, Sofia, Bulgaria. We analyzed the medical records of 110 women diagnosed with GDM, who gave birth in the period between January 2017–January 2019. Patients were divided into two groups, depending on the treatment plan—metformin group ($n = 70$) and insulin group ($n = 40$). We compared maternal characteristics, including fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c), measured at diagnosis of GDM, and at the end of pregnancy. A comparative analysis of the maternal and neonatal outcomes between the two groups was also performed.

Results: The mean FPG levels at diagnosis of GDM were significantly lower in the metformin-treated group compared to women receiving insulin therapy (5.72 vs. 6.69 mmol/L, $p < 0.001$). The same results were found when the baseline HbA1c levels were compared (5.61% vs. 6.29%, $p < 0.001$). There was no difference between the metformin-treated group and the insulin-treated group regarding the mode of conception, mode of delivery, gestational weeks at delivery, and incidence of neonatal hypoglycemia. The neonates of the mothers treated with metformin were with significantly lower mean birthweight comparing those in the insulin group (3154 vs. 3421 g, $p = 0.03$). The incidence of macrosomia was higher in the insulin group than in the metformin group ($p < 0.01$). There were no differences between the groups regarding Apgar scores and small-for-gestational-age neonates.

Conclusion: The results of this retrospective study suggest that metformin could be a safe and effective alternative to insulin in the treatment of GDM. No short-term complications have been observed in neonates born from women treated with metformin.

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Breastfeeding Women’s Knowledge Toward Spontaneous Reporting of Adverse Drug Reactions—a Pilot Study from Bulgaria

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Introduction: It is well-known fact that breastfeeding is beneficial for both the mother and infant. [1] Many breastfeeding women require

medications. Almost all medications are excreted into breast milk to some extent and this may pose a risk to a breastfed infant. [2, 3] In addition, this may raise questions about the safety of commonly used medications during breastfeeding.

Objective: To assess Bulgarian breastfeeding women’s knowledge and experience regarding spontaneous reporting of adverse drug reactions (ADRs).

Methods: A cross-sectional, questionnaire-based study was performed between June 2021 and September 2021. A pre-validated, anonymous questionnaire was distributed among breastfeeding women using a web-based platform. Data on demographics of participants, knowledge, and factors that may influence spontaneous reporting of ADRs were collected. Descriptive statistics and a chi-square test were used to analyze the data.

Results: A total of 96 breastfeeding women completed the survey. The overall mean age was 29.3 years ranging from 24 to 43. The majority of breastfeeding women reported a lack of knowledge regarding the ADRs reporting process. Only 25% of survey participants were aware of the possibility of reporting ADRs directly to the Bulgarian Drug Agency and this was significantly associated with education level ($P < 0.001$). ADRs reporting rate during breastfeeding was poor (12.5%). For the majority of women, the primary source of information about drug safety during breastfeeding were the health care professionals (92.7%) followed by a package leaflet (53.1%) and social media, e.g., discussion forums (47.9%). The majority of surveyed women (84.4%) reported the need for additional information on drug safety during breastfeeding.

Conclusion: The results from this suggest that Bulgarian breastfeeding women have insufficient knowledge regarding spontaneous ADRs reporting. Educational campaigns and additional information are needed to increase breastfeeding women’s awareness of drug safety, self-medication and the ADRs reporting process.

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Drug-Induced Liver Injury (DILI) and Ulipristal: A Cautionary Tale

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Introduction: In September of 2017, the French Medicines Agency (ANSM) received a case of fulminant hepatitis leading to hepatic transplantation in a patient treated with Ulipristal for uterine fibroids. Cumulatively, 3 cases of liver transplant associated with Ulipristal

were detected in EudraVigilance, which led to in-depth investigation by the European Medicines Agency (EMA), resulting in the restriction of indication and several other risk minimisation measures (RMM)(1). Ulipristal is an orally-active selective progesterone receptor modulator for treating symptoms of uterine fibroids. It is extensively metabolized by the liver and no signal of hepatotoxicity was identified before marketing authorization (MA).

Objective: We aim to explore if searching for DILI related MedDRA terms (Table 1) would've allowed for anticipatory detection of DILI cases and describe EudraVigilance spontaneous reports with DILI related adverse reaction terms before and after the safety issue was raised.

Table 1 - DILI related PT

Acute hepatic failure;	Alanine aminotransferase increased;	Autoimmune hepatitis;	Blood alkaline phosphatase increased;
Blood bilirubin increased;	Cholestatic liver injury;	Drug-induced liver injury (DILI);	Gamma-glutamyltransferase increased;
Hepatic cytolysis;	Hepatic enzyme abnormal;	Hepatic enzyme increased;	Hepatic failure;
Hepatitis;	Hepatitis cholestatic;	Hepatitis fulminant;	Hepatocellular injury;
Hepatotoxicity;	Hyperbilirubinemia;	Hypertransaminasemia;	Jaundice;
Liver failure;	Liver function test;	Liver function test abnormal;	Liver function test increased;
Liver injury;	Liver transplant;	Transaminases increased;	

Methods: We conducted a retrospective search of EudraVigilance using 27 preferred terms (PT) associated with DILI in two time frames: from MA of ulipristal in February 2012 up to September 2017, when the safety issue was raised, and from that point up until 31/12/2021. In the analysis of the first time frame, for those which fulfilled biochemical criteria for DILI, we used the RUCAM score (2) for causality assessment.

Results: We found 24 individual case safety reports (ICSR) with DILI related PT, with 7 of them including either the PT “drug-induced liver injury” or “hepatotoxicity”. Of these 24 ICSR, 4 did not have enough data to assess criteria fulfillment, 7 did not fulfill biochemical criteria. From the remaining 13 ICSR, 3 corresponded to the transplants. Of these 10 remaining ICSR, 2 had a RUCAM score of, at least, “Possible” and other 2 were auto-immune hepatitis but had no information regarding corticosteroid therapy or tapering. In the second time frame, after the safety issue was raised, we found 449 ICSR which included PT associated with DILI and 13 including either the PT “drug-induced liver injury” or “hepatotoxicity”.

Conclusion: Medicines such as ulipristal, metabolized by the liver, require careful monitoring for DILI. The use of DILI related terms can be used as sentinel in the attempt of anticipating possible liver injury. In this research we found that there are not many therapeutic options for patients with uterine fibroids who cannot undergo surgery or embolization. Regardless of RMM, this work highlights the need for safer treatment alternatives for patients with uterine fibroids.

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Pharmacovigilance of Selective Serotonin Reuptake Inhibitors and Gender Differences in Stroke Incidence

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Introduction: Selective Serotonin Reuptake Inhibitors (SSRI), commonly used for treating depression, have better tolerability and fewer adverse drug-related reactions (ADRs) compared to other antidepressants [1]; however, some severe ADRs can occur, such as QT interval prolongation [2]. It has been also suggested that people treated with SSRI are at an increased risk of ischemic stroke and having a stroke with unfavorable outcomes [3].

Objective: To investigate sex differences in the incidence of stroke and SSRI use.

Methods: A retrospective case-non-case observational study of ADRs reported to the World Health Organization Vigibase database from March 1988 to March 2022. Cases were defined as all “Central nervous system hemorrhages and cerebrovascular conditions” using the Standardized MedDRA Query (SMQ), while all other severe ADRs were included as non-cases. Cases were then divided into ischemic or hemorrhagic cerebrovascular conditions. Studied drugs were: citalopram, escitalopram, sertraline, paroxetine, fluoxetine, fluvoxamine. Age-adjusted reporting odds ratios and 95% confidence intervals (aROR, 95% CI) were calculated for each condition and sex, and ratios of aROR (RROR) were used for investigating gender differences in stroke incidence related to SSRI use. I^2 and Cochran Q were used to investigate the heterogeneity between drugs aROR and RROR.

Results: Overall, escitalopram and citalopram were associated with higher stroke aROR (1.87, 1.70–2.04 and 1.48, 1.35–1.63; respectively) compared to sertraline, paroxetine, fluoxetine, and fluvoxamine (1.10, 1.01–1.19; 1.11, 1.02–1.21; 0.96, 0.88–1.05; and 0.36, 0.25–0.52; respectively) ($I^2 = 99\%$; $P < 0.0001$). Overall, escitalopram and citalopram were associated with greater aROR for hemorrhagic strokes (1.99, 1.79–2.21 and 1.42, 1.27–1.60; respectively) compared to other antidepressants (sertraline, 1.16, 1.05–1.27; paroxetine, 1.14, 1.03–1.26; fluoxetine, 0.98, 0.88–1.08; and fluvoxamine, 0.31, 0.20–0.50; respectively) ($I^2 = 98.7\%$; $P < 0.0001$). Females using escitalopram and citalopram had increased RROR for ischemic stroke (1.48, 1.08–2.03 and 1.42, 1.05–1.90; respectively) compared to males; the other drugs did not present a different reporting risk between sex (sertraline, RROR = 0.83, 0.67–1.04; paroxetine, 0.77, 0.60–0.99; fluoxetine, 1.04, 0.81–1.32; and fluvoxamine, 1.50, 0.53–4.27; respectively) ($I^2 = 90.1\%$; $P = 0.002$).

Conclusion: This study has identified gender differences in reporting central nervous system hemorrhages and cerebrovascular conditions during SSRI treatment, as females treated with escitalopram and citalopram had an increased risk of ischemic stroke compared to males.

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Safety of Painkillers during Pregnancy a Retrospective Analysis of Reports from the Italian Veneto Region and VigiBase

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Introduction: Most women take at least one drug throughout pregnancy [1,2,3,4] with analgesics playing a special role, both because pain is a common complaint during pregnancy and because of their prescription status (Rx and OTC). Data on the safety of drugs in pregnancy are limited and the majority of data derive from spontaneous reporting.

Objective: To review the safety of analgesics in pregnancy using real world pharmacovigilance data from the Italian Veneto region and from VigiBase, the WHO global database of suspected adverse reactions of medicinal products between January 1st, 2014 and July 31st, 2020.

Methods: Individual case safety reports (ICSRs) were retrieved from the Italian Pharmacovigilance Database (RNF), according to the presence of pregnancy flag, or to the reporting of adverse reactions associated to pregnancy (by MedDRA SMQs). In VigiBase reports were identified only according to the reported reactions and the patients' characteristics. In both databases analgesic drugs were identified through ATC codes.

Results: During the study period, the RNF included 39,017 ICSRs from Veneto region, 42 (0.11%) of which concerning pregnant women and only 5 (0.01%) associated to analgesics' use. None of these reports were classified as serious. The most reported event was urticaria/pruritus (n = 3).

VigiBase, included 13,979,729 ICSRs, 61,005 (0.44%) of which related to pregnant women and 4,123 (0.03%) associated to analgesics' use. The majority of these (n = 3,040; 73.7%) were serious. The most reported reactions were abortion spontaneous (n = 450), premature delivery (n = 381), premature labour (n = 155).

The most reported drugs were paracetamol (n = 3) in Veneto and non-steroidal anti-inflammatory drugs (NSAIDs) (acetylsalicylic acid n = 700, ibuprofen n = 119), opioids (buprenorphine n = 727, fentanyl n = 260 and morphine n = 136), paracetamol (n = 430) and adjuvants in pain therapy (pregabalin n = 95) in VigiBase.

Conclusion: Pregnancy-related reporting is low, particularly in Veneto region and it reflects national differences in analgesics' use.

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Pharmacovigilance of Medicines for Controlled Ovarian Hyperstimulation—a Study of Patients' Perspective

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Introduction: Infertility can be nominated as the modern “beast of burden” of the 21st century. Between 50 and 70 million couples¹ worldwide suffer from inability to conceive, with a steady trend in increasing the number of newly diagnosed cases of sterility. Yet patient engagement in pharmacovigilance surveillance systems still needs to be fully explored.²

Objective: The current study aims to evaluate the type, incidence and severity of suspected adverse drug reactions (ADRs) during controlled ovarian hyperstimulation (COH). Patients' awareness of the System for spontaneous reporting of ADRs has been tested.

Methods: This is a cross-sectional study, based on results generated through a direct interview with 659 patients for a study period of 14 months. Statistical analysis of data, generated by the completion of a validated questionnaire has been performed. The following statistical analyses have been applied: Pearson's chi-square analysis (when investigating relationships between descriptive data with two or more categories), Student's T-test (for comparison of two groups of observations), Mann-Whitney test (to compare quantitative variables between two groups) and Kruskal-Wallis test (for quantitative analysis of variables among three different groups).

Results: Almost 40 % of participants reported a suspected ADR as a consequence of stimulation hormone application. The mean number of reported ADRs per patient is 1.27. As far as patients who reported an ADR are concerned, 213 respondents (82.2%) have indicated a direct causal relationship between the application of a particular stimulation preparation and a specific adverse effect. In 90% of cases of an experienced ADR, participants would evaluate the adverse effect as mild. Suspected ADRs have led to therapy termination in 3.8 % of investigated cases in the study. More than 2/3 of experienced ADRs are associated with local injection site reaction (63.1%), followed by reports of headache (9.8%), gastro-intestinal discomfort (5.8%) and nausea (4.7%). Women who underwent therapy for assisted reproduction are not well aware of the functional principles of the System for spontaneous ADR reporting and are not motivated enough to directly report a suspected ADR.

Conclusion: From a patient perspective treatment for COH is associated with a low incidence of mild ADRs that are not significant

enough for cycle cancellation. Levels of direct reporting of ADRs remain extremely low. Women, who underwent treatment for assisted reproduction are not well aware of the principles of drug safety surveillance systems.

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DNA Barcoding as a Tool to Overcome the Challenges of Phytovigilance of Natural Health Products Quality: The Example of Saffron

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Introduction: The quality of herbal medicines (HM) is one of the main challenges to the pharmacovigilance of HM [1]. The best example is the substitution of the target or marked species by another species and the addition of species along with the target or marked species [2]. These substitutions and additions are driven by the growing demand for herbs and the limited supply of many wild-harvested species [3]. When the demand for a specific herb exceeds the supply, there is an increased likelihood that adulterants or poor quality material will be used [4]. Recent developments in the molecular identification of plants using DNA sequence data allow accurate identification of plant species from medicinal plants using defined DNA markers [5]. Identification of multiple constituent species of compounded medicinal plant products using an amplicon metabarcode allows verification of labeled ingredients and detection of substituted, adulterated, and added species [6].

Objective: To investigate and detect the substitution on the market of several samples of *Crocus sativus* L. available on the Moroccan market.

Methods: A molecular and bioinformatics study was carried out to differentiate 7 saffron (*Crocus sativus* L.) samples collected in 7 different cities in Morocco and to assess their authenticity using DNA barcoding. Three candidate markers were amplified using genomic DNA and gene sequencing of these markers.

Results: The polymerase chain reaction (PCR) amplification of samples using the three primers gave promising results. They were able to distinguish different accessions from analyzed samples. In all the phylogenetic trees, four samples were clearly grouped in a clade with high bootstrap values while the samples from three cities were classified in another distinct clade and these have been identified as containing non-authentic *Crocus sativus* L. and all of them were positive for *Carthamus*.

Conclusion: Non-authentic products may cause potential risks to consumers, induce adverse reactions, and further reduce the apparent effectiveness of saffron as an herbal remedy or spice. The molecular DNA barcoding approach could be a faster and more cost-effective method to authenticate saffron and detect its adulterants and can be

used in the pharmacovigilance of HM to ensure the safe use of medicinal plants in general, and saffron in particular. The combination of DNA barcoding with chromatographic fingerprinting, a popular and generally accepted technique for the evaluation and quality control of medicinal plants, will provide an effective solution to assess the authenticity and consistency of the quality of medicinal plants.

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"Title Case" = A Case of Death Following the Application of "Nicotiana Glauca"

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Introduction: Nicotinic and nicotinic-like alkaloids are present in a wide range of plant species, some of which have been reported to be toxic in humans. Of these plants, the most widely recognized is *Nicotiana Glauca*

Objective: We report a case of rare human poisoning collected in the pediatric intensive care unit of a 5-year-old child victim of a 2nd degree burn who, following the application of leaves of the tobacco plant "Nicotiana Glauca" on the burn had presented vomiting with Disorder of consciousness

Methods: a 5-year-old child, without remarkable medical history, victim of a severe burn by splashing hot water, with total body surface area (TBSA) at 20%. The interrogation with the family revealed the notion of application on the day of its burn of the leaves of a plant "N glauca" at the level of the front face of the thorax and the thigh. The patient developed vomit and disorder of consciousness a few minutes after applying N. glauca leaves collected around the house. On arrival at the hospital, the patient was in cardiopulmonary arrest with bilateral mydriasis. She received cardiopulmonary resuscitation, with boluses of adrenaline.

Results: The parts of the plant brought back make it possible to identify it. It is a Solanacea family. Anabasine is the main alkaloid; its lethality is 10 times greater than that of nicotine. It is a nicotinic receptor agonist that exerts its effect primarily by binding to nicotinic acetylcholine receptors. The onset of symptoms is usually rapid, within 5 min to 3 hours of ingestion or topical application. Out of 15 reported cases, seven resulted in death.[1] This is the case for our patient who died a few days after her admission

Conclusion: ingestion or application of *N. glauca* leaves has a toxic potential. The toxicity is mediated by the nicotine-like alkaloid “anabasine”.

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Surveillance of Suspected Adverse Reactions to Beehive Products

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Introduction: Royal jelly, propolis, and honey are beehive products rich in bioactive compounds (e.g., flavonoids and caffeic acid phenethyl ester) with potential antimicrobial, anti-inflammatory, and antioxidant activities [1,2]. Thus, they are widely used as food supplements to prevent various ailments in both adults and children [1,3,4]. Beehive products are characterized by a highly variable composition, depending on honeybee and botanical sources [1,2], which could be implicated into quality and safety characteristics. Moreover, also allergenic components can be present (e.g., bee venom and 1,1-dimethylallyl caffeic acid ester) and implicated in the adverse reactions (ARs) observed during years, particularly in atopic subjects [5,6].

Objective: To evaluate the suspected ARs associated with the consumption of products containing, among others, beehive ingredients to monitor their safety profile.

Methods: We analysed all spontaneous reports of ARs to beehive products gathered within the Italian Phytovigilance System (IPS), which deals with collecting and evaluating reactions to botanicals products (e.g food supplements). ARs can be reported online by health professionals, companies, and citizens on the website www.vigierbe.it. The ARs were coded according to the Medical Dictionary of Regulatory Activities (MedDRA).

Results: From April 2002 to March 2022, 54 spontaneous reports of suspected ARs related to beehive products were collected. A previous analysis included 18 cases was published [6]. The median age of patients who experienced ARs was 37 years (Inter Quartile Range = 10–55 years); women were involved in 26 cases, men in 25 while in 3 cases the information was lacking. Serious reactions occurred in 14 cases. The ARs reported (n = 104) were related to Immune system (37%), Skin and subcutaneous tissue (28%), respiratory disorders (17%), and others (18%). The products involved were food supplements (63%) and medical devices (13%), while in 24% no information on the product was reported. About the composition, propolis was present in 68% of products, while royal jelly in 33%. Only one product contained their combination and, most of the cases,

suspected products also contained different herbal extracts. Predisposing conditions, as atopy or allergies, were indicated in 43% of reports. Concomitant products were reported in 46% of cases. From the label analysis, only 6 suspected products indicated warnings for atopic subjects.

Conclusion: Present findings outline relevant information about the safety profile of beehive product consumption in atopic subjects that could be further worsened by the absence of warnings on the label. Moreover, these results strengthen the importance of IPS as an irreplaceable method to monitor food supplements' safety signals.

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Improving the Knowledge Attitude and Practice of Pharmacovigilance Amongst Herbal Medicine Practitioners in Lagos

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Introduction: The inclusion of herbal medicines in pharmacovigilance systems is becoming increasingly important given the growing use of herbal products and herbal medicines globally [1,2]. Literature have indicated lack of awareness as one of the major barriers to the practice pharmacovigilance [3].

Objective: This study evaluated the impact of an educational intervention in improving the knowledge and practice of pharmacovigilance among traditional medicine practitioners in Lagos State, Southwest Nigeria

Methods: About two hundred traditional medicine practitioners attended a one-day workshop on pharmacovigilance. A pre-tested questionnaire was used to obtain baseline and one-month post intervention information on knowledge, attitude and practice of pharmacovigilance among respondents. The study was carried out at the Lagos State traditional medicine board in South-Western senatorial district of Lagos state, Nigeria. Descriptive statistics and paired t-test using SPSS 23 was employed for analysis.

Results: About sixty percent (60.7%) of the respondents were females. Majority of the respondents were married (75%), and had tertiary education (59.7%). The one-month post-intervention assessment showed that Herbal medicine practitioners' knowledge of pharmacovigilance had improved significantly after the educational intervention from an overall means score of 4.0 ± 1.2 to 4.72 ± 1.5 ($p < 0.0001$). Ninety one percent (91%) and 78% of respondents could correctly define the terms "Pharmacovigilance" and "Adverse Drug Reaction" respectively post intervention. Majority (89%) of the respondents could state the difference between a side effect and an adverse drug reaction. Furthermore, respondents knowledge of medicinal plants in terms of their composition, efficacy and adverse effect had also improved significantly (3.87 ± 1.65 versus 5.90 ± 1.22 ; $p < 0.0001$). Only very few respondents believed that their medicinal plants don't expire compared to 80% pre-intervention

Conclusion: This study showed that an educational intervention improved herbal medicine practitioner's knowledge and attitudes towards pharmacovigilance in the studied population. It also improved their knowledge of the nature of their medicinal plants

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Safety of Therapies and Use of Supplements. The Pharmacy Clinical Desk Experience in the National Cancer Centre CRO Aviano

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Introduction: More and more cancer patients are using complementary and alternative medicine (CAM). CAM is mainly used in addition to conventional treatments to reduce side effects and improve quality of life [1]. The Clinical Pharmacy Desk (PCD) is a free consultancy service offered at the CRO Aviano to patients and health workers attending the facility. On the one hand, the service evaluates the safety of therapies by detecting possible interactions (drugs-supplements or other products) and the inappropriateness of use. Indeed, the intake of these products may not be safe when associated with conventional anticancer treatment [2]. On the other, it promotes patient empowerment and informed use of these products. The PCD activity contributes to the safety of care and safeguarding patients' quality of life.

Objective: Detect near misses (interactions and inappropriateness of use). Educate the patient on an informed use of supplements and other products. Detect adverse drug reactions (ADRs) resulting from the intake of these products.

Methods: The PCD carries out safety assessments by active interception through structured patient interviews and on-demand access. The current clinical surveillance program, active since June 2019, involves 278 patients in follow-up for 24 months. Clinical data are

periodically updated on a dedicated database by checking medical records and interviewing patients. Near misses are detected by evaluating multiple databases and reading the literature from relevant sources. The suspected ADRs are reported on the "VigiErbe" portal [3]. At the same time, feedback on the assessment is given to the patient, and personalized information is provided through interviews and dedicated informational materials. Sharing relevant information with the oncologist is done through discussion and implementation of the patient's medical record.

Results: The active surveillance program has detected 293 near misses. In particular, 242 possible interactions between drugs and natural products were identified. In 180 cases, consumption of these products was discouraged, and in 62 cases, monitoring of clinical parameters and side effects was suggested. Inappropriate use was found for 51 supplements or other products. Finally, the number of suspected adverse reactions reported in VigiErbe was 4 (50% serious and 50% non-serious).

Conclusion: Through active detection and personalized information, the PCD offers patients an assessment of the safety of CAM associated with conventional anticancer therapies. This service allows identifying near misses, contributing to increased safety of therapies and patient empowerment. This promotes the prevention of risks related to the intake of supplements and other products in patients treated at the CRO Aviano.

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The AOUI Verona Task Force for Improvement of Post-Market Clinical Surveillance for Medical Device

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Introduction: Post-marketing surveillance (PMS) is the practice of monitoring the safety of a pharmaceutical drug or medical device (MD) after it has been released on market and is an important part of science of pharmacovigilance. PMS is considered one of the most critical aspects of the new EU-MDR 2017/745.

In AOUI Verona the pharmacist in charge of MD vigilance reports adverse events to Pharmacovigilance's Regional Service and Ministry of Health.

For many years there has been a collaboration between Pharmacy and Hospital Risk Management by sharing clinical information about incidents, failures, serious deteriorations or potential deficiency related to MD safety use. This multidisciplinary collaboration is the fundamental aspect to improve protection of health and safety

patients, healthcare professionals and all users reducing the likelihood of reoccurring incidents. Unfortunately during Covid-19 a lack of training and staff awareness significantly reduced spontaneous incident reporting.

Objective: Aim of the present study is analyze PMS data and organize hospital staff training to increase PMS and spontaneous incident reporting.

Methods: Over the years Pharmacy and Risk Management keep a database for recording and monitoring data on MD adverse events. The Cross-check analysis of databases allows to intercept all incident or failure occurred.

Results: From 2019, recorded data show a decrease of 30% related to MD incidents or failures (2019: N = 120; 2020: N = 67; 2021: N = 45) and some Operating Units are less likely to reporting. In 2021 the clinical risk manager received 56 incident reports and only 45 of these to Pharmacy too. 22 were filled in by surgical departments, of which 4 by pediatricians and 18 by adult specialists. The total number of reports shows that 80% have reached the pharmacy office, while the percentage ratio between the two sectors is expected to be 100%.

Conclusion: The PMS management in AOUI requires a strong collaboration of all figures involved in this process. For this reason, training and awareness-raising must be carried out in a widespread and continuous way. In AOUI Hospitals we are organizing training meetings to sharing information between various professional skills so that any problems arising are quickly identified. One target for 2022 is a participation to training events for at least one doctor and nurse for each hospital unit.

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Risk-Based Quality and Safety Management in Clinical Trials with Combination Devices in Changing Global Regulatory Environment

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Introduction: Newly emerging products which combine drugs, devices, and biologics are expected to provide new opportunities in bridging device and drug capabilities and establish synergies, while bringing sophisticated combination products to consumers [1, 2]. The emergence of these novel products has triggered new regulatory, strategic, and technological challenges. While progress has been made at clarifying the issues that arise most frequently, regulatory authorities and product developers continue to struggle with complex regulatory and technical issues encompassing the development programs for combination products [2-4]. A risk-based approach requires not only a strategy but also tools to define key indicators to measure specific risks. Key risk indicators (KRIs) and risk-based quality and safety management systems should focus on safety of research subjects and data integrity during product development, and postmarketing [5, 6].

Objective: To identify risk factors associated with developing a serious adverse events in clinical trials with combination devices and develop a framework for risk-based quality and safety management.

Methods: We analyzed current regulatory guidelines throughout the lifecycle of combination products and compared old and new approaches to risk-based quality and safety management for current good manufacturing practices and during pre-clinical and clinical phases of combination products development. Cause-effect analysis for major risk categories in clinical trials with combination products was performed.

Results: The results of our analysis are based on observations from 25 clinical trials, which were conducted with combination products. Based on our findings, we proposed practical recommendations for the development of KRIs to improve conduct and ensure safety of research subjects in trials with combination products by utilizing risk-based quality and safety management approach.

Conclusion: Combination products, due to their specific nature, can increase risks while being tested in clinical trials. Metrics critical to risk-based quality and safety management should be linked to particular processes within development program for combination products. Ongoing collaboration between regulators, industry, and other stakeholders is essential to streamlining of the global combination entities development and approval process in a way that will produce safe and effective products for consumers.

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Reported Health Problems Associated with the Use of Copper Intrauterine Devices

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Introduction: The Dutch Reporting and Expertise Centre for Adverse Effects of Medical Implants (MEBI) was established in 2017 to facilitate early detection of adverse effects related to medical implants.

In March 2021 MEBI issued an alert about possible health complaints when using the copper intrauterine device (IUD) IUB™ Ballerine® MIDI after a relatively high number of reports were received about this copper IUD, mainly from healthcare professionals. In that alert MEBI called on healthcare professionals and the public to report problems associated with the use of copper IUDs [1].

Objective: To identify potential associations between the use of copper IUDs and health complaints.

Methods: Reports were submitted via online questionnaire and analyzed by a multidisciplinary expert team. Additional data were collected about potential risk factors for IUD dislocation, expulsion or uterine perforation.

Results: Between January 2020 and July 2021 MEBI received 253 reports about IUB™ Ballerine® and 110 reports about other copper IUDs. Health complaints related to IUB™ Ballerine® were more frequently related to a reduced functioning of the IUD, such as a (partial) expulsion or an unplanned pregnancy (see table 1) [2].

Conclusion: The nature of the complaints about IUB™ Ballerine® were different from those of other copper IUD's. To ascertain whether certain problems are more commonly associated with a certain IUD, their frequency needs to be calculated in relation to the total number of IUDs placed and eventually compared to other types of IUDs. Such analyses are not yet possible as no national data are available about IUD implantations. MEBI strives to provide insight and transparency into all received reports about IUB™ Ballerine® and other copper IUDs, and therefore published an update to the alert in November 2021 [2].

Table 1. Reported complaints about the functioning of the IUD and their percentage, for IUB™ Ballerine® and other copper IUDs

Complaints	Ballerine (N=295) Number of complaints (n) and percentage per total number of IUDs reported (n/295x100%)*	Other copper IUDs (N=113) Number of complaints (n) and percentage per total number of IUDs reported (n/113x100%)*
Dislocation within uterus	108 (37%)	17 (15%)
Partial expulsion	34 (12%)	10 (9%)
Full expulsion	38 (13%)	6 (5%)
Pregnancy with IUD in the right place	12 (4%)	5 (4%)
Pregnancy after IUD was (partly) expelled	59 (20%)	8 (7%)
Pregnancy with unknown location IUD	7 (2%)	1 (1%)
Ectopic pregnancy	3 (1%)	3 (3%)
Perforation of the uterus	8 (3%)	0 (0%)
Total number of complaints	269	50

* A given IUD can be associated with several complaints, that is why the number of complaints exceeds the number of reports received. The percentage shown indicates the percentage of copper IUDs for which the complaint in question was reported. As not all IUDs had complaints about their functioning, percentages do not add up to 100%.

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Insights into the Dutch Reporting and Expertise Centre for Adverse Effects of Medical Implants: A 5-Year Perspective

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Introduction: Implants placed for medical or cosmetic reasons can cause adverse effects. Some are detected only after an implant has been on the market for a considerable period of time and inserted in a large number of patients.

The Dutch Reporting and Expertise Centre for Adverse Effects of Medical Implants (MEBI) was established in July 2017 to facilitate early detection of adverse effects related to medical implants [1]. It was a collaboration between the Netherlands Pharmacovigilance Centre (Lareb) and the National Institute for Public Health and the Environment (RIVM), commissioned by the Ministry of Health.

Objective: Sharing the lessons learnt while establishing MEBI and providing an overview of the activities carried out during its operationalization.

Methods: Taking stock of the experience gained over the 5 years, we will describe the inception of MEBI as a spontaneous reporting centre, as well as its governance and structure.

Results: Furthermore, we will provide insights into steps taken to implement MEBI effectively such as team development and training, optimization of reporting mechanisms, development of ICT infrastructure, as well as the development of internal processes for knowledge generation and dissemination.

Conclusion: Finally, we will describe the processes around data collection and analysis and share the results and trends observed during the 5 years of operation (examples are shown in Figure 1 and Table 1), as well as the challenges faced when implementing our activities.

Figure 1. Overview of reports received per type of implant over 2021

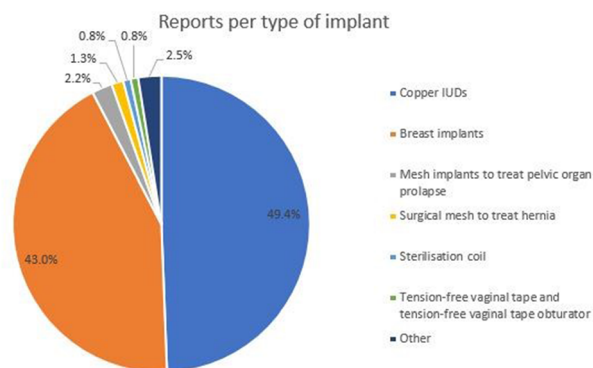


Table 1. Overview of reports received from 2017 to 2021

	2017 (Jul-Dec)	2018	2019	2020	2021
Total reports	240	162	397	248	714
Healthcare professional reports	2	11	25	46	139
% female	85	86	93	98	98
Average age	55	51	48	42	37
Top 3 reported medical implants	- Breast implants - Mesh implants for Pelvic Organ Prolapse - Hip prostheses	- Breast implants - Knee prostheses - Hip prostheses	- Breast implants - Copper IUDs - Mesh implants for Pelvic Organ Prolapse	- Breast implants - Copper IUDs - Mesh implants for Pelvic Organ Prolapse	- Copper IUDs - Breast implants - Mesh implants for Pelvic Organ Prolapse

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Consumer's Self-Assessment Form as a Source of COVID-19 Vaccine Surveillance Data in Iraq

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Introduction: Numerous routes for receiving and documenting COVID-19 vaccines AEFI reports were established within the Iraqi pharmacovigilance system as part of the national deployment and vaccination plan (NDVP). The plan entailed a workflow network connecting vaccination sites, health directorates with the ministry of health. Engaging the consumers in safety surveillance was unprecedented in Iraq due to multiple challenges.

Objective: To establish a feasible route to receive AEFI reports directly from the consumers.

Methods: A self-assessment form was developed to collect the necessary information for a valid AEFI report in four languages (Arabic, English, Kurdish, and Turkish). It was validated internally and externally. An instructional video was embedded within the form. The Iraqi pharmacovigilance center's WhatsApp account was used to disseminate this form. When the consumer messages the number, an automatic message will appear containing the form link. The public were introduced to this communication method through different means; placing the WhatsApp number on the back of the vaccination cards; educational video screened in the vaccination sites waiting area, and posted on social media.

A pharmacovigilance officer from the national pharmacovigilance center would reply back through WhatsApp. An appropriate individualized consultation was provided to each consumer as required. Adverse events were addressed. The consumers were encouraged to fill out the form. The responses are subsequently received by the regional center in the capture area and entered into the national database. Cases requiring further investigation were forwarded to the concerned organizations.

Results: From April 2021 until April 2022, a total of 2877 unique self-assessment reports were shared by the consumers, with an average of 9.5 reports per day. 70 consumers per day reached out through WhatsApp from April 2021 until September 2021 after which

decreased to around 30 per day. Some were concerning procedural and non-safety-related inquiries.

63.7% of the reports were less than 40 years old. Male were predominant (62%). 79.3% were regarding first dose. The reported vaccine types were: PfizerBioNTech (58.3%), AstraZeneca (28%), and Sinopharm (13.3%). The reported AEFIs contained both expected and non-expected ones, in addition to potential signals. The resulting AEFI reports comprised 22% of the total COVID-19 vaccines safety data in the national database.

Conclusion: Using the available social media channels to stimulate reporting (WhatsApp messaging) was successful in allowing the consumers to; report AEFIs; increase the scope of COVID-19 vaccines AEFI reports; show positive engagement and positive attitude toward the experience.

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First Patient Reports in Montenegro

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Introduction: In August 2020, the new Law on Medicines was adopted in Montenegro, which for the first time allows patients to report suspected adverse drug reactions (ADRs) directly to the Institute for Medicines and Medical Devices (CInMED) [1]. According to the experience of many countries, patient reports are an important source of information on the safety of medicines [2, 3, 4].

Objective: Analyze reports submitted to CInMED by patients

Methods: A retrospective analysis of reports submitted by patients from August 2020 to May 2022 was performed. Reported ADRs were coded using the appropriate Lowest Level Term (LLT) of the MedDRA. Results were analysed at MedDRA Preferred Term (PT) level. Important Medical Events (IME) list was used in assessing seriousness of cases. Descriptive statistics were used.

Results: All reports submitted by patients were valid. In the mentioned period, patients submitted 45 reports, which contained 200 reactions (4.4 reactions per report). Of these, 40 reports (88.9%) were related to adverse events following immunization (AEFIs) with COVID-19 vaccines. This represents 9.1% of the total number of reported AEFIs for COVID-19 vaccines in Montenegro. The majority of patient reports (32; 71.1%) were submitted via the eReporting module for VigiFlow [5]. Women submitted 28 (62.2%) reports, and men 17 (37.8%). Reports were mostly submitted by adult patients, 18–64 years old (34; 75.5%). A total of 8 (17.8%) reports described serious adverse reactions. In 14 (31.1%) cases, a follow-up request was made and patients provided additional information. Although the majority of reported adverse reactions were expected, 72 of 176 (40.9%) reactions to COVID-19 vaccines reported by patients were

unexpected—not listed in the relevant Summary of Product Characteristics at the time of reporting (e.g. chest pain, chest discomfort, arrhythmia, face oedema, hypoaesthesia, musculoskeletal stiffness, pain in extremity).

Conclusion: Patient reports are of good quality. Patients prefer the electronic way of reporting and are willing to answer follow-up inquiries. Patient reports are valuable source of new information on the safety of medicines and can be precious for signal detection, especially when it comes to new medicines. Further promotion of patient reporting and cooperation with patient associations are needed to increase the number of patient reports.

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Pharmacovigilance Evolution: Patient-Oriented Opportunities in Pharmaceutical Industry

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Introduction: European Union PV legislation recommends a proactive, transparent, risk proportionate and patient-centered approach with the main purpose to protect the public health [1]. Patient engagement in PV activities should go beyond opening up the reporting systems for them, and should include patient point of view in drug development, clinical research, and in the regulatory processes [2].

Objective: The tenth anniversary of the revised PV legislation is the right time to ask the following questions: are we sure that patients understand the meaning of pharmacovigilance and how to report adverse events? which are the opportunities for a pharmaceutical industry to become more patient-oriented?

Patients have limited knowledge on how they can participate in PV activities [3]. Patient Associations (PAs) could represent key facilitators to spread safety topics, and help patients in a better understanding of PV processes: they have the purpose to represent patients affected by specific diseases, to promote their rights and to offer services to these patients, and they therefore have the infrastructure, the networks, and trust of patients.

“Patient Safety Council” is a successful example of collaboration between PAs and Pharma Industry. The initiative, supported by Roche, involves 5 PAs, representing patients affected by major pathologies, with the aim to promote patient engagement on PV, increase the awareness on PV topics and the dialogue between patients and HCPs on safety & tolerability.

Methods: Patient Safety Council addressed the topic of awareness of PV processes in a structured way: from a specific survey [4], to initiatives for addressing the unmet need underlined, to events for raising discussion among experts, patients and institutional stakeholders.

Results: The Patient Safety Council set up projects like information material for patients, educational webinar with PV experts for patients and PAs members, communication of real PV examples, in order to overcome language and technical barriers in healthcare and to address some of the needs identified and stimulate patient engagement. The future goal is to identify new safety needs related to healthcare models in development (e.g. home treatments, telemedicine).

Conclusion: Bringing PV stakeholders and PAs together could create a “culture” of PV. It is important to establish a trustful and transparent environment where patients can become advocates and advisors, providing scientifically reliable, objective, comprehensive information on medicines research and development.

The evolution of PV lies in becoming multidisciplinary, not limited to clinical experts, finding solutions of mutual value for patients with Regulatory Authorities, PAs and key players of the Health System.

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Patients' Attitudes Towards Deprescribing—A Cross-sectional Study in Older Patients in Romania

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Introduction: The process of deprescribing has gained increasing interest as the solution to reduce polypharmacy and medication-related harm, but its success depends greatly on the patients' willingness to accept deprescribing.

Objective: To investigate Romanian patients' attitudes toward deprescribing using the revised Patients' Attitudes Towards Deprescribing (rPATD) questionnaire.

Methods: We conducted a cross-sectional study of patients 65 years and older with at least one chronic condition and one chronic medication referred to two Internal Medicine departments in a large University hospital. We applied a survey that contained questions on participant demographic characteristics, the rPATD questionnaire, and the Beliefs about Medicines Questionnaire (BMQ) specific concerns section. The rPATD was translated/back-translated into Romanian and cross-culturally adapted for the study. It consists of 22 questions grouped into 4 factors: *perceived burden of medication*, *concerns about stopping medications*, *involvement in decisions about medications*, and *appropriateness of medications* (each scored 1–5) and two global questions. A higher factor score indicates a greater perceived burden, concerns about stopping, involvement and appropriateness. The BMQ specific concerns questionnaire, previously validated in Romanian is scored 5–25 with higher scores indicating stronger concerns about the medication's potential adverse consequences.

Results: Most (217, 99%) of the 219 participants were retired, with a mean age of 72 years (standard deviation [SD] = 5.51). The majority were women (58%), living with family (72%) and from urban residency (62%). Participants reported a median of 6 (interquartile range [IQR] 4–7.5) chronic conditions and 7 (IQR 5–9) chronic medications. The highest scores were for the *involvement in decisions about medications* factor (median 4.6, IQR 4.2–5), followed by the *appropriateness* (median 3.4, IQR 2.8–4), *burden* (median 2.6, IQR 1.6–3.6), and *concerns about stopping* (median 2.4, IQR 1.8–2.8) factors. 84% of the patients responded “strongly agree” to the question “If my doctor said it was possible, I would be willing to stop one or more of my regular medicines”, and 68.95% of the patients responded “strongly agree” to “I am satisfied with my current medication”. The mean BMQ-specific concerns scale score was 11.

Conclusion: The great majority of patients would be willing to stop their medication if their doctor said it was possible. However, participants generally felt that their medications were appropriate, and the majority felt satisfied with their current medication. These findings may inform future research into how to best engage Romanian patients in the deprescribing process. Psychometric properties of the Romanian version of rPATD will be further evaluated.

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Not applicable.

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Quasi-experiment Study on Use of Toll-free Phone Systems for Adverse Event Reporting by Patients and Clinicians

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Introduction: African populations are the largest global recipients of antiretroviral therapy (ART) yet contribute less than 1% of post licensing adverse event (AE) reports to the WHO PV database VigibaseTM (1, 2). Dolutegravir (DTG) was rolled out for use in African ART programmes, however there's a paucity of studies providing AE information from those populations. Direct reporting by patients to the national regulator has not been widely adopted in African countries but has improved reporting and detection of new signals elsewhere (3, 4). Use of mobile phone systems has also been proposed as an intervention to improve reporting (5, 6).

Objective: To determine whether an intervention of clinicians and patients using toll-free phone systems results in improved reporting of AEs compared to clinicians using standard paper-based reporting methods.

Methods: We conducted a quasi-experiment study between May–November 2021 at three health centers in Kampala, Uganda with similar baseline reporting rates. We trained clinicians working in the HIV clinic with a standard package on pharmacovigilance and DTG AEs, at one health center (HC1) and also provided details of the toll-free number based at the National Drug Authority. In the second center (HC2) we provided the same training to patients on DTG-based regimens and the toll-free number. In the third center (control) we trained clinicians and encouraged use of existing paper-based reporting methods (HC3). We compared the monthly reporting rates from the two intervention centers to the control using 2-sample Wilcoxon rank-sum test. We summarized the AEs to DTG reported and compared them with the manufacturer's drug information label for new signals.

Results: We trained four clinicians in HC1 and another four in HC3. In HC2, 493 patients were enrolled with the majority female (430/493, 87%) and of median age 32 years (IQR 27–39). Monthly reporting rates were significantly higher in HC2 (138 reports received) compared to HC3 (0 reports) ($p = 0.003$). While reports in HC1 (3 reports received) were not significantly different compared to HC3 ($p = 0.317$). HC2 reports were made by 137 patients (87% female) of median age 34 years (IQR 28–40). Patients reported a total of 346 AEs with a median number of 2 AEs per patient (IQR 2–4). New signals emerging reported by patients included forgetfulness (5), loss of libido (8) and menstrual cycle changes (10). One report of forgetfulness was received from HC1.

Conclusion: Patients engagement in AE reporting in Uganda using toll-free phone systems can significantly increase reporting rates to the regulator with new signals emerging.

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Reporting ADR as a Citizen: Analysis of Data from Sardinian Region

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Introduction: European legislation on pharmacovigilance was amended with the adoption of EU Regulation 2010/1235 [1], which introduced significant changes in the active participation of patients and healthcare professionals to the Adverse Drug Reaction (ADR) reporting process. In recent years a new trend has established worldwide, allowing patients to directly report ADRs to national pharmacovigilance authorities [2]. A consumer, defined as a non-healthcare professional, is now also considered as a source of information on the safety of a medicinal product [3].

Objective: To identify numerosity and level of the involvement of citizens in ADR reporting in Sardinia.

Methods: We extracted data using Vigiseg platform from the Sardinian Region, from 2013 to 2021, for ADRs, stratified by year and qualification of the signaler. ADRs were also analyzed by severity, outcome, SOC (System Organ Classification) and ATC2 (Anatomical Therapeutic Chemical Classification System, level 2).

Results: In Sardinia, from 2013 to 2021, 6.591 ADR reports were recorded, 1093 (17%) of which were by citizens. Among those reports, 75% were classified as “not serious” and 37% had resolved completely. From 2013 to 2021, citizen participation in ADR reporting changed significantly, from 1 to 26% (Table).

Table. Citizen ADR reporting in Sardinia from 2013 to 2021.

Year	Total ADRs	ADRs from citizens (total number)	ADRs from citizens (%)
2013	369	4	1%
2014	447	8	2%
2015	440	33	8%
2016	523	64	12%
2017	517	100	19%
2018	462	40	9%
2019	531	33	6%
2020	281	16	6%
2021	3021	795	26%

In this period, most SOC reported by citizens were “General pathologies and conditions related to site of administration” (596), “Pathologies of nervous system” (421), “Pathologies of musculoskeletal system and connective tissue” (328). As for SOC “Pathologies of reproductive system and breast”, a significant increase in reporting was recorded: from 0% in 2013 to 73% in 2021. In this period, citizen reporting of pathologies of reproductive system and breast constituted 49% of the total reports. In absolute terms, the ATC J07 Vaccine was the most reported by citizens with 799 reports (2737 in 2021). Reports by citizens for homeostatic calcium drugs (H05) account for 81% (48 ADRs) of the total reports for this ATC. **Conclusion:** Increase in citizen reporting in 2017 and 2021 can be traced back to the information activities of the Regional Center following the introduction of mandatory vaccination and the awareness campaign for Covid-19 vaccines. Such increase reflects the growing importance of pharmacovigilance among citizens, meaning that an increasing number of citizens have now acquired the necessary tools to ADR reporting, thus becoming a significant source of information on the safety of drugs and vaccines.

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Assessment of Safety of Use of Antismoking Drug Cytisine in a Hospital Setting

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Introduction: Tobacco is one of the world’s largest preventable causes of premature death, which provoked more than 8 million deaths each year [1]. To effectively stop smoking, an integrated approach that includes psychological and pharmacological

intervention is required. Cytisine, selective partial agonist at nicotinic acetylcholine receptors, has been shown to reduce smoking withdrawal symptoms and tobacco use satisfaction [2].

Objective: To assess safety profile of cytosine treatment on a hospital setting; the efficacy and compliance have been also assessed.

Methods: A monocentric, observational, prospective study in smoking patients hospitalized in the medical school hospital of Verona (AOUI) treated with cytosine. For each patient, eligibility for treatment with cytosine and subsequently eligibility for the observational study is assessed. The smoker is asked to sign the informed consent form and the therapeutic plan is defined by the physician. The galenic cytosine preparation is prepared by AOUI Verona pharmacy. The primary endpoint is the number of adverse events and adverse drug reactions (ADRs) in the 12-month time period following start of treatment (quit day). ADRs are characterized by type of reaction, day of onset, severity and outcome.

Results: In total, 300 subjects will be enrolled. In the first six months of recruitment, 94 smoking patients with relevant comorbidities hospitalized in different departments of AOUI Verona (including cardiology, rheumatology, nephrology) were enrolled. From preliminary data analysis, the safety profile of cytosine is consistent with literature data. The most common ADR is nausea, followed by initial insomnia and sleep disorder. Most cases occurred within 3 days from the quit day. No serious ADRs have been reported.

Conclusion: To our knowledge, this is the first observational study with cytosine in a hospital setting. Findings from this study support the safety profile of cytosine, and preliminary data confirm the efficacy of the cytosine in this treatment context.

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Evaluating the Impact of Pharmaceutical Interventions on the Clinical Outcomes of Palliative Care Patients: A Single-Arm Clinical Trial

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Introduction: Palliative care is a multi-dimensional practice that aims at the improvement of the patient's quality of life. Given the level of reliance on drugs in this environment, clinical pharmacists can play an important role in assessing drug-related problems (DRPs). [1,2]

Objective: To evaluate pharmaceutical interventions on safety of drug therapy in palliative care patients admitted to a secondary hospital.

Methods: A single-arm clinical trial was carried out in the 10-bed palliative care ward of a secondary hospital in São Paulo, Brazil. All patients admitted to the ward from October 2021 to March 2022 were screened for eligibility (i.e., age > 18 years, hospitalization > 48 hours). To identify, solve and avoid DRPs, patients' pharmacotherapy was assessed by a clinical pharmacist according to Cipolle et al. (2004), and pharmaceutical care interventions were made towards the healthcare team, patients and caregivers. [3,4] The impact of interventions was evaluated by the application of the Palliative Performance Scale (PPS), Karnofsky Performance Status (KPS), Palliative Prognostic Index (PPI), and Edmonton Symptom Assessment Scale (ESAS) in hospital admission and discharge. The present study was reviewed and approved by the Research Ethics Committee of the School of Pharmaceutical Sciences of Ribeirão Preto (protocol number 5.306.657).

Results: During the 6-month period, 120 patients were included. Most patients were female (n = 68; 56.7%), had a mean age of 71.0 years (19–97) with most (n = 69; 20.5%) experiencing neoplasms. Overall, 170 DRPs were identified in 68.3% (n = 82) of patients (median 2 DRPs/patient). After assessing DRPs, the pharmacist directly intervened 361 times and was successful in 78.1% (n = 282) interventions. Each patient received an average of 3.8 interventions (0–15), where the most common were adjustment of medication dose and suspension of drug therapy. An increase in the median scores of PPS and KPS scores was noticed, from 30% to 40% in hospital admission and discharge, respectively. When assessing disease severity, an improvement of survival prediction was observed—average PPI score from 5.4 to 2.9. In addition, the consultation in hospital discharge revealed a decrease in the report of all ESAS symptoms.

Conclusion: Pharmaceutical interventions helped to identify clinically relevant DRPs and resulted in optimized drug therapy, which had positive effects on palliative care performance, survival prediction and symptom control. Thus, the care of palliative patients by pharmacists may be interpreted as a promotion of drug therapy safety by reducing drug risks.

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How Do You Find Monitored Dosage Systems?

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Introduction: Monitored Dosage Systems (MDS) are used by millions of patients and carers in the UK (1). Concerns on their use and

safety have been published(2), but inevitably patients and carers depend on them (3). Healthcare is evolving and it is recognised that patient empowerment is a vital component in the success of treatment (4). Research in the use of MDS, from the patient and carer perspective appears to be sparse.

Objective: The aims of this study was to explore the perspectives of patients or their carers, regarding the use of MDS.

Methods: Qualitative research with semi-structured interviews was carried out with patients or their carers from the Belfast Health and Social Care Trust (BHSCT). The study occurred over a four month period from July 1st to October 31st, 2021. The overall objective of the interviews was to allow for patients or their carers an opportunity to talk freely about their experiences with their use of MDS. The interviews were transcribed and analysed using NVivo[®] and thematic analysis (5).

Results: A total of 14 interviews (8 patients and 6 carers) took place during the study period. From the analysis the main theme that emerged from both patients and carers was positivity regarding MDS use. In the patient cohort this ranged from 0.30 to 4.40% coverage. Patients' comments included examples such as, "Think they are the best thing ever". In the carer's cohort, positive comments regarding MDS use ranged from 0.84% to 7.82% and comments included, "I think it's brilliant". Many other themes emerged, and the analysis identified high coverage of negativity towards original pack use in both groups.

Conclusion: The study identified that for those patients or carers who use MDS, continuation of care is very much dependent on MDS. The study has highlighted that MDS play a vital role in medicines management and safety. All the participants spoke about how MDS have transformed their lives. Enabling patients and carers to speak about their use has strengthened the case that MDS should not be stopped without established alternatives which offer equal or superior support.

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Are Pharmaceutical Companies Engaged with Patients for Pharmacovigilance?—A Search on Industry Accomplishment Regarding Patient Reporting of ADRs

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Introduction: According to directive 2010/84/EU, marketing authorization holders (MAHs) must establish a pharmacovigilance system with the aim of supervising their medicines [1]. Thus, the

pharmaceutical industries must provide information and reporting forms and/or direct contact for the reporting of adverse reactions on their websites, so that patients can report [1].

Objective: Analyze the possibility for patients to report suspected adverse drug reactions through the Pharmaceutical Industry websites and assess how it facilitates the reporting.

Methods: An observational, cross-sectional study was conducted through a search on the websites of 80 pharmaceutical companies (60 at European level and 20 outside Europe). Industries from following countries were selected: Ireland, Spain, USA, UK, Canada, Germany, France and Portugal. It was applied an auto-fill questionnaire for assessment of 10 items.

Results: Comparison between brand and generic industries shown that only 30.4% of the branded industries and 25% of the generic industries surveyed present a reporting form and 23.2% and 16.7 % have contact of regulatory agencies present in their website. Only 31.7% of European industries and 20% of non-European industries have a reporting form and a total of 21.7% of and 20.0% have the information about the contact of national regulatory agencies, respectively. The option to use a research field appeared in 90% of European industries and 85% of non-European industries. Regarding the direct contact for pharmacovigilance (phone or email) to report a problem 73.3% of European industries and 85.0% of non-European industries have direct contact with pharmacovigilance.

Conclusion: In general, the pharmaceutical industries websites have contact for patients to report ADRs, however it was possible to acknowledge that a significant percentage of industries didn't provide reporting form that allows patients to report suspected ADRs or a direct contact to the National Regulatory Agency. Thus, industries must improve these parameters in order to facilitate and improve the reporting of ADRs. This was a exploratory study in the field that should be deepen with a higher number of industries and different parameters between industries.

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Spontaneous Reporting of Adverse Events Following Immunization in Veneto: Direct Transfer of Reports from the Local Vaccination Registry

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Introduction: Rapid changes that have occurred in digital world in recent years have had a dramatic impact on how case reports are collected and analyzed. Although the European legislation on pharmacovigilance has made mandatory the introduction of web reporting, a direct connection between electronic health records and spontaneous reporting systems might prove useful in reducing underreporting, particularly among healthcare professionals (HCPs) [1]. VigiFarmaco, a web reporting system, has been in place in Italy since 2015. In the Region of Veneto HCPs of local vaccination

centers can access the SIAVr (Sistema Informativo Anagrafe Vaccinale regionale), a web-based platform for the registration of vaccinations that includes a section where adverse events following immunization (AEFIs) can be recorded. Up to 2018 AEFI reports collected in vaccination centers in Veneto had to be forwarded to the Local Pharmacovigilance Authority and then manually entered by pharmacovigilance officers into the National Pharmacovigilance Network (Rete Nazionale di Farmacovigilanza, RNF), the national pharmacovigilance database. Since 2019 AEFI reports are directly transferred from the SIAVr to the RNF through an API software, thus facilitating reporting by HCPs.

Objective: To assess the impact that the direct transfer of AEFI reports from the SIAVr to the RNF had on spontaneous reporting in Veneto up to April 2022.

Methods: Spontaneous reports of vaccines collected in Veneto were extracted from the RNF and those that originated from the SIAVr were identified. Reports associated with COVID-19 vaccines were not included in the assessment.

Results: 1,738, 1,950 and 1,594 AEFI reports were collected in Veneto in 2016, 2017 and 2018, respectively. During this period, Veneto accounted for 28% of total Italian AEFI reports. AEFI reports collected in Veneto were 1,923 in 2019 (+ 21% compared with the previous year), 1,202 in 2020 (− 37%) and 1,410 in 2021 (+ 17%). The percentage of reports originated from the SIAVr and then submitted through an API software was 71% in 2019, 82% in 2020, 93% in 2021 and 93% in the first 4 months of 2022.

Conclusion: Data show that the implementation of an API-mediated link between the SIAVr and the RNF has proved incredibly useful since the very beginning. To date, more than 90% of AEFI reports in Veneto are submitted through this powerful tool. Compared with national data, the spontaneous reporting rate for non-COVID-19 vaccines in Veneto has been starkly high in recent years, showing a more limited effect of COVID-19 pandemic on spontaneous reporting in 2020.

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Am2P: A New Accredited Academic Training Program in Pharmacovigilance and Pharmacoepidemiology Designed for US, Canadian and Caribbean Healthcare Professionals

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Introduction: Pharmacovigilance (PV) is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem.

Objective: In November 2021, the North American Society of Pharmacovigilance (NASoP), a Chapter of the International Society of Pharmacovigilance (ISoP), launched PV courses for the education of North American stakeholders, in collaboration with Eu2P academic institutions.

Methods: The Am2P program (Am2P) follows WHO-ISoP Core Elements of a Comprehensive Modular Curriculum and subscribes to the Innovative Medicines Initiative (IMI) Education and Training quality standards, jointly developed by Eu2P and other IMI Education and Training projects to foster quality in lifelong learning and continuing professional development. Convenient online education in PV supports the mission of ISoP to foster PV scientifically and educationally and enhance the safe and proper use of medicines worldwide. Am2P was designed by experienced PV experts from multiple institutions within NASoP, in partnership with Eu2P instructors, to comprise North America-focused online courses that benefit from existing Eu2P material, education technology, and academic accreditation.

Results: Am2P offers two academic options: the Certificate degree and the Short Course certificate of achievement in PV. Four modular course programs are available on the Am2P website (<https://www.am2p-courses.com>) providing education on core and specialized PV topics with a focus on North America: Basic Pharmacovigilance (PV) & PV regulations; PV for Biologics; External databases/Real World Data/Real World Evidence; Benefit-Risk assessment. Program approval is ensured by the Eu2P Executive Board including academic representatives of the 6 Eu2P degree-awarding universities.

Am2P and Eu2P Certificate Courses hold the same academic value. A regular Certificate course involves 75h student workload over three months, recognized as 3 ECTS (European—Credit Transfer and Accumulation System) credits, equivalent to 1.5 American credits. Am2P Short Courses are bite-sized courses to provide or reinforce solid, current knowledge in PV focused on North America.

Conclusion: Am2P is a partnership between NASoP and Eu2P to build a set of North America-focused online courses offered in PV. Am2P offers accredited PV training of the highest standard, focused on North America, as an extension of the Eu2P program. Online PV training addresses needs of new entrants to PV, and seasoned personnel.

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Knowledge, Attitudes and Practices on Pharmacovigilance and Phytovigilance among students of MSc in Nursing Sciences

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Introduction: Spontaneous reporting of suspected Adverse Drug Reactions (ADRs) by healthcare professionals is a key activity for patient safety. All professionals involved in care and drug administration should play a proactive role in spontaneous reporting to create a more robust pharmacovigilance (PV) and Phytovigilance (PhyV) culture [1, 2]. Nurses are a potentially valuable source of ADR and Natural Products Adverse Reactions (NPAR) reports, because they administer drugs and are often present when an ADR/NPAR occurs [3]. Underreporting of ADRs among nurses could be mainly due to lack of knowledge and to health care settings that do not support them in this activity [4].

Objective: To describe the Knowledge, Attitude and Practice (KAP) of MSc nursing student about the spontaneous reporting of suspected adverse ADRs and NPARs.

Methods: A descriptive observational study with an online anonymous KAP survey was carried out. The questionnaire was administered during March 2022 to the MSc nursing students of the University of “Tor Vergata”.

Results: Preliminary data was collected in May 2022 on a sample of 56 students. The respondents’ age ranged from 23 to 58 years (mean = 33.8; SD = 9.52; median = 30.5), 71.4% were female and the area of nursing practice was medical (23; 41%), emergency (10; 17.8%), surgical (7; 12.5%), obstetrics and gynaecology (5; 8.9%), domiciliary care (5; 8.9%) and other (6; 8.9%). Knowledge was measured through 16 multiple-choice questions and only 23.2% (13) scored more than 65% correct answers. The 33.9% (19) of respondents considers that “ADR reporting is a bureaucratic process”, only 17.8% (10) thinks that they “don’t have time to report ADR” and only 3.5% (2) that “the data collected through the reporting system have little utility”. Only 8.9% (5) considers that “the report of ADR is an exclusive duty of the physician”. The 73.2% (41) of responders declared that they were aware of PV system but only 28.5% (16) know the PhyV system. Furthermore, 32.1% (18) know where to find the reporting form; 32.1% (18) how fill it in; 33.9%, (19) to whom and how to send the reporting form; 25% (14) who is the contact person of PV in their hospital. The majority (92.8%; 52), declared to be interested in training programs on PV and PhyV.

Conclusion: These results show that knowledge about PV and PhyV is relatively low among MSc Nursing students. Despite this, attitudes and practices show an interest that could be used as a motivator to promote specific training, starting from pre-service education.

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P331

Children’s Pill School Evaluation: Healthcare Professionals’ Views and Recommendations

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Introduction: The Children Pill School (PS) was developed at a UK paediatric hospital and was designed to support children aged 3–18 years in switching from oral liquids to pills (tablets/capsules) following a single swallowing training session using candies; > 90% of trained children successfully switched to pills [1].

Objective: To explore views and recommendations of healthcare professionals (HCPs), from secondary and primary settings, on implementing PS as a health care service provided to children as part of standard care.

Methods: A virtual focus group (FG) was conducted with purposive sampling of HCPs (doctors, nurses, and pharmacists) using a topic guide derived from the previous study [1]. The FG discussed HCPs views of the PS initiative and explored any concerns they might have regarding the rollout of the PS across the different clinical areas in the hospital. The FG was recorded and transcribed verbatim. Anonymised transcript was analysed using a content analysis approach to identify themes.

Results: Eight HCPs participated in the FG, seven from secondary-care settings [hospital doctors (n = 2); pharmacists (n = 2); nurses (n = 3)] and one from primary-care setting, a general practitioner. Three main themes were identified: (1) impact of PS initiative on child’s health; (2) potential barriers that might prevent PS service working effectively; (3) recommendations to overcome barriers and promote PS.

All participants shared a common view on the direct benefits of the PS on a child’s health outcomes, e.g., overcome taste issues of oral liquids, improve child’s adherence, improve dosing accuracy, and quality-of-life of children and their families.

Parents/children's resistance and time pressure in clinics were barriers recognised by HCPs that might limit PS service working effectively. Including PS as part of normal admission assessment and running PS classes in outpatient clinics were HCPs' recommendations to overcome barriers and promoting a culture of 'pill-first' thinking. **Conclusion:** This study highlights the importance and potential benefits of the developed PS initiative on the health outcomes of children's, consequently their quality-of-life. A change in practice in favour of pills promotes patient safety and increasing children's access to marketed solid formulations.

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When the Drug Becomes Toxic!: Lyell Syndrome in a Moroccan Context

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Introduction: Toxic epidermal necrolysis (NET) or Lyell's syndrome is a rare, unpredictable, and potentially fatal bullous toxiderma. The disease requires early management in an intensive care unit, at best in a burn resuscitation unit.

Objective: To describe the clinical, paraclinical, therapeutic, evolutionary data of patients hospitalized in the burn resuscitation department and establish the imputability of drugs in the occurrence of this adverse event.

Methods: Our work is a retrospective descriptive study over a two-year period from January 2020 to March 2022. All our cases were reported to the National Pharmacovigilance Center of Morocco and were the subject of an evaluation of the causal link between the appearance of Lyell syndrome and the drugs taken by patients according to the French method of study of imputability of adverse drug reactions in its updated version.

Results: Out of 500 patients admitted to the service, 05 cases of NET were identified, an incidence of 01%. The notion of drug intake was present in all our patients. The drugs incriminated were Sul-famethoxazole-Trimethoprim, paracetamol, rivaroxaban, a specialty anti-cold combining (Paracetamol + ChlorphenamineMaleate + Salicylamide + Phenylephrine) and amoxicillin + claclofan acid. All patients had erythematous macular and maculopapulous lesions, of varying sizes, spread throughout the body associated with mucous and ophthalmic involvement. The median assessment of burned skin surface was 80%. Two patients progressed to sepsis and broad-spectrum antibiotic therapy was started. Patients received early management with exclusive symptomatic treatment, with care for skin and oro-pharyngeal lesions. The evolution was almost favorable for all our patients.

Conclusion: NET is a rare pathology that can be fatal. This serious drug complication requires mandatory reporting to

pharmacovigilance. Several immunological and viral genetic factors are believed to be involved in the pathophysiological of Lyell Syndrome but which are still poorly elucidated. Raising public awareness of the risks associated with self-medication and of doctors of the risks of drug prescribing remains the best means of prevention.

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ADHD Medication Use and Psychiatric Comorbidity, Trauma and Mortality in Children and Young Adults: A Cohort Study from Quebec, Canada

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Introduction: Among the Canadian provinces, Quebec showed one of the highest trends in increased diagnostic rates of attention-deficit/hyperactivity disorder (ADHD) between 2000 and 2012 (1). Recent prevalence estimates of ADHD are 6.6%, 18.9%, and 15.5% for those aged ≤ 11, 12–17, and 18–24 years, respectively (2). Prescription rates for ADHD medications in Quebec have increased from 1.9 to 7.7% between 2000 and 2020 (3). The comorbidity and health outcomes of individuals using ADHD medications have not been described in Quebec.

Objective: The aim of this study was to describe the prevalence of comorbidity, trauma-related events and mortality according to ADHD medication use.

Methods: Data were drawn from the Quebec Integrated Chronic Disease Surveillance System of the National Public Health Institute of Quebec (4) between 2000 and 2020. The cohort included residents covered under the public drug insurance plan between April 1st, 2000, and March 31st, 2020. Individuals between 1 and 24 years entered the cohort at either a first physician claim, hospital diagnosis of ADHD, or an ADHD medication claim. Medications included amphetamine-derivatives, methylphenidate-based psychostimulants and non-psychostimulants (5). The study population was categorized concerning the presence of an ADHD medication and diagnosis [ADHD

medication only, $n = 34,528$; ADHD diagnosis only, $n = 20,574$; both an ADHD medication and diagnosis, $n = 59,610$ (the majority had medications and diagnosis within 90 days)]. We estimated prevalence rates of psychiatric comorbidities, trauma-related events (ambulatory records), and mortality rates (all-cause; trauma-related without suicide) according to the presence of ADHD medication and ADHD diagnosis. Differences were based on 99% confidence intervals (CIs) around estimates.

Results: The prevalence of lifetime psychiatric comorbidities in individuals with ADHD medication only, diagnosis only and both medication and diagnosis were 78.5%, 65.8%, and 79.3%, respectively. Traumatic-related events were present in 48.3% of individuals with ADHD medication only, 49.4% of those with ADHD diagnosis only, and 59.0% of those with both. The prevalence of all-cause mortality was higher in those with ADHD diagnosis only (0.33% vs 0.19% in ADHD medication only, and 0.17% in both diagnosis and medication). Similar results among groups were found for trauma-related mortality, being 0.06% among individuals with ADHD medications, 0.05% among those with diagnosis only, and 0.07% among those with both.

Conclusion: Differences exist in the psychiatric comorbidities, traumatic-related events and mortality between individuals using ADHD medications and those who do not. Within-subject analyses are underway and will allow for assessing the association between ADHD medication use, suicide behaviours, trauma and mortality.

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Medication-Induced Delirium in Older People Hospitalized in General Wards Care: A Systematic Review

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Introduction: Delirium is a syndrome characterized by acute impairment of consciousness, attention and cognitive functions [1]. The occurrence of delirium in patients is multifactorial, which includes polypharmacy, clinical conditions and procedures [2]. Furthermore, medication-induced delirium is one of the most frequent adverse drug reactions in older hospitalized patients [3]. However, there is no consensus in the literature on how polypharmacy and medication with anticholinergic activity contribute to this syndrome [3,4,5].

Objective: Identify medication-induced delirium among older people hospitalized in general wards care.

Methods: This systematic review was based on the Cochrane manual and the search for articles was performed in the LILACS, PUBMED, Embase, Web of Science, Cochrane and Angeline Cochrane databases, without restriction of publication date. Two independent reviewers performed the selection of articles and the extraction of interest variables: medication, drug-related problems, time of hospitalization, and clinical outcomes.

Results: The initial search retrieved 10,461 studies. After eligibility assessment, only five met the inclusion criteria and were further included for the qualitative analysis. A total of 1,435 participants were assessed in the studies, of which 839 (58.5%) were women. Most studies ($n = 3$) were conducted in North America. The incidence of medication-induced delirium ranged between 7% and 19.7%. Four studies used the Confusion Assessment Method (CAM) scale, and no study reported the delirium subtype neither its gravity. Regarding clinical outcomes, three studies identified an increase in length of hospitalization, one study reported reduction of functional impairment after hospital discharge, and one study revealed an increase in mortality. The main pharmacological classes reported were: narcotic, antihistamine, anticonvulsant, benzodiazepine, sedatives, antibiotics, antihypertensives and anticholinergic. The most drug-related problems that contributed to delirium were of necessity (unnecessary polypharmacy and untreated health condition) and safety (anticholinergic drug load and adverse drug reaction). Furthermore, it was possible to observe that the modifiable risk factors for the occurrence of delirium related to pharmacotherapy were poorly described in the studies (e.g., dosage, route of administration, number of drugs used), as well as the instruments used to assess causality.

Conclusion: The lack of harmonization in the report of clinical outcomes, pharmacotherapy and the delirium characteristics impaired the causal imputation and identification of drug-related problems related to the syndrome. However, safe and necessity drug problems might have precipitated delirium. Narcotics were the most recurrent pharmacological class in the occurrence of the syndrome, which may increased length of hospitalization, disabilities and death among older people.

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P335

Applying a Launch Excellence Framework in Patient Safety

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Introduction: Following BMS' acquisition of several late-stage development assets, the need to enhance pharmacovigilance (PV) product launch preparation and support to enable improved safety communications with HCPs post-approval became more apparent. Communications between Safety and other functions, primarily Medical Affairs, was inconsistent and, often, reactive.

Objective: To develop and test a conceptual launch framework that will enhance the creation and exchange of safety information to better inform clinicians' healthcare decisions.

Methods: A current state assessment of launch activities in the pre- and peri-launch settings revealed several best practices, gaps, and opportunities that were used to guide the development of a new framework. This new framework, including new roles, processes, and tools, creates a dedicated launch capability for PV:

- Establish a single point of contact for coordinating and connecting safety launch activities.
- Assign clear launch accountabilities to existing roles on the asset safety management team.
- Build a Medical Collaboration Model to formalize engagement opportunities between the Safety and Medical Affairs functions.
- Development of a simple 10-step process to direct asset teams in value-driven safety activities surrounding launch.
- Creation of Complex Medical Query Rapid Response Model to streamline the communication and safety response for complex medical queries.
- Identification of new sources and new uses for existing data sources to further inform launch teams of safety topics.

Once the framework was created, the concepts were piloted at varying stages of asset launch for refinement before broad scale up and implementation.

Results: The new framework has been applied to 2 assets to date, resulting in improved stakeholder engagement and collaboration with (a) greater transparency on safety data gaps from the perspective of HCPs and patients, (b) opportunity to share information and expertise regarding the safety profile based on safety surveillance activities (c) alignment on medical and scientific communication opportunities including publications. Both teams identified opportunities to enhance safety communications and exchange insights for the asset.

Conclusion: Ensuring patient safety is critical in the development, approval, and commercialization of new medicines. By forming a launch capability framework, the team created structure that will trigger cross functional connectivity based on the unique safety needs of each new product preparing for market. Alignment on unmet data needs, data generation and scientific and medical communications surrounding the safety profile are key drivers of success. This new

capability will ensure valuable safety data and insights are effectively and efficiently shared across functions at BMS.

References/Further Sources of Information

Not applicable.

P336

Development of a Framework for the Integration of Two Major Biopharmaceutical Organizations and Guidance for Pharmacovigilance

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Introduction: Large mergers and acquisitions, including the largest in 2019, the acquisition of Celgene by BMS for \$74 Billion, continue to re-shape the pharmaceutical industry landscape. Health authorities closely monitor such integrations to ensure medicines continue to be developed, marketed, and distributed as per regulations.

Objective: To create a robust guidance for the integration of patient safety organizations to allow continued operations and maintain regulatory compliance.

Methods: The following framework has been established to enable successful and timely integration: day 1 planning and inspection readiness; integration planning and governance; initiative execution; and change management (Table)

Results: Application of this new framework within our organization has helped us reach the targeted end state in 2 years with complete business continuity, while realizing several people, process, technology and financial benefits:

- Optimized processes for receiving, monitoring and reporting patient safety information.
- Assessment resulted in the retirement of 85% of procedural documents.
- Reporting and multi-venue collaboration.
- Enhanced use of technology at integrated state: 5 IT solutions were integrated and deployed to automate, support, and enhance processes such as Risk Management, Pharmacovigilance Agreements, PV Quality, Signal Detection, and a multi-tenant Global Safety Database. These IT systems serve as a single source of data, providing standardized reports, and real time metrics.

Adoption of an extensible Change Management capability across the organization, enabling a predictable and consistent change experience throughout integration.

Conclusion: Successful completion of the largest Biopharma patient safety integration, inclusive of global safety systems, was achieved within 28 months by utilizing our innovative framework for executing on PV integrations. Development and application of this integration framework has been critical to ensuring that our large organization of 8 patient safety sub-functions and over 700 employees worldwide maintained business continuity, quality, compliance, and inspection readiness, and kept on track to reach our target end state, while maintaining our guiding principles:

- Focus on the priority of achieving a single PV system.
- Select best practices between the two heritage organizations.
- Identify sources for value capture/synergies.
- Minimize impact on day-to-day business operations.

This framework has since been applied to integrate a smaller PV organization at a much faster rate of approximately 6 months. This methodology may be adapted to support any patient safety integration and further applied beyond patient safety organizations, create

efficiency and reduce operational costs associated with integration planning and execution.

Torres et al—Integration Framework—ISoP 2022—Table

References/Further Sources of Information

Not applicable.

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Let's Make a PV Agreement: Three Solutions You Can Use to Enhance Your PVA Process

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Introduction: TransCelerate has launched a suite of solutions designed to help organizations enhance their PV agreement process. These solutions can help organizations improve their processes and potentially achieve more efficient negotiations with their business partners.

Session participants will be able to:

- Navigate each primary solution (Process Map, Glossary, and Table of Contents).
- Discuss and determine how they can apply these solutions to help enhance their PVA processes, help support negotiations, and potentially generate efficiencies across the PVA lifecycle.

Objective: The volume and complexity of PV agreements (PVAs) continually increase year over year. Inefficiencies in negotiating and complying with PVAs wastes resources and contributes to non-value-added work due to:

- Ambiguous contractual terms and definitions can lead to non-compliance.
- Lengthy negotiation periods & contractual maintenance discussions may lead to delays and potentially compromise business relationships.
- Lack of stakeholders' awareness and data around operational timelines often used in PVAs can lead to negotiation inefficiencies.
- Complexity of PVA structures and content leads to challenges in review & negotiating terms.

Methods: Through extensive collaboration, TransCelerate developed a suite of solutions including the Process Map, Glossary and Table of Contents. Each of the solutions was created by taking into consideration information collected from PVA templates and/or subject matter expertise. The objective is to offer a comprehensive and flexible framework to support the development, maintenance and lifecycle of PVAs.

Results: TransCelerate's Pharmacovigilance Agreements Optimization (PVAO) Initiative has produced a suite of customizable solutions for organizations that could be used to inform and/or streamline their end-to-end PVA process. The primary solutions are:

Process Map: An interactive tool that illustrates the end-to-end PVA lifecycle and key considerations throughout the development of PVAs.

Glossary: List of key definitions & synonyms often incorporated into PVAs.

Table of Contents: A framework of headings and points to consider for potential incorporation into PVAs, including regulatory citations.

Conclusion: By leveraging these solutions, PV stakeholders could potentially realize benefits, such as:

- Reducing drafting and negotiation time, thereby potentially improving the timeliness and reducing the risk of delays to key milestones.
- Increasing awareness of considerations that may impact PVA development.
- Serving as a resource for those involved in the PVA lifecycle.
- Support improvement of accuracy and completeness of PVAs.
- Better support patient safety through improved PVAs.

This session will discuss each of the primary solutions within the suite and enable participants to use these solutions to help enhance their PVA lifecycle activities.

References/Further Sources of Information

This project was a TransCelerate Initiative and submitted on behalf of TransCelerate.

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Facial Paralysis Associated with Pembrolizumab Use: Adverse Events-Signal Review

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Introduction: Facial paralysis is a loss of facial movement due to nerve damage. Common causes of facial paralysis include infection or inflammation of the facial nerve, head trauma, head or neck tumor, or stroke (1). Pembrolizumab is an antineoplastic agent. It is a humanized monoclonal antibody that binds to the programmed cell death-1 (PD-1) receptor. A signal of Pembrolizumab and facial paralysis was found in the medical literature. Saudi Food and Drug Authority (SFDA) has conducted this safety review based on that.

Objective: The purpose of this review is to evaluate the risk of facial paralysis in association with Pembrolizumab use

Methods: SFDA performed a search of the national ADRs database, World Health Organization (WHO) global ADRs database, and literature screening in order to review all related information to investigate the causality of drug-event combination

Results: Local Cases: The search in the National Pharmacovigilance Center (NPC) database resulted in zero cases. Global Cases: A search in the World Health Organization (WHO) database (Vigibase) was conducted to retrieve all reported cases between 2015 and 2021 via signal detection tool (Vigilyze). The search resulted in 28 Individualized Case Safety Reports (ICSRs). The author applied the WHO causality assessment, resulting in one case with probable association, six cases with the possible association, and five cases with unlikely association. Sixteen cases were unassessable due to a lack of information. **Data mining:** Information Component (IC) value was measured using the method for disproportionality analysis developed by Uppsala Monitoring Center (UMC). Zero value for spontaneous reporting suggests that the reported cases of facial paralysis have been observed equally with Pembrolizumab when compared to other medications in the WHO database. **Literature:** Upon conducting a literature search, two relevant studies were found. This signal was detected from a phase 3 double-blind trial entitled (Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma). Facial paralysis was one of the identified serious adverse events (4). A case report of a 44-year-old male patient was diagnosed with extensive-stage small-cell lung cancer (ES-SCLC). 6 months after receiving pembrolizumab, he developed facial paralysis and facial numbness. Pembrolizumab was stopped (5).

Conclusion: The weighted cumulative evidence identified from the causality assessment of the reported cases, and literature are sufficient

to support a causal association between Pembrolizumab and the risk of facial paralysis. Health regulators and health care professionals must be aware of this potential risk and it is advisable to monitor any signs or symptoms in treated patients

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Perception and Behavior towards Risk Information in the Patient Information Leaflet in Saudi Arabia

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Introduction: Accurate and consistent medication information is essential to prevent medical errors and to ensure the safe and effective use of marketed products. ⁽¹⁾ Patient Information Leaflet (PIL) is a printed material that contains information according to regulatory guidelines for the safe and effective use of a product. It must be compiled and distributed by the drug manufacturer after regulatory body approval. ⁽²⁾

Objective: The primary objective of this study was to explore the perception and drug intake behavior of adults toward risk information in the PIL in Saudi Arabia

Methods: This is a cross-sectional survey in form of an electronic questionnaire. A sample of adult consumers (aged > 18 years) was included in different regions of Saudi Arabia. We collected 521 responses. However, we excluded all participants who didn't read the leaflet and that resulted in 447 responses.

Results: A total of 523 adults participated in this cross-sectional study, of these 447 adults were included in the analysis since participants who did not read the product information leaflet were excluded. 92.8% considered that reading the risk information increases their understanding of the drug. 43% of participants who read the side effect section continue to take the medication, while 7% do not. Subjects with an educational level of university and post-graduate levels were more concerned about medication use than lower education levels (P-value = 0.008)

Conclusion: Almost half of the participants read the drug leaflet if the drug was used for the first time, and most-read the whole content of the drug leaflet and use the medication despite reading the side effects section.

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P340

Sexual Disorders with Selective Serotonin Reuptake Inhibitors: A Comparative Study

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Introduction: Sexual dysfunction may be a symptom of major depression. Moreover, sexual disorders occurring in association with selective serotonin reuptake inhibitors (SSRIs) therapy is well-known but underreported.

In pharmacovigilance, the phenomenon of underreporting is known, but reporting rates depend amongst other things, on the frequency with which adverse drug reactions (ADRs) occur.

Objective: The aim of this study was to determine and compare the reporting rate of sexual disorders in association with SSRIs.

Methods: The data were extracted from the WHO pharmacovigilance database, Vigibase, from 1967 to December 2021. Sexual disorders were identified and extracted from the database using the standardized MedDRA Query (SMQ) “sexual dysfunction”. First of all, we analyzed data. We calculated the rate of reported sexual disorders as a percentage of the total adverse drug reactions (ADRs) for each drug. We performed a disproportionality analysis through the calculation of reporting odds ratio (ROR) with 95% confidence intervals (CIs).

Results: A total of 337 832 ADRs with the SMQ sexual dysfunction were reported during the period of which 12 963 with SSRIs. The medication with the most frequently ADRs were paroxetine (n = 3937), sertraline (n = 3418) and fluoxetine (n = 2763). The most frequently ADRs reported were libido decreased and erectile dysfunction. The physicians reported only 25% of cases. All the SSRIs have a ROR statistically significant. The highest ROR were observed with paroxetine (ROR 4.00, 95% CI 3.88–4.13), sertraline (ROR 3.27, 95% CI 3.16–3.38) and escitalopram (ROR 2.86, 95% CI 2.71–3.02).

Conclusion: Sexual disorders occurring with SSRIs therapy are known but underestimated. Sexual side effect have sexual, psychological and social consequences.

Physicians must report this type of ADR and improve the clinical management.

References/Further Sources of Information

Not applicable.

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Future of Healthcare and Opportunities/Challenges for Pharmacovigilance in the Digital Age

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Introduction: In 2000, the Da-Vinci surgical robot was first introduced, revolutionizing how precision surgery, difficult positional surgery is conducted. Since then, there have been major advances in the role of technology, devices and digital in healthcare. The real-time streaming and sharing of RWD has enabled a patient centric connected care approach where wearables, diagnostic devices, EHR and laboratory findings can be consolidated, interrogated rapidly to assist clinical decisions. Novel therapies are often combination of biologics, devices and wellness.

Objective: Approaches to pharmacovigilance and risk management needs to evolve with the advent of novel therapeutics from a medical pharmacological approach to a multidisciplinary approach where medical, scientific, technology and community play a significant role. Integrated therapeutic solutions may include gaming, AR/VR, 3D printing, devices/SaMDs and digital solutions. Pharmacovigilance can play a key role in redesign of such solutions to maximize benefit-risk and optimize outcomes.

Methods: Pharmacovigilance processes like adverse event processing, signal detection, aggregate analysis and risk management needs to be re-evaluated for these novel therapeutics, and new sources of knowledge needs to be leveraged. On the other hand, there is also an opportunity to re-think risk management of drugs where digital devices/approaches could help early detection of safety risks, continuous monitoring and prevent serious outcomes.

Results: Digital and technological advances present opportunities for novel approaches to drug pharmacovigilance, personalized healthcare and optimization of benefit-risk-outcome. As some of these digital solutions are approved as SaMDs, there are also challenges in redefining the PV processes for such digital health products. Predictive science and use of AI/ML methodologies could also transform patient profiling, risk assessment, clinical decisions and safety analysis.

Conclusion: It is important to consider healthcare stakeholders beyond pharmaceuticals/biotech/regulators to also include technology startups, SaMD providers, wellness companies, healthcare education and include them in refining pharmacovigilance processes for digital solutions so that safety principles are embedded in the design process. Cross-industry collaboration and engagement with regulators is essential to prepare for these digital advances, and the future is now. There is a potential to transform healthcare and benefit patients, HCPs and wider society by leveraging these advances while managing the uncertainties these new approaches may bring.

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The Global Pharmacovigilance Professional Certification (GPPC)

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Introduction: As part of its mission to elevate pharmacovigilance career, the Institute of Pharmacovigilance, a non-profit non-governmental organization (NGO), is developing a Global Pharmacovigilance Professional Certification system (GPPC) for ISoP.

Objective: The goal of GPPC is to elevate the pharmacovigilance profession by defining roles & competencies, and testing against them.

Methods: The process begins with defining standards for various seniority levels and roles within the field of pharmacovigilance. These standards include prerequisites, expected knowledge and its depth, required skills, and desired personality traits for a given role. All mandatory prerequisites are checked prior to the admission to the certification process and then the candidate's knowledge is evaluated via an online, AI proctored multiple-choice test. For specific roles, the required skills are tested on a real-life scenario, which presents the candidates with a task they need to address followed by an oral examination. Once the candidates pass the complete examination process, they will be issued a certificate. The whole process is managed by the Institute of Pharmacovigilance with the contribution of recognized experts serving as members of the GPPC Examination Boards, and newly established ISoP Scientific Board overseeing the project.

Results: The GPPC is planned to be deployed by June 2022 via pilot programs. One of the crucial steps was setting up the framework for role standards in cooperation with ISoP Special Interest Group on Career Framework in Pharmacovigilance. At the same time, over 1,000 items (multiple-choice questions) have been generated and are to be validated by GPPC Examination board(s) and ISoP Scientific board. An online testing platform, including AI proctoring solution, has been selected and adapted to the needs of GPPC.

Future development will focus on completing competency standards for a wider range of roles and identifying areas of knowledge for testing. As soon as a new role competency standard is defined, this role can be easily added to the portfolio for testing.

The other stream of development is spreading across different countries and regions. The system is designed bearing in mind the possible need for localization and offering certification in local languages. The global recognition of GPPC will also be supported by a strong marketing campaign and outreach activities.

Conclusion: GPPC is on the course to contribute to the goal of elevating pharmacovigilance profession as well as providing benchmarks for individual roles. In the future, the certification will be accepted as the new pharmacovigilance qualification standard all over the world.

References/Further Sources of Information

Latest updates and published documents can always be found on our website <https://pharmacovigilance.instituteorourLinkedInprofile>.

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PVReg: A Comprehensive Global Pharmacovigilance Requirement Profiling and Analysis System

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Introduction: A core mission of the Institute of Pharmacovigilance (IPV), a non-profit non-governmental organization (NGO), is to develop a Global Pharmacovigilance Professional Certification (GPPC) which, when fully developed, will be using a pool of 5000 questions reflecting the wide scope of pharmacovigilance knowledge. A key component of the knowledge to be covered is safety regulatory compliance. To gather the relevant information with a global scope, the comprehensive global pharmacovigilance requirements profiling tool (PVReg-profiler) described in this paper was developed.

Objective: The purpose of the PVReg-profiler includes: (a) Constitute a core element of the Knowledge Management System supporting the GPPC; (b) Master the evolution of the diverse global safety regulatory environment; (c) Measure the impact of regulatory strengthening policies, serving the needs of Regional and National Regulatory Authorities, International Public Health Stakeholders and Market Authorisation Holders.

Methods: The concept was designed for collecting any compliance-critical pharmacovigilance-relevant requirement from any national or regional regulatory system, and to be able to evolve as regulatory frameworks are rapidly strengthening. Questions were formulated in order to serve as basis for generating multiple choice questions and standardised country safety requirement profiles for making comparative analyses across countries. A unique item numbering system was developed to allow for comparing items across versions. An initial set of 350 questions was created involving a panel of pilot experts invited to test it and provide feedback. The main challenge faced during the development phase was to address the actual diversity of requirement across countries by capturing compliance relevant details without inflating the number of items to be assessed. This was resolved by allowing for structured comments.

Results: The PVReg-profiler has entered its production phase including (i) the collection by appointed country experts of the relevant information, (ii) the validation of the profile by the National Regulatory Authority, (iii) the use of the information by item makers, (iv) the use of the available profiles by stakeholders interested such as holders of medicinal product licenses and public health stakeholders involved in regulatory convergence and strengthening.

Conclusion: Beyond its primary utility as a source of safety regulatory knowledge for the GPPC, this key component of IPV's ecosystem is intended to be used by Public Health stakeholders to facilitate identifying priorities for regulatory convergence and strengthening and monitor its progress.

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A Comprehensive Global Repository of Pharmacovigilance-Relevant Regulations

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Introduction: The context of rapid and diversified regulatory strengthening [1] makes increasingly necessary to create a comprehensive global repository of pharmacovigilance-relevant regulations including laws, ordinances, good vigilance practice documents, and guidelines. No such repository had been developed before our initiative to launch the *PVRegulations* repository subsequently incorporated into the *PVReg* ecosystem developed by the Institute of Pharmacovigilance (IPV), a not-for-profit non-governmental organisation establishing a Global Pharmacovigilance Professional Certification (GPPC).

Objective: In addition to constituting a resource of knowledge backing the GPPC, the *PVReg-repository* is of interest for public health and Industry stakeholders, as well as for academic institutions involved in regulatory science and research. National Regulatory Authorities (NRAs) and National Pharmacovigilance Centres (NPVCs) are welcome to access the *PVReg-repository* by reaching PVRegulations@outlook.com. Dialogue between IPV and NRA/NPVCs is welcome especially in countries where documents are issued in national language when format issues make challenging to generate English translation

Methods: The *PVReg-repository* was designed according to a consistent architecture aimed at providing rapid and easy access to targeted documents without the need for specific training. To reach this goal, a consistent, informative, and intuitive document naming system was developed. Besides the document architecture, methods were developed for overcoming the multiple issues resulting from the diversity of the formats of the document released by NRAs from all over the world. Different translation software applications were evaluated for generating English translations. The *PVReg-repository* was launched on a dedicated MS365 Standard Business platform making it accessible via OneDrive/SharePoint, pending access via the IPV website. The next step will consist in migrating the current folder architecture to a document management system making possible to associate metadata to the documents in order to enable advance search.

Results: The repository is populated and maintained taking advantage from multiple sources including systematic screening of NRA websites, input from IPV's network, and direct collaboration with NRAs. Currently, the *PVReg-repository* includes more than 2000 documents. Whilst the primary focus consists in pharmacovigilance regulations, the scope is being extended to regulations relative to Clinical Trials, Medical Devices, and Medical App.

Conclusion: We believe using the *PVReg-repository* combined with profiles generated by the global pharmacovigilance requirement profiling tool will become the most resource-efficient way for Public Health stakeholders as well as holders of medicinal product licenses to monitor the change of the safety regulatory environment.

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Pilot Implementation of the Global Pharmacovigilance Professional Certification (GPPC)

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Introduction: A core mission of the Institute of Pharmacovigilance (IPV), a non-profit non-governmental organization (NGO), is the development of a Global Pharmacovigilance Professional Certification system (GPPC) which, when fully developed, will be using a pool of 5000 questions reflecting the wide scope of pharmacovigilance knowledge.

Objective: The purpose of this paper is to describe the principles followed for the implementation and provide a status of pilot implementation in the EU countries followed by other regions.

Methods: Pilot countries were selected based upon criteria including (i) the availability of a local ISoP chapter/members interested in supporting it, (ii) a well-established networking relationship with Competent Authorities (CAs) and the interest expressed for implementing the GPPC to improve regulatory compliance. The PV requirement profiling tool (PVReg-profiler) (Abstract 1) was completed by relevant Experts. Multiple-Choice Questions (items) were generated according to the process described in Abstract 3.

Results: The first wave of implementation is aimed at EU member states followed by subsequent waves in other regions. Status as of September 2022 will be presented at the ISoP 2022 Annual Conference in Verona.

Conclusion: The lessons learned from this pilot implementation phase will be used to guide the subsequent global implementation of the GPPC.

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Proactive Drug Safety Monitoring of Adverse Drug Events in Saudi Arabia: 2021 Experience

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Introduction: The proactive drug safety monitoring program was established by Saudi Food and Drug Authority (SFDA) for post-marketing monitoring of the safety of registered medications, to create a strategy to monitor the safety of medicinal products proactively with higher efficiency. AdisInsight is an integrated database that aggregates scientifically-based content assembled from different sources to enable access to relevant, unbiased studies and case reports with citations and links to the original source.

Objective: To assess the relatedness of adverse drug event (ADE) case reports in AdisInsight database to a group of medications approved by SFDA.

Methods: A list of medicines registered by SFDA from 2015 to 2021 was selected. The main pharmacological categories of the included medications were monoclonal antibodies, antineoplastic agents, vaccines, and immunomodulatory agents. The ADE case reports of the selected medications was retrieved from AdisInsight database. First, the listedness assessment was performed on the retrieved ADEs lists by crosschecking the U.S. Food and Drug Administration (FDA),

European medicines agency and local label information to exclude listed ADEs. Then, a comprehensive drug safety review for the unlisted ADEs was performed using several evidence sources including unpublished clinical trial, literature, local and global spontaneous reports and periodic benefit-risk evaluation reports.

Results: A total of 110 medications were selected with 13,535 reported ADE case reports retrieved from AdisInsight database. The listedness assessment resulted in requesting of label update for 40 medicines (36.4%). A total of 64 comprehensive drug safety reviews were performed for 141 potential safety signals. The safety review recommendations were an update in the product safety information (n = 4 signals); request additional data from pharmaceutical companies (n = 23 signals), routine monitoring of the risk (n = 79), and no regulatory action needed (n = 35 signals).

Conclusion: The proactive drug safety monitoring program in SFDA successfully improved the identification of new safety information for medicinal products.

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Sertraline and the Potential Risk of Pulmonary Eosinophilia Drug-Induced

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Introduction: Sertraline is a selective serotonin reuptake inhibitor (SSRI) antidepressant, approved by the Saudi Food and Drug Authority (SFDA) for the treatment of major depressive episodes, panic attacks, obsessive-compulsive disorder, and social anxiety disorder (1). Pulmonary eosinophilia results from the infiltration of the lung tissue by eosinophils. It is a rare disease with a prevalence of less than 2.5% of interstitial lung disease reported cases (2).

Objective: This research aims to evaluate the association between sertraline use and the potential risk of pulmonary eosinophilia as a part of the proactive monitoring program adopted by the SFDA.

Methods: First, a systematic literature search was conducted from inception until January 2022, using PubMed, Google Scholar, and Cochrane library and we also searched in Adis Insight database to include English publications and studies on humans that reported the targeted adverse event with the use of sertraline. In addition to that, searching the local adverse drug reactions database and World Health Organization (WHO) database was performed on April 2022 via signal detection tool (Vigilyze) using the terms sertraline (substance (WHO Drug) [AND] “pulmonary eosinophilia” (reaction preferred term (PT) (MedDRA)).

Results: Six published case reports of pulmonary eosinophilia with the use of sertraline were found. Most of the cases were female (n = 4). The mean age was 57.1 (range 33–76). All of the cases showed a reasonable temporal relationship, three cases reported positive de-challenge, and one case had partial improvement only after the drug is withdrawn. None of the cases re-challenged with the drug. Using concomitant medications associated with known risk of pneumonia was present in two cases such as clomipramine and risperidone.

Globally, we retrieved 20 cases reported pulmonary eosinophilia with the use of sertraline. The WHO causality assessment was performed for five cases with a completeness score ≥ 0.5 . Based on the WHO–

UMC causality assessment, two cases had a probable causality assessment with reasonable temporality and positive de-challenge, two cases had a possible causality with reasonable temporality and one case could not be assessed because the information available was insufficient. No local cases were reported to the SFDA.

Conclusion: Based on the available evidence, the potential association between sertraline and pulmonary eosinophilia cannot be ruled out. Further epidemiological studies are needed to assess this potential association.

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The Antidepressant Effects of Hypoglycaemic Agents: New Insights from an Analysis of the FDA Adverse Event Reporting System (FAERS) Database

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Introduction: Based on recent preclinical and clinical evidence linking together metabolic regulations and psychopathological mechanisms, a potential antidepressant role for glucagon-like peptide 1 (GLP-1) functional agonists (i.e., GLP-1 agonists and dipeptidyl peptidase 4-DPP-4 inhibitors) has been hypothesized [1-4].

Objective: To investigate the antidepressant effects of GLP-1 functional agonists in a huge population scale data from the FDA Adverse Event Reporting System (FAERS) database, in a large period of observation (from 1967 to 2021).

Methods: From the primary cohort of patients treated with antidepressants (N = 536,240) (drugs were reported as suspect drugs in the occurrence of any adverse event), we identified *cases* i.e., depressed patients experiencing therapy failure and *non-cases* i.e., depressed patients experiencing any other adverse event. We then calculated and compared the ratio of the reporting odds ratios (ROR) as well as the ratio of 5% and 95% CI ROR values for cases versus non-cases in relation to the concurrent exposure to GLP-1 functional agonists (ATC codes: A10BJ and A10BH). Using the ratio of the 5% CI ROR value for non-cases and the 95% ROR CI value for cases is an adaptation of the Interaction Signal Score which represents interaction strength as the ratio of the 5% CI value of the disproportionality score for an event occurring with a pair of interacting drugs and the 95% CI value of the disproportionality score for the same event with the corresponding individual drugs [5].

Results: The results showed that the difference between cases and non-cases with respect to their association with antidiabetic drugs can be considered statistically significant (non-overlapping 90% confidence intervals of ROR values of non-cases compared to cases) for both drug classes. GLP-1 agonists: ROR/ROR = 2,921; ROR05/ROR95 = 1,961; DPP-4 inhibitors: ROR/ROR = 1,623; ROR05/ROR95 = 1,628.

With regard to the selected antidiabetic agents, drugs mainly involved in the decreased ROR for the occurrence of depression and therapy failure were vildagliptin (ROR/ROR = 9,9662; ROR05/ROR95 = 2,482) and liraglutide (ROR/ROR = 3,099; ROR05/ROR95 = 1,717). It is likely to suppose that these antidiabetic drugs might exert beneficial antidepressant effects to patients with diabetes.

Conclusion: This study has provided promising preliminary findings that may contribute to supporting the hypoglycaemic drug repurposing in the field of neuropsychiatric disorders

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Drug-Induced Canalculitis : An Observational Postmarketing Study

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Introduction: The canaliculus is the channel that connects eye to lacrimal sac. Canaliculitis is a lacrimal duct inflammation may be associated with stenosis. This adverse drug reaction (ADRs) has been described with 5-fluorouracil and docetaxel. The drug ocular toxicity is poorly documented, in particular canaliculitis.

Objective: The objective of the study is to investigate the association between drug and canaliculitis and to determine drugs implicated.

Methods: We used the World Health Organization pharmacovigilance database (Vigibase) comprising more than 29 millions of ADRs to identify canaliculitis related to drug exposure. Reported ADRs are coded using Medical Dictionary for Regulatory Activities (MedDRA). Cases of canaliculitis were selected by using the following Preferred Term (PT) “Dacryocanaliculitis” until December 2021. The association between drug and canaliculitis was evaluated. We performed a disproportionality analysis through the calculation of reporting odds ratio (ROR) with 95% confidence intervals (95% CI). A ROR was defined positive when the number of cases is more than 3.

Results: Of 29,758,968 reports, 94 reports corresponded to the PT. The drugs most frequently associated with canaliculitis were: etanercept (n = 8), dexamethasone (n = 6), infliximab (n = 6), rebamipide (n = 4) and adalimumab (n = 4). We found a significant ROR with etanercept (ROR 4.93, 95% CI 2.39–10.17),

dexamethasone (ROR 21.56, 95% CI 9.43–49.31) infliximab (ROR 11.27, 95% CI 4.93–25.76) and rebamipide (ROR 114.63, 95% CI 42.10–318.12).

Conclusion: Our study first describes the occurrence of canaliculitis after drug treatment. Canaliculitis is most often of bacterial origin. The limitation of the study is the number of reports. However, disproportionality analysis on Vigibase has proven its capacity in detecting increased risk of ADRs. This study still confirms the risk of infection by using Anti-Tumor necrosis factor- α (TNF α). These findings should activate healthcare professionals to report ocular toxicity.

References/Further Sources of Information

Not applicable.

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Spontaneous Reports vs Cohort Event Monitoring: Differences in Collecting Information on Adverse Drug Reactions of Non-Vitamin K Oral Anticoagulants

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Introduction: In the post-marketing phase of a drug it is important to monitor the safety in the general population. Besides the spontaneous reporting system (SRS), the Netherlands Pharmacovigilance Centre Lareb has a Cohort Event Monitoring (CEM) system to collect real-world information about adverse drug reactions (ADRs). For the SRS, ADRs are reported at one moment in time by healthcare professionals and patients. In the CEM system, patients are followed for a period of time in which they complete several questionnaires about their experienced ADRs. Data from both systems can be used for signal detection. There is however a gap in knowledge in type and quality of information collected by both systems.

Objective: To analyse the differences in type and quality of information collected by the SRS and CEM system and determine their usefulness for signal detection of possible ADRs of non-vitamin K oral anticoagulants (NOACs).

Methods: A retrospective comparative study was performed using information of ADRs of NOACs collected by the Dutch SRS and CEM system between March 2017 and October 2019. Reported information was compared on type and quality; patient characteristics (gender and age) and ADR information (type of ADR, outcome and burden of ADR, and action taken on the NOAC). Chi-square test or fisher-exact test were performed with a significance level of < 0.05, using RStudio with R version 4.1.3.

Results: A total of 1630 ADRs were reported through the SRS and 1149 ADRs in the CEM system (Table 1). For SRS, the median age of patients and the frequency of haemorrhagic ADRs were higher. For CEM, the number of male reporters, non-haemorrhagic ADRs listed in the Summary of Product Characteristics, and patients that recovered or were recovering from the ADR without discontinuing the NOAC was higher compared to SRS. Also, more burden scores and outcomes of ADRs were reported in CEM. Reporters experienced a higher burden of ADRs in the SRS than in CEM.

Table 1. Overview of the characteristics of the reporters/participants and specific information on ADRs of NOACs in CEM and SRS.

	CEM	SRS
Participants	1133	-
Reports [†]	627	784
Adverse drug reactions	1149	1630
Median age in years (interquartile range)	67 (59-72)	71 (62-78)
Gender		
Male (participants)	724/1133 (63.9%)	-
Male (ADR reporters)	365/627 (58.2%)	396/784 (50.5%) *
Haemorrhagic ADR	123/1149 (10.7%)	227/1630 (13.9%) *
Listed non-haemorrhagic ADR	432/1026 (42.1%)	428/1403 (30.5%) *
Burden score reported [‡]	1146/1149 (99.7%)	401/488(82.2%) *
High burden [§]	227/1146 (19.8%)	242/401 (60.3%) *
Outcome reported [¶]	1165/1210 (96.3%)	1366/1630 (83.8%) *
Recovered/recovering while continuing NOAC	744/809 (92.0%)	188/976 (19.3%) *

[†]Out of 1133 participants in CEM, 627 participants reported (an) ADR(s).

[‡]Total ADRs of 488 is lower than 784, since burden score was not implemented in SRS before November 2017.

[§]Very or extremely burdensome (score 4 and 5 on a 5-point Likert scale).

[¶]The total of 1210 is higher than 1149, since some patients experienced recurrent ADRs.

*Indicates statistical significance (p < 0.05) by chi-square test, or fisher-exact for burden score.

Conclusion: This study demonstrated that both systems provide different type and quality of information about ADRs. The SRS included a higher amount of ADRs, while the CEM system provided more specific information about the time course and burden. Both systems are unique in their methodologies and combining data collected by both systems would strengthen signal detection in pharmacovigilance.

References/Further Sources of Information

Not applicable.

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Eritrea's Experience in Safety Monitoring of Mass Administration of Praziquantel

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Introduction: Adverse events (AEs) following mass administration of praziquantel, used as preventive chemotherapy for schistosomiasis, are generally mild and transient with rare serious problems [1,2]. Serious AEs are less likely to be tolerated by the general public as the product is usually administered to healthy individuals. Moreover, co-incident events may be falsely attributed to praziquantel. If such AEs are left uninvestigated, they could compromise public confidence and endanger the success of public health programs.

Objective: This report shares Eritrea's experience in safety monitoring of praziquantel used in mass drug administration (MDA) and provides a summary profile of the AEs associated with praziquantel by analyzing data retrieved from Vigibase, the WHO global database.

Methods: Brainstorming and desk review of existing documents and tools were exercised to clearly understand the strategies employed, limitations/challenges, areas of improvement, and lessons learned during praziquantel mass administration. Moreover, data mining on Vigibase was carried out with search criteria 'praziquantel' as a drug substance and 'Eritrea' as a reporting country on May 01, 2022.

Results: Integration of pharmacovigilance activities into the neglected tropical diseases (NTD) control program was initiated in 2017. Under the umbrella of integrated systems, the introduction of a stimulated passive surveillance system during campaigns was the main strategy used to monitor AEs related to the mass administration of praziquantel. About 76% of the globally reported AEs related to praziquantel in Vigibase were submitted by Eritrea. Almost all

(99.4%) of the AEs were non-serious and a few serious AEs were left uninvestigated. Almost all cases (99.8%) were submitted to VigiBase following the integration in 2017. The most commonly reported AEs, according to MedDRA, were gastrointestinal (71.5%) and nervous system (33.19%) disorders and some of these AEs were either undocumented or poorly documented.

Conclusion: Integrating pharmacovigilance into the NTD control program along with some surveillance strategies resulted in a surge of AE reports, the majority of which were non-serious reflecting the product was generally tolerable in the Eritrean population. The integration was also helpful in identifying some AEs of praziquantel that seemed to be previously undocumented or poorly documented thus; triggering signal assessment. The few serious AEs were all left uninvestigated and thus, it was unknown whether they were related to praziquantel, administration error, and/or other alternative causes. Future campaigns are recommended to investigate cases of interest at the earliest possible time to prevent further harm and address false blame from coincidental events.

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Pharmacovigilance in no Profit Clinical Trial: Duties and Responsibilities for the Research Team

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Introduction: The pharmacovigilance (PV) activities in no profit clinical trials mainly concern the identification and collection of safety events, signal detection and management, Suspected Unexpected Serious Adverse Reaction (SUSAR) reporting to EudraVigilance, development of Safety Update Reports (DSUR), evaluation of drug risk/benefit balance. In this context, the presence of a trained and specialized research team is essential to manage and monitor patient safety and represents a legal requirement for centers promoting no profit clinical trials.

Objective: This project aims to evaluate the state of the art regarding duties and responsibilities of the research team in the management of pharmacovigilance activities in the no profit clinical trials.

Methods: On April 2022, the Italian Group of Data Manager and Clinical Research Coordinator launched an anonymous online survey, consisting of 20 multiple choice questions to healthcare professionals operating in no profit clinical trials at experimental sites.

Results: A total of 47 professionals have completed the survey (51.1%, n = 24 from northern Italy). Most of them were clinical

research coordinators (63.8%, n = 32) followed by responsible person for pharmacovigilance (12.5%, n = 7), pharmacists (8.5%, n = 5) and physicians (6.4%, n = 3). More than half of the participants (53.2%, n = 27) operate in oncological centers and perform the following tasks: collection of adverse events data (66%, n = 31), reporting of serious adverse events (59.6%, n = 28), implementation of Standard Operating Procedures (SOP) (42.6%, n = 20), submitting of DSUR (34%, n = 16), SUSAR reporting in EudraVigilance (31.9%, n = 15). Regarding pharmacovigilance activities, 68.1% (n = 32) of respondents confirmed the presence in the team of professionals with EudraVigilance certification (40.4%, n = 19) and qualified for SUSAR reporting (44.7%, n = 21). The most important barriers reported by participants are the lack of a multidisciplinary team to support safety management (66%, n = 31) and insufficient on training pharmacovigilance (49%, n = 23). 55.3% (n = 26) of professionals have not performed pharmacovigilance trainings at least in the last year. In addition, 70.2% (n = 33) have never been subject to a pharmacovigilance audit.

Conclusion: Promoting a no profit clinical trial represents an opportunity for a clinical center and an important chance for improvement. Because of the explorative nature of the survey, the results are limited to a representative sample. However, the project highlight an adequate organization of pharmacovigilance processes but also the need to ensure the recruitment of new resources and implement a specific training program. In this context, upgrading and guaranteeing continuous pharmacovigilance training is pinnacle to keep professionals updated thus optimizing activities at sites.

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Safety of Bempedoic Acid: Post-marketing Analysis of the FDA Adverse Event Reporting System

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Introduction: Bempedoic acid (BA) is an oral lipid modifying drug, approved in early 2020 by the Food and Drug Administration (FDA) and the European Medicines Agency, for primary hypercholesterolemia or mixed dyslipidemia in statin-intolerant subjects or patients unable to reach therapeutic goal on maximum-tolerated statin therapy [1]. BA inhibits adenosine triphosphate citrate lyase, expressed primarily in the liver and not in skeletal muscle, thus making myopathy less likely to occur. In pivotal studies, an increase in serum uric acid, liver enzymes, creatine phosphokinase, and creatinine emerged as adverse events of special interest (AESI) [2].

Objective: To characterize the post-marketing safety profile of BA, with a focus on AESI and the identification of unexpected events.

Methods: After duplicate removal, we collected spontaneous reports with BA reported to the FDA Adverse Event Reporting System (FAERS; April 2020–December 2021). Descriptive analysis was

performed to characterize demographic and clinical features: age, gender, comorbidities, co-medications, seriousness, discontinuation, and time to onset (with interquartile range, IQR). Disproportionality analysis was carried out by calculating the Reporting Odds Ratio, using the lower limit of the 95% confidence interval > 1 as the threshold for statistical significance (Bonferroni correction). Three groups were identified for comparison: all drugs in FAERS, other lipid-lowering agents, and statins.

Results: Over the 21-month post-marketing period, 460 adverse events to BA were identified (out of 157,433 with other lipid-lowering agents), almost exclusively as suspect (94.6%), with large contribution from females (62.66% vs 52.94% for other lipid-lowering drugs), subjects aged ≥ 65 years (63.89% vs 62.09%), clinicians (53.38% vs 25.04%), North America (92.61% vs 75.53%). Cardiovascular agents (56.09%) and ezetimibe (40.7%) were the most frequently reported co-medications. Hospitalization and death were recorded in 22.35% and 1.18% of the cases, respectively (vs 40.76% and 12.71% with other lipid-lowering drugs). Discontinuation was reported in 33% of the cases. A disproportionality signal, consistent across analyses, was found for 16 adverse events and different AESI, including musculoskeletal events (arthralgia, tendon rupture, myalgia, muscle spasms) and gout/hyperuricemia, with highly variable onset [median 9 days for gout ($N = 13$; IQR = 1–31) and 96 days for arthralgia (39; 1–238)].

Conclusion: While no new safety issues emerged with BA, the considerable discontinuation rate and variegated latency of AESI, including musculoskeletal events, underline the need to pursue proactive and regular monitoring by clinicians and pharmacovigilance experts.

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Marketing Authorization Holders: The Pharmacovigilance Performance Pattern According to their Geographic Classification

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Introduction: Saudi Food & Drug Authority (SFDA) initiated the pharmacovigilance (PV) inspection department as an independent section under the national pharmacovigilance center (NPC) at the end of 2018. This section aimed to monitor and enhance the PV activities among different Marketing Authorization Holders (MAH), by reviewing the procedures, systems, personnel and facilities in place and determine their compliance with SFDA obligations. The review aim is to identify the performance pattern of MAHs based on geographic classification from SFDA perspective (1,2,3).

Objective: Identify the performance pattern among MAHs based on geographic classification from December 2018 to December 2021.

Methods: A retrospective observational review of the documentation of various inspectional findings during the inspection of MAH, in the Saudi market, from December 2018 to December 2021. The actual inspections for the global MAHs were started in December 2018, while the regional and the local ones started in 2019. All registered MAHs in the Saudi market, global, regional, or local, were included. The inspection team examined several elements during the inspection planning:

- The MAH's portfolio.
- ADRs reporting rate.
- The QPPV turnover.
- Compliance history.
- No more than five years from the last inspection.

Descriptive analyses were performed, including frequency/percentages for categorical variables and mean with standard deviation or median with range for continuous variables.

Results: SFDA have conducted thirty-six inspections, among them more than half were global (36:57%), regional (16:25%), and local (16:18%). The average number of reported findings per inspection increased over time, 5.5 findings in 2018 and 8.3 in 2021 (percentage change (PC): 51% increase). In depth, global MAHs, The average number of findings per inspection was 5.5 in 2018 and 12.5 in 2021 (PC: 127% increase). While in regional MAHs, average findings was 22.4 in 2019 and 18.2 in 2021 (PC: 18.75% decrease). For local MAHs, average number of findings was 8.5 per inspection in 2019 and 14.5 in 2021 (70.5% increase).

Conclusion: The study has identified variations in the PV performance, developing distinguish patterns between these classifications. The inspection team considers that the significant variation in regional MAHs was due to lack of harmonization of the PV system in their countries with the global one. The inspection team will use the data to create an educational plan to deliver the targeted recommendation for each MAH category.

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Pharmacovigilance Capacity Building in Indonesia 2017–2021: Overview and Impact Trend Analysis

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Introduction: From 2017–2021, ISOP Indonesia Chapter (ISOP ID) held 4 workshops related to pharmacovigilance (PV) in Indonesia. The workshops were intended for multi-stakeholders in Indonesia and

training materials were developed based on ISOP Curricula on PV in consultation with ISOP Global.

Objective: To give an overview on PV capacity building activities held by ISOP ID from 2017 to 2021 and analyse its impact.

Methods: Analysis of ISOP training documents and 2022 Training Impact Assessment survey.

Results: In total, there are 170 registered participants in the workshops. More than 95.9 % of them came from the pharmaceutical industry and Contract Research Organization (CRO), the rest were academics and none was health care practitioners.

The workshops in 2017 and 2019 focused on basic PV, with full attendance rate of 91.5% and 81.5%. In 2017 workshop, participants had an increased median pre-post-test scores score from 14 to 20 (6 points out of total score of 25). In 2019, there was no difference in pre-post test scores of participants, (median score of 7 in pre-test and median score of 8 in the post-test; total score of 10).

The workshops in 2018 and 2021 focused on PV system establishment in Pharmaceutical Industry and practice of PV in clinical trials. The events were held for a small group of practitioners from local industry-CRO and had 100% rate of full attendance. Overall evaluation of the workshops shows medium to high satisfaction on the materials delivered in the training.

Based on 2022 Training Impact Assessment Survey preliminary results, from 44 respondents, 81.8 % of the participants were still working in PV. Nineteen (43.2%) of the respondents were able to directly apply the knowledge from the workshops to their daily work, while 5 (11.4%) said they did not directly apply the knowledge as institutional changes were needed. About 40 (90.9%) of respondents relayed the knowledge from the workshops to their colleagues and 14 (31.8 %) respondents relayed the knowledge to others outside their own institution.

Thirty-four (77.3 %) respondents had additional PV training after the workshops. The main reasons for additional training were the need for knowledge refreshment (16 respondents-36.4%) and company requirement (9 respondents-20.4%).

Conclusion: There is a continuous need for PV training in Indonesia, especially from Industry. The awareness and capacity building program need to be intensified for the health care practitioners, academics and policy makers. The workshops give a trend of positive impact for further implementation of PV in Indonesia.

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Drug Safety in Geriatric Patients and the Need for a New ISoP Special Interest Group

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Introduction: Elderly patients respond differently than adults to many medications because of age-related physiological pharmacokinetics and pharmacodynamic changes. As people grow older, their gastric pH and body fat increase while their body mass, gastrointestinal tract motility, serum albumin, and total body water decrease.1 Furthermore, the elderly are characterized by a reduction in liver mass, hepatic perfusion, and hepatic clearance.1 Most importantly, with aging, creatinine clearance decreases up to nearly 50%. In the elderly, receptor sensitivity, second messenger response, and cellular response can cause an alteration of the pharmacodynamic response.2 Aging is characterized by increased comorbidities and, consequently, polypharmacy. Therefore, also drug-disease and drug-drug interactions increase the risk of experiencing adverse reactions. Benzodiazepines (BZDs) and nonsteroidal anti-inflammatory drugs (NSAIDs) are examples of drugs that can bear an increased risk of adverse reactions in the elderly.

Objective: The sensitivity of BZD receptors increases as people get older. Because of elderly's increased body fat and decreased body water, intermediate and long-acting BZDs are more likely to accumulate and remain in the body longer, resulting in prolonged sedation.3 Long-acting BZDs have shown to have hangover effects that impair postural control and cognitive function, resulting in more falls as compared to short-acting BZDs.3

Methods: NSAIDs are another example of drugs to which elderly patients respond differently as compared to adults. NSAIDs are bound to plasma proteins and are metabolized in the liver before being renally excreted. They accumulate more quickly in the elderly than in the adults because of lower-body water, less protein binding, decreased volume distribution, and reduced renal function.1 NSAIDs cause renal vasoconstriction and reduced renal functionality. In addition, considering that diseases common in the elderly such as hypertension and atherosclerosis also contribute to reduced renal function, it is not surprising that NSAIDs intake in these patients is associated with an increased risk of renal impairment.1

Results: Not applicable.

Conclusion: Geriatric patients, especially frail and polymorbid, are still underrepresented in clinical trials despite responding differently to drugs than adults and being the subpopulation that consumes more medicines.2 Therefore, unfortunately, due to lack of data, a thorough drug benefit-risk assessment cannot always be performed in this patient subpopulation. The primary goal of the ISoP Geriatric Pharmacovigilance Special Interest Group is to promote safer use of medications in the elderly by raising awareness of why geriatric patients respond differently to drugs as compared to adults, stimulating more research in this area, and fostering a tailored use of medications in the elderly.

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P360**Developing Training Material for Community Health Workers on Adverse Drug Reaction Reporting: A Pilot Project**

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Introduction: The concept of community health workers (CHWs) is not new, it dates back to the early 1920's in China. Their roles and responsibilities have evolved globally. The WHO encouraged task-shifting with the introduction of CHWs to alleviate overstretched health systems [1] and low-and middle-income countries incorporated CHWs to assist and integrate HIV care at the primary healthcare level [2].

The role of CHWs in southern African health systems is crucial with regard to health promotion, supporting primary health care services and as vehicles of community participation within their own settings [1,3]. However, despite the important monitoring roles they play with patients on relatively new treatments, especially antiretroviral and tuberculosis medicines, they have almost no training in adverse drug reactions (ADRs) and little material is available on this topic for this level of health worker.

Objective: To develop a pilot training presentation on ADR reporting for CHWs and to receive feedback from the attendees to amend and improve the training material for CHWs.

Methods: Pilot training material was developed and peer reviewed internally by facilitators and partners from *Strengthening pharmacovigilance and regulatory capacities in four Southern African countries* (SPaRCS) project funded by EDCTP-2 in collaboration with the non-profit organization, TB HIV Care in Cape Town. The training day session included: an introduction to the CHWs, an ice-breaker session on real-world experiences and ADR reporting in their communities. Completion of a pre-test prior to the presentation with a roleplay scenario midway through the training. A question and answer session and a post-test followed. Feedback on a Likert-type scale questionnaire (n = 14) as well as fill-in questions (n = 3) pertaining specifically to the content of the training material, handouts and presentation were included.

Results: Ten CHW volunteers from across the Cape Town Metropole and two training managers attended the training session on 26 January 2022 in Cape Town. 81.8% (9/11) indicated that they had experience of a home-care patient with a suspected ADR. There was an improvement in the marks for 63.6% (7/11) of the attendees (pre-test vs post-test). 83.3% (10/12) fully agreed that the objectives of the training presentation were achieved and that adequate information was included on the slides. Everyone (12/12) fully agreed that the information on the slides were easy to understand.

Conclusion: The general feedback from the CHWs was positive and appreciative. They were eager to learn and requested follow-up sessions and more training material on ADR reporting.

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P362**Pediatric Drug Safety Surveillance: A Ten-years Analysis of Adverse Drug Reaction Reporting Data in Calabria, Southern Italy**

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Introduction: The paucity of pediatric clinical trials has led to many medicines frequently prescribed to children without a license for use in pediatrics [1-3], resulting in an increased risk of adverse drug reactions (ADRs) [4,5]. Pharmacovigilance databases remain, among others, a valuable tool for evaluating pediatric drug safety in the real-life setting [6].

Objective: To characterize pediatric ADR reports sent to the Italian Pharmacovigilance Database (RNF, *Rete Nazionale di Farmacovigilanza*) by Calabria Region (Southern Italy) over 10-year period and to compare them to ADR reports in adults.

Methods: The RNF was screened for all suspected ADR reports concerning individuals aged 0-17 years, as registered in the database coming from Calabria Region during the period 2010-2019. Adult reports (≥ 18 years) were also extracted for comparison. After exclusion of duplicates, vaccines and reports with missing age data, pediatric reports were analyzed with respect to time, sex, ADR seriousness and outcome, type of reporter, suspected drug [by the Anatomical Therapeutic Chemical (ATC) classification] and category of ADR [by the Medical Dictionary for Regulatory Activities (MedDRA[®])]. Main analyses were stratified according the following age groups: newborns (≤ 27 days), infants (28 days–23 months), children (2–11 years) and adolescents (12–17 years). A case-by-case clinical evaluation of pediatric reports was also performed to identify possible ADRs resulting from off-label/unlicensed drug use.

Results: Among 6529 selected reports, 395 pediatric reports corresponding to 556 ADRs were analyzed. From 2010 to 2015 an increasing number of pediatric reports were observed, but the reporting rate declined after 2015. The highest proportion of the reports concerned children and adolescents. Around 47% of reports involved girls: trend observed in all age groups excluding newborns. Sixty reports were serious and among them, 75% required hospitalization. Improvement was the most commonly reported outcome (57.7%). Most of reports were issued by physicians (64.1%). *Anti-infectives for systemic use* (38.5%) was the most frequently reported drug group in children. In adults, the most frequently implicated drugs belonged to the *Nervous system* ATC group. Skin disorders were the

most frequently reported ADRs both in children and adults; however, these reports were proportionally higher in children. Off-label/unlicensed drug use was recognized in 3.5% of pediatric reports.

Conclusion: This study provides an overview of ADRs reported in the pediatric population of Calabria Region, emphasizing the need for using a drug-, gender- or age-specific approach when analyzing pharmacovigilance databases to evaluate the safety of drugs in pediatric patients.

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Educational Interventions to Improve the Report, Attitude, and Knowledge of Adverse Drug Reactions in Healthcare Professionals: Systematic Review and Meta-Analysis

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Introduction: Adverse drug reaction (ADR) reports are the cornerstone of pharmacovigilance, however, underreporting limits and delays signal detection [1–3].

Objective: To synthesize the evidence of the efficacy of educational interventions (EI) in health professionals to increase ADR reporting, attitudes, and knowledge of pharmacovigilance.

Methods: A systematic literature review was carried out in database PubMed, LILACS, CENTRAL, Scopus, and Epistemonikos since inception to January 2022. In addition, gray literature was searched in Scopus Conference and ScienceDirect. Randomized clinical trials (RCT), including multi-arm trials, evaluating efficacy of EI in pharmacovigilance in health professionals to improve ADR reports, changes in the knowledge and attitude in pharmacovigilance. ADR reports were pooled by calculating odds ratios (OR) with 95% confidence intervals (95% CI), while pharmacovigilance knowledge and

attitude were pooled by calculating a mean difference (MD) with 95% CI. Heterogeneity between studies was estimated using the I^2 test. In addition, the sub-analysis was performed by EI type. An analysis of ADR report efficacy overtime was also performed. Meta-analysis was performed with RevMan 5.4 software [4] (PROSPERO: CRD42021254270).

Results: Eight hundred and seventy-five articles were identified as potentially relevant, 11 were included in the review. Most of the studies were conducted in Europe, mainly in physicians and pharmacists, with a maximum follow-up of sixteen months. Metanalysis showed significance in the increased reporting of ADRs by EI (OR = 4.74, [95% CI 2.46–9.12], I^2 = 93%). In subgroup analysis, the workshops (OR = 6.26, [95% CI 4.03–9.73], I^2 = 57%) increased ADR reporting more than telephone interviews (OR = 2.59, [95% CI 0.77–8.73], I^2 = 29%) or combined interventions (OR = 5.14, [95% CI 0.97–27.26], I^2 = 93%). No difference was observed in pharmacovigilance knowledge (MD = 1.72, [95% CI, – 0.04 to 3.47], I^2 = 98%), however, the sub-analysis revealed that the workshops increase pharmacovigilance knowledge (MD = 2.68 [95% CI 2.21–3.15]). EI efficacy to stimulate ADR reporting varies over time, workshops increased reporting continuously up to 16 months (OR = 3.14, [95% CI 1.31–7.52]), while for telephone interviews only seen up to 4 months (OR = 6.26, [95% CI 4.03–9.73]). Interestingly, the combined intervention did not increase the ADR reports at the beginning, but after 12 months the ADR reports increased (OR = 3.96, [95% CI 2.27–6.94]). Only one study evaluated ADR reporting attitude among participants and showed a positive effect on attitude after the intervention.

Conclusion: EI improve ADR report and increase pharmacovigilance knowledge. Workshops are the most effective EI to increase ADR reporting.

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International Harmonization of Good Pharmacovigilance Practices: Impact on Brazil

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Introduction: As in other areas of health management, in Pharmacovigilance it is essential to know the results of interventions carried out and evaluate their impact on decision-making. In this regard, the World Health Organization (WHO) has published references to key performance indicators (KPIs) for Pharmacovigilance systems [1,2]. In Brazil, the Pharmacovigilance Office (GFARM) of the Brazilian Health Regulatory Agency (Anvisa) published, in 2020, a Brazilian standard on good pharmacovigilance practices (GVP) that are in line with the world's leading regulatory agencies.

Objective: To evaluate the impact of the change in Brazilian Pharmacovigilance regulations on the demand for post-marketing monitoring of drugs at the Anvisa.

Methods: This is a before-and-after descriptive, retrospective, documentary analysis study. In it, the impact of Resolution RDC 406/20, a new standard for GVP published in July 2020, was evaluated using a set of seven KPIs focused on the internal demands of GFARM/Anvisa. The analyzed period was divided into a before (from July 2019 to June 2020– n_b) and an after (from August 2020 to July 2021– n_a).

Results: In the comparison, it was possible to observe an increase in all the KPIs analyzed: 10.0% for the number of risk communications made ($n_b = 20$; $n_a = 22$), 85.5% for the number of Adverse Drug Reaction (ADR) received ($n_b = 30035$; $n_a = 55723$), 38.0% for the number of non-serious ADR ($n_b = 24257$; $n_a = 33476$), 285.0% for the number of severe ADR ($n_b = 5778$; $n_a = 22247$), 84.1% for the number of notifications of ADR per million inhabitants ($n_b = 142.4$; $n_a = 262.2$), 26.0% for the number of technical processes ($n_b = 998$; $n_a = 1257$), and 9.5% for the number of technical documents generated ($n_b = 483$; $n_a = 529$). Furthermore, when analyzing the number of professionals involved in the demands in each period, a reduction of 10.3% in the average number of GFARM professionals was confirmed ($n_b = 14.5$; $n_a = 13$).

Conclusion: Although there was a reduction in the team, there was an increase in the demand from GFARM/Anvisa with the change in Pharmacovigilance regulations. This may have occurred because of rules in line with the world's leading standards, but also because of the demand of the Covid-19 pandemic. Once implemented, management through KPIs must be ongoing to qualify the management process and the area's decision-making.

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Use of Psychotropic Medications before and after Self-Harm in a Regional Cohort of Older Adults Aged 75+

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Introduction: Non-fatal self-harm (SH) is a major risk factor for late-life suicide. Research on use of psychotropic medications in older adults who self-harmed is sparse.

Objective: To assess psychotropic drug use during the year before and after non-fatal SH in a cohort of Swedish older adults aged 75+.

Methods: Adults aged ≥ 75 years who visited healthcare settings for an episode of SH between 2007 and 2016 were identified from the regional register VEGA. Their data were linked with several national population registers using their unique personal identity number. Redeemed psychotropic drugs were retrieved from the Swedish Prescribed Drug Register and their use was assessed during the year before and after the index SH episode.

Results: There were 659 older adults who self-harmed. Drug overdose was the main method of self-harm. The overall use of psychotropic medications was high; about eight out of ten used at least one psychotropic medication before the index episode, and this proportion remained unchanged during the year that followed the SH episode in both genders and across age groups (75–84/85+).

The most frequently prescribed type of psychotropic medication was hypnotics, used by about six of ten older adults who subsequently self-harmed. Antidepressants were used by four out of ten before SH and increased to 60% after the SH episode. Use of antipsychotics increased after the SH episode. Less than 5% of those who self-harmed used medications to treat substance/alcohol use disorders or mood stabilisers (including lithium).

Conclusion: Our research contributes to inform healthcare professionals on the clinical management of older adults with non-fatal self-harm, in order to enhance the safe use of medicines in both primary and specialised care. The high use of hypnotics, known to be associated with increased risk of SH and suicide should be reviewed and reduced when possible. Since drug poisoning is the main method of self-harm, our findings advocate the need for medication reviews for older adults with depression and/or suicidal behavior, for the consideration of the benefit-risk balance as well as safer medication alternatives when possible.

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Not applicable.

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Interdisciplinary Collaboration for Benefit-Risk Assessment Planning During the Medical Product Lifecycle: Results from a Survey

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Introduction: A Drug Information Association-American Statistical Association joint scientific working group from both the US and EU, established in 2017, has been examining benefit-risk assessment throughout the medical product lifecycle with a focus on developing recommendations for a benefit-assessment plan (BRAP). We have been assessing how such a BRAP proposal fits in with recently published FDA guidelines and how it can be integrated with previously developed Aggregated Safety Assessment Planning tool (ASAP), as well as how the Benefit Risk Assessment Tool Suite (BRATS) may assist the efforts during the drug development process.

Objective: We present here an industry survey on current practice and future plans of various companies as a part of overall efforts in the wider system.

Methods: A survey was conducted using Survey Monkey, from January to May 2020 asking about current state of participant organizations on structured BR assessment (sBRA) practices and areas for future opportunities. Each company was asked to complete a single survey based on the input and understanding across key company representatives involved in benefit-risk assessment.

Results: A total of 26 companies were included in analysis respondent group. About 80% of respondent companies are conducting structured benefit-risk-assessment (sBRAs). About 67% of companies use the FDA Framework. Five companies have created their own ‘internal’ or ‘company framework’ which includes their unique elements. Most (86%) of the responding companies that conduct sBRAs have a dedicated benefit-risk (management) group or designated specialist(s) who lead the sBRA effort. Most (80–85%) companies have document templates, sBRA training and dedicated team meetings in place to assist with sBRA. Most companies use sBRAs for decision-making and discussion with internal safety/benefit-risk committees and regulators. Feedback received from the survey indicates the need for more detailed guidance from guidelines such as ICH M4E on benefit-risk assessment, reasonable expectation for related discussion between regulators and sponsors before regulatory submission, guidance on how and when to use sBRA and/or quantitative approaches to demonstrate the value of a medical product and guidance on how benefit-risk trade-off can inform pre & post-approval strategic decisions.

Conclusion: The results from this survey confirmed a wide use of sBRA by companies involved in research and development of medical products. Qualitative structured frameworks are mostly preferred. Nevertheless, the topic is evolving and so several future opportunities and challenges were identified.

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Not applicable.

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Pharmacovigilance Challenges in Cannabis Medicinal Products—A Narrative Review

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Introduction: Cannabis is considered an illicit drug in most countries; however, it also has pharmacological properties, which has promoted research and debate on its use for therapeutic purposes in the last years. [1] This plant is composed of numerous components, named cannabinoids, with two of them of significant importance: THC (tetrahydrocannabinol), which is mainly responsible for the psychotropic effects of the plant, and CBD (cannabidiol), which appears to have therapeutic properties, despite of action mechanisms of certain cannabinoids remains unclear.[2,3] In Portugal, since 2018, cannabis has been approved as medicine under oral spray solution, whose objective is to mitigate the symptoms of muscle stiffness resulting from multiple sclerosis, among other indications. [4]

Objective: To understand the pharmacological composition of cannabis-based drugs, their adverse effects and to determine the safety profile of these drugs at the therapeutic level.

Methods: Bibliographic search in PubMed® and Google Scholar® databases of scientific articles, with full text in English or Portuguese, whose publication was between 2000 to 2020, using keywords such as

“cannabis”, “CBD”, “THC”, “adverse effects”, “legislation”, “legalization”. A total of 14 articles were selected for analysis. Data selection, extraction, management and extraction were performed by two independent reviewers. Data synthesis were presented as tables, including the information of population of the study, main results, described adverse effects and extract type used.

Results: The results of this review are based on the efficacy and safety of cannabis-based drugs in several chronic pathologies, such as cancer, multiple sclerosis, fibromyalgia and schizophrenia. Most of the products are constituted by THC and CBD extracts, used in different pharmaceutical dosage forms as capsules, spray, inhalers and solutions. Throughout the study, each drug’s adverse effects were described to understand what their benefit/risk ratio through the evaluation of the pharmaceutical form, type of extract, administration, and therapeutic indication. Most frequent described adverse effects were dizziness, drowsiness, nausea, spasticity, mental confusion, dyspnoea and vomiting.

Conclusion: With this review, it was possible to verify that cannabis presented a favourable benefit/risk ratio in the studies analysed, despite of the symptoms described. Those symptoms were not as severe as the symptoms of treated pathologies and cannabis when using drugs with compounds from this plant for the diseases to which its use is approved.

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Occurrence and Characteristics of Linezolid Toxicity in Clinical Practice: Interim Analysis of a Prospective Multicentric Study

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Introduction: Linezolid is a last-resort antibiotic for Gram-positive infections, which can cause adverse drug reactions (ADRs) such as hematological disorders, with associated risk factors including treatment duration, renal impairment at the beginning of the treatment and presence of comorbidities (evaluated by Charlson index (1)). The Buzelé score, which includes an age-adjusted Charlson comorbidity index and treatment duration, has been suggested as a useful tool for clinicians to assess the pre-therapeutic risk of linezolid-related ADRs

(score ≥ 7) (2). Through linezolid levels ($C_{\min}$) > 9 mg/L increase the risk of hematological toxicity (3).

Objective: To assess in clinical practice the rate of ADRs and risk factors associated with their development, and to relate them to $C_{\min}$ values.

Methods: Patients (in- and outpatients) undergoing linezolid therapy were enrolled from 2 hospitals (May 2021–March 2022 [still ongoing study]). They were prospectively followed over time to monitor the development of ADRs. $C_{\min}$ values were measured (4) every 7 days for inpatients and at follow-up visits for outpatients. Causality assessment was performed using the Naranjo probability scale (5).

Results: We report here an interim analysis on 19 patients. They received 600 mg linezolid BID orally or intravenously. 11 patients developed at least 1 ADR (for a total of 23 ADRs) during their treatment (4 patients—1 ADR, 4 patients—2 ADRs, 1 patient—3 ADRs, 2 patients—4 ADRs). 16/23 ADRs were probably associated and 7, possibly associated to linezolid based on Naranjo scores. 4 patients stopped their treatment due to toxicity (1 paresthesia, 3 medullar toxicities—including thrombocytopenia). The Table shows the most frequent and serious ADRs, with values of parameters identified as possible risk factors. Median treatment duration was longer and $C_{\min}$ higher (except for paresthesia) for patients with an ADR (although the difference was not always significant due to the small number of patients). Renal function tended to be reduced in patients experiencing metallic taste or blood counts abnormalities. The median Buzel score was ≥ 7 for all patients.

Table: Most Frequent ADRs and Potential Risk Factors

ADR (number)	Treatment duration (days) Median (min-max)	$C_{\min}$ (mg/L) Median (min-max)	GFR (ml/min) Median (min-max)	Buzel score Median (min-max)
No ADR (8 patients)	7.5 (4-19)	4.15 (1-10.1)	75 (41-115)	5 (4-9)
Metallic taste (3)	28 (15-53)	12.3 (10.6-34)	44 (10-78)	8 (10-19)
GI disorders (7)	28 (8-121) *	10.6 (4.9-34)	78 (10-118)	8 (1-19)
Anemia (4)	22.5 (10-28)	13.8 (7.7-25.4)	38 (23-118)	7 (4-8)
Thrombocytopenia (5)	28 (23-53) *	12.4 (10.6-27.4) *	44 (15-78)	8 (4-11)
Paresthesia (1)	109	4.9	72	17

*Pvalue < 0.05 with Mann-Whitney U test

Conclusion: These preliminary data suggest that ADRs are much frequent in clinical practice than reported in the SmPC (6) and occur more often in patients with long treatment duration and high $C_{\min}$. The analysis of the full sample (100 patients) will help to confirm these trends as well as the potential interest of therapeutic drug monitoring and follow-up of blood counts and renal function to help preventing ADRs or detecting at-risk patients.

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Developing Practical Pharmacovigilance Skills at a Distance: Description and Evaluation of UMC's Instructor-Led Online Learning

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Introduction: Uppsala Monitoring Centre (UMC) has been offering onsite pharmacovigilance (PV) courses since 1993 and in 2017 also launched online theoretical self-paced courses to increase global access to PV training [1]. In response to requests from the self-paced courses and increased PV needs due to the Covid-19 pandemic, the UMC developed instructor-led online training to assist national and regional PV centre staff to advance from theory to practice in various topics including signal detection and causality assessment.

Objective: To deliver instructor-led online courses focusing on applying concepts of signal detection and causality assessment followed by evaluation of their relevance.

Methods: Courses were delivered using Matrix Learning Management System in English and Spanish [2]. These were organized as instructor-led two-weeks of part-time study. National and regional PV centre staff that had completed the required theoretical UMC online courses could participate. The courses consisted of short videos and quizzes, individual assignments, and live discussions. All course elements except the discussion meetings were asynchronous. Individual assignments were the core with personal feedback from instructors to help reach the expected standard. Each course centred around analysis of a drug-ADR combination from VigiBase, the WHO global database of reported potential side effects of medicinal products [3]. The analytical process followed accepted structured approaches and used relevant functionalities in VigiLyze [4] and Bradford Hill criteria [5], resources which participants could re-apply to analysis of their national data analyses after the course. Evaluation of the course by the participants followed the Kirkpatrick evaluation model [6].

Results: Three courses focusing on signal detection and causality assessment were delivered during 2021. Fifty-nine participants from 35 countries completed either the English courses or the Spanish course. The course quality was rated as excellent by 94% of participants. The responses from all participants showed that the instructor-led parts, i.e., the individual assignments where each person needed to apply the theory and obtain personal guidance during the learning process, provided high educational value. The same applied to live sessions that provided an opportunity for participants and instructors to discuss the assignments, focusing on difficulties and possible conclusions (Table 1). Furthermore, the individual asynchronous tasks allowed more flexibility compared to scheduled group workshops.

Table 1. Evaluation by the participants

Evaluation Questions	Yes, to a great extent	Yes, to some extent	No
Did the individual assignments aid your learning?*			
English course 1 (Total: 21*)	18	3	0
English course 2 (Total: 22)	21	1	0
Spanish course (Total: 13)	11	2	0
Did the live session aid your learning?*	Yes, to a great extent	Yes, to some extent	No
English course 1 (Total: 22)	16	6	0
English course 2 (Total: 21*)	16	5	0
Spanish course (Total: 13)	13	0	0

*Both questions focus on the case series assessment part during the course.

*One person skipped the question.

*A person missed the meeting and could not provide an opinion.

Conclusion: UMC instructor-led online courses with emphasis on PV analysis skills development have provided a valuable educational alternative to onsite workshop-based courses. They demonstrate new advantages from the educational perspective, the flexibility aspect and availability geographically and linguistically.

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An Exceptional DRESS syndrome to Potaba with Positive Patch Test

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Introduction: Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome) is a hypersensitivity syndrome, defined as drug reaction with rash, eosinophilia, and systemic symptoms, mostly related to anticonvulsant drugs and also to antibiotics or allopurinol. Potassium-Paraaminobenzoic acid (Potaba) is a potassium salt used as a systemic treatment for fibrotic skin disease. DRESS syndrome to Potaba has exceptionally been reported.

Objective: We described a case of a DRESS syndrome following the administration of Potaba, colchicine, amoxicilline and paracetamol.

Methods: This case was notified to the National Centre of Pharmacovigilance of Tunis and was analyzed according to the updated French method of imputability

Results: A 44-year-old man was prescribed an oral therapy with Potaba-Glenwood® 12 g daily and Colchicine 1mg daily for Peyronie's disease. Four weeks later he took amoxicilline and paracetamol for angina.

Three days later, he was admitted to the hospital with fever, generalized rash and facial edema.

On physical examination, the patient had fever at 39°C, a generalized maculopapular exanthema. Laboratory tests revealed eosinophilia at 1297/micro L. Alanine aminotransferase level was 474 U/L (normal range, 40 U/L) and the aspartate aminotransferase level was 145 U/L (normal range, 45 U/L).

The infectious investigations were all negative and the abdominal ultrasound was normal.

All the medications were discontinued. The skin lesions improved within 14 days and laboratory tests returned to normal levels in 4 weeks. The skin biopsy showed spongiform dermatitis compatible with drug origin. Based on the RegiSCAR study group, the diagnosis of drug induced Dress Syndrome was confirmed with a score of 5 (probable).

The case was notified to the pharmacovigilance and the drug imputability analysis concluded to the probable responsibility of Potaba or Colchicine with an intrinsic imputation score of 12 compared with the other associated drugs.

One year later, patch tests were performed to potaba, colchicine, amoxicilline and paracetamol.

A strongly positive reaction to Potaba was observed on 48 hours (++) and 72 hours (+++) with multiple papulovesicles.

Conclusion: Our case was a complete and typical clinical, histologic, and laboratory findings case of Dress syndrome to Potaba. Skin tests were helpful to confirm the drug origin in our patient with polytherapy.

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Has Piperine a Role to Play Against Breast Cancer?

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Introduction: Spices were introduced in ancient times to improve the smell, taste and color of food, and some of them have made a huge contribution to cancer prevention and treatment (1). Breast cancer is one of the most common cancers in women with four principal therapies surgery, chemotherapy, radiotherapy, and hormonal therapy. Although there has been a multidrug resistance, studies are being developed for new chemotherapeutic agents (2). Piperine, a pungent alkaloid, has many therapeutic actions, such as anti-cancer activities and has been reported to inhibit the proliferation and survival of many types of cancer cells through its influence on the activation of apoptotic signaling and inhibition of cell cycle progression (3). Piperine plays a role in different enzymes and transcription factors, inhibiting invasion, metastasis, and angiogenesis (3). Because it is a potent inhibitor of p-glycoprotein, it reverses the resistance of cancer cells, acting as an enabler for chemotherapy (3). Preclinical research indicated that PP has the potential to become an anti-cancer agent (4).

Objective: Highlight the state-of-the-art of the potential effect of piperine in the prevention of breast cancer.

Methods: This literature review was performed on “PubMed” and “Science Direct”, using as keywords “Piperine”, “Breast Cancer”, and “Chemotherapy”, which led us to choose eleven full articles published between 2011 and 2020.

Results: Studies on piperine concerning breast cancer have discovered the formation of reactive oxygen species (ROS) in various types of cancer cells (1,3,5). ROS formation leads to depolarization of

membrane potential, releasing cytochrome c, activating caspases, and inducing apoptosis (1). At the molecular level, piperine can influence many effector proteins engaged in the apoptotic process. It can activate both intrinsic and extrinsic pathways of apoptosis (3) and inhibit tumor growth by inducing cell apoptosis and cell cycle blockage (6). Piperine also induced apoptosis in triple-negative breast cancer cells via the mitochondrial pathway (1). Piperine has the potential for inhibiting cancer stem cells (CSCs) self-renewal (3). Another study investigated the synergy effect between piperine and piperlongumine, proving these two natural alkaloids show better anticancer potential (4).

Conclusion: In short, piperine seems to have potential effectiveness in treating breast cancer. The role in apoptotic processes is confirmed in different studies highlighting the potential for breast cancer treatment. The synergism between piperine and piperlongumine shows a more effective approach than monotherapy.

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Is There an Important Role Played by Thiamine (Vit B1) in Alzheimer's Disease?

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Introduction: Alzheimer's is a neurodegenerative disease that mainly affects the elderly inducing gradual cognitive deficits and progressive amnesic dementia (1). The first and perhaps the best example of the interaction between nutrition and dementia is related to thiamine, an essential micronutrient playing a major role in energy metabolism (2). Thiamine-dependent enzymes are important components in glucose metabolism (3) that are reduced in the brains of Alzheimer's patients who also have thiamine deficiency (4). Therefore, its decline may be responsible for reducing this metabolism and thus reducing the cognitive deficits associated with Alzheimer's (4).

Objective: To understand the relationship, and the effect, between thiamine deficiency and Alzheimer's disease, as both are associated

with cognitive deficits and reductions in cerebral glucose metabolism and what are their possible causes.

Methods: This literature review was accomplished on the Pubmed and ScienceDirect during the period between 2011 to 2018, using the keywords “thiamine”, “Alzheimer's disease”, “cognitive deficits”, and “thiamine deficiency” for inclusion criteria. Ten full papers were considered for this review.

Results: Several studies have been conducted to analyze the possibility of delaying this pathology with thiamine enrichment (2,4,5). It has been shown that the effects of thiamine administered orally had a mild beneficial effect on the disease (4), but if it is long term, there are no effects recorded in slowing their progression. Despite improving cognitive function (3), oral thiamine supplementation did not lead to substantial changes in brain thiamine (4). On the other hand, if treatment is given early enough, deficits related to thiamine deficiency can be reversed (4). Thiamine deficiency depresses glucose utilization by the brain. However, with the administration of thiamine, there is an induction of an improvement in the capacity to use glucose, the decrease in neuritic plaques, phosphorylation of TAU protein and the reversal of memory deficit (1).

Conclusion: Further studies are needed to determine the benefits of using parenteral thiamine as a possible therapy for treating Alzheimer's disease. In short, a diet rich in nutrients that modulate degenerative processes with appropriate pharmacological therapy can increase well-being and health through a possible delay of Alzheimer's in the patient or even as an adjunct in the prevention of this pathology.

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A System for Reporting Adverse Drug Reactions to Emergency: Pilot Project

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Introduction: The Emergency Room (ER) represents a privileged observatory of Adverse Drug Reactions (ADRs) in the area, bearing in mind however that it is difficult to estimate the actual quantity of ADRs since not all patients with adverse reactions access an ER. From the currently available national and international published

data, it emerges that there is an objective difficulty in obtaining effective reporting of ADRs in the ER [1-3].

Objective: Description of the frequency and characteristics of the ADRs that led to access to the ER and detection of the drugs most involved through an online system.

Methods: We conducted an experimental project of ADRs reported to the Italian Medicines Agency through the National Pharmacovigilance Network in the period from April 2021 to March 2022. The data and ADRs were extrapolated from the corporate IT platform PS Web, were analyzed in collaboration with the working group and included in the National Pharmacovigilance Network. All clinical events and types of ADR, diagnoses and symptoms were analyzed and grouped by SOC (System Organ Class) and PT (Preferred Term), subsequently entered a database. All ADRs that led to hospitalization, an observation period of at least 4 hours (starting from the first PS visit and not from triage assignment) and which led to at least one parenteral drug administration were considered as “serious”. For all the reports made, the consequences of the adverse event were reported, as well as the outcome, and follow-up. Descriptive statistics were performed through elaborations and formulas with Microsoft Excel.

Results: The number of reactions entered by our healthcare company in the period considered is equal to 214; of these 199 (93%) were intercepted thanks to the project. The results showed: 73,1% referred to serious ADRs (n = 141). Most of these serious adverse reactions were caused by drugs belonging to the ATC M (22%), J (40%) and N (20%) and other class drugs (17%) groups. Of the serious ADRs, the causal link was evaluated with the Naranjo algorithm. The relationship between serious adverse reactions, demographics, patient gender and corporate health expenditure of ADRs was also explored.

Conclusion: With this project and the creation of a direct relationship between pharmacist and doctor of the ER, it has made it possible to find useful information for the purpose of reporting, significantly improving the quality of the reports.

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What's up in Celiac Disease Treatment?

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Introduction: Celiac disease is a chronic disease that involves the dysregulation of the immune system associated with inflammation of the small intestine on exposure to an environmental factor: the gluten protein, in individuals with a specific genetic background (1,2,3). The clinical presentation of the disease varies broadly and may include an array of intestinal and extraintestinal manifestations (1). It is considered a multifactorial disease with a broad spectrum of symptoms.

The effective treatment for celiac disease is a gluten-free diet which is restrictive, difficult to assure and nutritionally weak (4).

Objective: The goal was to state of the art and highlight the research on new therapeutic alternatives, pharmacological ones, that promote greater adherence and effectiveness in Celiac Disease.

Methods: This literature review was performed through scientific databases such as Pubmed and ScienceDirect. In this review were included 10 full papers. Articles were selected out of the last decade, using the following keywords Celiac Disease; Novel Treatments; Pharmacological Treatments, Intraluminal Therapies, Gluten-sequestering polymers.

Results: Several new promising pharmacological therapies have been discovered and developed for the treatment of this disease, namely, therapies based on the modification of gluten; modulation of intestinal permeability (1,3,6,7); modulation of the adaptive immune response (1); Intraluminal therapies; Immunomodulation and gluten tolerance (5). However, our focus will be on Intraluminal Therapies: Gluten-sequestering polymers (BL-7010) (5) and antibodies that neutralize gluten or the use of polyphenols to protect against Celiac disease (7). At this point, questions remain to be answered. It is not yet clear why only 5 to 10% of predisposing HLA patients will develop gluten-specific CD4+ T cells and tissue damage (2).

Conclusion: Steps on new treatments are on the road to be available for the Celiac disease patients, improving is quality of life. As the development of a novel medication for Celiac disease is still under preclinical and clinical phases, the conventional dietary treatment will hold its place for the time being. As an endpoint, in the long run, it is expected that novel therapies provide the possibility to include gluten in Celiac disease patients' diets.

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Current Pharmacovigilance Outsourcing Practices in Arab Countries

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Introduction: Outsourcing in Pharmacovigilance has grown in the last decade. However, standards and references are lacking in this area, both for initiating and maintaining a long term outsource relationship (1). The worldwide pharmacovigilance outsourcing market is anticipated to surpass US \$7.5 billion by 2024, according to the latest research available at Market Study Report LLC, the report provides extensive data on market share, growth, trends and forecasts for the period 2018–2024 (2). Pharmacovigilance has received much attention in Arab countries recently due to the development of new regulations. However, there are differences in the progression of pharmacovigilance systems by regulatory agencies in these countries because only some can meet the requirements for conducting pharmacovigilance activities.

Objective: The aim of this research was to provide an overview of the current pharmacovigilance outsourcing regulations in Arab countries. As well, recommending a draft guideline for good PV outsourcing practices that can be used as a starting point for the preparation of pharmacovigilance outsourcing process standard.

Methods: The study was an observational study conducted during the period of from 1st of April 2020 to 31st July 2020 on twenty-two countries which are considered members of Arab league. Regulatory Authorities websites were used as source of information regarding the Pharmacovigilance guidelines. Several documents were reviewed including the Arab guideline on good pharmacovigilance practices (GVP), version 2, guidelines for countries that have their discrete guidelines (e.g., Saudi Arabia, United Arab Emirates (UAE), Algeria, Tunisia, Iraq, Oman and Morocco). Additionally, a list of questions was designed and then approaching different Arab health authorities with questions regarding their current guidelines about Pharmacovigilance outsourcing.

Results: Of the twenty-two Arab countries, eleven countries have pharmacovigilance guidelines, of which eight countries have pharmacovigilance guidelines with outsourcing sections. The Arab League guideline and Saudi Food and Drug Authority Guideline on good pharmacovigilance practices contain seven modules with outsourcing sections mentioned while other Arab guidelines for Iraq, Algeria and Tunisia contain only one module with outsourcing section mentioned.

Conclusion: Based on our results and conclusions from other articles, we concluded the need for a unified guideline for Pharmacovigilance outsourcing not only in Arab countries but also in other parts of the world.

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Outsourcing of Pharmacovigilance Activities for Pharmaceutical Industries in Brazil

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Introduction: With the Brazilian Pharmacovigilance legislation update in 2020, companies have increased pharmacovigilance activities outsourcing, pursuing better compliance with growing work demands in the department [1]. Several factors lead companies to outsource Pharmacovigilance activities such as cost savings, lack of internal resources, and flexibility to deal with high workloads [2, 3]. A research was conducted to demonstrate data on outsourcing of Pharmacovigilance services in Brazil.

Objective: To present data on the outsourcing of Pharmacovigilance activities by pharmaceutical industries in Brazil

Methods: A survey with 53 pharmaceutical companies operating in Brazil was conducted in April 2022 to investigate data on outsourcing of Pharmacovigilance activities. The research was performed through an online questionnaire sent to companies associated with an union representing pharmaceutical industries in São Paulo (Brazil). The questionnaire included 9 questions, referring to data on outsourced Pharmacovigilance activities and important requirements when selecting Pharmacovigilance service providers. To protect the confidentiality of the survey data, names of companies and respondents' contact details were not accessed.

Results: Results showed that of all participant companies, 70% outsource some or all of the Pharmacovigilance activities, with the most outsourced activities being case processing (63%; 19 of 30 respondents), literature screening (53%; 16 of 30 respondents) and regulatory submissions of reports (23%; 7 of 30 respondents). It was observed that 60% of respondents have outsourced Pharmacovigilance activities for more than 5 years. For companies that do not outsource activities (n = 16), the main reasons being work demand are absorbed internally (36%), low volume of activities (29%), and company policy (21%). Companies outsource Pharmacovigilance activities especially to optimize resources for the internal team to work on strategic actions (30%; 9 of 30) and due to increased work volume (23%; 7 of 30). Amongst the important requirements when selecting a vendor are expertise in 67% (20 of 30), compliance in 30% (9 of 30) and quality in 23% (7 of 30). Good communication, flexibility and price were also mentioned. The main advantage observed (60% of respondents) when outsourcing Pharmacovigilance activities was the increased availability of the Pharmacovigilance team for strategic activities (signal detection and benefit-risk analysis).

Conclusion: Outsourcing Pharmacovigilance activities is shown to be a beneficial alternative to the pharmaceutical industries in Brazil, demonstrating reduction of the routine activities burden for the team, thus allowing Marketing Authorisation Holders to focus on products safety profile analysis and risk management, directly impacting patient well-being and safety.

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Safety of Antiangiogenic Drugs in Pediatric Patients with Solid Tumors: A Systematic Review and Meta-analysis

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Introduction: Cancer is a clinical condition which can benefit from anti-angiogenic drugs (AADs). Given the low prevalence and the heterogeneity of childhood cancers, information about safety of these drugs in pediatric patients is only partially assessed.

Objective: The objective of this study is to evaluate the safety of AADs in pediatric patients with solid tumors.

Methods: Using PRISMA guidelines we conducted a systematic review of the literature, and a protocol was registered in PROSPERO website. Clinical trials and observational studies reporting information on the severity/seriousness of adverse events in pediatric patients with solid tumors in treatment with AADs were searched in PubMed, ISI Web of Science and clinicaltrials.gov. Two authors screened all titles and abstracts of the references retrieved. For each included study, quality will be assessed (Risk of Bias tool, MINORS tool or New-Ottawa scale tool). Subgroup analysis will be performed by type AAD, combination regimens and type of tumors.

Results: Fifty-six studies (forty-nine published articles and seven clinical studies with published results) were retrieved. Most part were phase I trials (22 out of 56), and only five observational studies were found. Twenty studies reported the number of adverse events of antiangiogenic drugs used as monotherapy, twenty-eight in combination with standard chemotherapy and eight in combination with different regimens (e.g., target therapies). Forty-five studies were included for the evaluation of severity, while twenty-six for the evaluation of seriousness of adverse events. The quality assessment of the included studies is ongoing.

Conclusion: The high number of studies included in this systematic review will allow the assessment of the incidence of adverse events and will clarify the safety of AAD drugs in pediatric patients.

References/Further Sources of Information

Not applicable.

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Pharmacovigilance in Hospital: Monitoring Reports of Adverse Drugs and Vaccines Reactions Collected in an Active Pharmacovigilance Project

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Introduction: By using pharmacist monitors, active pharmacovigilance projects make possible to detect many adverse drugs and vaccines reactions (ADRs) that otherwise would go unreported and to

improve the quality of the reports entered in the Italian National Pharmacovigilance Network [1]. In our healthcare facility, the pharmacist was responsible for catalysing the process of reporting suspected ADRs by doctors and healthcare workers operating in Emergency and Acceptance Department. Since such adverse drugs and vaccines reactions could potentially have caused the patient to access the emergency department, they were responsible for a part of the requests in charge of the emergency system.

Objective: The aim of this paper is to analyse the reports of adverse drugs and vaccines reactions (ADRs) that caused patients to enter the emergency department of our facility during the last 10 months.

Methods: Suspected ADRs were identified by the analysis of emergency room reports written by clinicians at Careggi University Hospital during the period from May 2021 to February 2022. ADRs reports were loaded into the Italian National Pharmacovigilance Network and were subsequently analysed according to the reported drug/vaccine, the Anatomical Therapeutic Chemical Classification System (ATC) class and the severity of the reaction, as well as stratified according to patients' sex and age.

Results: The total number of ADRs reports collected during the analysed period and entered in the Pharmacovigilance Network was 76, of which 38 (50%) related to drugs, 35 (46%) to vaccines used for immunisation against Sars-CoV-2, and 3 (4%) to contrast media for diagnostic use. In terms of severity, only 17 ADRs were classified as serious (22,4 %). Most ADRs were detected in female patients and in adults aged between 30 and 60 years.

Conclusion: The active pharmacovigilance project called FARO enabled to intercept a good number of ADRs causing patients to access the emergency department, increasing the quantity and quality of reports entered into the Italian National Pharmacovigilance Network. In the period May 2021-February 2022, almost half of the intercepted ADRs concerned vaccines for immunisation against SARS-CoV-2. However, ADRs from drugs remained prevalent, and concerned molecules belonging to various ATC classes, in particular the class of drugs affecting the nervous and cardiovascular systems. The majority of ADRs were classified as non-serious (77.6%), indicating that many emergency room admissions were inappropriate. This highlights the need of strengthening territorial medicine and continuity of care services, which should ensure adequate care of patients with mild problems.

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Drug Use in Patients before and after Starting Chronic Dialysis, Lazio Regional Dialysis and Transplant Registry, 2008-2020

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Introduction: Dialytic patients present a complex clinical picture and are considered particularly fragile. The Lazio Regional Dialysis and Transplant Registry (RRDTL) offers the opportunity to analyse drug use in a large cohort of dialytic patients, before starting dialysis and afterwards, with a focus on specific drugs used in these patients (1). The present analysis is part of a study co-funded by the Italian

Medicines Agency in the context of the regional Pharmacovigilance call 2012–2013–2014 (ETELDIA project).

Objective: Describing the use of 25 drugs prescribed to patients with renal failure before and after starting chronic dialysis.

Methods: From RRDTL, patients initiating dialysis between 2008–2020 and in charge of a dialysis centre were enrolled (day of dialysis initiation = index date). Cases with renal transplantation before the index date, those who stopped dialysis within three months after the index date, and those who died in the first year after the index date were excluded. The drugs of interest are the 25 drugs registered in the RRDTL (1). For each patient information on drug use in the year before and after the index date was retrieved from the regional drug claims register. The proportion of patients using any of the 25 drugs in the year before and after the index date was calculated.

Results: A cohort of 10,334 dialytic patients was obtained. In the year before dialysis, more than 50% of subjects prescribed with drugs for the cardiovascular system (diuretics, ACEIs/ARBs, Ca-antagonists), anti-infectives, and drugs for blood and blood forming organs (anti-thrombotics, erythropoietins). After initiating dialysis, a considerable increase in the number of drugs was observed respect to the year before (mean number increased significantly from 8.5 (95% CI 8.4–8.5) to 10.3 (95% CI 10.3–10.4)). The most evident increases in proportions of drug use after initiating dialysis were observed for vitamin B (from 0.05 to 0.9%), anti-parathyroid agents (cinacalcet from 0.6 to 7.9%, paricalcitol from 6.0 to 29.3%, etelcalcetide from 0 to 2.5%, authorised in 2017), iron preparations (from 29.6 to 65.2%), treatment of hyperkalemia and hyperphosphatemia (from 26.8 to 58.4%), calcium (from 13.4 to 23.4%) and erythropoietins (from 53.6 to 82.6%).

Conclusion: Starting dialysis is associated with an increase in drug consumption and often requests specific drug therapy. In the ETELDIA project we will further investigate drug patterns and perform a comparative effectiveness and safety study of etelcalcetide and cinacalcet. This will provide useful information to health policies.

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ICSR and Pharmacovigilance Data: Challenges for Pharmaceutical Companies

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Introduction: Current Pharmacovigilance (PV) legislation asks to pharmaceutical companies to collect every day PV data in a structured format and handling them following a defined workflow in secure and validated environment. The number of data to be collected is ever greater and requirements for its handling are increasingly demanding. PV database suppliers are evolving more and more to make their products capable, safe and in compliance with such requirements. Data should be structured in a way it can be analyzable in aggregate reports and signal detection activities by the company itself and competent authorities. The company must therefore have the ability to keep up with requirements, selecting tools and suppliers that best meet its internal needs but, at the same time, keep up with technological and regulatory developments.

Among biggest challenges facing every pharmacovigilance department in this period there are *data format*, *data location* and *data migration*.

Data format: to be compliant to ICHE2B (R3) and IDMP standards

As of 30 June 2022, use of the ISO Individual Case Safety Report (ICSR) standard based on the ICH E2B (R3) modalities will be mandatory for ICSR reporting to/from EudraVigilance [1, 2]. Moreover, the ISO standard terminology for pharmaceutical forms and route of administration will become mandatory at the same time as a further step toward standardization in all ISO countries of structure and terminology of marketed medicinal products [3].

Data location: cloud computing services

GxP companies are subjected to extensive regulatory oversight and are required to analyze all risks thoroughly before adopting any new technology. Nevertheless, industries are compelled to streamline their business process and reduce costs. One way to optimize complex processes has been the adoption of cloud computing services. Potential benefits of this technology include for example cost savings, flexibility, multi-redundant sites to support business continuity and disaster recovery. On the other side, some risks may exist, e.g. lack of oversight on the software maintenance and data center governance, and cybersecurity risks.

Data migration for M&A and safety upgrades

Pharmaceutical companies are moving towards mergers and acquisition for potential business expansion in various countries. This implies large amount of data (PV data included) needs to be transferred from one company to another. Data migration activity becomes a challenge-based approach with many iterative phases. Main factors can lead to migration failure, e.g. inappropriate data migration planning, or inadequate data checking & validation.

Objective: Not applicable.

Methods: Not applicable.

Results: Not applicable.

Conclusion: Not applicable.

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Real-World Efficacy and Safety of Off-Label Use of Immune Checkpoint Inhibitors (ICI) in Cancer: A Retrospective Cohort Study in Qatar

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Introduction: Immunotherapy has been an attractive choice for cancer treatment based on an increased understanding of T cell biology and tumor immunology (1). The occurrence of Off-label prescribing in Oncology is higher than other disciplines for many

reasons, such as difficulty to conduct studies, cancer have variety of types and stages, protocol combinations and lines of treatment (2-3). Off-label use of Immune Checkpoint Inhibitors (ICI) has been inevitable since their first FDA approval a decade ago. The evaluation of efficacy and safety of ICI in off-label indications is lacking. In this study, we will address this gap in literature.

Objective: Evaluate the implications of off-label use of ICIs in terms of efficacy and safety in real-world practice. Primary objective is to evaluate efficacy: Complete response (CR), Partial response (PR), Progression disease (PD), Stable disease (SD), and safety: number of immune-related adverse events (irAEs) (Quantitative) and severity of irAEs (Qualitative).

Methods: Retrospective cohort study. Our population included all adult patients who received one or more of the ICIs (Atezolizumab, Avelumab, Durvalumab, Ipilimumab, Nivolumab, Pembrolizumab) without an approved indication between 01/01/2017 and 30/06/2021. Data were collected through electronic medical records, pooled in data collection sheet, and analyzed using SPSS.

Results: Over the study period, 836 cycles of ICI were evaluated for 103 patients. The most frequent identified indications were colorectal cancer (12.6%), hepatocellular carcinoma (12.6%) and breast cancer (11.7%). Pembrolizumab was the most prescribed ICI with (47.6%). Clinical response reported as 4 patients CR (3.88%), 14 patients PR (13.59%), 13 patients SD (12.62%); 57 patients progressed (55.33%). Safety data showed that 35 patients experienced 38 irAEs, of which 19 patients (48.7%) were treated with Nivolumab. Severity of irAEs were as follows; 19 severe (50%), 17 moderate (44.74%), 2 mild (5.26%). The most common irAEs were hepatic toxicities (23.68%), thyroid toxicities (15.78%) and hematological toxicities (10.53%).

Conclusion: ICI might be efficacious in more indications yet to be approved in cancer management. However, the use of ICI out of the approved indications might not be as safe considering increased potential of irAEs. Further studies on extended use of ICI are needed.

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Pharmacovigilance Funding Landscape in Africa—A Survey

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Introduction: The growth of pharmacovigilance (PV) in resource limited settings (RLS) in Africa has been slow. It is yet to achieve the maturity required to ensure safety of medicines deployed in the setting. One of the key factors highlighted as hindering this growth is the inadequacy of funding [1,2].

Objective: This paper presents the result of a survey assessing the prevailing pharmacovigilance funding landscape in African countries, including factors hindering and measures likely to improve sustainable funding.

Methods: A standardized questionnaire was developed in English with French and Portuguese translations and effectively distributed to 35 African countries during the period July 2020 to October 2021. The information sought related to features and operation of the PV system, sources of and factors impacting on PV funding. Suggestions were solicited in free text format on hindrances and measures to improve sustainable PV financing. The information was requested from the Head of the National Pharmacovigilance Centres (NPC). The data collected were handled qualitatively, analysed and presented descriptively. Values were expressed as range and median. A thematic synthesis was carried out to aggregate the free text responses.

Results: The questionnaire was completed by NPCs in 24 African countries (response rate of 68.6%); with National Medicines Regulatory Agency (NMRA) and NPC in 22/24 (91.7%) and 20/24 (83.3%) countries respectively. Again, 20/24 (83.3%) countries are in the WHO Programme for International Monitoring (PIDM). Number of staff/NPC was 5 with staff ratio NPC:NMRA of 1:11. PV activities were funded mainly by Governments and donor agencies. The mode of support was by cash grants, technical and other logistics channelled mainly through the NMRA and Public Health Programmes (PHP). Few countries 9/23 (39.1%) had a clear budget line within government budgets and 85.7% had their funding linked to the NMRA.

Factors identified as hindering PV funding included—lack of awareness of the importance of PV and poor prioritisation in the national scheme, unfavourable legal environment, non-generation of revenue, poor budgetary allocation, diversion of funds etc. Measures suggested to improve PV financing include adequate prioritisation and political goodwill, improved legal environment with increased annual budgetary allocation, revenue generating activities etc.

Conclusion: In all, funding of pharmacovigilance in Africa is inadequate, seemingly arbitrary, lacking legislative provisions and tied to the NMRA with significant donor funding channelled through the NMRA and PHP. There is need for PV financing to be backed by statute which will ensure sustainable funding and implementation of measures likely to improve funding

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Characterization of Factors Associated with Long-Term Prescription Opioid Use in Support of Risk Mitigation Strategies in the Non-Cancer Population

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Introduction: Long-term prescription opioid use in the non-cancer population is highly controversial as it is a known risk factor for opioid-related harms. The identification of modifiable and non-modifiable factors associated with long-term use may inform risk mitigation strategies when initiating or continuing treatment.

Objective: In patients without cancer who initiate a prescription opioid, to estimate the incidence of progressing to long-term use and to identify associated factors.

Methods: A systematic review and meta-analysis were conducted. Medline and Embase electronic databases were searched from 01 January 2009 to 15 January 2020. Additional sources were sought through pragmatic searches. Observational studies on long-term prescription opioid use in the non-cancer population of all ages, community-dwelling or institutionalized, and reporting a definition for long-term use of prescription opioids (LTPO), incidence estimates and/or associated factors were eligible. Two authors independently screened titles and abstracts, with conflicts resolved by a third author. Data were extracted by one author and validated by a second author. Methodological quality of individual studies was assessed using the Joanna Briggs Institute critical appraisal tools. For potential risk factors investigated in at least two studies, a meta-analysis of adjusted measures of association was conducted using a random effect model, and expressed as an odds ratio (OR) with corresponding 95% confidence interval (CI). Statistical heterogeneity of estimates was assessed using the I^2 statistics.

Results: A total of 64 observational studies including from 96 to 1,353,902 opioid users without cancer were included in the review. Among prescription opioid users, the incidence of progressing to long-term use ranged from 0.2 to 703.4 per 10,000 person-years (median: 41.6), with the highest incidence found in the post-surgical setting. Factors associated with long-term use were: obesity (OR 1.32; 95% CI 1.23–1.42), tobacco use (1.60; 1.42–1.80), anxiety (1.36; 1.14–1.61) and prescription for “any pain” (1.64; 1.39–1.95), with no evidence of statistical heterogeneity across studies. In a subgroup analysis based on sociodemographic characteristics, LTPO definition and quality assessment, the following associated factors were also found: male sex, concomitant psychiatric disorder, pre-existing substance use disorder and back pain indication.

Conclusion: This review demonstrated that long-term prescription opioid use is frequent, especially in post-surgical patients. Tangible

risk factors have been identified, some of which are actionable at the point of care.

References/Further Sources of Information

Not applicable.

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Post-Marketing Safety of Innovative Drugs: Analysis of Pembrolizumab Related ADRs in a University Hospital

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Introduction: Innovative drugs represent the most advanced pharmacological treatment available for patients since these drugs are characterised by a benefit and a therapeutic need compared to other marketed medicines [1]. In the context of innovative drugs, Pembrolizumab increased its authorised innovative indications during the years 2020–2021. Pembrolizumab is subject to additional monitoring in order to increase and improve the post-marketing vigilance phase. Therefore, pharmacovigilance [2] is fundamental for detecting any changes in the efficacy/safety balance since in the real world drugs are used in a larger number of patients compared to clinical trials.

Objective: The aim of this work is to assess the safety of treatment with Pembrolizumab, in a high-level hospital, through the analysis of suspected ADR (Adverse Drug Reaction) reports received by the local pharmacovigilance office.

Methods: The list of innovative therapeutic indications of Pembrolizumab for the years 2020–2021 was consulted on official sources [4]. For the mentioned period, all ADRs entered in the Italian National Pharmacovigilance Network (RNF) were analysed. By using company software, it was also possible to trace the total number of patients enrolled in chemotherapy protocols including Pembrolizumab with both innovative and non-innovative indications.

Results: Because of the expansion of Pembrolizumab innovative therapeutic indications, the number of patients treated in our University Hospital increased from 193 in 2020 to 317 in 2021. The 14 ADRs reports about Pembrolizumab (7 of which related to 2020 and 7 to 2021) involved patients with an average age of 68 years; 79% of patients were male, whereas 21% were female. In addition, 4 of reported ADRs were classified as non-serious (29%) and 10 as serious (71%). The serious ADRs resulted in the hospitalization of patients and, in one case, in the patient's death. In contrast, the 4 non-serious ADRs recovered and completely resolved.

Conclusion: The present analysis showed that the number of Pembrolizumab related ADRs remained constant over the period analysed even though the number of patients treated with Pembrolizumab increased. Therefore, the drug safety profile has maintained unchanged despite the expansion of innovative therapeutic indications and the consequent increase in Pembrolizumab-based treatments.

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Analysis of the Reports of Suspected Adverse Drugs Reactions of 2021 in a Tuscan University Hospital

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Introduction: In an efficient pharmacovigilance system (FV) [1], reports of suspected adverse drugs reactions (ADRs) play a fundamental role in highly specialized hospitals: indeed, in these structures, the most innovative and recently marketed drugs are prescribed, needing an implementation of post-marketing efficacy and safety data.

Objective: The purpose of this work is to analyse reports of suspected ADRs in a University Hospital, collected by the Italian National Pharmacovigilance Network (RNF) [2], in 2021 according to the following criteria: the Anatomical Therapeutic Chemical (ATC) classification, the severity of ADRs, patient's sex and reporter's qualification.

Methods: During the period under study, all ADRs forms collected by the Qualified Person for FV were analysed through an Excel database including the following information: RNF code, date of reporting, date of ADR onset, patient's sex, severity of ADR, outcome of ADR, suspected and/or concomitant drug and respective therapeutic indications, route of administration, ADR information and reporter's qualification. Moreover, in order to encourage healthcare operators to report ADRs, the VigiFarmaco platform link was indicated directly on the Excel folder.

Results: The total number of ADRs reports collected by RNF in 2021 was 383. The majority of the above-mentioned ADRs were not serious (74%), while among severe ADRs (26%) there were 28 reactions, which caused or lengthened patients' hospitalization. Most of the ADRs reports concerned drugs belonging to the following ATC classes: J class (anti-infective drugs for systemic use) with 234 reported ADRs, followed by L class (antineoplastic and immunomodulating agents) with 66 reported ADRs. ADRs reports were mainly about female patients (69%) and were made almost completely by physicians (92%), others healthcare operators (7%) and pharmacists (1%).

Conclusion: Most of the ADRs reports collected by the University Hospital in 2021 concerned drugs belonging to the ATC J class, followed by the L class. Hospital physicians were responsible for the majority of ADRs reports, also thanks to the introduction of the VigiFarmaco link in the Excel folder. However, considering the importance of post-marketing drugs surveillance, it is necessary to encourage also other healthcare operators of highly specialized hospitals to report suspected ADRs.

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Knowledge, Attitude, and Practice Regarding Pharmacovigilance among Health Care Professionals of Nepal: A Cross-Sectional Study

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Introduction: Pharmacovigilance plays a crucial role in improving patient care and safety associated with medicine use. However, the pharmacovigilance system of Nepal seems to be ineffective owing to the limited number of adverse drug reaction (ADR) cases reported so far. To address the current reporting gap, it is necessary to assess the knowledge, attitude, and practice of Health Care Professionals on pharmacovigilance which has an impact on reporting. In Nepal, such studies on the wider population are limited [1,2].

Objective: To assess knowledge, attitude, and practice of pharmacovigilance among Health Care Professionals of Nepal.

Methods: A cross-sectional baseline survey was conducted among the health care professionals of 26 centers (12 Regional pharmacovigilance centers and 14 non-regional pharmacovigilance centers) in Nepal. The study sites were selected purposively and the study participants were selected conveniently from all the study sites. The sample size for this study was 2109. Data was obtained using semi-structured self-administered questionnaires as well as online Google forms. The descriptive and analytical analysis was performed using SPSS version 22.

Results: The result showed that out of 2017 participants, the majority (87.80%) correctly answered 50% of knowledge questions. While, 3.37% of participants could answer all the questions related to knowledge on pharmacovigilance correctly; 0.15% could not answer any of the questions correctly. The attitude score showed that 66.52% (out of 2055) participants were inclined towards a poor attitude regarding the pharmacovigilance system. Moreover, out of 865 participants who observed ADR, only 12.31% reported to a pharmacovigilance center during their professional practice. Health Care Professionals of regional pharmacovigilance centers were found to have more knowledge along with a better attitude regarding pharmacovigilance than Health Care Professionals of non-regional pharmacovigilance centers.

Conclusion: Although the knowledge of pharmacovigilance was found to be good among health care professionals, the majority of the participants had a poor attitude towards the pharmacovigilance system. The reporting was lacking even when adverse drug reactions were identified. Thus, immediate actions are necessary to improve the pharmacovigilance system in Nepal.

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Phase-Wise Implementation of a Quality Management System to Improve the National Program for Adverse Events Following Immunization Surveillance in India

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Introduction: India is the largest developing country manufacturer of vaccines [1]. The Universal Immunization Program (UIP) of India, targets more than 26 million children and the national Adverse Events Following Immunization (AEFI) Surveillance Program within it receives reporting of AEFIs from both the government as well as private sector health care facilities [2]. Post marketing surveillance of vaccine safety, encompassing AEFI surveillance is one of the criteria for benchmarking a country's National Regulatory Authority [3]. The Indian AEFI Surveillance program initiated the development and implementation of a roadmap for quality management system (QMS) across the chain of AEFI processes—notification, reporting, investigation and causality assessment, management, feedback and action [2].

Objective: Quality in healthcare is defined as activities and programs intended to assure or improve the quality of care in a defined medical setting or program [4]. Though clinical healthcare delivery services have benefited comprehensively from application of Quality-Improvement (QI) techniques for accrediting quality of services, public health care delivery programs have lagged behind [5,6]. We aimed to establish this Quality Management System for AEFI program at different administrative levels and understand the challenges during the implementation process.

Methods: Considering the niche area of AEFI surveillance, and a lack of existing benchmarks for AEFI tasks the *National QMS committee* was established, and *dedicated human resources* were hired and leveraged for the task. Core and support quality processes in AEFI surveillance were outlined and benchmarked against global or regional standards. Further, a *Standards Formulation committee* was established with representatives from national, sub-national and field level with expertise on program management, immunization, surveillance, vaccine safety communication and clinical practice. A pragmatic approach for a phased implementation plan from national-field level with as-is mapping and quality audit was planned at national level.

Results: AEFI reporting, investigation and causality assessment processes improved substantially during the establishment of QMS program. Precise benchmarks for performance assessment were developed as National Standards for the AEFI surveillance program at national, sub-national and field level were recommended. Standard Operating Procedures (SOPs) were established for AEFI surveillance

activities and the national level of the program successfully achieved the Quality certificate (NQAS/AEFI/2016/01) from National Quality assurance standards (NQAS) in the country and the next phase for state level certification has been initiated.

Conclusion: Establishment of Standards for AEFI surveillance and Quality Audit improved AEFI surveillance at national level and phase wise implementation will benefit the program.

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Developing Kidney-Specific Causality Assessment Tool

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Introduction: Kidneys have crucial roles in maintaining homeostasis. If there is deterioration in their roles due to drugs or their metabolites, drug-induced acute kidney injury (DIKI) is observed. Once DIKI is observed, the causality between the drug and the effect should be evaluated. Causality is assessed by causality assessment tools (CAT) which could be nonspecific or organ-specific. Although there are successfully used liver-specific CAT, there is no kidney-specific causality assessment tool (KSCAT). Furthermore, current nonspecific CATs lack the assessment of DIKI and don't cover the recently expanded adverse drug reactions (ADR) definition by European Medicine Agency (EMA). We recently published an editorial letter addressing the need for developing KSCAT (1).

Objective: To suggest the possible required parameters and outline the path for developing KSCAT.

Methods: We performed a screening of previously published articles on nonspecific and liver-specific causality assessment tools to define possible parameters of KSCAT.

Results: According to our screening, CATs fall into 3 categories: expert judgment; algorithms; probabilistic methods. We suggest KSCAT parameters in 3 categories: (1) drug-related; (2) kidney-related; and (3) terminology. We created a tri-polar method that consists of definitive ADRs, terminology, and without ADRs so the new KSCAT be efficient, specific, user friendly, and less time-consuming. Finally, we suggest a pyramid model to offer the perspectives of experts in the fields of pharmacovigilance, pharmacoepidemiology, and nephrology, as well as decision makers, while developing a KSCAT.

Conclusion: Relating causality between drug(s) and DIAKI may be difficult and may not be assessed appropriately with the use of non-specific tools or approaches. We reiterate the need for KSCAT development and propose the associated steps by stating the main principles: namely, the definition of ADR, suggested parameters to be included in the KSCAT, and integration of technology. An interdisciplinary consortium of selected experts from the leading organizations EMA, ISoP, ISPE, and KDIGO, and technology will be created, meeting regularly as the initial step for the development of KSCAT. The tool should then be tested for its usability, specificity, and practicality. Finally, it should be used in real-life pharmacovigilance practices, as well as in research by health authorities, regulators, decision-makers, scientists, and clinicians. A standardized KSCAT would support providing reliable and reproducible measures of the relationship likelihood in suspected cases of ADR to overcome uncertainty and provide a standardized approach.

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FLASH PRESENTATION

P039

Smart Safety Surveillance of Vaccines in Mass Immunization Campaigns: Eritrea's Evolving Experience in a Nutshell

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Introduction: Monitoring safety of vaccines during mass immunization campaigns is challenging. Immunization programs usually focus on vaccination coverages and seldom invest time and effort in identifying and managing immunization-related safety issues. The safety surveillance initiatives taken by the Eritrean Pharmacovigilance Centre (EPC) following its integration into the Expanded Program on Immunization (EPI) in late 2016 involved tactics that evolved with the deployment of newer vaccines over the years. Currently, Eritrea's experience collectively enabled the country to operate in a higher level of proactivity, implementing strategies that go in line with principles of the latest concept of Smart Safety Surveillance (3S).

Objective: This report shares Eritrea's experience in monitoring adverse events following immunization (AEFI) during mass campaigns in 3S approach, presenting a lesson that can be learned for COVID-19 vaccine deployment.

Methods: Tools, principles, AEFI-line lists, integration progresses, practices, and strategies used in Eritrea for AEFI surveillance during immunization campaigns were reviewed. The evolution of the AEFI surveillance system in Eritrea was tracked to observe the changes that the EPC introduced in every growth stage of its system. Moreover,

search was made on VigiBase to demonstrate trends of AEFIs reporting overtime.

Results: In the kickoff, the EPC started small in harnessing its integration with the EPI. In the first two years following integration, the center received only a few tens of AEFI reports through an entirely passive approach of spontaneous reporting. In 2018, the center opted for a more ambitious plan and implemented an active surveillance of newly introduced measles and rubella vaccine. Although it collected 916 AEFIs in a few days, serious cases warranting investigation were left uninvestigated. In 2019, in another highly ambitious turn, the EPC optimized its system to a more proactive approach that employs principles of 3S. Through the 3S approach, the EPC implemented strategies that enabled prevention and management of AEFIs more efficiently. Following investigation, several serious cases that would otherwise have compromised the immunization program were found to be coincidental. Of the more than 3600 AEFIs received following meningococcal-A vaccination campaign, several serious cases were successfully investigated and timely communicated. The reports represent about 80% of all the globally reported cases to the vaccine in VigiBase.

Conclusion: 3S approach was found to be effective in monitoring and mitigating immunization campaign-related problems in Eritrea. Considering Eritrea's strategies might be helpful for countries having similar setting in establishing a robust vaccine safety surveillance system during COVID-19 vaccine deployment.

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P091

Association between SARS-CoV-2 Vaccines and Myo- and Pericarditis; a Large Observational Study Using Electronic Healthcare Data from Four European Countries

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Introduction: Some COVID-19 vaccines (Moderna and Pfizer) have been associated with an elevated risk of myocarditis in younger adults. However, observational studies were unable to stratify by dose

and had limited ability to evaluate the effect of adenovirus-based COVID-19 vaccines due to the limited distribution of these in their study populations [1–4].

Objective: Estimate the incidence rates (IR), rate differences (RD) and incidence rate ratios (IRR) of myocarditis and pericarditis before and after each dose of mRNA (Pfizer and Moderna) and adenovirus-platform (AstraZeneca and Janssen) COVID-19 vaccines.

Methods: We conducted a population-based cohort design with nested self-controlled risk interval (SCRI) study. Participants were followed from 1st January 2020 to 31st December 2021. Data were derived from healthcare data from five population-based data sources in four European countries: Italy, the Netherlands, the United Kingdom (UK), and Spain. The main outcome was first occurrence of myocarditis or pericarditis. RD and IR before COVID-19 disease and after each COVID-19 vaccine dose in those without COVID-19 were calculated. The SCRI calculated IRR with 60-day control period prior to vaccination and 28-day risk windows, with adjustment for seasonality. All analyses were stratified by age (< 30 and ≥ 30 years) and in the cohorts refined age-bands for < 30 were utilised.

Results: The study cohort comprised 35,365,669 persons with median age between 39–49 years, 57.4% received at least one COVID-19 vaccine dose and 77.6% of these received two. Myocarditis background rates were highest in persons 18–29 years (IR 2.8, 95% CI [1.5–4.1] to 6.4 [3.8–9.0] across UK, the Netherlands and Spain, and for 12–17 years in Italy (IR = 9.9 [5.3–14.4]). Pericarditis rates were higher in persons > 30 years (standardised IR from 11.6 [10.9–12.4] to 29.7 [19.8–22.1] across databases). RD of myocarditis were significantly elevated after Moderna dose 2 in persons between 18–29 years in Italy. Significantly reduced RD of pericarditis in the age group above 30 years was seen for Pfizer, Moderna and AstraZeneca. The SCRI showed significantly higher myocarditis IRR after dose 1 of Pfizer (IRR = 3.3 [1.2–9.4]), and also after dose 2 of Pfizer and Moderna in persons 12–29 years (IRR of 7.8 [2.6–23.5] and 6.1 [1.1–33.5], respectively). No association was observed between COVID-19 vaccination and pericarditis in the SCRI. In a sensitivity analysis, occasional significant association was seen for AstraZeneca dose 2 and myocarditis.

Conclusion: Myocarditis is rare, but rates were increased significantly after both doses of Pfizer and the second dose of Moderna vaccines in persons below 30 years of age. This was not seen for pericarditis.

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P092

Covid-Vaccine-Monitor: a Cohort Event Monitoring Safety Study of COVID-19 Vaccines in Twelve European Countries

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Introduction: Since the WHO declared the COVID-19 global pandemic in March 2020, vaccines to prevent severe SARS-CoV-2 infection have been developed at unprecedented speed. Several vaccines have been conditionally authorized by regulators in December 2020 already. The large-scale vaccination campaigns have undeniably raised the importance of post-authorization evaluations not only through spontaneous reporting but also by cohort event monitoring to obtain more in-depth vaccine safety information, rapidly after launch.

Objective: To monitor COVID-19 vaccine safety and estimate the frequency of solicited and non-solicited, non-serious and serious reactions.

Methods: We designed a prospective cohort event monitoring (CEM) study as part of the Covid-Vaccine-Monitor (CVM) project. The CEM collects baseline data, adverse reactions (ADRs) of authorized COVID-19 vaccines in the general and special populations (pregnant and lactating women, children, and adolescents, immunocompromised, allergic, and prior COVID-19 infection people) in twelve countries (Germany, Croatia, Netherlands, Belgium, Italy, France, Spain, Portugal, Slovakia, Romania, Switzerland, and UK). The current results comprise data from February 2021–February 2022.

Depending on the dose and cohort, two data collection platforms are used: the Lareb-managed Intensive Monitoring (LIM) and the UMC Utrecht Research Online (RO). Germany and Croatia used their national tools. Participants meet local age criteria, have a first vaccination cycle or a booster dose within 48 hours, and are followed up for 6 months. Data are pooled, stratified by special cohorts, and analyzed.

Results: We included more than 30,000 general population participants data from Belgium, Croatia, France, Italy, Netherlands, and UK, and more than 520,000 from Germany with the first vaccinations. Across different vaccines, 0.2–0.3% reported at least one serious ADR after receiving the first doses. More than 7,400 special cohorts vaccinees participated. 0.2% and 0.4% reported at least one serious ADR and adverse event of special interest (AESI), respectively, after the first vaccinations. The most-reported ADRs among vaccinees were injection site pain, locally, and fatigue, headache, malaise, and myalgia, systemically. Serious ADRs and AESIs were uncommon. More than 11,100 vaccinees from general and special cohorts receiving a booster dose were also included. Among different cohorts, children/adolescents reported the lowest number of ADRs, while lactating women reported the highest.

Conclusion: We collected and analyzed COVID-19 vaccines safety evidence in more than 550,000 general and special population persons after the first cycle and booster doses, combining data from twelve countries. Data confirm common ADR rates that are already listed in the summary of product characteristics, and that serious reactions are uncommon. Additional follow-up is ongoing.

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P093

How the United States' Vaccine Adverse Event Reporting System (VAERS) Database Has Been Used to Study SARS-CoV-2 Vaccine Safety

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Introduction: The rapid development and deployment of SARS-CoV-2 vaccines elevated reliance on pharmacovigilance to inform benefit-risk assessments and national vaccine policy recommendations. During the mass vaccination program against pandemic coronavirus, the VAERS received an unprecedented number of adverse event reports. The VAERS database doubled in size in 2021 and accumulated 856,340 SARS-CoV-2 vaccine reports (54.3% of all VAERS reports) as of May 6, 2022 (HHS 2022). This publicly available resource has been heavily relied upon to inform US vaccine policy.

Objective: To understand how VAERS has been used to study the safety of the SARS-CoV-2 vaccines.

Methods: Publications containing the terms "Vaccine Adverse Event Reporting System" or VAERS and COVID-19 or SARS-CoV-2 were identified from PubMed. Non-research articles, publications that did not use VAERS or did not study SARS-CoV-2 vaccines, and withdrawn publications were excluded. Key data fields were abstracted from the remaining articles and summarized through descriptive statistics.

Results: 88 publications were identified with 27 excluded upon review; 1 was withdrawn, 9 were commentaries/editorials, and the remainder did not study SARS-CoV-2 vaccines in VAERS. Approximately one-half of the 61 included publications focused on one or more Adverse Events of Special Interest (e.g., anaphylaxis, facial nerve palsy, Guillain-Barré syndrome, myocarditis/pericarditis, etc.) or death rather than all events or signal detection. Several special populations were studied including children, adolescents, and "pregnant persons." Methods ranged from constructing a case series for clinical review to modeling. Adverse event reporting rates were calculated in 36 studies (58%). Denominators were derived from state or national vaccine administration data (CDC 2022), and included estimates of doses administered, number of persons vaccinated, and person-years. In more than one-third of the publications that calculated adverse event reporting rates, these values were misreported or

misinterpreted by the study authors as estimates of incidence rates or cumulative incidence (risk).

Conclusion: The rapid nationwide SARS-CoV-2 vaccine rollout resulted in an unprecedented volume of VAERS reports, which have been relied upon to investigate rare adverse events and inform vaccination policy. The methods and scientific rigor of vaccine adverse event studies varied considerably. Despite the inability to calculate incidence or risk using voluntary adverse event reports, these terms were frequently used instead of, or interchangeably with, reporting rate. Where a causal relationship exists, relying on reporting rates as a proxy for incidence may substantially distort estimates of harms (Weiss 2022).

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P094

Real-life Safety of Oral Antivirals for COVID19: a Retrospective Cohort Study

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Introduction: Molnupiravir and nirmatrelvir/ritonavir are two new oral antivirals approved for the treatment of COVID-19 infections in adult, non-hospitalized patients at high risk for disease progression. Since their release, they have proven to be an effective strategy to prevent hospitalizations. Although clinical trials granted their efficacy and safety, real-life data on the possible effect of these drugs are lacking [1,2].

Objective: To evaluate the real-life safety of oral antivirals for COVID-19 by retrospectively assessing the number and type of adverse drug reactions (ADRs) detected in clinical practice.

Methods: We conducted a retrospective study of patients referred to the outpatient clinic for the early treatment of COVID-19 at the Infectious Diseases Unit of the University Hospital of Padua. Patients' clinical data and ADRs were collected. Each ADR was recorded in the National Pharmacovigilance Network. Data were anonymized and subsequently analyzed through R software. Qualitative variables were expressed as absolute numbers and percentages and compared using the Chi-square test. Quantitative variables were expressed as mean or median and compared by T-test or Mann-Whitney test whenever it was more appropriate.

Results: 109 consecutive patients with a median age of 73 years were included. 49 were male and 15 were unvaccinated for COVID-19. 74 (67.9%, Group1) patients received nirmatrelvir/ritonavir and 35 (32.1%,) molnupiravir (Group2). Median age was significantly higher for group2. Regarding ADRs analysis, a total of 49 (44.9%) patients reported at least one adverse event, of which 7 belonged to Group 2 and 42 to Group 1 ($p < 0.01$). No statistically significant difference between the two groups was found regarding serious ADRs and ADRs leading to discontinuation of therapy. The most frequent ADR

in the nirmatrelvir/ritonavir group was dysgeusia (37.8% of patients in this group) whereas in the molnupiravir group it was nausea (11.4%). For further information see Table 1.

Table 1 - "Cohort characteristics and outcomes"

	Molnupiravir (n=35)	Nirmatrelvir /ritonavir (n=74)	P
Female sex, n (%)	20 (57.1)	40 (54.0)	0.76
Median age, yr (IQR)	82 (71.5-87)	68 (52.5-76.75)	<0.001
Time since first symptom < 4 days, n (%)	20 (57.1)	49 (66.2)	0.36
Patients vaccinated for COVID-19, n (%)	27 (77.1)	67 (90.5)	0.06
Symptoms resolved within 7 days, n (%)	28 (80.0)	64 (86.5)	0.38
Patients with adverse events, n (%)	7 (20.0)	42 (56.8)	<0.001
Patients with serious adverse events, n (%)	1 (2.8)	3 (4.3)	0.52
Patients who discontinued the antiviral because of an adverse event, n (%)	3 (8.5)	9 (12.9)	0.42
Patients who experienced more than one adverse event, n (%)	3 (8.5)	13 (18.6)	0.13

Conclusion: The evidence emerging from our study suggests a higher frequency of ADRs compared to RCTs, especially in patients treated with nirmatrelvir/ritonavir. In these patients, we observed several cases of dysgeusia, much more than reported in the literature (37.8% vs 5.6%) [2]. Molnupiravir was associated with fewer side effects than nirmatrelvir/ritonavir even if administered to an older population. These findings suggest that molnupiravir may be considered a safe early treatment option in elderly people. Further analysis on larger cohorts, also taking into account possible confounding factors, need to be performed in order to better assess the real-life safety profile of these drugs

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P095

Allergic History and Anaphylaxis in COVID-19 Vaccines: A Disproportionality Analysis in the FDA Vaccine Adverse Event Reporting System

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Introduction: Many pre- and post-marketing studies on Covid-19 vaccines investigated their safety in the overall population. Little information is available on cohorts with specific comorbidities. Few studies evaluate the safety in allergic subjects, in particular as related to the anaphylaxis risk.

Objective: To investigate the association between anaphylaxis after Covid-19 vaccines and the history of hypersensitivity reactions to the most common allergens.

Methods: The Vaccine Adverse Event Reporting System (VAERS, January 2020-December 2021) was downloaded and cleaned. We focused on reports of Adverse Events Following Immunization (AEFIs) following COVID-19 vaccination in subjects > 12 years old with history of allergy. We performed a descriptive analysis and calculated the Reporting Odds Ratio (ROR) to identify demographic characteristics and allergic histories disproportionally reported with anaphylaxis for each Covid-19 vaccine and the most recorded allergens.

Results: We retrieved 183,860 AEFI reports recording any allergic history (864 anaphylaxis reports among cases vs 6,162 in Covid-19 reports without history of allergy). They concerned mostly women (81.3%) and adults (74.0%). Almost all reports were submitted in the US (99.7%) and 38.3% of them resulted in hospitalization. Covid-19 vaccines administered were Spikevax (49.3%), Comirnaty (42.1%), and Janssen (8.4%). The antigens most recorded as allergens were penicillins (49,407), sulfa drugs (37,365), opioids (26,398), seafood (12,039), latex (11,442), NSAIDs (11,319), cephalosporins (8,379), quinolones (8,023), macrolides (7,586). Seafood allergy resulted associated with anaphylaxis for Comirnaty (ROR = 2.80; 95% CI 2.20–3.56), Spikevax (2.57; 1.88–3.51), and Janssen (2.67; 1.39–5.11). Latex allergy was associated with anaphylaxis for Comirnaty (ROR = 1.92; 95% CI 1.45–2.55).

Conclusion: We gathered evidence pointing towards a preferential development of anaphylaxis in patients with an history of hypersensitivity to seafood (for all Covid-19 vaccines) or latex (restricted to Comirnaty). Whether confirmed by further studies, this knowledge may drive a more practical anamnesis and a prompt management of anaphylactic reactions.

References/Further Sources of Information

Not applicable.

P096

Role of Background Incidence in Signal Detection; Observed/Expected Analysis of Classical Thromboembolism with COVID 19 Vaccines in The Netherlands

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Introduction: Spontaneous reporting (SR) is a key method for monitoring the safety of COVID-19 vaccines used in the pandemic in 2021. SR led to early warnings of vaccine-induced-thrombosis-with-thrombocytopenia (VITT) with the vector vaccines of AstraZeneca and Janssen [1-3]. In addition, an increase of reports of other thromboembolic events with both vector and mRNA vaccines was seen. For now, venous thromboembolism (VTE) is labelled for

Janssen and cerebral-venous-thrombosis (CVST) for the AstraZeneca vaccines [4,5]. Because a large population is vaccinated in a short period of time and the fact that venous (VTE) and arterial thrombosis (ATE) are quite common conditions, the number of reports should be compared with background incidence rates as part of signal detection.

Objective: We evaluated the use of Standardised Morbidity Rates (SMR) to compare spontaneously reported cases of thromboembolism with COVID-19 vaccines with stratified Dutch background incidence rates from 2019 in the vaccine exposed population.

Methods: SMRs are calculated by dividing the reported as observed (O) cases by the expected (E) number within risk windows of 14/28 days following each dose and vaccine. $SMR > 1$ indicates that more cases were reported than expected [6].

Results: Until 9 December 2021, 2080 reports were received concerning at least one thromboembolic event with 24 million administered COVID-19 vaccines. These concerned 1000 of VTE, 956 of ATE, 19 of CVST and 134 reports of miscellaneous forms of thrombosis. Cases of VITT (TTS) were excluded. In the table the main results are summarized and highlighted. For AstraZeneca, SMRs reach or exceed 1 for VTE, ATE and CVST, especially in people aged < 60 years. With the second dose of mRNA vaccines more cases of the rare condition CVST were observed in men, although absolute numbers are low; $n = 3$ for men with 2nd dose of Pfizer (14 days) and $n = 1$ for men with 2nd dose of Moderna (28 days).

Table	1.	Standardised	Morbidity	Rates	(SMR)
		VTE	ATE	CVST	
PFI_1		0.20 (0.18-0.23)	0.10 (0.09-0.11)	0.22 (0.03-0.80)	
PFI_2		0.15 (0.12-0.17)	0.06 (0.05-0.07)	0.61 (0.20-1.42)	
o male (14 days)				0.88 (0.18-2.58)	
MOD_1		0.29 (0.18-0.41)	0.13 (0.08-0.19)	0	
MOD_2		0.31 (0.20-0.44)	0.12 (0.07-0.18)	0	
o male (28 days)				1.01 (0.03-5.63)	
AZ_1		0.70 (0.58-0.83)	0.24 (0.19-0.29)	4.18 (0.27-60.17)	
o (fe)male < 60 y (14 days)		1.69 (1.19-2.28)	0.91 (0.48-1.49)	5.03 (0.60-18.18)	
AZ_2		0.28 (0.20-0.36)	0.06 (0.04-0.09)	0	
JAN_1		0.66 (0.46-0.90)	0.18 (0.10-0.29)	0	

Table 1. Standardised Morbidity Rates (SMR) for venous thrombosis (VTE), arterial thrombosis (ATE) and cerebral venous thrombosis (CVST) following COVID-19 vaccination. Results are shown per vaccine and dose with a risk period/time to onset of 14 days (unless otherwise specified).

Conclusion: SMRs can be used when the exposed population is defined, stratified background incidence rates are available and the reporting rate is substantial. The rate of underreporting is unknown, differs in population subgroups, and is influenced by media attention. Therefore, SMRs near 1 are also considered to be 'high'. Our data cannot confirm nor exclude a potential signal of other types of thromboembolism with COVID-19 vaccines. But the potential signal initiated further epidemiological research to confirm and quantify a potential increased risk of thromboembolism with COVID-19 vaccines.

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P098

Adverse Events of Special Interests (AESIs) Reported in Pediatrics with Pfizer Biontech COVID-19 Vaccine: Insights from VAERS Database

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Introduction: Pediatrics are always a difficult yet important population to observe in any study for any safety concerns that could impact their future lives. To offset real or perceived safety issues, it is critical to be prepared to respond quickly, especially when dealing with adverse events of special interest (AESIs) as defined by World Health Organization WHO. Vaccine Adverse Event Reporting System VAERS is a passive reporting system, which means that it relies on people to report their experiences to the CDC and FDA.

Objective: This study aims to identify AESIs in children aged 5 years old to less than 18 years old who were vaccinated with Pfizer Biontech COVID-19 Vaccine in the United States according to VAERS database.

Methods: VAERS data on the Pfizer Biontech COVID-19 vaccine in children (aged 5 years old and less than 18 years old) were identified and saved. We retrieved all reports from 2020 to May 13, 2022. The analysis excluded reports with incomplete event details, age, or duplicate reports. The World Health Organization's COVID-19 vaccines safety surveillance manual, 2nd edition, was used to define AESIs. The frequency of AESIs was calculated as a percentage of the total number of reported adverse events in the database. The chi-square test was used to assess correlations between other reported demographic information. Statistical significance is defined as a P-value of less than 0.05.

Results: A total of 33,101 (50.4% males, 47.2% females) unique VAERS ID pediatric primary cases aged 5 years old and less than 18 years old were identified taking Pfizer Biontech COVID-19 vaccine and included in the final analysis. Most of the patients reported taking one dose of the vaccine 16,238 (49.1%) and two doses 9,844 (29.7%). Most reported cases were aged 14-18 years old 46.3% ($N = 15,342$). Overall number of reported adverse events were 110,467 events, while overall reported AESIs identified 1497 (1.36% of overall reported adverse events). Most common reported AESIs were acute cardiovascular injury with 689 reported events most of which accounted to myocarditis (614 cases), coagulation disorders (173), Multisystem inflammatory syndrome in children (143), ageusia (79),

anaphylaxis (75), generalized convulsion (73), thrombocytopenia (70), anosmia (67), and Guillain Barré Syndrome (31).

Conclusion: AESIs is alarming in pediatric population and should be further investigated, particularly acute cardiovascular injury, coagulation disorders, and multisystem inflammatory syndrome in children.

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P211

Healthcare Utilization Databases for Medical Product Safety Surveillance: A Pilot Analysis from Lombardy

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Introduction: One use of healthcare utilization data is for “near real-time” sequential postmarket safety surveillance of medical products. Sequential Database Surveillance (SDS) assesses evidence of association with respect to exposure–outcome pair. During surveillance, the incidence rate of the exposure–outcome pair is continuously compared with a historical, concurrent, or self-control population as data accrue. If a statistical signal of excess risk is identified, the null hypothesis of “no excess risk” is rejected. If not, the SDS ends at a predetermined stopping point while failing to reject the null. Any detected statistical signal is followed by confirmatory assessments to validate or refute the finding.

Objective: To identify which is the more optimal configuration of healthcare databases for obtaining a surveillance system for post-market safety surveillance of medical products in Lombardy

Methods: A SDS has been performed in Lombardy (10 million inhabitants) by investigators of the Regional Epidemiologic Observatory and the University of Milano-Bicocca.

Optimal design and analysis aspects of postmarket SDS are less developed than sequentially monitored clinical trials. The key difference is that clinical trials typically prioritize power and sample size whereas postmarket SDS places a high priority on power and the time to detect a signal. This attention to the calendar time to detect a signal is important because of potential harm to the general population from delayed detection of a safety problem.

Results: The postmarket SDS has been performed in our observational setting, where the investigator has no control over information accrual within each data source. Investigators must select how many observational healthcare databases to monitor and the duration of monitoring. First, the investigator must consider each database’s contribution to sample size, which depends on the size of the population of interest. Secondary attributes, such as delays and misclassification errors in data capture, also are important. Finally, the database-specific cost may increase considerably if medical chart validation accompanies surveillance.

To illustrate these design choices, our research group wished to detect a given incidence rate ratio of myocarditis among citizens who received mRNA vaccine with 80% power, which required a given amount of person-years of exposure to vaccine.

Conclusion: This pilot project will attempt to answer to the question: “which is the more optimal configuration of healthcare databases for obtaining a surveillance system for postmarket safety surveillance of medical products of Lombardy?”

To support quick detection, SDS analyses depend on amassing sufficient information (sample size) to reach a stopping point, either by rejecting the null or ending surveillance.

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P212

Use of ICD-10 Codes for Tracking Adverse Drug Events (ADEs): a Computational Approach to Searching Large Health Databases in Brazil

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Introduction: In recent years, interest has grown in the development of methods and tools capable of overcoming the challenges of traditional systems used in drug surveillance. Among these challenges is the underreporting of ADE, which in some cases can be greater than 90% 1–7. In Brazil, several studies have pointed out the problem of underreporting of ADEs in the National Pharmacovigilance System (SINAF) 8–10.

Objective: To evaluate the potential of selected ICD-10 codes to track suspected cases of Adverse Drug Events (ADEs) in the Hospital Information System of the Unified Health System (SIH), in the Mortality System (SIM) and in the Surveillance Notification System Sanitary (Notivisa)

Methods: The study is described according to the STROBE guideline. This is a cross-sectional, descriptive study, using information obtained from hospitalizations data (SIH), mortality data from the SIM, extracted from the DATASUS website and from the suspected cases of ADE reported in the Notification System in Health Surveillance (Notivisa) In Brazil, from 2009 to 2018.

Results: A total of 84,396 ADE notifications were evaluated in Notivisa and 593,159 hospitalizations and 31,764 deaths with

suspected ADE were tracked in 10 years. The pharmacist was the highest notifier of ADE in Notivisa. The average notification rate in Notivisa was 40.9 notifications/1 million inhabitants in Brazil, while the proportion of ADE identification in hospital data was 0.52%. The Southeast region presented the highest rate, as opposed to the North region with the lowest. All regions had EAM underreporting issues. ADRs and drug intoxications were the most identified events in all systems. Women were the most affected by ADE in Notivisa, while men were more affected by severe ADE. The age group most identified with ADE was 30–59 years. The vast majority of ADE reported in Notivisa originated from Sentinel Hospitals (55.6%), while in SIH and SIM the vast majority were from data from “Other hospitals”.

Conclusion: The list of triggers prepared for this study proved to be an applicable, simple and low-cost approach that allows the screening of ADE in any health database, using the ICD-10 as the diagnostic classification system. The results of this study are important in this moment of strengthening the patient safety culture, together with the growth of computer technology applied to electronic health records, which can facilitate the management of these events in the hospital environment and contribute to the capture of relevant information for the WHO drug monitoring program and strengthening pharmacovigilance in Brazil.

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Cohort Event Monitoring on Adverse Reactions to COVID-19 Vaccines in Seven European Countries: Pooled Results on First Dose

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Introduction: COVID-19 vaccines were rapidly authorized leaving many questions and the need to monitor safety intensively.

Objective: Multi-national collaboration was established with the aim to monitor the safety of the COVID-19 vaccines through prospective cohort event monitoring in Europe.

Methods: A prospective cohort event monitoring study was conducted with primary consented data collection in seven countries between December 2020 and November 2021. Participants in Belgium, France, Italy, the Netherlands and United Kingdom registered using the LIM web app and received follow-up questionnaires for six months. Participants from Croatia and Germany registered with the OPeN and SafeVac2.0 apps respectively. Rates of self-reported reactions were described by type (solicited, non-solicited), adverse event of special interest (AESI), seriousness, and stratified by vaccine brand. The rate of self-reported adverse reaction was calculated after dose 1 and prior to dose 2 among all subjects who responded with at least one questionnaire.

Results: 117,791 participants were included and responded to the first questionnaires after baseline: 88,196 from Germany, 27,588 from the Netherlands, 984 from France, 570 from Italy, 326 from Croatia, 89 from the United Kingdom and 38 from Belgium. 89,377 respondents received AstraZeneca, 14,658 BioNTech/Pfizer, 11,266 Moderna and 2490 Janssen. Reporting included all vaccine brands from all countries, except Germany which only included data on Moderna until May 2021 and AstraZeneca until September 2021. Median time to completion was 8 days for the first questionnaire after dose 1 (Netherlands, Belgium, Italy, France, United Kingdom) and 3 days in Croatia. Median age category was 40–49 for all vaccine exposed groups except for BioNTech/Pfizer where median age was 70–79. Fatigue and headache were the most commonly reported solicited systemic adverse reactions, injection site reactions the most common solicited local reaction. AESIs were very rare (< 0.1%) and serious adverse reactions were uncommon (< 1%) across all vaccine brands.

Conclusion: This study that collated self-reported data from more than 100,000 COVID-19 vaccine recipients, demonstrated feasibility of setting up and conducting cohort event monitoring across multiple European countries to collect safety data on novel vaccines that are rolled out at scale in populations which may not have been included in pivotal trials. Different vaccination schedules in countries and different web applications resulted in some heterogeneity. The study confirmed the safety information in the product labels: reactogenic reactions, related to immunogenic response, and local injection site reactions were very common across all vaccines, whereas serious reactions or AESIs were (very) rare.

References/Further Sources of Information

Not applicable.

P214

Cohort Event Monitoring of COVID-19 Vaccine Safety in Special Cohorts in Italy

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Introduction: Marketed COVID-19 vaccines showed an overall favourable safety profile in pivotal trials. However, those trials did not include high risk/fragile patient categories; hence, close monitoring of COVID-19 vaccine safety in those special cohorts in real-world setting is needed. The European Medicines Agency-funded “Covid-Vaccine-Monitor” project was set up to prospectively measure the incidence of solicited/unsolicited adverse events following COVID-19 vaccination in several European Countries as reported by vaccinees through web-based questionnaires. Italy is one of the Countries participating in the project as a large network named “ilmiovaccinocovid19 collaborating group”.

Objective: To measure the incidence of vaccinee-reported adverse events following immunization (AEFIs) with marketed COVID-19 vaccines in pregnant and lactating women, pediatrics, immunocompromised, people with history of allergy and people with prior SARS-CoV-2 infection in Italy.

Methods: We performed a prospective cohort study of the above-mentioned categories of vaccinees, who were recruited at multiple vaccination centers within 48 hours from either the first or booster COVID-19 vaccine dose administration. After providing informed consent and get registered into the web-app, vaccinees were asked to fill in an electronic baseline questionnaire and 6 follow-up questionnaires at different time points, within 6-month from vaccine administration, in which information on potential vaccine-related AEFIs were collected. We explored and compared the frequency of local and systemic solicited adverse events following first or booster dose for each special cohort and vaccine brands.

Results: Overall, 1,331 vaccinees (40.4% first dose and 59.6% booster dose) were included in the analysis. Of these, 8.4% were immunocompromised, 32.0% had history of allergy, 25.5% had prior SARS-CoV-2 infection, 23.4% were children/adolescents, 6.2% were pregnant and 4.6% were lactating women (non-mutually exclusive cohorts). Of subjects belonging to at least one cohort, 52.3% reported at least one AEFI following either the first or booster dose. Among all special cohorts, injection site pain was the most frequently reported solicited local AEFI, after both the first (37.5%) and booster (39.5%) dose. As solicited systemic AEFIs, headache (19.0%) was the most frequently reported after the first dose, while malaise (23.7%) and fatigue (23.7%) after the booster dose. The frequency of severe AEFIs was very low following both first dose (0.8%) and booster dose (0.6%).

Conclusion: Overall, this study confirmed the favourable safety profile of COVID-19 vaccines also in the above-mentioned special

categories who have not (or marginally) been included in pivotal trials.

References/Further Sources of Information

Not applicable.

P248

Flash presentation: Impact of 2018 EU Risk Minimisation Measures and Revised Pregnancy Prevention Programme on Utilisation and Prescribing Trends of Valproates

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Introduction: Due to the established teratogenic effects of valproates [1], the European risk minimisation measures (RMMs) for valproates were updated in March 2018 [2]. This included assessment of patients’ potential to become pregnant, pregnancy testing, contraceptive use and annual review of ongoing treatment.

Objective: To investigate the effectiveness of the 2018 RMMs in five European countries/regions.

Methods: An observational pharmacoepidemiological times-series study of females of childbearing age (12–55 years) was conducted using electronic healthcare databases from five countries/regions (Jan. 2010–Dec. 2020): Denmark (DNR), Italy (ARS Tuscany), the Netherlands (PHARMO), Spain (BIFAP), and the UK (CPRD). Clinical and demographic information from each source was transformed to the ConcePTION common data model [3], quality checks were conducted and a distributed analysis was performed using common analysis scripts. Incidence and prevalence rates of valproate use, proportion of valproate discontinuers and switchers to alternative medicine, frequency of pregnancy testing and contraception prior to and after valproate use, and occurrence of pregnancies during valproate exposure were estimated per month. Interrupted time series analyses were conducted to estimate the level or trend change in the mentioned outcome measures.

Results: There were 69,533 valproate users out of 9,699,371 female subjects of childbearing age from the five participating centres (median follow-up 3.5–10.0 years, mean age at baseline ≥ 30 years). We observed a statistically significant decline in prevalent use of valproates in all countries/regions, but no significant decreasing trend in incident use after the 2018 RMMs compared to the period before. The monthly proportion of compliant valproate prescriptions/dispensings with a contraceptive coverage was low (ranged between 0.5–25%), without an increasing trend after the 2018 RMMs across the studied databases. Pregnancy testing was insufficiently captured to analyse.

The only significant increase in trend in switching rates from valproates to alternative medicine after the 2018 RMMs was observed in ARS Tuscany. There was a substantial number of concurrent pregnancies during valproate exposure, but with a declining rate after the 2018 RMMs in ARS Tuscany (0.70 per 1000 valproate users pre- and 0.27 post-intervention), BIFAP (0.48 and 0.13) and PHARMO (0.34 and 0.00), and an increasing rate in CPRD (1.13 and 5.07).

Conclusion: There was a small impact of the 2018 RMMs on valproate use in the studied European countries/regions. Despite the declining rates of concurrent pregnancies with valproate use after the 2018 intervention, the occurrence of a substantial number of such events warrants a careful monitoring of the existing policies and regulations on valproate use in Europe.

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Inter-Year Comparison of Adverse Reactions Associated with Legal Cannabis Products Reported to Health Canada, 2018–2019 to 2021

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Introduction: Since the legalization of cannabis for non-medical purposes in Canada on October 17, 2018, there have been changes in the landscape including increasing availability of legal cannabis products, ongoing public knowledge and education on cannabis, an outbreak of vaping-associated lung illness and the covid-19 pandemic. These shifting contexts may have influenced cannabis use behaviours, and the number and type of cannabis adverse reactions (ARs) reported since legalization. Health Canada's (HC) Vigilance Framework for Cannabis Products allows for the monitoring, detection, assessment and risk management of ARs to support regulatory decision-making, knowledge translation and public communication of the safety of cannabis products.

Objective: The objective of this presentation is to provide an inter-year comparison of ARs associated with legal cannabis products reported to HC during the first year (October 17, 2018–December 31, 2019), second year (January 1, 2020–December 31, 2020) and third year (January 1, 2021–December 31, 2021) of legalization.

Methods: A descriptive, comparative analysis of AR cases involving legal cannabis products received by HC from October 17, 2018 to December 31, 2019 (referred to as 2018–2019), January 1, 2020 to December 31, 2020 and January 1, 2021–December 31, 2021 was conducted to characterize ARs across these three reporting periods.

Results: The total number of cases received by HC increased across reporting periods (n = 151 in 2018–2019, n = 161 in 2020, n = 174 in 2021), with serious cases increasing 36% overall between 2018–2019 and 2021 despite 2018–2019 having covered a longer reporting period. Cases more frequently involved females than males in all periods, while AR cases in 2020 and 2021 more frequently involved older adults (65+ years), whereas middle age adults (35 to 64 years) accounted for the largest proportion of cases in 2018–2019. Ingestible cannabis extracts (e.g., cannabis oils in liquid or capsules) were the most frequently reported suspect cannabis product in AR cases across three reporting periods despite widening availability of other types of legal cannabis products (cannabis topicals, other extracts such as cannabis vaping products and edibles) as of October 17, 2019.

Conclusion: While the total number of cases of ARs associated with legal cannabis products submitted to HC have increased across reporting periods, other variables have remained stable or have decreased. Health Canada will continue to monitor and analyse trends in cannabis ARs and publish these results in future years.

References/Further Sources of Information

Not applicable.

P312

Diarrhea and Apixaban; Using Combined Data from Spontaneous Reporting and Cohort Event Monitoring for Signal Detection in Pharmacovigilance

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Introduction: Apixaban, edoxaban and rivaroxaban are non-vitamin K oral anticoagulants (NOACs) that belong to the group of Factor Xa Inhibitors. Diarrhea is mentioned in the Summary of Product Characteristics (SmPC) of rivaroxaban, but not for apixaban and edoxaban. However, a significant number of reports about diarrhea associated with the use of apixaban have been reported to the Netherlands Pharmacovigilance Centre Lareb. Besides the spontaneous reporting system (SRS), Lareb performed a cohort event monitoring (CEM) study on the safety profile of NOACs in daily practice. Both systems could provide other types of information regarding signal detection in pharmacovigilance.

Objective: To explore how combined data from the Dutch SRS and a CEM study on NOACs can be used to analyze the possible association between diarrhea and apixaban.

Methods: The SRS included reports of possible adverse drug reactions (ADRs) spontaneously reported by healthcare professionals and patients to the Netherlands Pharmacovigilance Centre. The CEM study included 1133 NOAC users, of which 339 apixaban users, who had been followed for 6 months after start of the NOAC. During this period, they received 4 questionnaires about possible ADRs.

Results: The SRS included 18 reports of diarrhea associated with apixaban. In 7 reports the time to onset (TTO) was reported (median 5 days). Four reports out of these 18 mentioned a positive dechallenge. The CEM study included 7 cases of diarrhea. TTO and outcome were reported for all patients and demonstrated a median TTO of 7 days. All patient continued the use of apixaban and recovery was reported for 6 patients with a median time to recovery of 8 days. The TTO and recovery of the diarrhea associated with apixaban was compared with

that of rivaroxaban, using CEM data, and were found to be comparable (Table 1).

Table 1. Comparison CEM data on diarrhea between apixaban and rivaroxaban

Number of cases	apixaban number (%)	rivaroxaban number (%)
Participants in CEM study	339	445
Diarrhea cases CEM	7 (2%)	16 (4%)
Median time to onset (days)*	7	3
Time to onset < 1 week*	6 (86%)	12 (86%)
Time to onset > 1 week*	1 (14%)	2 (14%)
Continuation of NOAC therapy	7 (100%)	16 (100%)
Recovery of diarrhea	6 (86%)	9 (56%)
Diarrhea is less	1 (14%)	5 (31%)
Diarrhea not recovered	0 (0%)	2 (13%)

*For rivaroxaban known for 14 cases

Conclusion: The SRS and CEM system are complementary for signal detection purposes. Where the SRS gives a higher number of reports, the CEM system gives more insight into the time course. Because diarrhea is not described in the SmPC of apixaban, healthcare professionals might switch to this drug when patients experience diarrhea using rivaroxaban. It is important to further analyze this possible association to decide if adding diarrhea to the SmPC of apixaban is advised.

References/Further Sources of Information

Not applicable.

P313

VigiNetWork: a Community Pharmacists-Network on Pharmacovigilance in Emilia-Romagna and Veneto Region

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Introduction: The literature shows that in Italy community pharmacists and patients are not active enough in reporting adverse drug reactions (ADRs) [1-3]. To improve these replies it has been set up VigiNetWork project (September 2020–September 2022): it is a multiregional (Emilia-Romagna and Veneto Region) pharmacovigilance (PV) project funded by the Italian Medicines Agency, joining pharmacists and citizens in pharmacovigilance activities within the community pharmacies.

Objective: To develop a pharmacovigilance network among community pharmacies, to promote spontaneous ADRs reporting by pharmacists and patients and to improve pharmacists' knowledge on drug safety.

Methods: The project has been promoted through social networks, webinars, local newspapers, and the Category Professional Associations. An information leaflet explaining its characteristics, a free access to two e-learning courses and a personal access to a website (www.vigirete.it) have been made available to enrolled pharmacists. A similar leaflet has been developed for patients. To evaluate the

effectiveness of VigiNetWork we assessed the number of enrolled community pharmacies/pharmacists and of ADR reports submitted by them, their participation to e-learning courses and their visits to the website.

Results: From September 2020 to March 2022 a total of 669 and 371 community pharmacies were enrolled respectively in Emilia-Romagna and Veneto Region (Table 1). A total of 339 and 516 (about 90% of total reports from community pharmacists) ADR reports were submitted from the pharmacists of VigiNetWork respectively in Emilia-Romagna and Veneto Region and an increase in comparison to the previous 18 months was observed. The impact of the project in patient reporting was presumed, but not assessable. In our study period 40% and 58% of enrolled pharmacists registered for distance learning courses respectively in Emilia-Romagna and Veneto Region, even if only about 5% of them completed the training in both Regions. The website reached 2113 (86% of enrolled pharmacists) unique visitors.

Picture 1 - "Table 1: numbers of enrolled community pharmacies and pharmacists from September 2020 to March 2022"

Region	Total number of pharmacies in the Region	Number of enrolled pharmacies	Number of enrolled pharmacists	% enrolled pharmacies
Emilia-Romagna	1367	669	1502	49%
Veneto	1521	371	949	24%
Total	2888	1040	2451	36%

Conclusion: Our project showed a great attention of community pharmacists to PV, increased also due to COVID-19 pandemic. The total number of submitted reports, even if limited, represented almost the totality of all reports from community pharmacists in both Regions and their interest in our website contents was appreciable. More efforts could be done to continue these activities in daily practice.

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P326

Acquired Hemophilia A and COVID19 Vaccines: A Possible Safety Signal or a Notoriety/Detection Bias?

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Introduction: Acquired hemophilia A (AHA) is a rare autoimmune hemorrhagic condition (1-2 cases/million person/year)¹. Several cases

of AHA diagnosed following the administration of the COVID19 vaccines were described. Incidence of AHA diagnoses possibly higher than expected was also reported^{2,3}. Indeed, higher attention to, and/or screening for, coagulation disorders during the vaccination campaign (i.e. notoriety/detection bias) might have increased the probability of AHA diagnosis and reporting compared to the past.

Objective: To observe the utilization of AHA laboratory tests and incidence of AHA cases in Tuscany region during 2017–2021 and compare the rate of AHA in patients tested for AHA during COVID19 immunization campaign (2021) with that observed in 2019–2017.

Methods: A retrospective cohort study was performed using population-based administrative data from Tuscany region (3.7million inhab), Italy. Per each year between 2017 and 2021, patients active into the database at 1st January, with ≥ 5 years of age and 2 years of look-back were included. Subjects with ≥ 1 laboratory tests used for diagnosing AHA¹ were identified. Due to the absence of a AHA ICD9CM codes, possible AHA cases were identified combining information from different databanks. Cumulative annual incidence of both patients tested for AHA and possible AHA cases was respectively calculated. The rates of incident AHA cases on patients tested for AHA observed in 2021 and in 2017–2019 were calculated. All estimates were standardized by age and sex (std.). 95% confidence intervals (95% CIs) were estimated with Poissons method (statistical difference = no 95% CIs overlap).

Results: A total of 126 possible AHA cases and 1.081.878 incident patients with ≥ 1 laboratory test for AHA were identified between 2017 and 2021. Calendar year 2020 was clearly non-representative of the pre-immunization campaign period due to pandemic waves, thus it was excluded from the analyses. In 2021, std. incidence of tested patients (6067/million inhab/year; 95% CI 60412–60913) and std. Incidence of possible AHA cases (5.6/million inhab/year; 95% CI 3.4–8.7) showed the lowest point estimates, though only the former was statistically significant compared to any other year of the observation period. The std. rate of possible AHA cases on patients tested for AHA in 2021 was 5.6/100million (95% CI 3.4–8.7) was not statistically different from that observed in 2017–2019 (7.6/100million; 95% CI 5–11).

Conclusion: No increased incidence of possible AHA cases during the COVID19 immunization campaign was observed in Tuscany. Findings from this study do not suggest neither a possible detection bias nor a possible safety signal. Notoriety of other known vaccine-induced coagulation disorders may explain the increased reporting of AHA following COVID19 vaccines.

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Safety and Tolerability Profile of Paliperidone Palmitate: An Analysis on Publicly Accessible EudraVigilance Data

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Introduction: Long-acting injectable antipsychotics (LAIs) represent effective strategies to maintain treatment adherence in patients with chronic schizophrenia [1]. Among the second generation LAIs (SGA-LAIs), paliperidone palmitate (PP) is available as one- (PP1M) and 3-month (PP3M) formulations. These newer formulations seem to be effective, safe and well tolerated [2]. However, real-world studies regarding the safety and tolerability profile of PP1M and PP3M are few and mostly conducted on small samples.

Objective: To better understand the safety and tolerability profile of PP, with a focus on PP3M.

Methods: We analyzed the Individual Case Safety Reports (ICSRs) publicly available on EudraVigilance. ICSRs uploaded between 2011 and 2021, presenting PP1M and PP3M as suspected drugs were evaluated. ICSRs relative to LAI formulations of aripiprazole, olanzapine and risperidone reported between 2003 and 2021 were also examined as reference group. ICSRs derived from literature were excluded. Data were evaluated with a descriptive analysis, then, as disproportionality measures, crude reporting odds ratio (ROR) and 95% confidence interval (CI) were calculated. Chi² tests were also performed to compare ICSR characteristics between PP1M and PP3M.

Results: A total of 7.836 ICSR were retrieved. Of those, 6.095 (77.8%) presented as suspected drug PP1M and 1.655 (21.1%) PP3M, while 86 ICSR indicated both PP formulations as suspected drugs. The majority of ICSR regarded male patients (n = 4.616; 58.9%) in the 18–64 years age group (n = 5.079; 64.8%). After grouping the observed adverse drug reactions into System Organ Class (SOC) terms, the most frequently detected ones were “Psychiatric Disorders” (n = 2.817; 19.5%), “General disorders and administration site conditions” (n = 2.493; 17.3%) and “Nervous system disorders” (n = 1.867; 12.9%). The disproportionality analysis showed significant values for the SOC “Reproductive system and breast disorders” (ROR = 1.17; 95% CI 1.04–1.30) and “Endocrine disorders” (ROR = 1.45; 95% CI 1.21–1.73). The sub-analysis conducted using Chi² showed increased reporting frequencies for PP3M over PP1M regarding the SOC “Psychiatric disorders” [n = 772 (27.9%) vs n = 2.011 (17.5%); p < 0.001] and “General disorders and administration site conditions” [n = 602 (21.8%) vs n = 1.862 (16.2%); p < 0.001].

Conclusion: Our analysis shows that the safety and tolerability profile of PP, while being similar overall to those of the other SGA-LAIs, could present differences in key areas for tolerability such as the endocrine system. Furthermore, some differences in the ICSR reporting pattern between PP1M and PP3M seems to emerge from this analysis.

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Is Pegylation of Drugs Associated to Hypersensitivity Reactions? An Analysis of The Italian National Spontaneous Adverse Drug Reaction Reporting System

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Introduction: Increasing evidence highlights the allergenic potential of pegylated drugs as a result of the production of anti-PEG immunoglobulins [1-3].

Objective: To investigate the risk of hypersensitivity reactions of pegylated drugs using the Italian spontaneous adverse drug reaction (ADR) reporting system database (SRS).

Methods: We selected ADR reports attributed to medicinal products containing pegylated active substances and/or pegylated liposomes from the Italian SRS in the period between its inception and March 2021. As comparators, we extracted ADR reports of medicinal products containing the same non-pegylated active substances and/or non-pegylated liposomes (if not available, compounds belonging to the same mechanistic class). A descriptive analysis of all ADR reports, and of hypersensitivity reactions specifically, was carried out. Reporting rates and time to onset of hypersensitivity reactions for each medicinal product were also calculated. As a measure of hypersensitivity reactions reporting disproportionality, we also calculated the reporting odds ratio. Furthermore, the relationship between the proportion of hypersensitivity reactions for the study drugs and their PEG size was assessed.

Results: Overall, 3,865 ADR reports were related to pegylated medicinal products and 11,961 to their non-pegylated comparators. Concerning both overall ADRs and hypersensitivity reactions reports, around two-thirds of patients were females and they mostly concerned patients aged between 46 and 64 years. The frequency of hypersensitivity reactions reporting was higher among pegylated vs. non-pegylated medicinal products (11.7% vs. 9.4%, $p < 0.0001$) and the proportion of serious hypersensitivity reactions was two times higher for pegylated vs. non-pegylated medicinal products (33.0% vs. 16.3%; $p < 0.0001$). The hypersensitivity reaction reporting rates were always higher for pegylated vs. non-pegylated medicinal products, with reporting rate ratios ranging from 1.4 (95% CI 0.8–2.5) for pegfilgrastim vs. filgrastim to 20.0 (95% CI 2.8–143.5) for peginterferon alpha-2a vs. interferon alpha-2a. The median time to onset of hypersensitivity reactions ranged from < 1 day and 69 days for pegylated medicinal products, and from < 1 day and 345 days for non-pegylated comparators. Disproportionality analysis showed that both pegylated and non-pegylated medicinal products were not associated with an increased reporting trend of hypersensitivity reactions. Moreover, higher PEG molecular weights were not statistically associated with an increased risk of hypersensitivity reaction reporting.

Conclusion: Although disproportionality analysis showed that neither pegylated nor non-pegylated medicinal products were associated with an increased hypersensitivity reactions reporting trend, findings of

this study suggest a potential involvement for pegylation in triggering drug-related hypersensitivity reactions, especially clinically relevant ones. However, further clinical assessment is required to validate pharmacovigilance data.

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