Chapter 29: Knowledge gaps and priorities for research on prevention of HPV infection and cervical cancer

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Abstract

The recognition that human papillomavirus (HPV) infection is the necessary cause of cervical cancer brought new prevention paradigms in screening and HPV immunization. We now face many questions about how to implement an ambitious evidence-based agenda for cervical cancer prevention. Much is known about the epidemiology and natural history of HPV infection but several key variables remain to be elucidated. Research on HPV transmission requires new study designs to provide useful insights into preventive strategies. HPV testing has carved a niche in clinical practice but to consolidate its role in screening still requires evidence of long-term benefit. The rapidly evolving field of HPV diagnostics has contributed useful information concerning the value of HPV typing. Other screening methods hold promise in specific settings. The decade-long process that brought HPV vaccines to the doorstep of public health application is over. Many questions remain concerning long-term efficacy, correlates of protection, age of vaccination, and delivery. As vaccination makes inroads as a cancer control strategy, screening practices must be reformulated to maximize the synergy between primary and secondary prevention. Research on how to achieve an efficient combination of these modalities is yet to begin, but mathematical models have provided a useful road map for field-testing of promising algorithms. Daunting questions loom large concerning delivery of vaccines to those populations that need it the most. The field of HPV and cervical cancer prevention has never been so multi-disciplinary. A new era has begun and the challenges are many.

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1. Preamble

In the past 20 years basic, clinical, and population health research on the prevention of cervical cancer have progressed rapidly. The recognition that H infection was the central necessary cause of cervical cancer created new fronts for prevention via improved screening methods and immunization against HPV via vaccination. Owing to this successful track record the research community now faces a long list of needs and priorities from policymakers to assist them in implementing an ambitious evidence-based agenda for cervical cancer prevention. This chapter provides a summary of gaps in knowledge and needed research directions on HPV
and cervical cancer. It was written by this monograph’s section editors as a consensus document that collected views expressed by international experts in all areas of cervical cancer control and prevention. The headings below reflect key methodological and content areas covered in the monograph. The few references are given to inform readers about main sources of reading material that contain pointers to other primary documents. The individual monograph chapters contain an extensive, yet selected, bibliography concerning the individual topics of relevance in cervical cancer control.

2. HPV as a major public health problem

This section included chapters that provided an overview of knowledge concerning the burden of illness associated with HPV infection with a focus on cervical and other anogenital cancers. Although much is known about the role of HPV infection as the primary driver of the natural history of cervical neoplasia, there are significant gaps in our understanding (Table 1).

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<thead>
<tr>
<th>Research areas</th>
<th>Findings that are essential to assist prevention efforts</th>
<th>Gaps in knowledge and research priorities</th>
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<tbody>
<tr>
<td>Burden of cervical cancer</td>
<td>Methods to estimate the number of new cases per world region; secular trends for countries with well-developed cancer registries</td>
<td>Estimates from extensively populated areas in the world (i.e., China and India); HPV-type distributions in individual regions/countries in cervical cancer; relative contributions of HPV-16/18 per region/country</td>
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<td>Role of HPV in cervical cancer</td>
<td>HPV genotypes associated with risk; persistent infection as the key causal intermediate; knowledge that most important HPV types are relatively constant in etiologic fraction throughout the world</td>
<td>Risk factors for progression to invasion; role of cofactors acting “downstream” from HPV infection; duration of lesion sojourn time; role of cofactors upstream from HPV infection</td>
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<td>Role of HPV in other anogenital cancers</td>
<td>Lower but substantial etiologic fraction for cancers of the vulva, vagina, anus, and penis</td>
<td>Concerted multi-centre studies to pool cases and controls to obtain more accurate estimates of risks for these rarer tumors attributed to different HPV types and the role of cofactors</td>
</tr>
<tr>
<td>Epidemiology of genital HPV infection</td>
<td>Sexual activity is the key behavioural risk factor with strong mediating role of age; HPV type distribution among lesion-free women reasonably well established across continents</td>
<td>Identify immunological factors and other determinants of regression, persistence and progression; geographical differences among the minor oncogenic HPV to inform composition of next generation vaccines; differences among HPV types in risk factors and oncogenic potential; distribution of HPV types in atypical squamous cells of undetermined significance (ASCUS) smears to help inform next generation of HPV typing tests for triage; geographical information on the burden of genital warts and HPV type attribution</td>
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<tr>
<td>Natural history of HPV infection</td>
<td>Duration of HPV infection is 8–16 months on average, high-risk (HR)-HPVs more persistent than low-risk (LR)-HPVs; HPV-16 more persistent in some populations; most infections clear within 1 year</td>
<td>Does HPV infection segregate to the basal layer of the epithelium and becomes undetectable (concept of latent infection); What is the genesis of infections later in life? Can new acquisition be differentiated from reactivation later in life? Standardization of research on HPV persistence (frequency and mode of sampling and testing); role of antibody and cell-mediated immunity</td>
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<td>Transmission of HPV infection</td>
<td>Sexual transmissibility likely to be among the highest among all STIs</td>
<td>Studies in forming couples to determine infectivity, risk factor for transmission; relation between infectivity and viral load; role of sexual networks; importance of non-sexual routes in transmission; differences between HR- and LR-HPVs; inconsistent findings regarding condom protection</td>
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2.1. What is established

In spite of the existing efforts to register and monitor trends in the incidence of cervical cancer, extensive areas of the world still suffer from considerable uncertainty in this respect. These include large populations in Asia and Africa as well as some populations in Eastern Europe and Latin America. Case–control studies and independent cohort investigations have conclusively established that infection by high-risk HPV types is the necessary causal precursor in cervical carcinogenesis (reviewed in [1,2]). These studies have unveiled a wealth of information concerning the ancillary role of cofactors and on the epidemiology of HPV infection. Table 1 summarizes the main research achievements that are of relevance in prevention and gaps in our knowledge. The main thrust of research in epidemiology has been the demonstration of the causal role of HPV infection in cervical cancer. Natural history research has dealt with assessment of viral exposure as an intermediate endpoint on the basis of constantly evolving HPV DNA tests that have reached a very
high level of molecular sensitivity and specificity. Some of these assays have found a niche in clinical practice. Much is known about viral cofactors, such as intratypic molecular variants and viral load, and about hormonal, genetic, diet, and infectious cofactors. There is also substantial agreement among studies, despite their heterogeneity, with respect to the duration of HPV infection episodes in young women. Molecular epidemiology studies have also contributed to our understanding that a substantial proportion of other anogenital cancers is also caused by HPV infection.

2.2. What remains to be understood

Despite the wealth of findings on cofactors, we tend to know more about whether or not they are credible risk determinants or modifiers than about their placement in a natural history model. Case-control investigations are robust study designs to test hypotheses related to causality but, because HPV exposure cannot be accurately measured retrospectively, they provide only limited knowledge on the latency of effects mediated by cofactors. Much of what we have learned about whether cofactors act upstream or downstream from HPV infection in cervical carcinogenesis has been obtained from innovative uses of HPV-restricted subset analyses, which do not permit an adequate assessment of the “position” of causal variables in an etiologic model that considers latency of effects. Cohort studies are more capable of generating this type of information. However, because of their limited statistical power and need to restrict to pre-invasive lesion endpoints, the information provided can only be considered preliminary at this stage. As the large cohort investigations that began in the late 1980s and early 1990s accrue lesion events, this situation may change. Such cohort studies will also enhance our understanding of what constitutes latent infections. As women who cleared their infections are being followed for long periods of time that exceed 10 years, these cohort studies will have an excellent opportunity to monitor new HPV infection episodes and verify if they are related to earlier infections or represent new exposures.

We still need more consistency with respect to the findings on HLA markers of susceptibility to HPV infection and cervical cancer risk. Likewise, more research is needed to elucidate humoral and cell-mediated immunological factors that are involved in clearance, maintenance of latency, and progression of infection. We need better documentation of the predictive role of viral integration and related molecular markers that can be used in clinical practice. Epidemiologic research on HPV infection as an outcome in itself has recently refocused from the realm of cross-sectional and cohort studies to investigations in which viral transmission (and not acquisition or prevalence) is the variable of interest. Studies of forming couples will help shed light on the modes of transmission, degree of infectivity and on the protective effect of condoms.

3. Screening for cervical cancer

This section includes chapters that review the role of Pap cytology and the potential for competing screening technologies as secondary cervical cancer prevention strategies. Details of key facts and research priorities are shown in Table 2. Emphasis is given on the circumstances in which the available technologies deliver on their promises or fail because of unfavorable aspects of their performance in specific settings. A more complete picture of the role of screening, either independently or as a complementary preventive strategy to HPV vaccination appears in chapters in Section 4 (see below).

3.1. What is established

Despite never having passed the proof of randomized controlled trial testing, a standard of evidence now required of all health technologies, conventional Pap cytology quickly became the most widely used medical test. Second only to tobacco smoking cessation, cytology screening is unequivocally a public health success in cancer control. On the other hand, cytology screening has not provided the expected goals of cervical cancer control in developing and middle-resource countries, primarily because of problems related to coverage, lack of quality assurance, and management of those positive at screening. Many competing technologies have appeared in the last 15 years, the most promising of which are liquid-based cytology and HPV testing. These two methods have gained wide acceptance in industrialized countries, mostly because of a large knowledge-base of studies providing evidence that they either improved the efficiency (liquid-based cytology) or lowered (HPV testing) the false negative rate of conventional cytology. Other low-technology approaches, such as visual inspection and its variations have shown promise in developing countries where cytopathology resources are not adequate or are nonexistent [3].

3.2. What remains to be understood

As shown in Table 2, there are several areas that can be considered as priority for research on screening methods. There is an urgent need for research that can improve the implementation and delivery of screening in developing countries, where diagnostic services, laboratory infrastructure, and trained personnel are resources that cannot be counted on. Studies of screen-and-treat approaches must demonstrate benefit beyond the simple observation that more lesions can be detected and immediately treated. Follow-up investigations of treated women must be maintained to ascertain long-term benefit in morbidity and mortality reduction. Research on visual inspection methods must also be delivered as demonstration projects with long-term observation and continued quality control.

Cytology-based approaches that improve efficiency and eliminate manual scanning of smears hold great promise,
4. Prophylactic HPV vaccines

This section includes chapters that summarized key historical aspects and the current state of clinical development in the field of prophylactic HPV vaccines. Despite the solid gains that have made vaccine availability a reality in the near future there are many unknowns that require further research and attention to potential difficulties in vaccine delivery (Table 3).

4.1. What is established

The decade-long process that brought the two candidate vaccines to the doorstep of public health application stemmed from the discovery that immunization with the viral L1 protein in the context of virus-like particles produced by recombinant DNA technologies induces a strong and long-lasting immune response. The reader is referred to chapters in Section 3 for a detailed account of research on prophylactic HPV vaccines. In brief, the two candidate vaccines are very safe and highly efficacious for periods likely extending much beyond 5 years in protecting against HPV infection of types 16/18 and their associated precancerous lesions.

4.2. What remains to be understood

The many questions and research priorities outlined in Table 3 refer essentially to our need to urgently expand our knowledge concerning the effectiveness of HPV vaccines across a wide range of conditions. There are several questions related to age of vaccination, minimum number of doses

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<tr>
<td>Role of Pap cytology</td>
<td>Conventional cytology has been the mainstay of cervical cancer prevention for decades; large population coverage, centralized coordination, and quality assurance are the essential components of an effective screening programme; implementation often unsuccessful in middle-resource or developing countries; liquid-base cytology helps improve efficiency of screening</td>
<td>Strategies to achieve high coverage and to eliminate disparities in access; strategies to empower women in developing countries to enable them to have access to screening; experience with screen-and-treat approaches; experience with liquid-based cytology in resource-limited settings; cost-effectiveness of liquid-based cytology and automated cytology; performance parameters of cytology under conditions of low lesion prevalence, such as those likely to follow vaccination</td>
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<td>HPV testing in screening</td>
<td>Substantially more sensitive and slightly less specific than cytology in primary screening; efficacious in triaging women with atypical squamous cells of undetermined significance (ASCUS) smears; efficacious in monitoring lesion recurrence in women treated for cervical neoplasia (CIN)</td>
<td>Determine safety of follow-up periods above 3 years for women who are HPV and cytology negative; determine optimal follow-up for HPV-positive, cytology-negative women; effectiveness of self-collected samples in different settings; efficacy of point-of-care, simpler HPV testing technologies; Can HPV testing be used as the primary screening test followed by cytologic triage of HPV-positive women? Demonstration projects to monitor cancer incidence; cost-effectiveness of screening algorithms among HPV-vaccinated women; role of HPV typing as prognostic tool; evaluate utility of differential surveillance for infections with HPV's 16, 18, and 45; utility of viral load measurements in triage; evaluate health promotion strategies that minimize anxiety related to screening and HPV testing</td>
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<tr>
<td>Visual inspection</td>
<td>With adequate training and continued quality assurance can be effective in prevention</td>
<td>Effectiveness in combination with screen-and-treat strategies; comparison with HPV testing in low resource areas</td>
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<td>Role of molecular markers, physico-optical methods in screening</td>
<td>HPV mRNA, p16, proliferation markers are good markers and predictors of high grade lesions; physico-optical methods are promising as real-time tools</td>
<td>Performance characteristics under a wide range of clinical settings and in screening conditions; evidence that they represent cost-effective additions to cervical cancer control; research on microarray technology to improve prognosis</td>
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that can achieve protection, duration of protection in different circumstances determined by disease or the normal ageing process, the extent of cross-protection against other types, and efficacy in men. Are there correlates of protection that can be measured conveniently via neutralization or other assays or immune markers? These questions have enormous implications for the logistics of vaccine delivery and monitoring of its effectiveness. This is the first time that a vaccine that targets a sexually transmitted infection is primarily intended as an anti-cancer agent. Will it be more efficiently delivered as a school-age vaccine? This is likely to be the case in many countries but immunization must be timed in such a way that women will be adequately protected when they are first exposed to HPV. Determining whether initial doses can be given in childhood and the booster doses just prior to the onset of sexual exposure is one of many research questions for long-term studies and demonstration projects. As shown by research on hepatitis B vaccination, many key answers only became known at least 10 years after the vaccine first became available. The interested reader is referred to chapters in Section 6 for a comprehensive list of research priorities on HPV vaccination, many of which are already the focus of large scale studies.

5. Integrating HPV vaccines and screening

Assuming that the answers from research on HPV vaccination, as outlined above, will continue to indicate that it represents a promising primary cancer prevention strategy, we will have to consider what to do with existing screening programmes. Health authorities of many western industrialized countries have a reason to be proud of the effective way with which their organized Pap cytology screening programmes have reduced human suffering from cervical cancer. On the other hand, many middle-resource countries have spent vast resources to bring their screening programmes. Health authorities of many western industrialized countries have a reason to be proud of the effective way with which their organized Pap cytology screening programmes have reduced human suffering from cervical cancer. On the other hand, many middle-resource countries have spent vast resources to bring their screening programmes to meet desirable standards but have not achieved the obvious goals of reducing disease morbidity and mortality. While the decision to adopt HPV vaccination may be easier to reach in countries with no screening, the advent of HPV vaccination poses new challenges for countries with complex screening infrastructures in place. Such decisions can be guided by modern tools of decision science. Section 4 chapters deal with the important duality of cervical cancer control approaches and of how to achieve synergy between vaccination and screening in a cost-effective way.
5.1. What is established

Mathematical models of preventive interventions for cervical cancer have evolved considerably in the last 10 years. At core, these models incorporate highly complex knowledge from a solid body of molecular epidemiologic studies on HPV and cervical cancer and parameters of screening and vaccination efficacy that have emerged from clinical studies. These models are extensively validated and have become essential for rational, scientifically sound projections of cost per expected benefit. In general, these models have indicated that the cost-benefit relation is highly contextual and very sensitive to assumptions related to the type of screening test and desire to juxtapose technologies to prevent cancer. Simple and low cost solutions for substantial reductions in disease burden exist for developing countries. Solutions for developed countries generally incur higher costs for marginal gains because of the societal need to prevent as many cases of disease as possible.

5.2. What remains to be understood?

The validity and range of uses of the decision models has constantly improved as a function of the accrued high-quality data that is incorporated into the models and of their increasing methodological sophistication. However, these models continue to be based on knowledge obtained from screening and vaccination studies that comes as independent information without the expected interaction that one technology (vaccination) can have on the other (screening). Table 4 summarizes the importance of research on the expected interaction between these two prevention fronts. Future models will have to assess the impact of different algorithms for screening between vaccinated and unvaccinated women as if two separate population strata existed. Such models must also contemplate potential pitfalls that may ensue if vaccine uptake is primarily among women destined to be compliant of screening. The role of HPV testing in screening, already an important consideration before the vaccination era, may become a more urgent priority because of the possibility that the current cytology-based paradigm may falter. Much research is needed in the form of demonstration projects to obtain empirical evidence for the relative performance of cytology and HPV testing among vaccinated and unvaccinated women. Randomized trials may not be possible for this purpose for ethical reasons.

6. Public health aspects of HPV vaccine introduction

The scientific evidence generated in the process of bringing HPV vaccines to the licensing stage is but one component of the knowledge-base to be considered for the introduction of vaccination in individual countries. National regulatory authorities in different countries will examine the evidence concerning efficacy and safety to advise local and federal governments with respect to the merits of including HPV vaccination as part of existing immunization practices. Programmatic decisions concerning adoption of HPV vaccination and centralized funding for delivery of vaccination are far more complex because they depend on the relative merits of funding such a programme against a backdrop of limited

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<td>Cost effectiveness of interventions</td>
<td>Balance of marginal benefits for combining HPV vaccination to screening; current inequity; cost-effective interventions are available but unused in developing countries, whereas expensive interventions often used in developed countries for marginal gains; wider international problem of lack of equity in healthcare in developing countries</td>
<td>What are the cost implications for screening being met from a different source than those covering costs for HPV vaccines? How will a vaccine against HPV compete for resources with other vaccines aimed mainly at preventing childhood disease and mortality? Operational research on the design and acceptability of services; research on how to increase coverage of screening; demonstration projects to show that disease incidence will not increase from less aggressive screening and treatment with new technologies; research on screening follow-up algorithms (see Table 2)</td>
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<td>Impact of vaccination on screening</td>
<td>Screening will have to continue because of lack of vaccine coverage for all oncogenic HPV types, presumed lack of therapeutic efficacy, and to monitor loss of protection; decrease in prevalence of cervical precancerous lesions will lower the positive predictive value of cytology; potential situation to avoid: favoring vaccine uptake among women who are more likely to be screened while not doing enough to promote vaccination among those who fail to comply with screening</td>
<td>Will the performance characteristics of cytology suffer in conditions of low lesion prevalence? Can liquid-based cytology and automated technologies help prevent the possible loss of sensitivity and specificity of cytology? Can HPV testing followed by cytologic triage serve as a more rational approach to screen vaccinated women? Can age of screening onset be raised in vaccinated women? Can infection and cytology registries serve as a surveillance tool to monitor the effectiveness of vaccination? Health promotion studies of barriers to vaccine uptake and screening</td>
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budgets and other healthcare priorities. Section 5 addresses the substantial obstacles facing policy makers when considering the complexity of HPV vaccination delivery.

6.1. What is established

Individual countries will assess the merits of adopting HPV vaccination based on perceived importance of the burden of disease that it will prevent, the cost-effectiveness of vaccination vis-à-vis other priorities, and the sustainability of vaccination programs. Unlike other vaccine-preventable diseases, cervical cancer is already the target for preventative actions (screening) that mobilize substantial resources in the public health sector of many countries. Therefore, in addition to the above variables used in policy making, decisions may also have to ponder the costs and synergy with existing screening programs. Table 5 outlines some key public health areas that will need to be examined by national and supra-national health authorities in order to achieve high population uptake of HPV vaccination and cost-effective deployment of vaccines.

6.2. What remains to be understood?

A concerted effort must be made to ensure efficient communication of the scientific facts concerning HPV, cervical cancer, and vaccine safety and efficacy to health authorities, health providers, and the public to prevent misconceptions that may hamper successful implementation of vaccination programmes. Unfortunately, much is yet to be achieved in the area of communication and health promotion. Many misconceptions exist about the sexually transmitted mode of acquisition of HPV and the stigma that it represents in certain populations.

An effective and integrated post-market surveillance system must be executed to compile valuable information regarding long-term safety and efficacy under less than optimal conditions of vaccine delivery. Key information regarding efficacy against other HPV-induced diseases, protection of individuals with immunocompromising conditions, blockage of transmission to susceptible males, and protection under suboptimal doses will be provided by pooling together surveillance data in countries that implement vaccination (Table 5). Such phase IV studies will not be as controlled

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<tbody>
<tr>
<td>Decision making</td>
<td>World Health Organization (WHO) establishes licensing criteria based on best available scientific evidence for advising member countries; key criteria: vaccine efficacy from phase III trials, disease burden and cost-effectiveness</td>
<td>Proper quantification of cervical cancer burden, cost-effectiveness, and sustainability of vaccination in light of existing cervical cancer control programmes must be country and setting specific; need to establish population-based tumor registries in sentinel areas to monitor post-vaccination effects</td>
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<td>Safety, quality and efficacy of vaccines</td>
<td>Meeting vaccine performance standards is the responsibility of manufacturers; adopt guidelines proposed by WHO for National Regulatory Authorities (NRA)</td>
<td>Should individual countries that can afford the costs of independent monitoring establish their own NRAs? International agreement on immunological correlates of protection and feasible trial endpoints</td>
</tr>
<tr>
<td>Post-market surveillance</td>
<td>Post-licensing monitoring must be done via phase IV studies</td>
<td>Need to determine efficacy and safety in conditions such as: (i) incomplete doses, (ii) simultaneous administration of other vaccines, (iii) underlying chronic and infectious diseases that may compromise immune response or affect safety, (iv) long-term follow-up, (v) suboptimal delivery; determine efficacy against other HPV-induced diseases; determine risk of diseases that could be linked to side effects of vaccination</td>
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<td>Vaccine acceptability</td>
<td>Misunderstanding and misconceptions about transmission of HPV, its role in cervical cancer, and need for vaccination may hamper vaccine acceptability</td>
<td>Determine societal determinants of vaccine acceptability; Inform decision makers about the benefits of vaccination to prevent delayed implementation; Determine most effective means of communicating HPV- and cervical cancer-related information to healthcare providers and the population; Determine factors contributing to refusal to vaccinate</td>
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<td>Delivery costs</td>
<td>Experience with tiered-pricing and pooled procurement used for other vaccine-preventable diseases</td>
<td>Concerted effort among WHO, GAVI, country stakeholders and vaccine suppliers to secure affordable vaccine costs for developing countries; provide incentives for developing countries to accelerate the introduction of HPV vaccines; investigate feasibility of a strategy of advanced market commitment to guarantee vaccine availability at a reasonable cost</td>
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as phase III studies, and thus, they will be more prone to eliciting controversy concerning the validity of their findings.

The experience with other vaccine-preventable diseases provides a valuable knowledge-base that will assist policymakers in avoiding mistakes of the past. The lessons from the implementation and post-market surveillance with hepatitis B vaccination are one valuable example that has many similarities with the situation with HPV vaccination, i.e., the sexually transmitted mode of acquisition and cancer as long-term clinical outcome. The collective experience of the Global Alliance for Vaccines and Immunization (GAVI), the World Health Organization, other supranational bodies, and member countries may also provide valuable insights in obtaining innovative funding mechanisms to guarantee long-term availability of vaccines at a low unit cost for developing countries. Taken together, the daunting complexities related to successful implementation and sustainability of HPV vaccination can be minimized via concerted efforts among all stakeholders, private and public, commercial and non-commercial. While much remains to be done, the collective wisdom accumulated through decades of experience with other vaccines may make the new model of cervical cancer prevention via vaccination one of the most successful stories in modern preventive medicine. The future will tell.

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GPG: Consultant (GlaxoSmithKline, Merck and Co., Inc., Sanofi-Pasteur MSD, Sanofi-Pasteur); Research Grants (GlaxoSmithKline)

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