Approaches to monitoring biological outcomes for HPV vaccination: Challenges of early adopter countries


In this review, we describe plans to monitor the impact of human papillomavirus (HPV) vaccine on biologic outcomes in selected international areas (Australia, Canada, Mexico, the Nordic countries, Scotland, and the United States) that have adopted this vaccine. This summary of monitoring plans provides a background for discussing the challenges of vaccine monitoring in settings where resources and capacity may vary. A variety of approaches that depend on existing infrastructure and resources are planned or underway for monitoring HPV vaccine impact. Monitoring HPV vaccine impact on biologic outcomes is a complex and challenging task, but also plays an important role in documenting the benefit of vaccination, monitoring the progress of vaccination programs, and providing data to inform vaccination and disease prevention policies.

Published by Elsevier Ltd.

Contents

1. Introduction ........................................................................................................................................... 00
2. Methods .................................................................................................................................................. 00
3. Summary of monitoring plans from selected jurisdictions ................................................................. 00
  3.1. Implementation strategies for HPV vaccination ................................................................................. 00
  3.2. Infrastructure for monitoring ............................................................................................................ 00
  3.3. Outcomes to be monitored ................................................................................................................ 00
4. Challenges to monitoring HPV vaccine impact .................................................................................. 00
  4.1. General challenges .......................................................................................................................... 00
  4.2. Type-specific HPV infection ............................................................................................................ 00
  4.3. High grade cervical lesions .............................................................................................................. 00
  4.4. Invasive cervical cancer ................................................................................................................... 00
  4.5. Other HPV-associated cancers and precancers .............................................................................. 00
  4.6. Anogenital warts ............................................................................................................................ 00
  4.7. Recurrent respiratory papillomatosis ............................................................................................. 00
5. Discussion ................................................................................................................................................ 00
Acknowledgements ..................................................................................................................................... 00
References .................................................................................................................................................... 00

* The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
* Corresponding author at: 4770 Buford Highway, Mailstop K-55, Atlanta, GA 30341, USA. Tel.: +1 770 488 4293; fax: +1 770 488 4639.
E-mail addresses: MSaraiya@cdc.gov, yzs2@cdc.gov (M. Saraiya).

0264-410X/$ – see front matter. Published by Elsevier Ltd.
doi:10.1016/j.vaccine.2010.10.018
1. Introduction

Two prophylactic human papillomavirus (HPV) vaccines are currently available worldwide: a bivalent vaccine (HPV 16 and 18), and a quadrivalent vaccine (HPV 6, 11, 16, and 18). Randomized controlled trials conducted on several continents have demonstrated that these vaccines are highly efficacious in preventing vaccine-type high grade cervical intraepithelial neoplasia (CIN 2/3) [1–6]. In addition, the quadrivalent vaccine has been shown to prevent vaccine-type vaginal and vulvar intraepithelial neoplasia and external genital lesions, including genital warts, in women and men [6,7]. Worldwide, over 493,000 cervical cancers occur every year, most in settings where there is limited or no cervical cancer screening [8]. Current HPV vaccines have the potential to significantly reduce the burden of HPV-associated conditions, including prevention of up to 70% of cervical cancers [9].

The HPV vaccines have been licensed in over 100 countries and incorporated into national immunization programs in many high-income countries (as well as some low and middle-income countries) [10]. In April 2009, the World Health Organization (WHO) recommended inclusion of HPV vaccination in national immunization programs where cervical cancer and HPV-related disease are a public health priority and where vaccine introduction is feasible, sustainable financing secured, and cost-effectiveness considered [11]. In May and July 2009, respectively, both the quadrivalent vaccine and bivalent vaccine were awarded WHO pre-qualification, which denotes vaccine eligibility for procurement by organizations, such as United Nations Children’s Fund (UNICEF) or Pan American Health Organization Revolving Fund, for use in national immunization programs [12]. In 2009, the Global Alliance for Vaccines and Immunization (GAVI) stated that it aims to make the HPV vaccine available to girls in developing nations, pending available funding [13].

With the WHO recommendation and pre-qualification status, implementation of HPV vaccine is expected to increase worldwide, although high cost and unique implementation challenges continue to impede HPV vaccine introduction in resource-constrained settings with competing public health priorities [14]. Along with addressing the challenges for vaccine implementation, a strategy for monitoring the impact of HPV vaccine on biologic outcomes merits discussion and planning [15–20]. Impact monitoring cannot be interpreted without coverage and safety data; these components of comprehensive vaccine monitoring are addressed elsewhere [21,22] and in a recent WHO technical guidance document on monitoring HPV vaccine coverage [23]. Thus, here, ‘vaccine impact monitoring’ refers to the monitoring of biologic outcomes.

For HPV vaccine impact monitoring, biologic outcomes include HPV infection and HPV–associated diseases. Each biologic endpoint has its own opportunities and challenges [16,18–20,24–27], and the most appropriate outcomes to monitor, if any, may differ by setting. Cervical cancer develops in steps: HPV infection of the cervical epithelium, persistence of the infection, progression of the persistently infected epithelium to cervical intraepithelial neoplasia (CIN), and invasion through the basement membrane to result in invasive cervical cancer [28]. Hence, cervical cancer and high- and low-grade CIN lesions are outcomes that may be monitored. Vaccines directed against HPV types 16 and 18 also have the potential to reduce other HPV–associated cancers (vulvar, vaginal, anal, penile, and oropharyngeal). Anogenital warts and recurrent respiratory papillomatosis (RPP) are biologic outcomes that can be monitored in men and women for vaccines that prevent HPV types 6 and 11.

For several reasons, the ideal approach for monitoring vaccine impact must be carefully considered where HPV vaccine implementation is ongoing or soon will be. According to the WHO, surveillance of HPV outcomes is not a prerequisite to initiate HPV vaccination programs; however, monitoring, particularly for HPV infection and cervical cancer, should be considered [23]. Well done impact monitoring across each global region in at least some areas that have achieved a range of HPV vaccine coverage would be desirable for the benefit of all countries. Surveillance data for HPV–associated diseases collected at local or regional levels may help garner political will and public support in favor of implementation and sustain vaccination program policies by demonstrating HPV–associated disease burden. Baseline data may also establish benchmarks for monitoring vaccine impact [19]. In the present paper, we describe plans to monitor HPV vaccine impact on biologic outcomes in selected areas internationally (Australia, Canada, Mexico, Scotland, the Nordic countries, and the United States) as background for discussing the challenges of monitoring in settings where resources and capacity may vary.

2. Methods

From February to May 2009, 22 key stakeholders involved in HPV vaccination and/or cervical cancer from low-, middle- and high-resource countries were identified by the co-authors (MS, ED, SH) and interviewed (CW, MS, ED, SH) regarding vaccine monitoring activities. Additional information sources, including published manuscripts, unpublished documents, health ministry websites, press releases, plus websites and documents from public health authorities such as the WHO, were reviewed. Information is presented from: (i) these sources noted above; (ii) discussions at a CDC-sponsored satellite symposium at the 25th International Papillomavirus (IPV) Conference in May 2009 – HPV Vaccine Monitoring: Biological Outcomes; (iii) key issues from two meetings on HPV surveillance and monitoring at the WHO [23,29]. The term “jurisdiction” is used to refer to geographic areas, such as a country, groups of countries (i.e., the Nordic countries or the UK) or provinces, since vaccination and monitoring may be implemented at different levels of administration. Although we attempted to capture all available data useful for this report, the information presented is cross-sectional and not complete due to the evolving nature of HPV vaccine implementation and monitoring plans internationally.

3. Summary of monitoring plans from selected jurisdictions

HPV vaccine implementation, infrastructure, and monitoring plans in selected jurisdictions that adopted HPV vaccine are presented in Table 1 to provide context in which to discuss the challenges of impact monitoring. These settings were chosen because they have developed at least preliminary plans for monitoring impact.

3.1. Implementation strategies for HPV vaccination

Implementation across these predominantly high-resource settings, with the exception of Mexico, has varied. In Australia, Canada, the Nordic countries, and Scotland, HPV vaccine programs are mostly offered as part of school-based immunization for girls ages 9–12 years, some with catch-up vaccination through age 17 or 26 years (Table 1) [30–33]. Vaccine coverage with the 3-dose series in these countries has been moderate to high, ranging between 50 and 90% from 2007 to 2009 [30–35]. In the United States, HPV vaccination is recommended to girls at ages 11 or 12 years, with catch-up vaccination through age 26 years [40,41]. Vaccination is provided primarily in clinic–based settings by primary care providers; in 2008, coverage with 3 doses of quadrivalent vaccine among 13–17-yr-olds was 17% [36]. Mexico has been gradually implementing an
Table 1
Human papillomavirus (HPV) vaccine monitoring plans in select areas—implementation, infrastructure and biologic outcomes to monitor.

<table>
<thead>
<tr>
<th>Country</th>
<th>HPV vaccine implementation strategy</th>
<th>Infrastructure and plans for monitoring impact</th>
<th>Biologic outcomes to monitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia [39]</td>
<td>Quadrivalent (or, in future, bivalent vaccine)</td>
<td>National HPV vaccination program register</td>
<td>HPV genotypes in general population</td>
</tr>
<tr>
<td></td>
<td>Target population: 12–13 yr old females</td>
<td>WHO regional HPV reference laboratory</td>
<td>HPV genotypes in Pap test abnormalities and cervical cancer</td>
</tr>
<tr>
<td></td>
<td>Catch-up population 2007-09: 13–26 yr old females</td>
<td>National cervical screening programs with state-based Pap test registries with national data collection</td>
<td>Pap test abnormalities</td>
</tr>
<tr>
<td></td>
<td>Delivery strategy: School-based, 12–18 yr old females; PCPs, 18–26 yr old females</td>
<td>State-based cancer registries and registries of death with national data collection</td>
<td>High grade cervical disease (CIN 2/CIN 3, AIS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>National hospitalization data</td>
<td>Cervical cancer cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medicare claims data (numbers of procedures billed for)</td>
<td>Cervical cancer deaths</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Legislative underpinning to link vaccination registry to Pap test and cancer registries</td>
<td>Other HPV-associated cancer cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HPV genotypes in Pap test abnormalities and cervical cancer</td>
<td>Anogenital warts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HPV genotypes in Pap test abnormalities and cervical cancer</td>
<td>RRP</td>
</tr>
<tr>
<td>Canada</td>
<td>Quadrivalent vaccine (federal funding) Bivalent vaccine approved</td>
<td>Vaccine registries (varies by province and territory)</td>
<td>HPV genotypes in selected populations</td>
</tr>
<tr>
<td></td>
<td>Target population: 9–13 yr old females</td>
<td>Laboratory infrastructure varies across provinces and territories</td>
<td>Pap test abnormalities</td>
</tr>
<tr>
<td></td>
<td>Catch-up population: 13–26 yr old females</td>
<td>Pathology registries (varies by province and territory)</td>
<td>High grade cervical disease (CIN 2/3, AIS)</td>
</tr>
<tr>
<td></td>
<td>Delivery strategy: immunization programs responsibility of provinces and territories (varies). School-based, 9–14 yr old girls; PCPs, 12–18 yrs not in school or missed school dose, 18–26 yr olds</td>
<td>Cervical cancer screening databases and/or registries</td>
<td>Cervical cancer cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HPV genotypes in general population</td>
<td>Cervical cancer deaths</td>
</tr>
<tr>
<td>Mexico</td>
<td>Quadrivalent or bivalent vaccine</td>
<td>Comprehensive cancer registries</td>
<td>Other HPV-associated cancer cases</td>
</tr>
<tr>
<td></td>
<td>Target population: 2008 – 12–16 yr old females in 125 municipalities; vaccine administered at 0, 2, 6 months 2009 – 9–12 yr old females in 180 municipalities; vaccine administered at 0, 6, 60 months</td>
<td>High grade vaginal and vulvar intraepithelial lesions</td>
<td>Anogenital warts</td>
</tr>
<tr>
<td></td>
<td>Delivery strategy: school-based through Ministry of Health to ~220,000 girls in target population</td>
<td>HPV genotypes in selected populations</td>
<td>RRP</td>
</tr>
<tr>
<td>Nordic Countries (Denmark, Iceland, Norway, Sweden)</td>
<td>Quadrivalent vaccine in Denmark and Norway. Recommendation for a specific vaccine is underway in Sweden. In Iceland no recommendation is currently available</td>
<td>Central Person Register (personal identification number)</td>
<td>HPV genotypes in general population</td>
</tr>
<tr>
<td></td>
<td>Denmark: 12 yr old females; 13–15 yr old females catch-up</td>
<td>WHO global HPV reference laboratory in Sweden</td>
<td>HPV genotypes in CIN 2/3 and cervical cancer</td>
</tr>
<tr>
<td></td>
<td>Target population: Sweden: 12 yr old females; 13–17 yr old females catch-up Norway: 11–12 yr old females; No catch-up</td>
<td>Organized cervical cancer screening program</td>
<td>High grade cervical disease (CIN 2/3)</td>
</tr>
<tr>
<td></td>
<td>Delivery strategy: PCPs through invitation from National Board of Health (Denmark)</td>
<td>Cancer registry</td>
<td>Cervical cancer cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Linkage of all databases by means of unique personal identification number</td>
<td>Vaginal and vulvar cancers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vaccine Impact on Population study: Phase IV study to measure impact of quadrivalent HPV vaccine on CIN 2/3, cervical cancer, vaginal/vulvar high-grade lesions and cancer</td>
<td>Anogenital warts</td>
</tr>
<tr>
<td></td>
<td>Scotland</td>
<td>Bivalent vaccine</td>
<td>HPV genotypes in general population</td>
</tr>
<tr>
<td></td>
<td>Target population: 12–13 yr old females</td>
<td>Comprehensive school based vaccine registry</td>
<td>HPV genotypes in general population</td>
</tr>
<tr>
<td></td>
<td>Catch-up population: 13–26 yr old females</td>
<td>National reference laboratory</td>
<td>High grade cervical disease (CIN 2/3)</td>
</tr>
<tr>
<td></td>
<td>Delivery strategy: school-based, 12–13 yr old girls; Mixture of school based and community settings, 13–17 yr old girls</td>
<td>Organized cervical cancer screening program with centralized call recall system</td>
<td>Cervical cancer cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HPV genotypes in CIN 2/3 and cervical cancer</td>
<td>Cervical cancer deaths</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cancer registry</td>
<td>Other HPV-associated cancer cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surveillance of high grade cervical lesions</td>
<td>Sentinel sites for type specific precancer monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cancer registry</td>
<td>Administration claims databases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potential linkage of vaccine with cervical screening and cancer registries</td>
<td>Managed care organizations with electronic medical records</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HPV genotypes in general population</td>
<td>National health surveys</td>
</tr>
<tr>
<td>United States [20]</td>
<td>Quadrivalent or bivalent vaccine</td>
<td>WHO global HPV reference laboratory</td>
<td>HPV genotypes in general population</td>
</tr>
<tr>
<td></td>
<td>Target population: 11–12 yr old females</td>
<td>Comprehensive cancer registries</td>
<td>HPV genotypes in CIN 2/3, AIS, cervical cancer and other HPV-associated cancers</td>
</tr>
<tr>
<td></td>
<td>Catch-up population: 13–26 yr old females</td>
<td>STD surveillance network–includes anogenital warts</td>
<td>High grade cervical disease (CIN 2/3, AIS)</td>
</tr>
<tr>
<td></td>
<td>Delivery strategy: PCPs, 9–26 yr old girls;</td>
<td>Sentinel sites for type specific precancer monitoring</td>
<td>Cervical cancer cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cervical cancer deaths</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other HPV-associated cancer cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anogenital warts</td>
</tr>
</tbody>
</table>


Please refer to Section 3.1 for further details on HPV vaccine implementation and coverage.
HPV vaccine program, beginning with selected municipalities in 2008 and extending in 2009 to more women not covered by social security and to areas of high cervical cancer mortality. Mexico plans to increase the number of 9 year-old girls vaccinated each year, using a schedule with extended vaccination intervals (0, 6, and 60 months) in schools and clinic-based settings [37,38].

3.2. Infrastructure for monitoring

The countries presented in Table 1 that are developing or have implemented systematic monitoring plans generally have available many of the following high-quality systems: vaccination programs or registries, advanced laboratory capacity, cervical cancer screening programs, cancer registries, population-based surveys and/or administrative data sets. Examples of accessible administrative data sets include the health claims data in the U.S. or health services billing data in Canada. Jurisdictions with existing infrastructure are able to utilize, adapt or strengthen their systems to monitor vaccine outcomes. In some settings, monitoring has been incorpo rated into routine national public health disease surveillance activities, or biologic outcomes have become reportable conditions to allow for data collection as a public health mandate. As an example of the various monitoring activities and data sources, Australia will use a national HPV vaccination registry, national cervical screening program with state-based cytology registries, state-based cancer registries, and a regional WHO HPV reference laboratory [39]. The Nordic countries have some of the most comprehensive national health registries, which they will be able to use for monitoring [40].

Despite the ability to undertake some type of population-based surveillance in certain jurisdictions, using existing surveillance infrastructure and data has many challenges. For example, Canada and the UK must coordinate and assemble data from provincial/regional registries. In Canada, immunization programs are implemented as part of the public health system, at the level of provincial and territorial governments; however, laboratory infrastructure varies by province/territory and may be public, private, or a combination of both. Challenges also exist where certain surveillance systems are not available. For example, the United States, does not have a national vaccine or Pap test registry for population level monitoring. Where required infrastructure is not present, some settings are developing systems de novo for the purpose of impact monitoring.

The ability to link biologic outcomes databases to an accurately recorded HPV vaccination status is not common, but where present, may facilitate monitoring. In Nordic countries, a comprehensive national health care records system and a unique personal identifier assigned to each citizen at birth allow linkage across any registry, such as vaccine, screening, pathology, and cancer registries [41]. Scotland has a Community Health Index that assigns a unique patient identifier and can permit similar linkages [42]. Australia established a national HPV vaccine registry to allow linkages with state-based Pap test and cancer registries [43].

3.3. Outcomes to be monitored

Among the variety of outcomes that will be monitored, incidence and mortality of cervical cancers will take the longest to observe but are viewed as the most important given that the prevention of cervical cancer is the primary aim of vaccination; these are being monitored by all jurisdictions presented in Table 1. Early and intermediate endpoints allow a more proximal impact measure, such as the prevalence of HPV infection in the general public and in specific populations, as well as the incidence of high grade lesions associated with vaccine-related HPV types, i.e., CIN 2/3 and adenocarcinoma in situ (AIS). Other HPV-associated cancers and high grade lesions, such as vulvar, vaginal, anal, penile, and oropharyngeal cancer, are being monitored in some areas. For areas using the quadrivalent vaccine, anogenital warts and recurrent respiratory papillomatosis (RRP) are other biologic outcomes that are being monitored where the necessary infrastructure exists or special studies are in place.

4. Challenges to monitoring HPV vaccine impact

4.1. General challenges

Monitoring HPV vaccine impact requires collaboration among several sectors [16,18,24]. Diverse experts in vaccination, cancer screening, cancer surveillance, infectious disease, virology, sexually transmitted infection, child and adolescent medicine, reproductive health, and policy-making bodies need to work together to consider the methodological, clinical, and feasibility issues surrounding various biologic outcomes to be monitored. Well-organized technical support and information systems, such as data tracking and recording systems, would facilitate all monitoring efforts.

There are several monitoring challenges related to the long interval between HPV infection and associated diseases. Since some endpoints take years or decades to develop, maintaining complete and accurate vaccination status data, perhaps through vaccine registries with linkage capabilities to biologic outcomes as mentioned earlier, is important. Other challenges include the need for consistent sampling and methodology, as well as sustained resources and follow-up. Additionally, area-specific baseline data prior to widespread vaccine use is often unavailable for many HPV vaccine biologic endpoints, though baseline data in older females could be obtained after vaccine introduction in settings that do not implement catch-up vaccination programs. As monitoring continues, an important consideration when interpreting cervical disease trends is that screening recommendations and utilization are likely to evolve as vaccination becomes more widespread and various screening strategies (HPV or Pap test-based) become available and are implemented [44–47]. Further, changes in the level of vaccine coverage, the availability of new vaccines, and the duration of vaccine protection may influence the interpretation of impact monitoring data.

4.2. Type-specific HPV infection

Reduced prevalence of vaccine-type HPV infection is the earliest indicator of vaccine effectiveness. Though HPV genotype prevalence is not a direct measure of impact on disease, it is not affected by changes in cervical cancer screening practice and utilization, in contrast to cervical disease endpoints. However, HPV infection is often asymptomatic and laboratory testing for detecting HPV type-specific infection is currently unavailable or not recommended in many settings; therefore, impact monitoring using this outcome would entail special research evaluations, such as sentinel surveillance [48]. Mexico, for example, has initiated HPV testing in women 35–64 years-old as part of a national cervical screening program in 125 municipalities where vaccination was first implemented and expanded to other states in 2009 and 2010 [37].

In other settings, the target age group for HPV infection vaccine impact monitoring will often be younger than one that is typically targeted for cervical cancer screening. Given the high prevalence of HPV infection and increased probability of infection clearance in younger women, challenges exist for testing this population as well as addressing the ethical issues related to reporting test results and appropriate follow up [48,49]. Having the capacity and/or assessing the need to provide evidence-based information and follow-up services after HPV testing, such as additional screening, treatment or referral, may be especially challenging in settings.
without organized and integrated cervical cancer prevention and screening programs.

HPV genotype testing requires DNA collection from the anatomic site of infection, which may be resource-intensive. In addition, HPV genotype testing (PCR-based) used for epidemiologic surveillance is optimally standardized and more sensitive than clinically relevant pooled HPV tests in use (e.g., Hybrid Capture 2 [Digene Corporation, Gaithersburg, MD]) or point of care tests that may become available [56]. The ability to use new tests or technology and minimize variation in test performance will require laboratory capacity, testing standards, trained personnel, and sustained financial support [50]. Early discussions with laboratory personnel will be essential to monitoring activities.

Since laboratory capacity will be a unique need and challenge for HPV vaccine monitoring, the WHO launched the global HPV Laboratory Network in 2006 to “contribute to improving quality of laboratory services for effective surveillance and monitoring of HPV vaccination impact, through enhanced, state-of-the-art laboratory support” [50–52]. The HPV laboratory network may be an important partner for vaccine impact monitoring. Labs in the United States and Sweden serve as global WHO HPV reference laboratories [51].

### 4.3. High grade cervical lesions

Relative to cervical cancer, high grade cervical lesions are an intermediate measure of vaccine impact. These may be monitored through reports of cytologic (high grade squamous intraepithelial lesion—HSIL) or histologic (CIN 2/3 or AIS) outcomes. An HSIL diagnosis usually may represent either CIN 2 or CIN 3 when histologic evaluation takes place [53]. For the purposes of monitoring, histology-based outcomes would be ideal. CIN 3 is more predictive than CIN 2 as a precursor to cervical cancer and is the optimal endpoint for evaluating vaccine impact on cervical disease [61,62]. However, resource-limited areas may be unable to support the collection and accurate, reproducible diagnosis of histology or cytology specimens; quality assurance in cytology is a major challenge even in well-resourced settings [54]. Standardized terminology, coding, and centralized review for histology or cytology results could reduce variation in readings observed across laboratories.

The incidence of high grade CIN can be monitored through a variety of methods. In some areas, including Scotland and Finland, high grade cervical lesions (CIN 3) are reported to cancer registries [55]. More often, jurisdictions plan to use their cervical cancer screening programs as the foundation for monitoring high grade cervical lesions. Australian cervical screening registries routinely record histopathology results including CIN 2/3 and AIS [56]. Denmark can utilize their pathology data bank, which contains information on all normal and abnormal cervical cytology samples taken (both from organized and opportunistic Pap test screening) and all cervical histology since at least 1997. In Iceland and Sweden, histology registries have been established since 1985 and 1990, respectively. Mexico established national surveillance of high grade CIN lesions detected in their screening program in 2004. Some provinces in Canada have enabled the comprehensive collection of histopathology data as part of their cervical screening program, but implementation varies by province. In areas with established screening but no or limited screening registries, sentinel surveillance may be an appropriate approach, similar to the population-based monitoring model used in selected U.S. states through the cancer registries or established Emerging Infections Program network [20].

Monitoring will be even more challenging in settings that lack organized cervical screening [57–59]. Some countries are directing their efforts towards strengthening or implementing cervical cancer screening programs that would allow for a coordinated approach with vaccine implementation and monitoring. If cervical cancer screening is initiated at the same time as vaccine introduction, it may be difficult to interpret the relative impact of screening versus vaccination on changes in disease incidence because a pre-vaccine baseline was not established. However, since reduction of high grade cervical lesions and cancers is the ultimate goal, distinguishing the impact of a new screening program versus vaccination program may be less important.

In resource-limited settings, researchers face other unique challenges in monitoring high grade cervical lesions. Where cervical cancer screening targets an older cohort of women (over 35 years) with few lifetime screenings, a longer period of monitoring may be required to see vaccine impact on high grade lesions. Other settings use alternative screening, such as visual inspection with acetic acid (VIA) and “see-and-treat” programs [68,69]. In these programs, suspicious lesions are often diagnosed clinically and treated at the time of screening without collecting a biopsy sample. In jurisdictions where screening is prohibitively difficult, vaccination may provide an opportunity for other alternative screening methods, such as primary screening with HPV testing [46]. Such screening algorithms would still allow for impact monitoring of high grade lesions, though interpretation of results will need to take into account changes in screening practices.

Because high grade lesions are caused by various HPV types, examination of HPV type distribution in these lesions can contribute to assessing vaccine impact. With this in mind, the Nordic countries are using a central laboratory to test pathology samples from the pathology databank for 14 HPV types [40]. The Emerging Infections Program network in the U.S. will monitor HPV genotype trends in CIN 2/3 and AIS in 5 sites [20]. Periodic monitoring or sentinel surveillance models may be the best approach for countries able to monitor this outcome. In areas unable to monitor type-specific cervical lesions, monitoring the general outcome of reduced cervical lesions, abnormal Pap test results, or associated procedures may provide sufficient impact monitoring data.

### 4.4. Invasive cervical cancer

The most important potential benefit of HPV vaccine is to reduce the incidence of invasive cervical cancer. Due to the natural history of cervical carcinogenesis, decreased incidence is not expected until vaccinated cohorts (usually young adolescents) reach the age when cervical cancer is typically diagnosed, generally over 35 years of age [70–72]. Monitoring cervical cancer incidence will be challenging in areas without high-quality population-based cancer registries. Such registries require consistent coding of cervical cancer diagnoses in medical records and high levels population coverage in the registry, which can be difficult to achieve. Currently, less than 40% of countries in Latin America and Africa have well-functioning cancer registries [60]. However, the number of registries collecting data solely on cervical cancer may be higher than those monitoring all cancer types. For example, Mexico has established national cervical and breast cancer registries, but does not have a general cancer registry for other cancer sites. The geographic coverage of general cancer and cervical cancer registries can differ, and cervical cancer registries could be designed to be more limited geographically if needed. Since the most desired outcome of vaccination is prevention of cervical cancer, establishing or improving cervical cancer registries, even if more limited in scope, should be a high priority. Any changes made to registries must be taken into account when interpreting the affected cancer monitoring data.

HPV-typing of invasive cervical cancer specimens may be another component of HPV vaccine monitoring to establish any decrease in vaccine-targeted genotypes. For example, Australia has proposed HPV typing of all cases of cervical cancer. Though they are
able to consider this option because of their infrastructure, resource allocation, and relatively low incidence of invasive cervical cancer in Australia, considerable effort will still be required to establish systems with adequate quality assurance, suitably prepared and typed specimens, and central notification of typing results to cancer registries. In other settings, evaluations in special populations or specific regions may be more feasible. In the U.S., for example, HPV typing will be done on cervical cancers in selected population-based geographic sites [20]. Where resources are limited, it may be worthwhile to prioritize HPV typing of cancers in younger women because cervical cancers in women under 50 years of age are typically associated with HPV types 16 and 18 [61,62], and focusing on this group would allow for earlier impact data as these women are closer to the recommended age for vaccination.

4.5. Other HPV-associated cancers and precancers

Though HPV vaccines are primarily intended to prevent cervical cancers, there is also great potential for preventing other cancers in women and men [6]. However, the non-cervical HPV-associated cancers (vulvar, vaginal, anal, penile, and oropharyngeal) may be challenging to monitor. HPV is associated with varying proportions of each of these cancers, ranging from 35% of oropharyngeal cancers to 90% of anal cancers [63,64]. For all anatomic sites, most non-cervical cancers are associated with HPV types 16 and 18 [65]. The potentially precancerous outcomes for these cancers, such as vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VAIN), could serve as more proximal endpoints, although they can be difficult to evaluate since they are only sometimes captured in routine health care data sets.

Cancer registries are the most obvious system to use for monitoring HPV-associated cancers. For jurisdictions with general cancer registries that record all types of cancer, surveillance of HPV-associated cancers may not require much additional work. Capturing high grade lesions for these anatomic sites in the cancer registries may also be possible, similar to high grade cervical lesions that are recorded in cancer registries. International comparisons will, however, require a consensus agreement on which specific histology and anatomic site codes to include, especially when considering oropharyngeal cancers. Efforts to improve reporting may be needed where cancer registries do not include these selected cancer diagnoses. In areas without an established cancer registry, monitoring these non-cervical cancers may be impossible or impractical, though there may be time to develop new or limited registries, since reduced cancer incidence is not expected for some years. Similar to cervical cancer, HPV genotyping of representative samples of other cancer specimens pre- and post-vaccination may add to the assessment of vaccine impact on these cancers. The U.S., for example, has undertaken a pilot study of HPV genotyping these cancers diagnosed prior to 2005 in 5 state cancer registries [20].

4.6. Anogenital warts

Since HPV types 6 and 11 cause approximately 90% of genital warts and the time from HPV exposure to development of genital warts is brief (2–3 months) [66], reduced incidence of anogenital warts may be one of the earliest indicators of quadrivalent HPV vaccine impact on disease [67]. Though no laboratory test is required, the burden of anogenital warts prior to vaccine implementation is unknown, as most countries do not routinely conduct anogenital wart surveillance. An exception is the UK, which has anogenital warts data with differentiation of first and repeat episodes from all warts data with differentiation of first and repeat episodes from all sexually transmitted infection clinics in their jurisdiction [68]. Due to the lack of population-level surveillance infrastructure in other settings, opportunistic clinic-based monitoring or use of administrative health care databases may be a more feasible option. In the U.S., a surveillance network of 40 sexually transmitted disease (STD) clinics in 12 geographic areas have been collaborating since 2007 to monitor the prevalence and incidence of genital warts [20]. Genital warts surveillance in Canada using hospital and physician billing databases has been reported [69,70]. Australia has published early efforts to monitor the incidence of anogenital warts through a network of sexual health clinics; they found a rapid and notable reduction in the incidence of genital warts in women as well as some reduction in heterosexual men after HPV vaccine program implementation [71].

4.7. Recurrent respiratory papillomatosis

Juvenile-onset recurrent respiratory papillomatosis (JORRP) is due to HPV 6 or 11 infection acquired through vertical transmission at or before birth [72], and typically occurs in vaginally delivered first-born infants with teenage mothers [73]. Adult-onset RRP typically occurs in young males in their 20s to 30s [67] and is acquired through oral-genital transmission of HPV 6 and 11. In areas where the quadrivalent vaccine is used, monitoring the impact of HPV vaccination on RRP may be even more challenging than the impact on anogenital warts because RRP is rare, and there is a longer interval from immunization to development of this outcome [74–76]. Among other challenges, there are few countries with RRP surveillance or baseline data to use as a benchmark for monitoring, and there are no distinct International Classification of Diseases Codes for RRP, which makes administrative data difficult to use. Canada has established [77], and Europe and Australia are considering establishing, an RRP register or dedicated surveillance system to facilitate prospective and comprehensive surveillance [78,79]. Otherwise, special studies may be needed to monitor HPV vaccine impact on RRP.

5. Discussion

Monitoring HPV vaccine impact on biologic outcomes is a complex and challenging task. However, it can also play an important role in documenting the benefit of vaccination, monitoring the progress of vaccination programs, and providing data to inform vaccination and disease prevention policies. Comprehensively monitoring vaccine impact at the population level requires a well-established surveillance infrastructure and sustained resources, and therefore may not be feasible in many settings. Sentinel studies are often a useful and appropriate alternative, although still logistically difficult and prohibitively costly in some areas. Some jurisdictions are seeking guidance on minimal impact monitoring priorities. Where biologic impact monitoring is not possible, vaccine delivery along with monitoring vaccine safety and coverage should be the focus; biologic impact monitoring in nearby or similar populations, such as at the regional level, may provide useful information. Importantly, lack of biologic outcomes monitoring capacity should not delay vaccine introduction [80].

Sustainable financial support for biologic impact monitoring of HPV vaccine will be a special challenge. Many of the activities described in Table 1 are proposed and dependent on secure funding. Some jurisdictions with implementation and monitoring plans have used partners, such as public health organizations or pharmaceutical companies. Some of the monitoring projects in the Nordic countries mentioned above are supported by the vaccine manufacturer as long-term follow-up of clinical trial studies [40]. Although pharmaceutical funding could be used for great public health benefit, it would be ideal for governments to secure independent funding for HPV vaccine monitoring. One strategy successfully used by Scotland included identifying the integral role of monitoring as part of the overall new HPV vaccination program and...
concurrently planning and securing national funding for implementation and monitoring.

Public health authorities can play a vital role in coordinating, standardizing, and providing guidance on setting-appropriate approaches to vaccine monitoring. An objective of the WHO meetings in 2009 was to identify partners and resources for HPV surveillance and monitoring, with primary focus on low- and middle-resource settings [29,81]. One type of partnership that could be useful is collaborative networks between countries. In meetings, higher-resource jurisdictions expressed interest in partnering with lower-resource areas to build capacity and provide technical guidance to facilitate impact monitoring. The Vaccine European New Integrated Collaboration Effort (VENICE) is a network of 28 European countries working to enhance the exchange of information on vaccination; they have completed studies on each country’s available infrastructure that could be used to monitor vaccine impact [82,83].

Some countries have already published results from their vaccine impact monitoring activities [71]. Caution is needed when interpreting and presenting early monitoring results. Monitoring data from women vaccinated in catch-up programs, i.e., women more likely to have been infected with HPV prior to vaccination, will likely underestimate the eventual impact and value of vaccinating HPV-naïve women in whom the vaccine has higher efficacy [2,4]. Monitoring results may also be confounded by a variety of issues, such as dynamic changes in vaccination, screening, and registries, as mentioned earlier. Though there may be limitations to early monitoring results, study findings should be disseminated in a timely manner to effectively improve vaccination and monitoring programs.

A variety of approaches are planned or underway for monitoring the impact of HPV vaccine on biologic outcomes, a task that is complex and presents several unique challenges. Where monitoring has been initiated, key stakeholders recognize that mistakes will be made and lessons learned. This knowledge will be valuable to share with members of the HPV vaccine community as the challenges of evaluating HPV vaccination programs are addressed elsewhere. To determine the best methods for vaccine impact monitoring in high, medium-, and low-resource settings, a dialogue on vaccine monitoring must be maintained, as HPV vaccine implementation continues around the world.

Acknowledgements

We would like to thank Dr. Eduardo Franco and Dr. Elizabeth Unger for sharing their presentations from the CDC-sponsored satellite symposium at the 2009 IPV conference. Charlene Wong completed this project during her one-year fellowship The CDC Experience, a public/private partnership supported by a grant to the CDC Foundation from External Medical Affairs, Pfizer Inc.

References


