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Vaccine 24S3 (2006) S3/233–S3/241
Vaccine
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Chapter 28: Studies to assess the long-term efficacy and effectiveness of HPV vaccination in developed and developing countries

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Received 6 March 2006; accepted 15 May 2006

Abstract

We review studies of the implementation of human papillomavirus (HPV) vaccination programmes in developed and developing countries. The review spans the period from establishment of long-term vaccine efficacy follow-up studies, operational research on issues of vaccine preparedness, and relevant predictive modelling studies during the pre-licensure phase to plans of phase IV effectiveness trials, forms of epidemiological surveillance, and further operational research in the post-licensure phase. Much of the research is already ongoing. Depending on the results of the planned immuno bridging studies among HIV-negative and HIV-positive women, further phase III and/or phase IV trials may be warranted.
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Keywords: Cervical cancer; Vaccination; Effectiveness; Efficacy

1. Introduction

Participants in ongoing phase III studies of HPV vaccination are screened frequently and lesions are therefore detected and treated at an early stage, which makes it difficult to define vaccine efficacy (VE) against cervical intraepithelial neoplasia grade 3 (CIN-3) or invasive cervical cancer (ICC) and to predict the population-level impact of HPV vaccination on total morbidity [1–3]. However, in some population-based trials, screening other than by conventional programmes will not take place in the long run, hence the use of personal identifiers to link vaccinated/unvaccinated cohorts to country-wide registries achieves virtually complete long-term follow-up [4,5], and yields VE against major health problems, including ≥CIN-3, earlier than post-licensure surveillance.

The duration and HPV type-specificity of immune protection following HPV vaccination are also important long-term efficacy issues. Population-based long-term efficacy trials performed in the Nordic countries and in Guanacaste, Costa Rica, conducted in parallel with the ongoing phase III studies, will also address these questions.

In developing countries other endemic infections, such as malaria and HIV infection, act as immunological modulators, and HPV vaccine safety, immunogenicity, efficacy and effectiveness remain to be determined. However, it will be important to consider the impact that widespread use of HPV vaccines may have in terms of herd immunity and reducing the prevalence of high-risk (HR) HPV types circulating in the

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doi:10.1016/j.vaccine.2006.05.109

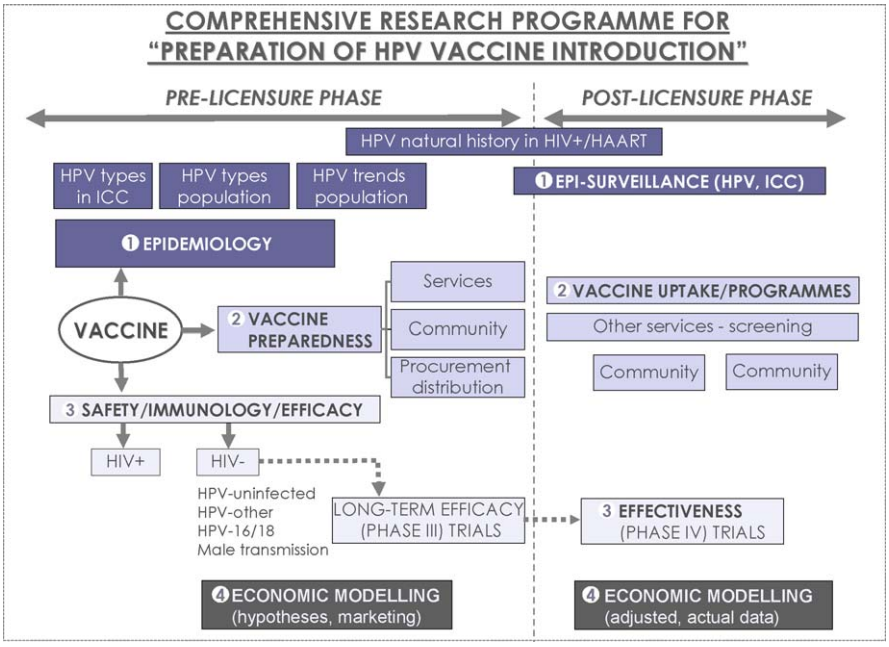

Fig. 1. Comprehensive research programme for "Preparation of HPV vaccine introduction". The figure stretches over time from epidemiological studies and phase II/III trials, including establishment of the long-term vaccine efficacy follow-up, operational research on issues of vaccine preparedness, and some predictive modelling studies during the pre-licensure phase, to phase IV effectiveness trials, or some form of epidemiological surveillance and further operational research or economical modelling using actual data in the post-licensure phase. Box background indicates the four blocks (1–4) of research areas. Some of the research has already been conducted. Depending on the results of the planned immuno-bridging studies among HIV-negative women in Africa, further phase III or phase IV trials may be warranted.

population both for developed and developing countries [6]. The elimination of several common childhood diseases by the Nordic vaccination programmes is an excellent example [7].

This chapter summarizes some of the largest ongoing population-based long-term efficacy projects on HPV vaccination, and discusses planned effectiveness studies both for developed and developing countries in the context of a wider HPV vaccine introduction research agenda (Fig. 1).

2. Long-term efficacy trials

2.1. The Nordic HPV vaccine trials

There are two ongoing Nordic trials, which have been established as double-blinded, controlled, population-based phase III efficacy studies of the upcoming vaccines against HPV types 6/11/16/18 (Merck & Co. Inc.) and 16/18 (GlaxoSmithKline, GSK, Biologicals). The trials are being conducted as separate studies between national research institutes and the vaccine manufacturers in unvaccinated young women; cohort studies are also ongoing [4,5].

In 2002–2004, 45,000 16–17-year-old women in 18 communities in Finland and 10,000 18–23-year-old women in the Scandinavian countries (Denmark, Iceland, Norway and Sweden) were invited to participate at different stages. Consenting women were randomized to receive either the HPV-6/11/16/18 L1 VLP vaccine or placebo between September 2002 and March 2003 (5,570 Scandinavian and 1,750 Finnish women), or the HPV-16/18 L1/AS04 vaccine or hepatitis A virus (HAV) vaccine between May 2004 and May 2005 (4,875 Finnish women; Fig. 2). Three vaccine doses were given, the first at enrolment, the second at 1 or 2 months and the third dose 6 months later. Active follow-up in both trials is for 4 years with 6-monthly (later 12-monthly) visit intervals. Women with cervical lesions are referred for colposcopy and appropriate diagnostic/treatment procedures following the local standard of care. After 4 years, follow-up will continue through national cancer registries.

In May 2003 and 2005, 31,000 and 59,000 unvaccinated 18–19-year-old Finnish women were invited to participate in a cohort study of unvaccinated women, and to complete a questionnaire about their willingness to receive HPV vaccine, living conditions, lifestyles and sexual behaviour [4,5]; 17,000 women agreed to participate and returned the questionnaire. A large number (69,500) of 18–45-year-old Scandinavian women were also invited. These women will be followed-up by cancer registries through which any incident ≥CIN-3 will be ascertained.

2.2. The Guanacaste HPV vaccine trial

The Guanacaste (CVT-PEG) trial in Costa Rica is a randomized, double-blinded, controlled, population-based efficacy trial of the HPV vaccine against types 16/18 from GSK Biologicals. This trial is being conducted as a collaboration between the National Cancer Institute and several institutions

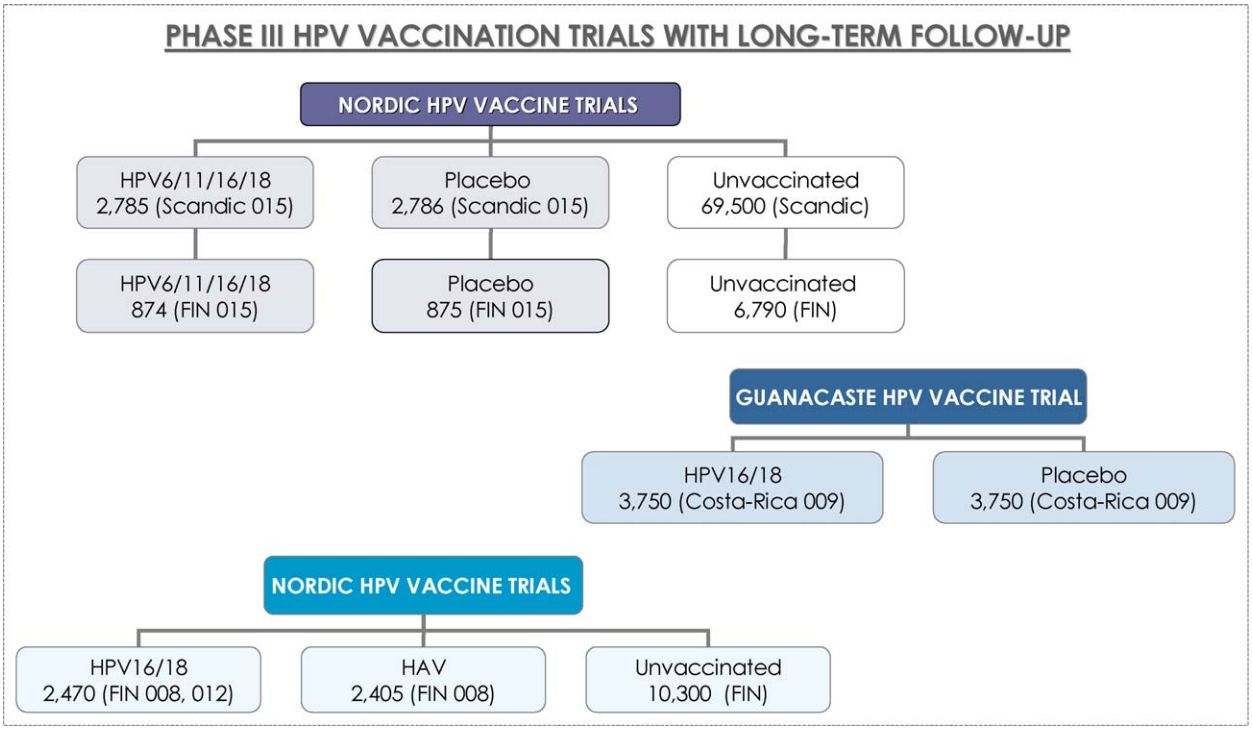

Fig. 2. Phase III HPV vaccination trials with long-term efficacy follow-up. Cohorts of female HPV-6/11/16/18 or HPV-16/18 vaccine/placebo recipients and unvaccinated controls in Finland (16–19-year olds), Scandinavia (Denmark, Iceland, Norway and Sweden, 18–45-year olds) and Costa Rica (18–25-year olds) were enrolled in a population-based fashion (Finland, Iceland, Sweden, Costa Rica) and subjected to long-term follow-up as described [4,5]. [§]Indicates the number of questionnaires sent out.

in Costa Rica (mainly Fundación INCIENSA and the University of Costa Rica).

Between June 2004 and December 2005 women aged 18–25 years residing in the province of Guanacaste and parts of nearby Puntarenas were invited to participate at home, and after informed consent, they were randomized to receive either the HPV vaccine or HAV vaccine. Vaccine doses were given at enrollment and at 1 and 6 months. Enrolment included 7,467 women (Fig. 2), and follow-up is planned for 4 years. Follow-up is carried out once a year, although more frequently for those with minor cytological abnormalities. Women with significant cervical lesions are referred for colposcopy and treated wherever indicated.

2.3. Objectives of the long-term efficacy trials

The main objective of the phase III studies is to determine the efficacy of the HPV vaccines to prevent histologically confirmed CIN-2 or worse lesions associated with HPV-16/18 in 4 years. A number of objectives for the follow-up beyond 4 years for the participants in the above trials are listed here and discussed in more detail in Chapter 28. They are:

- evaluating duration of protection;
- evaluating protection against non-vaccine HPV types;
- defining immunologic mechanisms of action;
- evaluating the therapeutic efficacy of vaccination in those previously infected with HPV.

There are, however, a number of other objectives for the long-term follow-up that benefit from the population-based nature of these trials, the national health registries and healthcare. These are discussed below.

2.3.1. Evaluating long-term efficacy of HPV vaccination

The Nordic trials will have high power to detect the impact of vaccination on ≥CIN-3 by 2015–2020 utilizing the Nordic healthcare/health registry infrastructure for long-term follow-up [4,5]. The peak of HPV infections will have passed during the active 4-year follow-up in the phase III vaccination studies. After that, VE against ≥CIN-3 will be compared using ≥CIN-3 incidences for women in the HPV vaccine cohorts and for women in the unvaccinated cohort (probably including the placebo/HAV vaccine cohorts) according to the equation: $VE = 1 - (\text{incidence rate}_{\text{vaccinated}}/\text{incidence rate}_{\text{unvaccaccinated}})$ [8,9].

Women who did not receive HPV vaccine in the Finnish phase III studies may not be offered free vaccine at the end of the 4-year active follow-up. The justification for this is that organized screening for ≥CIN-3 starts at the age of 25 years in Finland (20–23 years in Scandinavian countries) with 3–5-year intervals [10]. At least half of all lifetime HPV infections in the placebo/HAV vaccine arms will have been acquired by the end of the phase III studies, i.e. ages 21–27 [11]. All vaccine recipients and unvaccinated controls will receive letters of invitation for ≥CIN-3 screening. This is the established

most-effective means for prevention of cervical neoplasia [10]. The Finnish national ethical review board will assess whether or not HPV vaccination after the trial confers significant health benefit for placebo/HAV vaccinees; it is not currently planned for the end of the phase III studies. There may be systematic post-trial HPV vaccination in the other Nordic countries, but this would only decrease the power of the long-term efficacy trials because of the existence of parallel unvaccinated control cohorts.

2.3.2. Defining genetic determinants of successful vaccination

High hereditability estimates of cervical carcinoma may be explained by shared environmental and behavioural risk factors but also by known (e.g. human leukocyte antigen HLA) and unknown gene associations with ≥CIN-3 [12,13]. In both the Nordic and Guanacaste trials, the impact of host factors on the risk of acquiring breakthrough HPV infections and on infection with non-vaccine HPV types in vaccinated individuals will be assessed. Controls will comprise of a random sub-sample of subjects who have been successfully immunized and women who have received placebo/HAV vaccination. The groups will be compared to each other to identify any genetic polymorphism associated with breakthrough infection and/or non-vaccine type infections.

2.3.3. Evaluating overall protection against cervical lesions

HPV-16/18 are responsible for at least 70% of cervical cancers. Assuming no cross-protection, in spite of some recent promising results [14], complete prevention of infections with these two types should reduce incidence of disease in vaccinated women by approximately that amount. However, if other HR-HPV types occupy the vacant ecological niche of HPV-16/18 the net effect of the vaccine in preventing ≥CIN-3 could be reduced. Thus, VE against all cervical lesions independent of the HPV types will be evaluated.

The duration of protection is also an unresolved issue. Within 5, 10 and 15 years post-vaccination 25%, 50% and 60%, respectively, of the vaccine recipients will become pregnant and donate serum samples for the population-based screening of congenital infections [15]. These samples, together with the cervical samples collected in organized screening for cervical cancer, will enable surveillance of HPV antibody levels and cervical neoplasia occurrence in the vaccinated individuals.

2.3.4. Evaluating safety/pharmacovigilance of licensed vaccines

One of the main objectives of the phase III studies is to evaluate vaccine safety. Long-term safety will be assessed in the Nordic trials by using the personal identifiers to link vaccine recipients to the national health registers to detect possible differences in the incidence of major chronic diseases and adverse pregnancy outcomes in the vaccinated and unvaccinated individuals.

3. Post-licensure studies

3.1. Modelling studies

The potential impact of vaccination on HPV infection and cervical neoplasia can be explored through mathematical modelling analyses, as discussed in Chapter 21. Transmission models account for both the direct and indirect (herd-immunity) effects of vaccination, although models that consider HPV types separately [16,17] may fail to capture direct or indirect interactions of different HPV types [18]. While these studies are calibrated against observed HPV and ≥CIN-3 incidences over time [17,19], they are limited by the model structure and underlying parameter values. For the forthcoming phase IV (effectiveness) studies in Finland, modelling analyses have estimated the impact of varying the population coverage of vaccination and varying the age at vaccination on HPV infection (Fig. 3) and ≥CIN-3 [17] incidence.

3.2. Effectiveness studies measuring reduction in HPV prevalence

Post-licensure studies need to determine the effectiveness of HPV vaccination in the context of implementing vaccination into national vaccination programmes. It will be important to measure the reduction in the prevalence of HR-HPV types in the birth cohorts of early adolescents entering sexually active life, and to assess the role of herd immunity/vaccine coverage in this reduction. The effectiveness of different methods of implementing mass vaccination can be evaluated as protective efficacy (PE) in community randomized trials [9], as originally described by Brookmeyer and Chen [20].

In the forthcoming phase IV studies in Nordic countries, communities will be randomized to different HPV vaccination policies, taking into account time trends of HPV seroprevalence. These will be assessed for each community in random sub-samples of Finnish and Swedish maternity cohorts [19,21]. Serum samples of 15,000 young pregnant women are being used for the determination of HPV seroprevalence and to assess the spatio-temporal nature of HR-HPV epidemics in the sexually active population (Fig. 4); they will also be used to evaluate the impact of HPV vaccination. Maps from the pre-vaccination era show that HPV-16 and -18 have spread rapidly in time and space within birth cohorts born after 1960 [21]. The population of target communities for randomization to HPV vaccination or hepatitis B virus (HBV) vaccination varies between 50,000 and 150,000.

Phase IV HPV vaccination will take place at secondary schools in the target communities, and the study subjects will be early adolescents, among whom the coverage of national vaccination programme in Finland is 93%. Considering both direct VE and herd immunity, the number of communities required for the demonstration of a significant reduction in the prevalence of vaccine HPV types has been calculated with the following assumptions [9]: (1) vaccination will take place

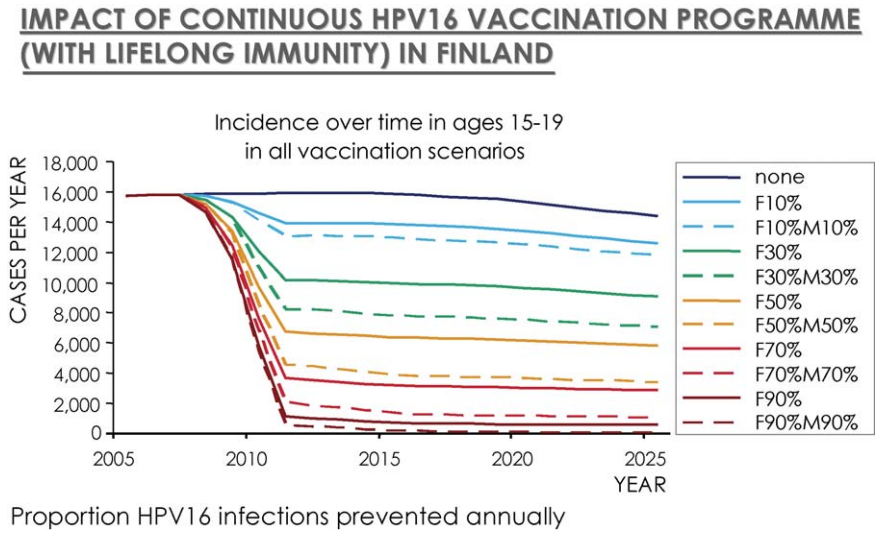

Fig. 3. Model of the impact of HPV-16 vaccination by vaccine coverage in females (F) and males (M) on reducing the number of HPV-16 infections in adolescents. Adaped from [17].

before sexual debut at age 13–14 years with an HPV-16/18 vaccine (70% coverage per community) or with an HBV vaccine; (2) randomization is by communities stratified for overtime sexually transmitted infection (STI) seroprevalence; (3) over 50% of HR-HPV infections are acquired within four years of sexual debut from 3-year-older or -younger partners in the same community with a population mixing of 15%; (4) direct VE is 95%; (5) the expected prevalence of HPV-16/18 in unvaccinated 18–19-year olds is 15%. Communities in Finland will be randomized into one of three groups: (A) HPV girls and HBV boys, (B) HPV girls and boys and (C) HBV girls and boys. Comparison of (A) with (C) requires seven communities per arm to yield 80% power for demonstrating 85% reduction in HPV-16/18 prevalence [9]. In Sweden,

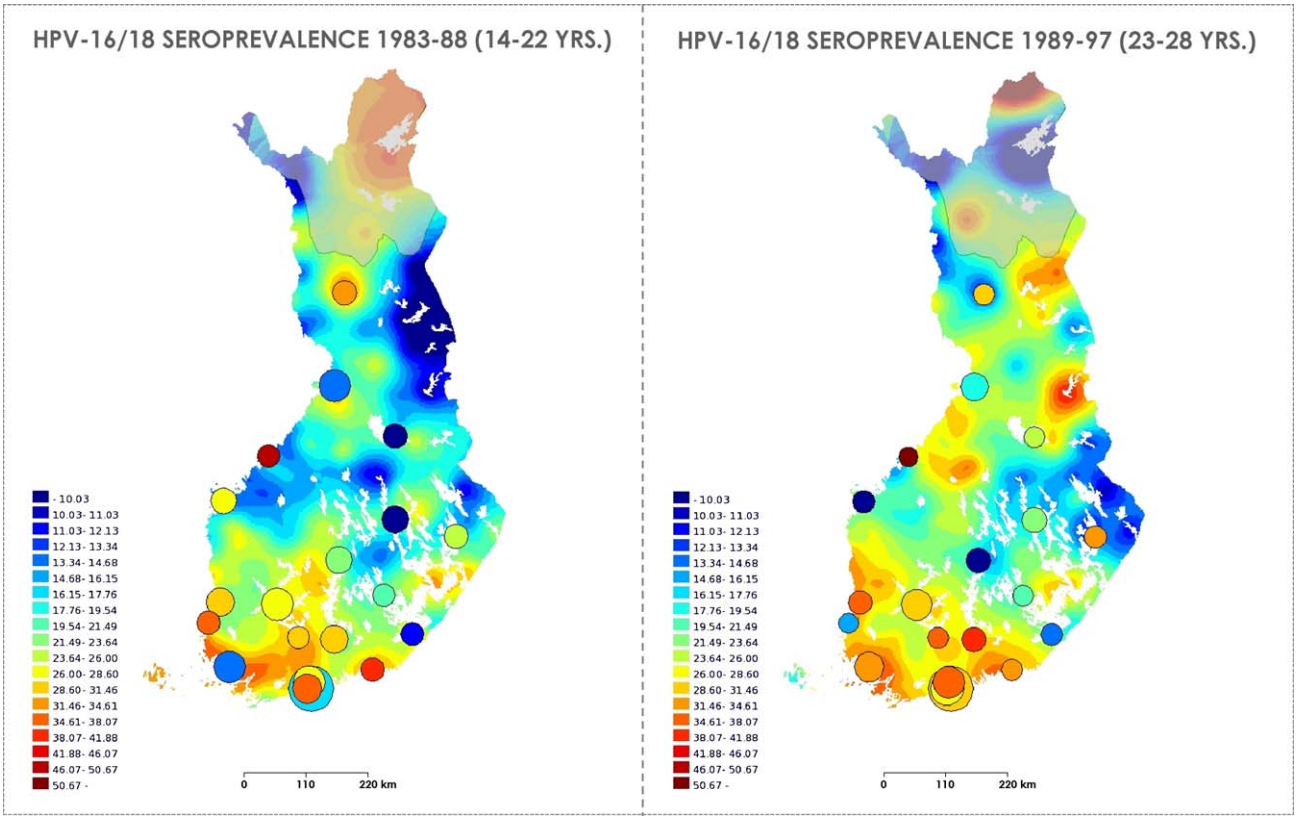

Fig. 4. HPV-16/18 seroprevalence maps of Finland in the 1980s and 1990s for the birth cohorts born in 1961–1974. Communities (>35,000 inhabitants) with phase HPV vaccination study sites are indicated with rings. Adapted from [21].

communities will be randomized to evaluate the impact of one or both sex vaccination strategies, as well as the impact of catch-up vaccination strategies.

Using the Finnish data [17,19,21] the effectiveness of vaccinating early adolescents has been modelled among 15–19-year-old adolescents in the community randomized setting by vaccine coverage (Fig. 3). The reduction in HR-HPV prevalence at 18 years of age will be compared to HR-HPV prevalence in communities in the HBV-vaccinated arm. It should be emphasized that for these communities cross-over vaccination with the HPV-16/18 (and HBV) vaccines needs to be guaranteed due to the young age of the vaccine recipients.

In this context, the aim of active surveillance could be to determine the causes of changes in the prevalence of vaccine and non-vaccine HPV types following vaccination. The community randomized trial also gives the opportunity to define immunocorrelates for protection. Identification of the neutralizing antibody titre at which there will be breakthrough infections (as in the HBV context) may be crucial to establish booster and re-vaccination schedules [22].

4. The challenge in developing countries

Developing countries carry the burden of disease with the highest ICC incidence rates and nearly 80% of global deaths ([23], Chapter 8). In most of the poorest developing countries ICC is the most common cancer among women, where cases present late, facilities for treatment are very limited and prognosis is poor. Most countries lack the resources to develop mass screening programmes and thus the widespread deployment of a preventive HPV vaccine could have an enormous long-term impact on ≥CIN-3 rates.

4.1. Challenges of implementing HPV vaccination

4.1.1. Delay in impact and targeting adolescents

The demands on the health budgets of developing countries greatly exceed the resources available. For HBV vaccination, it was many years after the causal association with liver cancer (the most common cancer in many African countries) was established that cheap HBV vaccines became available and widely introduced into infant vaccination programmes, largely through the promotion and funding by the global alliance on vaccines and immunization (GAVI). New interventions can only be funded if the expected health benefits merit this, but over the next two decades, the reduction in ≥CIN-3 rates and mortality by vaccination will be very small and the priority of HPV vaccination is low. The situation for HPV vaccination is even more difficult than that for HBV vaccine. First, HPV vaccines may be more expensive. Second, even at greatly subsidized costs, delivery of the vaccine to the adolescent target group itself will be much more difficult and costly than the delivery of HBV vaccine to infants combined with other infant vaccines. Ultimately, the HPV vaccine can also be given in infancy with other vaccines, but the first target group of adolescents will be a group for which there is little experience or infrastructure on which to base vaccination programmes.

4.1.2. Uncertainty about efficacy

4.1.2.1. Disease attributable to HPV types in vaccine. There are currently no data on the efficacy of HPV vaccine against ≥CIN-3, although there is limited information on the predominant HPV types circulating in the developing countries and on the types most commonly found in ≥CIN-3. While HPV-16/18 probably are the predominant types, more data are required to make estimates of the impact that an efficacious vaccine might have on disease rates.

4.1.2.2. Environmental influences on response to vaccination. The immune response, and adverse reactions, to HPV vaccines might be influenced in developing country populations by the high prevalence of other endemic infections, such as malaria, helminth infections, tuberculosis and other STIs, especially HIV. A programme of research is required to investigate such potential interactions before mass vaccination programmes with HPV vaccine are instigated (Fig. 1).

4.1.2.3. Duration of protection. HPV vaccination programmes will be implemented in developed countries before there is information available on the duration of protection and whether booster vaccinations will be required. The ongoing phase III studies will give information on short-term protection to inform the immediate vaccination strategy but decisions on deployment will have to be made in the absence of evidence of long-lasting immunity. The same will be true in developing countries, and again it would be wise to set up systems for monitoring immunity over time and also to monitor the long-term impact on disease rates.

4.1.3. The research agenda

Much of what is presented above depicts a comprehensive research programme to answer the key questions that a Ministry of Health official in a developing country might consider as HPV vaccines are being licensed. The HPV vaccine demonstration projects should be set-up to address issues such as

- Will the vaccine change morbidity and mortality? (epidemiological impact)
- What is required for vaccine delivery and what will its effect be on other services? (systems impact)
- What are the necessary investments, costs and savings? (economic impact)
- What will be the reaction of various constituencies? (societal/community impact)
- What will happen to (or be required for) special groups? (e.g. people living with HIV/AIDS)

4.1.3.1. Epidemiology of infection and disease. Although high in absolute terms, the prevalence of HPV-16 relative

to other HPV types appears to be lowest in Africa [24–26], which could suggest limited effectiveness for current vaccines (see Chapter 3). The IARC plans to support a multicentre study in African countries to determine the distribution of HPV types in ≥CIN-3, and whether this differs by HIV status. The HPV epidemiological heterogeneity may be related to complex and poorly studied factors (e.g. virological variants, immunogenetic factors) compounded by various possible causes of cellular impairment (due to parasitic infections, such as malaria or helminth infections, malnutrition, or chronic cervical inflammation caused by HIV, other STIs or genital schistosomiasis). These factors may also influence the immunological response to vaccines. In particular, the role of HIV in HPV acquisition, progression to ≥CIN-3 and response to vaccine (see Chapter 16) should be studied closely in a severely affected continent. Moreover, in the era of increased access to antiretrovirals, studies should be conducted to determine how highly active antiretroviral therapy (HAART) might impact the natural history of HPV and progression to ≥CIN-3, whether the increased survival afforded by HAART will be accompanied by corresponding increases in CIN and ≥CIN-3 rates, and how such an epidemic should be contained. HIV-infected women might represent a special priority group for vaccination.

4.1.3.2. Immuno-bridging studies. While the efficacy of company-sponsored vaccines is being established in ongoing trials in North America, Europe, Asia and Latin America, the delay in vaccine evaluation in Africa will lead to the delayed introduction of an important public health intervention. Bridging studies (phase IIB or IIIB) that would assess the tolerance, safety and immunogenicity of current vaccines in African populations are a priority. In particular, these studies should determine whether vaccine responses may be influenced by background malaria, parasitic infections, coexisting cervico-vaginal STIs and nutritional status. A number of studies are planned among HIV-negative young women in Senegal, Tanzania and South Africa. Importantly, immunobridging studies should also be conducted in HIV-positive adolescents and young women to determine the safety of the vaccines as it is unlikely that HIV-positive subjects will be excluded from vaccination programmes.

It is debatable whether bridging studies should also include boys and young men in Africa. Some data might be required to demonstrate immunogenicity of the Merck vaccine in particular, that targets HPV types 6 and 11, which might represent significant associated-morbidity (e.g. genital warts) in high-incidence HIV settings.

4.1.3.3. How to deliver vaccination to adolescents and other populations. The challenges represented by vaccination of adolescent populations in countries where such groups have not been traditionally targeted are described elsewhere in this monograph (see Chapter 14). Data are needed on the feasibility, acceptability and likely integration of HPV vaccination into other existing programmes, and should be obtained through operational research. These data would inform the future introduction and branding of other "teenage" STI vaccines (e.g. HIV). Issues of possible stigmatisation of girls through women-only vaccination strategies should be addressed. Some of these studies could be repeated during the roll-out phase of the vaccine to check on conditions that determine good uptake and coverage of vaccination programmes (Fig. 1).

4.1.3.4. Phase III/IV trials. Every effort should be made to make HPV vaccines available in developing countries as soon as possible after satisfactory immunogenicity and safety profiles have been established. However, based on previous experience with the introduction of new vaccines of this kind, it seems unlikely that wide coverage will be achieved for some years, especially given the challenges of delivering the vaccines to adolescents. Urgent consideration should be given to setting up demonstration projects that would seek to introduce HPV vaccination in specific countries or regions of a country to investigate the effectiveness of different delivery systems. Such projects, if carefully planned, could also be used to monitor changes in immune responses at different times after vaccination, and to verify the VE in different developing country settings.

A possible model for this would be the phased introduction of HBV vaccination into the routine infant immunization programme in the Gambia [27,28] or the follow-up of vaccinated cohorts in Taiwan [29]. In the mid-1980s, when few African countries included HBV vaccine in their routine vaccines, a vaccine manufacturer made available, free of charge, sufficient HBV vaccine to introduce the vaccine into the expanded programme on immunization (EPI) in a phased way, vaccination team by vaccination team, over a 4-year period. Records were made of all children coming for routine vaccination, regardless of whether or not HBV vaccine had yet been implemented by the vaccination team. Thus, over this period, two large cohorts of infants were defined, one of which had received HBV vaccine and the other not. The plan is to detect, through a national cancer registration system, the occurrence of liver cancer among those in the two cohorts over 30 or 40 years to measure the protective effect of the vaccine against this cancer. In the shorter term, selected samples of children in the cohorts have been resurveyed to ascertain the occurrence of new HBV infections and to measure the protective effect of the vaccine against the hepatitis B carrier state at different times after vaccination. Any children in the unvaccinated cohort in these surveys who have been found to require vaccination have been vaccinated and a different sample of unvaccinated children has been selected for each resurvey. Infant HBV vaccination has provided continuing protection against the hepatitis B carrier state, which is the main risk factor for liver cancer, for at least 15 years [30].

There would potentially be great value in implementing a similar study for HPV vaccination, although the details would depend upon the way in which HPV vaccination might eventually be implemented in national programmes. If catch-up

vaccination were to be introduced then it would be difficult to design a long-term study of this kind. However, if, as is common in the introduction of new vaccines in developing countries, the vaccine is administered to the main target group, such as adolescents before they leave school, and vaccination of earlier cohorts who have left school is not envisaged, then it would be possible to define vaccinated and unvaccinated populations on whom long-term studies might be undertaken, including passive surveillance of ≥CIN-3 and specific studies to look at the impact on persistent infection and on CIN through screening, treating and vaccinating subgroups of the cohorts.

The ethical aspects of such a study would have to be given serious consideration. The HBV study in the Gambia greatly accelerated the national introduction of the vaccine and a similar study might serve to accelerate the introduction of HPV vaccines into a specific country or region of a country and demonstrate the feasibility of a large vaccination programme serving as a model to speed introduction of the vaccine more widely in developing countries.

5. Concluding remarks

HPV vaccination may well be the next major public health breakthrough, with the potential to prevent the millions of deaths due to ICC and other cancers worldwide. However, the process to assure safety, efficacy and effectiveness of HPV eradication programmes has only just begun. In particular, given that current data have determined VE against precursor lesions in intensively screened cohorts, cost-effectiveness will, to a very large extent, depend on which vaccination strategies and concomitant cervical screening strategies are actually implemented. Optimizing and evaluating such strategies will require efficient and long-term sustainable evaluation systems after the vaccines have been registered. Multiple challenges remain to make sure the vaccine is implemented in all populations in the most cost-efficient manner, especially in the developing countries where it is most needed.

Disclosed potential conflict of interest

ML: Research Grants (GlaxoSmithKline Biologicals, Merck and Co., Inc.)

RH: Research Grants (GlaxoSmithKline); (RB): Consultant (Sanofi-Pasteur MSD)

JD: Consultant (Merck and Co., Inc., Sanofi-Pasteur MSD)

JP: Consultant (GlaxoSmithKline Biologicals, Merck and Co., Inc.)

Acknowledgments

The authors thank Dr. Pentti Koskela, Marjo Kaasila, Kari Pasanen and Toni Patama for providing the HPV prevalence maps, and Dr. Katherine French for providing the HPV prevalence reduction estimates. This work was supported by the Nordic Cancer Union.

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