REVIEW

How to best measure the effectiveness of male human papillomavirus vaccine programmes?

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Abstract

In many countries now, vaccination of young adolescent girls with prophylactic human papillomavirus (HPV) vaccines has been rolled out as a public health programme. In countries where coverage has been high, this has led to dramatic reductions in cervical high-grade precancerous lesions, as well as genital warts. A reduction in circulating vaccine-related HPV types has also been demonstrated. With the introduction of gender-neutral approaches incorporating universal vaccination of pre-adolescent boys in some countries, implementation of post-vaccine monitoring will be critical to evaluate the incremental impact of male vaccination. In contrast to cervical screening programmes, population-wide screening for HPV infection or related disease in males is not recommended; hence real-time monitoring of HPV vaccine effectiveness in males will require dedicated surveillance strategies. Monitoring the prevalence of circulating genital HPV types using a sentinel surveillance model could offer a good surrogate marker of early vaccine effectiveness in males. However, such an approach requires careful consideration of the most appropriate anatomical sites from which to collect specimens, the best sampling methods and the most sensitive assays to use. Additionally, in assessing an accurate measure of the impact of HPV vaccination in the male population, the effect of herd protection will need to be assessed, as most male programmes will commence in the setting of established female programmes. This poses an interesting epidemiological challenge.

Keywords: Genoprevalence, human papillomavirus, males, sentinel surveillance, vaccination programmes, vaccine effectiveness
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Introduction

The implementation of prophylactic vaccines against human papillomavirus (HPV) is arguably one of the most significant developments in cancer prevention of our time. HPV is largely a sexually transmitted infection, with disease manifestations in both genders. In addition to the well-known relationship between HPV and cervical disease, anogenital HPVs are the causative agent of genital warts, a proportion of anal, penile, vaginal and vulvar cancers, as well as some oropharyngeal cancers [1]. With proven efficacy in preventing male disease [2,3], licensure of HPV vaccines for males has followed that for females, with many countries now funding or recommending universal vaccination of pre-adolescent boys.

Male vaccination has not been without controversy however, with some arguing that the incremental benefit of adding males to female vaccination campaigns does not justify the cost [4]. To inform debate on the benefit of the male programme, it is critical that the effects of male vaccination are properly measured. In this review we discuss the efficacy and safety of HPV vaccines in males and summarize the current status of implementation, as a prelude to considering how best to measure the effectiveness of male HPV vaccination.

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HPV clinical vaccine trials

Prophylactic bivalent (2vHPV) and quadrivalent (4vHPV) HPV vaccines have been shown in phase III clinical vaccine trials to be safe, efficacious and immunogenic in young women 18–26 years of age [5–8], with safety, efficacy and immunogenicity also demonstrated in mature women, up to 45 years of age [9,10]. Moreover the effectiveness of female vaccination in real world settings is not only evident in the translation to significant reductions in vaccine-related HPV infections, but also disease manifestations such as genital warts and cervical intraepithelial neoplasia [11–14]. In addition, where 4vHPV coverage of the target female population has been high, a parallel reduction in genital warts has been observed in heterosexual males: a consequence of herd protection [15]. Surprisingly, decreases in the rates of genital wart diagnoses among vaccine-eligible females and same-aged males has been observed in England following 2vHPV vaccination [16]. Moderate 2vHPV vaccine efficacy against low-risk HPV types, through cross protection or cell-mediated immunity, may help to explain this observation [17].

Although these vaccines were developed to reduce the burden of disease from cervical cancers, the vast majority of which are caused by infection with high-risk HPVs (HPV types 16 and 18 contribute to 70% worldwide), a proportion of other anogenital cancers are also caused by the same HPV types. These include approximately 70% of cancers of the vagina, 43% of vulvar, 50% of penis, 88% of the anus and 13–56% of the base of tongue and oropharynx [1]. As a result, current vaccines have the potential to significantly reduce the burden of HPV-associated diseases in both men and women.

The 4vHPV vaccine has been evaluated in young men aged 16–26 years, in similarly designed phase III clinical trials to those used in females and has been shown to be similarly immunogenic, efficacious and safe, not only in preventing vaccine-related HPV infections, but also genital warts and anal intraepithelial neoplasia [2,3]. In a subgroup analysis of men who have sex with men (MSM), an 89% reduction in genital warts (95% CI 8.8–95.4) and ~75% reduction in high-grade anal lesions (anal intraepithelial neoplasia stage 2/3) (95% CI 65.3–97.9) was reported [2]. Consequently the 4vHPV vaccine was licenced in October 2009 by the US Food and Drug Administration for use in males aged 9–26 years in the USA, with several other countries following thereafter.

A next-generation vaccine, the nonavalent (9vHPV) has recently been reported in phase III trials to be safe, efficacious, immunogenic and non-inferior to the 4vHPV vaccine in young women aged 16–26 years [18]. Preliminary unpublished but presented results of other studies indicate that safety and immunogenicity also extend to men aged 16–26 years and girls and boys aged 9–15 years (EUROGIN 2015 Congress, abstracts 0C 6-6 Castellsague et al. and 0C 6-3 Olsson et al., respectively). Based on these findings, licensure occurred in the USA by the US Food and Drug Administration in December 2014 [19] and by Health Canada in February 2015 [20], with the US Advisory Committee on Immunization Practices voting in February 2015 to include the 9vHPV vaccine in recommended routine vaccination for 11- to 12-year-old girls and boys [21]. We await the pricing relative to the 4vHPV vaccine.

Current male vaccination implementation in public health programmes

To date, very few countries have implemented male 4vHPV vaccination as part of national public health programmes. Implementation of male 4vHPV vaccination into public health programmes followed that of the female programme in the USA, with endorsement by the US Advisory Committee on Immunization Practices in October 2011 for routine vaccination of males aged 11–12 years, in a clinic-based delivery system [22] with some state and federal funding available. Coverage for boys stands at approximately half the rate for girls according to the most recent data (13.9% for males aged 13–17 years in 2013, 37.6% for females [23]). In Australia, implementation of male vaccination occurred in December 2012, with the Australian Technical Advisory Group on Immunisation (ATAGI) endorsing an ongoing school-based government-funded programme commencing in February 2013. This programme targets 12- to 13-year-old boys and included a 2-year catch-up for 14- to 15-year-olds to the end of 2014. Although population-based estimates are not yet available, preliminary data suggest coverage of the school-based male vaccination programme is only slightly lower than that achieved to date in the female programme [24]. In 2012, Austria announced that it planned to introduce a national publicly funded HPV vaccination programme covering both males and females from the outset [25]. Other countries are beginning to follow suit with two of 13 provinces in Canada currently offering publicly funded campaigns [25] and ongoing debate in the UK about whether to extend publicly funded vaccination to males [26].

How best to measure HPV vaccine effectiveness in males?

Vaccine safety and effectiveness are key to any successful immunization programme. Although pre-clinical end-point efficacy

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