Available online at www.sciencedirect.com
ScienceDirect
Vaccine 25 (2007) 5399–5408
Vaccine
www.elsevier.com/locate/vaccine

The potential cost-effectiveness of prophylactic human papillomavirus vaccines in Canada

Marc Brisson [a,b,*], Nicolas Van de Velde [a,c], Philippe De Wals [a,c], Marie-Claude Boily [d]

[a] *Département de médecine sociale et préventive, Université Laval, Que., Canada*
[b] *Unité de recherche en santé des populations, Centre hospitalier affilié universitaire de Québec, Que., Canada*
[c] *Unité de recherche en santé publique et santé environnementale, Centre hospitalier universitaire de Québec, Que., Canada*
[d] *Department of Infectious Disease Epidemiology, Imperial College, London, UK*

Received 16 March 2007; received in revised form 24 April 2007; accepted 26 April 2007
Available online 22 May 2007

Abstract

Aim: Clinical trials have shown prophylactic human papillomavirus (HPV) vaccines to be effective against infection and disease. We examined whether HPV vaccination has the potential to be cost-effective.
Methods: A cohort model of the natural history of HPV was developed, which fits simultaneously Canadian age and type-specific data for infection, cervical intraepithelial neoplasia, cervical cancer (CC) and genital warts (GW). Quality-Adjusted Life-Years (QALYs) lost and costs were estimated using data from the literature.
Results: Vaccinating 12-year-old girls (efficacy = 95%, no waning, cost/course = CAN$ 400) against HPV-16/18 and HPV-6/11/16/18 is estimated to cost the health provider CAN$ 31,000 (80%CrI: 15,000–55,000) and CAN$ 21,000 (80%CrI: 11,000–33,000) per QALY-gained, respectively. Results were most sensitive to age at vaccination, duration of vaccine protection, vaccine cost and QALY-lost due to GW, and were least sensitive to the medical costs.
Conclusion: Vaccinating adolescent girls against HPV is likely to be cost-effective. The main benefit of vaccination will be in reducing CC mortality. However, unless screening is modified, the treatment costs saved through vaccination will be insignificant compared to the cost of HPV immunization.

Keywords: Human papillomavirus (HPV); Vaccination; Cost-effectiveness

1. Introduction

Human papillomavirus (HPV) causes cervical intraepithelial neoplasia (CIN), cervical [1] and other anogenital cancers (vulva, vaginal, anus, penile) [2,3], head and neck cancers [4], genital warts [5,6], and recurrent respiratory papillomatoses [7,8]. In Canada and other developed countries, cervical cancer screening programmes have substantially reduced the incidence and mortality of cervical cancer over the past 50 years [9]. However, the marked declines seen until the 1990s have been slowing in recent years [9]. In Canada, cervical cancer is currently the third most common cancer in women aged 20–49 and, each year, there are approximately 1400 new cases and 400 deaths from the disease [10]. High risk types HPV-16/18 account for approximately 70% of all cervical cancers [11–13]. Low oncogenic risk types HPV-6/11 are responsible for approximately 90% of genital warts [6,14].

Two HPV prophylactic vaccines, which target HPV-16/18 (Cervarix®) and HPV-6/11/16/18 (Gardasil®), have been shown to be highly effective in clinical trials [15–18]. With promising safety and efficacy results from these trials and the licensure of Gardasil® in Canada, the US and many other countries [19–21], policymakers will be asked to make rec-

* Corresponding author at: Unité de recherche en santé des populations, Centre hospitalier affilié universitaire de Québec, Hôpital Saint-Sacrement, 1050 Chemin Sainte-Foy, Que., Canada G1S 4L8. Tel.: +1 418 682 7511.
E-mail address: marc.brisson@uresp.ulaval.ca (M. Brisson).

0264-410X/$ – see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.vaccine.2007.04.086

ommendations and decisions regarding the introduction of HPV vaccines. The main criteria considered in such decisions include safety, effectiveness, cost-effectiveness, affordability, programmatic feasibility, equity, public preferences, and the political consequences of decisions [22,23]. In this study, we focus on examining the potential cost-effectiveness of prophylactic HPV vaccination in Canada. The goal of cost-effectiveness analysis is to compare the health and economic impact of different interventions in order to identify which interventions maximize the health of the population, in a context of limited resources. The specific policy questions that we examine in this study are: What is the cost-effectiveness of introducing HPV vaccination, under the current conventional cytology-based screening programs in Canada? What is the relative cost-effectiveness of a quadrivalent vaccine (HPV-6/11/16/18) compared to a bivalent vaccine (HPV-16/18)? What is the impact of age at vaccination on the cost-effectiveness results?

Because many of the benefits of prophylactic HPV vaccines occur in the medium to long term, mathematical models are needed to project the impact of vaccination beyond the time horizon of clinical trials. The development of models are based on assumptions, which necessarily introduce uncertainty regarding the conclusions that can be drawn from their results [24]. It is therefore important to examine the uncertainty of model predictions to provide policy makers with the necessary information to make appropriate decisions. In the case of HPV, it is particularly important to quantify uncertainty due to the complex natural history of HPV infection (encompasses numerous stages of disease which depend on HPV-type, screening and treatment) and the limited data on age and type-specific HPV natural history. Given these considerations, an additional aim of this study is to quantify the uncertainty around model predictions.

2. Methods

2.1. Epidemiologic model structure

We used a compartmental deterministic model that follows a cohort of 10-year-old women through different cervical infection and disease states (susceptible, infected, immune, genital warts, CIN1, CIN2/3, cervical cancer) for four classes of HPV genotypes (HPV-16, HPV-18, Low Oncogenic Risk (LR) types and other High Oncogenic Risk (HR) types). We assume that there is no cross-protection between HPV types, co-infection can occur, and women can develop lifelong immunity following infection. The model also accounts for screening and treatment outcomes. That is, women have an age-specific rate of screening and a lesion-specific test sensitivity of being detected. We assume that screening practice and compliance is unaffected by vaccination status. The epidemiologic model is identical to a previously model published by Van de Velde et al. [25] and Brisson et al. [26].

2.2. Economic analysis

We performed the analyses from the perspectives of the ministry of health, which includes all direct medical costs. Personal medical costs are not included in the analysis. Future costs and outcomes are discounted at 3% per year over the lifetime of the target population. We chose cost-utility analysis (cost per QALY-gained) as our analytic technique.

2.3. Vaccine strategies

We compare the quadrivalent (HPV-6/11/16/18) and the bivalent (HPV-16/18) vaccines to no vaccination, under current conventional cytology-based screening rates in Canada. The base case vaccine strategy assumes vaccination of 12-year-old girls. Sensitivity analysis is performed to evaluate the impact of age at vaccination and a booster dose (assumed to be at age 22 years if duration of protection is less than lifelong). We did not conduct an incremental cost-effectiveness analysis of the quadrivalent over a bivalent vaccine as the prices of these vaccines are unknown. To compare the bivalent and quadrivalent vaccines we estimate the cost per course these vaccines must have to produce equivalent cost per QALY-gained ratios.

2.4. Vaccine characteristics

Base case vaccine characteristics are assumed to be as follows: (1) the proportion of individuals protected following immunization (take) is 100%; (2) vaccine duration is lifelong; and (3) reduction in susceptibility to HPV-6/11/16/18 and HPV-16/18 (vaccine efficacy) is 95%. A sensitivity analysis was performed to explore the impact of vaccine parameters on predictions. Vaccine duration is varied by assuming a constant waning of vaccine protection, resulting in an exponential decay of the protected population. Because we are modeling prophylactic HPV vaccines, we do not include any therapeutic benefits to vaccinees already infected with the vaccine types. Furthermore, we assume that the natural history of disease is unaltered following vaccine failure or loss of vaccine-induced immunity.

2.5. Demographic, screening and treatment parameters

Demographic, screening and treatment parameters were taken from available Canadian-specific data [25]. If no Canadian data were available, US data were used.

2.6. Natural history parameters

All natural history parameters are type (HPV-16, 18, HR, LR) and age-specific. An extensive fitting procedure, described elsewhere [25,26], was performed to identify different natural history parameter sets that fit adequately to available Canadian prevalence and incidence of HPV, genital warts, CIN and cervical cancer. The 209 parameter sets

Table 1
QALY-weight lost per health state

	Base (%)	Min[a] (%)	Max[a] (%)	References
Genital warts	10	5	15	See methods[b]; [31]
CIN[c] 1[d]	9	0	9	[28–30]
CIN2/3	13	0	13	[28–30]
Cervical cancer				
Stage I	32	19	51	[27,29,30]
Stage II and III	43	30	58	[27,29,30]
Stage IV	49	38	64	[27,29,30]

[a] Min and Max are the minimum and maximum values of the triangular distributions used in the probability sensitivity analysis. For genital warts, Min and Max represent the 95% confidence interval. For the other values, Min and Max represent the maximum and minimum values found in the literature.

[b] Preliminary results from a multi-center prospective cohort study, which aims at recruiting 300 patients across Canada to measure the psychosocial impact of having genital warts [44]. Interim results, presented here, are for the first 31 women recruited in the study. The women were aged between 19 and 62 years (median = 24 years). Patients were asked to complete the EQ-5D questionnaire.

[c] CIN, cervical intraepithelial neoplasia.

[d] False positives were assumed to incur the same QALY-weight loss as a CIN1 patient.

identified can loosely be considered as different models that allow thorough investigation of the impact of natural history assumptions and parameter uncertainty on model predictions. Furthermore, these parameter sets can also be considered to reproduce the variability in the epidemiology of HPV, CIN, cervical cancer and genital warts in Canada.

2.7. Outcome measures

Utility estimates are presented in Table 1. The average QALY-weight lost for a false positive results, CIN and cervical cancer were taken from the literature [27–30]. To estimate the QALY-weight lost for genital warts, we recruited 31 women presenting at their physicians office with genital warts. QALY-weights were estimated using the EQ-5D questionnaire. For each woman who responded to the questionnaire, their QALY-weight lost was estimated as the difference between the average population QALY-weight and the estimated QALY-weight with genital warts, matched on age and gender. We estimate that the QALY-weight lost due to genital warts is 0.10 (95%CI: 0.05–0.15), which is similar to the 0.09 reported by Myers et al. [31]. The average duration of a diagnosed genital wart episode was assumed to be 6 months (varied between 4 and 8 months in the sensitivity analysis) [32]. In the cost-effectiveness analysis, we only attribute QALY-losses to women who are diagnosed with genital warts, CIN or cervical cancer. An extensive sensitivity analysis was performed on all utility estimates.

2.8. Cost data and assumptions

Unit costs are presented in Table 2 and are in 2005 $CAN. Costs are inflated to 2005 $CAN using the Canadian Consumer Price Index for Health [33]. Where available, Canadian costs were used. This includes the cost of conventional cytology, colposcopy, biopsy and the treatment following CIN2/3 [34–36]. In the absence of Canadian-specific data, we adjusted missing costs proportionally based on the relationship between known costs in Canada and those from the US. For example, Canadian cytology, colposcopy and biopsy costs were, on average, 50% of published US costs. Based on the relative costs between Canada and the US, we scaled down the average US published costs by half. The costs estimated using this technique are very similar to those from a costing study yet to be published by Jacobs et al. (Dr. Jacobs, personal communication). Given the high degree of uncertainty surrounding the unit costs of screening and treatment of CIN, cervical cancer and genital warts in Canada, extensive sensitivity and uncertainty analysis was conducted on these parameters. In the sensitivity analysis, we varied all costs between CAN$ 0 and the maximum costs found in the literature.

Table 2
Unit costs (2005 $CAN)

	Base[a]	Min[b]	Max[b]	References
Genital warts	338	457	866	[45–47]
Conventional cytology	57	17	105	[27,30,35,36,48–52]
Colpolscopy and biopsy	148	53	599	[27,29,34,35,49–52]
Diagnosed CIN[c] 1	852	865	2,759	[27,29,30,48]
Diagnosed CIN2/3	1,181	819	4,868	[27,29,30,35,48,49,52]
False positives	198	316	493	[30,48]
Cervical cancer				[27,29,30,48,49,52]
Stage I	9,999	4,500	28,233	
Stage II and III	15,819	16,592	43,222	
Stage IV	21,616	25,922	64,317	

[a] The base case is the average unit cost taken from the literature. In the absence of Canadian-specific data, we adjusted missing costs proportionally based on the relationship between known costs.

[b] Min and Max represent the maximum and minimum values found in the literature. Costs from other countries were converted to Canadian dollars using the currency exchange rate. Min and Max are the minimum and maximum values of the triangular distributions used in the probability sensitivity analysis.

[c] CIN, cervical intraepithelial neoplasia.

In our base case analysis, we assume that the quadrivalent and bivalent vaccines cost CAN$ 400 per course (varied in the sensitivity analysis), which includes the cost of the vaccine and administration fees. We assume that a booster dose costs CAN$ 167 (i.e. CAN$ 33 more that an adolescent dose to reflect the additional vaccine administration costs for adults).

2.9. Sensitivity analysis

We performed probabilistic sensitivity analysis, using triangular distributions around unit costs and QALY-weights (see Tables 1 and 2 for input distributions). Results are presented with 80% credibility intervals (CrI), which show the 10th and 90th percentile taken from the distribution of results from 209,000 simulations (209 "good fit" natural history parameter sets × 1000 simulations of the probabilistic sensitivity analysis). Credibility intervals are the Bayesian analog to classical frequentist confidence intervals. We used an 80%CrI instead of the 95% criterion as it illustrates the uncertainty of model predictions without giving excessive weight to outliers.

3. Results

3.1. Vaccine effectiveness

Under base-case assumptions, the model predicts that vaccinating a cohort of 100,000 girls aged 12 years against HPV-6/11/16/18 would prevent 18,000 episodes of genital warts (0 without HPV-6/11 types in the vaccine), 20,000 CIN1 (16,000 without HPV-6/11), 13,000 CIN2/3, 310 cervical cancer cases and 140 cervical cancer deaths over their lifetime (Table 3). This corresponds to lifetime risk reductions of 86% (0% without HPV-6/11), 24% (19% without HPV-6/11), 47%, and 62% for genital warts, CIN1, CIN2/3 and cervical cancer, respectively. The greatest gains in reduction of morbidity (as measured in terms of QALYs-gained) are through the prevention of cervical cancer deaths and QALY-adjusted life-expectancy (Fig. 1a).

3.2. Base case cost-effectiveness analysis

Table 3 shows the predicted health outcomes and costs prevented by vaccination. Under base case assumptions, vaccinating 100,000 girls aged 12 years results in 1400 (1800) discounted QALYs-saved over their lifetime, using a bivalent (quadrivalent) vaccine. This is estimated to result in direct medical cost offsets of CAN$ 4.4 million for the bivalent vaccine and CAN$ 7.2 million for the quadrivalent, but at a cost of vaccination of CAN$ 40.0 million (Table 3). Thus, the cost-utility ratios for the bivalent and quadrivalent vaccines are estimated to be approximately CAN$ 31,000 (80%CrI: 15,000–55,000) and CAN$ 21,000 (80%CrI: 11,000–33,000) per QALY-gained, respectively (Table 3).

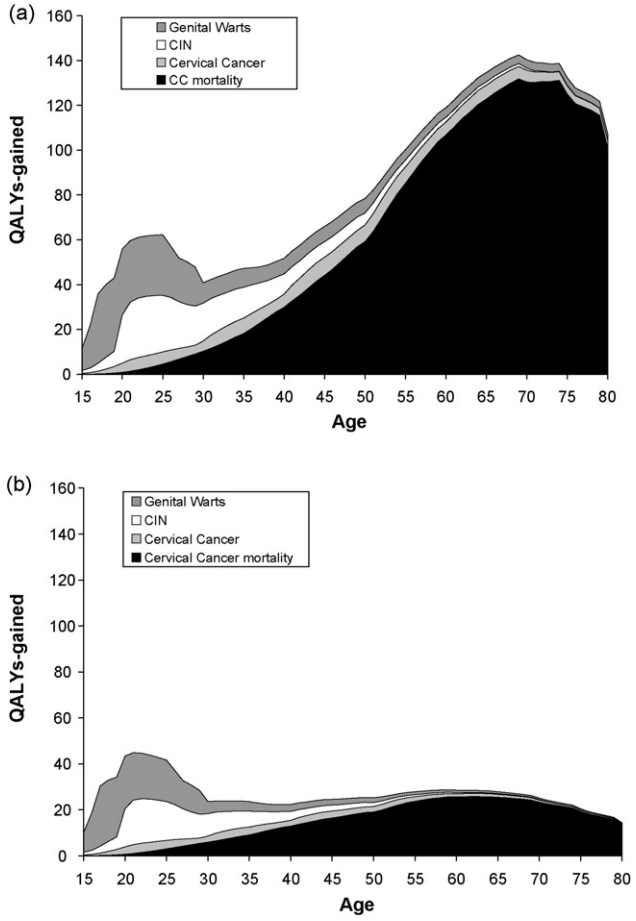

Fig. 1. Estimated (a) undiscounted and (b) discounted QALYs-gained in a cohort of 100,000 girls vaccinated at 12 years of age (vaccine efficacy = 95%, average duration of vaccine protection = Life). Genital warts, CIN, cervical cancer and cervical cancer deaths represent 21% (12%), 16% (9%), 8% (7%), 55% (72%) of the cumulative QALYs-gained using a 3% (0%) discount rate. Note that the gains in QALYs due to prevention of genital warts are the result of the 6/11 component of the HPV-6/11/16/18 vaccine. QALY, Quality-Adjusted Life-Years.

3.3. Impact of vaccine characteristics and vaccination scenarios

The cost-effectiveness of HPV vaccination is especially sensitive to the duration of vaccine protection (Table 3 and Fig. 2). The cost-utility ratio when assuming duration of vaccine protection is 30 years are three to four times higher than those assuming protection is lifelong (Table 3). The uncertainty around model predictions also increases when waning vaccine induced immunity is assumed (Fig. 2a). This is because a vaccine with limited duration will move the pool of susceptibles towards older ages allowing for age-specific natural history of cervical cancer to influence model predictions. If the force of HPV infection remains high among older women and/or if progression rates towards cervical cancer are greater in older women, then waning immunity will greatly reduce vaccine effectiveness. If waning immunity occurs, adding a booster dose is predicted to improve

Table 3
Lifetime discounted (3%) health outcomes and costs saved by vaccinating a cohort of 100,000 12-year-old girls

	Average duration of vaccine protection		
	Life	30 years[a]	30 years and booster
Health outcomes prevented			
Infection	110,189	55,439	90,745
Genital warts (HPV[c]-6/11)	9,962	6,352	8,485
Diagnosed CIN[c] 1			
Bivalent (HPV-16/18)	3,417	1,853	2,695
Quadrivalent (HPV-6/11/16/18)	4,090	2,216	3,277
Diagnosed CIN2/3	1,871	1,080	1,500
Cervical cancer	122	33	89
Cervical cancer deaths	45	9	32
LY[c]-gained	1,321	465	998
QALY[c]-gained			
QALY-gained preventing death	1,079	397	819
Genital warts (HPV-6/11)	382	243	325
Diagnosed CIN1			
Bivalent (HPV-16/18)	94	52	74
Quadrivalent (HPV-6/11/16/18)	116	64	93
Diagnosed CIN2/3	187	108	150
False positive	−11[d]	−6[d]	−9[d]
Cervical cancer	91	22	65
Total			
Bivalent (HPV-16/18)	1,441	572	1,100
Quadrivalent (HPV-6/11/16/18)	1,844	828	1,444
Cost offsets (million CAN$)			
Negative Pap[c] tests	−0.30	−0.17	−0.24
False positive	−0.05[d]	−0.03[d]	−0.04[d]
Treatment and diagnosis			
Genital warts	2.53	1.61	2.15
CIN1	1.28	0.68	1.03
CIN2/3	2.21	1.28	1.77
Cervical cancer	1.54	0.41	1.12
Total			
Bivalent (HPV-16/18)	4.44	2.04	3.43
Quadrivalent (HPV-6/11/16/18)	7.21	3.79	5.80
Cost of vaccination (million CAN$)	40.00	40.00	52.21
Cost per LY-gained (CAN$)[b]	34,496	222,273	65,750
Cost per QALY-gained (CAN$)			
Bivalent (HPV-16/18)	31,060	114,846	56,028
Quadrivalent (HPV-6/11/16/18)	20,512	64,584	36,981

Vaccine efficacy = 95%, cost per course = CAN$ 400, booster = CAN$ 167.
[a] Average duration of vaccine protection of 30 years corresponds to a waning rate of 0.033 per year.
[b] Cost per LY-gained is the same for the HPV-6/11/16/18 and HPV-16/18 vaccines.
[c] HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia. LY, life-year; QALY, Quality-adjusted life-year; Pap, Papanicolaou.
[d] False positives will increase after vaccination if prevalence of CIN declines and the specificity remains constant.

dramatically the cost-utility ratios (Table 3 and Fig. 2). On the other hand, varying vaccine efficacy between 90% and 100% has little impact on the cost-effectiveness predictions.

Under base case vaccine characteristics, results suggest that there is relatively little difference between vaccinating at 12 or 15 years of age (Fig. 2a). However, vaccinating women at 25 years of age rather than at 15 years increases the cost per QALY-gained from CAN$ 32,000 (80%CrI: 15,000–59,000) to CAN$ 65,000 (80%CrI: 24,000–125,000) using the bivalent vaccine, and from CAN$ 21,000 (80%CrI: 12,000–34,000) to CAN$ 44,000 (80%CrI: 21,000–83,000) using the quadrivalent vaccine (Fig. 2a). The cost-utility ratios, and related uncertainty, increase with age at vaccination because older women have a greater chance of having been infected and thus being immune to at least one of the HPV types included in the vaccine. The increased uncertainty reflects the limited understanding of the epidemiology

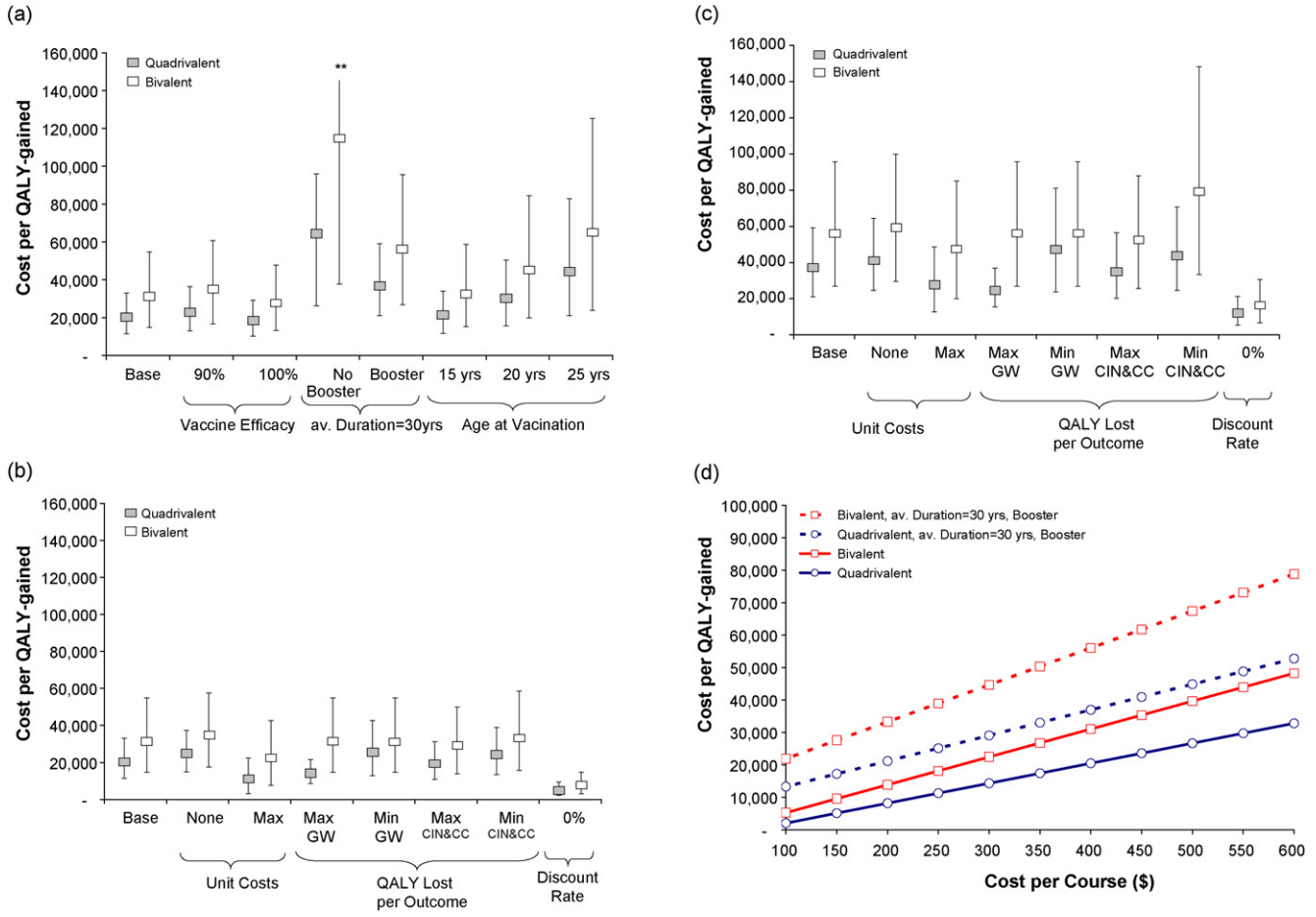

Fig. 2. Univariate sensitivity analysis: (a) vaccine characteristics and scenarios, (b) health economic parameters: lifelong vaccine protection, (c) economic parameters assuming average duration is 30 years and a booster dose is given, (d) vaccine cost per course. Base: VE = 95%, VD = Life, VA = 12 years, cost per course = CAN$ 400. In the univariate sensitivity analyses, parameters were varied one at a time, holding other parameter values at the base case level. The 80% credibility intervals (CrI) represents the variability related to the 209 "good fit" natural history parameter sets. In the sensitivity analysis the cost of a booster dose is assumed to be CAN$ 167.

of HPV infection and disease in older women (e.g. percentage of cervical cancer attributable to infection at older ages).

3.4. Impact of economic parameters

Cost-effectiveness results are relatively insensitive to large variations in direct medical costs and the QALYs lost due to CIN and cervical cancer (Fig. 2b and c). Cost-effectiveness is however very sensitive to the discount rate, as the greatest benefits related to HPV vaccination (i.e. prevention of cervical cancer deaths) occur decades after vaccination (Fig. 1 illustrates the impact of discounting on the estimated QALYs-gained through vaccination). It should be noted that when discount rates are very small, the relative difference in the cost-effectiveness between the bivalent and quadrivalent vaccines is diminished (Fig. 2b and c) because the relative contribution of the QALYs-gained from preventing genital warts is reduced compared to the QALYs-gained from preventing cervical cancer.

Predictably, the vaccine's cost per course has a major influence on cost-effectiveness estimates (Fig. 2d). Under base case assumptions, each increase (or decrease) of CAN$ 50 in the cost per course of the bivalent and quadrivalent vaccines will produce an increase (or decrease) of CAN$ 4000 and CAN$ 3000 per QALY-gained, respectively (Fig. 2d). The cost per course of the bivalent and quadrivalent vaccines will probably not be identical. Assuming the quadrivalent is CAN$ 400 per course, we estimate that the cost per course of the bivalent vaccine must be approximately CAN$ 295 (80%CrI: 235–347) in order for the vaccines to produce equivalent cost-utility ratios (results not shown). This result is highly sensitive to the average QALY-lost to genital warts but not to the cost of treatment. If we use the minimum QALY-lost for genital warts (see Table 1) or assume that genital warts does not lead to direct costs to the health care system, the cost per course of the bivalent vaccine to produce the same cost-utility ratio as a quadrivalent that costs CAN$ 400, must be CAN$ 343 (80%CrI: 312–371) or CAN$ 313 (80%CrI: 259–360), respectively (results not shown).

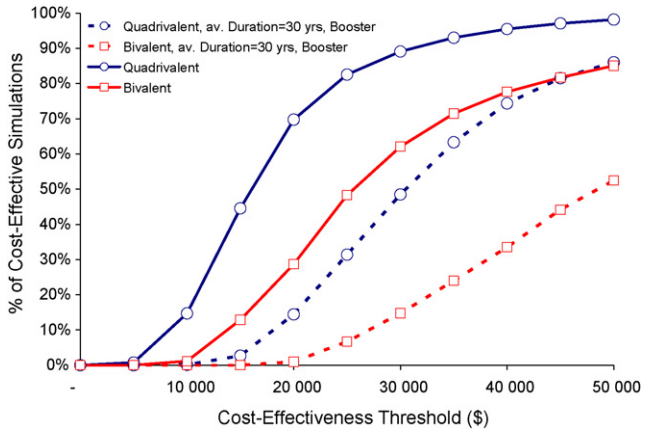

Fig. 3. Probabilistic sensitivity analysis: proportion of simulations that would be deemed cost-effective for different threshold values of cost per QALY-gained (VE = 95%, VA = 12 years, cost per course = CAN$ 400). In the sensitivity analysis the cost of a booster dose is assumed to be CAN$ 167. The figure can be loosely interpreted as showing the probability that HPV vaccination would be deemed cost-effective for alternative values of society's maximum willingness to pay for a QALY-gained.

3.5. Multivariate sensitivity analysis

Fig. 3 summarizes the results of the multivariate sensitivity analyses. Although no guidelines are available for the maximum amount that decision makers are prepared to pay for an additional QALY-gained, a commonly cited rule of thumb is that interventions are "very cost-effective" if they have cost-effectiveness ratios less than the per capita GDP [37,38]. Using CAN$ 40,000 (Canadian per capita GDP [39]) as strong evidence for cost-effectiveness, vaccinating 12-year-old girls against HPV-16/18 or HPV-6/11/16/18 is likely to be cost-effective (Fig. 3).

4. Discussion

We developed a cohort model to help inform policy decisions and recommendations regarding HPV vaccination. Results suggest that vaccinating adolescent girls against HPV is likely to be cost-effective under current cytology-based screening programs in Canada. Furthermore, the main benefit of HPV vaccination will be in preventing cervical cancer mortality rather than reducing the direct health care costs related to screening and treatment of HPV-related disease (assuming screening is not changed). Using CAN$ 40,000 per QALY-gained as strong evidence for cost-effectiveness, HPV vaccination is estimated to be cost-effective under a wide range of parameter assumptions and vaccination scenarios. These results are sensitive to assumptions regarding duration of vaccine protection and the cost per course of vaccination. If waning of vaccine protection occurs then a booster dose will be needed in order for HPV vaccination to be cost-effective (Fig. 2).

Our cost-utility ratios are slightly higher than those from US cohort-based cost-effectiveness analyses of HPV-16/18 vaccination [27,40]. Goldie et al. [27], and Sanders and Taira [30] predicted that vaccinating 12 year old girls against HPV-16/18 will cost US$ 24,000 and US$ 23,000 per QALY-gained, respectively (using similar vaccine characteristics). The higher cost-utility ratios estimated in our study are partly due to the lower screening and treatment costs in Canada compared to the US. When using the costs reported in Goldie et al. [27], we estimate that the cost per QALY-gained by vaccinating 12-year-old girls against HPV-16/18 is US$ 25,000 (80%CrI: 11,100–46,000).

The main limitation of our modeling approach is that it does not take into account the change in the transmission dynamics of infection following vaccination, which limits the research questions that can be addressed [41]. However, because model predictions are based on a static model, which does not account for herd-immunity effects, our results can be considered as conservative (previous US studies have shown that including transmission dynamics reduces HPV vaccine cost-utility ratios [40–42]). Given that our model does not include herd-immunity effects, we did not examine the incremental cost-effectiveness of vaccinating boys or optimal catch-up strategies. US modeling studies have predicted that if coverage rates can reach 90% (which would be expected in Canada if universal routine immunization is implemented), including boys in a vaccination program would not be cost-effective [40]. Results should be similar (or worse) for Canada as health care cost are lower than in the US and HPV vaccine effectiveness predictions are similar [25]. Although, we did not investigate different catch-up strategies, we did examine different ages at vaccination. Results suggest that HPV vaccination is likely to be cost-effective if given to girls/women 12–20 years of age (using the CAN$ 40,000 per QALY-gained threshold) and, therefore, that a catch-up strategy within these age groups has the potential to be cost-effective. However, to accurately estimate optimal catch-up strategies, good programmatic feasibility and cost data is required, in addition to dynamic modeling. Another potential limitation of this study is that data on the costs of screening and treatment of CIN, cervical cancer and genital warts are sparse and incomplete in Canada. However, extensive sensitivity and uncertainty analysis show that these unit costs have little to no impact on model conclusions regarding the cost-effectiveness of HPV vaccination under current screening strategies in Canada. Treatment and screening costs will most likely have an impact when examining the cost-effectiveness of optimal screening strategies.

Our modeling study has three main strengths. First, and most importantly, we perform an extensive fitting procedure that identifies multiple parameter sets (that reproduce Canadian epidemiological data), which enable thorough investigation of the impact of natural history assumptions and parameter uncertainty on cost-effectiveness predictions. Secondly, we do not assume, a priori, age dependencies in our progression and regression rates as no conclusive evidence

exists as to these associations. This advantage enables us to explore the impact of age-specific natural history assumptions. The wide credibility intervals when waning efficacy is assumed or vaccination is given to "older" women reflect the uncertainty in the natural history of HPV in older adults and suggest that more research is needed in this area. Thirdly, we performed extensive sensitivity and uncertainty analysis, which allow us to illustrate the robustness of conclusions, given our model structure.

We provide a comparison of the cost-effectiveness of a bivalent versus a quadrivalent vaccine. Policy makers will have to decide, given their respective characteristics and costs, whether none, one or both of these vaccines should be included into the routine vaccine schedule. Base case results predict that the cost per course of the bivalent vaccine would have to be CAN$ 105 less than that of a quadrivalent (assuming the quadrivalent costs CAN$ 400) to produce equivalent cost per QALY-gained ratios. A source of uncertainty regarding this result is the potential impact of cross-protection. Harper et al. [16], have published evidence which suggests that the bivalent vaccine (HPV-16/18) is protective against incident HPV-31/45 infection. Clinical trials have yet to show whether the quadrivalent vaccine is protective against HPV-31/45 infection or that the current bivalent and quadrivalent vaccines are cross-protective against persistent HPV-31/45 infection and associated diseases. If we assume that only the bivalent vaccine produces cross-protection against HPV-31/45, that this reduces cervical cancer and associated mortality by an extra 4% (as predicted by Kohli et al. [43]) and that genital warts do not incur costs to the health care system, then the bivalent vaccine is predicted to have to be CAN$ 75 (80%CrI: 27–133) less than that of a quadrivalent (assuming the quadrivalent costs CAN$ 400) to produce equivalent cost per QALY-gained ratios. Using these same assumptions, we estimate that the incremental cost per course of the quadrivalent (compared to the bivalent) would have to be CAN$ 63 to produce an incremental cost-effectiveness ratio of CAN$ 20,000 per QALY-gained (age at vaccination = 12 years, 95% efficacy, duration of vaccine protection = life). The relative cost-effectiveness of the bivalent and quadrivalent vaccines are highly sensitive to the QALYs lost to genital warts, for which there is limited data in the literature. Clearly, more research should be focused on understanding the quality of life impact of genital warts.

To our knowledge this is the first Canadian study that examines the potential cost-effectiveness of prophylactic HPV vaccines. Results indicate that HPV vaccination of adolescent girls, in addition to current cytology-based screening in Canada, is likely to be a cost-effective use of limited health care resources. The main benefit of vaccination will be in reducing cervical cancer mortality. However, unless screening is modified (e.g. later age of initiation or wider screening intervals), the cost of HPV immunization will strongly outweigh the direct costs saved through reduced health care resource use. Finally, more studies should be focused on: (1) quantifying the duration of vaccine protection, (2) estimating the QALYs-lost and costs related to genital warts to better understand the relative cost-effectiveness of the HPV-16/18 and HPV-6/11/16/18 vaccines, and (3) using dynamic models to examine the efficiencies and cost-efficiencies of different screening and vaccine strategies in reducing HPV-related disease.

Acknowledgments

Conflicts of interest: Dr. Brisson was an employee of Merck Frosst Canada Ltd. during the analysis. He is now associate professor at Laval University. He has consulted for Merck Frosst and has received reimbursement for travel expenses from GlaxoSmithKline. Dr. De Wals has received research grants, reimbursement for travel expenses, and honoraria for conferences from vaccine manufacturers that include Aventis Pasteur, GlaxoSmithKline, Shire, Chiron, Baxter, Merck Frosst, and Wyeth-Ayerst. Dr. Boily has received HPV unrestricted research grants from Merck Frosst Canada Ltd. Nicolas Van de Velde has no conflicts of interest to declare.

References

[1] Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999;189(1):12–9.
[2] Carter JJ, Madeleine MM, Shera K, Schwartz SM, Cushing-Haugen KL, Wipf GC, et al. Human papillomavirus 16 and 18 L1 serology compared across anogenital cancer sites. Cancer Res 2001;61(5):1934–40.
[3] Schiffman M, Kjaer SK. Chapter 2: natural history of anogenital human papillomavirus infection and neoplasia. J Natl Cancer Inst Monogr 2003;(31):14–9.
[4] Herrero R. Chapter 7: human papillomavirus and cancer of the upper aerodigestive tract. J Natl Cancer Inst Monogr 2003;(31):47–51.
[5] Brown DR, Schroeder JM, Bryan JT, Stoler MH, Fife KH. Detection of multiple human papillomavirus types in Condylomata acuminata lesions from otherwise healthy and immunosuppressed patients. J Clin Microbiol 1999;37(10):3316–22.
[6] Greer CE, Wheeler CM, Ladner MB, Beutner K, Coyne MY, Liang H, et al. Human papillomavirus (HPV) type distribution and serological response to HPV type 6 virus-like particles in patients with genital warts. J Clin Microbiol 1995;33(8):2058–63.
[7] Pou AM, Rimell FL, Jordan JA, Shoemaker DL, Johnson JT, Barua P., et al. Adult respiratory papillomatosis: human papillomavirus type and viral coinfections as predictors of prognosis. Ann Otol Rhinol Laryngol 1995;104(10 (Pt. 1)):758–62.
[8] Rimell FL, Shoemaker DL, Pou AM, Jordan JA, Post JC, Ehrlich GD. Pediatric respiratory papillomatosis: prognostic role of viral typing and cofactors. Laryngoscope 1997;107(7):915–8.
[9] Franco EL, Duarte-Franco E, Ferenczy A. Cervical cancer: epidemiology, prevention and the role of human papillomavirus infection. CMAJ 2001;164(7):1017–25.
[10] Canadian Cancer Society/National Cancer Institute of Canada. Canadian Cancer Statistics 2006, ISSN 0835-2976; April 2006 [http://www.cancer.ca/vgn/images/portal/cit_86751114/31/21/935505792cw_2006stats_en.pdf.pdf].
[11] Munoz N, Bosch FX, de Sanjose S, Herrero R, Castellsague X, Shah KV, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med 2003;348(6):518–27.

[12] Burd EM. Human papillomavirus and cervical cancer. Clin Microbiol Rev 2003;16(1):1–17.
[13] Clifford GM, Smith JS, Aguado T, Franceschi S. Comparison of HPV type distribution in high-grade cervical lesions and cervical cancer: a meta-analysis. Br J Cancer 2003;89(1):101–5.
[14] von Krogh G, Lacey CJ, Gross G, Barrasso R, Schneider A. European course on HPV associated pathology: guidelines for primary care physicians for the diagnosis and management of anogenital warts. Sex Transm Infect 2000;76(3):162–8.
[15] Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind A, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. Lancet 2004;364(9447):1757–65.
[16] Harper DM, Franco EL, Wheeler CM, Moscicki AB, Romanowski B, Roteli-Martins CM, et al. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. Lancet 2006;367(9518):1247–55.
[17] Koutsky LA, Ault KA, Wheeler CM, Brown DR, Barr E, Alvarez FB, et al. A controlled trial of a human papillomavirus type 16 vaccine. N Engl J Med 2002;347(21):1645–51.
[18] Villa LL, Costa RL, Petta CA, Andrade RP, Ault KA, Giuliano AR, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncol 2005;6(5):271–8.
[19] Health Canada. Drugs and Health Products. Notice of Compliance (NOC). Gardasil. Recombinant human papillomavirus vaccine (Types 6, 11, 16, 18). DIN: 02283190 [accessed March 15, 2007, http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/txt/[36]prodpharma/bio2006et.txt].
[20] Koutsky LA, Harper DM. Chapter 13: current findings from prophylactic HPV vaccine trials. Vaccine 2006;24(Suppl. 3):S114–21.
[21] US Food Drug Administration. Center for Biologics Evaluation and Research. Product Approval Information. Licensing Action. GARDASIL. Label. Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine 9682300; STN: 125126/0 [accessed March 15, 2007, http://www.fda.gov/cber/products/hpvmer060806.htm].
[22] Erickson LJ, De Wals P, Farand L. An analytical framework for immunization programs in Canada. Vaccine 2005;23(19):2470–6.
[23] National Advisory Committee on Immunization (NACI). Statement on Human Papillomavirus Vaccine. Canada Communicable Disease Report; 2007. p. 33.
[24] Brisson M, Edmunds WJ. Impact of model, methodological, and parameter uncertainty in the economic analysis of vaccination programs. Med Decis Making 2006;26(5):434–46.
[25] Van de Velde N, Brisson M, Boily MC. Modeling human papillomavirus vaccine effectiveness: quantifying the impact of parameter uncertainty. Am J Epidemiol 2007.
[26] Brisson M, Van de Velde N, Boily MC, De Wals P. Estimating the number needed to vaccinate to prevent human papillomavirus related disease and mortality, submitted for publication.
[27] Goldie SJ, Kohli M, Grima D, Weinstein MC, Wright TC, Bosch FX, et al. Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. J Natl Cancer Inst 2004;96(8):604–15.
[28] Insinga RP, Glass AG, Rush BB. Health state transitions following an abnormal Pap smear: implications for health utility assessment in cost-effectiveness analyses. In: 22nd International Papillomavirus Conference. 2007.
[29] Kulasingam SL, Myers ER. Potential health and economic impact of adding a human papillomavirus vaccine to screening programs. JAMA 2003;290(6):781–9.
[30] Sanders GD, Taira AV. Cost-effectiveness of a potential vaccine for human papillomavirus. Emerg Infect Dis 2003;9(1):37–48.
[31] Myers ER, Green S, Lipkus I. Patient preferences for health states related to HPV infection: visual analogue scales versus time trade-off elicitation. In: Proceedings of the 21st International Papillomavirus Conference. 2004.
[32] Winer RL, Kiviat NB, Hughes JP, Adam DE, Lee SK, Kuypers JM, et al. Development and duration of human papillomavirus lesions, after initial infection. J Infect Dis 2005;191(5):731–8.
[33] Statistics Canada. Consumer Price Index [accessed March 15, 2007, http://www.statcan.ca/english/Subjects/Cpi/cpi-en.htm].
[34] Benedet JL, Bertrand MA, Matisic JM, Garner D. Costs of colposcopy services and their impact on the incidence and mortality rate of cervical cancer in Canada. J Low Genit Tract Dis 2005;9(3):160–6.
[35] Lytwyn A, Sellors JW, Mahony JB, Daya D, Chapman W, Howard M, et al. Adjunctive human papillomavirus testing in the 2-year follow-up of women with low-grade cervical cytologic abnormalities: a randomized trial and economic evaluation. Arch Pathol Lab Med 2003;127(9):1169–75.
[36] The Society of Obstetricians and Gynaecologists of Canada. Human Papillomavirus: the most common sexually transmitted infection [accessed March 15, 2007, http://www.sogc.org/health/pdf/HPV_e.pdf].
[37] WHO (World Health Organization). Investing in Health for Economic Development. Report of the Commission on Macroeconomics and Health. Geneva, Switzerland; 2001.
[38] WHO (World Health Organization). WHO-CHOICE: World Health Organization statistical information system: choosing interventions that are cost effective [4-21-2006, http://www.who.int/whosis/en].
[39] Baldwin JR, Brown M, Maynard JP. Insights on the Canadian Economy: interprovincial differences in GDP per capita, labour productivity and work intensity: 1990–2003. StatCan Catalogue No. 11-624-MIE-No. 011; 2005.
[40] Taira AV, Neukermans CP, Sanders GD. Evaluating human papillomavirus vaccination programs. Emerg Infect Dis 2004;10(11):1915–23.
[41] Newall AT, Beutels P, Wood JG, Edmunds WJ, MacIntyre CR. Cost-effectiveness analyses of human papillomavirus vaccination. Lancet Infect Dis 2007;7(4):289–96.
[42] Elbasha EH. Model for assessing human papillomavirus vaccination strategies. Emerg Infect Dis 2007;(13):28–41.
[43] Kohli M, Ferko N, Martin A, Franco EL, Jenkins D, Gallivan S, et al. Estimating the long-term impact of a prophylactic human papillomavirus 16/18 vaccine on the burden of cervical cancer in the UK. Br J Cancer 2007;96(1):143–50.
[44] Sénécal M, Maunsell E, Ferenczy A, Franco E, Ratnam S, Coutlée F, et al. Psychological impact of cervical screening and condylomas: an epidemiological study (PISCES). In: 23rd International Papillomavirus Conference. 2006.
[45] Brown RE, Breugelmans JG, Theodoratou D, Benard S. Costs of detection and treatment of cervical cancer, cervical dysplasia and genital warts in the UK. Curr Med Res Opin 2006;22(4):663–70.
[46] Chesson HW, Blandford JM, Gift TL, Tao G, Irwin KL. The estimated direct medical cost of sexually transmitted diseases among American youth, 2000. Perspect Sex Reprod Health 2004;36(1):11–9.
[47] Insinga RP, Dasbach EJ, Myers ER. The health and economic burden of genital warts in a set of private health plans in the United States. Clin Infect Dis 2003;36(11):1397–403.
[48] Insinga RP, Glass AG, Rush BB. The health care costs of cervical human papillomavirus-related disease. Am J Obstet Gynecol 2004;191(1):114–20.
[49] Kim JJ, Wright TC, Goldie SJ. Cost-effectiveness of human papillomavirus DNA testing in the United Kingdom, The Netherlands, France, and Italy. J Natl Cancer Inst 2005;97(12):888–95.
[50] Kleinberg MJ, Straughn Jr JM, Stringer JS, Partridge EE. A cost-effectiveness analysis of management strategies for cervical intraepithelial neoplasia grades 2 and 3. Am J Obstet Gynecol 2003;188(5):1186–8.

[51] Kulasingam SL, Myers ER, Lawson HW, McConnell KJ, Kerlikowske K, Melnikow J, et al. Cost-effectiveness of extending cervical cancer screening intervals among women with prior normal pap tests. Obstet Gynecol 2006;107(2 (Pt. 1)):321–8.

[52] Legood R, Gray A, Wolstenholme J, Moss S. Lifetime effects, costs, and cost effectiveness of testing for human papillomavirus to manage low grade cytological abnormalities: results of the NHS pilot studies. BMJ 2006;332(7533):79–85.