Population-level impact, herd immunity, and elimination after human papillomavirus vaccination: a systematic review and meta-analysis of predictions from transmission-dynamic models

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Summary

Background Modelling studies have been widely used to inform human papillomavirus (HPV) vaccination policy decisions; however, many models exist and it is not known whether they produce consistent predictions of population-level effectiveness and herd effects. We did a systematic review and meta-analysis of model predictions of the long-term population-level effectiveness of vaccination against HPV 16, 18, 6, and 11 infection in women and men, to examine the variability in predicted herd effects, incremental benefit of vaccinating boys, and potential for HPV-vaccine-type elimination.

Methods We searched MEDLINE and Embase for transmission-dynamic modelling studies published between Jan 1, 2009, and April 28, 2015, that predicted the population-level impact of vaccination on HPV 6, 11, 16, and 18 infections in high-income countries. We contacted authors to determine whether they were willing to produce new predictions for standardised scenarios. Strategies investigated were girls-only vaccination and girls and boys vaccination at age 12 years. Base-case vaccine characteristics were 100% efficacy and lifetime protection. We did sensitivity analyses by varying vaccination coverage, vaccine efficacy, and duration of protection. For all scenarios we pooled model predictions of relative reductions in HPV prevalence (RR_{prev}) over time after vaccination and summarised results using the median and 10th and 90th percentiles (80% uncertainty intervals [UI]).

Findings 16 of 19 eligible models from ten high-income countries provided predictions. Under base-case assumptions, 40% vaccination coverage and girls-only vaccination, the RR_{prev} of HPV 16 among women and men was 0·53 (80% UI 0·46–0·68) and 0·36 (0·28–0·61), respectively, after 70 years. With 80% girls-only vaccination coverage, the RR_{prev} of HPV 16 among women and men was 0·93 (0·90–1·00) and 0·83 (0·75–1·00), respectively. Vaccinating boys in addition to girls increased the RR_{prev} of HPV 16 among women and men by 0·18 (0·13–0·32) and 0·35 (0·27–0·39) for 40% coverage, and 0·07 (0·00–0·10) and 0·16 (0·01–0·25) for 80% coverage, respectively. The RR_{prev} were greater for HPV 6, 11, and 18 than for HPV 16 for all scenarios investigated. Finally at 80% coverage, most models predicted that girls and boys vaccination would eliminate HPV 6, 11, 16, and 18, with a median RR_{prev} of 1·00 for women and men for all four HPV types. Variability in pooled findings was low, but increased with lower vaccination coverage and shorter vaccine protection (from lifetime to 20 years).

Interpretation Although HPV models differ in structure, data used for calibration, and settings, our population-level predictions were generally concordant and suggest that strong herd effects are expected from vaccinating girls only, even with coverage as low as 20%. Elimination of HPV 16, 18, 6, and 11 is possible if 80% coverage in girls and boys is reached and if high vaccine efficacy is maintained over time.

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Introduction

Since 2006, two prophylactic human papillomavirus (HPV) vaccines have been widely used worldwide: the bivalent and quadrivalent vaccines. Both vaccines target HPV 16 and 18, which cause about 50% of high-grade cervical lesions, 70% of cervical cancers, and 40–80% of other HPV-related cancers.[1–5] The quadrivalent vaccine

also targets HPV 6 and 11, which are associated with 80–90% of anogenital wart cases.[6] Large randomised controlled clinical trials have shown that both vaccines are highly effective in protecting against vaccine-type persistent HPV infection and precancerous lesions in women and men (vaccine efficacy 93–100%).[7,8] More than 65 countries have introduced HPV vaccination

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Research in context

Evidence before this study

Many models have been developed over the past decade to understand HPV epidemiology and to help guide policy decisions concerning HPV vaccination. However, it is unknown whether these models are giving consistent results in terms of HPV vaccination population-level effectiveness, herd effects, incremental benefit of vaccinating boys in addition to girls, and elimination. To examine this question, we conducted a systematic review and meta-analysis of HPV transmission-dynamic model predictions of the long-term population-level effectiveness of HPV vaccination against HPV 6, 11, 16, and 18 infection in women and men. To our knowledge, this is the first meta-analysis of HPV model predictions, and is the first to examine the potential for elimination.

Added value of the study

Our study shows that the HPV models give generally consistent results, which can be reassuring for decision makers using these models for vaccination policy decisions. Results suggest that HPV vaccination will produce strong herd effects leading to substantial long-term reductions in HPV infection and related diseases in unimmunised women and men. Herd effects are predicted even with vaccination coverage as low as 20%.

Given the substantial herd effects of girls-only vaccination when coverage is moderate to high, the incremental benefit of vaccinating boys is predicted to be small. To our knowledge, our study is the first to suggest that elimination of vaccine-targeted HPV types is possible if vaccination coverage of girls and boys reaches 80%. Finally, our study includes a greater number of models than any published comparison of infectious disease models, reflecting the influential role modelling has played in HPV vaccination policy decisions.

Implications of available evidence

HPV vaccination is likely to have a strong direct and indirect impact across different countries and coverage levels. The case for vaccinating boys could mainly depend on other issues besides the predicted additional benefit for heterosexual males, such as cost of the vaccine for boys, feasibility of increasing coverage in girls, and equity for men who have sex with men. Although early post-HPV vaccination surveillance data do not show herd effects in settings with low coverage, our study suggests that this is probably because herd effects take longer to become evident when coverage is lower. Policy makers might want to examine whether to set objectives to eliminate HPV vaccine types in their jurisdictions.

programmes.[9,10] Most programmes target girls only, with only a handful of countries vaccinating both girls and boys (eg, the USA, Australia, Switzerland, Austria, and Canada).[11–17] These decisions have been made with substantial input from mathematical models.[11,18–22] Recently, a nonavalent vaccine, which targets HPV 31, 33, 45, 52, and 58 also, has been licensed and recommended for use in the USA[23] after reports of strong efficacy and immunogenicity from large trials.[24]

Mathematical models have consistently predicted that vaccinating girls against HPV is highly cost-effective,[25–27] however, the picture is less clear for vaccinating boys.[28–35] This is because the cost-effectiveness of vaccinating girls is mainly driven by the direct benefit of HPV vaccination among vaccinated women, which depends on well quantified parameters such as vaccine efficacy and the proportion of cervical cancer due to the vaccine types.[27] The incremental effectiveness and cost-effectiveness of vaccinating boys is influenced largely by the magnitude of indirect protection conferred to men by vaccinating girls (herd immunity), which depends on a complex combination of factors (eg, vaccination coverage and sexual behaviour).[28,35,36] Modelling studies have shown that if vaccinating girls significantly reduces the burden of HPV-related diseases in men through herd immunity, then vaccinating boys will produce limited additional population-level benefits for heterosexual men and women and thus will not be cost-effective at the same vaccine price.[28,30,35] However, it is unclear what vaccination coverage is necessary to achieve substantial herd effects, and whether models are consistent in their predictions.

A systematic review of population-level HPV post-vaccination surveillance data has shown significant reductions in anogenital warts in young men in the first 4 years after girls-only quadrivalent vaccination programmes with high coverage (≥50%).[37] In countries with low vaccination coverage (<50%) there was no indication of herd effects.[37] In Australia, where quadrivalent vaccination coverage among girls has been consistently higher than 70%, anogenital warts consultations among heterosexual men declined by more than 80% within the first 5 years of the programme (before vaccination of boys).[38] These results suggest that HPV vaccination can produce important herd effects for the anogenital warts associated types (HPV 6 and 11), and that elimination of these types might be achievable.

Better understanding the potential long-term population-level effectiveness of HPV vaccination, including herd effects, is crucial to help inform future vaccine policy decisions such as the inclusion of boys in vaccination programmes, incremental impact of increasing vaccination coverage and optimal combinations of HPV vaccination and cervical cancer screening strategies. Mathematical models provide a formal framework to examine these questions, which cannot be answered in trial settings. However, models require many assumptions, which might lead to questions about the validity of predictions and uncertainty for decision makers. A large number of HPV models have been developed over the past decade, but it is still unclear whether the models are giving consistent results and whether we can draw general principles from them. We conducted a systematic review

and meta-analysis of model predictions of the long-term population-level effectiveness of HPV vaccination against HPV 6, 11, 16, and 18 infection in women and men, to examine the robustness and variability of predicted herd effects, incremental benefit of vaccinating boys, and potential for HPV vaccine-type elimination.

Methods

Search strategy and selection criteria

In this systematic review and meta-analysis, we used a three-step systematic process to identify independently developed HPV transmission-dynamic mathematical models from the published literature, which we report in accordance with the PRISMA guidelines.[39] First, we systematically reviewed the literature. Modelling studies were eligible for inclusion if the model: (1) was an HPV transmission-dynamic model; (2) produced predictions of the population-level impact of vaccination on HPV 16, 18, 6, or 11 infections among women or men or both; and (3) was developed to examine the impact of HPV vaccination in a high-income country. We searched MEDLINE and Embase databases using a combination of the following MeSH terms, title or abstract words, without restriction on the language of the articles: ("models, theoretical" or "mathematical model" or "models, statistical" or "cost-benefit analysis" or "cost-effectiveness" or "risk-benefit analysis") and ("papillomavirus vaccines" or "papillomavirus vaccination" or "human papillomavirus vaccine" or "HPV vaccine" or "HPV vaccination"); the exact search for both databases is presented in the appendix p 2. We included models published between Jan 1, 2009, and April 28, 2015, because the authors were likely to use their model to inform future policy decisions. We identified eligible studies through review of titles and abstracts. To identify additional studies, we reviewed the references of selected articles and hand searched the abstracts from the main HPV conferences (Eurogin Congress 2013; Florence, Italy; Nov 3–5; and International Papillomavirus Conference 2014; Seattle, WA, USA; Aug 20–25). MB, ÉB, and MD assessed the eligibility of all studies.

Second, we decided a priori to group the selected studies by research team. Teams were not selected if they used a model previously developed by another team. MB contacted the senior or corresponding authors of all teams to determine whether they were willing to produce new predictions using a standardised-input dataset. The ability to provide new standardised predictions was a prerequisite for inclusion of a model in this meta-analysis, to adequately compare and pool model results. Third, when modelling teams had different versions of their models, we included only their most recent published model in the meta-analysis to ensure independence between model predictions.

### Data collection and quality assessment

All eligible and participating teams were asked to fill a standardised form to describe their models in detail.

Additionally, MB and ÉB provided the modelling teams with 19 predetermined vaccination scenarios and asked them to transfer these new results using a standardised format (appendix p 3). Our primary outcome was the relative reduction in the overall prevalence (RR_{prev}) of HPV 16, 18, 6, and 11 among heterosexual women and men after 70 years of vaccination (*vs* no vaccination). We decided, a priori, to stratify outcomes by HPV type and sex. Results were stratified by sex to investigate the herd effects of vaccinating girls only on RR_{prev} among heterosexual men, and were stratified by type to examine if model predictions of herd immunity or elimination differed between HPV vaccine types. Base-case vaccine characteristics used by all groups were 100% vaccine efficacy and lifetime duration of protection. In the sensitivity analyses, we varied vaccine efficacy (to 90%)

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See **Online** for appendix
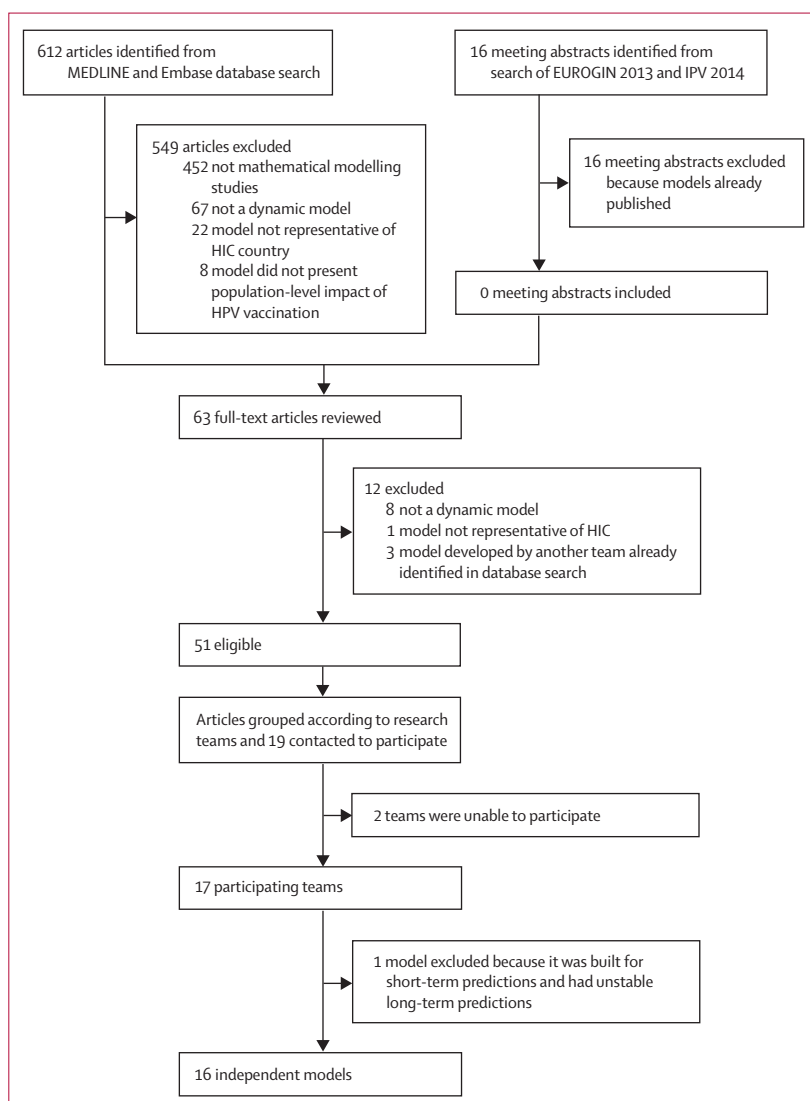
Figure 1: **Model selection**
HPV=human papillomavirus. HIC=high-income country. EUROGIN=Eurogin International Multidisciplinary Congress. IPV=International Papillomavirus Conference.
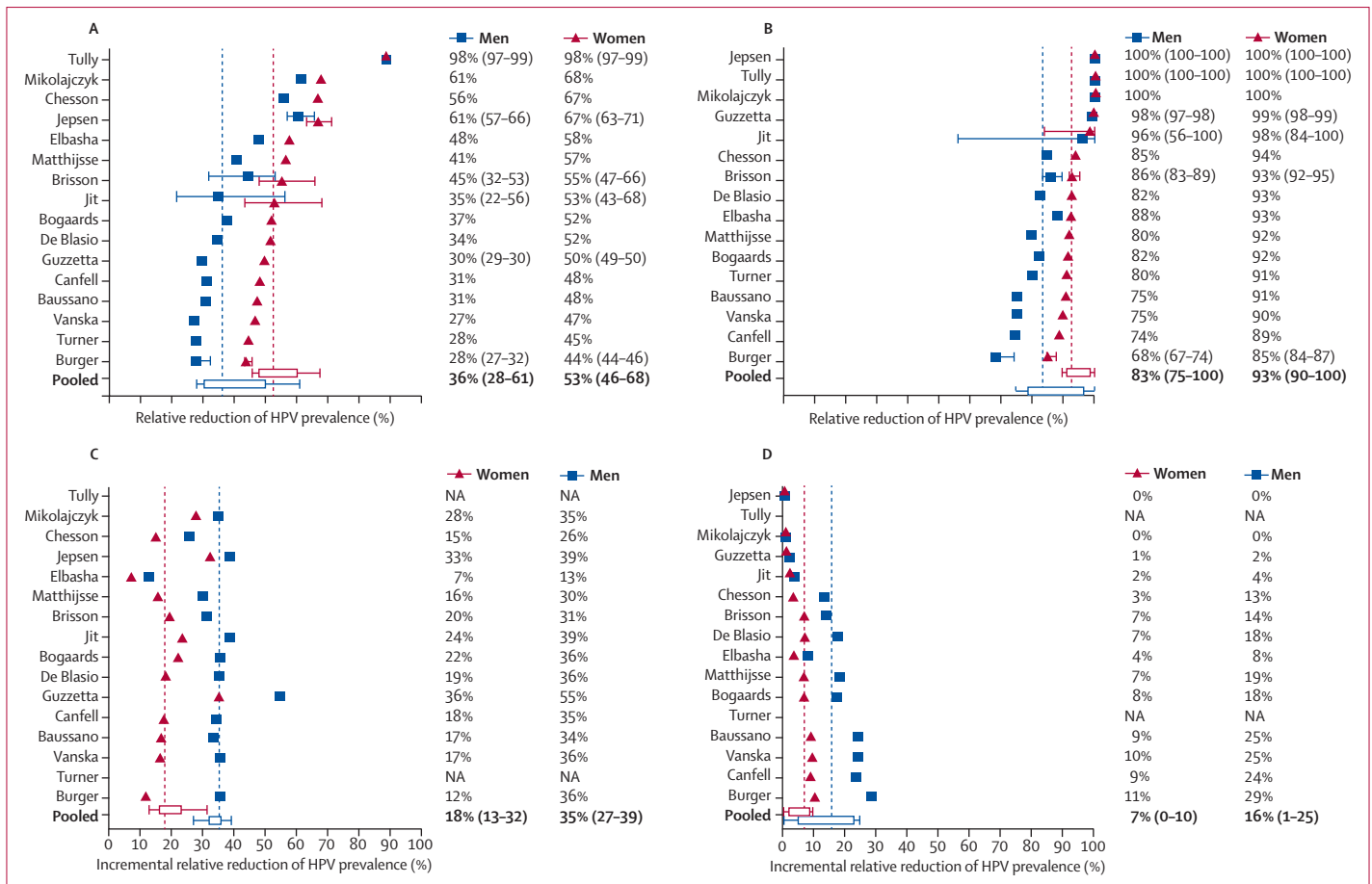
Figure 2: Population-level impact of HPV vaccination of girls only (A, B) and boys and girls (C, D)
Predicted relative reduction in the prevalence (RR$_{prev}$) of HPV 16 among women and men after 70 years of girls-only vaccination, assuming 40% (A) and 80% (B) vaccination coverage; and predicted incremental relative reduction in the prevalence of HPV 16 among women and men after 70 years by vaccinating boys in addition to girls only, assuming 40% (C) and 80% (D) vaccination coverage. The pooled estimates are medians and 80% uncertainty intervals (10% and 90% percentile) of predictions. Models with error bars provided uncertainty intervals (10th and 90th percentile) around their median model predictions. When a model's results includes a median estimate and uncertainty range, the pooled results used the median value. HPV=human papillomavirus. NA=not available.

and duration of protection (to 20 years) for fixed vaccination coverage of 40% and 80%. As a secondary outcome, we present RR$_{prev}$ over time since the introduction of vaccination.

Before contacting modelling teams, MB and ÉB assessed if the studies were of sufficient methodological quality to be included in the pooled analysis. Following recommendations from the International Society for Pharmacoeconomics and Outcomes Research and Society for Medical Decision Making (ISPOR-SMDM) modelling good research practices task force,[40] the main quality criteria were that the models had to be transmission-dynamic mathematical models and be calibrated to epidemiological data. Given that an objective of the meta-analysis was to examine herd effects and HPV elimination, the transmission-dynamic model criterion was included as an eligibility criterion. Finally, once model results were obtained from the participating modelling teams, MB and ÉB assessed the construct validity of predictions.

Data analysis

We derived pooled predictions of HPV vaccination population-level impact by calculating the median and 10th, 25th, 75th, and 90th percentiles of the predictions of the models, and present RR$_{prev}$ with 80% uncertainty intervals (80% UI; the 10th and 90th percentiles). These pooled results illustrate the central tendency and variability or robustness of model predictions, with all models having equal weight. These pooled results are different to summary estimates from classical meta-analysis of empirical studies, which are pooled with weights based on sample size or variance. Incremental RR$_{prev}$ were obtained by subtracting the RR$_{prev}$ of girls-only vaccination from the RR$_{prev}$ of girls and boys vaccination.

We used univariate linear meta-regressions to identify potential sources of heterogeneity among the different models' predictions for HPV 16, giving equal weight to all models. We looked at model characteristics in univariate analysis and examined the potential interactions between each characteristic and vaccination

coverage (40% and 80%), and between each characteristic and vaccination strategy (girls only and girls and boys). Given the number of models, it was not possible to perform multivariate analysis. We verified that our results were similar when using HPV 18. We used SAS version 9.4 for all analyses.

Role of the funding source
The funders of the study had no role in the study design, data collection, analysis and interpretation, or writing of the report. MB, ÉB, and MD had full access to all the data in the study and MB had final responsibility for the decision to submit for publication.

Results
Our search led to the identification of 51 articles published by 19 different research teams (figure 1). Of the 19 teams contacted to participate in the meta-analysis, 17 provided new standardised model predictions. All models met the main methodological quality criteria. However, one model[41] was excluded because it was built for short-term predictions, and demographic change assumptions produced unstable long-term predictions. The 16 models included in the meta-analysis vary in terms of type (deterministic or stochastic), structure (assumptions about sexual activity, partnership formation and dissolution, transmission, and natural immunity), and baseline HPV prevalence, and were developed in ten countries (Australia, Canada, Finland, Germany, Ireland, Italy, Netherlands, Norway, UK, and USA; appendix pp 4–5). HPV 16, 18, 6, and 11 were included in 16, 13, five, and three models, respectively.

Among women after 70 years of girls-only vaccination, the overall predicted prevalence of HPV 16 decreased by 53% (RR$_{prev}$ 0·53 [80% UI 0·46–0·68]) assuming 40% coverage, and by 93% (RR$_{prev}$ 0·93 [80% UI 0·90–1·00]) assuming 80% coverage (figure 2). At 40% coverage, the corresponding RR$_{prev}$ for HPV 6, 11, and 18 were 7 to 28 percentage points greater than HPV 16, and at 80% coverage these types were eliminated (HPV 11) or close to elimination (HPV 18 and 6; figure 3A, appendix pp 6–13). Given that population-level effectiveness (RR$_{prev}$) was substantially greater than vaccination coverage for all HPV vaccine-targeted types, these results indicate that girls-only vaccination is expected to produce substantial herd effects for unvaccinated women even at low coverage, with greater herd immunity effects for HPV 18, 6, and 11 than for HPV 16 (figure 3A, appendix p 14).

Important herd effects were also predicted in men after girls-only vaccination for both low and high coverage scenarios (figures 2, 3). Among men, the overall prevalence of HPV 16 decreased by 36% after 70 years of girls-only vaccination assuming 40% coverage (RR$_{prev}$ 0·36 [80% UI 0·28–0·61]), and by 83% assuming 80% coverage (0·83 [0·75–1·00]; figure 2). The RR$_{prev}$ of HPV 18, 6, and 11 were again greater than that of HPV 16 (figure 3A, appendix p 14).

Post-vaccination reduction in HPV prevalence over time after girls-only vaccination was faster for women than men, for types HPV 6 and 11 compared with HPV 16 and 18, and at higher coverage than at lower coverage (appendix pp 15–16).

Vaccinating 40% of boys in addition to 40% of girls (girls and boys strategy) resulted in incremental reductions of HPV 16 prevalence of 18% among women (incremental RR$_{prev}$ 0·18 [80% UI 0·13–0·32]) and 35% among men (0·35 [0·27–0·39]) after 70 years (figure 2C). Given the important herd effects following girls-only vaccination with 80% coverage, vaccinating 80% of boys in addition to girls produced small incremental reductions in HPV 16
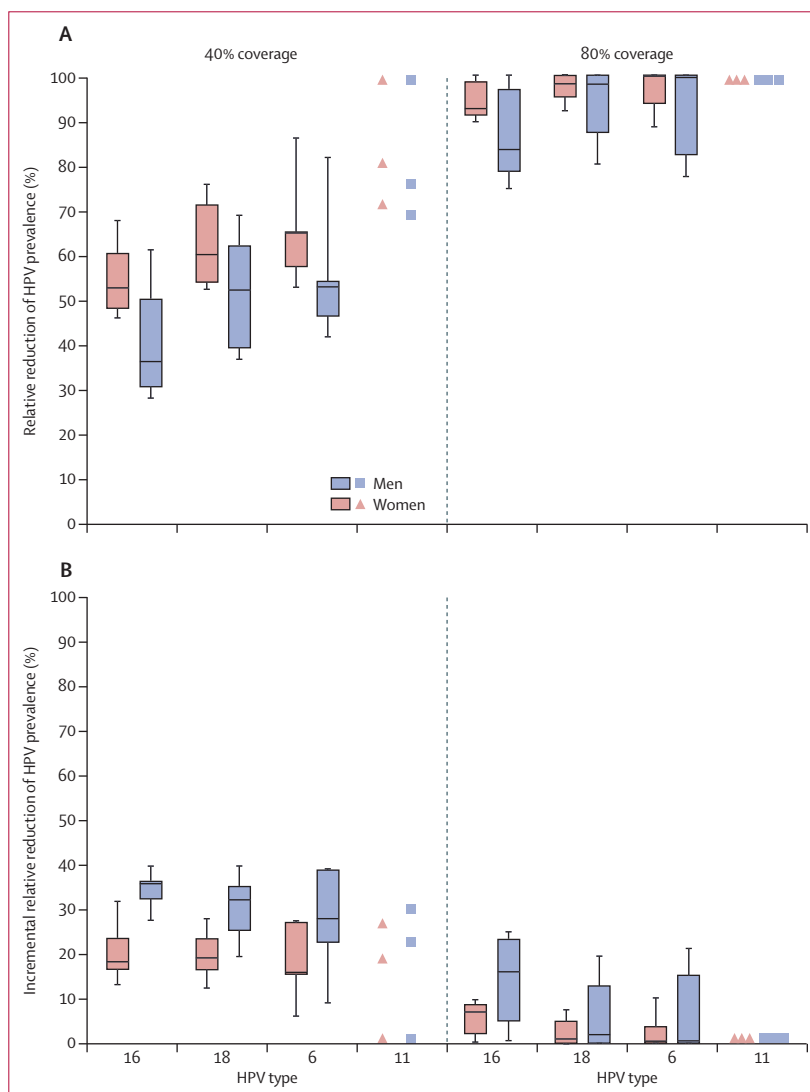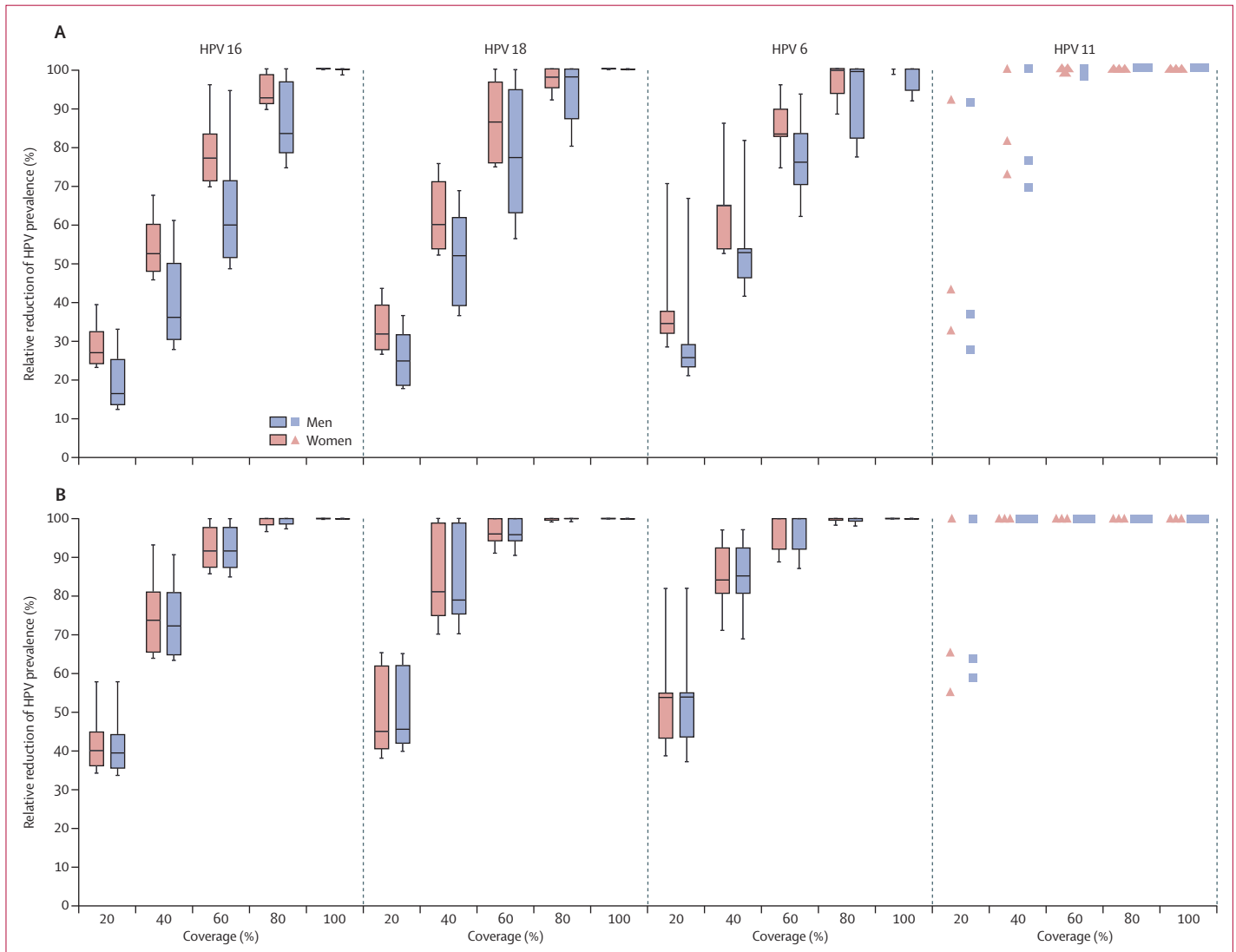

Figure 3: Pooled predictions of the vaccine-type-specific population-level impact of HPV vaccination
Relative reduction of HPV prevalence among women and men after 70 years of girls-only vaccination (A), and incremental relative reduction in HPV prevalence among women and men after 70 years by vaccinating boys in addition to girls only (B). Shown here are median (line) and 25th and 75th percentiles (box) and 10th and 90th percentiles (whiskers) of the predictions of the models. HPV 11 results have a different presentation due to the few models that include this outcome. See appendix pp 6–9 for forest plots of model predictions for types HPV 16, 18, 6, and 11; and appendix pp 10–13 for values of pooled estimates and uncertainty intervals. HPV=human papillomavirus.

prevalence (incremental RR$_{prev}$ of 0·07 [80% 0·00–0·10] for women and 0·16 [80% 0·01–0·25] for men), after 70 years (figure 2D). The incremental population-level effectiveness of vaccinating boys in addition to girls was similar between the HPV vaccine types when assuming 40% coverage, but was substantially higher for HPV 16 (*vs* HPV 18, 6, 11) when assuming 80% coverage (figure 3B). Vaccinating boys in addition to girls produced a slightly faster decline in vaccine-type-specific prevalence among women and men (appendix pp 15–16).

For the same number of additional vaccinated individuals, increasing coverage in a girls-only strategy was predicted to provide greater population-level benefits than was including boys in a vaccination programme. The models predicted that increasing girls-only

vaccination coverage by 40% (from 40% to 80%) reduced HPV 16, 18, 6, and 11 prevalence in women by an additional 40%, 38%, 35%, and 19%, respectively; higher than the incremental benefits of vaccinating 40% of boys in addition to 40% of girls (figure 4; appendix pp 10–13, 15–16). The same increase in girls-only vaccination coverage from 40% to 80% was also more effective in reducing HPV 16, 18, and 6 prevalence in men than the incremental benefit of vaccinating 40% of boys in addition to 40% of girls, and the strategies were equally effective for HPV 11 (figure 4, appendix pp 10–13).

Increasing coverage considerably improved population-level effectiveness up to 80% for girls-only vaccination and 60% for girls and boys vaccination, after which, increasing coverage had very little marginal benefit

Figure 4: **Pooled predictions according to vaccination coverage and vaccine type**
Relative reduction of HPV prevalence among women and men after girls-only vaccination (A) and after vaccination of boys in addition to girls (B). Shown here are median (line) and 25th and 75th percentiles (box) and 10th and 90th percentiles (whiskers) of the predictions of the models. HPV 11 results have a different presentation due to the limited number of models that include this outcome. See appendix pp 6–9 for forest plots of model predictions for types HPV 16, 18, 6, and 11; and appendix pp 10–13 for values of pooled estimates and uncertainty intervals. HPV=human papillomavirus.

(figure 4). Substantial herd effects were predicted with girls-only vaccination coverage as low as 20% (figure 4, appendix pp 10–13). Interestingly, 19% (three of 16), 46% (six of 13), 60% (three of five), and 100% (three of three) of models predicted that HPV 16, 18, 6, and 11, respectively, would be eliminated among heterosexual populations if girls-only vaccination reaches 80% coverage (figure 4, appendix p 14). The girls and boys strategy substantially increased the predicted potential for elimination; 64%, 92%, 80%, and 100% of models predicted that HPV 16, 18, 6, and 11 would be eliminated with 80% coverage, and a few models predicted elimination of types HPV 18, 6, and 11 with 60% coverage (figure 4, appendix p 14).

Predicted population-level effectiveness and herd effects were much lower and more variable across the models when assuming that vaccine duration of protection was 20 years compared with lifelong protection (appendix p 17). However, reducing vaccine efficacy from 100% to 90% had little impact on the pooled predictions (appendix p 17).

In the meta-regression analysis, vaccination coverage and vaccination strategies were the main sources of heterogeneity between the predictions of the models (data not shown). However, the meta-regression results are presented separately by vaccination coverage and vaccination strategy, given that significant interactions were observed between these variables and the other model characteristics (appendix pp 18–19). Across all vaccination scenarios, the main source of heterogeneity in predictions for women and men was whether the transmission-dynamic models included (or not) different sexual activity risk groups (appendix pp 18–19). Models that did not include risk groups for sexual activity predicted significantly higher population-level HPV vaccination effectiveness and herd effects. Population-level effectiveness was also significantly higher among models that assume lower natural immunity among women (mostly when vaccine protection is assumed lifelong), or include the natural history of cervical cancer (when vaccine protection is 20 years). These results were similar when examining model predictions for HPV 18.

Discussion

The findings from our systematic review and meta-analysis suggest that HPV vaccination will produce strong herd effects leading to substantial long-term reductions in HPV infection and related diseases in unimmunised women and men. Herd effects are predicted even with vaccination coverage as low as 20%, and to be greater for HPV 18, 6, and 11 types than for HPV 16. Given the substantial herd effects of girls-only vaccination when coverage is moderate to high, the incremental benefit of vaccinating boys is predicted to be small. However, most models predict that vaccinating boys in addition to girls could eliminate HPV 16, 18, 6, and 11, as long as

80% coverage is achieved in both sexes and the vaccine confers long-term protection.

Our findings have important policy implications. First, because of the important herd effects from girls-only vaccination, our models predict that increasing HPV vaccination coverage among girls has greater incremental benefit for both male and female individuals than adding boys to a vaccination programme. The herd effects for heterosexual men are predicted to be about the same magnitude as the level of girls-only vaccination coverage. Given this, the epidemiological and economic considerations about vaccinating boys should focus on the following issues: the feasibility and incremental marginal costs of increasing vaccination coverage among girls versus introducing a gender-neutral programme;[42] whether the price of the vaccine can be reduced for boys for the strategy to be cost-effective; and the importance placed on achieving equal protection for men who have sex with men (MSM).

Second, our models suggest that elimination of HPV 6, 11, and 18 is likely if vaccination coverage of girls and boys reaches 80% and the vaccine provides long-term protection. However, vaccination coverage might have to be slightly higher than 80% to eliminate HPV 16, the type responsible for most of the HPV-related burden. These results also have implications for the recently licensed nonavalent vaccine. Given their prevalence and biological characteristics, the additional types are expected to behave similarly to type HPV 18 and thus be easier to eliminate than HPV 16. It should also be noted that the time to elimination might be shorter than was predicted in the meta-analysis (appendix pp 15–16), because we did not include scenarios with catch-up programmes. Policy makers might want to examine whether to set objectives to eliminate HPV vaccine types in their jurisdictions and set vaccination coverage targets.

Third, post-vaccination reduction of HPV 6 and 11 infections was predicted to be steeper than for HPV 16 and 18 infections, which is due to the shorter durations of infectiousness and lower transmissibility of these low oncogenic risk types.[43] Hence, HPV 6 and 11-related disease (eg, anogenital warts) trends are a poor proxy of change in HPV 16 and 18 and related diseases, and should not be directly extrapolated to inform policy decisions regarding prevention of HPV-related cancers and its precursors.

Fourth, the models predicted substantial herd effects even at relatively lower coverage (40%). However, a recent meta-analysis found evidence of significant herd effects only in higher-coverage settings.[37] Our study findings suggest this difference is likely to be because herd effects take longer to become evident where coverage is lower. Early programme impact data should not be used to rule out herd effects in settings where coverage is low.

This study addresses a key source of concern when using mathematical model results for decision making:

the robustness and validity of predictions. By system-atically identifying published HPV transmission-dynamic models that were independently developed from one another and presenting the distribution of predictions, our analysis provides decision makers with a measure of uncertainty and robustness surrounding model predictions. Reassuringly, the key conclusions of this systematic review were consistent among the models, even though the models were built to represent different countries and varied in structure and assumptions.

According to good modelling practice guidelines, model validation should include between-model corroboration using independent models and, if possible, external or predictive validation.[44] Our systematic review shows high consistency in HPV model predictions of population-level reductions in HPV vaccine types among women and men when vaccination coverage is 80% or higher for girls only and 60% or higher for girls and boys vaccination. The models also consistently predict that post-vaccination reductions will be smaller for HPV 16 than the other vaccine types. However, there is substantial variability in predictions when vaccination coverage is between 40–60%, and when duration of vaccine protection is 20 years. Our meta-regression identified two key model choices or parameters that explain this variability: inclusion of sexual activity risk groups in the model and the level of natural immunity among women. Sexual activity has been shown to be very heterogeneous in populations (eg, skewed distribution of number of partners), leading most models built for prediction of interventions against sexually transmitted diseases to include sexual risk groups. Furthermore, a recent meta-analysis found that the proportion of women who develop natural immunity against a subsequent HPV 16 or 18 infection is greater than 35% when controlling for potential confounders or using neutralising assays.[45] When considering only the predictions of models that include different sexual activity risk groups and that assume that the proportion of women who develop natural immunity is greater than 35%, the variability in predictions is substantially reduced with little impact on the median pooled estimates (eg, at 40% vaccination coverage, the RR_{prev} of HPV 16 among women after girls-only vaccination is 0·52 [80% UI 0·45–0·58] vs 0·53 [0·46–0·68] when considering all predictions (appendix pp 20–21). Finally, although external or predictive validation was beyond the scope of the paper, the descriptive results of the pooled analysis are in line with results from a recent meta-analysis of post-HPV vaccination data,[37] showing strong herd effects shortly after vaccination in countries with high vaccination coverage and very little evidence of herd effects in this timeframe where coverage is low. In addition, models included in the systematic review have previously shown that they reproduce the reduction in HPV 16 and 18 infection[46,47] and anogenital warts consultations observed in the first 5 years after HPV vaccination introduction.[48]

Our main findings are likely generalisable to most high-income countries given that they are based on models from ten of these countries and very little heterogeneity remains when results are stratified by vaccination coverage, vaccination strategy, and key model characteristics. In addition, there are similarities in sexual behaviour,[49] HPV type distribution,[50,51] and age profile of HPV prevalence[52] among high-income countries. However, our predicted herd effects and potential for elimination should be extrapolated to low-income and middle-income countries (LMIC) with caution, because there are important differences between high-income countries and LMICs in sexual behaviour and potential cofactors of HPV such as high HIV prevalence.[49,53,54]

The study has two main limitations that should be considered, in addition to those inherent in meta-analysis.[55,56] First, although the models were built independently from one another and showed variability in their structures, similarities remain in key structural assumptions, which could contribute to the consistency of findings. None of the models included MSM, incorporated multisite infection or transmission (transmission between oral, anal, and genital sites), or the possibility of reactivation. Modelling HPV transmission between men would be unlikely to have an effect on predictions about the herd effects of girls-only vaccination, but could slightly impact predictions about elimination. Including higher risk groups or MSM, who have greater HPV prevalence (and higher R_0), would make it more difficult to eliminate HPV, and therefore the coverage required for elimination could be higher than estimated by the models in the systematic review. On the other hand, recent modelling studies suggest that adding multisite transmission or reactivation would probably have very little impact on long-term predictions about the population-level effectiveness of HPV vaccination.[57,58] Second, we purposely decided to examine the predicted impact of vaccination on HPV infection rather than disease endpoints, as the main focus of the paper is on herd effects and elimination of HPV vaccine types. Additional uncertainty in HPV model predictions, when examining the impact of vaccination on disease endpoints, will be in the absolute reduction of HPV burden of disease (related to country specific pre-vaccination burden of disease and proportion due to the vaccine types) and the timing of these benefits (related to assumptions about progression from infection to lesions or cancer).

To our knowledge, our study includes a greater number of models than any published comparison of infectious disease models, reflecting the influential role that modelling has played in HPV vaccination policy decisions. Furthermore, this is the first model comparison study in which systematic review methodology was used to identify all potentially eligible mathematical models (reducing possible selection bias); independence of models was controlled for by including

only one model per team and producing predictions for predetermined and standardised scenarios without prior harmonisation of model structures or natural history parameters; and meta-analytic techniques were used to describe the central tendency and variability of predictions and identify sources of heterogeneity in results. Finally, our study shows that the HPV models developed over the past decade give consistent results in terms of population-level effectiveness against infection, herd effects, and the possibility of elimination, which could be reassuring for decision makers using these models for vaccination policy decisions. We also identified key HPV modelling choices (ie, inclusion of sexual risk groups, natural history of cervical cancer, and natural immunity) that have the greatest influence on model predictions, which should guide the future development of models.

In conclusion, the results of this study indicate strong promise for the long-term population-level impact of HPV vaccination programmes. However, it will be important to continue to validate HPV model predictions and to compare them to post-vaccination surveillance data, as many policy decisions about HPV vaccination (ie, number of doses, which vaccine to use, and vaccination of boys) and cervical cancer screening remain.

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