

# HPV vaccination in women treated for Cervical Intraepithelial Neoplasia grade 2 or 3: evidence-based recommendation from the Multisociety Italian Guidelines for cervical cancer prevention

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DOI: [10.31083/j.ejgo4205153](https://doi.org/10.31083/j.ejgo4205153)

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Submitted: 30 March 2021 Revised: 23 April 2021 Accepted: 29 April 2021 Published: 15 October 2021

**Objective:** Women treated for Cervical Intraepithelial Neoplasia (CIN) grade 2 or 3 are at increased risk of CIN and cervical cancer. Human Papillomavirus (HPV) vaccination is effective in preventing CIN in women who are not infected by HPV. Some studies suggested that vaccination may reduce the risk of CIN2 or 3 in women treated for CIN. A working group including all Italian scientific societies involved in tackling cervical cancer developed a recommendation on vaccination against HPV for women treated for CIN2 or CIN3. **Data sources, methods of study selection:** The group conducted a systematic review of the literature published from January 2006 to May 2019. Evidence on safety outcomes was retrieved by a recent Cochrane Review on vaccination in the general population. To develop the final recommendation, evidences were appraised and integrated by a Panel of Experts using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evidence to Decision framework. **Tabulation, integration and results:** Six eligible studies were included. Four were RCTs and two were cohort studies, with different timing of vaccination. An additional study, published in October 2019, was taken into consideration after external review. A reduction of 70% CIN2+ in the treatment group was estimated; the vaccine was considered safe. **Conclusion:** The working group recommends the use of HPV vaccination in women treated for CIN2 or 3. The strong recommendation is based on large estimated desirable effects and trivial anticipated undesirable effects (moderate certainty of evidence), negligible costs and savings (no studies included), and a positive judgment in terms of feasibility, acceptability, and impact on equity.

## Keywords

Cervical cancer; Screening; Human papillomavirus; Vaccination

## 1. Introduction

In Italy, approximately 1,700,000 women are screened for cervical cancer every year within organized programs with a detection rate of 3.4 per thousand pre-neoplastic lesions, for more than seven thousand treatments overall [1]. In addition, data from the Italian nationwide surveillance PASSI suggest that almost the same amount of cervical pre-neoplastic lesions are identified and treated every year in Italy outside organised screening programs [2].

The HPV vaccine was shown to be effective in preventing new infections and CIN associated with HPV 16 and 18 infection. Instead, the vaccine showed no therapeutic effect on infections and lesions already present at the time of vaccination [3]. Thus, vaccine effectiveness in women treated for CIN2 and CIN3 is uncertain and challenging to assess, given the difficulty of classifying lesions identified after treatment as a new pathology or persistence of the treated lesion.

The rationale for vaccinating women treated for CIN2 and CIN3 derives from the evidence of an increased risk of CIN lesions and cancer persisting for many years [4, 5].

A meta-analysis conducted by the Italian Group for Cervical Cancer Screening (GISCi), reported an average viral clearance of 76.5% at 6 months after treatment, and an 8.4% risk of developing CIN2+ at 24 months in women treated for CIN2 and CIN3 [6]. The risk of recurrence of CIN2+ lesions differs by HPV test and cytology results, ranging from a 0.9% to 30% at 24 months after treatment, in women with a negative or positive first HPV test after treatment, respectively [7].

The main Italian scientific societies (**Supplementary Table 1**) involved in tackling cervical cancer instituted a project to develop recommendations on cervical cancer prevention. The project aims at integrating the European guidelines for quality assurance in screening and the Italian Ministry of Health guidelines for screening on all those specific aspects that are not included in the scope of these two frameworks setting guidelines [8–11]. This paper describes the development of an evidence-based recommendation on vaccination against HPV for women treated for CIN2 or CIN3.

## 2. Methods

### 2.1. Structured question and outcomes prioritization

The clinical question “Should HPV vaccination be used in women treated for Cervical Intraepithelial Neoplasia 2 or 3?” was structured according to the Population, Intervention, Comparison and Outcomes (PICO) framework (Table 1, Ref. [7]).

**Table 1. Clinical question.**

Population: women treated for CIN2 or CIN3
Intervention: HPV vaccine (2-, 4-, 9-valent), including full vaccination course with 3 doses and incomplete vaccination courses
Comparator: no HPV vaccination
Outcomes prioritised in the scoping phase: <ul style="list-style-type: none"> <li>■ Incidence of invasive cervical cancers (Rating: CRITICAL)</li> <li>■ Incidence of CIN2 and CIN3 (Rating: CRITICAL)</li> <li>■ Safety Outcomes (Proposed in the prioritization phase) [7]           <ul style="list-style-type: none"> <li>○ Local/injection site adverse events</li> <li>○ Overall systematic event and general symptoms</li> <li>○ Serious adverse events</li> <li>○ Deaths</li> </ul> </li> </ul>
All the outcomes proposed in the prioritization phase were included and none were excluded.

## 2.2. Systematic review

### 2.2.1 Review protocol and amendments

The review protocol was registered in PROSPERO—International prospective register of systematic reviews of the National Institute for Health Research, with ID CRD42019135870 [12].

The outcomes were prioritized by the Guidelines Development Group (GDG) as suggested by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [13–15].

According to external reviewers' comments, the GDG integrated the protocol on 17/01/2020 to include the description of sources and methods to collect background information, safety outcomes and timing of vaccination.

### 2.2.2 Data sources and searches

To quantify the actual population potentially targeted by the intervention in the background section of the Evidence-To-Decision (EtD) table, two nationwide sources were used. The 2017 national report of the National Centre for Screening Monitoring (ONS) provided data about organised cervical cancer screening programs [1], while the database of "PASSI" national surveillance [2] was used to quantify lesions and treatments deriving from non-programmatic (i.e., non-organised) screening.

To synthesize evidence on effectiveness and safety of the intervention, a systematic search was performed on 31 May 2019 in the following databases: MEDLINE (accessed through PubMed), The Cochrane Library (accessed through [cochranelibrary.com](http://cochranelibrary.com)), EMBASE (accessed through [embase.com](http://embase.com)) and Scopus (accessed through [Scopus.com](http://Scopus.com)). A pre-defined search strategy was adapted to achieve the requirements of each database (**Supplementary Table 2**).

### 2.2.3 Study selection

Studies were included if published after 2006, the year of publication of the first trials on HPV vaccines marketed in the European Union.

Two reviewers independently screened for eligibility all titles/abstracts of studies identified using the search strategy, and those from the reference lists. The full texts of poten-

tially eligible studies were then assessed by two members of the Evidence Review Team (ERT). Any disagreement or uncertainty over eligibility was discussed between the reviewers and, when consensus was not reached, the project leader was involved in the discussion.

The result of this process is reported in the PRISMA flowchart (Fig. 1).

### 2.2.4 Data extraction

Data extraction was done by one reviewer using a pre-defined form including: first author and year of publication, country, study design, study aims, study population and sample size, description of intervention, descriptions of comparators, study outcomes and times of measurement, main results, results in population subgroups, and quality of the study. It was not necessary to contact study authors to retrieve additional information.

### 2.2.5 Data analysis

The efficacy outcomes of interest were the risks histologically confirmed CIN2 or CIN3 and of invasive cervical cancer in vaccinated and non-vaccinated women after treatment of CIN2 and CIN3. As categorical outcomes, the effect measure was synthesized calculating the pooled Risk Ratio and the Absolute Risk Difference. The 95% confidence intervals were calculated to report the effect size with its precision.

The pooled estimates were reported for each outcome in the Summary of Findings table using the GRADEpro online software tool, along with the certainty of the evidence items [16].

The evidence on safety outcomes was retrieved as reported in the Cochrane review [3].

A narrative synthesis was performed for costs and resource consumption, not included in the meta-analysis.

### 2.2.6 Risk of bias assessment and certainty of the evidence

The risk of bias was assessed using the Cochrane Risk of Bias RoB 2.0 tool (Cochrane Collaboration, London, UK) [17] for Randomized Controlled Trials (RCT), and the ROBINS-I tool (v. 1.0) (Cochrane Collaboration) for non-randomized studies [18]. The quality assessment results were

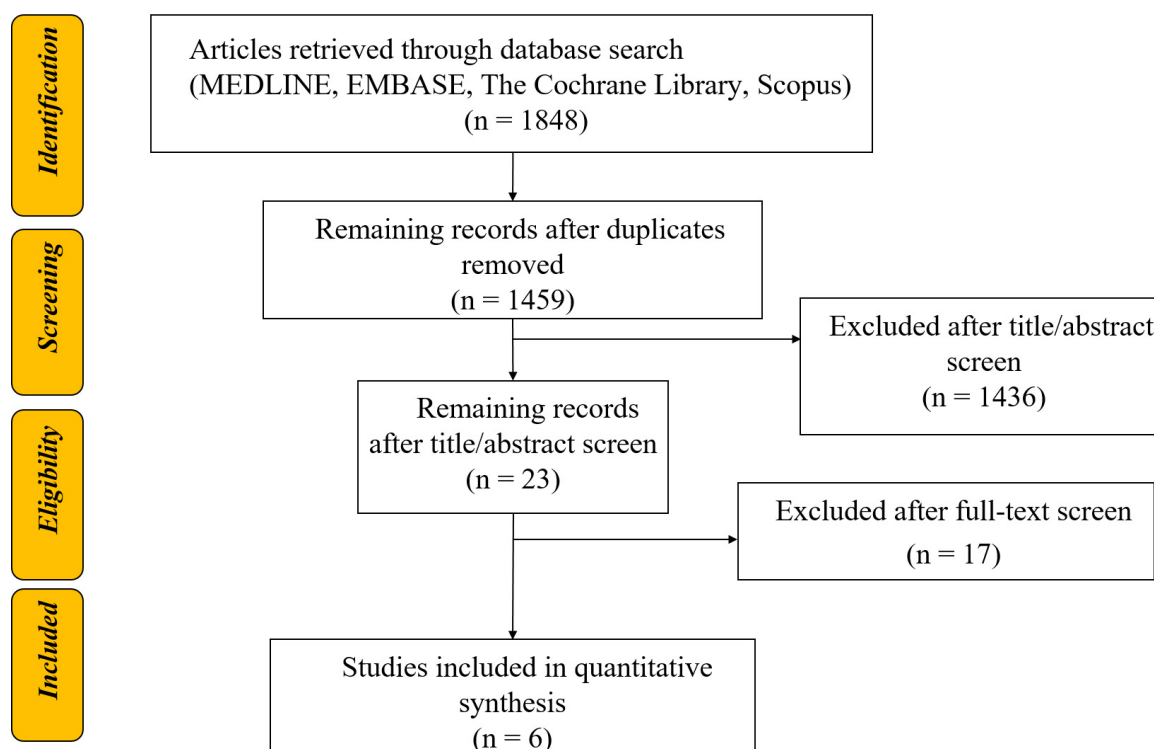


Fig. 1. PRISMA Flow chart Results of the study selection process.

reported in the “Risk of bias”, “Inconsistency”, “Indirectness”, and “Imprecision” items of the “Summary-of-Findings” (SoF) table using the GRADEpro software tool (v. 1.0) (McMaster University and Evidence Prime Inc., Hamilton, ON, Canada) [16].

The overall certainty of evidence per outcome was rated using the GRADE approach and presented to the Panel of Experts using the SoF table [16, 19–21].

### 2.3 Evidence to decision framework and recommendation development

The process used by the GDG to formulate recommendations was described in a dedicated article published elsewhere [13]. In brief, a Technical Scientific Committee (TSC) with representatives from nine scientific societies involved in tackling cervical cancer defined the scope of the process and set up the GDG subgroups, assessing conflict of interest (COI) disclosures. One of the GDG subgroups, the Evidence Review Team, including experts on the topic and methodologists, was responsible for the systematic review and completion of the first draft of the SoF table and the EtD framework [19–21]. The tables were presented during plenary meetings to the Panel of Experts including clinicians and informed patients, supporting the appraisal of EtD criteria and the recommendation formulation. Subsequently, the whole process was reviewed by Independent External Reviewers invited by the TSC, and feedbacks were used to improve the quality of recommendation. Then, a final document was sent to the Italian National System of Guidelines (SNLG) review-

ers, starting an iterative process of feedbacks and revisions done by the GDG, until final approval by SNLG reviewers and publication of the final recommendation on the Italian SNLG guidelines database [22].

## 3. Results

### 3.1 Results from the systematic review of efficacy

#### 3.1.1 Included studies

Six eligible studies were included in the systematic review of the literature, including one RCT [23] and two cohort studies [24, 25] evaluating the effectiveness of post-treatment HPV vaccination and three RCTs evaluating the effectiveness of pre-treatment HPV vaccination in reducing recurrences [26–28] (**Supplementary Table 3**).

The total number of women included in the systematic review was 1427 in the intervention group and 1663 in the control group. Since no invasive cancer was identified in any considered study, this outcome was excluded from the quality assessment of the evidence on efficacy.

On 17 January 2020, during the external review process, a study published after the literature search date was signalled, showing a smaller protection than previous studies (Hazard Ratio 0.86; 95% CI 0.67–1.09) [29]. In plenary meeting, the GDG expressed 13 out of 16 votes in favour of the inclusion of the study in the additional considerations without updating the systematic review neither changing the criteria of the recommendation.

**Table 2. Evidence synthesis on safety from a Cochrane Systematic Review by Arbyn et al. 2018. [3].**

Outcomes	Absolute risk/per 10,000		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	placebo	vaccinated			
Overall local/injection site adverse events	6847	8080	1.18 (1.16 to 1.20)	18,113 (8 studies)	⊕⊕⊕○ moderate
Pain at injection site	6505	8782	1.35 (1.23 to 1.49)	25,691 (13 studies)	⊕⊕⊕○ moderate
Swelling at injection site	1582	2737	1.73 (1.32 to 2.27)	22,106 (9 studies)	⊕⊕⊕○ moderate
Redness at injection site	1938	3333	1.72 (1.50 to 1.97)	19,996 (6 studies)	⊕⊕⊕○ moderate
Overall systematic event and general symptoms	6102	6224	1.02 (0.98 to 1.07)	18,191 (8 studies)	⊕⊕⊕○ moderate
Serious adverse events	605	611	1.01 (0.95 to 1.07)	6978 (21 studies)	⊕⊕⊕⊕ high
Deaths	11	13	1.25 (0.81 to 1.93)	71,452 (23 studies)	⊕⊕○○ low

CI, Confidence interval; RR, Risk Ratio.

### 3.1.2 Evidence synthesis

By comparing the risks of CIN2 and CIN3, the intervention was associated with a reduction in risk in all studies, with consistent estimates. The pooled estimates showed a Relative Risk (RR) of 0.32 (95% CI 0.15–0.66) for RCTs assessing the effectiveness of pre-treatment HPV vaccination, a RR of 0.00 (0.00–1.45) for the RCT and RR 0.30 (0.15–0.58) for the cohort studies assessing of post-treatment HPV vaccination.

The pooled estimates of RR for lesions related to HPV types included in the vaccine, showed a higher reduction of risk in vaccinated women compared to non-vaccinated (**Supplementary Table 4**).

The overall certainty of evidence assessed according to GRADE approach was rated as moderate.

### 3.2 Results from the systematic review of safety

#### 3.2.1 Included studies

The sample size of the studies included in the systematic review of efficacy was too small to show significant results on serious adverse effects. Nevertheless, none of the included study reported serious adverse effects in women vaccinated after treatment [23–28].

However, the evidence synthesised in a recent Cochrane review on the safety of HPV vaccination was considered transferable to the population included in the PICO defined by the GDG (Table 2) [3].

#### 3.2.2 Evidence synthesis

The Cochrane review on the safety of HPV vaccination showed an increased risk of local adverse events for vaccination compared to placebo (RR 1.18; 95% CI 1.16–1.20), as assessed in 8 studies and 18113 women, with moderate certainty of evidence. Conversely, no differences in the risk of systemic adverse events were reported (RR 1.02; 95% CI 0.98–1.07) in 8 studies and 18191 women, with a moderate certainty of evidence. Finally, there was no statistically significant increase in the risk of death (RR 1.25; 95% CI 0.81–1.93) in 23 studies and 71452 women, with an overall low certainty of evidence [3] (Table 2).

#### 3.3 Certainty of evidence

The overall certainty of evidence was rated as moderate.

The main concerns across studies were related to the tim-

ing of vaccination and study design. Three out of four included RCTs assessed the effectiveness of pre-diagnosis and pre-treatment HPV vaccination [26–28] and evidence on post-treatment were mainly available from cohort studies [24, 25], with potential selection and attrition biases [25] (**Supplementary Figs. 1,2**).

The evidence was consequently downgraded for indirectness because the largest randomized studies were conducted on a pre-treatment vaccination and then restricting the analysis to a sub-population of treated women, so the evidence was not direct considering the intervention under evaluation, i.e., treatment of women who already have been treated or who are undergoing the treatment. On the other hand, the GDG noted that there was no heterogeneity between results independently from the timing of the intervention. Thus, evidence was not downgraded for heterogeneity. The effect was considered large in all subgroups thus the certainty was upgraded to moderate.

Moreover, no evidence of difference in the risk of cervical cancer was retrieved due to the sample size of included studies and low expected incidence of cancer in this population. Notwithstanding, the pooled estimates showed consistent results toward reduction of CIN2 and CIN3 risk in the intervention group, internationally validated endpoints as proxy for cervical cancer.

#### 3.4 Results for economic evidence

A systematic review of the literature on economic evidence was not performed.

The appraisal of economics criteria was conducted during plenary meeting, starting from data on costs retrieved by public tenders for 4-valent (€ 33.5 per dose) and 9-valent HPV vaccine (€ 63 per dose) purchase by regional health-care services and costs for CIN treatment reported by an Italian Health Technology Assessment (HTA) report on cervical cancer screening [10, 30, 31].

The GDG highlighted that costs did not include counselling on vaccination and dose administration.

Considering the current costs of HPV vaccines, approximately 2500/5000 euros are needed to prevent one CIN2+ lesion. The estimates considering CIN2+ incidence at 6% and vaccine protection at 60%, ranged from € 2792 if a vaccine



CRITERIA	SUMMARY OF JUDGEMENTS						IMPORTANCE FOR DECISION				
	PROBLEM	DESIRABLE EFFECTS	UNDESIRABLE EFFECTS	CERTAINTY OF EVIDENCE	VALUES	BALANCE OF EFFECTS		RESOURCES REQUIRED	CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	COST EFFECTIVENESS	EQUITY
	No	Probably no	Probably yes	Yes	Varies	Don't know					
	Trivial	Small	Moderate	Large	Varies	Don't know					
	Large	Moderate	Small	Trivial	Varies	Don't know					
	Very low	Low	Moderate	High	No included studies						
	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability							
	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know				
	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know				
	Very low	Low	Moderate	High	No included studies						
	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies				
	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know				
	No	Probably no	Probably yes	Yes	Varies	Don't know					
	No	Probably no	Probably yes	Yes	Varies	Don't know					

**Fig. 2. Summary of judgments from the Evidence-to-Decision framework by Panel of experts [16].** The final judgment for each criterion is marked with colors: blue was used for criteria with neutral meaning while yellow or green were used for criteria expressing a balance against or in favor of the intervention.

dose costs € 33.5, up to € 5250 if vaccine costs € 63 per dose. Considering a CIN2+ incidence of 8% and vaccine protection at 60%, the corresponding costs ranged from € 2094 to € 3938.

The GDG reported that there were also unquantified avoided costs (second treatments and treatment related to obstetric outcomes). According the Italian HTA report, the cost of treating a CIN2+, including follow up, was € 1785 (2010 currency) [10], while costs related to reproductive outcomes avoided by reducing re-treatments were not quantified.

The Panel of Experts judged as negligible the costs for HPV vaccinations needed to avoid a CIN treatment compared to the costs related to treatment its health consequences, leading to a judgment of cost-effectiveness in favour of intervention [21] (Fig. 2).

The GDG also stated that a more in-depth economic analysis should be conducted, since the current evaluations were based on a rapid cost-consequences analysis and on the opinion of the panel's experts assessing available data.

### 3.5 Equity, acceptability, and feasibility

Equity was considered to increase since a free access to vaccine with active proposal by the screening service would decrease economic and health literacy barriers, in analogy to the documented effect of population-based screening programs [32, 33] and to active invitation to HPV vaccination in Italy in reducing health inequalities [34].

The intervention was considered as largely acceptable by all the three relevant involved stakeholders groups: health professionals were in large part in favour of the intervention

as reflected by the panellists; included studies showed that most women accepted the intervention; finally, in Italy several regional health services were already providing the intervention for free, showing that also policy makers accepted the intervention (Fig. 2, Ref. [16]).

## 4. Discussion

### 4.1 Recommendation and justification

The GDG expressed a strong recommendation in favour of the use of HPV vaccination in women treated for CIN2/3, mainly considering the large expected desired effects, and the negligible undesirable events (Fig. 2).

Although the outcome assessed as "incidence of invasive cancers" had a "very low" quality of evidence, the panel unanimously assessed that the outcomes "CIN2 and CIN3 lesions" were valid proxies of the risk of invasive cancer. This decision was consistent with decisions taken by other panels in the development of international recommendations for the prevention of cervical cancer [35–37]. Furthermore, given the preventive efficacy of post-treatment follow-up, it was not reasonable to expect incident cancers in women treated for CIN2 and CIN3 in controlled studies.

#### 4.1.1 Desirable effects

The GDG judged as large the desirable effects expected from the implementation of HPV vaccination in women treated for CIN2/3, mainly based on the results of the three included studies assessing vaccination performed after treatment, thus with population and intervention consistent with the PICO [23–25].

The GDG also considered the increased risk of premature births and negative pregnancy outcomes resulting from repeated cervical treatments in women of childbearing age [38].

Finally, the potential increase in the desired effects compared to those reported in the included studies, resulting from the introduction of the 9-valent HPV vaccine was considered for the final judgment.

#### 4.1.2 Undesirable effects

The GDG judged as trivial the undesirable effects of HPV vaccination in women treated for CIN2/3 based on the evidence reported by a Cochrane review published in 2018 on HPV vaccination safety. Despite the Cochrane review assessed safety outcomes in the general population [3], the GDG considered the results transferable to the target population of the recommendation (Fig. 2).

#### 4.1.3 Resources required

Although direct assessments of all the costs and savings consequent to vaccination in women treated for CIN2/3 was not available, the GDG considered the costs related to the HPV vaccination implementation to be negligible. This judgment was based on the opinion of the Panel of Experts, considering the limited costs related to the vaccination purchase and counselling, and of the avoided (although not quantified) costs resulting from the reduction in repeated treatments in the management of related obstetric outcomes (Fig. 2).

Finally, although no direct assessment of the cost-effectiveness of HPV vaccination was available in women treated for CIN2/3, the GDG evaluated the cost-effectiveness in favour of the intervention.

#### 4.2 Strengths and weaknesses

Neither a systematic review of cost-effectiveness of the intervention nor a proper cost-effectiveness analysis were conducted. A rapid cost-consequence estimate was produced by the panellists, which suggested that a proper cost-effectiveness analysis should be conducted, even if the budget impact of the intervention would not be large in terms of absolute cost for the NHS.

Similarly, no systematic review was conducted for evidence on how women value the included outcomes. Nevertheless, cancer incidence and reproductive outcomes were considered hard outcomes that most women would rate as critical.

Finally, the systematic review search was closed on May 2019 even if studies published after that date were considered in the final evaluation [29], according to external reviewers' suggestion. After the publication of the recommendation, two further studies were published and identified by the ERT. Their results go in the same direction of the included studies [39, 40].

#### 4.2.1 Subgroup considerations

Although not considered in the PICO, the populations of the included trials include also women treated for AIS (ade-

nocarcinoma *in situ*) and microinvasive cancers. The GDG stated that the final recommendation could be extended to these women too.

In women of non-reproductive age, the overall impact of the intervention is lower, making the balance between desirable and undesirable effects, as well as between benefits and costs, less favourable.

#### 4.2.2 Implementation considerations

The timing of vaccination in trials was close to treatment (before or within three months after surgery). There was no evidence for vaccinations after this time frame. Thus, to ensure timeliness in HPV vaccination, it is advisable to identify a care pathway, defining the roles of the health services to involve. The steps to be defined include the identification of target women, the referral to vaccination services, the counselling and HPV vaccine administration. In this regard, the GDG recalled how the issue of reaching specific high risk groups emerged in other vaccinations targeting as hepatitis B vaccination [41, 42]. Moreover, the GDG highlighted how issues related to care pathway organization can be greater in some opportunistic screening settings.

#### 4.2.3 Monitoring and evaluation

The GDG stated that HPV vaccination coverage in women treated for CIN2/3 should be calculated in organised screening programs.

#### 4.3 Relationship with other guidelines

The ERT found that the most important agencies and scientific societies do not mention the use of HPV vaccine in women treated for CIN2 or CIN3. The American Cancer Society does not recommend vaccination for women over 26, actually excluding the vast majority of the potential target of the proposed intervention [43, 44]; similarly the US Advisory Committee on Immunization Practices (ACIP) does not recommend catch-up HPV vaccination for all adults aged >26 years; but recommends shared clinical decision-making regarding HPV vaccination for some adults aged 27 through 45 years who are not adequately vaccinated [44]. Similarly, European Centre for Disease Control (ECDC) limits the vaccination to women below 26, but it mentions the need to study strategies to vaccinate high-risk groups in addition to mass vaccination of girls and boys [45].

At National level, Spain introduced free vaccination of women treated for CIN2 and CIN3 in 2017 [46].

The Austrian HTA agency in 2020 issued a report concluding that there "is moderate evidence that HPV vaccination in women treated for high-grade cervical cancer lesions reduces the risk of future HPV related high-grade CIN and is more effective than usual care", but it is also cautious about safety in this group, since vaccine has been administered mostly to younger women, and on long term effectiveness [47].

Moreover, the European Society of Gynaecologic Oncology and the European Federation for Colposcopy published

in 2019 a position paper on HPV vaccine in which they suggest offering vaccination, on individual basis, to women with HPV-related disease and prior local treatment [48].

Finally, moreover, the 2020 position paper of the Italian Society of Colposcopy and Cervico-Vaginal Pathology (SICPCV) suggested HPV vaccination for women aged 27–45 years, on individual request, even after local treatment for high-grade CIN, without distracting resources from the primary objective of vaccination and cervical cancer screening programs [37].

#### 4.4 Unanswered questions and future research

The main gap of knowledge emerged during the recommendation development process was related to the optimal timing for vaccination, for which evidence from new studies is needed.

Moreover, to have stronger evidence on the effectiveness of HPV vaccination in the natural history of the disease after treatment of CIN2/3, it is important to be able to distinguish recurrences due to inadequate treatment and/or persistence of the HPV infection that caused the treated lesion, from recurrences due to new infections. To this end, it would be advisable to perform HPV typing on samples collected before and after treatment in future studies or in re-analyses of already published studies.

Finally, the GDG reported that an updated of the recommendation will be necessary when new evidence coming from ongoing or planned prospective randomized trials will be available. Relevant evidence will come from the HOPE9 Trial planned in Italy [49] and from the NOVEL trial in Sweden and UK [50].

### Abbreviations

CIN, Cervical Intraepithelial Neoplasia; ERT, Evidence Review Team; GDG, Guidelines Development Group; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HPV, Human Papillomavirus; RCT, Randomized Controlled Trials; TSC, Technical Scientific Committee.

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### Ethics approval and consent to participate

The work reported in this paper does not need ethical approval. The guideline development project has been submitted to and approved by the Italian National System of Guidelines (SNLG) of the National Institute of Health (ISS) (Sistema Nazionale Linee Guida, Istituto Superiore di Sanità). This specific recommendation has been submitted to the SNLG and published on the web platform of the Italian recognized guidelines database: <https://snlg.iss.it/>.

## Acknowledgment

Thanks to all the participants to the GDG, peer reviewers for their opinions and suggestions.

## Funding

This research received no external funding.

## Conflict of interest

The authors declare no conflict of interest.

## Supplementary material

Supplementary material associated with this article can be found, in the online version, at <https://ejgo.imrpress.com/EN/10.31083/j.ejgo4205153>.

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