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HPV vaccination in boys and men

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Human papillomaviruses are DNA viruses that infect skin or mucosal cells. In the genital tract HPV (especially types 6 and 11) cause genital warts, the commonest viral sexually transmitted disease. At least 13 of the more than 100 known HPV genotypes are oncogenic “high-risk” genotypes. The 2 most common of these (genotypes 16 and 18) cause approximately 70% of all cervical cancers. Oncogenic HPVs particularly HPV 16 are associated with other anogenital cancers, anus, vagina, vulva and penis, and cancers of the head and neck and current estimates are that 5.2% of all cancers are HPV associated. In industrialised countries cervical cancer is controlled by secondary intervention other HPV associated malignancies are increasing in incidence and the burden of HPV associated disease in men is now comparable to that in women in economically developed countries. Randomized control trials with the quadrivalent HPV VLP vaccine demonstrate robust antibody responses and high efficacy against genital warts anal precancers in men. Few countries have recommended male vaccination on the basis that this is not cost effective. However gender-neutral vaccination has been recommended in the USA, Canada, Austria, and Australia. Careful cost effective modeling has preceded these decisions showing that when the burden of disease in men is included in the models then, depending upon coverage, vaccine price, and other factors male vaccination can become cost effective.

Introduction

Human papillomaviruses are a large family of small double stranded DNA viruses that infect squamous epithelia (or cells with the potential for squamous maturation) including the skin and the mucosae of the ano-genital tract and upper respiratory tract.¹ More than 100 HPVs have been isolated from clinical biopsies, they are classified by DNA sequence and numbered in the sequence in which they were isolated e.g., HPV 1, HPV 2 etc. About 30–40 HPVs regularly or sporadically infect the genital tract and here they fall into 2 groups. There are low-risk viruses such as HPV 6 and 11 that cause genital warts, the commonest viral sexually transmitted disease with a lifetime risk of acquisition of 10% representing a huge disease burden in men and women. The second group is high-risk HPVs associated with

ano-genital cancer. Infection with one of a subset of mucosal high-risk human papillomaviruses (HPVs), principally 16 and 18, is the cause of almost all cervical cancers in women; it is the major etiological agent in squamous cell carcinoma of the anus, tonsil, and base of the tongue and a significant contributor to squamous cell carcinoma of the vulva, vagina, penis, larynx and head, and neck.² Altogether HPV is estimated to be the causal agent in 5% of all human cancers with HPV16 by far and away the major player.

In economically developed countries the incidence of cervical cancer in women has been significantly reduced as a result of cervical screening programs to detect and then treat high grade cervical intra-epithelial neoplasms (CIN) the obligate precursor to invasive cancer.³ However, the other cancers associated with HPV are not amenable to screening and the incidence of these is rising in both men and women.⁴ More than 90% of cases of anal carcinoma are attributable to HPV infection, mainly HPV 16.⁵ This is a rare cancer but the incidence worldwide is increasing; women have a higher incidence than men in age groups greater than 50⁶ but men dominate the 20–49 y age group and this incidence is rising. Rates of anal cancer are highest in men who have sex with men (MSM) and the incidence in this group is estimated to be equivalent to that of cervical cancer in an unscreened population and is even higher in HIV infected MSM.⁷

Squamous cell cancers of the oral cavity (OCC) and of the oropharynx (OPSCC) are the sixth commonest cancers worldwide with an estimated 400 000 cases per annum and 230 000 deaths.⁸ Heavy tobacco and alcohol use and poor dentition are strong risk factors for both OCC and OPSCC.⁹ The incidence of OCC has declined or stabilized in many parts of the world in the recent past and this coincides with the decline in tobacco use in those localities. In contrast, OPSCC incidence has increased in several countries predominantly in developed countries such as Northern Europe,¹⁰ Australia,¹¹ and the USA.¹² These increases correlate strongly with increase in the proportion of HPV positive, OPSCC over the period from 1980 onwards. The rise is greater, 2–3-fold, in men than women and in contrast to HPV negative cancers, HPV positive OPSCC occur in younger age groups <60 y and are not associated strongly with tobacco or alcohol use but with oral sex.¹³ In the USA incidence of HPV OPSCC is higher in men than women as is the prevalence of oral HPV infection and it is projected that in the US the annual number of HPV-positive OPSCC will surpass that of cervical cancers by the year 2020.¹⁴

There are interesting differences between men and women in the immune response to natural genital HPV infection. HPV infection varies with age in women with the peak prevalence in

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the late teens and twenties declining steadily throughout the subsequent decades,¹⁵ in contrast men acquire infection in the late teens and the prevalence remains constant throughout the subsequent decades.^{16,17} The majority of women $\geq 70\%$ seroconvert after detectable cervical HPV infection with antibody to the major coat protein L1¹⁸ but only $\geq 20\text{--}30\%$ of men do so.¹⁹ Highly effective prophylactic HPV vaccines that target HPV 16 and 18 only or HPV 6, 11, 16, and 18 have been developed and are licensed products globally; these vaccines are highly effective with early evidence of reduction in disease^{20,21} and infection²² in vaccinated women and girls. Despite the poor antibody response in natural infection, men make robust humoral immune responses to VLP vaccines with virtually 100% sero-conversion.²³ Trials with the quadrivalent vaccine Gardasil have shown efficacy against infection and disease in men who have sex with women (MSW)²⁴ and MSM²⁵ preventing 6/11 genital warts and 6/11/16/18 anal intraepithelial neoplasia, respectively.

Men clearly will benefit from HPV vaccination but despite the widespread introduction of national HPV immunization programs for girls and women few countries have recommendations for boys and men. Gender-neutral vaccination is a controversial issue. If the reduction in female cancer is the only public health benefit to be considered then mathematical models²⁶ indicate that male vaccination provides only a small added benefit in the rate of disease reduction since, with a sexually transmitted infection (STI), immunizing one gender at high coverage should with time engender herd immunity and block transmission.²⁷ However as in women, men develop HPV attributable cancers of the anus, the oral cavity and the oropharynx and they have an equivalent burden to women of genital warts. Most health economic models conclude that vaccination of boys is not cost effective when female vaccination coverage is high.²⁸ However, MSM in that scenario receive little benefit from herd protection and remain vulnerable to preventable HPV associated disease. The cost effectiveness case is that gender neutral vaccination is not justified since with time MSW will be protected since they

are the partners of vaccinated women. This scenario seems to be supported with data from Australia where after vaccination the incidence of genital warts in young (<21-y-old) women and MSW, declined by >90% over a 3-y period but no decline occurred in MSM or older, presumably non-vaccinated women.²⁹ In contrast, in Denmark, despite high vaccine coverage and a precipitous decline in genital warts in young women <18 y little decline in warts in men has been detected.³⁰ Gender neutral vaccination has been recommended in some countries notably the USA, Canada, and Australia. Careful cost effective modeling has preceded these decisions showing that when the burden of disease in men is included in the models then, depending upon coverage, vaccine price, and other factors male vaccination can become cost effective.³¹

In developed countries such as those in Western Europe the burden of HPV associated cancers in men is comparable to that in women. Cervical cancer, the dominant cancer in women, can be prevented both by vaccination to prevent infection and screening to treat precancerous lesions but there is no screening for anal cancer and OPSCC, the malignancies increasing in incidence particularly in men.³² Furthermore, compared with HPV negative cancers at these sites HPV associated cancers tend to occur in younger age groups—40 to 60 y—present at later stage with associated mortality and show a very significant morbidity after therapy with impaired quality of life. All men irrespective of sexual orientation have a significant burden of HPV associated disease, this burden is increasing in developed countries but could be substantially reduced if boys were immunized.³³ This would result in true herd immunity with rapid decline in viral load in the population. In this context failure to implement male vaccination looks like a missed public health opportunity.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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