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ORIGINAL ARTICLE

Cost-effectiveness analysis of adding a quadrivalent HPV vaccine to the cervical cancer screening programme in Switzerland

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ABSTRACT

Objective: Based on positive safety and efficacy data, a quadrivalent Human PapillomaVirus (HPV) vaccine has been approved in Switzerland to prevent HPV types 6, 11, 16 and 18 infections. The objective of this study was to explore the cost-effectiveness of an HPV vaccination in Switzerland.

Design and methods: A Markov model of the natural history of HPV infection was adapted to the Swiss context and followed a hypothetical cohort of 41 200 girls aged 11 years over their lifetime. Main epidemiological and economic parameters were extracted from the literature. Two strategies were compared: conventional cytological screening only and HPV vaccination followed by conventional cytological screening. A coverage rate of 80% was used and the vaccine was assumed to provide a lifelong protection. Analyses were performed from the direct health care cost perspective including only direct medical costs.

Results: Compared to screening only, adding a quadrivalent HPV vaccine could prevent over lifetime 62% of cervical cancers and related deaths, 19% of Cervical Intraepithelial Neoplasia (CIN 1), 43% of CIN 2, 45% of CIN 3 and 66% of genital warts per cohort. Incremental cost-effectiveness ratios (ICER) were estimated to be CHF 45 008 per Life Year Gained (LYG) and CHF 26 005 per Quality Adjusted Life Year (QALY) gained. Sensitivity analyses demonstrated that the ICER was robust to all parameters, but was most sensitive to the need for a booster and discount rates.

Conclusions: Compared to commonly accepted standard thresholds in Europe and other vaccination strategies implemented in Switzerland, adding a quadrivalent HPV vaccine alongside the current cervical cancer screening programme is likely to be cost-effective in Switzerland.

Introduction

Approximately 300 new cases of cervical cancer and almost 88 related deaths are diagnosed in Switzerland yearly[1]. Human PapillomaVirus (HPV) has a key role in cervical carcinogenesis and is detected in over 99% of cervical cancer cases[2]. HPV infection is a sexually transmitted disease and is, therefore, strongly influenced by sexual activity. More than 70% of the sexually active population could be infected with HPV during their life[3]. Most HPV infections are cleared spontaneously within 1 or 2 years[2]. However, in a small percentage of women, HPV infection may persist and lead to cervical precancerous lesions (cervical intraepithelial neoplasia – CIN) and if it is not treated, progress to invasive cervical cancer. HPV may also cause vulvar, vaginal, anal, penile, head and neck cancers as well as genital warts[4]. It is estimated that about 1% of the sexually active men and women population

(15–49 years) could be infected with genital warts, which are disfiguring and can have psychosocial sequelae[5,6].

Based on their oncogenic potential, HPV types have been classified into low-risk and high-risk HPV types. The low-risk HPV types rarely cause precancerous and cancerous lesions, but are often associated with genital warts. The high-risk HPV types have a higher oncogenic potential and are often linked to the development of cervix, anal, penile, vaginal and vulvar precancerous lesions (intraepithelial neoplasia) and cancers. Most HPV related diseases may be attributable to four HPV types: 6, 11, 16 and 18. High risk HPV types 16 and 18 account for approximately 75% of all cervical cancers[7] and 55% of CIN 2/3[8]. Low risk HPV types 6 and 11 are responsible for approximately 90% of genital warts[9]. It is also estimated that HPV types 6, 11, 16 and 18 may be responsible for approximately 35% of CIN 1[10].

In Switzerland, a cervical cancer screening programme has been implemented to reduce the cervical cancer incidence and related mortality rate. Women are recommended to be screened every 3 years to detect and treat precancerous cervical lesions before the development of cervical cancer[11]. However, despite important benefits from the cervical cancer screening programme, cervical cancers still occur in Switzerland and women continue to die from this disease.

A quadrivalent prophylactic recombinant HPV vaccine (Gardasil*) which targets HPV types 6, 11, 16 and 18 has recently been approved in Switzerland, designed for the prevention of cervical cancer, CIN, genital warts and other HPV related diseases. This vaccine was shown to be highly effective in phase III clinical trials[12,13]. Regarding the safety and the high efficacy of this vaccine, policymakers recommended to vaccinate all adolescent girls aged between 11 and 14 years of age in Switzerland in June 2007[1].

The objective of this study was to explore the cost-effectiveness of adding an HPV vaccination programme with the quadrivalent HPV vaccine to adolescent girls aged 11 years alongside the current cervical cancer screening programme from the direct health care cost perspective in Switzerland.

Material and methods

Structure of the model

A previously published and validated US Markov model[14,15] simulating the natural history of HPV infection and cervical cancer and estimating economic consequences of HPV related diseases was recently adapted to the European context[16]. Compared to the original[14,15], this model was revised to separate high-grade CIN into CIN 2 and CIN 3 and to integrate genital warts. This revised model was used to assess the cost-effectiveness of an HPV vaccination programme in Switzerland and was also adapted structurally to reflect the local screening and treatment pathway. The model was programmed using the software TreeAge Pro (TreeAge Software Inc., Williamstown, MA, USA).

A hypothetical cohort of 41 200 girls aged 11 years old[17] was followed until death through different health states corresponding to the natural history of HPV infection (i.e. well state, infected, CIN 1, CIN 2, CIN 3, cervical cancer and death). Movements between health states were based on yearly transition probabilities. Women who were normal (i.e. did not have CIN or cervical cancer) were at risk for developing genital warts.

Women infected with HPV can have their infection clear, progress or persist. For those women whose infections persist or progress, HPV infection may progress to CIN 1 or genital wart and rarely to CIN 2 directly. For women developing genital warts, we assumed that the disease would be cured within a year. Women who develop CIN 1, CIN 2 or CIN 3 can have their disease progress (to CIN 2, CIN 3 or cervical cancer, respectively), regress or persist. Cervical cancer (FIGO stages I–IV) can be detected during screening or by a doctor after becoming symptomatic. Women who do not have their disease detected and remain asymptomatic can progress to the next stage; remain in the same stage or die of cervical cancer. Additionally, each year women face an age-specific risk of dying from other causes.

The adaptation of the model to the Swiss context allowed comparing outcomes of two strategies among the same cohort followed over their lifetime:

- the current cervical cancer screening programme alone;
- adding a quadrivalent HPV vaccine alongside the current cervical cancer screening programme.

Natural history of HPV

Due to the lack of available country specific data, we assumed that the natural history of HPV was similar between all European countries[18]. First, transition probabilities data were extracted from the UK model[16] as no data were available in literature for Switzerland. In a second step, the model was empirically calibrated in a hierarchical fashion to fit the age specific cancer incidence curve observed in Switzerland alongside the current cervical cancer screening alone[19]. Although we assumed that the underlying natural history of cervical cancer is fundamentally the same across countries, we acknowledged that patterns of sexual behaviour and age of sexual debut vary[18]. To reflect this variation, we adjusted incidence rates of HPV infection. The probability

* Gardasil is a registered Trademark of Merck & co., inc, USA

of progressing from CIN 3 to cancer FIGO I was also hierarchically calibrated to fit the age-specific cervical cancer incidence curve. Yearly transition probabilities used in the model are presented in Table 1.

No data were available for 5 year survival rates for patients with cervical cancer and age-specific incidence rates of genital warts in Switzerland. Therefore, these parameters were derived from observed data in France

Table 1. *HPV natural history parameters*

Parameters	Ages (years)	Annual transition probabilities
HPV infection		
Well to HPV infected state[calibrated from 53]	13–16	0.030–0.05
	17–18	0.085
	19	0.230
	20–22	0.250
	23	0.220
	24–29	0.190
	30–33	0.045
	34–49	0.029
	50+	0.008
HPV infection to CIN 1 or CIN 2[53]	All	0.0959
HPV infected state to well[based on 14,53]	12–24	0.4666
	25–29	0.3333
	30–39	0.2666
	40–49	0.1800
	50+	0.0666
Proportion of HSIL that are CIN 2[based on 14,53]	All	0.1350
CIN		
CIN 1 to CIN 2[53]	16–34	0.0297
	35+	0.1485
CIN 1 to CIN 3[53]	All	0.0301
CIN 1 to well or HPV infected state[53]	16–34	0.2248
	35+	0.1124
Proportion CIN 1 regressing directly to well[53]	All	0.9000
CIN 2 to CIN 3[53]	16–34	0.0389
	35–44	0.0797
	45+	0.1062
CIN 2 to CIN 1[53]	All	0.2430
CIN 2 to well or HPV infected state[53]	All	0.1901
Proportion CIN 2 regressing directly to well[53]	All	0.9000
CIN 3 to CIN 1[53]	All	0.0000
CIN 3 to CIN 2[53]	All	0.0135
CIN 3 to well or HPV infected state[53]	16–44	0.0135
	45+	0.0100
Proportion CIN 3 regressing directly to well[53]	All	0.5000
CIN 3 to invasive cervical cancer[calibrated from 53]	All	0.0120
Cervical cancer		
Probability of symptoms[based on 14,53]		
Figo stage I		0.11
Figo stage II		0.23
Figo stage III		0.66
Figo stage IV		0.90
Progression and time of progression between[based on 14]		
Figo stage I and II		0.90/48 months
Figo stage II and III		0.90/36 months
Figo stage III and IV		0.90/15 months

CIN: cervical intraepithelial neoplasia

Table 2. Estimated age-specific incidence of genital warts in women in Switzerland[based on 24,25]

Age group (years)	Genital warts incidence (/100 000)
16–20	239
20–24	630
25–29	563
30–34	366
35–39	225
40–44	157
45–49	89
50–54	61
55+	45

and Germany as the epidemiology was assumed to be similar between these countries. Five year survival rates for patients with cervical cancer FIGO I, II, III and IV were assumed to be 90.9%, 64.8%, 44.2% and 20.0% in Switzerland, respectively[20–22]. Age-specific mortality rates from all causes in the general female population were based on WHO estimates[23]. Age-specific incidence rates of genital warts[24,25] used in the model are presented in Table 2. Furthermore, we assumed that all women with symptomatic warts would be treated and that the treatment would be 100% effective.

Women who undergo benign hysterectomy would not develop cervical cancer and were controlled for in the model. Age-specific incidence rates of hysterectomy in Switzerland were obtained from the National Office of Swiss Statistics[17] and were estimated to be between 0.07 per 1000 and 9.26 per 1000 in the general population aged 20 years and over.

Screening programme

In Switzerland, cervical cancer screening is recommended every 3 years for women aged 18–69 years[11]. However, the frequency of screening was estimated to be every 2 years in the model based on expert opinions. The cervical cancer screening coverage rate for women screened was extracted from a survey conducted in 1997 in Switzerland[26]. The sensitivity and specificity of diagnostic tests used were extracted from the literature and are presented in Table 3.

Vaccine parameters and vaccination programme

Based on results from recent Phase III clinical trials, the quadrivalent HPV vaccine was found to be 100% effective in preventing precancerous lesions, cervical cancers and genital warts due to HPV types 6, 11, 16 and 18[12,13]. In the model, we adopted a conservative approach by assuming that the vaccine was 95% effective. The vaccine efficacy was tested between 90% and 100% in sensitivity analyses.

Based on the proportion of precancerous lesions, invasive cancers and genital warts attributable to HPV 6, 11, 16 and 18 infections and a 95% vaccine efficacy[7–10], we modelled a reduction of approximately 33% for CIN 1, 52% for CIN 2/3, 71% for cervical cancer and 86% for genital warts. The duration of protection is likely to be lifelong without the need for a booster and was considered in the base case model. This approach is supported by recent efficacy data seen 5 years post study entry[27]. As some uncertainties still exist on the duration of protection provided by vaccination, a strategy assuming the need for a booster 10 years after first doses to provide a lifelong duration was tested in sensitivity analyses.

Vaccine coverage was assumed to be 80% for all Swiss adolescent girls aged 11 years. The vaccine was assumed to be administered by general practitioners (GP) for 50% of the girl cohort and by gynaecologists for the remaining girls.

Management of HPV related diseases and cost of cervical cancer screening, diseases management and vaccination programme

Costs are presented in Table 3. The management of HPV related precancerous lesions were estimated based on a retrospective data collection among the colposcopic clinic in the Centre Hospitalier Universitaire Vaudois (CHUV, Lausanne, Switzerland) including 8000 patients who had consultations over a 5-year period[28]. The data were completed and/or validated by 2 Swiss experts (Dr Gerber and Pr Heinzl)[29] and valued with TARMED[30]. The cost of a gynaecologist visit for screening was estimated to be CHF 155.00[28]. For the screening, we made the assumption that gynaecologists used in the same proportion conventional pap smear and Liquid Based Cytology (LBC). The cost of a routine pap smear test was estimated to be CHF 54.50, including CHF 32.50 for the test[30] and CHF 22.00 for its analysis[28]. The cost for a colposcopy/biopsy and for an HPV DNA test was estimated to be CHF 80.00 and CHF 170.00, respectively[30]. The management of abnormal pap smears in Switzerland is presented in Table 4. Furthermore, we assumed that 35% of women presenting with CIN 1, 95% with CIN 2 and 100% with CIN 3 were treated respectively and the treatment of CIN was 100% effective. The management of genital warts was based on interviews using a structured questionnaire with the 2 Swiss experts (Dr Gerber and Pr Heinzl)[29]. Health care consumptions were then valued with TARMED[30] and Swiss Compendium[31].

Table 3. *Sensitivity and specificity of screening and diagnostic tests, unit costs and utility values*

Sensitivity and specificity of tests used	
Pap smear	
Sensitivity[54]	0.590
Specificity[15,55]	0.957
HPV DNA test[56]	
Sensitivity	0.948
Specificity	0.673
Colposcopy/biopsy	
Sensitivity[57]	0.900
Specificity[15,58]	1.000
Cost parameters	
Unit costs	
Pap smear[28,30]	CHF 54.50
Gynaecologist visit (for screening)[28]	CHF 155.00
HPV DNA test[30]	CHF 170.00
Colposcopy[30]	CHF 70.00
Colposcopy/biopsy[30]	CHF 80.00
Treatment costs	
CIN 1[28-30]	CHF 529.85
CIN 2[28-30]	CHF 1150.70
CIN 3[28-30]	CHF 2237.60
Cervical cancer[29]	CHF 20000
Genital warts[29-31]	CHF 387.50
Vaccine and administration cost (per dose)	
Vaccine cost[31]	CHF 236.85
Vaccine administration[30]	CHF 45.00
Utility values and duration[based on 35]	
Routine screening pap smear	0.9764 (1 month)
ASC-US diagnosis from pap smear	0.9404 (2 months)
LSIL/HSIL diagnosis from pap smear	0.9062 (2 months)
genital warts	0.9142 (85 days)
CIN 1	0.9333 (2 months with 10 months follow up)
CIN 2/3	0.8658 (2 months)
FIGO I	0.7598 (5 years)
FIGO II-IV	0.6693 (5 years)

ASCUS: atypical squamous intraepithelial lesion
LSIL: low-grade intraepithelial lesion
HSIL: high-grade intraepithelial lesion
CIN: cervical intraepithelial neoplasia

The management of CIN 1, CIN 2, CIN 3 and genital wart cases was estimated to cost CHF 530, CHF 1151, CHF 2238 and CHF 387, respectively from the direct health care cost perspective (including only direct medical costs). The cost of cervical cancer management was estimated by experts to be CHF 20 000, as no data existed for Switzerland[29]. This estimate was compared to the cost of cervical cancer management observed in France[32], Germany[33] and the United Kingdom[34] and was slightly lower.

Regarding vaccination costs, three doses of the vaccine are necessary to provide a complete protection against HPV types 6, 11, 16 and 18. In Switzerland the cost per vaccine dose is assumed to be CHF 236.85[31]. Administration cost per vaccine dose was assumed to be CHF 45 based on GP and gynaecologist consultation costs[28].

Table 4. Management of abnormal pap smear results in Switzerland[based on 28,29]

Pap smear results	Follow up	Proportion
LSIL (4.0%)	No follow up	5%
	Follow-up	95%
	Colposcopy and/or biopsy	85%
	repeat pap smear	15%
HSIL (1.1%)	No follow up	5%
	Follow-up	95%
	Colposcopy and/or biopsy	100%
ASCUS (5.0%)	No follow up	10%
	Follow-up	90%
	HPV test	55%
	repeat pap smear	45%
Inadequate (2.3%)	Repeat screening	100%

ASCUS: atypical squamous intraepithelial lesion

LSIL: low-grade intraepithelial lesion

HSIL: high-grade intraepithelial lesion

Utility scores

Utility scores are necessary to calculate quality-adjusted life years (QALY). However, at the time of this analysis, no European data were available. We, therefore, used utility scores derived from a US study[35] as done in recent similar cost-effectiveness analyses in the UK[16] and in France[36] (Table 3). The utility for those surviving cervical cancer was set as 1.0[15]. As women having a routine pap smear and results of the test may impact the utility of screened women, our model took into account the disutility associated with having a routine pap smear and effect of the diagnosis as a result of the smear. Furthermore, as genital warts, CIN and cervical cancer (FIGO I, II, III, IV) may impact considerably the utility of women, they were considered in our analysis.

Analysis

First, the model was validated by checking that predictions for a screened modelled population were similar to the observed epidemiological data in Switzerland, notably for cervical cancer age-specific incidence and mortality rates based on Pury *et al.*[19]. It was not possible to calibrate the model according to precancerous cervical lesions incidence rates as no Swiss data were available.

For both strategies, the model calculated the following health and economic outcomes among the same cohort of girls followed over their lifetime: cervical cancer cases and lifetime risks, cervical cancer related deaths, CIN 1, CIN 2, CIN 3 and genital wart cases and lifetime risks. The model calculated also the cost associated with the two strategies (including costs related to screening, HPV diseases and vaccination), the number of Life Years Gained (LYG) and the number of QALY gained.

The cost-effectiveness of adding HPV vaccine to the current cervical cancer screening programme was assessed in terms of cost per LYG and per QALY gained from the direct health care cost perspective. Indirect costs were not included.

In the base case, an annual discount rate of 3% and 1.5% was used for costs and benefits, respectively. There are no guidelines in Switzerland, but this approach is more conservative than other published cost-effectiveness analyses for vaccines in Switzerland[37,38]. Different discount rates were tested in the sensitivity analysis.

Sensitivity analysis

Univariate sensitivity analyses were performed since some parameters may present some uncertainties. The vaccine efficacy was tested between 90% and 100%. The impact of a scenario whereby a booster vaccine is required to achieve a lifetime protection was also explored. The booster vaccine was assumed to be administered to 50% of females originally vaccinated.

Management costs per cervical cancer, CIN 1, CIN 2, CIN 3 and genital wart cases were varied between ±20%. Utilities were also varied using either cervical cancer utility scores (0.68 for FIGO I, 0.57 for FIGO II and III and 0.51 for FIGO IV) or duration of genital warts (6 months) derived from a recent Canadian study[39].

As some girls may be vaccinated through a school programme, the impact of the administration of the vaccine for 30% of girls during a school programme was examined. The possibility of a co-administration of 2 doses with the Hepatitis B vaccine for all girls was also explored.

Finally, discount rates were varied for both costs and benefits ranging from 0 to 5%.

Results

Validation of the model

Probabilities of becoming infected with HPV and yearly transition probabilities from 'CIN 3' health state to 'cervical cancer' health state were calibrated empirically to fit with the observed cervical cancer incidence in Switzerland. Predictions of the model are presented in Figure 1 and indicate comparable age-specific cervical cancer incidence and mortality rates

in Switzerland[19]. Our model predicts an incidence rate of 7.5/100 000 for cervical cancer for a screened population, whereas the observed incidence rate in 2001–2003 was 8.4/100 000 in Switzerland[19].

Base case analysis

Lifetime risks for developing invasive cervical cancer and related deaths were estimated to be 0.64% and 0.19%, respectively, with the cervical cancer screening programme alone. Adding a HPV vaccination to 80% of adolescent girls aged 11 years to the current cervical cancer screening programme could reduce lifetime risks by approximately 62% in Switzerland, leading to a lifetime risk of 0.24% for cervical cancer and 0.07% for related deaths.

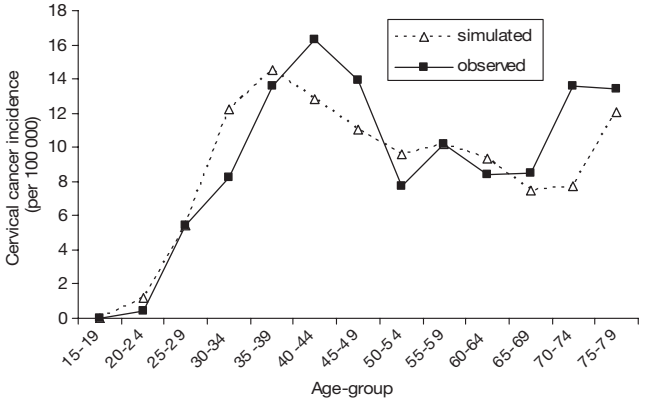

Figure 1. *Model predicted and observed cervical cancer incidence in a screened population in Switzerland[19]*

Our model predicts that approximately 264 cervical cancers, 76 related deaths, 7271 CIN 1, 3439 CIN 2, 3059 CIN 3 and 3255 genital warts occurred per cohort of adolescent girls with cervical screening only aged 11 years followed over their lifetime (Table 5). Adding HPV vaccine to the screening could prevent among the same cohort about 164 cervical cancers (62%) and 47 related deaths (62%), 1348 CIN 1 (19%), 1493 CIN 2 (43%), 1365 CIN 3 (45%) and 2142 genital warts (66%). Compared to screening only, the model also predicts that adding an HPV vaccine results in an incremental 0.013 LYG and an incremental 0.020 QALY gained per patient.

The incremental cost per patient of the introduction of an HPV vaccination programme would be 520.10 CHF compared to screening only.

Introducing a quadrivalent HPV vaccine alongside the current cervical cancer screening programme in Switzerland would result in incremental cost-effectiveness ratios (ICER) of CHF 45 008 per LYG and CHF 26 005 per QALY gained from the direct health care cost perspective versus screening only.

Sensitivity analysis

Results are sensitive to the need for a booster 10 years after first doses to provide a lifetime protection (Table 6). Assumption that a booster is administered to 50% of vaccinated females in order to provide a lifetime protection, resulted in an increase of the cost-effectiveness ratio (CHF 45 400 per QALY gained), but kept below commonly accepted threshold.

Table 5. *Incremental health, economic and cost-effectiveness outcomes associated with a quadrivalent HPV vaccine under base case in Switzerland*

Outcomes	Screening	Screening + HPV vaccination	Incremental outcomes
Health outcomes (per cohort)			
Genital warts	3255	1113	2142
CIN 1	7271	5923	1348
CIN 2	3439	1946	1493
CIN 3	3059	1694	1365
Cervical cancers	264	100	164
Cervical cancer deaths	76	29	47
Cost-effectiveness outcomes			
Total direct costs (CHF per patient)	1809.00	2329.10	520.10
Life years (per patient)	43.030	43.043	0.013
ICER (CHF / LYG)	–	–	40 008
QALY (per patient)	42.987	43.007	0.020
ICER (CHF / QALY)	–	–	26 005

CIN: cervical intraepithelial neoplasia

ICER: incremental cost-effectiveness ratio

QALY: quality-adjusted life year

Table 6. Incremental cost-effectiveness ratios under base case and sensitivity analysis

Parameters	Cost (in CHF) / QALY
Base case	26 005
Sensitivity analysis	
Duration of efficacy	
Lifetime achieved with booster	45 400
Vaccine efficacy	
90%	27 400
100%	24 800
Utilities	
Cervical cancer utility scores (0.68 for FIGO I, 0.57 for FIGO II and III and 0.51 for FIGO IV)	24 770
Duration of genital warts (6 months)	24 889
Management costs	
+20%	24 670
–20%	27 565
Discount rate for costs/benefits	
0/0%	7900
3/3%	47 725
3/0%	13 000
5/0%	14 800
5/5%	105 145
Administration	
School programme	23 150
Co-administration with the Hepatitis B vaccine	22 400

QALY: quality-adjusted life year

The ICER was not modified a lot when management costs were varied by ±20% (CHF 24 670–CHF 27 565 per QALY gained), when cervical cancer utility values from a Canadian study[39] were used (CHF 24 770) or when using a 6 month duration for genital warts[39] (CHF 24 889).

The vaccine efficacy was also tested between 90% and 100% and showed a slight impact on results (CHF 24 800–27 400 per QALY gained respectively). If 30% of vaccinated females received the vaccine through a school vaccination programme, the ICER would be reduced from CHF 26 005 per QALY gained to CHF 23 150 per QALY gained. A second vaccination scenario was also tested considering the co-administration of two doses of the vaccine with the Hepatitis B vaccine and resulted in an ICER of CHF 22 400 per QALY gained.

The ICER was most sensitive to the change in discount rates. If the same discount rate of 5% was used for both costs and benefits, the ICER would be CHF 105 145 per QALY gained. However, if costs and benefits are not discounted, the ICER would be about CHF 7900 per QALY gained.

Discussion

Introducing a quadrivalent HPV vaccine alongside the current cervical cancer screening programme may considerably reduce HPV related diseases burden in Switzerland (cervical cancer, CIN, genital warts) due to HPV types 6, 11, 16 and 18. Compared to the current cervical cancer screening programme alone, an HPV vaccination strategy in addition to the cervical cancer screening would cost approximately CHF 45 000 per LYG and CHF 26 000 per QALY gained from the direct health care cost perspective assuming a lifelong duration of protection.

This study is the first exploring the cost-effectiveness associated with the introduction of an HPV vaccine in addition to the current cervical cancer screening programme in Switzerland. To date, no officially accepted threshold exists in Switzerland below which an intervention should be adopted and considered as cost-effective. In Europe, a standard threshold value of €50 000 per QALY gained is often used to explore the cost-effectiveness of health interventions. In the Netherlands, an informal threshold of €20 000/QALY[40]

is commonly accepted and in the UK, the official upper limit of the acceptable ratio is £30 000/QALY[41]. Based on these European figures, our results suggest the quadrivalent HPV vaccine to be likely cost effective when added to the current cervical cancer screening under base case assumptions, as observed in other cost-effectiveness studies performed in Europe[16,36,42–44]. Furthermore, the ICER found in our study may be highly acceptable when it is compared to the ICER associated with recent vaccination implementations such as with pneumococcal conjugate immunisation program for infants in Switzerland[37].

HPV vaccination would likely be cost-effective under most assumptions and vaccination scenarios tested. An HPV vaccination in addition to the screening in Switzerland would remain cost-effective whether or not a booster will be required 10 years after first doses to provide a lifetime protection. Furthermore, the cost-effectiveness ratio could be improved if the vaccine would be administered through a school programme or in co-administration with the hepatitis B vaccine.

Our model presents some limitations. First, no data were available in Switzerland for the natural history of HPV and was ,therefore, derived from UK epidemiological parameters[16]. However, predictions of the model were close to the observed cervical cancer incidence and mortality rates in a Swiss screened population[19]. Furthermore, screening and treatment pathways were estimated from the activity over 5 years of the colposcopic clinic in the CHUV of Lausanne[28] and expert opinions[29] which could potentially under or over estimate management costs. Estimated management costs in Switzerland were compared to those observed in France[24,34,45], Germany[25,33] and the United Kingdom[34] and were in the same range. Furthermore, management costs were tested in sensitivity analysis by ±20% and showed a slight impact on overall results.

It was not possible to perform a probabilistic sensitivity analysis. Although one study to date has conducted this kind of simulation[39], there is a lack of information to determine the appropriate distributions to use in such complex models. This analysis used triangular distributions, although these have well known limitations. This highlights the need for epidemiologic and economic studies to include information on the distributions as well as point estimates and confidence intervals.

In our study, the calibration was performed by an empirical approach. First, transition probabilities data were extracted from the UK model[16] as no data were available in the literature for Switzerland. In a second step, the model was empirically calibrated in a hierarchical fashion to fit the age specific cancer incidence curve observed in Switzerland by adjusting incidence rates of HPV infection and yearly transition probability of progressing from 'CIN 3' to 'cancer FIGO I'. A recent work using a probabilistic sensitivity analysis to determine credible intervals for the natural history component of a model[47], demonstrated that more than 164 parameter sets could model results within the prespecified target. This emphasises a huge need to collect natural history parameters.

A recent review highlighted these difficulties and pitfalls for HPV cost-effectiveness analyses[48]. Although our study presents some identified limits, the results are very helpful for decision makers, in line with European Centre for Disease Prevention and Control guidelines, recommending country-specific health-economic analyses before introducing HPV vaccines[49].

It would be extremely useful to have European utilities scores to calculate the QALY lost. In our study it can be argued that US data might not reflect the morbidity associated with cancer, CIN and genital warts in Switzerland. However, utilities were tested using either cervical cancer utility scores or duration of a genital wart case derived from a recent Canadian cost-effectiveness study[39] and showed a slight impact on the ICER. Furthermore, we assumed that women who survive to cervical cancer have a utility of 1.0, which is a very conservative assumption.

Our analysis was based on the assumption that HPV vaccination will be added to the current cervical cancer screening programme and efforts should be made for continued screening in order to ensure gains from adding vaccination to cervical cancer screening.

The health and economic outcomes associated with the introduction of an HPV vaccine are probably underestimated since our model does not take into account the effect of 'herd immunity', or changes in the population over time. These limitations can be addressed with the use of a transmission dynamic model. In the US[35] and recently in the UK[46], the cost-effectiveness of an HPV vaccine was assessed using such a model. These studies showed a high impact of the herd immunity on overall results and that benefits from a quadrivalent HPV vaccine could be achieved quickly after its introduction because of its ability to prevent, in the short term, genital warts and low-grade squamous intraepithelial lesions (CIN 1). The early prevention of CIN is all the more important as the treatment of CIN is associated with increased pregnancy related morbidity which can have significant consequences on the future health of women and their newborns[50]. The risk of preterm delivery and low birth weight was increased after any cervical treatments for CIN (conization, ablation...). Furthermore, the risk of extremely preterm delivery and very preterm delivery increases after conisation[50]. A recent study conducted in the US demonstrated high hospitalisation costs per preterm delivery and low birth weight in the US,

averaging $ 15 100[51]. Hospitalisation costs were higher for extremely preterm infants, about $ 65 600[51]. The increased risk of preterm delivery and low birth weight after treatment of CIN were not taken into account in our model which could, therefore, potentially underestimate HPV burden in Switzerland and potential health and economic benefits from the introduction of HPV vaccination.

Recent analyses showed that the HPV quadrivalent vaccine (6, 11, 16 and 18) has a cross protection effect against other HPV types which was not considered in our analysis and may consequently underestimate health outcomes associated with the introduction of an HPV vaccination in Switzerland[52]. Furthermore, model estimates may be conservative as other potential preventive benefits of HPV 6, 11, 16 and 18 related diseases as the prevention for VIN (Vulvar Intraepithelial Neoplasia), VaIN (Vaginal Intraepithelial Neoplasia), vulvar cancer, vaginal cancer or laryngeal papillomas were not considered.

The cost-effectiveness analysis was performed from the direct health care cost perspective. Benefits from a HPV vaccination could be much higher considering indirect costs in terms of productivity lost.

Conclusion

This study provides evidence regarding the potential health and economic benefits associated with the introduction of a quadrivalent HPV vaccine in Switzerland alongside the current cervical cancer screening programme. From the direct health care cost perspective, an HPV vaccination strategy is likely to be cost-effective considering the commonly acceptable standard threshold in Europe and other health interventions implemented in Switzerland[37].

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Thomas Szucs supervised this work and validated the model inputs and outputs. Nathalie Largeron calibrated the model and ran the analyses. Konstantin Dedes validated the model inputs from a clinical point of view. Stève Bénard and Rachid Rafia collected model inputs from different Swiss sources, validated the analysis plan, wrote the report to Swiss Health Authorities and also drafted the article. All authors read and approved the final version of the article.

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