EXECUTIVE SUMMARY

Modelling estimates of the incremental effectiveness & cost-effectiveness of HPV vaccination

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BACKGROUND

Since 2007, 65 out of 195 countries worldwide have implemented human papillomavirus vaccination (HPV)[1, 2]. A recent systematic review and meta-analysis of the observed population-level impact of HPV vaccination has provided compelling empirical evidence from high income countries (HIC). This evidence suggests that girls-only HPV vaccination programs are 1) effective at the population-level and 2) provide herd effects against HPV 16/18 infection and anogenital warts, and 3) that the impact of vaccination follows a dose-response relationship with vaccination coverage (i.e., greater effects with higher coverage/greater percent of the population that is vaccinated)[3]. More specifically, in countries with high vaccination coverage among girls (≥ 50%), significant decreases in HPV-16/18 infections (reduction of 68%), anogenital warts (reduction of 61% vs pre-vaccination) and CIN2+ lesions (reduction of 31%) have been observed in girls aged 15-19 years, over the first 4 years of vaccination[3]. Significant reductions were also noted for older women aged 20-24. Among boys aged 15-19 years old, anogenital warts decreased significantly by 34% and new data from Australia show non-significant decreases in HPV-16/18 (reduction of 63%) between the pre- and post-vaccination periods[4]. In countries with lower coverage among girls (<50%), significant decreases were observed for HPV-16/18 infections (reduction of 50% vs pre-vaccination) and anogenital warts (reduction of 14%) among girls 15-19 years of age, but no significant herd effects were observed. The systematic review did not identify differences between the bivalent and quadrivalent HPV vaccines in their population-level effectiveness against HPV-16/18, and HPV-31/33/45; all the studies were conducted prior to the introduction of the nonavalent vaccine.

At this time, there is very little empirical data on the added population-level impact of a gender-neutral compared to a girls-only HPV vaccination program. A recent update of the systematic review of the population-level impact of HPV vaccination identified eligible studies in only 3 countries (Australia, USA and Canada) having recently implemented gender-neutral programs [5]. Unfortunately, the maximum follow-up available in the identified eligible articles was 1-2 years following a switch from girls-only to gender neutral vaccination, which makes it impossible to measure the added impact of vaccinating boys. In addition, the updated systemic review was unable to isolate the population-level impact of vaccinating multiple age cohorts (which can amount to catch-up vaccination when implemented outside of the primary age target of 9-13 years) from routine immunization of a single cohorts, as the great majority of countries with high vaccination coverage (6/8) also have included catch-up vaccination (i.e., too few countries with no catch-up for comparisons). Finally, the systematic review did not find studies comparing pre- and post-vaccination periods from low to middle income countries (LMIC).

There are, thus, many remaining questions: What is the incremental effectiveness and cost-effectiveness of 1) different HPV vaccines based on girls-only immunization, 2) gender-neutral vs girls-only HPV immunization, and 3) vaccinating multiple age cohorts versus a single age cohort in HIC and LMIC? Mathematical models provide a formal framework to examine these questions, which cannot be answered in trials, or, for the time being, in post-introduction impact evaluations.

OBJECTIVES

We used mathematical modeling and literature reviews to examine the potential incremental effectiveness and cost-effectiveness of:

   a. <u>different HPV vaccines</u> for girls-only vaccination (cervical cancer prevention)
   b. <u>gender-neutral</u> vs girls-only vaccination (prevention of HPV-related diseases)
   c. <u>multiple female cohorts</u> (multiple age cohorts within a defined age range) compared to single age cohort immunization of girls aged 9–13 years (cervical cancer prevention)

METHODS

Results for HIC are mainly based on a systematic review and meta-analysis of transmission-dynamic modeling studies (published between 2009-2015) that predicted the population-level impact of vaccination on HPV6/11/16/18 infections in high-income countries[6]. Additional results are based on HPV-ADVISE (Agent-based Dynamic model for VaccInation and Screening Evaluation). The model has been extensively described [7-9] and has been used to inform previous HPV vaccine policy decisions in the United States and Canada [8-13]. HPV-ADVISE is an individual-based transmission-dynamic model of HPV infection and disease. It includes 18 HPV genotypes (including the 9 types in the 9-valent vaccine: 6/11/16/18/31/33/45/52/58). In addition, a literature review was conducted to identify previously published cost-effectiveness studies of HPV vaccination.

For LMIC, population-level effectiveness and cost-effectiveness predictions are based on two models: HPV-ADVISE LMIC and PRIME (Papillomavirus Rapid Interface for Modelling and Economics)[14]. For HPV-ADVISE LMIC, HPV-ADVISE was calibrated to India, Vietnam, Uganda, Tanzania, and Benin, using comprehensive demographic, sexual behavior and epidemiological data available from international databases (Demographic and Health Surveys (DHS)[15], ICO information Centre on HPV and Cancer[16], Multiple Indicator Survey (MICS)[17], United Nations Statistics Division[18], HIV and AIDS HUB for Asia Pacific-Evidence to action[19]; WHO Global Health Observatory data repository[20]) and original studies[21-26]. PRIME (Papillomavirus Rapid Interface for Modelling and Economics) is a static proportional impact model developed in collaboration with WHO to estimate the impact and cost-effectiveness of introducing HPV vaccination to girls prior to sexual debut in 94 of the original 179 countries across the world[14].

SUMMARY OF FINDINGS
Girls-only immunization

Girls-only HPV vaccination (vs no vaccination):

- <u>Population-level effectiveness</u>. The systematic review and meta-analysis, representing pooled predictions from 16 independent transmission-dynamic models from 10 HIC[6], suggests that HPV vaccination will produce strong herd effects leading to substantial long-term reductions in HPV infection and related diseases in unimmunized women and men (Figure 1). Herd effects are predicted even with vaccination coverage as low as 40%, and to be greater for HPV18, HPV6 and HPV11 than

HPV16 (Figure 1). Results from HPV-ADVISE LMIC (India, Vietnam, Uganda, Tanzania, and Benin) are consistent with those from the HIC models.

- Cost-effectiveness. Despite variations in methods, modeling studies from HIC[27-41] and LMIC (PRIME)[14] are producing consistent conclusions. At current prices of the 2- and 4-valent vaccines, girls-only vaccination is cost-effective (vs no vaccination) irrespective of the vaccine used, even when assuming no cross-protection or herd protection. In a global analysis using PRIME[14], girls-only vaccination was cost-effective even when including only the direct impact on vaccinated women and cervical cancer as an outcome, and using different cost-effectiveness thresholds.
- The main driver of the population-level benefit and cost-effectiveness of Girls-only HPV vaccination is the prevention of HPV-16/18 related cervical cancer.

9-valent Girls-only vaccination (vs 2- or 4-valent)

- Very few modeling studies have examined the incremental population-level effectiveness and cost-effectiveness of 9-valent vaccination vs 2- or 4-valent vaccination[10, 12, 42-45].
- Population-level effectiveness. Current models from HIC[10, 12, 42-44] and LMIC (PRIME)[14] predict that switching to a 9-valent vaccination strategy would further reduce precancerous cervical lesions and cervical cancer, with very little impact on non-cervical HPV-related outcomes. However, importantly, the magnitude of the incremental benefits of the 9-valent at preventing cervical cancer outcomes strongly depends on assumptions regarding the level and duration of cross-protection provided by 2- or 4-valent vaccines.
- Cost-effectiveness. In HIC, switching to a 9-valent program is predicted to be cost-effective in Canada, Austria, and cost saving in the U.S., if the cost/dose of the 9-valent is assumed to be 10-15% greater than the 4-valent [10, 12, 42-44]. In a global analysis using PRIME[14], Girls-only 9-valent vaccination was estimated to be cost-effective in LMIC (vs 2-valent or 4-valent, using 1xGDP as the cost-effectiveness threshold), assuming 2-dose vaccination and the cost/dose of the 9-valent was in the same range as the 2- and 4-valent vaccines. The 9-valent was not cost-effective (vs 2-valent), under assumptions of maximum cross-protection for the 2-valent vaccine.

Gender-neutral immunization

- Population-level effectiveness. Given the predicted substantial herd effects of Girls-only vaccination when coverage is moderate to high, the incremental benefit of vaccinating adolescent boys is predicted to be limited in HIC (Figure 1a - Systematic review of models in HIC). Results from LMIC suggest that Girls-only vaccination may produce lower herd–effects than in HIC (Figure 1b, example for HPV-ADVISE INDIA). However, this result depends on sexual behaviour, which is highly variable between LMIC. In some LMIC, where a large proportion of females marry (having had no pre-marital sex partners) and have no other sexual partner in their lifetime. In these countries, HPV transmission is predicted to be through the husbands who have concurrent partnerships or are clients of sex workers. In these cases, gender-neutral vaccination that includes adolescent boys may provide

substantial benefits for women (in particular if vaccination coverage is low among at-risk girls who are harder to reach with vaccination).

- Potential for HPV elimination: Importantly, the majority of models in the systematic review predict that vaccinating boys in addition to girls in HIC could eliminate HPV16/18/6/11, provided 80% coverage is achieved in both sexes and the vaccine confers long-term protection (Figure 1a). This result was not found in the LMIC that were modelled (Figure 1b, example for HPV-ADVISE INDIA)).

- Cost-effectiveness: Models from HIC have consistently shown that, if the HPV vaccination coverage in girls is greater than approximately 50%, gender-neutral vaccination is unlikely to be cost-effective (vs Girls-only vaccination [40, 41].

- The epidemiological and economic considerations about vaccinating boys should focus on the following issues: 1) the feasibility and incremental marginal costs of increasing vaccination coverage among girls versus introducing a gender-neutral program[46], 2) whether the price of the vaccine can be sufficiently reduced for boys in order for the strategy to be cost-effective, and 3) importance placed on achieving equal protection for MSM.

**Single and multiple age cohort immunization**

- Population-level effectiveness. In HIC and LMIC, vaccinating multiple age cohorts is predicted to result in a substantially shorter time in achieving the impact of the vaccination than vaccination of single age cohorts (Figure 1). However, the impact of multiple age cohort vaccination could be reduced in countries with early age at HPV infection.

- Cost-effectiveness. In a global analysis using PRIME, vaccinating multiple cohorts of girls is cost-effective in the age range of 9–14 years (vs single age cohort), particularly when a 2-dose schedule is used. The incremental cost-effectiveness for additional age cohort of girls and women aged ≥15 years is reduced as 3-dose schedule are required and proportionally more girls/women will already have been infected.

FIGURE 1. Population-level impact and herd effects of Girls-only and Girls&Boys HPV vaccination.

A) High income Countries - Pooled predictions from 16 models.
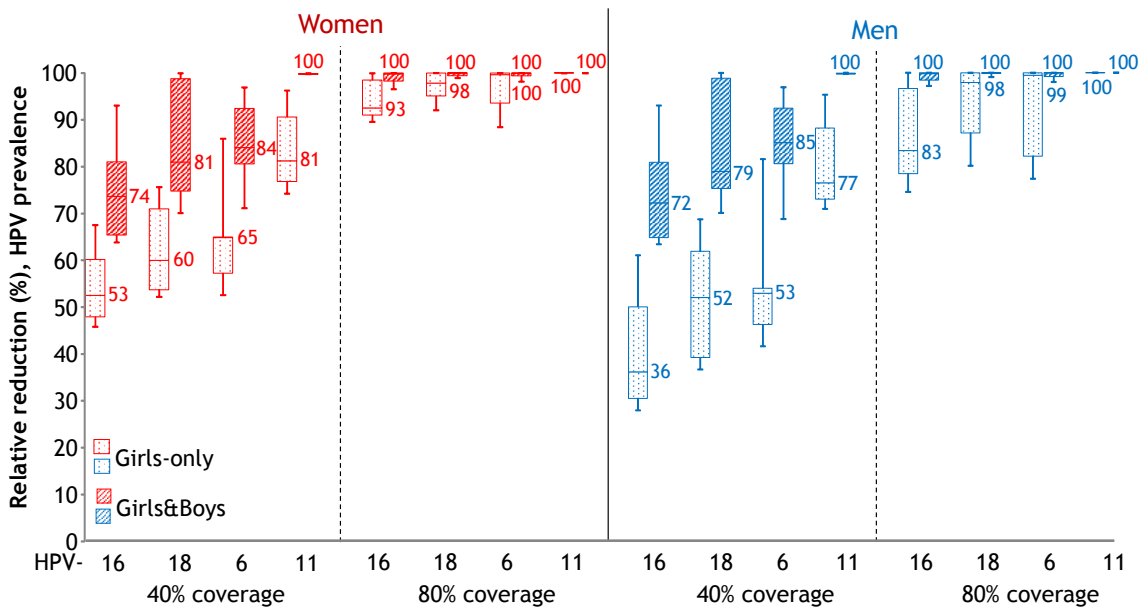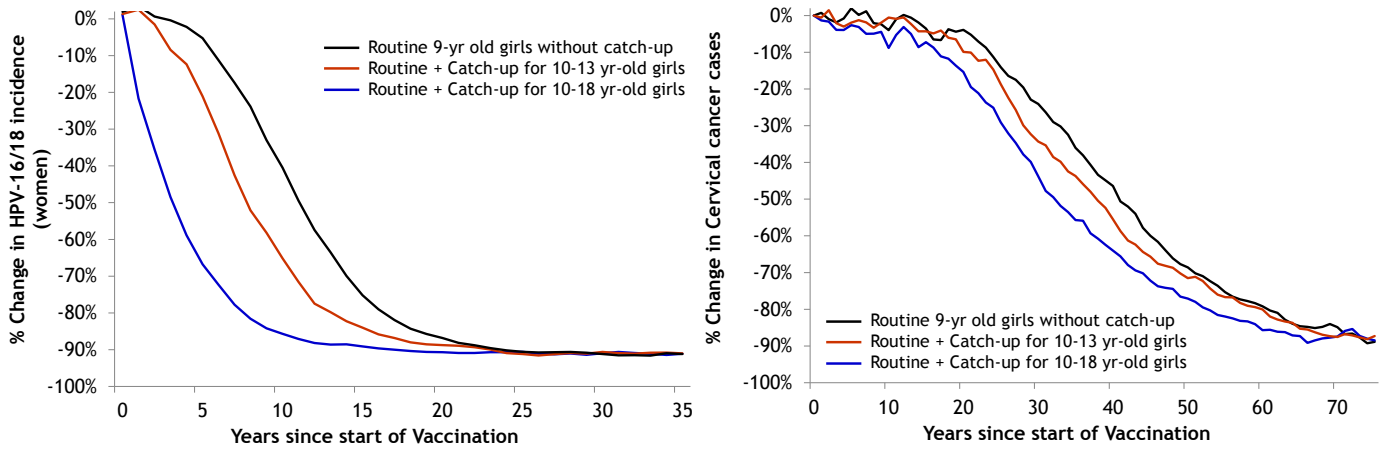
**B) Low to Middle Income Country (India) -** Predictions from HPV-ADVISE INDIA
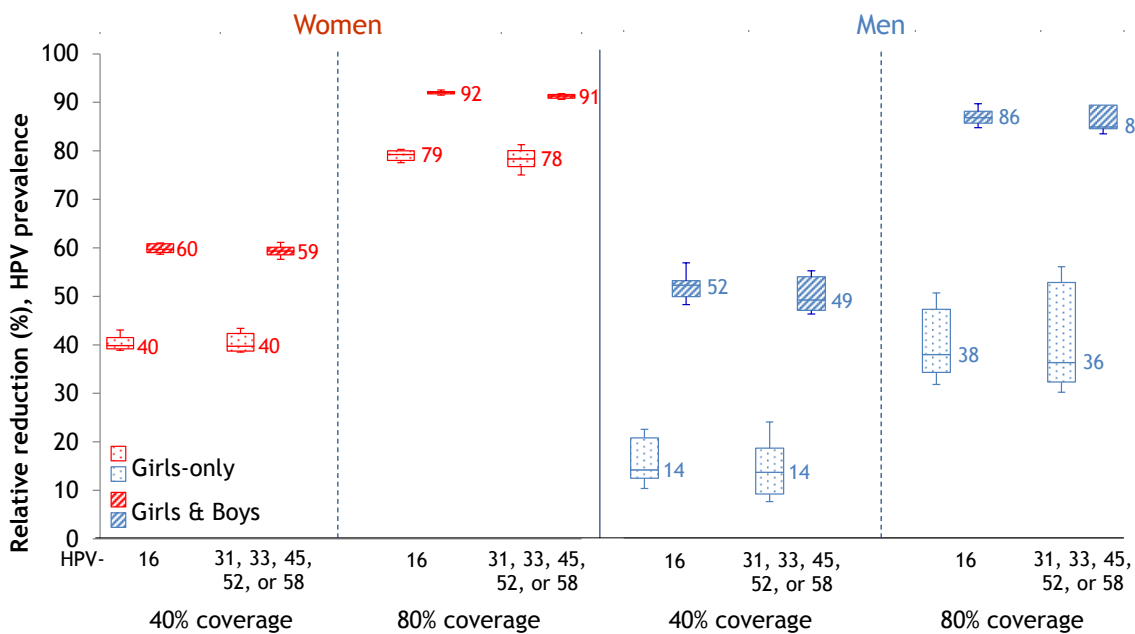
Relative reduction of HPV prevalence among women and men following 70 years of Girls-Only and Girls&Boys vaccination. Herd effects=reduction of HPV prevalence in Men with Girls-only vaccination. Girls-Only: Vaccination of girls only; Girls&Boys: Vaccination of girls and boys. The pooled estimates represent median and 10th, 25th, 75th, and 90th percentiles of the predictions of the 16 models in the systematic review (Figure 1A) and the best fitting parameter sets for HPV-ADVISE INDIA (Figure 1B). Predictions were performed using the following vaccine characteristics: Vaccine efficacy=100% and Duration of vaccine protection=Lifelong.

FIGURE 2. Population-level impact of single and multiple age cohort Girls-only HPV vaccination.

A) High income Countries (Canada) - Predictions from HPV-ADVISE Canada

B) Low to Middle Income Country (India) - Predictions from HPV-ADVISE INDIA
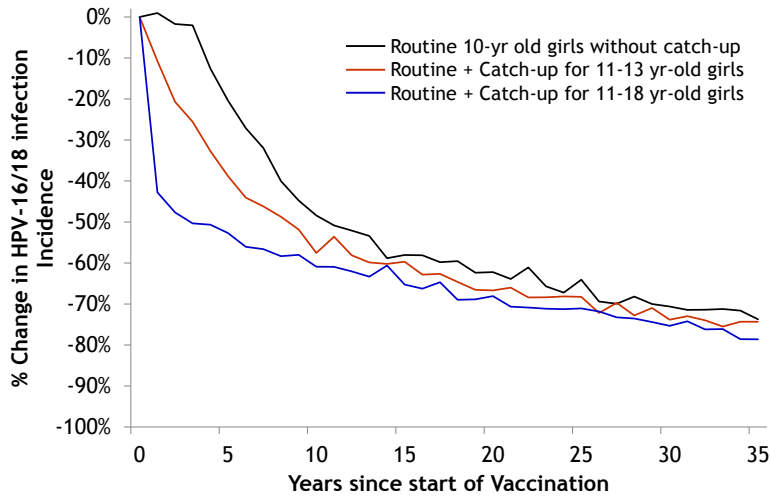
Reduction of HPV-16/18 prevalence and cervical cancer among women over time since vaccination. Girls-Only: Vaccination of girls only. Predictions were performed using the following vaccine characteristics: Vaccination coverage=80-%, Vaccine efficacy=95%, and Duration of vaccine protection=Lifelong.

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