Report
Efficacy and other milestones for human papillomavirus vaccine introduction

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Abstract
Last year, the World Health Organization (WHO) convened a gathering of experts, including scientists, national regulatory authorities, industry representatives, epidemiologists and government officials from both developed and developing countries to discuss appropriate endpoint measurements for HPV vaccine efficacy and effectiveness trials. The consultation also considered the regulatory requirements and public health issues that vaccine candidates should address before deployment, particularly in developing countries. This report summarizes the discussions and the conclusions reached over the course of the consultation.

The general consensus of the consultation was that it would be desirable to have a globally-agreed, measurable efficacy endpoint for considering deployment of HPV vaccines in public health settings. After hearing from experts about virological and clinical endpoints to be considered, requirements of regulatory authorities of various countries and endpoints used to measure efficacy and effectiveness for another known cancer vaccine (hepatitis B), the experts agreed that ethical and time considerations make it necessary to use a surrogate endpoint, and not invasive cervical cancer, to define efficacy of HPV vaccines. While regulatory authorities of each country ultimately will determine the endpoints required for licensure, the consultation recommended that the endpoint for efficacy in population-based studies be, based on current knowledge, histologically-classified cervical intraepithelial neoplasias (CIN) of moderate or high-grade, as well as cancer. Since persistent infection with the same high-risk type is considered a predictor for moderate or high-grade cervical dysplasias and cancer, they might represent a useful endpoint in future vaccine efficacy studies. Indeed, if vaccines prove to be effective against transient or persistent HPV infections, it is likely that they will protect women against cervical cancer. The consultation recognized that in the context of many developing countries, efficacy alone might not provide enough information for countries to decide whether or not to adopt HPV vaccines as a public health prevention tool against cervical cancer. The consultation unanimously agreed that additional clinical bridging studies as well as studies to clarify local epidemiology should be conducted in certain developing countries to determine the potential impact of vaccination. Such countries should also undertake targeted interventions to ensure acceptability and programmatic feasibility of the vaccination. Recognizing that upon vaccine introduction it will be some years before a reduction in cervical cancer is detectable at the population level, the consultation stressed the importance of maintaining existing cervical screening programmes while such long-term studies are conducted. The following paper explains the background and rationale behind these conclusions and elaborates on specific considerations for vaccine study and introduction in developing countries.

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1. Overview

1.1. Cervical cancer and human papillomavirus
Cervical cancer kills around 250,000 women every year worldwide and is the second most common type of cancer in women. About 80% of the 500,000 new cases of cervical
Cervical cancer is largely preventable through screening programmes designed to diagnose and treat cervical lesions that may progress to invasive cancer. In past decades this strategy has shown high success rates in some industrialized countries. However, it has been very challenging to establish and maintain effective screening programmes in many developing countries [2].

The primary cause of cervical cancer in women has recently been definitively linked to genital human papillomavirus (HPV) infections, a virus detected in over 99% of cases worldwide [3]. HPV fulfils the criteria for a carcinogenic agent defined by the International Agency for Research on Cancer [4], and in a few instances can also cause cancer of the anal canal, vulvae, penis and oropharynx.

Human papillomaviruses are non-enveloped double stranded DNA viruses that infect preferentially epithelial cells [5]. Among the nearly 100 types of papillomaviruses molecularly identified, about 40 types can infect the genital mucosa following sexual transmission, and about 16 are highly carcinogenic. Epidemiological studies on the prevalence of HPV types in cervical cancer show that a majority—65%—are related to just two HPV types: HPV 16 and HPV 18. Another 18% are related to HPV types 31, 33, 35, 45, 52 and 58, collectively (see Fig. 1) [6].

When a woman is infected with oncogenic HPV types, a spectrum of cellular and molecular events can result in dysplasia and, in a small subset of infected women, cervical cancer [7]. Natural history studies have reported that HPV infection occurs shortly after the onset of sexual debut, but the progression of HPV infection to cervical cancer can take many years.

In the developed world, the reported peak incidence of HPV infection occurs in the late teens and early twenties. The peak incidence of pre-cancerous lesions reported in a population is influenced by the timing and frequency of cervical cancer screening. In countries with less intensive screening, peak incidence of pre-cancerous lesions may be detected at later ages. In general, the most affected age groups are women 20–30 years for low-grade abnormalities, 30–40 years for high-grade dysplasia or carcinoma in situ, and 40–60 years for invasive cancer [8].

The link between HPV and cervical cancer has led experts to believe that vaccines designed to prevent infection with the most common HPV types will prevent cervical cancer and other HPV-related cancers.

Indeed, several years ago subunit HPV vaccines were prepared based on the recombinant viral capsid protein L1, also called virus-like particles (VLPs) [9]. The encouraging preclinical results from in vivo HPV VLP testing prompted both commercial and public institutions to develop and clinically-evaluate candidate vaccines against the most common oncogenic HPV types: 16 and 18. Results from phase I trials have confirmed the safety and tolerability of the recombinant viral proteins and shown excellent immunogenicity [10,11]. Phase II trials show homogeneous serological immune responses and highly effective protection against persistent HPV infections in women [12]. As phase III trials are already underway in the United States, Latin America and recently in Asia, the consultation agreed that there is a need to define an acceptable measurable endpoint for HPV vaccine efficacy in view of facilitating global introduction in public health programmes.
2. HPV vaccine efficacy

Traditionally, in etiological and cancer prevention studies, the measurable endpoint to determine efficacy of an intervention has been the incidence of cancer itself. But as cancer takes a long time to develop and is not common in a given population, trials with an endpoint of invasive cancer can be prohibitively large and lengthy. In the case of cervical cancer—a disease that can be prevented through proper detection and treatment—a study endpoint of cancer can be ethically impracticable. Therefore, to accelerate HPV vaccine development and introduction, alternative measurements of vaccine efficacy representing a disease-relevant surrogate endpoint would be appropriate, particularly for proof-of-concept studies.

2.1. What are the types of endpoints that could define HPV vaccine efficacy?

Given that there are several options for measuring HPV vaccine efficacy, the consultation reviewed and evaluated the full range of possible virological and clinical endpoints that could be studied. The group then discussed various external factors that could influence or inform a decision on endpoints, taking into account the endpoints that are being considered by manufacturers for current HPV vaccine candidates, endpoints that would meet the regulatory requirements for various countries when introducing HPV vaccines, and endpoints that were used for a previous cancer vaccine (hepatitis B).

The consultation noted that another factor to be considered beyond defining endpoints for HPV vaccine efficacy is the duration of protection conferred by vaccines. HPV infections may occur repeatedly over a number of years, and there is the possibility that vaccinated subjects may alter their sexual risk behaviour and further increase the lifelong risk for infection and cancer. This issue will need to be carefully followed in the near future.

The advantages and disadvantages of different possible endpoints for clinical studies of HPV vaccines were discussed and are outlined further.

2.1.1. Virological endpoints

There are two potential virological endpoints for prophylactic HPV vaccines: detection of incident HPV infection and persistent HPV infection. (a) Incident HPV infection is defined as new detection of HPV DNA in cervicovaginal cells in women previously shown to be HPV negative. Such infections are very common among sexually active subjects and are mostly asymptomatic. Over 90% are cleared spontaneously by the immune system within about 1 year without treatment. While the clinical, molecular, or host features that distinguish HPV infections that cause cancer as opposed to infections that will clear are unknown, HPV infection is definitely a precursor for the development of cervical cancer. HPV infection is relatively easy to measure, and occurs with sufficient frequency to allow for a rapid assessment of short term vaccine efficacy in a relatively small sample set (ca. 2000 subjects) followed for 1.5–2 years post vaccination. However, as only a small percentage of HPV infections have the potential to progress to cancer, only a vaccine with an efficacy of 100% against HPV infections will assure real impact on reducing cervical cancer rates.

(b) Persistent HPV infection is defined as detection of the same HPV DNA in cervicovaginal specimens obtained in follow-up visits 6–12 months apart in women who were naive for the relevant type at baseline. Since persistent infection with the same high-risk HPV type is accepted as a powerful predictor for moderate or high-grade dysplasias and cancer [8,12–15], it may represent a useful endpoint in vaccine efficacy studies. On the other hand, there is no formal evidence showing that selectively preventing persistent HPV infections has an impact on cervical cancer development. Such demonstration would require an increase of the robustness of the persistent HPV infection as an endpoint by long-term follow-up with repeated measurements of HPV. Clinical trials to measure protection against persistent infections by HPV vaccination would also require relatively few participants, about 2000, and performing such studies would take 2–3 years, if a long-term follow up is not required.

2.1.2. Clinical endpoints

Clinical endpoints can be assessed both cytologically (through Papanicolaou (Pap) testing) and histologically (through biopsy sampling). However, because the Pap test is only 70% sensitive (i.e., it will be negative in 30% of cases of CIN 2/3 on histology, see below) there can be discordance between the severity of dysplasia as manifested in cytology and histology. Hence, histology is accepted as the definitive diagnostic procedure evaluating cervical disease. Clinical endpoints appear to have an advantage over virological endpoints because they diagnose clinical diseases that require medical care.

Pre-cancerous cervical dysplasia lesions are histologically classified as cervical intraepithelial neoplasias (CIN) of mild (CIN 1), moderate (CIN 2) or high grade (CIN 3), which includes carcinoma in situ (see Fig. 2) [16].

CIN 1 (or low-grade dysplasia) is seen as the most common clinical manifestation of cervical HPV infections. CIN 1 lesions are accompanied by a high rate of clinical regression, as around 60% of low-grade dysplasias resolve without the need for treatment, and about 10% can progress to CIN 2 and 3 [17–19]. CIN 2 (moderate-grade dysplasia) also shows a high rate of regression, but women with CIN 2 are still at substantial risk for cervical cancer. A meta-analysis of cervical dysplasia natural history studies estimated that 22% of
In the context of a trial, CIN 2/3 cases would be identified from a work-up of patients with regular follow-up using colposcopy with biopsy of any suspicious lesions, and tested for HPV DNA corresponding to vaccine types. There are some data available to suggest that such a vaccine trial is feasible [12,22]. Obviously, in vaccination trials, an endpoint of high-grade dysplasia (CIN 2/3) or worse would require large numbers of participants, be resource-intensive and perhaps long in duration.

Both CIN 2/3 and persistent HPV infection were considered highly feasible endpoints for measuring HPV vaccine efficacy. CIN 2/3 was considered valid as an endpoint in light of studies among students that have shown that some women who developed CIN 2/3 in a 3-year follow-up [22] were tested HPV-negative in virological samples throughout the preceding period, and would have been missed looking at a virological endpoint only. Perhaps, this discrepancy may reflect low sensitivity of assays used to detect HPV DNA.

In addition, it was noted that it is difficult to measure the duration of an HPV infection with any certainty, because of the overlap in some diagnostic criteria between the two pathological states. [Stoler MH, Schiffman M. Atypical squamous cells of undetermined significance—low-grade squamous intraepithelial lesion triage study, (ALTS) Group. Interobserver reproducibility of cervical cytologic and histologic interpretations: realistic estimates from the ASCUS-LsIL Triage. J Am Med Assoc 2001;285(11):1500-5].

2 Some studies have indicated that CIN 2 may represent a heterogeneous group of HPV-related conditions, including lesions that regress spontaneously and others that progress to cancer. It is possible that this observation may be the result of a misclassified diagnosis of CIN 1 as CIN 2 due to the overlap in some diagnostic criteria between the two pathological states. [Stoler MH, Schiffman M. Atypical squamous cells of undetermined significance—low-grade squamous intraepithelial lesion triage study, (ALTS) Group. Interobserver reproducibility of cervical cytologic and histologic interpretations: realistic estimates from the ASCUS-LsIL Triage. J Am Med Assoc 2001;285(11):1500-5].

2.2 Which endpoints are currently being considered by vaccine manufacturers?

Two promising HPV vaccine candidates are reaching advanced clinical phases in development and will be measuring vaccine efficacy in field conditions. Following is a brief summary of the results of their trials.
Glia*SmithKline in co-development with MedImmune Inc. has developed an injectable, bivalent HPV 16 and 18 VLP vaccine candidate. The vaccine candidate was well-tolerated upon intramuscular administration at 0, 1, and 6 months, and vaccine-specific antibody responses were induced in 99.8% of subjects. The studies showed antibody titres 80-fold higher for HPV 18 and 101-fold higher for HPV 16 than those elicited by immune responses to natural viral infections. Efficacy against incident HPV 16 cervical infections was 100 and 89.6% against HPV 16 plus 18 infections. A 100% efficacy was seen against persistent infection with both virus types [23]. Efficacy endpoints for phase III clinical trials with this vaccine were not announced.

Merck & Co. Inc. has sponsored a proof-of-principle trial using the HPV 16 VLP vaccine candidate to measure efficacy against HPV infections and related dysplasias [12]. Dose-ranging studies showed that 20–80 μg of injected HPV 16 antigen at 1, 2 and 6 months formulated in alum elicits comparable immune responses. High-titre HPV antibodies were observed up to 145-fold higher than those following natural infection after the third vaccine dose. These antibody levels remain four to five-fold higher for at least 2 years after vaccination. A double-blind placebo-controlled study among women with both HPV-negative serology and negative for HPV DNA showed 100% protection against persistent HPV infections and related dysplasias. These results suggest that administering prophylactic HPV L1 VLP vaccines may substantially reduce the risk of infection, and cervical pre-cancer related to the HPV types included in the vaccine.

The company has now begun a multi-centre phase III clinical trial in several countries. More than 20,000 women will be enrolled to assess the protective efficacy of a quadrivalent HPV 6–11–16–18 vaccine candidate against CIN 2/3. The ongoing phase III vaccine studies are designed to demonstrate vaccine efficacy against CIN 2/3 in women enrolled in developed and developing countries (60 and 40% of the sample, respectively). These studies will assess vaccine effects in a diversity of ethnic and socio-economic backgrounds. About 13,000 subjects had received HPV vaccine candidates, and results showed that they are well tolerated.

Although vaccine manufacturers are willing to make HPV vaccines available in developing countries, their clinical trials are not designed to evaluate whether local co-factors will impact the level of benefit of HPV vaccination in certain regions. To address this issue, the consultation called for a series of bridging studies in developing countries that would go beyond phase III clinical trials. Such studies should also improve the regulatory process for developing countries and ensure that HPV vaccines adequately meet the needs of women in under-resourced countries.

2.3. Which endpoints would satisfy national regulatory authorities?

All vaccines must follow the regulatory requirements of a certain country or region in order to be licensed for use. Because national regulatory authorities (NRAs) can have different expectations for measuring efficacy of a new vaccine, the consultation heard the views of representatives of various national regulatory authorities concerning novel HPV candidate vaccines with a focus on advanced clinical phases.

The approach of the United States Food and Drug Administration (FDA) to licensing a prophylactic vaccine against HPV was the topic of an FDA Vaccines and Related Biological Products Advisory Committee Meeting, 28 and 29 November 2001. The main focus of this meeting was to select appropriate endpoints for phase III vaccine efficacy trials. Briefly, according to the requirements of the FDA, human clinical trials are conducted under Investigational New Drug (IND) regulations. There should be sufficient safety and immunogenicity data from phases I and II to support a phase III efficacy study, and relevant epidemiological background of the efficacy trial population should be available. The phase III efficacy protocol should clearly state primary and secondary endpoints to be studied. Also, the efficacy trial should have a prospective statistical plan. Standard operating procedures (SOPs) as well as validation of all assays used to measure the defined endpoint(s) in the context of vaccine studies should be well established before efficacy studies are initiated. It is worth noting that the phase III study often provides most of the safety data from pre-licensure clinical development.

Following completion of an efficacy trial and any other necessary trials, the sponsor may submit a Biologics License Application (BLA). The FDA will inspect the manufacturing facility and review the BLA within the mandated time frame of 6 months (priority) or 10 months (standard), depending on the application. After FDA’s review of the BLA and prior to any licensure decision, the FDA Vaccines and Related Biological Products Advisory Committee would consider the clinical data at a public meeting. Following licensure, the sponsor may conduct some specific clinical studies to address important issues not covered in pre-licensure development. The Vaccine Adverse Event Report System (VAERS) collects and analyses data from post-marketing reports of adverse events following vaccination. Post-approval facility inspections are conducted on a periodic basis.

The FDA recommends that sponsors meet with the FDA at critical times during drug development, especially (i) prior to submission of the IND, (ii) prior to initiation of a pivotal efficacy study and (iii) prior to submission of a BLA.

The FDA Vaccines and Related Biologicals Advisory Committee concluded that the primary endpoint for vaccine
licensure in the United States should be CIN 2/3 (or worse) histology detection accompanied by virus detection, with the data probably gathered in a single, large trial. This approach would address the possibility of an unanticipated effect of the vaccine on natural history of HPV disease. Also, the standard of care in the US and many other countries necessitates intervention for this histology endpoint. The larger trials and perhaps longer follow-ups required would allow accumulation of sufficient safety, immunogenicity and efficacy data before licensure.

The FDA stressed that the overall vaccine development programme should address critical areas including the following: (i) assays, (ii) manufacture and scale-up, and (iii) accumulation of sufficient safety, immunogenicity and efficacy data. Thus, in the process of US licensure, many important issues relevant for worldwide implementation would be addressed. However, clinical development to support US licensure would not include certain “regionally appropriate” clinical bridging studies in developing countries.

In Europe, a centralized procedure, through the European Medical Evaluation Agency (EMEA), is mandatory for evaluating and authorizing recombinant DNA products, genetically expressed bioactive products, and monoclonal antibodies. It is thus applicable to HPV vaccine candidates. The committee for proprietary medical products (CPMP), in charge of the evaluation, might agree on an accelerated evaluation procedure, taking into account seriousness of the target disease, absence of other therapeutic options, and expected high clinical benefit. In developing new vaccines for European Union (EU) licensure, manufacturers need to follow the requirements laid out in the Notes for Guidance on Clinical Evaluation of New Vaccines, which addresses points related to the clinical programme: the availability of an appropriate animal challenge model, testing in special groups, compliance with GCP guidelines, validation of immune correlates of protection, if any (when the licensure is based on such an endpoint), and matching antigenic components of vaccines with antigenic components of prevalent disease in Europe. In this respect, a well-validated correlate of protection would be extremely valuable. Indeed, if such a correlate was established then it could serve as an endpoint for a pivotal study for product licensure, although a clinical disease endpoint would be preferable.

Even if the pivotal phase III study is very large, the CPMP may still request post-licensure monitoring. The EMEA’s specific comment with respect to HPV vaccines was that a vaccine to be licensed based on data using high-grade dysplasia endpoint could only be promoted as a vaccine against dysplasias, not as a cancer vaccine. (Note: FDA would be supportive of a “cancer indication” for a definitive histological demonstration of prevention of high-grade dysplasia.) A formal EMEA position on this issue has not been determined; an official statement of the CPMP/EMEA would have to be announced.

National Regulatory Authorities in developing countries generally have fewer resources to properly review new vaccines and technologies. Because cervical cancer is the most commonly occurring female cancer mortality in developing countries, many NRAs may have an incentive to license HPV vaccines without proper review. It is imperative, however, that NRAs understand the local epidemiology of HPV types and cancer before approving vaccine trials and using the vaccine in a public health setting. Ideally, HPV vaccines should be demonstrably safe and effective in the local population, taking into account regional co-factors such as age of sexual debut and, where relevant, HIV prevalence. Representatives from developing country NRAs suggested that certain countries carry out “regionally-appropriate” clinical bridging studies beyond the pivotal phase III studies currently being conducted. There was discussion on the possibility of conducting bridging studies based on immunogenicity and virological and histological endpoints. While immunogenicity and virological endpoints might speed the process and facilitate vaccine availability, it was generally felt that histological endpoints would be most accurate and useful, especially in the effort to settle on a globally-agreed efficacy endpoint for pivotal trials.

In further discussions on vaccine introduction in developing countries, the group strongly suggested that developing countries consider the vaccine’s affordability, suitability for mass immunization and the potential impact on cervical screening programmes before rolling out public health programmes for HPV vaccination. Without such research, national health services are unlikely to introduce HPV vaccines based solely on phase III efficacy trials showing that HPV infection or CIN can be prevented. National Health Authorities should also be encouraged to begin building awareness of HPV disease burden in the local communities, assessing ultimate acceptability of an HPV vaccine, and assessing cost benefits of implementation and practical issues of vaccine availability and affordability.

2.4. What do we know about endpoints used for previous cancer vaccines?

Much of what we know about the process of licensing and adopting new vaccine stems from experience with other novel vaccines. In this case, much can be learned from the development and deployment of hepatitis B vaccines. Hepatitis B infection is similar to HPV infection in that it is also linked with cancer development. The development and rollout of hepatitis B (HepB) vaccine, declared effective 12 years ago, is often cited as relevant to the HPV vaccine field. There are major differences, however, between cervical cancer and liver cancer. Infection with hepatitis B virus (HBV) can cause acute hepatitis, which is symptomatic in 50% of cases (jaundice, pain, etc.) while chronic infection can lead to carcinogenesis.

6 http://www.emea.eu.int/pdfs/human/vp/046397EN.pdf.
7 Forty-fifth World Health Assembly, 4–14 May 1992 (WHA45.17 Immunization and vaccine quality).
in this case, liver cancer. Most critical is that in studies of liver cancer prevention there is no pre-cancerous condition (such as CIN 3) that could be used as surrogate endpoint for establishing vaccine efficacy. Also, unlike cervical pre-cancerous lesions, which can be treated, there is no treatment available for chronic hepatitis B infection. As a result, the only way to prove that hepatitis B vaccine prevented cancer was to monitor study participants until they did or did not develop cancer (sometimes upwards of 30 years), an ethical impracticality with HPV vaccine. As expected, these studies have taken a long time and will be completed in the next 10–20 years.

In Taiwan, where HBV infection had a high prevalence (90%) in liver cancer, a population-based study used age-specific incidence of cancer as the measurable outcome to study impact of HepB vaccination on hepatocellular carcinoma. This vaccine study evaluated the incidence of this cancer in children six years or older from 1981 to 1994, as a nationwide HepB vaccination program was implemented in Taiwan in July 1984. The incidence of hepatocellular carcinoma in children 6–9 years of age declined from 0.52 for those born between 1974 and 1984 to 0.13 for those born between 1984 and 1986 [24]. Vaccine efficacy was also measured as cumulative onset of persistent HepB sero-prevalence over a long time and will be completed in the next 10–20 years.

The Taiwan experience additionally showed that studies on effectiveness and cost-benefit are key elements for a successful national immunization programme, along with strengthening public health infrastructure, education, registration, evaluation and certification systems.

Further large studies were initiated in areas with a high incidence of liver cancer, one in Qidong county, China, and one in the Gambia, to demonstrate effectiveness of HepB vaccination against liver cancer. The Gambia Hepatitis Immunization Study (GHIS) was feasible because the infrastructure provided by the national immunization programme allowed for a population-based study. The results have suggested 94% efficacy measured against chronic carriage, which would translate into a 66% reduction in liver cancer incidence, assuming 80% of liver cancers attributable to HBV infection. The study has been designed to allow for 50% loss of subjects during the 30–35 year follow-up required for sufficient liver cancer cases to appear among the controls to demonstrate a significant reduction in incidence. Identifying individuals and linking cases with vaccinated cohorts after a 20-year follow-up have proven difficult and undoubtedly is a major drawback of studies designed to evaluate long-term endpoints in developing countries. The trial will continue until at least 2016.

Despite the lengthy trials, HepB vaccine was recommended by WHO for public health use because it prevents acute hepatitis, a disease that can be manifested clinically, varying in degree from mild to fulminating. Even so, it is taking most developing countries many years to introduce the vaccine and additional effectiveness studies in the Gambia and China are still incomplete.

The lessons from HepB vaccine studies suggest that HPV vaccines could face even greater challenges to introduction and use, because unlike acute hepatitis B, infection with HPV alone has no clinical manifestation and is not necessarily considered a disease or a serious condition. Moreover, HPV efficacy studies with an endpoint of cancer would be ethically controversial. In addition, without a public health commitment to support its use, and without an agreed surrogate endpoint for efficacy studies, HPV vaccines could take decades to be approved and introduced into public health programmes where it is most needed.

3. Recommendations

The consultation recognized that in the context of many developing countries, efficacy to surrogate endpoints might not provide enough information for countries to decide whether or not to adopt HPV vaccines as a public health prevention tool against cervical cancer. Furthermore, these vaccines will be expensive and underused without public health commitment. Therefore, a number of issues unlikely to be covered by studies sponsored by the vaccine manufacturers, but potentially relevant to the global impact of vaccines in a number of developing countries, need the attention from the scientific community and public sector. The consultation agreed unanimously that it seems impracticable to use invasive cervical cancer as a primary endpoint for vaccine efficacy studies towards licensure.

3.1. Evaluating HPV vaccine efficacy

The consultation generally agreed that CIN 2/3, as well as cancer, should be recommended as the globally defined endpoint for efficacy studies with an endpoint of cancer would be ethically controversial. In addition, without a public health commitment to support its use, and without an agreed surrogate endpoint for efficacy studies, HPV vaccines could take decades to be approved and introduced into public health programmes where it is most needed.
3.2. Additional research for evaluating HPV vaccines in developing countries

The consultation agreed that “regionally-appropriate” clinical bridging studies should be carried out to clarify immunogenicity and/or efficacy issues unlikely to be covered by clinical studies being sponsored by the vaccine manufacturers. For instance, in sub-Saharan Africa, immunogenicity levels of HPV vaccination might be altered in HIV-infected subjects. Similarly, other endemic infections such as hepatitis B or malaria that chronically alter the immune system of affected people may modify the patterns of immunogenicity or affect the safety profile of HPV vaccine candidates. Although there is no evidence to suggest that malnourished populations show lower efficacy levels of other vaccinations, there may be significant differences in HPV vaccine immune responses among malnourished, compared with better-nourished populations.

Furthermore, although the HPV types included in the current vaccine candidates are prevalent at similar levels across many studied countries and are likely to target the majority of cervical cancer cases worldwide, there are subtle regional differences in the distribution of oncogenic HPV types that should be further studied.

Taking into consideration the potential benefits of such bridging studies, experts recommended the following three studies on a short-term basis.

- Bridging studies\(^9\) to evaluate immunogenicity and possibly collect virology data in geographical areas or ethnic groups affected by debilitating health status and not represented in ongoing pivotal efficacy trials or other immunogenicity studies.
- Immunogenicity and limited safety studies in immunocompromised subjects (e.g., HIV-infected) at vaccination, particularly in endemic areas where HIV-infected subjects may not be using standard antiretroviral therapy.
- Feasibility studies of vaccinating adolescents who are poorly targeted by public vaccination programmes. Major cultural differences exist between countries that could impact the potential acceptability of HPV vaccination among minors. For example, HPV vaccination may be perceived as the promotion of sexual activity. Data on average age at first intercourse may help in determining the age to start vaccination.

3.3. Long-term studies

After discussing relevant short-term studies, the consultation realized that some additional longer-term studies would greatly benefit the field. Specifically, the experts recommended the following.

- Study the ability of the current vaccines to induce cross-immunity. The extent of cross immunity among different HPV types cannot be determined without study in populations with high prevalence of such types [6].
- Monitor the prevalence of HPV types in vaccinated and non-vaccinated populations by periodic sampling surveys. Following the introduction of HPV vaccination against two or four HPV types, vaccination could have an unexpected impact on shifting the prevalence of other HPV types in the general population.
- Evaluate the benefit of vaccinating previously infected women, preventing not only re-infection but also perpetuation or persistence of infection. While the current target group is young women before sexual debut, vaccination of a wider age range could have more immediate impact on cervical cancer (e.g., women 18–34 years).
- Document breakthrough cases following long periods after vaccination, and promote studies aimed at establishing immune correlates of protection. This is crucial for designing an appropriate vaccination schedule and would facilitate vaccine product improvements.

3.4. Duration of vaccine protection

Data generated over the last 3 years, show that vaccination prevents HPV infections or even related lesions over this period of time. However, the duration of vaccine efficacy remains a key issue that could have a major impact on the long-term implications of vaccination strategies and affordability.

The members of the consultation considered whether it was necessary to set up special studies to monitor the long-term effectiveness of vaccination over and above the expected evaluation and monitoring of every newly introduced cancer control measure, as recommended in the National Cancer Control Programme [16]. Recognizing that it will be some years before a reduction in cervical cancer is detectable at population level, the consultation stressed the importance of maintaining existing cervical screening programmes upon vaccine introduction and while such long-term studies are conducted. There are substantial differences in cervical screening strategies and their impact among various countries. Even in developed country settings, comprehensive screening programmes have not been able to completely eliminate cervical cancer. For this reason, cervical cancer may still be detected as an endpoint in any large-scale HPV vaccine effectiveness study. For population-based field trials (i.e. studies in which a protocol is not followed for screening), screening programmes may drive the choice and frequency of the endpoints. This will be easier to record in countries that have established cancer registries.

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\(^9\) The International Conference on Harmonization (ICH) E5 guideline defines a bridging study as a supplementary study conducted in a new region to provide pharmacodynamic or clinical data on efficacy, safety, dosage and dose regimen to allow extrapolation of the foreign clinical data to the population of the new region.
3.5. Ethical considerations for HPV vaccine efficacy trials

If randomized trials of an HPV vaccine in developing countries are contemplated, the ethical issues of including a control group will have to be addressed in each country. In general, the following should be considered:

- Monitoring the occurrence of invasive cervical cancer in specific early age groups could identify an early impact of vaccination on cancer (as in the Taiwan HepB study). A demonstration project where women living in one area are vaccinated and compared to those in unvaccinated areas or to historical controls would be ethically acceptable.
- As is the case in interventions of unknown efficacy, it would be acceptable for control groups to receive the care normally offered in each country. In most countries, this would be a cervical Pap smear.
- If long-term randomized studies are set up, cluster randomization might be the most feasible approach, although this does not necessarily remove the need to identify vaccinated or unvaccinated individuals.
- If studies prove that HPV vaccination prevents HPV-related disease(s), it would be ethical to begin vaccination of the control group at that point. However, if HPV vaccination were only effective within a certain age group (e.g., adolescents), then delayed vaccination would offer no benefit to the controls and would not need to be offered. However, in view of the high efficacy demonstrated so far, this may not be advisable for HPV vaccines, especially on a long-term basis.

Ethically and scientifically speaking there should be no differences in cervical cancer screening interventions between the two groups of field trials: vaccinated and control. For example, in a country with a policy not to screen before age 35, there would be no justification to introduce nationwide screening at an earlier age simply for HPV vaccine research purposes.

There was consensus that WHO should advise such countries on how to monitor disease if HPV vaccines are introduced. Evaluating the vaccine’s ability to prevent HPV infections could be then regarded as a suitable surrogate.

4. Conclusion

Evaluation of HPV vaccine efficacy using prevention of CIN2/3 dysplasias and cancer was recommended as the globally accepted endpoint for population-based studies. Since the time the meeting was held, discussions on this subject of cervical cancer and vaccine research have continued. Regulatory authorities of each country ultimately will determine the endpoints required for licensure. In particular, it may be possible that regulatory authorities of some countries will base registration of HPV vaccines on the demonstration of their capacity to protect against persistent virus infections, not to delay introduction of a potentially life-saving vaccine. This will be appropriate if results show that protection against persistent infection correlates with protection against development of high-grade cervical lesions. Regardless, of the endpoint used for registration, countries will face a decision on using HPV vaccines before efficacy against invasive cervical cancer is demonstrated. Initial evidence to support HPV vaccine introduction will be based on vaccine efficacy against surrogate endpoints as well as on feasibility studies or clinical bridging studies in developing countries with the highest disease burden. This may imply that, certain health authorities may not be able to justify adoption of vaccination against cervical cancer without demonstration of the clinical benefit of vaccination for the population and the public sector in the long term.

Without a public health commitment, then, to guide their introduction, HPV vaccines are in danger of being initially underused in developing countries, where most needed.

However, if developing countries are supported in their efforts to conduct bridging studies and conduct proper review of HPV vaccines, and if they make an effort to address acceptability issues, then HPV vaccines have the potential to significantly reduce cervical cancer cases throughout the world and greatly improve the lives of women, especially those most affected by the disease living in developing countries.

As novel evidence is being accumulated from advancing clinical trials and becomes public knowledge, some of these recommendations may become outdated and will be revisited, as appropriate, by a group of experts with cross cutting competences in all disciplines overarching cervical cancer prevention policy.

Appendix A. List of participants

Eliav Barr*, Blue Bell, USA; Xavier Bosh, Barcelona, Spain; Chien-Jen Chen, Taipei, Taiwan; Zvavahera Chirenje, Harare, Zimbabwe; Felicity Cutts, Banjul, Gambia; Gary Dubin*, King of Prussia, USA; Mario Festin, Manila, Philippines; Silvia Franceschi, Lyon, France; Eduardo Franco, Montreal, Canada; Ian Frazer, Queensland, Australia; Karen Goldenthal, Rockville, USA; Rolando Herrero, Santa Ana, Costa Rica; Julian Hickling*, Cambridge, UK; Allan Hildesheim, Bethesda, USA; Stephen Inglis, Hertfordshire, UK; Bettina Klug, London, UK; Marie-Therese Martin*, Rixensart, Belgium; Anthony Miller, Heidelberg, Germany; Denise Nandelli Haefliger, Lausanne, Switzerland; José Eluf Neto, Sao Paulo, Brazil; John Nieland*, Martinsried, Germany; Sue Nie Park, Seoul, Korea; Max Parkin, Lyon, France; Pimnee Pitisuttithum, Bangkok, Thailand; Douglas Pratt, Rockville, USA; Helen Rees, Johannesburg, South Africa; John Sellors, Seattle, USA; Keerti Shah, Baltimore, USA; Jennifer Smith, USA;

*Representatives of industry did NOT participate in the drafting of recommendations.
References


