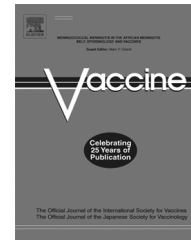


Part 1: EUROGIN 2007

Roadmap on Cervical Cancer Prevention

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FOREWORD

EUROGIN 2007 roadmap on cervical cancer prevention

The mission of EUROGIN is to promote excellence in the field of HPV infections, prevention and management of pre-cancers and cancers of the cervix and lower genital tract. EUROGIN is a forum for multidisciplinary exchange of knowledge and views, for consultation and for sharing experiences among experts, research scientists, and clinicians. It also represents a platform for genuine teaching, education and information for physicians, patients and public health authorities.

The demonstrated effectiveness of HPV prophylactic vaccination opens a new era of hope for both health professionals and women. It urges us to continue our ongoing efforts to promote information, training, communication, education and coordination of resources to ensure the best-practice solutions to prevent, control and treat genital pre-cancers and cervical cancers worldwide.

EUROGIN has a long record of experience in building consensus, since 1997. Our aim is to promote the highest standards in cervical cancer prevention by translating evidence-based data into clinical practice. The rapidly increasing volume and complexity of medical advancements in this area makes it difficult for physicians to incorporate data into the daily practice. Therefore, EUROGIN Consensus Conference Guidelines are proposed as a tool to assist physicians in the decision making process, and hence improve quality of care.

The process of developing guidelines includes needs' assessment, defining and evaluating implementation options, and thus revision is complex and requires a great deal of expertise and experience.

The main objectives of the EUROGIN guidelines are:

- To enhance professional learning, patient education and physician communication.
- To recognize the physician's responsibility to his/her patient, and balance the needs at the private and public health level.
- To reach a consensus in the field of cervical cancer prevention, based on high level of collective expertise.

- To coordinate strategies for implementation of the recommendations, emphasizing the role of patients, physicians and other healthcare providers.
- To promote the dissemination of information through traditional communication channels, networking and the internet.

EUROGIN 2007 roadmap on cervical cancer prevention

The EUROGIN consensus on prevention of cervical cancer was reviewed in 1997, 2000 and updated in 2003 and 2007 [1–6]. For the first time new options for Europe, including liquid-based cytology and HPV testing in clinical management and primary screening, were incorporated. Subsequently, vaccines against the most common cancer-causing HPV types have been developed, tested in clinical trials, and launched.

This year the EUROGIN Consensus Conference focused on HPV prophylactic vaccination against cervical neoplasia and cancer. Four specific topics were addressed: (1) age of HPV vaccination; (2) is viral status needed before vaccination; (3) screening approaches for vaccinated populations; and (4) monitoring of vaccinated women.

The choice of these topics was proposed in order to assist the physician, and to answer the main and urgent questions he/she has in the daily practice.

Chapters were developed on the above four conference topics and authors were directed to the following structure: background and rationale, current evidence-based medical practice, expert opinion, recommendations, directions for future research, clinical perspectives, references and disclosure of potential conflicts of interest.

The peer-review process included three levels: (A) two coordinators (J. Monsonego (France) and A. Singer (UK)) from the EUROGIN board of directors. Their role consisted of defining the general framework, determining the topics of interest and the oversight of compliance with timelines. (B)

Two independent chair persons who also participated in the review process (C. Wheeler (US) and S. Franceschi (France)). They had the role of acting as an interface between the authors and a working group of reviewers to reach a consensus. (C) Eight experts, as members of the drafting group, including two experts responsible for drafting each topic.¹

The choice of the authors was based on the following criteria:

- Proven experience of collaborating with EUROGIN.
- Clear commitment to a common cause of cervical cancer prevention and record of relevant publications.
- Capacity to elaborate on a scientific opinion, while being able to reconsider a personal opinion following the reviewers' comments.
- Ability to express an opinion in full independence, to serve the cause of cost-effective cervical cancer control, even when involved in disclosed partnerships with industry.
- A balance representation between clinicians and non-clinicians, and also between North America and Europe.

The strength of this project relied on a multidisciplinary team, in order to assist clinicians in the daily practical questions and decisions. In addition, a group of 47 selected independent reviewers aimed to ensure the representation of a variety of relevant disciplines. Their comments were taken into account by the chairs before finalizing the report.

Process

The authors provided a draft report on their respective topics, that was circulated through the reviewers' group by January'07. Modifications were made based on discussions, and the statements were approved before the EUROGIN Conference 2007.

The EUROGIN 2007 Roadmap contrasts with the former assignment of EUROGIN guidelines published in 1997, 2000 and 2003. The Roadmap designation represents an approach that provides direction to current and future best practices related to HPV vaccines while acknowledging the rapidly evolving landscape and evidence related to primary and secondary cancer prevention. As additional data on HPV vaccination becomes available from clinical trials, statements in the document will be updated as needed. The full report is published with a series of other papers presented here, and available at EUROGIN web site (www.eurogin.com) and at Elsevier web site (www.sciencedirect.com).

This collection of papers shall represent an independent synthesis of experts' views and opinions with sufficient sub-

stance, details on methodology and contextual information to aid clinicians and policymakers. The chairman endorses the conclusions as the EUROGIN 2007 roadmap is based on the current evidence, taking into account the views and opinions of the majority of the reviewers.

The challenges ahead are many, but let me highlight a few priorities:

1. To understand the burden of HPV disease and to recognize the respective role of primary and secondary prevention in the control of cervical cancer, ensuring the complementary and synergistic implementation of these two preventive measures to achieve the goal of eliminating the disease. In addition, to be aware of the importance of compliance and coverage of the target populations as a main issue to reach visible public health benefits.
2. To improve the level of knowledge of the physician by providing a simple and clear message through the communication channels available to date.
3. To promote an educational program for changing the attitude of the public—moving from a curative system to preventive approach.

Acknowledgements

The group of reviewers included the following persons: K. Ault (USA), F. Breitburd (France), X. Castellsague (France), C. Clavel (France), L. Denny (RSA), J. Dillner (Sweden), B. Duval (Canada), Elbasha (USA), A. Ferenczy (Canada), J.M. Foidard (Belgium), I. Frazer (Australia), G. Garnett (UK), S. Goldie (USA), A. Hildesheim (USA), P. Hillemans (Germany), E. Joura (Austria), H. Lawson (USA), Lehtinen (Finland), C. Meijer (Netherlands), A. Moscicki (USA), N. Munoz (France), D. Nardelli-Haeffliger (Switzerland), S. Pagliusi (Switzerland), J. Patnick (UK), K.U. Petry (Germany), W. Prendiville (Ireland), M. Quinn (Australia), G. Ronco (Italy), P. Sasieni (UK), M. Schiffmann (USA), J. Schiller (USA), A. Schneider (Germany), T. Schwarz (Germany), J. Sherris (USA), H. Strickler (Australia), S. Syrjänen (Finland) and J. Wardle (UK).

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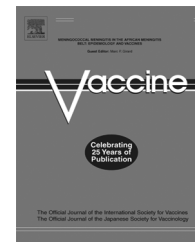
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¹ The paper on each topic was drafted by two authors:

- D. Harper (US) and J. Paavonen (Finland): age for vaccination.
- T. Wright (US) and X. Bosch (Spain): is viral status needed before vaccination?
- E. Franco (Canada) and J. Cuzick (UK): screening approaches for vaccinated populations.
- M. Stanley (UK) and L. Villa (Brazil): monitoring of vaccinated women.

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INTRODUCTION

The new challenges in the prevention of cervical cancer

In spite of the considerable success registered by the early detection procedures for cervical cancer prevention, the “smear” did not fulfill all hopes one could expect in reducing cancer incidence at large scale.

Cervical screening seems to benefit a minor part of the world female population, and yet a large proportion of women who benefit from it still prove its weaknesses [1].

At the level of the lower genital tract, infections by human papillomaviruses (HPV) are very frequent, and the most virulent types, 16 and 18, are responsible for two thirds of the cervical cancer cases worldwide. Condyloma acuminata (genital warts) induced by HPV 6 and 11 affect nearly 2–4% of boys and girls younger than age 25 years, and their clinical management is generally long and difficult. The burden and the weight of papillomavirus associated diseases are significant [2]. The psychological and emotional impact is also an important issue.

The fact that these genital lesions are the consequence of a chronic genital infection with HPV opens new and extraordinary opportunities for prevention through vaccination. The HPV vaccines are the first vaccines presented as an anti-cancer immunization. Indeed, these prophylactic vaccines, to protect against precancerous and cancerous lesions associated with HPV, shall save lives, reduce costly treatment interventions, and have an individual and collective benefit that should not be neglected.

The clinical studies of vaccines against papillomavirus based on the use of viral like particles (VLPs), constituted of the major protein L1 of the capsid of the virus, without any viral genetic material – immunogenic while not infectious and non-transforming – demonstrated their remarkable efficacy in preventing cervical precancers and cancers, as proven for the quadrivalent [against HPV types 6, 11, 16, 18] and the bivalent [against HPV types 16, 18] vaccines. Their level of clinical efficacy in the “per-protocol” analysis (consisting of women who were naive to vaccine targeted HPV types at baseline as determined by serology testing for the presence of HPV type-specific antibodies or polymerase chain reaction (PCR) testing of genital samples

for the presence of HPV DNA) is unprecedented in the history of vaccination: close to 100% [3–7].

The highest efficacy is demonstrated in young women naive to the virus types associated to the vaccines. The vaccines seem to have no therapeutic effect on existing lesions or on the course of viral infections already carried by healthy individuals [3, 4, 8, 9, 10]. The impact of vaccination is also relevant in vaginal and vulvar lesions [4] that, somewhat less frequent than cervical lesions, however cannot benefit from early detection programs and treatment, can be scattered and relapsing, and hence traumatizing. Data supporting additional cross protection vaccine efficacy have been reported in the conference and are expected to be published in short [5, 8, 11].

Four large trials of either a HPV 16 monovalent vaccine or the quadrivalent HPV vaccine demonstrated a vaccine efficacy of 44% for preventing HPV 16/18 associated CIN 2, 3 or AIS in the “intent-to-treat” population (consisting of all women who were enrolled into the trial) after a mean follow-up of 3 years [8]. Results with a limited benefit have been reported for the bivalent HPV 16 and 18 vaccine [7].

The vaccines also have been shown to not accelerate clearance of infections in women already infected with HPV 16 and 18 [12].

In practice the effectiveness of HPV vaccines are limited by two factors: all genital cancers and precancerous lesions are not induced exclusively by HPV types 16 or 18, and the optimal benefit is demonstrated in adolescents and young women before they have encountered these viruses.

In fact, delaying the period of vaccination could imply losing its maximal valuable protective effects. Nevertheless, in clinical practice it is necessary to interpret the trials’ results with a critical view. For instance, it is unlikely that a person has been exposed to all types of viruses included in the vaccines, and therefore a protective effect might be expected against the HPV types that have not been encountered [13]. In the clinical trials, about 70% of girls and young sexually active women under 26 years with

an average of two lifetime sexual partners were HPV DNA and serology negative (naïves) for HPV 16 and 18 vaccine types. Because approximately half of all individuals exposed to genital HPV infections never develop antibodies, 70% is an obvious underestimation of the actual cumulative HPV exposures in these populations. Thus although a reasonable proportion of women with few lifetime sex partners might be expected to benefit from HPV vaccines, the benefit will certainly decline as HPV exposures increase. Finally, among young women aged 14–25 years, the clearance rate of genital HPV infections is high, and disease occurs in a minority of women who can decrease their risk for cancer in settings where organized screening programs are available (REF) [1]. The question of vaccination before or after sexual debut is controversial, and depends on the concept of individual or collective benefits and arguments of effectiveness over efficacy. Regardless, continued cervical cancer screening is necessary in both vaccinated and unvaccinated populations.

The reported adverse effects of vaccination are generally minor. National and international plans for monitoring and evaluating risks linked to HPV vaccination are already in place, and will allow to measure within a few years the benefits of vaccination by age group.

Practical questions will need to be addressed, such as the potential for disease replacement through unmasking of oncogenic HPV types not included in current HPV vaccines, if effective, the need and cost-effectiveness of vaccinating boys, the duration of vaccine protection, the extent and longer term benefit of cross protection against HPV types not targeted by current vaccines, and most importantly access to vaccines in poor countries. In developed countries, possible negative effects of vaccination programs must be considered such as a decreased participation in cervical cancer screening programs by vaccinated women [14] and changes in the performance of screening methods [15].

If vaccination would be left to individual choice and initiative, the coverage would be low, and the benefit in reducing the frequency of this cancer would be barely perceived. We need to keep in mind that, in the context of public health, it may take several years to observe the benefits of preventing cervical cancer cases following vaccination of cohorts of adolescents with high coverage. Reductions in precancerous lesions could be significantly reduced within much shorter time period when vaccination is extended to broader age cohorts of women, consistent with clinical trial benefits observed over 2–4 years.

Thus, there is a need for vaccination policy, which is likely to differ in poor countries where the magnitude of disease represents a larger toll of disease and mortality, and in wealthy countries where screening programs have significantly reduced the frequency and mortality of this cancer.

The adoption of systematic or routine vaccination of girls aged 9–15 years, with a catch-up of cohorts of young women aged 16–26 years, correspond to date to the indication of the product as defined in the marketing authorization by the European Medicines Agency (EMA).

The success of vaccination as a public health intervention, will depend on its acceptability and on the degree of engagement of health professionals. A vast educational program for the general population, for patients and for health

professionals is needed. As vaccines will not protect from all possible HPV types associated to cervical cancer, the screening programs shall be maintained at current intervals and conditions. Vaccination and screening act complementary and synergistically, and constitute to date the new standards of disease prevention.

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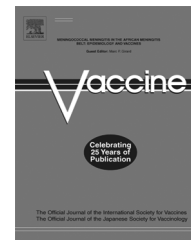
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Age for HPV vaccination

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KEYWORDS

HPV vaccination;
Prevention;
Prophylactic
vaccination;
Age;
Cervical cancer

Summary HPV vaccination of pre-pubescent girls will be effective for many girls. Vaccinating girls and women older than 12 years of age may accelerate the reduction in cervical cancer rates. Currently HPV vaccines are effective for at least 5 years in the prevention of HPV 16 and 18 associated precancerous lesions however the duration of vaccine protection is unknown. The need for booster shots must therefore be addressed with patients as unknown. Continued cervical cancer screening is necessary regardless of vaccination. Vaccination alone will not eliminate cervical cancer.

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Rationale

Historically, vaccination is a prophylactic measure to prevent fatal infectious diseases; and is dispensed when the person is not infected, before the fatal event, at a time when the person is at highest risk of exposure to the infectious disease. Thus, vaccines are typically prophylactic, not therapeutic. In contrast to the typical prophylactic vaccine, the HPV vaccine is designed to prevent a viral infection that may cause cervical cancer many years later. In addition to causing cervical cancer, the second most common cancer in women worldwide, HPV is closely linked to many other cancers including anogenital and oropharyngeal for which prophylactic vaccination may prove effective in future studies.

Current evidence based medicine

How are HPV infections detected?

Two standard laboratory methods have been used in epidemiology studies to identify HPV infection: HPV DNA detection and serum antibody detection. Type specific HPV DNA is identified in exfoliated cells sampled from the cervix or vagina by PCR consensus primers or occasionally performed after detection with a cocktail probe of multiple HPV types (Hybrid Capture[®] 2, Digene, Gaithersburg, MD). Seroprevalence is determined by ELISA to type specific HPV virus-like particles self-assembled in baculovirus manufacturing systems. Sero-epidemiology studies always indicate a lower prevalence than HPV DNA detection for three reasons [1]: (1) less than half of the epithelial HPV infections produce an antibody response, (2) if there will be a serologic response to a natural oncogenic HPV infection, it will occur many months after incident infection (8–12 months later) and usually after the concurrent HPV type specific DNA is no longer detectable, (3) antibody titers to type specific HPV infections can be lost after initial detection. The cumulative probability of losing the type specific antibody response within 3 years is almost 50% [2].

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What genders are infected by oncogenic HPV?

Approximately 90% of the cancers caused by oncogenic HPV affect women only; 2% of the cancers caused by oncogenic HPV affect men only; and 7% cause anal, oropharyngeal and oral cancers in both men and women. Clearly, majority of the fatal disease occurs in women. Genital wart manifestation of non-oncogenic HPV infections is much less common than cytologic manifestations of oncogenic HPV infections reported on Pap screening [3].

At what age are genital oncogenic HPV infections detected?

There is no one age at which all boys or girls are uninfected with oncogenic HPV types. Oncogenic HPV DNA has been reported in the epithelium of young girls and boys at an underlying prevalence between 3 and 10% [4–14]. Proposed, but unproven, transmission modes include vertical transmission during birth [5–7], genital skin to skin contact as well as sexual abuse in children [15]. In adolescence, the point prevalence of high risk HPV types peaks at 30–50% for young women in their second and third decades of life. This is mostly attributed to the onset of sexual exploration with one or more sexual partners, with up to 15% of the remaining infections not associated with penetrative penile intercourse.

The oncogenic HPV population prevalence in women drops to 15–20% for women 26–30 years of age, and 10–20% for women 31–35 years to an underlying population prevalence of 5–15% in later decades of life [16–19]. The cumulative prevalence rate to 50 years of age of oncogenic HPV infections approaches 80% [20–22].

Acquisition of high risk HPV parallels the prevalence statistics reported. Women under 25 years of age have the highest acquisition of high risk HPV at 4.5% per year, with a continuing infection rate of 1% per year for women older than 35 years [20]. At the same time, the risk of not clearing a high risk HPV infection increases with age. In women older than 30 years, 20% of their HPV 16 persistent infections and 15% of their HPV 18 persistent infections progress into CIN 3 lesions within 10 years [23].

The risk of HPV infection, whether from new exposures or auto-inoculated from prior exposure and being detected as incident or persistent infections, continues throughout a woman's lifetime. Past exposure to type specific HPV infections does not confer lifetime protection from future infection with the same HPV type [24].

What is the time from HPV infection to death due to cervical cancer?

Time from HPV infection to high grade precancerous dysplasia ranges from 6 months to decades, on average around 3 years [25]. Because CIN 2/3 triggers medical treatment, it is considered the surrogate clinical precancer marker for invasive cancer. Progression from CIN 2/3 to invasive cervical cancer has been described to take from 5 to 20 years [26].

In screened populations, cervical cancer has been reported, before 20 years of age [27], gradually increasing to a plateau level by the early 30s that does not decrease in the later years [28]. In unscreened populations, the incidence of cervical cancer continues to increase as a woman ages [29].

What determines whether the vaccine will be effective in a particular woman?

DNA negativity for the vaccine associated HPV types at the time of first vaccination is the sole determinant of vaccine efficacy for prevention of disease associated with those HPV types [30–36]. Complete vaccine efficacy for HPV 16 and 18 has been reported for both virgins and sexually active women 15–26 years old when the women are HPV DNA 16/18 negative at the time of vaccination. Vaccine efficacy in women younger than 15 years has not been established, but will be evaluated in upcoming studies.

Does vaccine immunogenicity determine vaccine efficacy?

HPV vaccine trials have established that both vaccines produce an immunologic response within weeks of complete vaccination, and are associated with 100% efficacy for 5 years at all titer responses [30,31,33,34]. Seroconversion is generated by HPV vaccination at any age in both genders. There is no immune correlation for efficacy to date. Vaccine induced immune titers to the specific HPV types are much higher than natural infection titers for 18 months of follow-up for both vaccines. Although each vaccine has a different profile of antibody response over the 5 years reported, the significance of this difference is unknown [37–39].

Do HPV vaccines offer protection for a woman's entire life?

This is unknown. Efficacy evidence of both HPV vaccines shows 100% protection from future disease caused by HPV 16 and 18 for at least 5 years in women negative for HPV 16 and 18 at the time of first vaccination. This is sufficient evidence to initiate vaccination implementation with concurrent surveillance programs. Duration of vaccine efficacy must be established to determine if, when, and for which HPV vaccine booster shots are necessary.

Do HPV vaccines clear current HPV infections or treat current CIN lesions?

No, both vaccines are entirely prophylactic. The HPV vaccines cannot cure current HPV infection [40], nor treat current CIN caused by vaccine associated HPV types [41].

Current recommendations

National regulatory agencies (e.g. FDA, EMEA,) approve commercial products based on safety and efficacy. Public health agencies recommending implementation policies for

vaccination (e.g. ACIP) include cost effectiveness in their deliberations. Gardasil™ has been approved in several countries by regulatory agencies including the FDA and EMEA for use in young women 9–26 years of age. Cervarix™ is currently under review by the FDA and has been approved by the EMEA for women 10–26 years of age. In Australia, Cervarix™ has been approved for women 10–45 years of age and there are approvals with no upper limit of age in several Asian countries. A few countries have approved Gardasil™ and Cervarix™ for use in boys 9–15 years of age.

Directions of future research

The safety and efficacy of co-administration of the HPV vaccines with other childhood and adolescent vaccines need to be established. Safety database reporting systems must be regionally in place to understand the more rare complications from HPV vaccination that could be reported in future years.

Randomized controlled trials provide optimal vaccine efficacy results. Population based trials, such as the NCI-sponsored Costa Rican vaccination trial and the long-term Nordic countries' follow-up studies will provide estimates of vaccine effectiveness in the prevention of cancer. In addition, the 80,000 girls and boys enrolled from the Nordic countries between the age of 12–15 years provide vaccine safety surveillance for rare adverse events to be documented should they occur. Phase IV trials will necessarily broaden the age and gender of populations studied, as well as the underlying co-morbid health states of vaccine recipients (e.g. diabetes, malaria, HIV infection, chronic diseases, etc.).

Implementation research needs to consider vaccination dosage interruptions for non-compliance or intervening health events such as abnormal Paps, pregnancy, lactation, or other disease treatments.

Population based public health research will evaluate the effectiveness of varying the number of initial vaccine doses in the context of the need for boosters and original age at vaccination.

The number and frequency of booster vaccines necessary after the initial series will be important to establish lifetime risk control. The logistics and expense for repeated boosters needs to be addressed scientifically, sociologically, and economically.

The delivery of the vaccine requires cold chain maintenance. Other potential routes of administration (intranasal, transgenic food carriers, topical applications) should be explored.

Clinical perspectives

- (1) Vaccinating pre-pubescent girls will be effective for many girls, and vaccinating women older than 12 years may accelerate the reduction in cervical cancer rates.
- (2) The HPV vaccines are effective for at least 5 years in the prevention of HPV 16 and 18 associated precancerous lesions. Duration of vaccine protection is unknown. The need for booster shots must be addressed with patients as unknown.

- (3) Continued cervical cancer screening is necessary regardless of vaccination. Vaccination alone will not eliminate cervical cancer.

Phase IV studies

As the phase IV studies in older women are published showing immunogenicity, efficacy and safety, as vaccine effectiveness studies of women 18 and older are continued in Costa Rica, and as community randomized trials are undertaken in Finland immunizing 12–15-year-old girls and boys establishing vaccine effectiveness against the development of cancer including duration of vaccine efficacy, we will gain data to understand the differential benefit of vaccinating different ages of women and men. Until then, natural history data and modeling data are useful surrogates to guide recommendations.

Modeling data show that the younger the age of vaccination, the more cervical cancers will be prevented (Fig. 1) [42]. Equally important is the time lapse before reducing the incident cervical cancers. It is estimated to take 100 years to maximally reduce cervical cancer incidence when vaccinating only 12-year-old girls. Modeling data clearly show that it is the duration of vaccine efficacy, not the age of vaccination, which drives the cost effectiveness of cervical cancer prevention in populations [43].

The serendipitous benefit in preventing other HPV associated cancers throughout the body will take decades to prove, but appears likely from early data [44] using surrogate precursor markers for other anogenital sites.

Expert opinion

HPV vaccines have been shown through clinical trials, leading to approval by national regulatory boards, to prevent infection and lesions of vaccine specific HPV types in women 15–26 years of age, who are not currently infected with the vaccine specific HPV types at the time of vaccination.

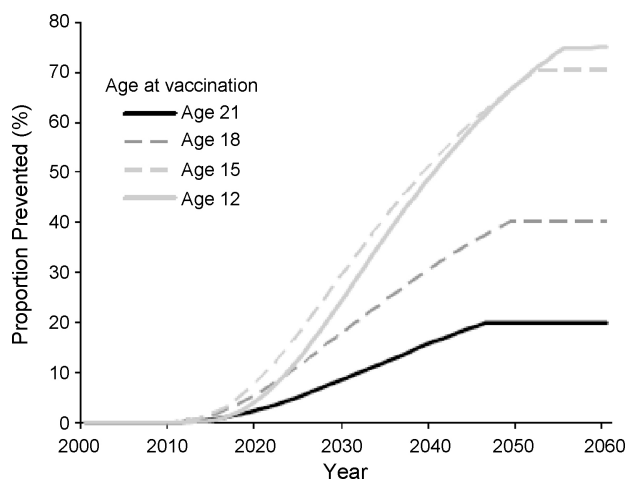


Fig. 1 Assuming 70% population coverage, the proportion of HPV 16 cervical cancers prevented by starting female vaccination at different ages. Model assumptions include 100% vaccine efficacy and lifetime protection with no catch up ages included. Source: French, et al. [42].

Because of the complete set of immunogenicity, safety and efficacy data, public health dollars may be spent to design and implement programs to immunize this group of women.

Immunobridging and safety data exist for females as young as nine years of age. Vaccination of young girls offers possible protection prior to the average age of peak HPV acquisition, but may require boosting to maintain protection throughout the period of acquisition, if started too young. Public health officials have assumed lifelong protection (*no further costs*) from both HPV vaccines and have implemented publicly funded programs to immunize young girls.

Similarly, immunobridging and safety data in women as old as 55 years are also supported by a similar efficacy for those women who are HPV DNA negative for the vaccine specific types at the time of vaccination. Because *the study methodologies are too limited* to determine whether the presence of antibody titers (either naturally induced or vaccine induced) prevents future type specific infections (either novel or by auto-inoculation of latent episomally active field infections), *we are unable to quantify the full benefit of vaccinating women* with prior type specific infections, but not infected at the time of vaccination. HPV vaccination is safe and may possibly offer a great benefit against future anogenital cancers [45,46]. Therefore, at this time, women older than 26 years are entitled to be offered the option of vaccination potentially at their own cost, as public health dollars for population coverage are rationed first to the youngest girls.

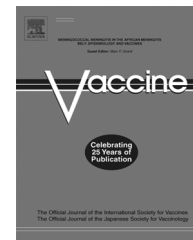
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Is viral status needed before vaccination?

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KEYWORDS

Human
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HPV;
HPV cervical cancer
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Summary Human Papillomavirus (HPV) testing prior to HPV vaccination is not recommended unless HPV tests are part of the established local routines for cervical cancer screening. The reasoning is based upon the very low frequency of women who, at the time of vaccination, would show markers of prior/current exposure (HPV DNA or serological tests) to the HPV types included in the vaccine. Thus at least one thousand women would need to be screened to find one that is HPV 16 and 18 DNA positive. The increase in cost and the other barriers afforded by a prior to vaccination test requirement would result in a lower coverage, the key indicator of a successful vaccination program.

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Rationale

It is widely accepted that the maximum benefit of Human Papillomavirus (HPV) vaccination will be achieved by vaccinating individuals prior to the onset of sexual activity. This is because the vaccines do not appear to have a measurable therapeutic effect and do not prevent either infection or lesions in females already infected with a given vaccine HPV type [1]. They also have been shown to not accelerate clearance of infections in women already infected with HPV 16 and 18 [2]. Therefore the principal target population for vaccination in most countries is adolescent females who have either not yet, or only recently, initiated sexually activity. The fact that the general population vaccine efficacy is higher when adolescent females are vaccinated does not indicate that the vaccine is failing to prevent incident infections with vaccine-targeted types of HPV in older women.

Instead it reflects the fact that the vaccine has no therapeutic effect in women already exposed to the vaccine-targeted types of HPV. Therefore it is likely that many sexually active women who have already initiated sexual activity will desire vaccination and in a few countries there are national recommendations for vaccinating these individuals [3]. Since the HPV vaccines are relatively expensive and the majority of women become infected with HPV within several years of initiating sexual activity [4,5], some clinicians are questioning whether viral status should be determined before vaccinating sexually active women.

Current evidence-based medicine

Impact of HPV status on vaccine efficacy

The results from Phase II and Phase III clinical trials of the two HPV vaccines indicate a lower efficacy in preventing either CIN lesions or vulvar/vaginal lesions associated with vaccine HPV types in individuals who have been previously exposed to vaccine-targeted HPV types at the time of vaccination [6–9]. A recent analysis of four large trials of either

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a HPV 16 monovalent vaccine or the quadrivalent HPV vaccine (6, 11, 16, 18) demonstrated a vaccine efficacy of 44% (95% CI 31–55%) for preventing HPV 16/18 associated CIN 2,3 or AIS in the “intent-to-treat” population (consisting of all women who were enrolled into the trial) after a mean follow-up of 3 years [10]. In contrast, the efficacy in the “per-protocol” (consisting of women who were naïve to vaccine-targeted HPV types at baseline as determined by serology testing for the presence of HPV type-specific antibodies or polymerase chain reaction (PCR) testing of genital samples for the presence of HPV DNA) was 99% (95% CI 93–100%). Although vaccine efficacy in the “intent-to-treat” population would be expected to increase over time as women in the placebo group continue to become infected with vaccine-targeted types of HPV and develop Cervical Intraepithelial Neoplasia (CIN) 2,3 lesions, vaccine effectiveness may be lower when sexually active women in the general population are vaccinated compared to the results obtained in the clinical trials to date. This is because the women enrolled in the Phase II and Phase III quadrivalent vaccine clinical trials were a relatively low-risk population for HPV infections based on age and sexual history. The average age of the 20,583 participants was 20 years, the mean age at first sexual intercourse was 16.7 years, and the median lifetime number of sexual partners in non-virginal enrollees was 2 [10]. Women with more than four lifetime sexual partners were not allowed to enroll in these trials.

Prevalence of HPV infections in sexually active individuals

Despite the relatively “low-risk” nature of the population enrolled into the pivotal vaccine trials, there was a relatively high prevalence of infection with vaccine types of HPV and cytological abnormalities found at entry into the study. The overall prevalence of positivity for HPV 16 or 18 by either PCR or serology in the four pivotal studies of the quadrivalent vaccine was 21% and 12% of the enrollees had an abnormal cervical cytology at entry [10]. A somewhat

lower prevalence of infection with vaccine types of HPV was observed in the Phase III trial of the bivalent vaccine [9]. Based on PCR using the SPF10-LiPA primer-detection system, HPV 16 was identified in 5% of the enrollees at entry and HPV 18 in 2%. However, 17% of the women were seropositive for HPV 16 antibodies by enzyme linked immunosorbent assay (ELISA) and 12% were seropositive of HPV 18 antibodies. There have been two studies that have reported the prevalence of HPV DNA positivity in representative, population-based studies in the U.S. One used stored urine specimens collected from sexually active women aged 18–25 years of age which were tested for HPV using a PCR-based MY09/MY11 with dot blot primer-detection system [11]. The prevalence of types 16 or 18 in this study was 7.8%. Another population-based study utilized women 14–59 years of age enrolled in NHANES, the Centers for Disease Control and Prevention’s National Health and Nutrition Examination Survey [12]. Self-collected vaginal swabs were tested for HPV DNA using PCR with a PGMY09/PGMY11 reverse line blot detection system. In this study the prevalence of HPV 16 and 18 was only 1.5% and 0.8%, respectively [12]. It is important to note, however, that both self-collected vaginal swabs and urine samples may underestimate the prevalence of HPV 16 and 18 compared to samples obtained directly from the cervix. Table 1 presents the prevalence of HPV 16 identified by either polymerase chain-reaction (PCR) DNA testing or serology in various recent studies. The HPV 16 DNA positivity rates range from 2% to 18% and the HPV 18 positivity rates range from 1% to 7%. It is important to recognize that these estimates are derived from cross-sectional surveys and do not provide an estimate of a woman’s cumulative lifetime exposure to HPV 16 or 18.

There are fewer serological studies of HPV 16 and 18 antibodies in women in the general population. Serology appears to underrepresent prior exposure to HPV since only approximately 60% of HPV DNA positive individuals develop a serological response [3]. In the recent bivalent vaccine study from Costa Rica, only two-thirds of the women who were HPV 16 or 18 DNA positive were seropositive for HPV 16 or 18 [2]. Unlike the prevalence of HPV DNA which declines

Table 1 Estimates of prevalence of infection with HPV 16 and 18

Author	Country	Median or mean age (years)	HPV 16 positivity (%)		HPV 18 positivity (%)	
			DNA	Serology	DNA	Serology
Kjaer et al. [18]	Denmark ^a	25	4	NA	2	NA
Koutsky et al. [1]	U.S.	20	11	13	NA	NA
Stone et al. [13]	U.S.	14–59	18	NA	NA	NA
Wang et al. [19]	Costa Rica	38	4	15	1	15
Manhart et al. [11]	U.S.	22	6	NA	2	NA
Naucler et al. [20]	Taiwan	48	NA	8	NA	15
Skjeldestad et al. [21]	Norway	21	16	16	7	6
FUTURE II [8]	Multicountry	20	9	11	4	4
Garland et al. [6]	Multicountry	20	9	12	3	3
Hildesheim et al. [2]	Costa Rica	21	7	NA	3	NA
Paavonen et al. [9]	Multicountry	20	5	17	2	12
Dunne et al. [12]	U.S.	14–59	2	NA	1	NA

Modified from Refs. [1,2,6,8,9,11–13,18–21].

^a Restricted to women who are cytologically normal.

with increasing age, seropositivity for antibodies against HPV 16 and 18 tends to remain stable with increasing age. In a representative sample of women 20–29 years of age in the U.S., 25% of individuals were seropositive for HPV 16 [13]. A population-based study of older women from Latvia has reported that the seropositivity rate for HPV 16 or 18 was 25% [14]. Although the cumulative lifetime exposure of women to HPV might be as high as 80%, the cumulative lifetime exposure to HPV 16 and/or 18 appears to be considerably lower. Table 1 also provides the prevalence of serological responses to HPV 16 or 18 in various recent studies. The prevalence of antibodies against HPV 16 ranges from 8% to 17% and from 3% to 15% for HPV 18. It is important to recognize that the prevalence of antibodies against a given HPV type probably underestimates cumulative exposure to that type of HPV since not all women exposed to HPV will seroconvert.

Limitations of current HPV detection methods

The HPV DNA detection methodologies such as Hybrid Capture II (Digene Diagnostics) or Amplicor (Roche Molecular Diagnostics) that are currently in clinical use are insufficiently sensitive to be used as a marker of infection. The detection methods that are currently being routinely utilized for clinical purposes have been specifically designed to identify a subset of HPV-infected women who are at greatest risk for developing high-grade cervical neoplasia or invasive cervical cancer [15,16]. Therefore these assays have been “detuned” in order to reduce their sensitivity for detecting low copy number HPV infections that are unlikely to be associated with high-grade neoplasia. For example, the sensitivity of Hybrid Capture II is approximately 5000 copies of high risk HPV DNA [16]. In contrast, the vaccine trials have utilized highly sensitive PCR assays that are designed to identify as many HPV-infected women as possible. The other issue is that HPV genotyping assays are not widely available for routine clinical use and the assays that are being occasionally used have not been validated in rigorous regulatory trials [15]. Therefore even if HPV DNA testing were to be routinely undertaken as a discriminate test prior to vaccination, it is unclear how valid the test results would be. There are similar issues with serological assays for HPV. Although research laboratories have developed highly reproducible two-step ELISA assays for HPV 16 and 18 antibodies that utilize L1 capsids as targets, these assays are not commercially available and they show considerable interlaboratory variation in estimated antibody levels [17]. An important step to developing validated commercially available serological assays for HPV 16 and 18 is the development of an International Standard for antibodies to HPV 16 and 18. This is currently being undertaken by the World Health Organization [17].

Safety of vaccinating women with prevalent vaccine-targeted HPV infections

A considerable number of women enrolled in the Phase II and Phase III trials had evidence of prevalent vaccine-targeted HPV infections at the time of vaccination. This data has been presented to the national regulatory bodies at the time

of vaccine registration and has documented no increase in adverse events when women already infected with vaccine-targeted HPV infections are vaccinated. Based on this safety data, some countries have recommended vaccination of sexually active women, as well as women with a history of abnormal cervical cytology or who are high-risk HPV DNA positive, although it is clear that the vaccine will have no therapeutic effect in already infected with vaccine-targeted HPV infections and that efficacy will be lower in such women compared to women who have not previously initiated sexual activity [3].

Recommendations

Despite the fact that infection with or evidence of exposure to any single type of vaccine-targeted HPV type is relatively high in the vaccine trials as well as various population-based studies, evidence for infection with both HPV 16 and 18 is relatively uncommon. Infection with both HPV 16 and 18 was encountered in only approximately 1% of the women in these trials and only about 1 in a 1000 had either serological or DNA evidence of exposure to all four types of HPV targeted by the quadrivalent HPV vaccine, HPV 6, 11, 16, and 18. This means that most women will receive some benefit from vaccination against HPV, although the level of benefit will decrease as the likelihood of prior exposure to HPV 16 increases [3]. Moreover, commercially available standardized tests for identifying HPV 16 and 18 DNA or antibodies against HPV 16 and 18 are currently not available for routine clinical use and there are currently no clinical indications for HPV serological testing other than research. Based on these considerations, HPV DNA testing or serology should not be used as a discriminate test prior to vaccinating sexually active women. However, sexually active women should be screened for cervical cancer at the time of vaccination in accordance with screening recommendations for a given country. Even though a woman has a history of cervical disease or an abnormal screening test result, they will still benefit from vaccination.

Directions of future research

1. Continue cohort studies to better understand the incidence of HPV 16 and 18 over time in different populations.
2. Conduct clinical research to evaluate cervical cancer screening protocols for vaccinated women in different age groups.
3. Conduct additional studies to determine relationships between HPV 16 and 18 DNA status and serological status and response to vaccination in older, sexually active women.

Clinical perspectives

1. Although most sexually active women will have been exposed to HPV, very few will have been exposed to all of the vaccine target types of HPV and almost all will receive some benefit from vaccination.

2. Pre vaccination testing for HPV (unless it is part of routine cervical cancer screening) is unnecessary and adds additional costs to the vaccination program.
3. Serological testing for HPV does not have any clinical application.
4. Vaccinating women who during routine screening are found to have either a high-risk HPV infection or CIN has not been associated with adverse events in the vaccine trials.

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Contributors: F.X.B.'s research unit is involved in vaccine trials organized by *GlaxoSmithKline* and *Merck/Sanofi Pasteur MSD*. He is member of the Steering Committee of *Merck/Sanofi Pasteur MSD*, and external advisor of *GlaxoSmithKline*.

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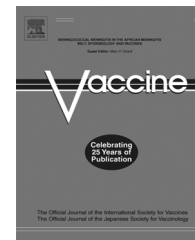
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Cervical cancer screening following prophylactic human papillomavirus vaccination

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KEYWORDS

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Pap cytology;
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Prevention

Summary The recognition that infection with certain human papillomavirus (HPV) types is a necessary cause of cervical cancer has opened new fronts for the prevention of this disease. Primary prevention is now possible via immunization with highly efficacious HPV vaccines and secondary prevention has gained impetus with the advent of sensitive HPV DNA testing to improve traditional Pap cytology screening programs. Although universal vaccination of teenagers and young women is a desirable policy cost remains a key obstacle. To achieve cost-effective reductions in the burden of cervical cancer prevention initiatives must consider screening and immunization as integrated and organized approaches that take advantage of HPV testing as primary screening test followed by triage with Pap cytology. This strategy has the added benefit of providing epidemiological surveillance of vaccinated populations.

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Introduction

The licensing of a first prophylactic vaccine (GardasilTM, Merck, Inc.) against the two most important oncogenic genotypes (16 and 18) of human papillomavirus (HPV) in 2006 has ushered a new era in cervical cancer prevention. A second vaccine (CervarixTM, GlaxoSmithKline, Inc.), which also targets these types, is expected to reach the market in 2007–2008 (already approved in Australia in May 2007 and received a favourable preliminary assessment in Europe). In clinical trials, these vaccines have been nearly 100% efficacious in preventing incident persistent infection with the target types (Cervarix) and the precancerous high-

grade lesions (both) that are caused by these viruses in women without prior exposure with the vaccine types [1–4]. Mathematical models of the impact of these vaccines have projected a substantial public health benefit in most geographical areas [5–7].

Despite the enthusiasm with the initial results with HPV vaccination it is generally accepted that cervical cancer screening will have to continue after vaccination. Both vaccines are fully effective as pre-exposure prophylaxis for disease caused by HPV types 16 and 18, when used before the onset of infection; however, women currently infected with these viruses may not derive any benefit [8]. Moreover, the target types included in the two vaccines are causally linked to about 70% of all cervical cancers [9]. Although some degree of cross-protection against infection with phylogenetically related HPVs (e.g., HPVs 45 and 31) could also exist [1], there is also a possibility of an increase in prevalence of other HPV types in vaccinated populations, as a result of the vacated ecologic niches following the progressive elimina-

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tion of HPVs 16 and 18 (a yet unproven phenomenon known as type replacement). There is also the possibility that the type-specific immunity conferred by vaccination may wane over periods extending beyond 5 years and no data are currently available on this.

Despite these caveats, it is expected that a vaccinated woman will experience much lower risks of developing cervical precancerous lesions over a period that may extend for a decade or longer. Thus, there is a sense that subsequent intensive screening via annual or biennial Pap cytology may waste resources while providing only marginal additional benefit over the next period of life during which immunization is exerting a protective effect. While much is yet to be learned about the above issues it is obvious that the incorporation of HPV vaccination will impose a substantial burden to the public health budgets of most countries. Proper planning of cervical cancer screening, an intervention that represents today a key healthcare expenditure, may help offset the costs that will stem from universal vaccination.

Rationale

Vaccination and screening should be complementary cancer control strategies

Gardasil, the first HPV vaccine to be licensed has been approved in most Western countries for vaccination of women aged 9–26 years, as pre-exposure prophylaxis. Current recommendations from immunization advisories place the emphasis on a 3-dose immunization regimen focused on girls aged between 11 and 15 years (e.g., the UK is likely to implement school-based vaccination for ages 12–15 years). At this writing, the second vaccine, Cervarix, had been approved in Australia for women 10–45 years of age. The latter country started a government-funded, school-based programme, with catch-up vaccination as of April 2007. This second vaccine has also received preliminary approval in Europe.

Implementation of HPV vaccination is likely to be a gradual and diverse process that will reflect specific health policy environments. In some countries, vaccination may be adopted as universal policy for all adolescents and young women and covered by a centrally managed health care system, either regional or national. School-based vaccination is a popular strategy in this regard because it permits reaching virtually all at-risk groups. In other settings, vaccination may be adopted as an opportunistic intervention implemented via the network of general practitioners or family physicians as they provide health care for their client bases. The cost of vaccination in these settings may be initially borne only by patients but over time cost-sharing with the public sector may be implemented as a result of policy decisions. Some countries may not be able to bear the costs of vaccination, in which case the recommendation to vaccinate will be left to the discretion of health care providers as they assess the potential benefits vis-à-vis their costs to their patients. Regardless of scenario, secondary prevention via frequent screening with Pap cytology is widely perceived as already providing adequate protection against the onset of invasive cervical cancer and may be used as argument against adopting universal vaccination.

The benefits of vaccine protection are likely to be maximal in women before the age of sexual debut and as yet, little is known about the benefits of vaccination in women older than 26 years of age since efficacy RCTs have covered the age range of 15–26, and only bridging immunogenicity studies are available to document immune response in older women. Despite these uncertainties, policy decisions concerning HPV vaccination would benefit from considering the changes in future screening practices that are likely to ensue if vaccination were to be adopted. This could permit more realistic projections about the potential reductions in cervical cancer control costs due to a reformulation of screening recommendations.

Concerns about Pap cytology in cervical cancer screening

In spite of its track record, Pap cytology has important limitations. It is based on the subjective interpretation of morphologic alterations present in cervical samples that must be collected with proper attention to sampling cells of the transformation zone. Also, the highly repetitive nature of the work of screening many smears leads to fatigue, which invariably causes errors in interpretation. The average sensitivity of Pap cytology to detect high grade cervical intraepithelial neoplasia (CIN2+) or invasive cervical cancer has been reported as 53% and its average specificity as 97%. In addition there is large heterogeneity in sensitivity from about 30% to 75% [10]. Therefore, the Pap test's high false negative rate is its most critical limitation. The advent of liquid-based cytology has helped to mitigate the problem of efficiency in processing cellular samples but because liquid-based cytology has not proven to be more sensitive than the conventional Pap smear the limitations of cytology remain the same [11]. This low sensitivity for an individual testing opportunity is compensated by the requirement in some countries (e.g., US and Canada) to have women entering screening age with an initially negative smear to repeat their tests at least twice over the next 2–3 years before they can be safely followed as part of an extended screening schedule. Examples of such safeguards can be found in guidelines by the Canadian screening programme [12] and the American Cancer Society [13].

Possible short-term impact of HPV vaccination on screening practices

As the successive cohorts of vaccinated young women reach screening age, the reduction in cervical lesions will lead to a decrease in rates of colposcopic referral to about 40–60% or less of the existing case loads in most Western countries, judging from attributable proportion estimates [14] and preliminary findings from the vaccination trials [3]. A small proportion of currently referred cases are associated with low oncogenic risk HPVs, such as HPV 6. Merck's Gardasil, which includes the latter type as immunogen, may thus lead to a more pronounced reduction in abnormalities than GSK's bivalent vaccine, perhaps by an extra 5–10% in absolute terms [14]. Such reductions are likely to translate into initial savings to the health care system or to individuals but the vaccine-induced decrease in cervical lesions may

lead to a degradation of performance characteristics of Pap cytology (because of a decreased expectation of abnormalities on a day's smear workload) with consequent concerns related to the need for heightened quality assurance. The positive predictive value (PPV) of Pap cytology will decline paralleling high vaccine uptake because clinically relevant lesions will become less common. This will lead to a decline in the performance of cytology because of a decrease in the signal (squamous abnormalities) to noise (inflammation and reactive atypias) ratio that characterizes the subjective and tedious work of reading and interpreting smears. In other words, a low lesion rate will lead to losses in sensitivity by causing a decrease in familiarity for recognizing abnormal cells as well as specificity, because fear of missing disease leads to more overcalls of benign abnormalities [15]. Fig. 1 illustrates the impact of combined changes in lesion prevalence and Pap performance on the positive predictive value of cytology screening. The lower PPV for cytology will require greater expertise to maintain good quality and this may be achieved by centralization of screening in larger lab-

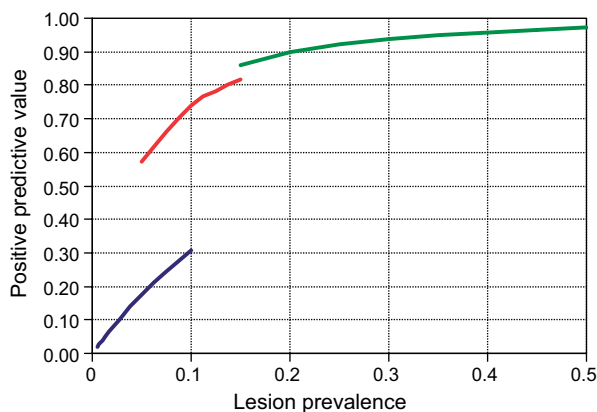


Figure 1 The impact of the joint effects of changes in cervical lesion prevalence (CIN1+) and in the sensitivity and specificity of Pap cytology on the positive predictive value (PPV) of screening (one of the most cost-influential screening performance parameters). Although CIN1 is not the typical outcome used to assess the impact of preventive interventions it was chosen because it represents the earliest threshold of lesion severity that merits clinical and public health attention as a driver of healthcare utilization via heightened surveillance by screening and frequent colposcopy referrals. The three curves show different combinations of sensitivity (Se) and specificity (Sp): red: Se = 51%, Sp = 98%; green: Se = 70%, Sp = 98%; blue: Se = 40%, Sp = 90%. The red curve reflects the performance characteristics that prevail around 10% lesion prevalence. The green curve reflects the screening performance in conditions of high lesion prevalence or in the artificial situation of cytologic triage of HPV-positive women. The blue curve shows decreased sensitivity and specificity expected in conditions of decreased lesion prevalence following HPV vaccination. As shown, the best performance of Pap cytology is seen in conditions of high lesion prevalence, particularly when smears are read with heightened attention, such as when triaging smears from HPV-positive patients. Although the scale would be different, the conclusions regarding the joint effects of prevalence, sensitivity, and specificity equally apply to CIN2+ lesions.

oratories. Use of liquid-based cytology may offset some of the problems but this technology is also likely to be affected. Likewise, use of automated cytology with optical recognition of abnormalities may reduce some of the problems related to rarity of relevant lesions but the altered signal-to-noise ratio expected post-vaccination may require recalibration of the computer-assisted recognition algorithms. Therefore, the negative impact on the PPV can be expected even with heightened quality control and improved cytology systems.

The above reductions in case loads will be a function primarily of two factors: (i) the overall uptake of HPV vaccination by the successive cohorts of adolescents and young women targeted by vaccination, and (ii) the time it will take for protected women to reach the age when they become eligible for screening [15]. In countries without a centrally managed health care system (e.g., the US) uptake of vaccination will require much effort in educating the public and health care providers. Vaccinated adolescents will reach the age of cervical cancer screening within 3 years after the onset of sexual activity. Therefore, the impact on screening and management case loads will be initially minimal for women vaccinated between the ages of 10 and 18 years. On the other hand, the benefits in risk reduction among young adult women receiving the vaccine will be realized almost immediately because of the short latency between the averted acquisition of HPV infection and the appearance of low grade or equivocal cervical abnormalities [15]. For countries where screening starts at age 30 or even 25 years (as happens in most of Europe), the effect on screening will be even more delayed.

Possible long-term public health outcomes of HPV vaccination

Even with high uptake, a statistically noticeable reduction of the burden of cervical cancer via HPV vaccination is unlikely to be observed for at least 10–15 years because of the dual facts that vaccination below age 20 will not affect high grade CIN rates appreciably for 5–10 years and another 5–15 years will be necessary for this to be translated into reductions in cancer incidence. A paradoxical situation may arise if high vaccine uptake occurs primarily among women who will eventually be adherent with screening recommendations. If adolescents and young women who are more likely to be vaccinated are the very ones destined to become screening-adherent the reduction in ASC-US and SIL abnormalities will be seen nearly exclusively among such women. There may be initial enthusiasm with the reduction in triage and management case loads consequent to the fewer abnormalities identified on screening. However, because of their high adherence with screening these women would not be the ones destined to develop cervical cancer. On the other hand, unprotected women may be less likely to be screened and their undetected precancerous lesions will progress until invasion occurs, when the attendant symptoms will then prompt the need for diagnosis [15]. This undesirable scenario of compounded inequity is unlikely to occur in countries that already enjoy the benefits of an organized screening program that reaches all women. Such countries are likely to adopt also an organized and universal vaccination program that benefits all segments of society.

Current evidence-based public health

HPV DNA testing as promising screening test

Of the molecular-based technologies for cervical cancer screening HPV DNA testing is the one eliciting the greatest interest. The Hybrid Capture™ (HC) assay (Digene, Inc., Gaithersburg, MD) is currently the most widely used in clinical and screening settings. It is a nucleic acid hybridization assay with signal amplification using microplate chemiluminescence for the qualitative detection in cervical specimens of HPV DNA of 13 high oncogenic risk genotypes, defined as those that are associated with cervical cancer: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. Other HPV DNA testing formats based on polymerase chain reaction (PCR) with Luminex detection platforms are beginning to be commercially available and will permit identifying infection with individual oncogenic types, which will help in defining the prognosis of HPV infections. HPV testing has 25–35% higher sensitivity than cytology in absolute terms but somewhat lower specificity, 5–10% lower for detecting high grade lesions [10,16–19]. Screening of women older than 30 years tends to improve the performance of HPV testing because viral infections in this age group are less likely to be of a transient nature than those in younger women and are more directly related to high grade CIN [20]. It is noteworthy that the combination of Pap and HPV testing (called co-testing) attains very high sensitivity and negative predictive values (approaching 100%). This feature could potentially allow increasing screening intervals safely, e.g., from 1–3 years to 3–5 years, depending on the population. The draw-

back is an increased number of patients who would need additional evaluation including possibly colposcopy, many of which will turn out to be lesion-free. Resource-rich countries can absorb the extra costs related to the secondary triage of cases that will be referred via a dual-testing screening approach because this strategy may be cost-saving over time, because of the reduced patient flow in primary screening clinics afforded by the extension in the screening interval for women who are cytology and HPV negative [21]. Additional triage tests such as HPV typing, HPV E6/E7 mRNA and p16 testing may help to identify women most likely to harbour high grade disease [19]. A Pap-HPV co-testing approach has been recently recommended in professional guidelines in the US [22]. Fig. 2 shows the opportunities for screening intervention via Pap and HPV testing and their performance characteristics in identifying the succession of intermediate endpoints in the natural history of cervical neoplasia.

Emerging evidence in support of HPV testing in screening

In addition to the aforementioned strong body of evidence already published regarding non-randomized studies, a few large randomized controlled trials of HPV testing in primary cervical cancer screening are currently ongoing in the Netherlands, UK, Sweden, Finland, Italy, Canada, and India [23–29] and have already produced strong evidence in support of the adoption of HPV testing in primary screening [30–32]. These RCTs, embedded in on-going opportunistic or organized screening programs, will likely further add to the strength of evidence necessary for public health pol-

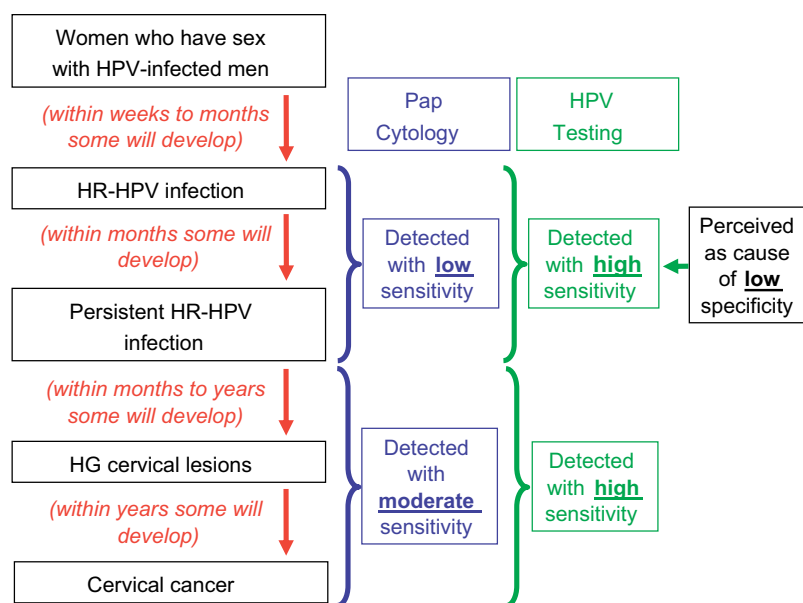


Figure 2 Pap cytology and HPV DNA testing in cervical cancer screening. Cytology relies on the recognition of morphological cellular abnormalities in a Pap test whereas HPV DNA testing detects DNA from oncogenic HPV types, which provides improved sensitivity compared with cytology. HPV testing is more “upstream” in the natural history of cervical neoplasia because it is based on detecting HPV DNA even before it becomes associated with morphological changes to the infected cervical epithelium. The downside of its greater sensitivity and in being more upstream than cytology is that it is less specific than the latter test. The extra referrals for colposcopy will lead to higher costs on initial screen that can be offset later on via extended screening intervals. Abbreviations: HR-HPV: infection with high oncogenic risk HPV types; HG: high grade.

icymakers to make informed decisions about the future of their cervical cancer screening programs. Evidently, all other features of organized screening programs, particularly coverage, quality assurance, and adequate case management also apply to any competing technology.

Recommendations

Primary screening via HPV testing followed by Pap cytology triage

Simply making cytology screening less frequent may not be a viable strategy to achieve a cost-effective combination of vaccination and screening in light of the aforementioned potential problems that may plague Pap cytology performance in conditions of low lesion prevalence (illustrated in Fig. 1). Although the “quantitative” effect shown in Fig. 1 will also negatively affect the PPV of HPV testing the latter is unlikely to be affected by the “qualitative” effects that further contribute to the decrease in PPV of cytology which are secondary to the degradation of sensitivity of specificity of the latter test due to the rarity of lesions (shown in the non-overlapping curves in Fig. 1). HPV testing has the screening performance characteristics that would make it an ideal primary cervical cancer screening test in such conditions. In addition, the interpretation of HPV testing results is objective and potentially automatable, which will make it less prone to the vagaries of subjective interpretation, particularly in conditions of low lesion prevalence. Pap cytology should be reserved for triage settings, i.e., in assisting management of HPV positive cases because it is more likely to perform with sufficient accuracy in conditions in which lesion prevalence is high, a situation that is artificially created when the workload includes only smears from women harbouring HPV infection (Fig. 1). The advantages of the approach of only using HPV testing as the primary screen and then triaging positive women with cytology have been described before [15,33–35] and are being evaluated in Finland [26], Northern Italy [27] and in British Columbia, Canada.

Integration of screening and follow-up of vaccinated populations

As a bonus, another key advantage of using HPV testing as the primary screening tool in prevention programs is the opportunity to create HPV infection registries with the provision to link test results from the same women over time, thus allowing an efficient and low-cost strategy to monitor long-term protection among vaccinated women. As HPV typing becomes incorporated in future HPV testing screening there will be an improved opportunity to manage HPV positive cases and to gain insights into the long-term effectiveness of vaccination [15].

Particularly for low resource regions in developing countries where screening is not very well established or effective, programmes which combine vaccination for adolescent girls with HPV-based screening of their mothers is very attractive. Given the difficulties with cytology, and the much higher sensitivity seen with HPV testing compared

to cytology or visual inspection [36], an attractive strategy would be screening of the mothers by a rapid HPV test (2-h assay time) in the morning (along with vaccination of daughters), followed by any required treatment (comparable to a See-and-Treat approach) in the afternoon of the same day, using visual inspection with acetic acid in women who were HPV positive.

Economies of scale and market forces will lower costs of HPV testing in screening

At present, the main obstacle for the adoption of the above policy is the high cost of HPV testing. The fact that the market is dominated by a single manufacturer of a clinically approved HPV assay (Digene) is certainly a deterrent for achieving lower prices for HPV testing. Another problem comes from the current practice guidelines in most countries which at most approve HPV testing for the triage of ASC-US abnormalities, an admittedly restricted niche market that represents at most 5% of the total patient population that can benefit from this technology in screening. It is expected that once HPV testing is deployed in the high volume of primary screening there will be a reduction in the cost of individual tests because of the market expansion following an economy of scale. Governments and managed care organizations may be able to negotiate with the manufacturer(s) lower prices conditioned to high volume purchasing. Furthermore, a change in market potential from simple ASC-US triage to wide-scale primary screening will inevitably bring other biotechnology companies to compete in the field by bringing their own molecular HPV tests for validation and regulatory approval. This is already happening even before this change in market is realized. A few biotechnology companies are already in advanced stages of regulatory application for novel molecular HPV tests to compete in the Pap-HPV co-testing market in the U.S. Taken together, the combination of shifting trends in screening practices, economies of scale, and perception of new market opportunities for companies will further contribute to a reduction in the overall cost of the “HPV followed by Pap” screening approach.

Directions for further research

The above proposal for changes in screening practices among vaccinated women has at present strong theoretical underpinnings (likely loss of performance of Pap cytology in vaccinated women) and empirical support (proven value of HPV DNA testing). At present, however, we only have a limited understanding of the natural history of cervical lesions in vaccinated women from the initial published findings of HPV vaccine trials. RCTs of HPV testing followed by cytology triage compared with favoured local screening paradigms must be conducted in general and also in vaccinated populations in order to provide the evidence base that will inform future screening algorithms in vaccinated women. Historically, new screening technologies and combinations thereof, as well as new screening algorithms that combine old and new approaches are slow to be accepted in clinical practice. Professional guidelines take time to be updated as a reflection of the available evidence from controlled

studies and are also responsive to perceptions related to cost-effectiveness, safety, liability for providers, and the degree of controversy that may surround the use of new methods. Considering the rapid transition of the field of cervical cancer prevention, the recommendations in this article are likely to need updating as new scientific information becomes available concerning duration of vaccine protection, cost of HPV testing, acceptability and proof of concept of HPV typing in screening, and empirical proof that the impact on cytology practices forecasted above may occur following vaccination. In this regard, the following important questions should be targeted by research studies.

Frequency of screening in vaccinated women

Because of its enhanced sensitivity and improved negative predictive value a policy of HPV screening followed by Pap triage could be done at 3–5-year intervals even in today's unvaccinated populations in North America. In Europe, even longer intervals could be possible because of the wide coverage of screening and proven effectiveness of policies with 5-year intervals when robust organized programs are in place. Pilot or demonstration projects and RCTs could be instrumental in demonstrating what could be acceptably safe intervals for both vaccinated and unvaccinated women as long as they remain negative. As these studies are implemented safety considerations dictate that extended screening intervals among vaccinated women should bear in mind the possibility of waning of immunity.

Age at initiation of screening

In women vaccinated as part of a school-based program screening will not have to start until 8–12 years later. Which approach should be used in this regard, traditional cytologic screening or the combined HPV-Pap algorithm described above? Should separate algorithms be envisaged for vaccinated and unvaccinated women? Should the screening interval be different between these two groups, e.g., 3–5 years for unvaccinated and 5–7 years for vaccinated women? With a high coverage of vaccination among young women it is likely that there will be a shift of the peak age of pre-cancerous lesions to older ages. Continued surveillance via the HPV with Pap triage approach will demonstrate whether this phenomenon will occur and the extent of the age shift in different populations.

Also germane to this discussion is the fact that HPV testing has been proven useful in women 30 years of age or older. Studies are ongoing that could perhaps permit cost-effective screening via HPV testing at age 25 years and older, particularly with cytologic triage, as proposed above.

Follow-up algorithm for HPV positive/Pap negative women

What should be the frequency of testing for a woman harbouring an oncogenic HPV infection but with no signs of cytological abnormalities? How soon after her last HPV test becomes negative should she be returned to the regular frequency of screening for average risk women? Much research

is needed to determine safe and cost-effective intervals for following up women who are found to harbour HPV or cytological abnormalities. Should different policies be evaluated for vaccinated and unvaccinated women? What is the value of adjunctive tests such as HPV E6/E7 mRNA, HPV typing, p16, and other biomarkers to triage those patients into those needing immediate referral, enhanced surveillance, or only routine screening? As of today, these tests have had only limited clinical testing for risk stratification and are yet to be validated as screening or triage tools. In particular, HPV typing may contribute to risk prediction in HPV positive/Pap negative women.

Clinical perspective

In conclusion, much has been achieved during the last 10 years from research on screening and prevention of cervical cancer. Progress in this area has been grounded on the recognition that HPV infection is the central, necessary cause of this important neoplastic disease. However, it is imperative that screening and primary preventive strategies be adapted to and meshed with one another in well-designed and managed organized programs to permit cost-effective reductions in the burden of cervical cancer. With the advent of HPV vaccination there may come a day when screening algorithms, such as described here, may be applied differently to vaccinated and unvaccinated women. There is always much hesitation to use complex risk-based approaches to decide on how to screen because they may cause confusion and fail to be properly applied in clinical practice. Common sense dictates that screening must be simple but policies should take into account prior history of vaccination to be able to be cost-effective. Breast and colorectal cancer screening practices are two examples in which risk-based differences in policies are already in place and widely promulgated by professional guidelines. Cervical cancer screening may eventually be added to the list. As research on the subject continues to provide additional evidence for public health action the next 5–10 years will bring many changes in practice standards and guidelines.

We realize that many of the predictions made in this article are based purely on theoretical grounds and epidemiologic principles of the performance of screening tests in conditions of varying prevalence. Much of our rationale is also based on current understanding of the value and robustness of HPV testing in screening. By definition, the subject matter of our article is one that requires writing about theoretical concerns and the indirect evidence that supports potential changes in practice. Many of our views, despite their theoretical underpinnings and some empirical support, may not be widely acceptable. Colleagues who are convinced that no changes are necessary to Pap cytology as a technology per se may view HPV testing as potentially causing many more colposcopy referrals than would be acceptable. Our arguments to the effect that this issue is offset by the extra safety margin of HPV testing (which would permit extended screening intervals and thus be cost saving in the long run) still require empirical support as suggested above. However, our proposal is made from a strong foundation of theory and practice which has emerged in recent years and underscores the importance of reaching

cost-effectiveness via a careful integration of primary (vaccination) and secondary (screening) prevention strategies. Therefore, the essential assumptions in our proposal are: (i) that HPV vaccination will have its intended effects as predicted above, (ii) that HPV testing will maintain its performance levels upon deployment as a primary screening test, and (iii) that Pap cytology would falter in the conditions of low lesion prevalence consequent to high vaccine uptake. Our statements should not be viewed as firm recommendations for practice guidelines but a roadmap for the merging of technologies in cervical cancer control that are likely to earn evidence-based status in the future.

Acknowledgments

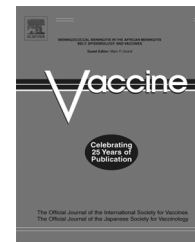
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Monitoring HPV vaccination

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KEYWORDS

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Summary The availability of two prophylactic HPV vaccines will require thorough considerations about monitoring and surveillance of those vaccinated and the general population, respectively. Vaccinated populations should be followed-up for long-term safety, sustained immune responses and vaccine efficacy. Effective monitoring will benefit from linkage of vaccination history and screening history, as well as precise measurement of HPV exposure, both DNA and serological testing. Lack of record linkage in many settings is one of the main obstacles for an effective surveillance program, though other surveillance activities can make contributions to assessing HPV vaccine effectiveness, including information from organized screening programs and phase IV studies.

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Current evidence-based medicine

Several clinical trials of two prophylactic HPV vaccines have been conducted in different countries including about 60,000 individuals. The per-protocol populations included women who were naïve to HPV 6, 11, 16, and 18 at baseline as determined by serology testing for presence of HPV type-specific antibodies or polymerase chain reaction (PCR) testing of genital samples for the presence of HPV DNA [1,2]. For both the bivalent and quadrivalent vaccines, results of different trials allow for the examination of broad trends in efficacy in preventing HPV 6/11/16/18-related disease in several groups of patients categorized according to their HPV status at baseline. The quadrivalent vaccine was 100% effective in reducing the incidence of HPV 6/11/16/18-related disease in HPV-naïve women as well as in women who had been previously exposed to at least 1 vaccine HPV

type at enrollment, but had no ongoing HPV infection (i.e., seropositive but HPV DNA negative by PCR) [3,4]. However, there was no clear evidence of protection from disease caused by HPV types for subjects that were HPV DNA positive by PCR and/or seropositive at baseline (Joura et al. [5]). Similar results were obtained for the bivalent vaccine (Harper et al. [6]). In a recent publication of a phase III trial, this vaccine showed 90% prophylactic efficacy against CIN2+ associated with HPV 16 or HPV 18th [7].

Despite these excellent efficacy results, it may take some time before these vaccines are administered to the general population worldwide. Moreover, women will still be at risk for developing cancers caused by other HPV types not included in the vaccine and hence, screening and monitoring strategies will be required. Finally, since at present the durability of these vaccines have been evaluated only for up to 5 years [6,8], monitoring of antibody levels and HPV infections in immunized individuals will be required over the next decades. Importantly, at present neither HPV serological assays nor HPV DNA tests can be used as clinically relevant tools. Studies to assess the long-term efficacy of HPV vaccination in developed and developing countries are ongoing [9].

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Populations to be monitored

1. Young individuals, previous to sexual exposure.
Immunization programs in several countries, with few exceptions, are targeting female preadolescents before their sexual debut. In addition, vaccine policy needs to consider the potential impact and benefits of including boys and men in these programs. Immunizing males and females may dramatically reduce transmission with high coverage.
2. Catch-up population
Even young women who are sexually active should be vaccinated because only a small percentage of them are likely to be infected by more than one HPV type at the time of immunization. Results from the quadrivalent vaccine trials have shown that only about 0.1% of the young women between 16 and 26 years of age, from different countries of the world, were positive for all four HPV types at baseline [10].
3. Older women
Recently, the bivalent vaccine has been approved in Australia and Indonesia for women between 10 and 45 years for the prevention of HPV types 16- and 18-related infections and disease. Additional phase III studies of the quadrivalent vaccine are being conducted in mid-adult women up to 45 years of age with results expected by end of 2008. The long-term safety and efficacy profile of these vaccines should be monitored in this group of individuals who are more likely to have been exposed to these viruses.

Recommendations

Monitoring of immune responses

Ideally, long-term follow-up of antibody status at least in selected cohorts of vaccinated persons should be the objective. These groups include adult women and representative cohorts from any population to which efficacy was bridged by means of comparison of immune responses. Vaccinated adolescent girls could be monitored 5–10 years after immunization in conjunction with cervical cancer screening (HPV testing followed by cytology).

At the present there is no agreed standard methodology for serological assays that measures vaccine induced antibody or that acquired in a present or past HPV infection although virtually all reported studies employ enzyme immunoassays. Before neutralizing antibody assays were made available [11], most serological assays were type-specific HPV VLP ELISA [12]. More recently, an automated multiplex assay based on the use of Luminex beads was developed for the detection of different serotypes with the same sensitivity and specificity achieved in the single-type assays [13].

Standardized methodologies that measure total serum antibody, neutralizing antibody and type-specific antibody concentrations will be necessary. Not all of these assays will be routine but if and when employed must be standard and consistent. These assays will require the establishment of an International Standard(s) with an arbitrarily assigned unit measure or International Units (IU). These issues

were recognized by the World Health Organization (WHO) who has established collaborative studies to evaluate reference reagents for type-specific HPV serologic assays (http://whqlibdoc.who.int/hq/2004/WHO_IVB_04.22.pdf and [14]).

Monitoring vaccine efficacy

Long-term assessment of vaccine efficacy to prevent CIN2/3, AIS, and cervical carcinoma could be achieved by following vaccinated women enrolled into clinical studies that employed histological endpoints. Linkage with screening programs and cancer registries would allow for proper efficacy measures along time. These exist as separate databases at the present and a key step will be to put in place infrastructure and procedures to link these records. Importantly, loss of screening performance may occur because of the expected reduction in cervical abnormalities in vaccinated populations. In this scenario, HPV testing has the potential to perform better as a primary screening test, followed by cytology for triage of HPV positive cases [15].

Studies of effectiveness should include virological assessments in order to establish whether disease cases in vaccinated individuals are caused by HPV types different from those contained in the vaccine. Moreover, widespread use of vaccines containing types 16 and 18 might lead to replacement of these as the predominant oncogenic HPV types. These data may also provide further information on the potential for types 16 and 18 to confer some degree of cross-protection against other HPV types.

Presently, the two methodologies most widely used for genital HPV types detection are Hybrid Capture™ version 2 (HC2) and PCR with generic primers. HC2 (DIGENE Co. Gaithersburg, MD, USA) is based on hybridization in solution of long synthetic RNA probes complementary to the genomic sequence of 13 high-risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) – high (B) probe cocktail – and five low-risk (6, 11, 42, 43, and 44) HPV types – low (A) probe cocktail. However, this assay cannot discriminate between individual HPV types and, therefore, is of little utility for the purpose of monitoring vaccinated individuals or surveillance of unvaccinated populations. PCR-based methods can detect a large number of individual HPV types, including a PCR-based line blot assay, capable of identifying 37 HPV genotypes (LINEAR ARRAY, Roche Diagnostics, Mannheim, Germany) [16], and the Roche's AmpliCor™ Human Papillomavirus test kit designed to amplify 13 high-risk genotypes. Consensus primers PCR include the GP5+/6+ system [17] and the Short PCR Fragment (SPF)-PCR, designed to discriminate a broad spectrum of HPVs by reverse line blot hybridization [21]. All the PCR-based assays described have, however, very high analytical sensitivities which is not ideal for monitoring and surveillance of naturally-exposed or vaccinated populations. It is clear that HPV type-specific PCR methods will be needed. The initiatives led by the World Health Organization may accelerate this process [14,18,20]. Candidate reference reagents for calibration of type-specific HPV DNA and serological assays will be essential in the establishment of monitoring and surveillance strategies.

Final recommendation

- Monitor young vaccinated women by type-specific HPV DNA testing followed by cytology (when HPV positive) at larger screening intervals.
- Surveillance in different countries with different vaccine coverage rates to evaluate HPV type replacement. Assess type-specific HPV prevalence in selected populations.
- Monitoring of sero status of vaccinated individuals by a centralized laboratory(ies) using an accepted and standardized methodology.
- Effective monitoring and surveillance will require record linkage between vaccination history and screening history/tumor registries.

Direction of future research

The next several decades will require the collection of data on the outcome in terms of HPV vaccine safety and effectiveness in the following situations:

- For those individuals that received fewer doses than recommended.
- That received more than one VLP vaccine.
- For women that received the vaccine while pregnant.
- When co-administered with other vaccines.
- To prevent other tumors (anal, head and neck, etc.).

It will be also important to define who will be responsible for post-marketing monitoring of HPV vaccines, pharmaceutical companies, government agencies, others.

Clinical perspectives

1. Clinicians must enforce the concept that cervical cancer screening programs must continue in addition to vaccination.
2. The clinician is crucial in long-term monitoring for effective and early reporting of putative vaccine associated adverse events.
3. Vaccine breakthroughs will be censored by clinicians, particularly gynecologists. Physicians should be aware of methodologies to properly classify and report these events. Ultimately, this will be essential to monitor changes in disease incidence.

Expert opinion

According to a recent publication, continuous monitoring will be crucial to evaluate any vaccination failures as well as to monitor HPV type replacement or the occurrence of escape mutants [19]. A reliable immunological correlate of protection, presently not available, will help in assessing the potential need for booster vaccinations. Besides, continuous evaluation of health care cost consumption will ultimately determine the success or failure of HPV prophylactic vaccination programs.

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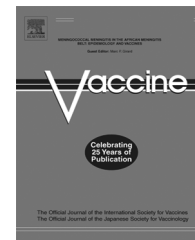
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EUROGIN 2007 roadmap—Conclusion

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Concluding remarks

Human papillomavirus (HPV) quadrivalent and bivalent vaccines effectively prevent HPV 16 and 18 associated with CIN2/3 in women naïve for HPV vaccine types for at least 5 years [1–7]. Duration of vaccine protection is unknown and to date no reliable correlate of vaccine immunity has been determined. The need for booster shots is also unknown, but additional data is expected over the next decade.

The greatest benefit from first generation HPV vaccines will be realized in sexually naïve populations. For this reason, vaccination of females with ages ranging from 9 to 14 represents the primary target population for routine systematic vaccination. The average age of initiation of sexual intercourse will vary among different populations, but it is expected that everywhere benefits from HPV vaccination will decline as HPV exposures increase with increasing age as will associated cost effectiveness. Presently there is no support for use of HPV testing prior to offering vaccination [8,9]. HPV type-specific testing by either polymerase chain reaction (PCR) for HPV DNA or serology for HPV-specific antibody is expensive and impractical. Furthermore, current HPV DNA status does not predict which women will benefit from HPV vaccination because it does not reflect cumulative HPV exposures.

Although models would predict that vaccinating girls/women older than 14 can reduce cervical cancer rates 10–20 years faster than vaccine programs including only 11, 12, 13 or 14 year olds, extending vaccination of current HPV vaccines to all sexually active populations would result in dramatic decreases in vaccine effectiveness at an incredible cost. Thus even in the wealthiest nations, limited health care resources and competing health care demands have for the most part resulted in a restriction of real world catch-up vaccination programs to women of younger age with lower lifetime HPV exposures. Presently, although it is known that individuals of any age can seroconvert after vaccination, efficacy and effectiveness of HPV vaccines to prevent pre-cancerous cervical lesions in women above age 26 or genital HPV infection in males of any age has not been demonstrated. Still undemonstrated, but of great potential usefulness, is also the efficacy of delivering HPV vaccines to infants and children, a much easier task than vaccinating girls, especially in developing countries.

Currently available HPV vaccines do not eliminate the risk of cervical cancer as they provide limited or no protection against a number of other common HPV types causing cervical cancer. Cervical screening where available, will therefore remain important under current guidelines in vaccinated and unvaccinated women to minimize cancer incidence. In countries where screening programs exist, if women at greatest risk fail to screen and also fail to vaccinate or if vaccinated young women opt out from regular screening, then vaccine benefit will be substantially reduced. Educational programs emphasizing the benefits of vaccination in primary population targets and the continued requirement for routine screening in both vaccinated

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and unvaccinated women will be important to avoid these potential unintended outcomes.

Overall cost-effective combination of vaccination in younger women and new screening strategies in older women will only be realized if economies of scale and market forces will lower the costs of these interventions. Assuming that HPV vaccine coverage will increase over time, the positive predictive value of any cervical screening test will be expected to decline. Part of the loss in the positive predictive value might be overridden by extending cervical screening intervals through the added reassurance achieved with HPV testing. In this regard, large randomized screening trials have recently provided overwhelming support for the use of HPV testing as a primary cervical cancer screening test in older women (~30 years old) and potential extension to women aged 25 and above might deserve consideration [10–13]. HPV testing and, in particular, novel low cost methods and once or twice in a lifetime screening programs can be rapidly adopted and best implemented in resource-poor settings where screening based on cytology continues to lack feasibility [14]. In developed countries, however, primary cervical screening is likely to continue using either cytology alone or with HPV testing performed adjunctively. In these settings, to specifically achieve the shift from existing cervical screening programs utilizing Pap tests to HPV testing-based screening programs will require a major reorganization process and therefore this change is likely to be delayed. Embedded in this statement are the financial concerns of those who perform Pap tests and of those who deliver these tests as an integral part of their clinical practice. HPV testing will not necessarily provide jobs for those who perform Pap tests and this is not, at present, simply a minor concern. Furthermore in a number of industrialized countries, cervical Pap screening plays an institutionalized role in the delivery of overall women's health care. Clinicians may be reluctant to rapidly adopt changes that for decades have formed the successful foundation of their current practice and that propose to turn regular practice referrals into extended interval referrals for which compliance with repeat screening is simply unknown. In the absence of organized screening that is accompanied by invited recall programs, resistance to adopting HPV testing as a primary screen and extension of screening intervals with any test is actually quite understandable. Before acceptance of HPV testing in many developed countries will be broadly embraced, additional clinical trials must be conducted that will allow establishment of algorithms defining specific screening intervals and that will evaluate reflex cytology with or without HPV genotyping. Extension of screening intervals specifically in vaccinated cohorts and potential effective differences in screening intervals for vaccinated and unvaccinated populations are anticipated but until these data become available screening will continue with no change in all women following current screening guidelines.

High coverage is the most important determinant of vaccination and screening success. In the absence of legal obligations, high coverage is the responsibility of clinical providers. In contrast, monitoring vaccine is a primary responsibility of public health entities and includes continuing surveillance to determine (1) safety; (2) population effectiveness (reductions in disease incidence); (3) long-

term immune responses; and (4) absolute and relative declines in vaccine HPV types and possible changes in non-vaccine HPV types (increases in case of unmasking or replacement or decreases were cross-protection substantial). Effective monitoring and public health surveillance will benefit from record linkage between vaccination and screening history (preferably through comprehensive registries) and over the long term, through tumor registries. It is however extremely important to note that although monitoring of HPV vaccination is important and necessary, it should not prevent vaccine introduction in nations where resources are limiting factors. It is expected that the most critical elements of surveillance data pertinent to global populations will be made available from those countries implementing high-level monitoring programs. In any case, monitoring will be different in developed countries where record linkage studies are possible versus developing countries where only sentinel surveys would be feasible.

Reduction or elimination of cervical cancer risk in any population through vaccination will require many decades and will ultimately be determined by several factors, including the baseline prevalence of carcinogenic HPV, the level of vaccination coverage in the population, the number of carcinogenic HPV types included in the vaccines, the duration of vaccine protection. The adequacy of accompanying provider, partner and patient education programs, the continuation of high-level screening practices, and the improvement of healthcare disparities will also play an important role. Looking toward the future, second and possibly third generation HPV vaccines targeting a broader spectrum of carcinogenic HPV types seem feasible and needed to expand the benefits of HPV prophylactic vaccines. HPV vaccines with expanded protection against HPV types causing nearly all cervical cancer would justify expansion of routine and catch-up vaccination programs to older age groups and would have a potential over the long term of eliminating cervical screening.

It must be stated that the benefits of prophylactic HPV vaccination and HPV testing remain limited because of a lack of resource availability among the nations and individuals that have the greatest need. The greatest burden of cervical cancer is found in underserved, resource-poor populations living in developing countries where women might never be screened in their lifetime. In total, over 80% of all incident cervical cancer and related mortality occurs in the developing world. In these nations, resources are required to provide access to HPV vaccines and tests, to develop novel and affordable alternatives, and to mount global campaigns and form multidisciplinary partnerships that enable their delivery. It is, to this extent, encouraging that the most important international donors of children vaccines are for the first time considering to support a vaccine like HPV vaccine meant to prevent cancer in adult women and that attempts to produce low-cost HPV vaccines in developing countries are being made. Within industrialized nations, reduction in cervical cancer morbidity and mortality will require that underserved and poor women are provided with both HPV vaccines and screening. Ultimately, for true success of primary and secondary cervical cancer interventions to be achieved, redistribution of resources and expansion of efforts to achieve global justice and equity are required.

The roadmap 2007 summary

The EUROGIN 2007 roadmap on cervical cancer prevention was developed following the preparation of the four preceding manuscripts [15–18]. The manuscripts present current data and the individual opinions of the expert authors. When the authors agreed with reviewer criticism or suggestions, the manuscripts were modified as a result of a broader review process. As chairs of the EUROGIN roadmap review process, under our assigned responsibilities, we have incorporated into the EUROGIN 2007 summary statement below, the balanced position formed through consolidation of (1) the manuscript author's perspectives, (2) the perspectives of the larger group of independent reviewers who represented a broad spectrum of clinical and scientific disciplines and (3) all available clinical and epidemiology evidence.

The roadmap provides direction to current and future best practices related to HPV vaccines and screening and summarizes the body of current evidence and future challenges related to primary and secondary cervical cancer prevention. Several key elements were considered. What age or range of age is appropriate for routine systematic versus catch-up vaccination? What if any potential utility does HPV testing have in determining who should be vaccinated? What current evidence exists and is suggested for the future to direct complementary and synergistic vaccination and screening strategies considering women of different ages and within countries with varied resources? Who is responsible for monitoring of vaccinated populations and what are the critical elements of post-licensure surveillance programs? The roadmap also considered individual and collective benefits of HPV vaccination and screening given competing needs and limited health care resources. An overall need for patient, partner and provider education must be highlighted as critical to all health care interventions. Future efforts of EUROGIN will focus on the complexity of educational and infrastructure resources needed to insure successful implementation of primary and secondary cervical cancer prevention. The EUROGIN 2007 roadmap summary is provided below.

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EUROGIN 2007 roadmap summary statement

Age of HPV vaccination

- Routine vaccination in females age 9–14 is supported with both public and private funding recommended.
- Catch-up vaccination in females age 15–18 is supported. When resources permit, use of both public and private funding is recommended.
- Catch-up vaccination in females age 19–26 (as authorized by regulatory agencies) can be supported by private funding however public funding is not recommended.
- Vaccination of females above age 26 is currently under evaluation.

Sexual activity is NOT a criterion to be used in setting public health prevention policy
Is viral status needed before HPV vaccination?

- DNA-, RNA- or serology-based HPV test methods should not be used under any circumstance as part of determining who should be vaccinated.
 - HPV tests are inaccurate measures of past or cumulative HPV type-specific exposures.

Cervical cancer screening following HPV vaccination

- Available evidence is currently insufficient to support changes in cervical cancer screening practices in vaccinated women thus presently no change is recommended. Vaccinated and unvaccinated women should continue in regular cervical screening programs under current guidelines.
- Future changes in screening are likely and are expected to include primary HPV screening, extended screening intervals and cost-effective combinations of screening and vaccination.
 - Cost-effective combination of vaccination in younger women and new screening strategies in older women will only be realized if economies of scale and market forces will lower the costs of these interventions.

Monitoring HPV vaccines

- Post-licensure vaccine surveillance should be conducted directly by or in collaboration with public health authorities. Monitoring of HPV vaccines should not be performed by individual scientists or clinicians.
 - Is necessary but should not prevent vaccine introduction.
 - Will be different in developed (record linkage studies) and developing countries (sentinel surveys).
 - Is critical to establishing long-term vaccine safety and to determining real world, not clinical trial population-based effectiveness.

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