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Monitoring the impact of HPV vaccine in males—Considerations and challenges

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ABSTRACT

In this article, we examine the issues involved if national or sub-national programs are considering extending post HPV vaccine introduction monitoring to include males. Vaccination programs are now being extended to include males in some countries, in order to improve population level HPV infection control and to directly prevent HPV-related disease in males such as anogenital warts and anal cancers. Coverage and adverse events surveillance are essential components of post-vaccination monitoring. Monitoring the impact of vaccination on HPV infection and disease in men raises some similar challenges to monitoring in females, such as the long time frame until cancer outcomes, and also different ones given that genital specimens suitable for monitoring HPV prevalence are not routinely collected for other diagnostic or screening purposes in males. Thus, dedicated surveillance strategies must be designed; the framework of these may be country-specific, dependent upon the male population that is offered vaccination, the health care infrastructure and existing models of disease surveillance such as STI networks. The primary objective of any male HPV surveillance program will be to document changes in the prevalence of HPV infection and disease due to vaccine targeted HPV types occurring post vaccination. The full spectrum of outcomes to be considered for inclusion in any surveillance plan includes HPV prevalence monitoring, anogenital warts, potentially pre-cancerous lesions such as anal squamous intraepithelial lesions (SIL), and cancers. Ideally, a combination of short term and long term outcome measures would be included. Surveillance over time in specific targeted populations of men who have sex with men and HIV-infected men (populations at high risk for HPV infection and associated disease) could be an efficient use of resources to demonstrate impact.

1. Introduction

Worldwide human papillomaviruses (HPV) cause multiple cancers and anogenital warts in men and women. By far cervical cancer contributes the largest number of cases to the global burden of HPV-related cancers annually. The main focus of global vaccine programs has been prevention of cervical cancer, through prevention of oncogenic HPV infection, the necessary cause of squamous and glandular cervical carcinomas [1,2]. Currently many countries have two prophylactic HPV vaccines licensed (a bivalent and a quadrivalent vaccine) that prevent infection with, and thus disease due to, HPV16 and 18, the two oncogenic types that cause most cancers [3,4]. In 2014, the US FDA licensed a 9-valent HPV vaccine (Gardasil 9) with expanded coverage against five additional HPV types that cause cervical cancer. The 9-valent vaccine has the potential to prevent up to 90% of cervical cancers worldwide [5]. If broadly disseminated, the bivalent and quadrivalent vaccines could potentially prevent over two-thirds of cervical cancer cases globally [4] and the majority of HPV-related vulvar, vaginal, and anal cancers in women.

With the growing recognition that HPV causes some cancers in men (i.e., anal, oropharyngeal, oral, and penile cancers) there has been increased interest in the potential to prevent other cancers in

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addition to cervical cancer in both men and women through HPV vaccination [6]. The quadrivalent vaccine has demonstrated efficacy in males and is licensed for use in males, as is the 9-valent vaccine. [7] Immunogenicity of the 9-valent vaccine in males was shown to be non-inferior to that in same age females, providing immunobridging to the female efficacy trial in women aged 16–26 years. [7–9]. Some public HPV vaccine programs are now including males, both to increase prevention of HPV infection in the population through herd immunity and to provide a direct benefit to males in prevention of HPV-related diseases and cancers of men [7,10]. These countries include Austria (recommended since 2011 but not funded until 2014) [11], Australia (commenced 2013) [12], the US (commenced 2011) [13], and parts of Canada (Alberta, Nova Scotia, British Columbia and Prince Edward Island) [14].

Worldwide, over 500,000 women develop cervical cancer yearly, and approximately 40,000 HPV related cancers occur in men, causing considerable personal and public health impact [15,16]. At present, there are no recommended screening programs for HPV-related cancers in men [17]. A particularly high risk population are men who have sex with men (MSM) who have a significantly higher incidence of anal and other cancers than other men or women [12,18,19]. Both men and women with HIV infection and other forms of immunosuppression are also at increased risk of HPV–related cancers [20]. Anogenital warts, which are caused by HPV 6 and 11 and prevented by the quadrivalent HPV and the 9-valent HPV vaccines, are a significant burden in both men and women. A systematic review of 32 studies found that the annual incidence of anogenital warts ranged from 160 to 289 per 100,000 [21].

Especially with HPV vaccination programs now being extended to include males in some countries, there is a need to define best practices for monitoring of HPV vaccine programs in males. Monitoring impact in males may be useful even in female only vaccination program settings, in order to measure the impact on males obtained through herd protection. As with any vaccination program, monitoring coverage and adverse events is the foundation of an HPV vaccine program for males. Measuring HPV vaccine effectiveness in females and males is challenging because of the variety of factors that need consideration, including different policies (vaccine recommendations, target ages), health system outcomes (uptake, series completion) and biologic outcomes (infection, warts, precancer, cancers.) In addition, depending on the selected biological outcomes, the time frames to detect impact can range from months to decades [22]. Because of its relative complexity and costs, vaccine effectiveness monitoring through HPV surveillance is not seen as an essential component of an HPV vaccination program by the World Health Organization [23]. Instead, jurisdictions are encouraged to rely on comprehensive post-vaccination surveillance systems in settings where infrastructure and resources allow this [23]. However, despite the challenges, many developed countries are considering methods to monitor impact in both females and males to demonstrate program effectiveness.

To date, aside from anogenital warts, monitoring for HPV vaccine impact has focused largely on women. In some settings, cervical screening programs have provided a means to monitor screen-detected cervical lesions and provide cervical samples for HPV testing and/or pathology to monitor HPV vaccine impact in women [24–28]. In men, this surveillance cannot generally be integrated into established routine screening programs as there are no recommendations for HPV-associated cancer screening for males. Although there is much interest in targeted approaches to screen men (and women) at high risk of anal cancer, the methods to use, ages to target, optimal treatments and effectiveness of screening to reduce cancer have not been defined [12].

We outline the objectives of male HPV vaccine effectiveness monitoring, identify the key challenges to be addressed and consider possible options for such surveillance programs.

2. Objectives of male HPV surveillance

The primary objective of any male HPV surveillance program will be to document changes in the prevalence of HPV infection and disease in males due to vaccine targeted HPV types occurring post vaccination, paralleling objectives developed for female surveillance internationally [22,24,26,29–31]. A secondary objective may be to investigate the additional impact of male vaccination on female HPV infection and disease. Information on vaccine impact can support vaccine programs and their sustainability. Dependent upon the setting and population targeted for vaccination, these changes may be entirely new (if a vaccine program targets both sexes from the outset or targets only men who have sex with men) or may build upon declines already achieved through herd protection following female only vaccine programs established prior to gender neutral vaccination.

Options for vaccine impact monitoring in males include HPV type surveillance in clinician or self-collected specimens, anogenital warts, precancer, and cancer surveillance. Within an overarching HPV vaccine impact monitoring program, different endpoints can be used to evaluate short, medium and long-term HPV-related health outcomes of interest. Table 1 presents different endpoints with reference to existing HPV surveillance programs for females, how they could be adapted for monitoring in males, and particular challenges in their assessment.

3. Challenges for monitoring HPV vaccine impact in males

Cancer, anogenital warts and recurrent respiratory papillomatosis surveillance can be conducted equally well in male populations because their diagnosis and reporting in cancer registries and in clinical records is similar for males and females (Table 1). Anogenital wart surveillance has already demonstrated a reduction in incidence in heterosexual males following female only HPV vaccination programs in some countries, reflecting herd protection through reduced transmission from females to male sexual partners [32–34]. The extent of disease reduction in males due to herd protection is female coverage dependent [34]. This will make differentiating the impact of male vaccination either introduced concurrently or as an incremental strategy challenging, particularly if a move from female only to gender neutral vaccination programs facilitates an overall increase in coverage in both sexes. Anogenital wart surveillance in MSM may be especially valuable as a means of relatively rapidly monitoring the impact of male vaccination programs, given that to date female vaccination programs have not convincingly demonstrated any herd immunity impact in this population [32]. However vaccine coverage achieved among MSM might differ from that achieved in other men.

Surveillance approaches for sexually transmitted infections (STIs) in women include: population based screening using large population based surveys; venue based screening at STI clinics; opportunistic testing at laboratories of specimens collected for another purpose; and, targeted screening of priority populations. While this has offered opportunities for HPV surveillance in women, for men HPV surveillance may pose new challenges as there are not routine clinical screening programs for HPV or HPV-related cancers in men. HPV type prevalence assessments in males will rely on new or structured efforts that collect biological specimens. Surveys in which biomedical specimens from are collected could include self-collected or provider-collected specimens for HPV testing of males. For example, the National Health and Nutrition