Strategies to achieve HPV-related disease control in Italy: results from an integrative approach

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ABSTRACT

Background: achieving Human Papilloma Virus (HPV) - related diseases control is an important challenge in public health. In Italy HPV vaccination uptake does not rise a sufficient level. The aim of this project is to identify strategies to promote HPV vaccination in Italy.
Methods: an integrated approach consisting of a systematic review and a two-step panel consultation was used to identify strategies to increase vaccination uptake among adolescents, population target of the national vaccination program, and to promote vaccination in additional targets. Overall, ten experts in the fields of Gynecology, Public Health, General Practice and Pediatrics were involved along with Patients representatives. Recommendations were elaborated according to a set of criteria drawn from the Evidence to Decision (EtD) framework.
Results: the systematic review led to the identification of three categories of strategies: reminds, education and multicomponent approaches respectively. A strong recommendation was formulated to use reminds tailored to vaccine recipients or their parents, and a moderate recommendation to use reminds directed to health professionals. A moderate recommendation was developed on the implementation of multicomponent interventions. A strong recommendation was yielded with respect to the promotion of HPV vaccination among women already treated for HPV-related diseases, fertile women not previously vaccinated and 25 year-old women undergoing cervical cancer screening. Lastly, a strong recommendation was formulated for catch-up initiatives targeted to women and men turning 18 years of age.
Conclusion: this project led to the identification of several valuable strategies to improve HPV vaccination and strengthen HPV-related diseases control at national level.

Key words: Immunization Programs, Papillomavirus Vaccines, Communicable Disease Control, Consensus, Implementation Science

INTRODUCTION

Worldwide, cervical cancer is the fourth more common cancer among women after breast cancer, colorectal cancer and lung cancer [1]. The World Health Organization (WHO) has recognized cervical cancer

as the first cancer totally attributable to an infection (HPV - Human papilloma virus) [2,3]. In particular, high-risk genotypes, namely HPV 16 and 18 overall, but also HPV 31, 33, 45, 52 and 58, might be responsible for potential preneoplastic lesions and following cancers.

In Italy, it is estimated that almost 5.000 cases/year are attributed to chronic infections by high-risk HPV genotype, with particular regard to cervical cancer and a variable proportion of cancer of anus, vagina, vulva, penis, and also oral cavity, pharynx and larynx [1].

Because of that, vaccination against HPV has been implemented worldwide since 2007. In Italy, since 2008, vaccination against HPV has been offered actively and free of charge to 12 years-old girls. Moreover, from 2015 onwards, some Italian Regions extended the free of charge offer to 12 years-old boys [4].

This extension of vaccination followed the position paper issued by the WHO in 2017 in which a main and secondary target of vaccination were identified. As the main target, the WHO has identified girls between 9 and 14 years of age while, as a secondary target if feasible, accessible, inexpensive and without consequences in terms of resources intended for vaccination of the primary target, girls aged ≥ 15 years and boys [3].

Currently the Italian National Immunization Plan (NIP) 2017-2019 recommends HPV vaccination to the whole population (females and males) in the twelfth year of life, women 25 years-old at the first screening for cervical cancer and subjects at risk (Men who have Sex with Men - MSM) [5]. The NIP also identifies vaccination coverage ≥ 95% as desirable goal.

Although free of charge since 2008, vaccination coverage has not reached this goal in any Region and a decreasing trend has been shown in the last year [4]. In particular, for older cohorts, from 1997 to 2011, vaccination coverage varies from 73% to 76% for at least one dose and between 69% and 72% for the complete vaccination cycle. Data about more recent cohorts (2003-2005) have shown a decreasing trend reaching the lowest value of 64.3% for the first dose and 49.9% for the complete cycle [4].

Therefore, targeted interventions to increase vaccination coverage would be worthwhile, taking into account that HPV vaccination, even if not included among mandatory vaccinations in Italy, is provided free of charge in the target population because included in the list of services deemed to be essential for the Italian population [4].

The achievement of vaccination coverage goal could allow controlling cervical cancer. Australia has been the first country worldwide to promote a national vaccination program against HPV in April 2007. Vaccination target originally included only girls aged 12-13 years, while boys of the same age were included from 2013 onwards. As reported by the National HPV Vaccination Program Register, in 2017, the first uptake reached 88.9% and 8% respectively among 15 years old girls and boys, whereas the 3-doses coverage was 80.2% and 75.9% respectively. The program has also included the catch up of women up to 26 years old for a while [6]. The campaign has led to a reduction of more than 90% of vaccine-targeted HPV types infections and ano-genital warts and 47% reduction in high-grade squamous cervical lesions [7,8]. Currently, vaccination in Australia is also recommended to immunocompromised individuals, MSMs and women already treated for HPV-related lesions.

A recent study has estimated that in Australia, while maintaining high coverage, it would be possible to fall below 1 in 100,000 cases – in that eliminate the disease - by 2066 (range 2054-2077), if the cohorts receiving the 9-valent vaccine are continued to be screened for cervical cancer [9].

In order to achieve the control of cervical cancer, a high vaccination coverage is indeed necessary, and strategies aimed at increasing it should be supported and implemented.

The results of a recent systematic review suggest many types of intervention can increase HPV vaccination coverage in different settings, and with modest cost, in United States. Interventions were effective especially when implemented in combination at both provider and community levels [10]. Alongside interventions to increase vaccination coverage among the targets of vaccination campaign, another way to make the control of cervical cancer possible could be to promote the vaccination in targets other than those already included in the NIP.

The aim of the present study was to formulate, through an integrative approach encompassing both the literature and stakeholders' opinions, national recommendations to increase HPV vaccination coverage in 12-year-olds and to promote vaccination to additional targets.

METHODS

In order to elaborate the recommendations, a consensus development method was adopted. Firstly, a systematic review on the available evidence on the interventions that increase vaccination coverage among 12-year-olds, and on the interventions to promote the vaccination to other targets that are not currently reached out by the NIP, was performed. Secondly, the results of the systematic review were used to identify possible interventions that were subsequently submitted to the evaluation of an expert panel for the development of a consensus. The latter was achieved through two consecutive face-to-face meetings. The first meeting involved a restricted group of experts and was aimed at elaborating a set of preliminary recommendations considering both the evidence and experts' opinions on possible uncertainties surrounding the evidence. The second meeting involved a larger number of experts with the goal to get a consensus and to formulate a final set of recommendations (Figure 1). The steps of the whole process are described hereafter.

FIGURE 1. Recommendations formulation process.

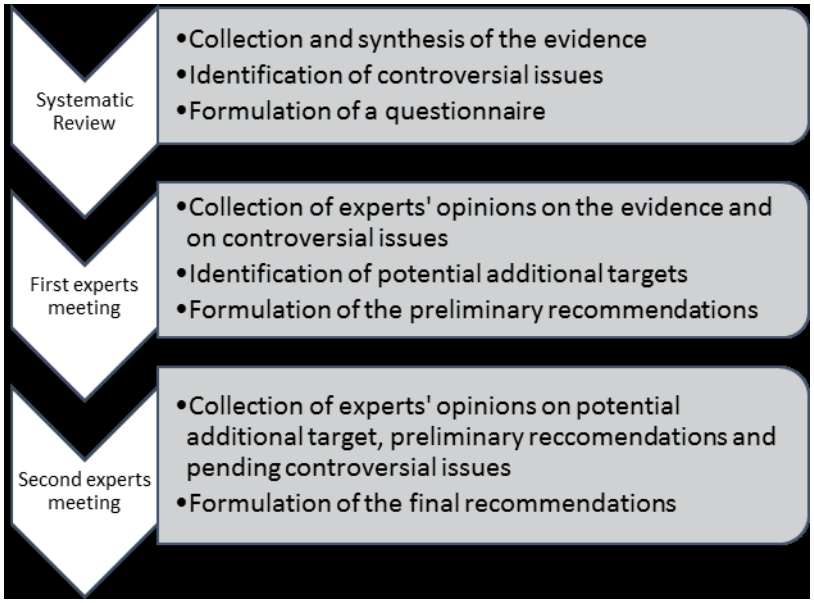


TABLE 1. Modified Evidence to Decision Framework

Domain	Judgments	Scale
Problem	Is the problem a priority?	No; Probably no; Probably yes; Yes; Varies; Don't know
Desirable Effects	How substantial are the desirable anticipated effects of the intervention?	Trivial; Small; Moderate; Large; Varies, Don't know
Certainty of evidence	What is the overall certainty of the evidence of effects?	Very low; Low; Moderate; High; No included studies
Resources required	How large are the resource requirements (costs)?	Large costs; Moderate costs; Negligible costs and savings; moderate savings; large savings; varies; Don't know
Equity	What would be the impact on health equity?	Reduced; Probably reduced; Probably no impact; Probably increased; Increased; Varies; Don't know
Acceptability	Is the intervention acceptable to key stakeholders?	No; Probably no; Probably yes; Varies; Don't know
Feasibility	Is the intervention feasible to implement?	No; Probably no; Probably yes; Yes; Varies; Don't know

1. Evidence collection

A systematic review was carried out by searching electronic databases (PubMed, Scopus, and Web of Science) using the keywords "papillomavirus vaccine", "HPV", "vaccination strategy" and "efficacy". Only articles conducted in high-income countries and evaluating the impact of one or more strategies on HPV vaccination coverage were included. Strategies identified through the review were categorized according to the target and the type of intervention.

2. First meeting methodology

During the first face-to face meeting, organized in Rome on December 2018, five selected experts from different disciplines (Public Health, Pediatrics, Gynecology, and General Practice), identified based on their leadership in the field, were first provided with an overview of project aims and available evidence and were subsequently submitted to a questionnaire. The questionnaire was anonymous and included two parts, one on types of strategies identified from the literature to increase vaccination coverage and one on potential additional targets of the vaccination. The first part was developed following the Evidence to Decision (EtD) Framework [11]. Particularly, the EtD framework was used to identify which criteria to submit to the consensus development because either critical or controversial. With this respect, seven out of the 12 domains proposed by the EtD were used (Table 1).

For each EtD domain an agreement among the experts was adjudicated when at least three over the five experts expressed the same judgment.

The second part encompassed several additional potential targets (namely women treated for HPV-related diseases, women at the moment of their first invitation to the cervical cancer screening, women at their first contact with the General Practitioner (GP), women discharged from obstetric/gynecological clinics or from Emergency Room for a gynecological condition, girls turning 18 years old, boys and girls until their 18th birthday) and relied on a scale from 1 (total disagreement) to 10 (total agreement) to collect experts' opinion on the opportunity to promote vaccination to each target. The responses were then dichotomized in "Not agree" or "Agree" based on a score $< \text{or} \geq 7$. The experts were considered to agree when at least three out of five did "agree" or "not agree" with suggested additional targets.

At the end of the first meeting, based on both the evidence from the literature and the experts' opinions, a preliminary list of recommendations was elaborated and modulated as strong, moderate or weak. Recommendations about strategies to increase vaccination coverage among 12-year-olds were modulated as strong if no critical points were highlighted, moderate if some criticisms were raised from experts in relation to domains other than desirable effects and certainty of evidence, and weak in presence of criticisms on desirable effects and certainty of evidence emerging from the literature itself.

3. Second meeting methodology

The second face-to-face meeting was held in Rome, Italy, on February 26th 2019. An extended group of ten experts from several contexts (Public Health, Pediatrics, Gynecology, General Practice, Ministry of Health and Patients Representative) participated in the meeting that was organized in two parts. During the first part, a summary of previous activities and results was presented to the participants and discussed by a chairperson. In the second part, a questionnaire was administered to the experts in order to collect their opinion. The questionnaire included two sections. Within the first one, the experts were asked to express their agreement or disagreement on promoting HPV vaccination to additional targets, as emerged during the first meeting. Furthermore, for each additional suggested target, they were asked to select one or more strategies considered valuable to reach out the target. The second section of the questionnaire was built as a series of statements reporting the preliminary recommendations (along with their modulation) yielded by the first meeting about strategies to improve vaccination coverage among 12-year-olds. Furthermore, for each statement, two or three ancillary statements were submitted to address critical points highlighted during the first meeting (e.g. economic sustainability, equity, acceptability and feasibility of the strategies). Experts' opinions were collected based on a 4-points Likert scale (agree, partially agree, partially disagree, or disagree). The responses were collected anonymously through a tele-voting system using Google Forms.

After the meeting, potential additional targets of HPV vaccination were identified based on the agreement of at least 70% of the experts and recommendable strategies to reach out the target were identified looking at the majority of answers given by the experts. As for the recommendations on the strategies for increasing HPV coverage among 12-year-olds, the preliminary recommendations were confirmed or downgraded based on the level of agreement reported by participating expert. If at least 70% of the experts expressed a total or partial agreement with the recommendation, that was confirmed. In the case that at least 50% but less than 70% of the experts reported to be partially or totally agree with the recommendation, then this was downgraded unless already weak. This process led to the definition of the final recommendations.

RESULTS

1. Evidence collection

The synthesis of evidence allowed to identify three types of interventions to implement HPV vaccination coverage, namely reminder-based, information and communication (I&C) and multicomponent interventions. Furthermore, two potential targets for these interventions were selected: vaccination recipients and their parents from one side and healthcare workers (HWCs) on the other side.

2. First Expert meeting

Results yielded by the first expert meeting are summarized in table 2 and described in more details hereafter.

Reminder-based interventions

The panel considered reminder-based interventions as valuable tools which can positively influence vaccination coverage. Particularly, benefits were expected to be higher if interventions are targeted to eligible individuals, irrespective of their age, and their parents. Furthermore, there was an agreement in considering reminder-based interventions effective, sustainable, fair in terms of access to vaccination, and acceptable. In contrast, disagreement emerged about effectiveness, feasibility and acceptability of this kind of interventions tailored to HCWs. Some experts pointed out that the intervention would require either electronic medical records or a digital vaccination

TABLE 2. Results from the collection of evidence and experts' opinions on interventions to increase HPV vaccination coverage among 12-year-olds

Questions	Is the problem a priority?	How substantial are the desirable anticipated effects?	What is the overall certainty of the evidence of effects?	How large are the resource requirements (costs)?	What would be the impact on health equity?	Is the intervention acceptable to key stakeholders?	Is the intervention feasible to implement?	Strength of preliminary recommendation
Reminder-based intervention								
for vaccination recipients and/or their parents	+/+	+/+	+/+	-/+	-/+	-/+	-/+	Strong recommendation
for HCWs	+/+	+/-	-/-	-/+	-/+	-/-	-/-	Moderate recommendation
Information and Communication (I&C) intervention								
to vaccination recipients and/or their parents	+/+	-/+	-/-	-/-	-/+	-/+	-/+	Weak recommendation
Mass campaigns	+/+	-/-	-/-	-/-	-/+	-/+	-/+	Weak recommendation
Multicomponent intervention								
targeted to vaccination recipients and/or their parents	+/+	+/-	+/-	-/-	-/+	-/+	-/-	Moderate recommendation
targeted to HCWs	+/+	+/+	+/+	-/+	-/+	-/+	-/+	Strong recommendation
targeted to vaccination recipients and/or their parents and to HCWs	+/+	+/+	-/-	-/-	-/+	-/+	-/+	Moderate recommendation

+/+ : Evidence and experts are in favor (high priority/moderate or high desirable effect/moderate or high certainty of the evidence/low required resources/probably increased health equity/moderate or high acceptability/moderate or high feasibility)
-/- : Lack or insufficient evidence and the experts are not in favor or disagree
+/- : Evidence in favor but the experts are not in favor or disagree
-/+ : Lack or insufficient evidence but experts are in favor

registry but, as of now, they are not homogeneously implemented across the country.

Information and communication strategies

The panel considered I&C strategies a pillar upon which to build HPV vaccination campaigns, particularly when eligible individuals and their parents are targeted by the intervention. As a general matter, the panel highlighted I&C as a key component of health promotion and that strong and empathetic relationships between HCWs and citizens might certainly play a major role. Nevertheless, amount and quality of evidence about their effectiveness were judged to be low or moderate and these strategies were considered requiring few resources. In contrast, a positive judgment of feasibility and acceptability were agreed upon since these interventions are already included in common health promotion activities in routine practice.

Concerning mass I&C strategies, i.e. campaigns carried out at population level, the expert panel did not achieve an agreement. Indeed, even if they agreed on the potential affordability in terms of resources needed, feasibility and acceptability, uncertainty was expressed about extent of effectiveness and quality of evidence.

Multicomponent interventions

Multicomponent interventions represent a wide and heterogeneous group of strategies. Experts agreed about the potential of this kind of interventions which could be regarded as the most effective strategies to be promoted. Indeed, these public health interventions are multifaceted in nature and their effectiveness in increasing vaccination coverage proportionally depends on the number and kind of strategies deployed. Particularly attractive are school-based interventions combined with education of vaccination recipients and/or their parents and proactive calls from primary care professionals. At this regard, the first encounter between teens and GPs is a key moment to raise awareness and offer vaccination. On the other hand,

experts affirmed that effectiveness, sustainability, feasibility and equity cannot be predicted as they largely depend on the specific combination of interventions used. As a matter of fact, costs could be overwhelming for local health authorities. Moreover, the panel judged the evidence to be of low quality as well as transferability.

Higher agreement was achieved about multicomponent interventions that target HCWs. Increasing HCWs' awareness is an important step towards the raise of positive attitude among citizens. Evidence from literature suggests the effectiveness of these interventions being moderate and its certainty was judged to be moderate/high. Similarly, to multicomponent interventions which target eligible individuals and/or their parents, resources needed, feasibility, equity and acceptability can vary according to the specific strategy used and the local context but might be affordable.

Other potential targets

The panel completely agreed (5/5) upon promoting vaccination in women affected by cervical HPV-related diseases who undergo treatment. The decision was also reasoned by the growing amount of evidence [13-17]that suggest that HPV vaccination, combined with the appropriate treatment, leads to a significant reduction of relapses and reinfections. Multicomponent interventions, I&C strategies, proactive calls and the involvement of GPs and gynecologists were considered as the most effective strategies.

The panel strongly agreed (4/5) to promote vaccination in girls up to 16 years old, 25-year-old women undergoing cervical cancer screening and boys and girls at their first medical visit by the GP.

The panel did not achieve an agreement (2/5) about promoting vaccination in women of 18 years of age or after childbirth (post-partum). None of the experts agreed on promoting vaccination either in those entering to the world of work or to those attending university as it could potentially lead to inequality in terms of access to vaccination.

First meeting conclusion

At the end of the meeting, 14 preliminary recommendations were formulated in the form of questions (Table 3). Seven questions and 16 sub-questions aimed at investigating expert's agreement with the strength of recommendations about strategies to increase HPV vaccination coverage in 12-year-olds. Seven questions and six sub-questions aimed at investigating expert's opinions about additional targets to include in vaccination promotion.

3. Second expert meeting

During the second meeting, experts were asked about the 14 preliminary recommendations.

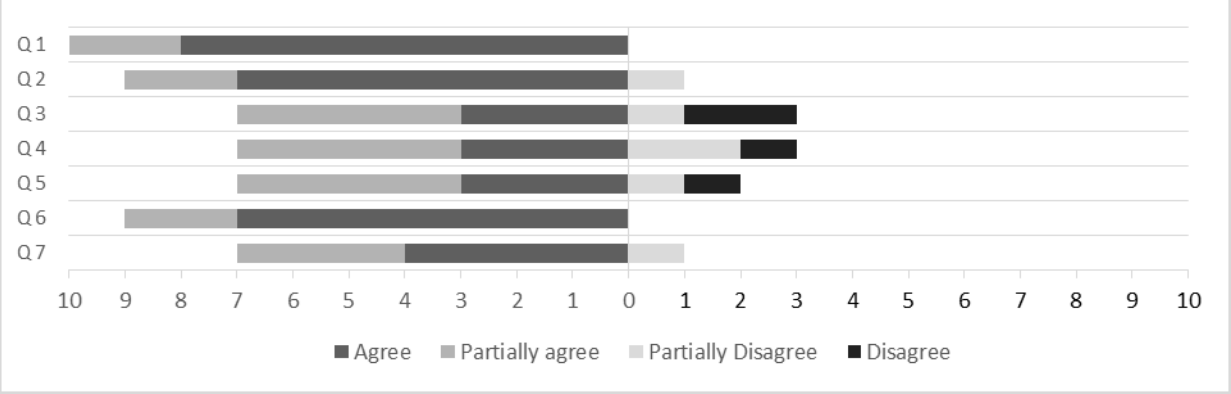
Section 1: Strategies to improve vaccination coverage among 12-year-olds

Figure 2 shows experts' opinions about preliminary recommendations on strategies to improve vaccination coverage among 12-year-olds:

Reminder-based interventions

The panel completely agreed (10/10) on the **strong recommendation** of promoting the implementation of reminder-based strategies tailored on vaccination recipients and/or to their parents. This kind of interventions was seen to be able to also improve a timely uptake of first and second doses and reduce missed opportunities. Particularly, all experts agreed in recommending it to all teens of 11-12 years and/or their parents to remind them the scheduled date of vaccination. In addition, most of

FIGURE 2. Experts' opinion on strategies to increase vaccination coverage among 12-year-olds.



Q n: question number n according to Table 3

the experts (9/10) concurred with the recommendation of using reminder-based tools to contact those who missed the vaccination appointment. In this sense, reminder-based interventions could be regarded to as key catch-up tools.

The panel was also in accord (9/10) with the **moderate recommendation** of targeting HCWs (e.g. through alert in electronic medical records). The most frequently mentioned HCWs were pediatricians (9/10), MDs in vaccination clinics (7/10) and GPs (6/10). On the contrary, only few experts would target gynecologists or medical doctors working in clinics and hospitals. Nonetheless, the experts agreed in considering these interventions costly (6/10), and with low feasibility (8/10) due to the need of a full implementation of the national digital vaccination registry and the population registers.

Information and communication strategies

The panel (7/10) agreed with the **weak recommendation** of implementing I&C strategies targeted to vaccination recipients and their parents. In particular, doubts were raised about costs and feasibility. In fact, according to the opinion of 7 out of 10, these interventions require trained personnel which would make costs arise and feasibility struggle in many contexts.

TABLE 3. Preliminary questions based upon first experts meeting

- Q1. Should strategies based on reminds for vaccination recipients and their parents be strongly *recommended* to increase HPV uptake?
  - It is *recommended* to send reminds to teens of 11-12 of age or their parents some days before the vaccination appointment scheduled with the healthcare practitioner at the moment of the proactive call. What is your opinion?
  - It is *recommended* to send reminds to teens of 11-12 of age or their parents in case of eligible individuals missing the scheduled vaccine appointment. What is your opinion?
- Q2. Shoud strategies based on reminds for HCWs be moderately *recommended* to increase HPV uptake?
  - In your opinion, which would be the most appropriate HCWs to be targeted by this intervention?
  - In your opinion, could this intervention encounter sustainability issues in terms of financial resources?
  - In your opinion, could this intervention be scarcely accepted by HCWs?
  - In your opinion, could this intervention encounter feasibility issues?
- Q3. Should information- and education-based strategies targeted to vaccination recipients and their parents be weakly *recommended* to increase HPV uptake?
  - In your opinion, could this intervention encounter sustainability issues in terms of financial resources?
  - Should these strategies be mostly based on a trustfully relationship between HCWs and targets/their parents?
  - Could these strategies be implemented at school-level?
- Q4. Should strategies based on information campaigns (through TV, journals, radio, social media, information sheets in healthcare clinics etc.) be weakly *recommended* to increase HPV uptake?
  - In your opinion, could this intervention encounter sustainability issues in terms of financial resources?
- Q5. Shold multicomponent-based strategies tailored on vaccination recipients and/or their parents be moderately recommended to increase HPV vaccination uptake?
  - In your opinion, could this intervention encounter sustainability issues in terms of financial resources?
  - In your opinion, could this intervention encounter feasibility issues?
  - Should multicomponent strategies be offered at school-level?
- Q6. Should multicomponent-based strategies tailored on HCWs be strongly recommended to increase HPV vaccination uptake?
  - In your opinion, could this intervention encounter feasibility issues?
- Q7. Should multicomponent-based strategies tailored either on HCWs and vaccination recipients and/or their parents be moderately recommended to increase HPV vaccination uptake?
  - In your opinion, could this intervention encounter sustainability issues in terms of financial resources?
  - In your opinion, could this intervention encounter feasibility issues?
- Q8. Should HPV vaccination be recommended to women undergoing treatment for HPV-related genital disease?
  - In your opinion, which would be the most effective interventions to promote vaccination offer to this target?
- Q9. Should HPV vaccination be recommended to all previously unvaccinated women aged 25 years undergoing cervical cancer screening?
  - In your opinion, which would be the most effective interventions to promote vaccination offer to this target?
- Q10. Should HPV vaccination be offered to previously unvaccinated women of childbearing age?
  - Could the first contact with the GP be a key moment to offer HPV vaccination?
  - In your opinion, which would be the most effective interventions to promote vaccination offer to this target?
- Q11. Should catch-up vaccinations be recommended for boys and girls, eligible for birth cohort, who did not receive the vaccine?
  - Which populations should be targeted by catch-up interventions?
  - In your opinion, which would be the most effective interventions to promote vaccination offer to this target?
- Q12. Should information and promotion of vaccination be recommended for all boys and girls aged 9 to 18 years old at their first medical visit by GP or by pediatrician or, if required by regional law, at the Health Balance visit?
- Q13. Should HPV vaccination be recommended to unvaccinated women being admitted or discharged from healthcare facilities (hospital, emergency room, ambulatory) for gynecologic or obstetric reasons?
- Q14. Should a life-course free vaccination offer be recommended to all individuals who were once eligible for birth cohort i.e. girls born after 1996/1997 and boys born after 2003/2004 (or before according to Regional Law)?

Furthermore, three experts expressed doubts about long-term effects of this kind of intervention. More benefits are expected by targeting HCWs because of the fact that they are already in charge of these activities. Indeed, 8 out of 10 experts pointed out that information is powered when it undergoes between a patient/citizen and his/her MD. However, I&C strategies remain a relevant tool to increase awareness, particularly when they are undertaken in schools. All experts agreed that the school, particularly for the sixth-grade scholars, is a key context to be taken advantage of. In this sense, teachers might act as key players to inform teens about vaccinations.

Regarding I&C strategies at population level (televisions, journals, radio, social media, brochure in health clinics, etc..), the panel agreed (7/10) with the **weak recommendation** about their implementation. Some doubts were expressed about effectiveness of mass campaigns, due to low quality and small amounts of evidence (7/10) and costs and long-term sustainability (7/10).

Multicomponent interventions

Nine out of ten experts responded questions about these strategies. The panel agreed (7/9) with the **moderate recommendation** of promoting multicomponent strategies targeted to vaccination recipients and/or their parents. In fact, these interventions were expected to be highly effective in increasing vaccination coverage. Nevertheless, 7 out of 9 experts underlined that the wide heterogeneity of these strategies could cause an unaffordable surge of costs and 8 out of 9 experts pointed out an impaired feasibility at local level. Noteworthy, the panel concurred (7/9) in recommending, as a part of these multi-component strategies, school-based interventions. According to experts' opinion, secondary schools should particularly be taken into account as they represent a key moment to inform, educate and actually offer vaccination. However, one expert claimed this intervention is not expected to be feasible in many schools across the country due to their financial and organizational constraints.

The panel coincided (9/9) in the **strong recommendation** of promoting multicomponent strategies tailored on HCWs. Indeed, HCWs are key actors in promoting vaccination and a high effectiveness is expected. However, when it comes to HCWs, tailored interventions are strongly required since they should specifically aim at increasing HCWs' awareness, knowledge (about vaccinations and common missed opportunities) and communication skills towards citizens. However, even for this type of intervention, feasibility was considered a possible problem to be addressed locally (6/9).

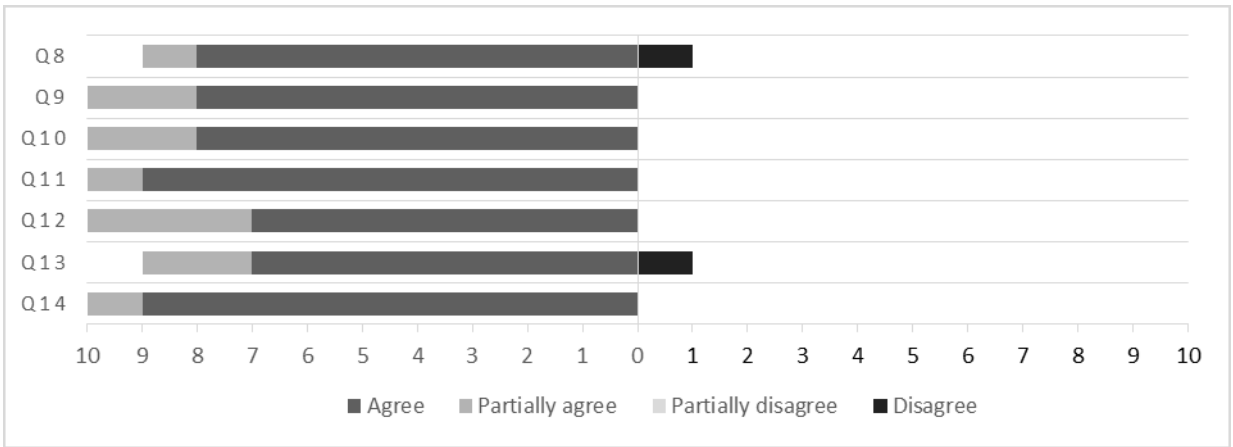
Finally, the panel agreed (7/9) upon the **moderate recommendation** of implementing multicomponent interventions targeted either to HCWs and vaccine recipients and/or their parents, as this multifaceted intervention could be more successful in achieving the final aim of increasing awareness and vaccination uptake. According to previous opinions about other multicomponent interventions, six out nine experts judged feasibility and financial sustainability as possible major issue.

Section 2: Promotion of HPV vaccination to additional targets

Figure 3 shows experts' opinion about the seven recommendations regarding promotion of HPV vaccination to other targets.

The panel was firstly asked about promoting vaccination to women affected by HPV-related genital diseases as a part of the treatment. Most of them agreed (9/10) with this **recommendation**. To achieve this goal, free vaccination offer (10/10), multicomponent interventions targeted to patients (8/10) or to HCWs (6/10) and reminder-based interventions targeted to

FIGURE 3. Experts' opinion about the seven recommendations regarding promotion of HPV vaccination to other targets.



Q n: question number n according to Table 3

childbearing women being admitted or discharged by healthcare facilities (6/10) were considered the most effective interventions.

When asked about the recommendation of promoting vaccination to women of 25 years of age at the moment of cervical cancer screening, the panel unanimously agreed (10/10). As effective interventions to reach this target, they mentioned: free vaccination offer (10/10) and multicomponent interventions targeted to women (6/10).

From an extended point of view, the panel also strongly (10/10) advocated the circular November 21st, 2018 issued by the Italian Ministry of Health that promotes HPV vaccination offer to all unvaccinated women of childbearing age, irrespective of their age. Of note, for most of the panel (6/10) attention should be given to the first time a woman meets her GP, as this is a key moment from a health promotion perspective. About other relevant interventions to carry out, they cited: free vaccination offer (8/10), multicomponent interventions targeted to women (6/10), I&C targeted to women (6/10) or to HCWs (6/10).

Afterwards, questions attempted to investigate experts' opinions about the promotion of vaccination in eligible individuals, irrespective of their gender, who did not get vaccinated at the scheduled age. The panel unanimously agreed (10/10) with the **recommendation** of promoting catch-up interventions for boys and girls who did not get vaccinated in the past, starting from eligible birth cohorts, i.e. those born in 1995 for girls and 2006 for boys. It was expected that this intervention could provide equity as it would give access to vaccination to people who failed to receive it in the past due to information or organization problems. Moreover, catch-up cohorts are a well-known tool to quickly increase vaccination coverage. For most of the experts (6/10) the best catch-up cohort would be at the age of 18 years, as this would reduce any possible parents' influence. Multicomponent interventions targeted to boys and girls and free vaccination offer would be the most effective strategies for most of the experts (8/10 and 7/10 respectively). Also, I&C strategies to HCWs (6/10) and multicomponent interventions targeted to HCWs and active calls (6/10) were regarded as valuable tools.

In order to decrease the occurrence of missing opportunities, the panel concurred (10/10) with the recommendation of informing and promoting HPV vaccination to any boys and girls from 9 to 18 years of age as for the first time they seek medical attention by GP or pediatrician. In addition, the regular health assessments made by pediatrician, referred to as Health Balance visit, were thought to be a valuable moment. However, experts underlined that this intervention requires complete implementation of a national vaccination registry and a full interoperability among electronic medical records used by the regions.

Besides age-based cohorts, experts were interviewed about promotion of vaccination in specific circumstances. Particularly, they were asked about promoting HPV vaccination to unvaccinated women being admitted or discharged from healthcare facilities (hospital, emergency room, ambulatory) for gynecologic or obstetric problems. The panel agreed (9/10) with this recommendation underling that it could represent a valuable catch-up opportunity. Nevertheless, interventions aimed at increasing HCWs' awareness are strongly required for this intervention to happen.

Lastly, the panel was invited to express its opinion about a life-course free vaccination offer to all individuals who were eligible for birth cohort i.e. girls born after 1996 and boys born after 2003 (or before according to Regional Law). The most of the experts agreed (9/10) with this recommendation as most of those people might have missed the opportunity due to problems related to lack of information or local contextual factors.

From this perspective, this intervention would have a high impact in terms of equity.

Second meeting conclusion

According to the results of the two face-to-face meetings, a strong recommendation was issued with respect to the promotion of vaccination in the following additional targets:

1. women treated for HPV-related lesions,
2. previously unvaccinated women of 25 years, at the time of cervical cancer screening,
3. previously unvaccinated women of childbearing age,
4. boys and girls born respectively from 1996/1997 and 2003/2004 who missed the opportunity at the eligible age also guaranteeing the vaccination free of charge,
5. unvaccinated women discharged from gynecologic or obstetric units or Emergency Rooms and health clinics for gynecological disease.
6. all boys and girls aged 9 to 18 years at the time of the Health Balance visit or, if not required by the Region, at every medical visit performed by the GP or by the pediatrician.

As for the strategies to increase vaccination coverage among 12-years-olds a strong recommendation was formulated with respect to reminder-based strategies for vaccination recipients and their parents and with respect to multicomponent interventions for HCWs. A moderate recommendation was issued with respect to reminder-based strategies for HCWs (e.g. alerts in electronic medical records) and multicomponent strategies tailored only to vaccination recipients and/or their parents, or also to HCWs. Eventually, I&C strategies and information campaigns were weakly recommended.

DISCUSSION

This project has allowed developing a consensus among key experts in the field of HPV-related diseases prevention and control with respect to the a) promotion of vaccination to additional targets and b) strategies to increase HPV vaccination coverage among 12-year-olds.

With respect to the additional vaccination targets, a clear indication emerged on the inclusion of women treated for HPV-related lesions and previously unvaccinated women of 25 years and of childbearing age. Furthermore, the need for catch up initiatives was pointed out to reach out boys and girls who missed the opportunity at the eligible age. In particular, girls and boys turning 18 years of age were identified as the most suitable cohort, and free offer was considered as a requisite.

Promoting HPV vaccination to additional targets represents a good opportunity to increase the HPV immunization level and, subsequently, to reduce HPV-related diseases. This objective should be pursued in parallel with any efforts aimed at improving vaccination coverage in the current primary target. Nowadays vaccination coverage in Italy is far from the goal of ≥ 95% reported by the 2017-2019 NIP in any Italian Region with a decreasing trend in the last years [4]. As far as the increase of vaccination coverage among 12 years-old, only one type of intervention was judged strongly recommendable, namely reminders tailored to the recipients and/or their parents.

As outlined before, reaching high HPV vaccination coverage allows achieving a better prevention and control of HPV-related diseases. This achievement is an important challenge on the agenda of several countries in the world, although further improvements are needed (18).

As at February 2019, worldwide, HPV vaccine for girls had been introduced in the NIP of 92 countries (47%) while, as at March 2017, it was offered also for boys only in 11 countries (6%) (18). Nevertheless, the implementation of HPV NIP in EU/EEA countries appears very heterogeneous [19].

The free offer of HPV vaccination is one important key aspect of the campaign and also our project pointed out that the maintenance of gratuitousness for birth cohorts that were entitled to receive free of charge vaccination at eligible age is highly desirable. Free of charge HPV vaccination was offered for the first time in Australia (20). In EU/EEA countries, free of charge vaccination is now available for boys and girls (variable age from 9 to 14 years) in Austria, Croatia, Czech Republic, Denmark, Italy, Luxemburg, Liechtenstein, Norway and United Kingdom. Other countries (including Belgium, Bulgaria, Cyprus, Finland, Netherlands, Portugal, Romania and Sweden) offer free vaccine only for girls. In Germany, HPV vaccination is included in statutory health insurance to all girls and boys aged 9–14 years. The vaccination is partially funded in France, with a reimbursement rate of 65% of the price, only for girls (11-14 years old) [19]. Despite the fact that the NIP are usually targeted to adolescents, during the last years, a trend toward expanding the HPV vaccination to subjects of other ages never vaccinated before could be described. Recently, the Food and Drug Administration also approved the use of the 9-valent HPV vaccine for HPV-diseases prevention in women and men aged 27-45 years [21]. Permanent or transitory catch-up initiatives have been implemented in several countries in order to offer vaccination to people never vaccinated before. Cohorts recommended as results of this project include previously unvaccinated women of 25 years, and girls and boys turning 18 years of age. Across European countries, these strategies include usually adolescents/adults from the age of primary target to a maximum age variable according to the countries from 15 years (such as in Austria) to 26 years. Although the major part of the countries offers catch-up vaccination until 18-20 years, adolescents turning 18 years of age are included only in the program of 3 out of 34 EU/EEA countries. Twenty-five years-old women, instead, are included in the NIP in two European countries (Lichtenstein and Norway) [19]. In Italy, the 2017-2019 NIP recommends HPV vaccination for 25 years-old women at the first screening for cervical cancer, but promotion strategies are needed in order to improve their adherence.

Despite the fact that, currently, catch-up programs in Italy are variable by Regions, our project has shown that they should be considered in order to make possible the control of HPV-related diseases.

Furthermore, offering catch-up vaccination free of charge is also a recommendable strategy. Free vaccination in offered in Denmark and Liechtenstein, while it is available at a reduced price in Austria, Belgium, Germany and in France.

Considering strategies directed to the primary target (e.g. adolescents 9-14 years-old) to increase vaccination coverage, during the last 15 years, several European countries have introduced, and are currently adopting, school-based vaccination programs. These include Austria, Belgium, Croatia, Cyprus, Estonia, Finland, Hungary, Iceland, Ireland, Latvia, Norway, Slovenia, Sweden, United Kingdom and some regions in Spain; however, the vaccination coverage is heterogeneous [19]. In Sweden, where a school-based immunization program was introduced in 5-6th grades, the vaccination coverage reaches 98% in girls aged 14 years and over [22]. In Italy, because of heterogeneity in schools facilities, resources and organization across the country, a school-based vaccination program could be difficult to implement and could likely lead to inequalities.

Nevertheless, schools could represent a suitable setting for education campaign. For example, in Canada, information is provided to parents of vaccination targets through school-based education programs. These programs seem to work better than media campaigns, widely used in United State to inform citizens about HPV vaccination

[23]. Actually, also our project has highlighted that media campaigns could be of limited value in promoting vaccination.

Strategies recommended within this document are developed integrating available evidence and experts' opinions. Despite the fact that multicomponent strategies are reported as effective strategies, their potentially high costs do not allow formulating a strong recommendation. On contrary, the feasibility and sustainability of reminder-based strategies, along with the available evidence about their efficacy, led to make a strong recommendation for this kind of interventions.

Our project has several limitations and advantages. With respect of limits, it should be noted that the systematic review used to inform the experts panel have not included gray evidence on strategies to implement HPV vaccination and that the framework used to assess the different criteria was adapted from the EtD one. Furthermore, the choice of face-to-face meeting could have introduced some bias in the delivery of judgment [24]. On the other hand, we should say that the evidence collected served only to shed light into the main types of interventions that could be supported for improving HPV vaccination and that, even though we opted for face-to-face meeting, the mutual influence among experts has been mitigated by the use of a questionnaire and a tele-voting systems respectively in the first and in the second meeting. As for the strengths, our project was the first one in Italy, to the best of our knowledge, to collate together evidence and expert's opinions on strategies to bring the control of HPV-related diseases in Italy forward in a transparent and reproducible way. Furthermore, the involvement of well-known Italian professionals in the field of prevention and control of HPV-related diseases adds validity to the consensus development (24) and a desirable number of experts were considered for the consensus development [25].

In conclusion, this project has released important and shared recommendations on how to promote HPV vaccination in Italy and it could serve as a valuable tool to support decision-making in the prevention and control of HPV-related diseases.

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