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Review

Human papillomavirus vaccination in men who have sex with men – what will be required by 2020 for the same dramatic changes seen in heterosexuals

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Abstract. This paper addresses the issue of whether men who have sex with men (MSM) will share the spectacular reductions in human papillomavirus (HPV) infection and its associated neoplasia that we are currently witnessing in heterosexuals. The reproductive rate for HPV infection in heterosexuals is not well established, but 70% vaccination coverage in women has resulted in a fall of more than 90% in genital warts and HPV types 16/18 in young women and 80% fall in young men indicating that the critical vaccination threshold has been exceeded for this group. Published data on the three elements of the reproductive rate for HPV infection (i.e. transmission probability per sexual partnership, rate of partner change and duration of infectiousness) suggest they are higher in MSM than heterosexuals. This indicates that the reproductive rate for HPV will be higher in MSM and hence the critical vaccination threshold will also be higher. But while vaccinating 70% of girls protect 70% of sexual partnerships in heterosexuals, vaccinating 70% of boys protect more than 70% of partnerships in MSM. Only 9% (30% by 30%) of sexual partnerships in MSM are not protected with 70% coverage. Therefore vaccinating 70% of boys will protect 91% of sexual partnerships in MSM. However the efficacy of the HPV vaccine is much lower when sexually active MSM are vaccinated rather than boys. We argue that if MSM are to have the same benefit from the HPV vaccine that heterosexuals had, boys and not adult MSM will need to be vaccinated.

Additional keywords: human papillomavirus vaccine, men who have sex with men.

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Introduction

This paper addresses the issue of whether men who have sex with men (MSM) will share the spectacular reductions in human papillomavirus (HPV) infection and its associated neoplasia that we are currently witnessing in heterosexuals. These reductions in heterosexuals have occurred because vaccination polices enabled the 'critical vaccination threshold' to be exceeded and therefore dramatic declines occurred. We will discuss what factors influence the critical vaccination threshold in MSM and what vaccination programs are most likely to exceed this threshold in MSM. Only by exceeding this threshold will MSM achieve equity in HPV health outcomes with heterosexuals.

There is no doubt that HPV causes a significant burden of disease in MSM. Not only are genital and anal warts three- to five-fold more common in MSM than in heterosexuals, but anal cancer is much more common.[1–3] In HIV-negative MSM, the incidence of anal cancer is approximately the same as cervical cancer was before Pap smear screening programs began (i.e. ~10 per 100 000 per person-years), but in MSM with HIV, the incidence may be of the order of ~100 per 100 000.[1] Oropharyngeal cancer has also been reported, albeit not significantly, to be more common in MSM and, worryingly, the proportion of these cancers due to HPV has been rising for some years.[4,5] However, with the right vaccination program in MSM, HPV infection, genital warts and the HPV-associated cancers may largely disappear and much unnecessary human suffering will be avoided; as is the likely scenario in heterosexuals.

Transmission dynamics and critical vaccination threshold

The critical vaccination threshold is the proportion of a population that needs to be vaccinated to prevent the persistence of the infection in that population. It is mostly used for infections, such as measles, to ensure that populations have

sufficient vaccine coverage so that when infectious cases are inevitably introduced into these populations, epidemics do not occur. The concept is equally relevant for HPV infection. This threshold depends on how easily an infection spreads in a population and is higher for infections that are easy to transmit, like measles, and lower for infections that are more difficult to spread, like small pox. The critical vaccination threshold is calculated by subtracting 1/Ro from one. The reproductive rate or Ro of an infection refers to how many secondary infections occur when an infection is first introduced into a susceptible population. The Ro for smallpox is ~3, so the critical vaccination threshold is ~67% (i.e. 1–1/3), but for measles with a Ro of more than 10, more than 90% (i.e. 1–1/10) of the population need to be vaccinated to prevent epidemics.[6] The reproductive rate for sexually transmissible infections is dependent on three factors: (i) the probability of transmission per sexual partnership; (ii) the rate of partner change; and (iii) the duration of infectiousness. Specifically, Ro is the product of these three numbers.

The reproductive rate for HPV infection in heterosexuals is not well established, but can be inferred from what has happened to the incidence of genital warts and HPV infection in heterosexuals following the introduction of the HPV vaccine. For example, genital warts and HPV types 16,18 largely disappeared in Australian-born women within 7 years of the vaccination program commencing in women.[7,8] Genital warts have fallen by more than 90%, and a similar magnitude of fall has been seen for HPV 16,18 in genital samples analysed from women; this change has occurred with ~70% of women having been vaccinated.[7,8] Importantly, declines of ~80% were also seen in genital warts and HPV 16/18 in young heterosexual men who had largely not received the HPV vaccine.[7,9] These dramatic falls are consistent with the vaccination coverage being greater than the critical vaccination threshold for both genital warts (largely HPV 6 or11) and the oncogenic HPV types, 16 and 18. Not surprisingly, little change in genital warts has occurred in MSM attending sexual health services in Australia.[10] Interpretation of all these studies requires caution, given that the detection of HPV in men is less sensitive and more difficult than in women, and different HPV types may have different HPV transmission rates.[3]

Several other countries have also seen large falls in genital warts in women and mostly unvaccinated men, but it has primarily been in countries that have vaccination coverage of at least 50%.[11]

Equity of outcome for MSM

The critical question now is how equity of health outcome from HPV vaccination can be achieved in MSM. It is important to appreciate that the reproductive rate of HPV infection and hence critical vaccination threshold required to prevent persistence of HPV in MSM will be different from heterosexuals because the reproductive rate is different. At least two of the three factors that determine the reproductive rate are higher in MSM. A recent Australian survey found that MSM have a median of 22 lifetime male partners, but women and heterosexual men have only four, and eight respectively.[12,13] The second element that determines the reproductive number is the probability of HPV transmission between partners; and several studies suggest this is higher for MSM. In one study, the ratio of genital warts in heterosexual men and women was ~1:1, but the ratio of anal warts to penile warts in MSM was ~3:1, suggesting that the anal epithelium may be particularly susceptible to infection.[14] This finding is also consistent with another cohort study of young MSM between 16 and 20 years of age, which found that anal HPV infection was much more common than penile infection and estimated that the probability of HPV transmission per partnership from the penis to the anus approached 100%.[3] Based on limited cohort studies, the duration of HPV infection at the anus may also be higher than in the female genital tract on the basis of limited cohort studies.[15]

It is therefore likely that the reproductive rate of HPV infection is higher in MSM, given that all of the three factors that determine the reproductive rate may be higher. And this necessarily raises the fundamental question for health departments; what vaccination coverage is required in MSM to exceed the critical vaccination threshold? It is important to appreciate that a vaccination coverage of 70% in women (or 35% of heterosexual men and women) translates to 70% of sexual partnerships being protected. However, if 70% of boys are vaccinated, the proportion of sexual partnerships in MSM that are protected is greater than 70%. This is because the proportion of the sexually active population vaccinated is double that of heterosexuals (70% vs 35%). But one must also consider that two vaccinated men may have sex together, unlike the scenario where only women are vaccinated and a vaccinated woman only has sex with an unvaccinated man. When these two factors are considered, ~91% (100% minus (30% by 30%)) of random partnerships involving MSM are protected with a vaccine coverage of 70%.[7] So if the vaccination coverage achieved in boys is the same as seen in girls, it is quite possible that this coverage may be sufficient to overcome the higher reproductive rate of HPV infection in MSM. Australia began vaccinating young boys in 2013 and the current vaccination coverage is at least 60%, so that within 5 years' studies looking at genital warts and HPV DNA, young MSM will be able to answer this question.[16]

Only Australia, Austria, Israel the US and four provinces of Canada have adopted vaccination programs for boys as well as girls. In other countries, vaccination of MSM will occur after sexual activity has commenced, which creates a significant problem because there is very rapid acquisition of HPV DNA in young MSM.[3] In the study with the youngest cohort, the incidence of HPV 16 or 18 approached 25% per year in a sample of 200 MSM aged 16–20 years.[3] The high prevalence of existing infection in young MSM explains why the efficacy of the vaccine was reduced in the HPV vaccine study in MSM who were already sexually active.[17] The efficacy of the HPV vaccine was only 59% in the intention-to-treat analysis, but 95% in the per-protocol analysis that excluded approximately one-third of individuals positive at baseline for HPV on either serology or HPV DNA.[17] Opportunistic vaccination of younger MSM is also unlikely to achieve substantial coverage even in countries where it is provided free. Not only are adult vaccination campaigns generally lower than childhood programs, but this vaccine would require a stigmatised group to present as young as possible to receive the vaccine.[18] An additional important issue to consider is that there are no studies of the efficacy of

the vaccine beyond 26 years of age despite considerable continuing HPV risk in those older than 26 years.[15]

Some important changes in sexual practices are occurring in MSM populations that may influence the reproductive rate of HPV infection and hence the critical vaccination threshold required in the future. These changes are associated with the increasing use of pre-exposure prophylaxis for HIV and Treatment as Prevention. Early data suggest these non-condom-based interventions are associated with reduced condom use and possibly an increase in the number of sexual partners, both of which will increase the reproductive rate of HPV infection and hence the proportion of the population that will need to be vaccinated.[19]

Unfortunately, the prospect of widespread and dramatic reductions in HPV incidence and HPV-associated cancers in MSM seem unlikely, with only five countries having adopted universal vaccination of boys before sexual activity. Some countries have adopted programs targeted at sexually active MSM, but with rapid acquisition of infection and reduced vaccine efficacy, it is unlikely that dramatic HPV reductions will occur outside those directly vaccinated. Our prediction for 2020 and beyond is that only countries with childhood HPV vaccination of boys will afford their future generations of MSM the same dramatic declines in anal and other cancers that will be seen in heterosexuals.

Conflicts of interest

CKF owns shares in CSL Biotherapies that market Gardasil in Australia. EPFC has received educational grant for HPV research from CSL Biotherapies to attend the 30th International Papillomavirus Conference (HPV 2015) and Seqirus to attend the EUORGIN 2016 Conference.

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