The Impact of Human Papillomavirus Catch-Up Vaccination in Australia: Implications for Introduction of Multiple Age Cohort Vaccination and Postvaccination Data Interpretation

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We used transmission-dynamic modeling to estimate the added effectiveness of vaccinating multiple cohorts of females (12–26 years) in Australia compared with the theoretical introduction of routine-only (12–13 years) vaccination. Our results suggest that vaccinating multiple cohorts produced markedly faster direct/indirect effects, and it added benefits that last for 20–70 years. Furthermore, the number needed to vaccinate to prevent 1 anogenital warts (AGW) case or cervical cancer (CC) was similar for routine + catch-up (AGW = 9.9, CC = 678) and routine-only vaccination (AGW = 9.9, CC = 677), thus providing similar levels of efficiency per person vaccinated.

Keywords: anogenital warts; cervical cancers; human papillomavirus; mathematical modeling; vaccination.

In October 2016, the World Health Organization’s Strategic Advisory Group of Experts on Immunization (SAGE) revised its position to recommend human papillomavirus (HPV) vaccination of multiple age cohorts of girls (9–14 years old) when introducing the vaccine in a country, rather than vaccination of a single cohort [1]. In addition, if resources are available, the age range could be expanded up to 18 years old [1]. Before this recommendation, several high-income countries had introduced multiple age-cohort HPV vaccination, mostly as catch-up campaigns, whereas lower- to middle-income countries have mostly introduced HPV vaccination for a single age cohort [2]. Among high-income countries, Australia had the most comprehensive HPV vaccination program, including school-based routine vaccination of 12- to 13-year-old girls and catch-up of 14- to 26-year-old females (2007–2009) [3]. Since 2013, the program also includes routine vaccination of 12- to 13-year-old boys and a catch-up of 14- to 15-year-old boys (2013–2014) [3].

As a result of its comprehensive quadrivalent HPV vaccination program and high vaccination coverage, Australia showed the sharpest postvaccination declines in HPV infections, anogenital warts (AGW), and precancerous cervical lesions among countries identified in a recent systematic review [4]. Using traditional epidemiological analyses of postvaccination surveillance data, it is impossible to estimate the added population-level benefits of vaccinating multiple cohorts (routine + catch-up) and those provided by the routine girls-only program. The aim of this study was to use mathematical modeling to estimate the incremental population-level effectiveness of catch-up vaccination in Australia on AGW and cervical cancer compared with routine (single age cohort) girls-only vaccination. This information can help countries decide whether or not to include multiple age cohort vaccination.

METHODS

We used HPV-Agent-based Dynamic model for Vaccination and Screening Evaluation (HPV-ADVISE), an individual-based transmission-dynamic model that includes 18 HPV types [5] (technical appendix: http://www.marc-brisson.net/HPVadvise.pdf). The model comprises 6 fully integrated components: sociodemographic characteristics, sexual behavior and HPV transmission, HPV-related diseases, vaccination, screening and treatments, and economics. To identify model parameters, the model was calibrated to 678 prespecified sexual behaviors, HPV epidemiology, and screening data targets (see [5] for details). Ten parameter sets, producing the best model fit to data, were used for model predictions [5]. In our base-case scenario, we assumed that the quadrivalent vaccine provides lifelong protection and 95% vaccine efficacy with 3 doses against HPV 6/11/16/18. Cross-protection against HPV 31/33/45/52/58 was taken from a systematic review of clinical trials [6]. Of note, for individuals <21 year old, we assumed 95% vaccine efficacy between the 1st–2nd and 2nd–3rd doses, whereas for individuals ≥21 years old, we assumed 95% vaccine efficacy after the 3rd dose, with no protection for <3 doses. These assumptions produced the best model fit to Australia’s time-specific declines in AGW and are in agreement with immunogenicity data showing noninferiority of less than 3 doses among girls compared with women [7].

We compared 2 vaccination scenarios: (1) routine + catch-up vaccination and (2) routine vaccination only. Table A1 in the Appendix presents the vaccination coverage data used for both scenarios, which are based on observed data from Australia [8].
Of note, for both scenarios, girls-only vaccination started in 2007 and was switched to the gender-neutral vaccination in 2013.

The percentage change in AGW and cervical cancer cases (both squamous cell carcinoma and adenocarcinoma) were used as primary model outcomes. The added benefit of the routine + catch-up compared with routine vaccination only was estimated by the difference in the percentage change in AGW and cervical cancer cases after vaccination between the 2 vaccination strategies. For AGW cases, we only considered the first consultation. We assumed that the delay between HPV infection and consultation was 4 months (minimum [min] = 0; maximum [max] = 8) for women and 10 months (min = 0; max = 29) for men [9, 10]. The maximum delay between HPV infection and consultation was obtained by using the 75th percentile of data from empirical studies [9, 10]. We used the number needed to vaccinate (NNV) to prevent 1 AGW or 1 cervical cancer case as a secondary outcome, to estimate the efficiency of the vaccination program (ie, effectiveness per person vaccinated). The NNV was calculated as the number of people vaccinated divided by the number of events prevented. The NNV predictions are presented using the mean (80% uncertainty interval [UI] = 10th–90th percentiles) of simulations.

RESULTS

Figure 1 illustrates the difference in the predicted reduction in AGW cases over time since the start of vaccination in Australia, with and without catch-up vaccination. Our model predictions reproduced the reported steep declines in age-specific AGW cases among Australian girls/women and boys/men with routine vaccination.

**Figure 1.** Short-term impact of human papillomavirus (HPV) vaccination in Australia on anogenital warts cases (routine vaccination with or without catch-up): model predictions compared with empirical data. (A) Girls aged <21 years old. (B) Boys aged <21 years old. (C) Women aged 21–30 years old. (D) Men aged 21–30 years old. BASE CASE: Vaccine efficacy against vaccine types = 95%; duration of protection = lifelong; percentage of anogenital warts (AGW) caused by HPV-6, -11 = 90%; delay between HPV infection and consultation = 3.9 and 9.8 months for women and men, respectively [9, 10]. Of note, for individuals <21 year old, we assumed 95% vaccine efficacy between the 1st–2nd and 2nd-3rd doses, whereas for individuals ≥21 years old, we assumed 95% vaccine efficacy after the 3rd dose, with no protection for <3 doses. AUSTRALIAN HPV VACCINATION PROGRAM MODELED: From 2007 to 2012: Girls-only vaccination (routine 12–13 years old, catch-up 14–26 years old 2007–2009); Since 2013: Gender-neutral program (routine girls and boys 12–13 years old, catch-up of boys 14–15 years old 2013–2015). PREDICTIONS: Median estimate generated by the 10 best-fitting parameter sets. Each parameter set run 20 times. Minimum (Min) of model predictions: minimal reductions in AGW obtained with the 90th percentile of model predictions; percentage of AGW caused by HPV-6, -11 = 85%; delay between HPV infection and consultation for AGW = 7.7 and 28.8 months for women and men, respectively. Maximum (Max) of model predictions: maximal reductions in AGW obtained with the 10th percentile of model predictions; percentage of AGW caused by HPV-6, -11 = 95%; no delay between HPV infection and consultation for AGW for women and men.
+ catch-up vaccination (Figure 1). Empirical data indicate that AGW decreased by 90% among girls aged <21 years old after 5 years of vaccination, whereas our model predicts an 87% (min = 82%; max = 93%) decrease (Figure 1A). On the other hand, when examining the counterfactual of routine vaccination only, our model predicts a 38% (min = 32%; max = 43%) decrease in AGW after 5 years of vaccination, resulting in an incremental reduction of AGW due to catch-up vaccination of 49 percentage points. Similarly, 5 years after the introduction of girls-only HPV vaccination, our model predicts an incremental reduction of AGW due to catch-up vaccination of 65 percentage points among men <21 years old and 59 and 56 percentage points among women and men ≥21–30 years old, respectively (Figure 1B–D). Our model also predicts considerable long-term benefits of catch-up vaccination on AGW and cervical cancer cases (Figure 2). Our model predicts that the incremental reductions in AGW cases (Figure 2A and B) and cervical cancers (Figure 2C) due to catch-up vaccination will persist up to 25 and 70 years after the introduction of HPV vaccination, respectively.

The vaccination efficiency (effectiveness per person vaccinated) was predicted to be relatively similar for the catch-up versus the routine-only vaccination program. The predicted NNV to prevent 1 AGW case and 1 cervical cancer are 9.9 (80% UI, 9.6–10.1) and 677 (80% UI, 549–802), respectively, for Australia's HPV vaccination program (routine + catch-up vaccination, girls-only 2007–2012; gender-neutral since 2013) (Appendix Table A2). For routine vaccination only, the predicted NNV to prevent 1 AGW case and 1 cervical cancer are 9.9 (80% UI, 9.5–10.1) and 678 (80% UI, 584–842), respectively. Finally, when examining the incremental NNV of catch-up vaccination, our model predicts that 1 additional case of AGW and 1 additional cervical cancer would be prevented for every 10.5 (80% UI, 9.5–10.9) and 512 (80% UI, 260–683) individuals vaccinated through catch-up vaccination, respectively.

Discussion

Our modeling analysis suggests that the rapid declines in AGW and strong herd effects observed in Australia are largely attributable to catch-up vaccination. In the short-term, our model reproduced the observed declines in AGW among girls/women, boys/men. Furthermore, our model estimated that, 5 years after the start of vaccination, Australia's catch-up program contributed to more than half of the observed reduction in AGW. In the long-term, our model predicts that the additional reductions in AGW cases and cervical cancers due to catch-up will persist for decades after the introduction of HPV vaccination.

Two possible arguments against multicohort vaccination programs are that they would be less efficient than a routine program, because a proportion of older individuals (1) will have previously been infected at the time of vaccination (vaccine would be ineffective as it is prophylactic) and/or (2) will be protected through herd effects from a routine program.
(redundancy in vaccine protection). Our model estimated that the catch-up component of Australia’s program was as efficient in terms of AGW and cervical cancer prevention as the routine program (eg, NNV in the catch-up cohorts to prevent an additional AGW case was 10.5 vs 9.9 for the NNV in the routine vaccination cohort). Given that these results depend on the age distribution of individuals in the multiple cohorts vaccinated in the catch-up, we further stratified the NNV into the routine only cohort, the catch-up cohort of 14- to 18-year-olds, and the catch-up cohort of 19- to 26-year-olds. The predicted incremental NNV to prevent 1 AGW case in Australia was 9.9 for routine-only vaccination, 6.8 for the catch-up cohort of 14- to 18-year-olds, and 20.0 for the catch-up cohort of 19- to 26-year-olds. For generalization to settings with girls-only vaccination, we also examined a girls-only scenario (using the female-only coverage in Australia without the introduction of adolescent male vaccination in 2013), and we estimated that the NNV to prevent 1 AGW for girls-only routine vaccination was 5.5, 4.9 for the catch-up cohort of 14- to 18-year-olds, and 18.2 for the catch-up cohort of 19- to 26-year-olds (see Appendix Table A2). These results suggest that losses in efficiency by vaccinating previously infected individuals is counterbalanced by the enhanced short-term herd effects of vaccinating multiple cohorts before age 18 years (but not after), and that vaccinating multiple cohorts up to 18 years of age is a highly efficient HPV vaccination strategy. These results are consistent with previous economic analyses, which indicate that catch-up vaccination of girls up to age 18 years produces is cost effective, but that HPV vaccination of 18- to 26-year-old women is unlikely to be cost effective [11].

To our knowledge, this is the first study to estimate the benefit of different vaccination strategies, by using mathematical modeling to produce counterfactual scenarios to observed postvaccination population-level surveillance data. As more postvaccination surveillance data become available, it will be important to validate and calibrate mathematical model predictions to observed postvaccination data to (1) help interpret and understand surveillance data and (2) increase robustness of model predictions for future vaccination decisions. A limitation of our analysis is that we used a model that was calibrated to Canada for predictions in Australia. However, the HPV epidemiological data and sexual activity are very similar between Australia and Canada [12], and the model perfectly reproduced short-term decreases in AGW observed in Australia, without recalibrating the model.

The results have 2 main implications. First, our results can be used by public health officials to make recommendations about whether to introduce multicohort vaccination. Second, our results show that both vaccination coverage and the number of cohorts vaccinated should be considered (percentage of individuals vaccinated) when examining differences in post-vaccination surveillance data between countries/regions rather than vaccination coverage in a specific age group. For example, in countries/regions with high vaccination coverage of a single cohort of girls, decreases in AGW were observed 4–5 years after the implementation of vaccination (eg, Ontario, Canada) [13], whereas in countries vaccinating multiple cohorts of girls with high coverage, substantial decreases and strong herd effects were observed in the year after the implementation of their vaccination programs (eg, Australia, Denmark) [14]. The percentage of individuals vaccinated is also important to understand why countries such as the United States, which have low to medium vaccination coverage but in multiple cohorts, have postvaccination effectiveness not dissimilar to countries with high coverage but with routine-only vaccination of 1 cohort [15].

**Conclusions**

In conclusion, the rapid declines in AGW and strong herd effects observed in Australia are largely attributable to catch-up vaccination, in combination with high routine vaccination coverage. Furthermore, the incremental benefits of catch-up vaccination (or multiple cohort vaccination) are expected to last for decades. Policymakers should consider multiple cohort vaccination (up to 18 years of age) to obtain faster population-level effects and stronger herd effects, because such a strategy is as efficient, in terms of effectiveness per person vaccinated, as routine vaccination of 1 cohort.

**Supplementary Data**

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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**Potential conflicts of interest.** During the past 3 years, M. D. has done consulting work once for GlaxoSmithKline (herpes zoster vaccine). During the past 3 years, J. M. L. B. has received partial, unrestricted research funding for human papillomavirus (HPV) typing in an epidemiological study of recurrent respiratory papillomatosis from Merck and for HPV typing...
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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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