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Brief Communication

BRIEF COMMUNICATION

Who Will Benefit From Expanding HPV Vaccination Programs to Boys?

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Abstract

Indications for human papillomavirus vaccination programs are expanding to boys. However, the rationale behind their inclusion is often not clear. Using a Bayesian synthesis framework and assuming equal vaccine coverage in both sexes, we assessed how the incremental number of cancer cases prevented and life-years gained from boys' vaccination are distributed between women, heterosexual men, and men who have sex with men (MSM). Below 60% coverage, at least 50% of the gains from boys' vaccination was attributable to cervical cancer prevention, whereas at 80% coverage, 50% of the gains was attributable to women, 15% to heterosexual men, and 35% to MSM. Above 90% coverage, 85–100% of the gains from boys' vaccination was attributable to anal and oropharyngeal cancer prevention, mainly in MSM. Sex-neutral vaccination can be advocated on grounds of bolstering herd protection to women and directly protecting men, particularly MSM, with the clinical significance of either argument determined by the coverage.

Human papillomavirus (HPV) infections are established carcinogens in the cervix, vulva, vagina, anus, oropharynx, and penis (1). HPV vaccines have proven to be effective in preventing anogenital HPV16/18-related precancerous lesions in both women and men, and the new nonavalent vaccine also protects against HPV31/33/45/52/58 (2,3). Considering the strong implication of HPV16 in the development of oropharyngeal disease, there is also potential for vaccination to prevent oropharyngeal cancer (4,5).

A widely used argument when advocating sex-neutral HPV vaccination is the direct benefit for male vaccinees (6) promoting health equity (7,8). Mathematical modelling studies, however, argued that the impact of sex-neutral vaccination will be limited when vaccine coverage among females is high (9–17): owing to the sexual transmission of HPV, female vaccination provides herd protection to heterosexual males. Men who have sex with men (MSM) do not, however, benefit and the current situation in many countries with an HPV vaccination program is that the coverage is only moderate, indicating scope for improved protection by vaccinating boys (18). Besides, HPV-related oropharyngeal and anal cancer incidence have increased rapidly lately (19–28), with men experiencing a stronger increase than women (29). These considerations strengthen the need for a delineation of the distribution of the health gains that may be achieved by expanding preadolescent vaccination programs to boys in terms of sexual orientation, tumor site, and vaccine coverage.

Using a previously published Bayesian synthesis framework, we assessed how the incremental number of cancer cases prevented and life-years (LYs) gained by sex-neutral vaccination will be distributed between women, heterosexual men, and MSM (30,31). The framework accounts for all cancers with strong evidence for causal involvement of HPV16/18/31/33/45/52/58 and takes account of model-based herd immunity effects that are expected when vaccinating boys along with girls. In the present analysis, we translated the HPV-related disease risks in men and the excess risks in MSM into separate risk attributions for heterosexual men and MSM. We stratified the incremental gain from sex-neutral vaccination with respect to women, heterosexual men, and MSM and with respect to the following cancer sites: anus, cervix, oropharynx, penis, vagina, and vulva. Finally, we estimated the distribution of cancer cases prevented

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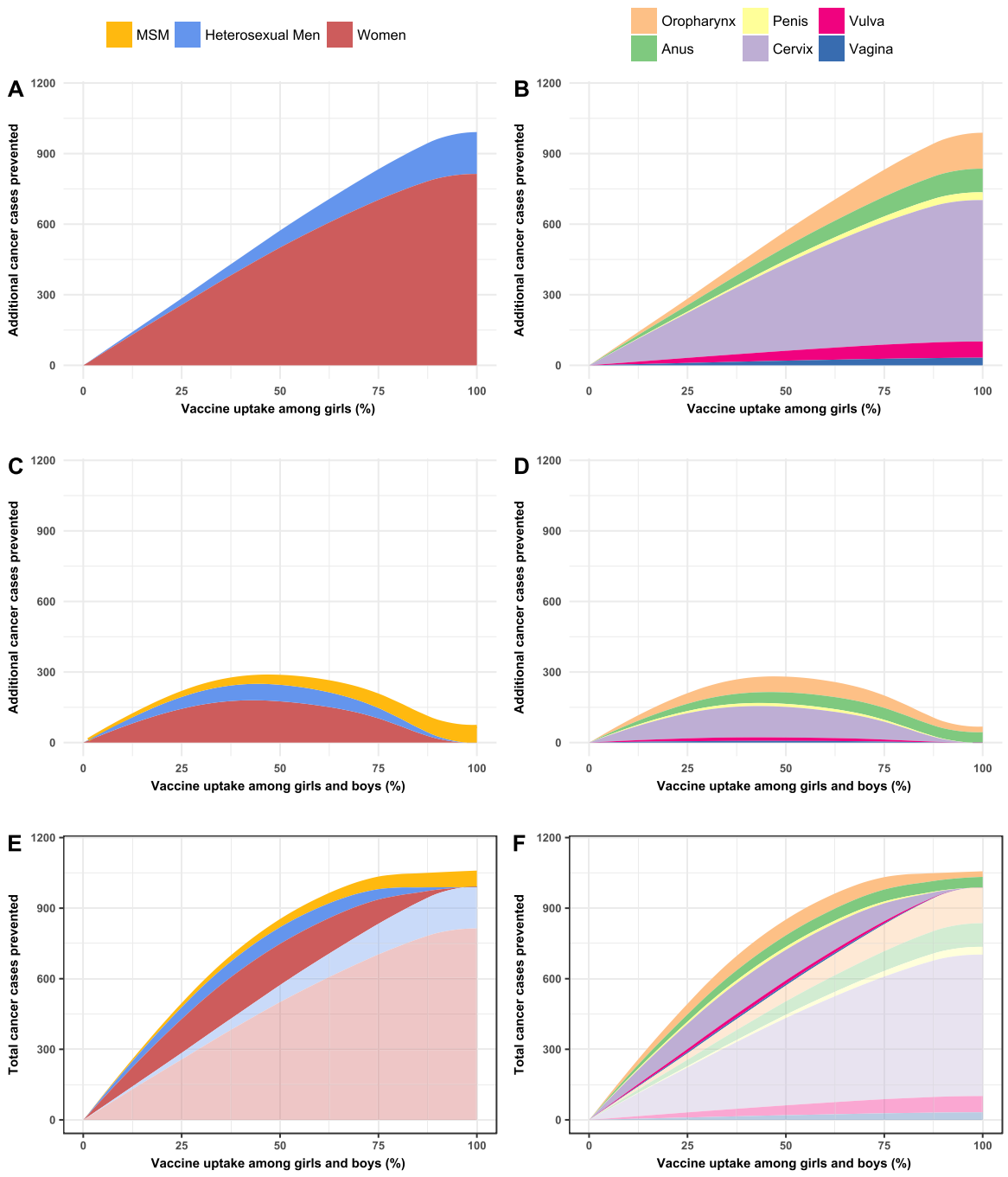

Figure 1. **A**) Gain from implementing girls-only vaccination in number of cancer cases prevented for women and heterosexual men compared with no vaccination (only cervical cancer screening). **B**) Gain from girls-only vaccination in number of cancer cases prevented for different human papillomavirus (HPV)-related anatomic sites compared with no vaccination. **C**) Incremental gain from implementing sex-neutral vaccination (under equal coverage in boys and girls) in number of cancer cases prevented for women, heterosexual men, and men who have sex with men (MSM) compared with girls-only vaccination. **D**) Incremental gain from implementing sex-neutral vaccination in number of cancer cases prevented for different HPV-related anatomic sites compared with girls-only vaccination. **E**) Total gain from implementing sex-neutral vaccination in number of cancer cases prevented for women, heterosexual men, and MSM compared with no vaccination. **F**) Total gain from implementing sex-neutral vaccination in number of cancer cases prevented for different HPV-related anatomic sites compared to no vaccination. Note that panel E combines panel A (transparent coloring) with C and panel F combines panel B (transparent coloring) with D.

and LYs gained under girls-only and sex-neutral vaccination as a function of vaccine coverage in preadolescent girls and boys. Coverage in girls and boys was considered equal under sex-neutral vaccination. Herd effects within the MSM network were omitted in the base-case analysis, but in the sensitivity analysis, we projected herd effects from men to women in the heterosexual network onto the MSM population. This scenario is expected to overestimate herd effects among MSM given their increased HPV prevalence compared with heterosexuals (32).

We estimated that 812 (95% credible interval (CrI) = 782 to 844), 180 (95% CrI] = 127 to 241) and 72 (95% CrI = 42 to 109) cancer cases per year were attributable to HPV16/18/31/33/45/52/58

infections in women, heterosexual men, and MSM in the Netherlands during the period 2005–2014. That number corresponded to 6547 (95% CrI = 6235 to 6891), 1102 (95% CrI = 652 to 1623), and 566 (95% CrI = 319 to 845) LYs lost due to HPV16/18/31/33/45/52/58-related cancers, respectively (31). Figure 1, A and B show the distribution of the health gains in number of cancer cases prevented from girls-only vaccination with varying coverage compared with no vaccination (only cervical cancer screening) (see Supplementary Figure 1 in the appendix for the distribution of LYs gained). Of the total gain, 85–90% was attributable to women, mostly due to cervical cancer prevention (Figure 1B), whereas only 10–15% was attributable to heterosexual men (Figure 1A). The gain in women and heterosexual men was almost linearly related to vaccine coverage in girls up to a coverage of 80%, at which point girls-only vaccination prevented over 80% of the disease burden in heterosexual men and over 90% of the disease burden in women (Figure 1A).

Figure 1, C and D show the respective distributions of the incremental gain from vaccinating boys at equal coverage as girls compared with girls-only vaccination. Vaccinating boys produced a substantial gain in women, depending on the coverage in girls. Below 60% coverage, at least 50% of the additional gains from boys' vaccination were attributable to cervical cancer prevention (Figure 1D) and at least 60% were attributable to cancers prevented in women (Figure 1C). When coverage in boys and girls was 80%, 50% of the gains was attributable to women, 15% to heterosexual men, and 35% to MSM. Above 90% coverage, the benefit of sex-neutral vaccination was concentrated in MSM: 85% of the additional health gains was attributable to prevention of oropharyngeal and anal cancer, for which MSM have increased risk. Projecting herd effects from the heterosexual network onto the MSM population produced higher gains for MSM at lower coverage and therefore slightly changed the relative distribution of the incremental health gains: at 80% coverage, 45% of the gains was attributable to women, 15% to heterosexual men, and 40% to MSM. Figure 1, E and F show the total number of cancer cases prevented from implementing sex-neutral vaccination compared with no vaccination (see Supplementary Figure 1 in the appendix for the distribution of LYs gained).

Thus, at moderate levels of vaccine coverage, as observed in several established HPV vaccination programs (18), vaccinating boys along with girls may provide a greater benefit to nonvaccinated women than to men themselves. This finding, counterintuitive at first sight, stems from the high burden of cervical cancer compared with other HPV-related cancers and from the notion that herd effects from vaccinating one sex are generally stronger in the opposite sex (10,31,33). The last also explains the strong impact of girls' vaccination on vaccine-preventable HPV infections in heterosexual men (34,35).

To conclude, this brief report calls for a careful consideration of the various arguments used to advocate sex-neutral HPV vaccination and strengthens the importance of using realistic assumptions in terms of achieved coverage in girls-only programs rather than target coverage when evaluating sex-neutral vaccination (36). Our estimates support that, in terms of health gain, sex-neutral vaccination can be advocated on two grounds: to bolster herd immunity to women and to directly protect men, particularly MSM, with the clinical significance of either argument determined by the achieved coverage. Although modeling studies have suggested that increasing coverage among girls is more efficient than implementing sex-neutral vaccination (9,10), real-world data from different countries show that, in practice, such a policy may not be achieved (18). These arguments aside, the reduction in the cost of vaccination, resulting from implementation of two-dose regimens and tendering for HPV vaccines in large-scale immunization programs (37), has substantially improved the cost-effectiveness profile of sex-neutral vaccination even in settings with acceptable coverage in girls-only programs (31,38,39). Finally, this report highlights a fundamental incentive inherent to large-scale vaccination programs: individuals are not only vaccinated to protect themselves but also to maximize herd protection in the population as a whole.

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