Incremental Impact of Adding Boys to Current Human Papillomavirus Vaccination Programs: Role of Herd Immunity

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(See the editorial commentary by Castle and Zhao, on pages 335–7.)

Our aim was to examine the potential incremental impact of vaccinating boys against human papillomavirus (HPV) on vaccine-type infection in females and males, using an individual-based HPV transmission-dynamic model. Under base assumptions (vaccine efficacy = 99%, duration of protection = 20 years, coverage = 70%), vaccinating 12-year-old boys, in addition to girls, resulted in an incremental reduction in HPV-16/18 (HPV-6/11) incidence over 70 years of 16% (3%) in females and 23% (4%) in males. The benefit of vaccinating boys decreased with improved vaccination coverage in girls. Given the important predicted herd immunity impact of vaccinating girls under moderate to high vaccine coverage, the potential incremental gains of vaccinating boys are limited.

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BRIEF REPORT

Infection with high–oncogenic-risk human papillomavirus (HPV) types, such as HPV-16 and -18, is a necessary cause of cervical cancer and is associated with anogenital and head and neck cancers [1–3]. Infections with low–oncogenic-risk HPV types, such as HPV-6 and -11, are associated with genital warts and recurrent respiratory papillomatosis [4]. It is well recognized that HPV causes a substantial burden of diseases in females, particularly due to cervical cancer. However, the burden in males is also considerable, particularly due to penile, anal, and oral cancers [5].

Two prophylactic HPV vaccines are currently licensed for use in females in many countries across the world: the bivalent and quadrivalent vaccines that protect against types HPV-16/18 and HPV-16/18/6/11, respectively. Given evidence that the vaccines are highly efficacious against persistent type-specific HPV infections and precancerous lesions, and cost-effective in preadolescent girls [6–8], most developed countries have introduced routine vaccination of girls. Recently, clinical trials have shown the HPV quadrivalent vaccine to be 86% effective at preventing vaccine-type persistent infection in young males (aged 16–26) [9]. Following these results, the quadrivalent vaccine has been licensed for use in boys and men in many countries [10, 11].

Currently, there is an intense debate on whether boys should be included in routine vaccination programs. A key factor that must be considered is the magnitude of herd immunity that will be conferred to males from female HPV vaccination strategies (ie, reduction in the risk of infection in males due to reduced exposure following vaccination of females). If vaccinating girls significantly reduces the burden of HPV-related diseases in males through herd immunity, vaccinating boys will produce limited additional reductions in morbidity/mortality and thus will not be cost-effective. The role of herd immunity has not been sufficiently addressed in previous modeling studies that have assessed the impact of vaccinating both genders. The objective of this study is to estimate the potential incremental gains of vaccinating boys against HPV-6/11/16/18, taking into account herd immunity effects.

METHODS

We developed an individual-based transmission-dynamic model of partnership formation and dissolution and a natural history of HPV infection (see [12]). The modeled population is heterosexual, open, and stable. Individuals enter the population prior to sexual debut and are attributed 2 different risk factors.
for HPV infection: gender and sexual activity level. HPV transmission is assumed to be dependent on sexual behavior (e.g., partner acquisition rates, mixing between age groups), per-partnership risk of transmission, duration of infectiousness, and natural immunity. Partnership formation and dissolution are based on gender-, age-, and sexual activity level–specific partner acquisition and separation rates and mixing patterns. Eighteen HPV types are modeled individually: 16/18/6/11/31/33/45/52/58/35/39/51/56/59/66/68/73/82. These HPV types are assumed to be independent with respect to transmission and persistence; thus, any combination of multiple co-infections is possible. Following clearance, individuals have a type-specific probability of developing natural immunity (i.e., individuals have a risk of being reinfected with a type they have previously cleared).

Our model calibration procedure identified multiple parameter sets that fit simultaneously age-specific sexual behavior and epidemiological data, including the proportion sexually active, number of partners in the last year, and type-specific HPV prevalence by sexual activity level [12]. Forty-four parameter sets produced results within the pre-specified targets of the data [12]. Model predictions are based on these 44 parameter sets. Parameter uncertainty surrounding model predictions is presented as the median, 10th and 90th percentiles of results from the posterior parameter sets (80% uncertainty intervals [UIs]).

Population-level vaccine effectiveness predictions are represented by 2 outcomes: the relative reduction in HPV prevalence at equilibrium compared with no vaccination and the relative reduction in the incidence of vaccine-type infection over the first 70 years after the start of the vaccination program compared with no vaccination. Vaccine program efficiency is represented by the following effectiveness–coverage ratio: reduction in vaccine-type prevalence at equilibrium ÷ vaccine coverage.

RESULTS

Under base assumptions (per-act vaccine efficacy = 99%, average duration of protection = 20 years, coverage = 70%), the model predicted that vaccinating 12-year-old girls only will produce a rapid decrease in vaccine-type-specific prevalence in females and males and that, at equilibrium, HPV-16/18 prevalence in females and males will be reduced by 65% (80% UI, 49–82) and 62% (80% UI, 45–81), respectively (Figure 1). Vaccinating 70% of 12-year-old boys in addition to girls produced a slightly faster decline in vaccine-type-specific prevalence and a larger reduction in HPV-16/18 prevalence at equilibrium: 85% (80% UI, 68–100) and 88% (80% UI, 72–100) in females and males, respectively (Figure 1). Under the above assumptions, vaccinating boys resulted in an incremental reduction in HPV-16/18 incidence over 70 years of 16% (80% UI, 10–20) in females and 23% (80% UI, 14–26) in males. HPV vaccine effectiveness is predicted to be significantly higher for HPV-6/11 compared with HPV-16/18 following the vaccination of girls alone (Figure 2A). Therefore, the incremental impact of vaccinating boys was estimated to be lower (Figure 2B).

Because the potential to achieve significant gains from vaccinating boys depends on the population-level effectiveness of girls-only vaccination, the incremental impact of vaccinating boys decreases significantly with improved vaccination characteristics. Figure 2 (A and B) clearly shows that increasing coverage considerably improved the effectiveness of girls-only vaccination but produced diminishing incremental gains when adding boys to the vaccination program. Similarly, the incremental benefit of adding boys to HPV vaccination programs also decreased when vaccine efficacy or duration of vaccine protection increased (Figure 2C). Of note, scenarios with lower vaccine efficacy or shorter duration can represent situations where a proportion of girls receive <3 doses.
Figure 2. Impact of vaccine coverage: A, reduction in vaccine-type incidence in females and males over the first 70 years of a girls-only vaccination program for different vaccine coverage (coverage = coverage in girls); B, incremental reduction in vaccine-type incidence in females and males over 70 years by vaccinating boys in addition to girls for different vaccine coverage (coverage in boys = coverage in girls); C, incremental reduction in vaccine-type incidence in males over 70 years by vaccinating boys in addition to girls for different vaccine characteristics (coverage in boys = coverage in girls); D, effectiveness–coverage ratio (reduction in vaccine-type prevalence at equilibrium ÷ population vaccine coverage) following a girls-only vaccination program; and E, incremental effectiveness–coverage ratio (incremental reduction in vaccine-type prevalence at equilibrium ÷ incremental population vaccine coverage) by vaccinating boys in addition to girls. Vaccination base assumptions: age at vaccination = 12 years, vaccine coverage = 70%, per-act vaccine efficacy (VE) = 99%, vaccine duration (VD) = 20 years. All vaccine efficacy parameters were assumed to be identical for girls and boys. G, coverage among girls; B, coverage among boys; and Overall, overall population coverage.
Although vaccinating boys in addition to girls produces incremental benefits, the return on investment is much smaller than that of vaccinating girls alone (Figure 2, D and E). Under base assumptions, our model predicts that by vaccinating 35% of the population (70% of 12-year-old girls and 0% of boys), overall HPV-16/18 prevalence is reduced by 64% (80% UI, 50–82) in the long term, which produces an effectiveness–coverage ratio of 1.8 (64% ÷ 35% coverage reduction in HPV-16/18 prevalence). An effectiveness–coverage ratio above 1 indicates that herd immunity is occurring because there are more individuals in the population protected than vaccinated. However, if the number of vaccinees is doubled by adding 12-year-old boys to the vaccination program (70% coverage in girls and boys), the incremental reduction in HPV-16/18 prevalence is predicted to be 24% (80% UI, 14–29), for an incremental effectiveness–coverage ratio of 0.7 (24% ÷ 35% = 24% reduction in HPV-16/18 prevalence ÷ [70%–35%] coverage). The incremental effectiveness–coverage ratio of vaccinating boys decreases substantially with increased vaccine coverage, indicating important diminishing returns on investment (Figure 2E).

**DISCUSSION**

Our modeling analysis indicates that vaccinating 12-year-old girls will produce significant herd effects, thus protecting males against HPV infection and disease. These herd effects increase with improved vaccine characteristics (including greater vaccine efficacy, longer duration of protection, higher coverage) and are greater for HPV-6/11 than HPV-16/18. Given the important herd immunity impact of female vaccination on males under moderate to high vaccine coverage, the incremental gains from vaccinating boys are predicted to be limited.

Our results explain why most cost-effectiveness studies have predicted that vaccinating boys is not cost-effective when coverage is moderate to high in girls (eg, >50%) [8]: The return on investment of adding boys to a vaccine program is much smaller than for vaccinating girls alone (Figure 2, C and D). This is because, if coverage in girls is high, many of the boys who would receive the vaccine would never become infected due to the herd effect of vaccinating girls. This means that including boys in a vaccine program would produce considerable losses in vaccine program efficiency (eg, decrease effectiveness–coverage ratios and increase cost-effectiveness ratios) and produce redundancy in vaccine delivery. Current evidence from Australia suggests that herd immunity effects are occurring in males following girls-only HPV vaccination programs [13].

Currently, in many developed countries, including the United States, HPV vaccine coverage is <50% among young girls [14]. In this situation, the incremental gains by vaccinating boys can be more substantial (Figure 2, B and D). However, increasing vaccine coverage in girls consistently produces greater population-level effectiveness than adding boys to the vaccination program. For example, under base case model assumptions, if overall coverage in 12-year-olds is increased from 25% to 50% by vaccinating 50% of boys in addition to 50% of girls, the incremental effectiveness–coverage ratio is predicted to be 0.9 (23% incremental reduction in HPV-16/18 at equilibrium ÷ 25% increase in overall coverage; Figure 2D). However, if overall coverage in 12-year-olds is increased from 25% to 50% by vaccinating girls only (ie, increasing coverage in girls from 50% to 100%), the model predicts that the incremental effectiveness–coverage ratio is 2.2 (54% incremental reduction in HPV-16/18 prevalence at equilibrium ÷ 25% increase in overall coverage [results not shown]). These results can be explained as follows. If 100% of girls and 0% of boys are vaccinated, then 100% of heterosexual partnerships have at least one person vaccinated. However, if 50% of girls and 50% of boys are vaccinated, then, on average, only 75% of heterosexual partnerships have at least one partner vaccinated (25% chance both are vaccinated, 50% chance that only one partner is vaccinated, and 25% chance that neither of the partners is vaccinated), assuming coverage and mixing are independent. These results illustrate why cost-effectiveness studies have shown that it is more cost-effective to increase coverage in girls than to add boys to the program [15]: Herd immunity effects are optimized by increasing coverage in girls rather than including boys in a program.

There are 2 key unknowns, which have yet to be included in HPV infection models that can reduce the predicted herd immunity impact of vaccinating girls and thus increase the incremental benefit of vaccinating boys. First, if vaccinated females can continue to have transient infections (ie, continue to be carriers) and transmit HPV, then herd effects may be smaller than predicted. Second, if coverage is low among subgroups of females who are highly sexually active (eg, core groups), then herd immunity may be limited even though population-level coverage is high.

It should be pointed out that the magnitude of herd effects predicted by our individual-based model is greater than in previous deterministic models. As previously shown this is mainly because, unlike previous models, we explicitly model partnership formation and dissolution and we do not group vaccine types together into one generic type [12]. Finally, we assume that vaccine coverage and mixing are independent, which may overestimate the incremental benefit of vaccinating boys. As vaccine uptake is likely to be associated with sociodemographic characteristics, extending vaccination to boys may disproportionately protect the sexual partners of vaccinated females, thus limiting the incremental benefit of male vaccination.

We purposely decided not to present the impact of vaccination on disease endpoints, such as cervical cancer, genital warts, or anal cancer. Rather, we examine the impact of vaccination on HPV infection to isolate the type-specific impact of vaccination without
the additional uncertainties related to the natural history of the different HPV-related diseases and to have a common outcome of vaccine effectiveness for comparison between males and females. Furthermore, by focusing on HPV infection we eliminate the debate on the relative burden of HPV disease in females and males.

Our results suggest that heterosexual males will benefit almost to the same extent as females from a girls-only vaccination program, due to herd immunity. However, we did not include males who have sex with males (MSM) in our model and thus have not estimated the impact of female vaccination on this population. It is highly likely, though, that the impact of vaccinating girls on the MSM population through bridge groups, such as bisexuals, will be limited. Clearly, more work is needed to better identify the most effective and cost-effective strategies to reduce HPV-related diseases among MSM.

In summary, given the important direct and herd immunity impact of vaccinating girls under moderate to high vaccine coverage, the incremental gains of vaccinating boys are limited. These results help explain why many modeling studies show that male vaccination is not cost-effective. In other words, although vaccinating boys can help further reduce the overall burden of HPV-related disease in females and males, vaccinating boys may not be the best investment of scarce health care resources due to diminishing returns caused by herd effects.

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