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Comparing the cost-effectiveness of two- and three-dose schedules of human papillomavirus vaccination: A transmission-dynamic modelling study

Jean-François Laprise[a], Mélanie Drolet[a,b], Marie-Claude Boily[c], Mark Jit[d,e], Chantal Sauvageau[a], Eduardo L. Franco[f], Philippe Lemieux-Mellouki[a,b], Talía Malagón[a,b], Marc Brisson[a,b,c,*]

[a] Centre de recherche du CHU de Québec, Québec, Canada
[b] Département de médecine sociale et préventive, Université Laval, Québec, Canada
[c] Department of Infectious Disease Epidemiology, Imperial College, London, United Kingdom
[d] Modelling and Economics Unit, Public Health England, United Kingdom
[e] Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom
[f] Division of Cancer Epidemiology, McGill University, Montreal, Canada

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ABSTRACT

Background: Recent evidence suggests that two doses of HPV vaccines may be as protective as three doses in the short-term. We estimated the incremental cost-effectiveness of two- and three-dose schedules of girls-only and girls & boys HPV vaccination programmes in Canada.
Methods: We used HPV-ADVISE, an individual-based transmission-dynamic model of multi-type HPV infection and diseases (anogenital warts, and cancers of the cervix, vulva, vagina, anus, penis and oropharynx). We conducted the analysis from the health payer perspective, with a 70-year time horizon and 3% discount rate, and performed extensive sensitivity analyses, including duration of vaccine protection and vaccine cost.
Findings: Assuming 80% coverage and a vaccine cost per dose of $85, two-dose girls-only vaccination (vs. no vaccination) produced cost/quality-adjusted life-year (QALY)-gained varying between $7900–24,300. The incremental cost-effectiveness ratio of giving the third dose to girls (vs. two doses) was below $40,000/QALY-gained when: (i) three doses provide longer protection than two doses and (ii) two-dose protection was shorter than 30 years. Vaccinating boys (with two or three doses) was not cost-effective (vs. girls-only vaccination) under most scenarios investigated.
Interpretation: Two-dose HPV vaccination is likely to be cost-effective if its duration of protection is at least 10 years. A third dose of HPV vaccine is unlikely to be cost-effective if two-dose duration of protection is longer than 30 years. Finally, two-dose girls & boys HPV vaccination is unlikely to be cost-effective unless the cost per dose for boys is substantially lower than the cost for girls.

1. Introduction

The majority of high income countries have introduced three-dose routine human papillomavirus (HPV) vaccination programmes [1]. Although most countries are vaccinating girls/women, only the US, Australia and one Canadian province (Prince Edward Island) have included boys in their routine HPV vaccination programmes. The most commonly used HPV vaccine in high income countries (including Canada, the UK, the US and Australia) is the quadrivalent [1], which protects against HPV-16/18 (responsible for more than 70% of cervical cancers [2] and associated with other anogenital [3,4] and head and neck cancers [5]) and HPV-6/11 (associated with more than 85% of anogenital warts [6]). Although vaccinating girls against HPV is expected to dramatically reduce the burden of HPV-associated diseases [7,8] and to be highly cost-effective [9–11], it nevertheless imposes an important financial strain on immunisation budgets. In Canada, HPV vaccine

* Corresponding author at: Centre de recherche du CHU de Québec, Axe Santé des populations et pratiques optimales en santé Québec, 1050 Chemin Sainte-Foy, Québec, Canada G1S 4L8. Tel.: +1 418 682 7386; fax: +1 418 682 7949.
E-mail addresses: marc.brisson@uresp.ulaval.ca, mbrisson@uresp.ulaval.ca (M. Brisson).

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represents 40% of the total cost to fully immunise a girl from infancy to adolescence (Dr. Bruno Turmel, Quebec Ministry of Health and Social Services, Personal communication) [12]. Decision-makers may thus be interested in the possibility of reducing doses of HPV vaccine to invest the funds on improving coverage to underserved populations, male HPV vaccination or other immunisation programmes.

Recent evidence suggests that two doses of HPV vaccine may be as protective as three doses in the short-term. A nested nonrandomised analysis within a phase III randomised clinical trial in Costa Rica suggested that two doses of HPV vaccine has similar high efficacy against vaccine-type persistent infections as three doses, four years after vaccination [13]. More recently, a phase III randomised trial examined the immunogenicity of two doses in girls 9–13 years compared to three doses in girls 9–13 years and three doses among young women 16–26 years. Results from the study showed that antibody responses for the vaccine-types among girls (9–13 years) who received two doses were noninferior to those among young women (16–26 years) who received three doses, over a period of three years after the last vaccine dose [14]. However, antibody responses to HPV-18 at two years and HPV-6 at three years were significantly lower for girls (9–13 years) who received two doses vs. girls (9–13 years) who received three doses. Because noninferiority did not persist over time for all vaccine types when directly comparing the two groups of girls aged 9–13 years, the authors of the clinical trial, and those from the accompanying editorial [15], concluded that more data on duration of protection is required before reduced-dose schedules are recommended or implemented. However, such information will not be available for several years. Furthermore, data on duration of protection is not typically available when new vaccines are introduced (e.g., duration of three-dose HPV vaccine protection is still unknown).

Mathematical models are particularly well-suited and increasingly used to provide timely evidence to inform immunisation policy-decisions when empirical data is scarce or incomplete [16], as they provide a formal framework to synthesise information from various sources (e.g., clinical trials, epidemiological studies) to make predictions about the population-level effectiveness and cost-effectiveness for different what-if scenarios (e.g., vaccinating girls-only or girls and boys, different durations of vaccine protection). To our knowledge, no model has examined the cost-effectiveness of two-dose HPV vaccination or the optimal combination of number of HPV vaccine doses and vaccination strategy (e.g., girls-only vs. girls and boys). The objectives of this study were to: (i) estimate the incremental cost-effectiveness of two- and three-dose schedules of girls-only and girls & boys HPV vaccination programmes, and (ii) identify the duration of two- and three-dose HPV vaccine protection necessary for a third dose to be cost-effective.

2. Methods

2.1. Study design & economic analysis

HPV-ADVISE, an individual-based transmission-dynamic model of multi-type HPV infection and disease, was used for model predictions [8,17,18]. Cost–utility analysis (cost/QALY-gained) was chosen as the analytic technique and the analysis was performed using the healthcare payer perspective. Costs were inflated to 2010 Canadian dollars using the Canadian Consumer Price Index for Health. Costs and outcomes were discounted at 3%/year. A 70-year time-horizon was chosen for our reference-case (average life-expectancy of the first cohort of vaccinated girls). Sensitivity analysis on the discount rate and time-horizon was conducted as per good-modelling practice [19]. As suggested by WHO guidelines [20,21], the Canadian per capita GDP was used as the cost-effectiveness threshold. Hence, vaccination strategies below $40,000/QALY-gained were considered cost-effective.

2.2. Strategies investigated

The incremental costs, benefits, and cost-effectiveness ratios of the following HPV vaccination strategies were examined:

(1) Two-dose girls-only vs. no vaccination
(2) Three-dose girls-only vs. two-dose girls-only vaccination
(3) Two-dose girls & boys vs. two-dose girls-only vaccination
(4) Three-dose girls & boys vs. three-dose girls-only or two-dose girls & boys vaccination

In our base-case scenario, routine vaccination is given at 9 years of age. Of note, all vaccination scenarios include a five-year three-dose catch-up campaign for 14-year-old girls. Vaccination coverage was 80%, similar to coverage in UK (79–91%) [22] and Australia (64–80%) [23]. Vaccination coverage, ages at vaccination, vaccination schedules and the catch-up campaign are based on the current girls-only HPV vaccination programme in Quebec, Canada [24]. However, vaccination coverage and the three-dose schedule were varied in sensitivity analysis. HPV vaccination was introduced five years ago in Canada (in 2008) and in many developed countries. Hence, all changes in vaccination strategies are modelled to occur during the 6th year of the programme. See Supplementary Fig. 1 for a detailed description of the vaccination strategies examined in our base-case scenario.

2.3. Model structure

The model structure of HPV-ADVISE is described in great detail elsewhere [8,17,18]. Briefly, individuals in the model are attributed four different risk factors for HPV infection and/or disease: gender, sexual orientation, sexual activity level and screening level. Eighteen HPV-types are modelled individually (including HPV-16/18/6/11/31/33/45/52/58). The diseases modelled are anogenital warts and cancers of the cervix, vulva, vagina, anus, penis, and oropharynx. Cytology was used for cervical cancer screening, which reflects current practice in Canada. Screening rates are a function of a woman's screening behaviour level, previous screening test results, and age. Finally, direct medical costs and Quality-Adjusted Life-Year (QALY) weights were attributed to outcomes (e.g., diagnosed lesions, cancer) over time.

2.4. Parameter values

Sexual behaviour, natural history and cervical screening parameters were identified by fitting the model to 782 sexual behaviour, HPV epidemiology and screening data target points, taken from the literature, population-based datasets, and original studies [25–37] (see Van de Velde et al. [8] and www.marc-brisson.net/HPVadviseCEA.pdf). Vaccine-type and cross-protective efficacy estimates were based on a recent meta-analysis [38] (see Supplementary Table 1), and assumed to be equal for two- and three-dose schedules based on the short-term results of the noninferiority trial [13]. Type-specific efficacy and cross-protection were assumed to be equal for cervical and non-cervical sites. The duration of vaccine-type efficacy and cross-protection remains uncertain for two and three doses. Currently, clinical data show no evidence of waning for three-dose vaccine-type efficacy after 9.5 years [39] and potential limited duration of cross-protective efficacy [38]. Given such uncertainty, we varied the average duration of vaccine-type efficacy for three doses between 20 years and lifelong, and for two doses between 10 years