Vaccine 32 (2014) 5845–5853

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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

ARTICLE INFO

Article history:
Received 22 April 2014
Received in revised form 15 July 2014
Accepted 30 July 2014
Available online 12 August 2014

Keywords:
Cost-effectiveness
Transmission-dynamic modelling
Human papillomavirus (HPV)
Immunisation
Vaccine schedules
Programme optimisation
Cervical cancer
Anogenital warts

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).

http://dx.doi.org/10.1016/j.vaccine.2014.07.099

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

and lifelong. It is important to note that duration of protection is calculated from the time of the first dose. Furthermore, in scenarios with limited vaccine duration, each vaccinated individual is given a specific duration of protection sampled from a normal distribution (μ = varied; σ = 5 years) [17], as not all individuals will lose protection at the same time after vaccination. In the base-case scenarios, cross-protection was assumed to last 10 years. A scenario was also examined where two-dose schedules do not provide cross-protection. The HPV vaccine cost per dose including administration was $85. QALY-weights and unit costs were taken from the literature [25,26,40–48] (see Supplementary Table 2).

2.5. Sensitivity & uncertainty analyses

In univariate sensitivity analysis, vaccine efficacy (for cervical and non-cervical sites), duration of protection, percent of anogenital warts due to HPV-6/11, proportion of the male population that are men-who-have-sex-with-men (MSM), relative risk of disease in MSM vs. heterosexual men, costs and QALY-weights were varied between their minimum and maximum values found in the literature (Supplementary Tables 1 and 2). Finally, favourable scenarios for vaccination of boys were examined in multivariate sensitivity analysis. Variability of model predictions due to natural history parameters is presented as the median, and first and third quartiles of simulation results, referred to as the interquartile ranges (IQR).

3. Results

3.1. Population-level impact and costs

Table 1 shows the potential population-level effectiveness of two- and three-dose schedules assuming different durations of protection (see Supplementary Fig. 2 for post-vaccination dynamics). Under our base-case (coverage = 80%, vaccine-type efficacy = 95%) and assuming two-dose vaccine duration of protection is 10 years, *two-dose girls-only* vaccination is predicted to prevent a cumulative 13% of HPV-related cancer cases (12% anogenital warts consultations) over 70 years. Over the same time-horizon, giving a *third dose* in a *girls-only* vaccination programme prevents between 13 and 15% extra HPV-related cancer cases, if the duration of protection from three doses is between 25 years and lifelong. The equivalent expanded reductions in anogenital warts consultations are between 54 and 60%. Switching to a *two-dose girls & boys* strategy would prevent an extra 3% HPV-related cancer cases and 9% anogenital warts consultations compared to a *two-dose girls-only* vaccination policy. However, when assuming the duration of protection of two doses is 20 or 30 years, the incremental benefits of giving a *third dose* to *girls-only* or switching to a *two-dose girls & boys* strategy are predicted to be relatively small (e.g., between 2 and 6% extra HPV-related cancer cases prevented; Table 1). Of note, the additional benefits provided by a *third dose to girls-only* are mostly among females whilst the majority of benefits of switching to a *two-dose girls & boys* strategy are among MSM.

Fig. 1 shows the discounted QALYs-gained and cost offsets for *girls-only* and *girls & boys* vaccination programmes using two- and three-dose schedules. The incremental QALYs-saved and cost offsets by giving a *third dose to girls-only* are relatively small when assuming that two-dose protection is 20 years or more, but would increase the overall cost of the programme by almost 30%. Unless two and three doses provide equal duration of protection, switching to a *two-dose girls & boys* vaccination strategy is predicted to provide similar or lower incremental discounted QALYs-gained and cost-offsets than adding a *third dose* to *girls-only*. However, because it requires providing twice the additional number of vaccine doses, giving two doses to boys would be more than twice the cost of adding a third dose to girls (incremental cost of a *third dose girls* = $109 million vs. *two-dose boys* = $256 million over 70 years of vaccination in a population of 10 million, results not shown).

3.2. Cost-effectiveness

Compared to *no vaccination*, all *two-* and *three-dose girls-only* and *girls & boys* HPV vaccination strategies investigated produce cost-effectiveness ratios below the $40,000/QALY-gained cost-effectiveness threshold (Fig. 2, and see Supplementary Table 3 for detailed results).

In the base-case, *two-dose girls-only* vaccination (vs. *no vaccination*) consistently produces the lowest incremental cost-effectiveness ratio with cost/QALY-gained varying between $7900 [IQR: 7000;9700] and $10,400 [IQR: 8800;13,400] (Fig. 2b–f). The only exception is when two-dose duration of protection is assumed to be 10 years (Fig. 2a). In the sensitivity analysis, *two-dose girls-only* vaccination cost-effectiveness ratios remained below $40,000/QALY-gained (Fig. 3a). The maximum cost per dose for *two-dose girls-only* vaccination to remain cost-effective (vs. *no vaccination*) is predicted to be $128, $218 and $252 assuming two-dose vaccine protection lasts 10, 20 and 30 years, respectively (see Supplementary Fig. 4 and Table 4).

The incremental cost-effectiveness ratio of giving the *third dose of vaccine to girls* (i.e., of *three-dose girls-only* vs. *two-dose girls-only*) is estimated to be below $40,000/QALY-gained if: (i) three doses provide longer protection than two doses (i.e., more than 5 years), and ii) two-dose protection is less than 30 years (Figs. 2c, d and 3b).

Under most scenarios, *two-dose girls & boys* vaccination (vs. *two-dose girls-only)* provides fewer or similar QALYs-gained and is more expensive than *three-dose girls-only* vaccination (i.e., is dominated; Figs. 2a, c–f and 3b). The only exceptions are: (i) if the third dose provides little or no additional protection to two doses, (ii) when extreme scenarios for burden of HPV-disease among MSM are assumed (e.g., 7% males are MSM, the relative risk of disease among MSM vs. male heterosexuals is 17, and girls-only vaccination is assumed to have no effect on HPV-related disease incidence in MSM) or (iii) when vaccine cost for boys is 10–40% of the cost for girls (Fig. 3b, Supplementary Fig. 3).

Finally, the incremental cost-effectiveness ratio of *three-dose girls & boys* vaccination (vs. *three-dose girls-only*) is greater than $100,000/QALY-gained under all base-case scenarios and most scenarios investigated in sensitivity analysis (Figs. 2 and 3c). In the sensitivity analysis, *three-dose girls & boys* vaccination is estimated to be less than $40,000/QALY-gained if the cost per dose for girls and boys is substantially reduced (Supplementary Fig. 4c).

4. Discussion

Our modelling analysis suggests that *two-dose girls-only* vaccination (compared to *no vaccination*) is likely to be cost-effective if vaccine protection is longer than 10 years. Furthermore, *two-dose girls & boys* is likely to provide similar or less QALYs-gained and to be more expensive than *three-dose girls-only* strategy, unless the third dose gives no added value or the price for boys is substantially less than the price for girls. Hence, the key question is: how long does two-dose protection have to be in order for the third dose to be cost-ineffective among girls? Our results suggest this threshold duration of protection for two doses is about 30 years. Hence, if two doses protect for more than 30 years, then the third dose will have to be priced substantially below $85 to be cost-effective. Finally, *three-dose girls & boys* HPV vaccination is unlikely to be cost-effective compared to *three-dose girls-only* vaccination, as shown by most modelling studies, unless the cost of the vaccine is substantially reduced [49–54].

Table 1
Health outcomes saved over 70 years after the start of HPV vaccination under base-case assumptions[a] (undiscounted; population = 10 million).

	2-Dose duration = 10 years					2-Dose duration = 20 years					2-Dose duration = 30 years			
	Cumulative reduction (%)	Additional cumulative reduction[b] (additional % cumulative reduction)[c]				Cumulative reduction (%)	Additional cumulative reduction[b] (additional % cumulative reduction)[c]				Cumulative reduction (%)	Additional cumulative reduction[b] (additional % cumulative reduction)[c]		
Strategy	2-dose Girls only	3-dose Girls only	3-dose Girls only	3-dose Girls only	2-dose Girls & boys	2-dose Girls only	3-dose Girls only	3-dose Girls only	3-dose Girls only	2-dose Girls & boys	2-dose Girls only	3-dose Girls only	3-dose Girls only	2-dose Girls & boys
Duration (vaccine types)	10 years[d]	25 years[d]	35 years[d]	Life[e]	10 years[d]	20 years[d]	25 years[d]	35 years[d]	Life[e]	20 years[d]	30 years[d]	35 years[d]	Life[e]	30 years[d]
AGW consultations	111,066 (11·6)	527,033 (53·9)	568,531 (57·0)	582,422 (60·0)	83,470 (8·6)	550,743 (57·5)	83,710 (8·7)	131,750 (13·7)	133,491 (13·9)	124,531 (13·0)	685,187 (71·4)	1414 (0·1)	776 (0·1)	49,596 (5·1)
Diagnosed CIN2/3	47,140 (15·4)	89,502 (25·9)	121,485 (32·8)	163,260 (42·0)	13,076 (3·8)	111,443 (32·6)	30,360 (8·2)	52,677 (14·9)	85,107 (23·2)	10,751 (2·8)	144,149 (42·0)	17,704 (5·1)	50,134 (13·3)	12,096 (3·6)
Cancers[f]														
Cervix	4606 (16·4)	4116 (18·2)	4617 (20·1)	5195 (22·5)	832 (2·9)	7266 (29·3)	1155 (4·8)	1696 (6·1)	2251 (8·6)	558 (2·0)	8261 (34·5)	596 (2·2)	1175 (4·5)	421 (1·6)
Anus	448 (10·2)	787 (9·2)	880 (10·3)	919 (10·8)	370 (4·4)	1444 (17·0)	193 (2·3)	281 (3·3)	328 (3·9)	443 (5·2)	1633 (19·3)	87 (1·0)	137 (1·6)	445 (5·2)
Oropharynx	847 (11·2)	1504 (10·3)	1657 (11·3)	1711 (11·7)	577 (3·9)	2736 (18·6)	334 (2·3)	485 (3·3)	541 (3·7)	568 (3·9)	3080 (21·0)	150 (1·0)	209 (1·4)	516 (3·5)
Vulva, vagina and penile	457 (9·6)	655 (7·1)	684 (7·5)	717 (7·7)	121 (1·4)	1392 (15·0)	162 (1·7)	193 (2·1)	229 (2·5)	106 (1·1)	1528 (16·5)	58 (0·6)	95 (1·4)	92 (1·0)
All cancers[g]	7961 (13·1)	7191 (12·9)	7890 (14·4)	8576 (15·3)	1954 (3·3)	12,807 (22·3)	1879 (3·2)	2747 (4·3)	3387 (5·6)	1667 (2·8)	14,556 (25·4)	899 (1·5)	1597 (2·7)	1509 (2·6)

AGW: anogenital warts; CIN2/3: cervical intraepithelial neoplasia of grade 2 or 3.

[a] Base-case: vaccination coverage = 80%, vaccine-type efficacy = 95%, cross-protective efficacy = see Supplementary Table 1.

[b] Cumulative reduction: median reduction in the cumulative incidence vs. 2-dose girls-only strategy over 70 years (each parameter set was run 50 times).

[c] Median of percentage differences compared to 2-dose girls-only. *Note*: We estimate the median of the differences for each simulation not the difference of medians.

[d] Duration of cross-protection = 10 years.

[e] Duration of cross-protection = lifelong.

[f] HPV positive cancers only.

[g] All cancers: median of totals. *Note*: We estimate the median of the sums of additional cancer cases prevented for each simulation not the sum of medians.

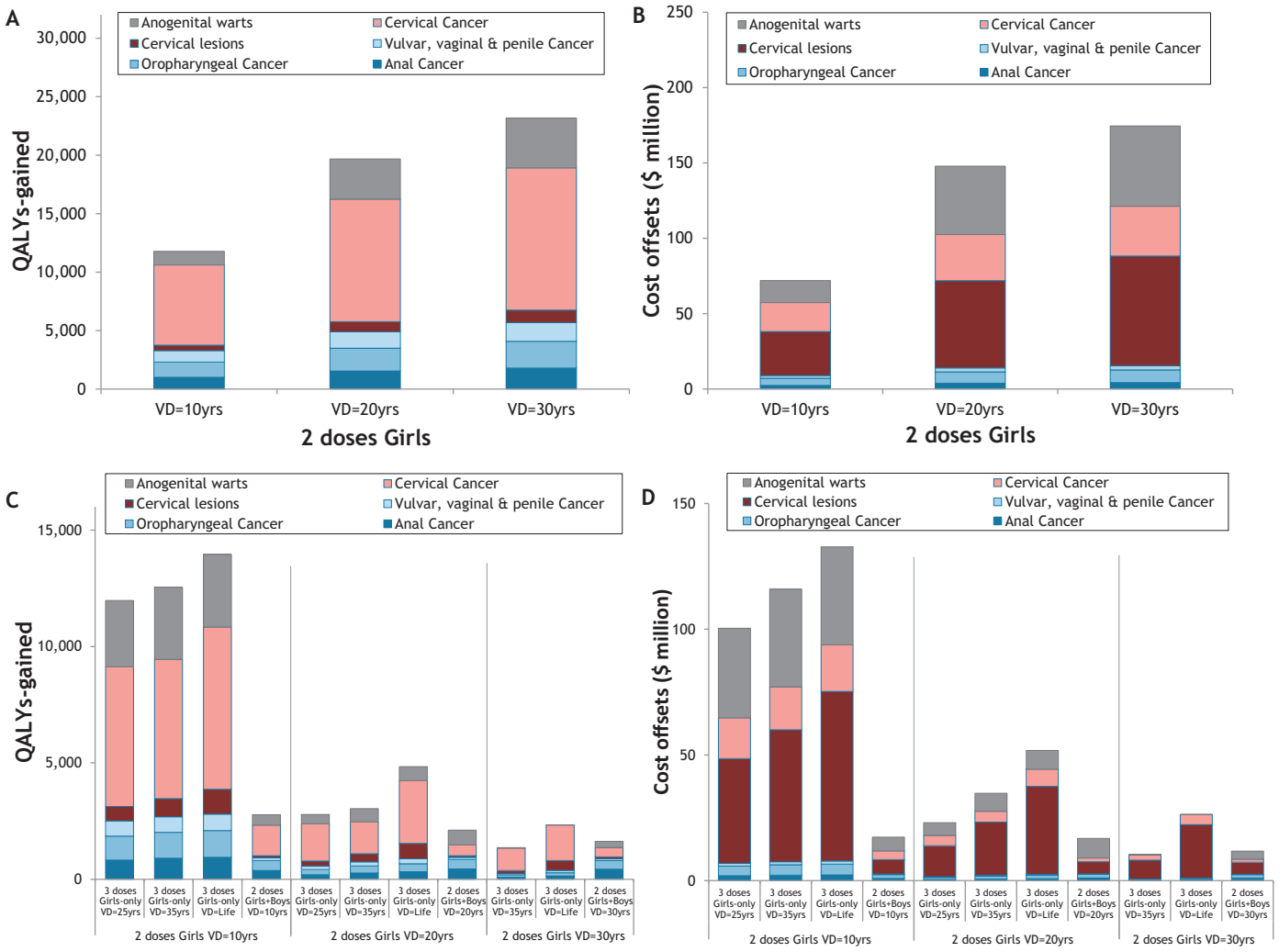

Fig. 1. Discounted QALYs-gained and cost offsets over 70 years after the start of HPV vaccination (population = 10 million). (a) QALYs-gained and (b) cost offsets for 2-dose girls-only vaccination protecting for 10 years, 20 years and 30 years; (c) incremental QALYs-gained and (d) cost offsets of giving the 3rd dose or adding 2-dose boys vaccination to girls programme. Base-case: vaccination coverage = 80%, vaccine-type efficacy = 95%, cross-protective efficacy = see Supplementary Table 1. Duration of cross-protection is assumed to be lifelong when vaccine-type duration of protection is lifelong, otherwise duration of cross-protection is assumed to be 10 years. VD: vaccine duration, QALY: quality-adjusted life-years.

Our results suggest that a two-dose schedule that provides protection for more than 30 years would likely prevent the majority of preventable vaccine-type HPV infections and diseases, which entails that the added value of the third dose would be limited. This is because, at 30 years duration of protection, two-dose vaccination would confer protection during a significant proportion of the peak years of sexual activity and HPV infection (18–35 years). Our results also indicate that *two-dose girls & boys* vaccination is likely dominated by a *three-dose girls-only* strategy, because adding two doses among boys costs twice as much as adding a third dose among girls. However, because these two strategies result in comparable QALYs-gained, the price for boys would need to be reduced by more than half (60%-90% depending on duration of protection, and assuming cost for girls ≥$30) to make a *two-dose girls & boys* strategy cost-effective vs. *three-dose girls-only*.

Two key issues must be considered when using these results for decision-making. First, the policy decisions regarding alternative HPV vaccine schedules will depend on the evaluation of risks and uncertainties related to the duration of protection of two and three doses. Policy-makers could decide that evidence is sufficient for the implementation of *two-dose girls-only* vaccination based on the following observations: (i) three doses in young women 16–26 years of age has shown sustained efficacy for almost 10 years [39], (ii) two doses in girls aged 9–13 years have shown noninferior immunogenicity compared to three doses in young women aged 16–26 years [14] and (iii) our results indicate that *two-dose girls-only* vaccination is cost-effective if the vaccine protects for longer than 10 years. On the other hand, the duration of vaccine protection with two doses remains uncertain. Should this duration be less than 20 years, a third dose extending the duration of protection (≥5 years) would likely produce substantial additional benefits. Second, for equity reasons, policy-makers' or society's willingness to pay for an additional QALY-gained may be higher for *two-dose girls & boys* vaccination than a *third dose* among girls-only. The potential additional benefits of the third dose occur among women and heterosexual men, who would also benefit from a *two-dose girls-only* strategy. However, adding boys to an HPV vaccination programme would extend benefits to MSM, who do not benefit from the herd effects of girls-only vaccination [55] and have a disproportionately high burden of HPV-related disease [56,57]. Hence, policy-makers may deem a *two-dose girls & boys* strategy worthwhile even though it is likely to be less cost-effective than a *three-dose girls-only* strategy.

To our knowledge, no study has examined the cost-effectiveness of different HPV vaccination schedules. However, a previous

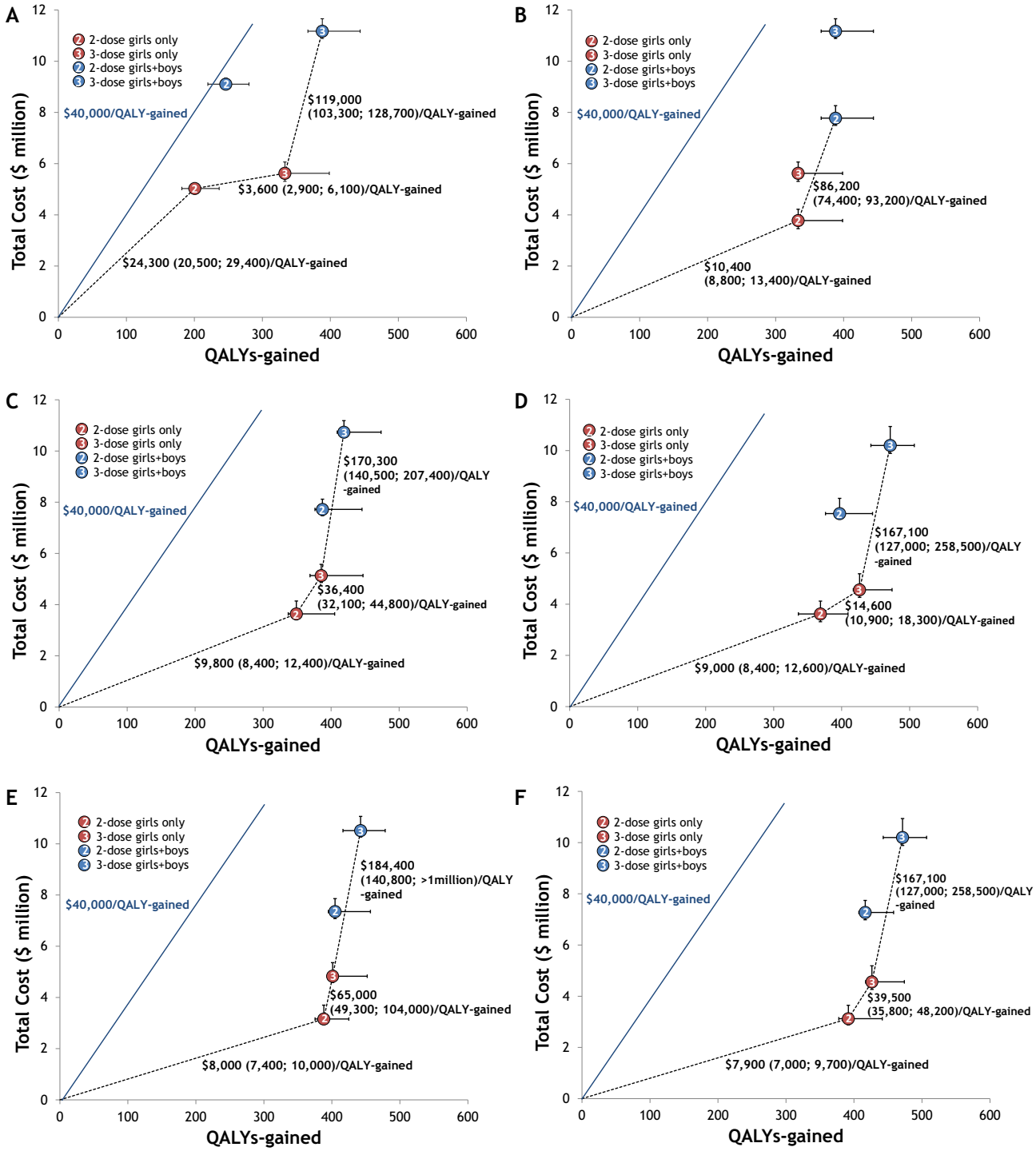

Fig. 2. Incremental cost-effectiveness of 2- and 3-dose vaccination strategies. (a) Duration of protection 2 doses = 10 years & 3 doses = 20 years, (b) duration of protection 2 doses = 20 years & 3 doses = 20 years, (c) duration of protection 2 doses = 20 years & 3 doses = 25 years, (d) duration of protection 2 doses = 20 years & 3 doses = life (e) duration of protection 2 doses = 30 years & 3 doses = 35 years, (f) duration of protection 2 doses = 30 years & 3 doses = Life. Base-case: vaccination coverage = 80%, vaccine-type efficacy = 95%, cross-protective efficacy = see Supplementary Table 1; duration of cross-protection is assumed to be lifelong when vaccine-type duration of protection is lifelong, otherwise duration of cross-protection is assumed to be 10 years. QALY: quality-adjusted life-years; population of 170,000 individuals. Each parameter set was run 50 times. Results are the median and interquartile range (1st and 3rd quartiles of model simulations). The blue line represents the cost-effectiveness threshold ($40,000/QALY-gained). All vaccination scenarios include a 5-year 3-dose catch-up campaign. Hence, the cost-effectiveness ratios of 2-dose programmes are slightly influenced by 3-dose catch-up vaccine efficacy and duration of protection. The comparator for *3-dose girls & boys* vaccination is the most cost-effective strategy between *3-dose girls-only* and *2-dose girls & boys*, as indicated by the dotted line connecting the vaccination strategies.

comparative modelling analysis, using our model and one from England [58], examined the potential population-level impact of *two-* and *three-dose girls-only* HPV vaccination. The conclusions of both models were similar when examining 40–80% vaccination coverage: the predicted added population-level effectiveness of a third dose at preventing cervical cancer is minimal if the duration of protection of two doses is at least 20–30 years.

The results from the comparative analysis and the robustness of our conclusions to vaccine costs/dose and vaccination coverage (between 50–80%; see Fig. 3 and Supplementary Table 3),

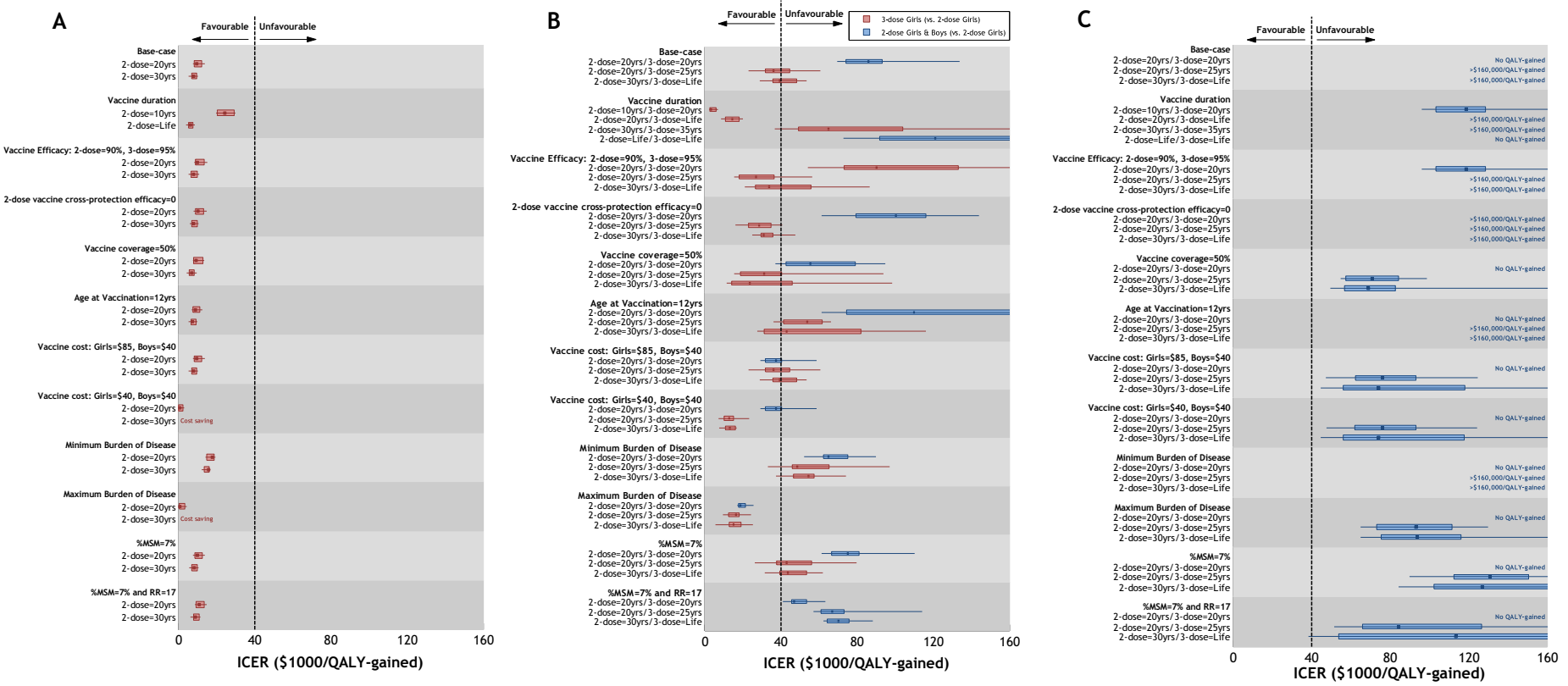

Fig. 3. Sensitivity analysis. Cost-effectiveness of (a) *2-dose girls-only* vaccination strategy, (b) *3-dose girls-only* and *2-dose girls & boys* vaccination strategies vs. *2-dose girls-only* (only the most cost-effective strategy is shown), and (c) *3-dose girls & boys* vaccination strategy vs. the most cost-effective strategy between *3-dose girls-only* and *2-dose girls & boys* (the comparator for *3-dose girls & boys* vaccination is the strategy shown in c). Base-case: coverage = 80%, vaccine-type efficacy = 95%, cross-protective efficacy = see Supplementary Table 1. Sensitivity analysis: in the sensitivity analyses, only the parameters indicated in the description were varied, holding other parameter values at the base-case level. Max (Min) burden of disease: all costs and QALYs-lost parameters, and % HPV-6/11 in AGW are given their maximum (minimum) values from the literature (Supplementary Table 2). Definitions. QALY: quality-adjusted life-years; coverage: vaccination coverage; AGW: anogenital warts; MSM: men-who-have-sex-with-men; RR: relative risk of disease in MSM vs. heterosexual males; ICER: incremental cost-effectiveness ratio. Each parameter set was run 50 times. Solid dots represent the median, boxes the 1st and 3rd quartiles of model simulations, and the "error-bars" the 10th and 90th percentiles of model simulations.

suggests that the main cost-effectiveness conclusions of this paper are likely to be generalisable to other high income countries with HPV epidemiology, health care costs and cervical screening similar to England and Canada. However, our results should not be extrapolated to resource-poor settings due to differences in sexual behaviour and HPV epidemiology.

A limitation of our analysis is the validity of data on the proportion of MSM in the population and the burden of disease within this population. However, even when the proportion of MSM was assumed to be high (7% vs. 3% in the base-case), vaccinating boys with two doses remained dominated by *three-dose girls-only* vaccination. A second limitation of the analysis is that our model assumes no herd-protection from girls-only vaccination to MSM. Herd-protection to MSM is only included in scenarios with male vaccination, potentially overestimating the impact of including boys in vaccination programmes. However, no herd-immunity has been observed in MSM following the introduction of girls-only HPV vaccination [59].

As recommended by good modelling practice, we conducted internal, between-model and external/predictive validation [60]. First, HPV-ADVISE was calibrated to highly-stratified Canadian data on sexual behaviour, natural history and cervical cancer screening (internal validation), and model predictions were performed using multiple good fitting parameter sets. Secondly, as discussed above, our two-dose effectiveness predictions are consistent with those from a model used to inform HPV immunisation decisions in England (between-model validation) [58]. Finally, our model qualitatively reproduces short-term post-vaccination data showing important and rapid declines in anogenital warts and herd effects in young heterosexual men from vaccinating girls-only with high coverage, such as those reported for Australia (external/predictive validation) [55,59,61] (see Supplementary Fig. 4).

Our cost-effectiveness analysis provides new evidence to help decision-makers weigh the potential risks and benefits of reducing HPV vaccination schedules from three to two doses for different assumptions about duration of protection. Independently of the schedule implemented, careful long-term surveillance is essential as duration of protection remains the key uncertainty in the effectiveness of HPV vaccination programmes.

Acknowledgements

We are indebted to Compute Canada for providing us with the power necessary to run the simulations. We would also like to acknowledge Dr. Van de Velde (NVDV) who programmed most components of HPV-ADVISE and helped design the model. Finally, we thank Drs. Vladimir Gilca, Marie-Hélène Mayrand and Patricia Goggin for comments on the analysis. *Contributors*: MB designed the study, co-drafted the article, had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. JFL, MD, MJ, MCB, TM, PLM, EF and CS commented on the study design and model structure. JFL and MD co-drafted the paper. MB, MCB and NVDV designed HPV-ADVISE. MB and JFL programmed the economic components of the model. EF provided the data necessary for the analysis. JFL and MB performed the analysis. All authors contributed to the interpretation of results, critically revised the manuscript for important intellectual content and approved the final version submitted for publication. *Conflict of interest statement*: MB and CS have consulted and received reimbursement for travel expenses from Merck Frosst and GlaxoSmithKline. EF has served as occasional consultant or advisory board member for Merck and GlaxoSmithKline JFL, MD, MJ, MCB, TM, and PLM have no conflicts of interest to declare. *Funding*: This work was supported by the Canada Research Chairs programme (support for MB), a team grant from the Canadian Institutes of Health Research (grant no. CRN-83320) and the Québec Ministry of Health and Social Services. The funders had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2014.07.099.

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