Monitoring HPV vaccination

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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 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].
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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