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Overcoming barriers in HPV vaccination and screening programs

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ABSTRACT

The Human Papillomavirus Prevention and Control Board brought together experts to discuss optimizing HPV vaccination and screening programs.

Board members reviewed the safety profile of licensed HPV vaccines based on clinical and post-marketing data, reaching a consensus that current safety data is reassuring.

Successful vaccination programs used well-coordinated communication campaigns, integrating (social) media to spread awareness. Communication of evidence supporting vaccine effectiveness had beneficial effects on the perception of the vaccine. However, anti-vaccination campaigns have threatened existing programs in many countries.

Measurement and monitoring of HPV vaccine confidence over time could help understand the nature and scale of waning confidence, define issues and intervene appropriately using context-specific evidence-based strategies. Finally, a broad group of stakeholders, such as teachers, health care providers and the media should also be provided with accurate information and training to help support prevention efforts through enhanced understanding of the risks and benefits of vaccination.

Similarly, while cervical cancer screening through population-based programs is highly effective, barriers to screening exist: awareness in countries with population-based screening programs, access for vulnerable populations, and access and affordability in low- and middle-income countries. Integration of primary and secondary prevention has the potential to accelerate the decrease in cervical cancer incidence.

1. Introduction

The HPV Prevention and Control Board was created in December 2015 [1] with the aim to share relevant information on HPV with a broad array of stakeholders, and to implement preventive strategies to reduce the HPV-related disease burden. Here we report the discussion that took place during the first official meeting, held on June 27 and 28, 2016, in Antwerp, Belgium.[1]

The objectives of the meeting were (a) to summarize the available adverse event profile and any reported safety concerns following HPV vaccination, (b) to summarize cultural, perceptual, infrastructural and financial barriers to the implementation of vaccination, (c) to identify factors that influence adherence to cervical screening programs, (d) to propose strategies to build public confidence in HPV prevention programs and address any vaccination and screening hesitancy, and (e) to discuss new approaches to improve HPV prevention and cervical cancer control.

2. Vaccine safety profile

The safety of new products is critical for licensure and successful implementation/uptake. Critical review of clinical trial data is the first step in this process. However, as clinical trials generally involve limited numbers, and participants may have health conditions different from those in the general population, post-marketing surveillance is essential.

While licensure has varied according to country, HPV vaccines have been available since 2006 beginning with the quadrivalent (4vHPV, Gardasil, Merck), followed by the bivalent (2vHPV, Cervarix, GSK) and the nonavalent (9vHPV, Gardasil9, Merck) vaccines. The clinical trial safety data for the 4vHPV and 2vHPV vaccines have been reported at length [2–4]. Pain at the injection site was the most frequently reported local adverse event (AE), and occurred significantly more frequently in the intervention group than in the control group. Serious AE were very infrequent, and were not reported more frequently in the intervention group compared to the control group. Clinical trials investigating the 9vHPV vaccine had lower numbers of participants, but the results were comparable to those obtained with 4vHPV [5–8]. In nearly 13,500 participants, three non-causally-related serious AE were noted: one case of tonsillitis, one case of asthma exacerbation, and one case of severe headache; all cases fully recovered.

A Cochrane review [9] assessed mortality after vaccination observed within the follow-up period of the randomized trials using data published in the peer-reviewed literature. The pooled relative risk of death in the group who received HPV vaccines versus the control group showed no

[1] The slides of the presentations are available on the HPV Prevention and Control Board website: https://www.uantwerpen.be/en/projects/hpv-prevention-control-board/meetings-/barriers-in-hpv-vacc/.

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significant decrease or increase. Relatively more deaths occurred in the HPV vaccine arm than in the control arm in trials that enrolled mid-adult women (older than 25 years). However, these findings were explained by the trial investigators and independent audits as a chance occurrence. None of the deaths were deemed related to vaccination (absence of pattern in death causes, causality considered biologically implausible, unclear temporal relation).

As millions of doses of the HPV vaccines have been administered globally, post-marketing data are available. Post-marketing surveillance can be performed in many ways, including spontaneous reporting databases, electronic health records, and record linkage between vaccine and morbidity registries. Passive surveillance is generally organized at the national level, e.g. the Yellow Card Scheme in the UK, set up in 1964 [10], and the Vaccine Adverse Event Reporting System (VAERS) in the USA, set up in 1990 [11]. Both the US Food and Drug Administration (FDA) and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) keep registers for post-marketing studies. These registers contain phase IV studies that vaccine manufacturers are either required, or committed, to perform by the regulatory bodies (e.g. FDA, EMA) as part of the post-licensure commitment.

The Global Advisory Committee on Vaccine Safety (GACVS) was set up in 1999 to provide the WHO with independent advice on vaccine safety issues. The role of the GACVS is both to analyze and to interpret reports of adverse effects of vaccines that impact global vaccination programs and strategies, and to foster the development of improved surveillance systems to detect any adverse effect of vaccines, particularly in low- and middle-income countries [12,13]. Since licensure of the HPV vaccines, GACVS has investigated a number of events, issues and allegations. This has led to the adaptation of recommendations, to improve the detection of potential safety issues and avoid or reduce false allegations. GACVS concluded that the safety profile of the HPV vaccines remained reassuring throughout the reviews, and that the benefit-risk assessment remains favorable. Nevertheless, continued pharmacovigilance remains important to ensure that concerns can be addressed in a timely way and with the best possible evidence. Finally GACVS published the statement that allegations of harm from vaccination based on weak evidence can lead to real harm when, as a result, safe and effective vaccines cease to be used [14].

Adequate assessment of possible vaccine safety concerns requires knowledge of the background rates of a disease and/or condition to determine whether the observed cases exceed the rates expected in the population in the absence of vaccination [15]. Background rates of selected medical events, stratified by age, sex, health status, and geographic location, help strengthen vaccine safety assessment, and provide an evidence-based focus for discussing the incremental risk of newly introduced vaccines [16]. To explore some of the recent concerns about HPV vaccine safety, a register-based retrospective cohort study was performed in Finland to assess the age- and sex-specific incidence rates of Guillain Barré Syndrome (GBS), Chronic Fatigue Syndrome (CFS), and Postural Orthostatic Tachycardia Syndrome (POTS) in the period 2002–2012 [17]. A significant increase in CFS and POTS was observed within the register-based data prior to introduction of HPV vaccination, indicating the importance of assessing fluctuations over time in specific conditions that may be due to factors unrelated to vaccination such as increased awareness, changes in diagnostic criteria and/or recording, or changes in catchment population. Therefore, registry-based disease rates investigated for association with vaccination should be interpreted with caution, especially for non-specific diagnostic entities without consensus case definitions or those that fluctuate over time. The European Medicines Agency reviewed the evidence surrounding reports of Complex Regional Pain Syndrome (CRPS) and POTS in young women who were immunized against HPV and concluded that the evidence did not support a causal link between the vaccines and development of CRPS or POTS [18]. Similar studies were performed looking at demyelinating diseases and autoimmune disorders [19–22]. None of these studies found an association between HPV vaccination and the conditions under investigation.

3. Country-level HPV vaccination programs

Experiences from a number of countries were discussed; a SWOT (Strengths, Weaknesses, Opportunities and Threats) analysis of all countries combined is presented in the following sections.

3.1. HPV vaccination program strengths

Many countries utilized strong evidence-based recommendations prior to the introduction of the HPV vaccine and were able to conduct well-coordinated immunization and communication campaigns. Those countries that included school-based programs generally had higher coverage. Nevertheless, some countries, such as Japan and Denmark, experienced high initial uptake using a community-based program. The use of institutional and social media to spread awareness was considered a strength. Evidence supporting vaccine effectiveness against genital warts and cervical lesions in a timely manner post-vaccine introduction [23–26] had beneficial effects on the community perception of the vaccine. Finally, before introduction of the HPV vaccine, some commentators suggested that the administration of the vaccine to young girls might lead to increased sexual promiscuity [27]. Therefore, the observation that promiscuity did not increase after vaccination in Canada, the UK and the US was welcomed [28–30].

3.2. HPV vaccination program weaknesses

Weaknesses in HPV vaccine programs are frequently due to low initial vaccine uptake, the extended time period between vaccine introduction and potential impact on clinical endpoints, insufficient data infrastructure to determine population-level vaccine effects as well as to contextualized perceived vaccine risks, and sub-optimal communication regarding the vaccine. Population-level reductions in HPV-related disease is contingent upon substantial uptake of the vaccine so that both direct and indirect effects can be realized. Limited risk communication for HPV infection and related disease, as well as negative perception of HPV vaccine safety can lead to low initial vaccine uptake and sustained coverage. Vaccination coverage among traditionally hard-to-reach communities, such as (illegal) immigrants and religious groups opposing vaccination, remains a concern. It is also imperative to document the population-level impact of the HPV vaccine on disease reduction which can be difficult due to the long time window between vaccine introduction initially in adolescents and the peak ages for which HPV-related pre-cancers are detected. Limited data infrastructure, such as poor local epidemiological data, the absence of vaccination registries, and the inability to link relevant data, can hinder timely evidence-based assessments of vaccine effectiveness as well as responses to vaccine scares which has occasionally led to decisions to suspend vaccination such as in Japan [31] and India [32]. Finally, in some countries the lack of vaccine advocates and the social taboo of sexuality in adolescent girls have impeded communication related to HPV risk and vaccine awareness.

3.3. HPV vaccination program opportunities

To strengthen HPV vaccine coverage, programmatic and awareness opportunities exist. Furthermore, advocacy with the media and community leaders has been developed in many settings, reinforcing awareness around the impact and seriousness of cervical cancer. The increased public concern about cervical cancer following the death of a celebrity is likely to increase awareness, as has been seen in Denmark, England and Scotland [33]. The political commitment of the Belgian government towards vaccination as a public health goal was also seen as an opportunity for strengthening local HPV vaccine programs. Finally, the (slow) transition from traditional, Pap smear-based screening towards high-risk HPV-based screening offers opportunities to integrate primary and secondary screening (see section 7).

3.4. HPV vaccination program threats

In all countries, the presence of anti-vaccination campaigns, usually well-organized and very active, is seen as the biggest threat to HPV vaccination programs, especially as concerns voiced on the Internet or case stories can be seen by the public as evidence against the vaccine. The perceived association of the vaccine with HIV (and the social stigma attached to this infection) and the idea that vaccination may be used to control fertility are both specific threats in India. The lack of response from the government to the anti-vaccination campaigns, as well as an unrestrained media environment [34] are threats to the HPV vaccination program in Japan. Finally, the lack of a strong provider recommendation to vaccinate against HPV was seen as a threat in the US.

4. Vaccine confidence

Wavering vaccine confidence is a global phenomenon with deep local roots. The history of public questioning of vaccines is as old as vaccination itself, but the speed and scope of any global spread of public concern is quickly changing due to the influence of rapid and wide-reaching communication channels, such as the Internet, television and social media. A growing number of people use the Internet to obtain health information, including information about vaccines [35]. The reasons for opposing vaccination in the 19th century were essentially the same as today, with vaccine safety as the major issue, although the current global environment suggests a greater level of public distrust and right-to-know mentality. Other relevant groups opposing vaccination are those who oppose based on religion, or those who oppose because they think vaccination is ‘unnatural’. The latter group can be engaged in a value-based campaign, although this may polarize attitudes towards vaccination [36].

The most commonly mentioned concern about vaccination in Europe was linked to the perceived safety and risks of vaccines. Those concerns are typically specific to the vaccine but could include perceived minor side effects such as the belief that influenza vaccination can cause flu-like symptoms, as well as perceived serious side effects such as fears of infertility following HPV vaccination. Other important factors related to low vaccine acceptance were a perceived: low likelihood of contracting the disease, low disease severity, concerns about vaccine safety, low confidence in vaccine efficacy, lack of information about the vaccine and/or the disease, lack of need for vaccination, and lack of evidence or testing of vaccines [37].

A systematic review showed a variety of factors as being associated with vaccine uptake [38]: socio-economic status, with both high and low income able to act as barrier or promoter of vaccination; level of education, similarly, both higher and lower education can serve as barrier or promoter; media coverage, in which case the content of the story determines whether it is a barrier or a promoter; costs of vaccine/being vaccinated, generally acting as a barrier; social/peer pressure, encouragement from others, or the feeling that immunization is a social norm acted as a promoter; beliefs, attitude and motivation around health issues, with greater health knowledge acting as promoter; knowledge/awareness of the need of vaccines, especially awareness of a vaccine-preventable disease acted as a promoter [38]. However, these factors did not allow for a complete classification and confirmation of their independent and relative strength of influence. It was concluded that determinants of vaccine hesitancy are complex and context-specific - varying across time, place and vaccines [38]. Determinants of HPV vaccine confidence differ from those of other vaccines and need to be addressed as such. Finally, determinants of HPV vaccine confidence also differ between cultures. For example, the fear around promiscuity was not prominent in Australia; in surveys prior to program implementation, very few parents mentioned concerns about promiscuity [39].

Confidence in HPV vaccine should be measured to understand the nature and scale of any reduction in order to detect and address drops in vaccine confidence quickly. Confidence in HPV vaccine can be measured by qualitative and epidemiological research, using for instance the SAGE open-ended questions, or the Parent Attitudes About Childhood Vaccines survey [40]. This type of data, while slow to acquire, can provide deep insights and predictions of vaccine hesitancy, social phenomena that can help or hinder vaccination campaigns, and long-term contextual factors that create “fertile ground” for a crisis of confidence. Internet surveys and media tracking can provide fast data; near-real-time estimates of public perception of vaccines [41], which could help immunization programs tailor more effective and timely strategies to address specific public concerns. Global news media monitoring on HPV vaccines is ongoing at the London School of Hygiene & Tropical Medicine and national examples of media monitoring of vaccines are on the rise.

When dealing with HPV vaccine confidence it is necessary to identify if and where pockets of vaccine hesitancy exist, to monitor public confidence, to develop an understanding of scope/context/root causes of vaccine hesitancy, and to use context-specific, evidence-based strategies (including, but not limited to, communication) to address underlying issues. This involves starting communication planning early, allowing for formative research to anticipate difficult issues, and building cross-sectoral team to integrate all relevant sectors. Finally, developing a plan for those girls the service does not reach is recommended, as they may be the girls who are at higher risk of developing cervical cancer and would benefit most from the vaccine. Communication is most likely to effectively reach these girls, and their parents, through channels that they identify with and trust. An example is provided in Box 1.

Information provided to those targeted for vaccination (or their parents) should explain what the benefits are (e.g. what does the vaccine prevent), why the vaccine is given at a young age (more robust immune response, need for fewer doses), why the HPV vaccine needs to be delivered before the start of sexual activity, why multiple doses are necessary, how effective it is, and what are the risks (e.g. the common and less frequent side effects). This may also be an opportunity to reinforce the importance of cervical cancer screening.

If HPV vaccine delivery is school-based, teachers and administrators will be on the front lines of the program. They may participate in training, and educate or remind girls about the vaccine. They may also coordinate information with health workers and with parents, for instance through parent-teacher organizations. As such, they may be a trusted source of information for pupils. Therefore, they should have formal opportunities to

Box 1
Communication and Education around HPV Vaccination, the Example of Scotland.

In Scotland, a multi-media campaign (including Internet, TV and cinema) was developed and implemented to raise awareness, understanding and acceptance of HPV immunization among girls and their parents, healthcare and education professionals. Professional communications included briefing key stakeholders, informing service providers through regular professional letters, and training immunizers (i.e. nurses providing vaccination in schools). A common strapline for all materials 'Together we can beat cervical cancer' and a brand image based on a schoolgirl talking to her friends were designed. Additional work was done to reach girls who had left school, including using pink camper-vans to promote awareness. Members included public communications experts, training experts, epidemiologists and representatives from schools, education, general practice, a national health telephone help-line (NHS24), health boards and other workstreams. The chair was a senior communications expert from the National Health Service.

coordinate with health workers (e.g. joint meetings) and access to materials they can use which both make them comfortable with the program and help them to engage and mobilize parents and daughters [42].

As GPs (and other health care professionals) are still the most trusted source of medical information [43], and in some countries are the sole HPV vaccine providers, they should be aware of the evidence available, and able to respond to questions and concerns. As they may have questions themselves about the HPV vaccine or about the biological links between HPV, the vaccine and cervical cancer they can benefit from training on HPV, cervical cancer as well as interpersonal communication skills with girls and families [42]. The way GPs and nurses approach patients can determine acceptance or refusal of the vaccine by the patients. Resistance to vaccination has been shown to be significantly lower when there is a presumptive offer of vaccines directly to patients [44]. However, if patients are resistant to a specific vaccine, it is important that GPs and nurses engage in discussions with their patients and listen to their concerns. GPs and nurses need to be appropriately trained to acquire these communication skills, especially as in most countries GPs and nurses may not be a target for awareness and educational campaigns.

The media play an important role in vaccine confidence. To avoid the type of situation that has occurred in Japan, it is essential to provide the media with accurate information, so that they are less likely to report misinformation from other sources. Especially in the case of a new vaccination campaign, such as HPV, it may be worthwhile to organize pre-campaign briefing sessions for journalists. It is also important to have trained media spokespeople ready, including scientific experts, who can be available to address concerns or misinformation quickly (although they should also to be aware of the danger of false balance in the media).

Guidance exists on best practices for communication, especially when providing information to the target population (as summarized in Table 1, adapted from [42]). Specific guidance is available for debunking of myths, as presenting the facts is often insufficient [45].

5. Key challenges to improve cervical cancer screening uptake

Country examples of cervical screening programs were presented. By screening, cervical precancerous lesions are detected and can then be successfully treated before the development of cancer. Population-based programs are more efficient in reducing cervical cancer incidence and mortality than opportunistic screening. Several countries are switching from cytology- to HPV-based screening.

In the UK, around 25% of women do not attend cervical cancer screening as recommended. Low screening compliance is found among younger women, those with low socio-economic status, and those from ethnic minorities. Reasons for non-attendance in UK screening programs were many

Table 1
Guidance for providing information about HPV vaccination to the target population. Source: Adapted from [45].

- Use every opportunity; don't only focus on official opportunities. For example, messages can be printed on the back of the girls' immunization card, the Minister of Health can talk about HPV vaccine in speeches about maternal and child health. But it is equally important to use informal ways, e.g. a short message at a concert by a singer popular with adolescent girls.
- Develop a frequently asked questions (FAQ) reference guide, with all possible questions, including challenging questions. The WHO plans to provide a basic FAQ to draw from.
- Use language and materials girls can relate to and have fun with, e.g. colourful materials with modern designs. In countries where text messaging is common, there may be opportunities for text-based quizzes and games in collaboration with mobile phone service providers.
- Set up a telephone hotline; some countries have experience setting up phone hotlines so that girls, parents and other audiences can call and ask questions. This can be an effective way for people to have a real conversation with an expert about HPV vaccine.
- A mix of channels is important, including radio and television, school, health workers and churches.
- Pay attention to underserved populations, to promote equity.
- Use Internet and social media; Facebook or Twitter accounts devoted to adolescent health, including HPV vaccine. Dedicate a web site to HPV vaccine (or to the vaccination program in general) where any audience can access evidence-based information, materials and FAQs. Keep this information up-to-date.
- Use gain-framed messaging, i.e. promoting the benefits of vaccination, rather than emphasising the consequences of not getting vaccinated. Build on positive perceptions of vaccines, which may be most effective in promoting vaccination and minimising stigma.

and varied [46]. The non-attenders fell into three groups: those who had made an active decision not to take part (who tended to be older), those who intended to be screened but did not attend (predominantly younger women), and finally those who were unaware of screening, despite great communication efforts by the screening programs [46]. In a systematic review of 39 papers from the UK, Australia, Sweden and Korea two broad themes were identified: (a) should I go for screening? and (b) screening is a big deal. Practical barriers affected whether women translated screening intentions into action. The variation in women's understanding and perceptions of cervical screening suggests that interventions tailored to decisional stage may be of value in increasing engagement with the invitation and uptake of screening in those who wish to take part [47]. Finally, addressing practical issues such as appointment systems and clinic times may have a positive impact on attendance in young women [48].

Vulnerable, hard-to-reach populations generally show low cervical cancer screening uptake and consequently higher risk of cervical cancer and mortality in many settings. This includes the First Nation population in Canada [49], Aboriginal and Torres Strait Islander women in Australia [50], Maori women in New Zealand [51], Native American or Alaskan Natives [52]. Enhanced outreach to, and compliance in, cervical cancer screening programs and vaccination among these vulnerable populations is imperative to reduce the disparity in risk of cervical cancer.

Working closely together with the community, HPV self-sampling was tested as an alternative to Pap smear screening in a First Nation population in Ontario, Canada. A pilot study showed that 87% of women felt that self-sampling was a better option that would lead to increase screening participation. Self-sample integrity was high (96%). Women whose sample tested positive for high-risk HPV (16.3%) were provided follow-up [53].

In Romania, screening is offered by family doctors, based on Pap smear screening once every 5 years to women aged 25–64 years. The uptake is currently around 50%. The strategy is to change to HPV primary screening within the 2017–2020 National Cancer Control Plan. However, the majority of Roma women and other disadvantaged groups of women are rarely screened. Within a current pilot project these women are offered self-sampling, or Pap smear collection in mobile units. The primary outcome is the screening uptake, measured as the proportion of women having a screening test within the mobile unit. As a secondary outcome, the HPV prevalence in different communities will be investigated, to serve as baseline in case HPV vaccination is (re)introduced.

6. Broadened scope for prevention of HPV-related cancers

HPV vaccination offers an enormous potential for HPV-associated cancer prevention. For industrialized regions it is estimated that 120,000 new cases of HPV-related cancer are diagnosed per year [54]. Although the largest burden is in cervical cancer, with 77,000 cases per year, other forms of cancer make up for a third of all HPV-related cancer cases. Among these, oropharyngeal cancers compose the largest burden (approximately 15,000 cases per year), followed closely by anal cancer (12,000), and vulvar and vaginal cancers (11,000), whereas HPV-associated penile cancer is less frequent [3200] [54]. As HPV-associated cancers also affect males, some countries have funded vaccination programs for boys, e.g. Australia, Austria and the USA.

The current target population for vaccination in many countries is females before the start of sexual activity: generally, girls between 11 and 14 years of age, where efficacy is highest. However, epidemiological modeling of catch-up vaccination of women 22–26 years of age showed that while reaching the same plateau of protection, this plateau would be reached 5–7 years earlier compared to a vaccination program without catch-up. Secondly, a program with catch-up is much more resilient to a temporary reduction in vaccination coverage, for instance due to some sort of media crisis [55].

Similarly, a substantial level of protection has been observed in subjects beyond the age of 26. Trials of HPV vaccination in women aged up to 55 years have shown more than 80% protection against cervical precancerous lesions caused by HPV16/18 among pre-vaccination HPV16/18-DNA-negative women [56,57].

Secondary prevention of cervical cancer, through Pap smear and/or HPV-based screening technology is effective, but can be further optimized through enhanced coverage of screening programs in many countries. Synergy between primary and secondary prevention is being explored, for instance by extending routine vaccination programs to women of up to 30 years of age (and to the 45-year in some settings), in combination with at least one HPV-screening test at age 30 years or older [58]. Preliminary studies are being undertaken in high income countries, but might be an attractive approach for middle-income countries in Central and Eastern Europe, Latin America, Asia, and Africa, in the presence of political will, adequate planning, and an affordable price of the vaccines.

7. Additional information

As this manuscript is a reflection of the meeting, it is also limited to what was said at the meeting. In this section, to provide the reader with the opportunity to explore issues relevant to effective HPV vaccination and cervical screening in more detail, we refer to further literature.

7.1. Practical and/or logistical barriers to vaccination

While the role of vaccine confidence and hesitancy as a barrier in vaccination was extensively discussed in the meeting, other factors may also lead to suboptimal uptake, especially issues of access, or practical and logistical barriers. These barriers can be a more important factor than refusal or hesitation in some settings, even for publicly-funded vaccines, where cost is less of a barrier [59,60].

Several interventions that could increase vaccine uptake have been reviewed by the US Community Preventive Services Task Force [61], with home visits and requirements for child care, school and college being recommended, whereas for client-held immunization records, community-wide education (when used alone), and monetary sanction policies, insufficient evidence is available to be recommended.

Weak provider recommendations for the HPV vaccine, particularly common among HCP in the US: many providers do not seem to recommend the HPV vaccine as strongly as other age-appropriate vaccines, or present it as an option rather than a recommended vaccine [62,63]. This finding led to the development of a Randomized Trial comparing announcement training with conversation training among HCP. The announcement training showed a significantly greater improvement of HPV vaccine uptake, both in girls and boys [64].

7.2. The role of advisory groups and governments in communication

Although not extensively discussed during the meeting, advisory groups and governments can play an important role in communication. As indicated by the example of Scotland, well-planned, designed and coordinated communication can promote screening and vaccination programs in a relevant and effective way.

7.3. The role of self-sampling in screening

At the meeting, the specific example of the addition of self-sampling to increase screening in Romania was discussed. Ample evidence exists on the accuracy of self-sampled versus clinician-sampled specimens [65,66], the acceptability of self-sampling to women [67], and the significant impact on participation in randomized trials, when self-sampling kits were sent to women [68]. Using an opt-in approach did not increase participation [68].

7.4. HPV genotyping in an HPV-based screening program

While integration of vaccination and screening was discussed during the meeting, the use of partial genotyping in an HPV-based screening program was not. Partial genotyping to identify the most oncogenic HPV types separately (HPV16/18) can further stratify women positive for these types into the highest risk group for further investigation. Partial genotyping information can also be used to monitor vaccine impact, and can act as a 'early warning system' to detect changes in prevalence of different HPV types, especially once vaccinated women come into the screening cohort. This approach will be rolled out in Australia [69] and New Zealand [70].

7.5. Interventions to improve screening uptake other than self-sampling

Although not discussed during the meeting, other interventions can be helpful to improve screening, such as the use of invitations and/or reminders and support and monitoring of the program by a centralized screening registry.

7.6. Addressing weaknesses of the vaccination program

The vaccination program weaknesses were listed in the meeting, but solutions were not specifically addressed. For instance, the long period between vaccine introduction and impact on clinical endpoints, necessitates appropriate data infrastructure to determine population-level vaccine effects and speedy communication of this impact of the vaccine. While this was done in several countries, e.g. Australia and Denmark, this infrastructure could be improved in many countries. A potential weakness not discussed during the meeting is the length of time over which HPV vaccination is offered. If the vaccine is offered for a short time window (e.g. at a particular age or in a particular school grade), it may encourage parents to decide, so their child does not miss the opportunity. On the other hand, some people might miss the opportunity if the time window over which the vaccine offered is too short.

A further potential weakness is the voluntary nature of vaccination. Some countries have implemented policies which mandate or strongly encourage vaccination (e.g. school entry mandates in the US; 'no jab no pay' and 'no jab no play' in Australia). However, the impact of these policies will be different in different cultures, and may turn out to be counterproductive in some cultures.

8. Conclusion

As for any other vaccine, before and during the introduction of the HPV vaccines, the safety profile has been closely monitored. Post-marketing data will remain under scrutiny to detect signals timely and to address concerns objectively. The safety profile of the HPV vaccines remains reassuring and the benefit-risk balance remains favorable. It is imperative that HPV vaccination programs and cancer prevention programs proactively provide up-to-date information on benefits and risks of vaccination to ensure that confidence remains high. Communication guidance related to cervical cancer, screening and vaccination program exist but the success of a national vaccine program requires many coordinated activities. These have been distilled from the SWOT analysis described above: careful planning including attitudinal work, well in advance of the start of the program; good communication, with all parties involved, with material that is suitable for each target group, and extra attention for hard-to-reach populations, as they may be at higher risk; delivery of the vaccine through a school-based system; an action plan to quickly and effectively handle anti-vaccine media alerts; and appropriate data management and linkage to facilitate early detection of signals, but also show impact of vaccination.

Similarly, cervical cancer screening through population-based programs is highly effective. Nevertheless, major barriers to screening exist: awareness in countries with population-based screening programs, access for vulnerable populations, as well as access *and* affordability in low- and middle-income countries. While resolving practical issues within existing secondary prevention programs may increase vaccine uptake, a considerable impact is expected from the introduction of self-sampling for HPV screening, as this will ensure convenience and control by the woman, increased sensitivity, and reduced cost due to less frequent screening intervals. Finally, integration of primary and secondary prevention has the potential to accelerate the decrease in cervical cancer incidence.

Conflict of interest

AV University of Antwerp obtained unrestricted educational grants from GSK, Merck and SPMSD; speakers fees from Merck were paid directly to an educational fund held by the University of Antwerp.

MA declares no conflict of interest

MB received medical writing fees from vaccine-producing pharmaceutical companies, including Merck, SPMSD and GSK.

XB received research funding via his institution from GSK, Merck, Qiagen, Roche, and SPMSD, and reimbursement of travel expenses for attending symposia, meetings and/or speaking at conferences from GSK, Merck, Qiagen, Roche, and SPMSD.

SDS received institutional grants from Merck and GSK

SH declares no conflict of interest

EK has received funding through her institution from Merck to convene a research symposium and from Merck and SPMSD for speaking at conferences, symposiums, and meetings.

PLL declares no conflict of interest

KGP received reimbursement of travelling expenses from Merck

JY declares no conflict of interest

PVD acts as principal investigator for HPV vaccine trials conducted on behalf of the University of Antwerp, for which the University obtained research grants from vaccine manufacturers; speakers fees for presentations were paid directly to an educational fund held by the University of Antwerp.

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