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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.

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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

Table 1
Outcomes for HPV monitoring: existing female strategies, possible male strategies and challenges.

HPV Outcome	Existing female methods	Male options	Challenges (M=males, F=females)*
Genital HPV infection (vaccine targeted types and non-targeted types)	a) HPV typing of liquid based samples obtained from cervical screening [13,56,57] b) HPV typing of self collected vaginal samples [37,58] c) HPV typing of urine samples from i) residual specimens from Chlamydia screening progams [36] ii) purpose collected specimens [59] d) HPV typing from oral specimen (e.g. rinse)	a) HPV typing of samples collected from external genitalia (glans, shaft, scrotum), self collected or clinician collected [60] b) HPV typing of anal swabs [61] c) HPV typing from oral specimen (e.g. rinse) [62] d) HPV typing of urine samples from i) residual specimens from Chlamydia screening progams [36] ii) purpose collected specimens [41]	1) Representativeness of study population (F+M, a,b,c,d) 2) Ensuring consistency of HPV typing methods over time so that results are comparable (F+M, a,b,c,d) 3) Availability of vaccination status and sexual history data from participants (F+M, a,b,c,d) 4) Distinguishing deposition from infection (F+M,a,b,c,d) 4) Standard collection method not established (M, a, b) 5) Urine has low sensitivity in males to detect the presence of genital HPV infection (M,d) and is therefore not a suitable specimen type for routine monitoring in males
Genital intraepithelial neoplasia	a) Trend analysis of CIN2+ in cervical screening registry data i) existing registers [63–65] ii) purpose built registers [66] b) Trend analysis of vaginal/vulval intraepithelial neoplasia in Nordic registers [22,67] c) Vaccine effectiveness estimation against CIN from registry based data linkage studies in vaccinated populations [28,68-70] d) HPV typing of CIN specimens to determine proportion due to vaccine preventable types over time [71]	a) Monitor rates of AIN diagnoses in populations using hospitalisation data, health insurance databases or population based health registry data (Nordic countries only) Because PIN is very rare and not screened for, monitoring rates (even where possible) is unlikely to provide useful monitoring data. b) Use data collected from trials of AIN screening in MSM in pre vs post vaccine periods to monitor AIN attributable to vaccine types over time	1) Ecological nature of register data/time trends in populations of abnormalities. Can be impacted by trends in diagnosis, participation, sexual activity etc (F a,b,c +M a) 2) Incomplete/inaccurate data linkage (F,c) 3) Lack of population based testing for AIN/PIN means no register data or stable diagnostic rates in most countries (M, a) 4) Monitoring rates of AIN due to HPV16/18 in MSM over time requires research studies being undertaken of screening at appropriate time points as HPV typing and screening is not routine clnical practice (M,b)
Genital warts	a) Trend analysis of genital warts/anogenital warts diagnoses in sentinel clinics [32] [72] b) Trend analysis of anogenital warts diagnosed in general practice [73] c) Trend analysis of diagnoses and treatment in insurance populations [74,75] d) Trend analysis of national hospitalisation data [33] e) Trend analysis of national health registry data (Nordic [76,77]) f) Vaccine effectiveness estimation against genital warts from registry based data linkage studies in vaccinated populations (Nordic) [78]	Female surveillance methods also applicable to males	1) Ecological nature of time trends of genital warts in populations. Can be impacted by trends in treatment modalities, access to health care services, sexual activity etc (F+M, a,b,c,d, e,f) 2) Representativeness of study population (F+M,a,b,c,d) 3) Need to obtain information about sexual orientation in order to monitor in MSM populations (M,a,b,c,d,e,f)
Recurrent respiratory papillomatosis	a) Monitoring hospitalisations over time [79] b) Register based RRP surveillance (Canada) c) Rare childhood diseases surveillance through ENT surgeons and paediatricians [80] d) Monitoring of HPV types in RRP lesions	Female surveillance methods (monitoring of incident cases of RRP) also applicable to males	1) Rare disease (F+M,a,b,c,d) 2) Ecological nature of time trends (F+M,a,b,c, d) 3) Usually no RRP surveillance/register established prior to vaccination programs to provide baseline data (F+M,b,c) 4) HPV typing of RRP lesions not routine in many countries (F+M,d)
Cancer	a) Use of cancer registries to monitor rates of cervical, vagnial, vulval, anal and HPV-associated head and neck cancers over time [22]	Female surveillance methods (analysis of cancer incidence data over time) also applicable to males. Add monitoring of penile cancers.	1) Data quality. In many countries cancer registries are incomplete, of poor quality or do not exist. (F+M,a) 2) Long time frame between HPV vaccination and impact on cancers. (M > F,a) 3) Consider systems to record vaccination status against cancers - e.g. for verifying and recording vaccination status on cancer registers. (F+M,a) 4) HPV typing of cancers is not routine- consider development of methods to record on registers. (F+M,a) 5) May be changes over time in which cancers are classified as HPV-related so care is needed in applying consistent inclusion critreria. Site-specific coding for head and neck cancers is incomplete in some registers. (F+M,a)
Cancer mortality	a) Use of cancer registries and cause of death registers to monitor rates of cervical, vagnial, vulval, anal and HPV-associated head and neck cancers over time [22].	Female surveillance methods (analysis of cause of death data over time) also applicable to males. Add monitoring of mortaliy from penile cancers.	1) Data quality. In many countries cause of death registries are incomplete, of poor quality or do not exist. (F+M,a) 2) Long time frame between HPV vaccination and death from cancers. (M > F,a)

* Letters in brackets refer to the subsections in the adjacent male and female surveillance columns.

Surveys (NHANES) in the US [35] and the National Surveys of Sexual Attitudes and Lifestyles (NATSAL) in the UK [36] both provide an opportunity to collect clinical samples appropriate for HPV testing from participants. Australia does not currently have a similar population survey infrastructure; therefore, HPV surveillance in Australia is dependent in the short term at least on dedicated HPV studies where specimens are obtained from clinic populations or through self-collected sampling from participants enrolled through in special studies, as has been achieved for HPV testing in young women [37]. Methods to confirm vaccination status will need setting specific consideration dependent upon the availability of vaccination registers, clinical or patient held records of vaccination. STI clinics and clinics that serve youth or MSM may be appropriate sites to obtain genital specimens.

4. Site and specimen collection for HPV detection in males

HPV infection prevalence differs significantly by anatomic site; infection prevalence is high at the external genital skin in both MSW and MSM (and is higher at the anus in MSM than in MSW or in women) and lowest at the oral epithelium (e.g., HPV 16 prevalence in MSW is 6% at external genital skin, 2% at anal canal, and 0.6% at oral epithelium [38]). In pre-licensure efficacy trials, the quadrivalent HPV vaccine was shown to provide protection against HPV infection and related lesions at the external genital skin and anal canal [39,40]. Given these data, and the relatively high prevalence of infection at these anatomic sites, the external genital skin and anal canal are appropriate to consider sampling in post-vaccine surveillance activities among males.

Male external genital specimens suitable for HPV testing are not routinely collected for other health purposes. Unfortunately, the readily obtainable urine specimen has been shown repeatedly to provide a poor reflection of HPV status in males [41–43]. Direct sampling of the external genital skin and anal canal are required to accurately estimate HPV infection in men. Several different methods of sampling the external genital skin have been investigated; sampling with pre-wetted Dacron swab alone or following mild abrasion of the genital skin, and dry swab sampling of the external genital skin. In addition, provider sampling and self-sampling using these methods have been explored. The collective evidence indicates that abrasive methods are not required in order to collect a specimen adequate for HPV detection from males [44–46]. However obtaining suitable specimens still relies on adequate technique, which may be facilitated by self-collection (allowing firmer swabbing) rather than clinician collection. Men may find self -collection more acceptable and less embarrassing [44,47]. A recent study found self-collection using dry swabs to be more acceptable to men, quicker to use and less painful, but just as effective as an emery-wet swab technique for HPV detection [44] and is being used in some monitoring programs [48]. Anal canal self sampling has been found to be acceptable to MSM in several studies and may be a useful sample type for monitoring given the high prevalence of HPV at this site in this population [49–51]. For surveillance purposes, whichever sampling and typing methods are used, the methods should be sufficiently sensitive, consistent over time and ideally consistent with other published studies to facilitate comparisons. A variety of issues can be considered for choice of HPV typing methods for males [52]. A pilot surveillance phase would be helpful to establish that the proposed methods are feasible, produce valid results, and are acceptable to participants, so that they can be consistently used for accurate surveillance over time. A pilot phase can also determine baseline prevalence to inform sample size estimates for the particular population. Comprehensive sampling of multiple sites with one swab (e.g. shaft of penis, tip, coronal sulcus, scrotum $\pm$ anus) may better reflect the overall HPV burden at the external genitals but may not be needed for monitoring vaccine impact as long as a consistent method over time is used [43].

5. Assessing reduction in clinical disease

HPV-related diseases such as the pre-cancers and anogenital warts, are not routinely reportable conditions in most countries (except in the case of cervical pre-cancers reportable to screening registers in those countries with registers integrated as part of the screening program). [22] Furthermore, with an absence of screening programs for HPV-associated neoplasia to detect pre-cancers in males, measuring any reduction in these lesions will be challenging in most settings. Also, where diagnosis of these lesions occurs in routine practice, these data are not systematically collected in registers or tested for HPV in most settings. Furthermore, any changes in screening practices for anal cancer would impact trends in anal pre-cancers lesions (as would changes in cervical screening programs impact upon apparent cervical pre-cancer lesion prevalence for women). Following introduction of vaccination programs, monitoring of HPV types in lesions in high risk populations, such as MSM and HIV-infected men, may be a suitable way to obtain indicators of vaccine impact. This type of monitoring may best be performed as repeated research studies over years as a part of formal anal screening evaluation studies [18] or targeted vaccination evaluations rather than using any routine population based health data sources. Care needs to be taken in ascribing HPV types to lesions during such focal surveillance studies in MSM populations, given existing evidence that HPV detected by anal swabs are frequently of multiple types and have poor concordance with HPV types that cause focal lesions as identified by analysis using laser- capture microdissection [53].

HPV related cancers, such as anal, penile, oropharyngeal cancers, are routinely reported in most countries as a part of cancer registries. Optimally, HPV related cancer rates in males will be monitored through such cancer registries. However, because non-cervical HPV-related cancers have an older median age of onset, the impact of HPV vaccination on cancer incidence among males will take comparatively longer to observe [54].

6. Design considerations for male HPV prevalence surveillance

Approaches to male HPV surveillance will depend upon the characteristics of the HPV vaccination program (i.e. target age group, universal approach from commencement or female vaccination first, years since commencement, uptake) and infrastructure for supporting collection of specimens from males. In many places no HPV prevalence data in young males will exist prior to male vaccination commencing and this may be a particular challenge if female vaccination has already been underway for some years (for example, in Australia and the US). Thus, collection of suitable specimens to establish baseline HPV prevalence in males, either pre HPV vaccine or following HPV vaccination of females, would be optimal. For example in Australia, the male vaccination program commenced in 2013 (following female vaccination since 2007). A catch up program was undertaken for boys up to age 15 years in 2013–2014. In order to compare pre and post male vaccination HPV prevalence in young males, a study was designed to commence as soon as possible, given that males aged 17–19 years would be unvaccinated in 2014–2016 (HPV prevalence reflecting impact of female vaccination only) but belong to vaccinated cohorts in 2017–2018 (personal communication, Marcus Chen). Australia is also currently piloting a predominantly clinic based surveillance system, supplemented with online recruitment

activities, for ongoing HPV prevalence monitoring. (http://www.health.gov.au/internet/main/publishing.nsf/Content/ohp-HPV.htm). Resulting HPV prevalence estimates will in turn help determine sample sizes necessary for ongoing monitoring of HPV prevalence post vaccination. For example, a five continent study of HPV prevalence in 16–24 year old males with 1–5 lifetime female sex partners found HPV 6/11/16 or 18 in 8.8%, 16 or 18 in 5.6% and HPV16 in just 3.8%. [45]. A baseline prevalence of 5% or lower would require a large sample size to detect a significant decline in HPV16/18 or 16 alone post vaccination (e.g., in a simple before-after design with equal sample sizes, 1077 would be required in each group to detect a fall of 50% (with 80% power, two-sided test)). If vaccine targeted HPV prevalence is relatively low, due to broad dissemination of vaccine to females, larger sample sizes may be needed and/or consideration given to recruiting a sentinel surveillance population that is relatively high-risk for HPV exposure, such as from an STI clinic setting [47]. Focused efforts in specific high-risk populations such as MSM, HIV-infected, or those attending STI clinics may be optimal in many settings for this reason [55].

7. Conclusion

Monitoring HPV vaccine impact in males will inform policy and programs worldwide by evaluating the benefits of vaccination through reduction of infection, disease or cancer in men. There were be different opportunities and challenges depending on the outcome and setting. The spectrum of outcomes to be considered for inclusion in any monitoring plan includes HPV prevalence, anogenital warts, and cancers. Specific consideration is needed to assess opportunities to monitor pre-cancer lesions such as AIN. Ideally a combination of short term and long term outcome measures would be included. Surveillance in specific targeted populations of MSM and HIV-infected men could be an efficient use of resources to demonstrate impact.

8. Conflict of interest statement

JMLB's institution has been a recipient of investigator initiated grant funding from bioCSL/Merck to support epidemiological HPV research but she has never received any personal financial benefits. ARG is a member of Merck & CO, Inc. advisory boards and her institution receives grant funding for investigator initiated studies. LEM, EFD and GSO have no conflicts of interest.

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