Vaccine 31 (2013) 3922–3927

Contents lists available at SciVerse ScienceDirect

Vaccine

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

Cost–effectiveness of the prophylactic HPV vaccine: An application to the Netherlands taking non-cervical cancers and cross-protection into account

J. Luttjeboer[a], T.A. Westra[a,b], J.C. Wilschut[b], H.W. Nijman[c], T. Daemen[b], M.J. Postma[a,d,*]

[a] Unit of PharmacoEpidemiology & PharmacoEconomics (PE2), Department of Pharmacy, University of Groningen, Groningen, The Netherlands
[b] Department of Medical Microbiology, Molecular Virology Section, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[c] Department of Gynaecology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[d] Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

ARTICLE INFO

Article history:
Received 17 February 2013
Received in revised form 31 May 2013
Accepted 12 June 2013
Available online 24 June 2013

Keywords:
HPV
Cross-protection
Non-cervical cancers
Cost–effectiveness analysis

ABSTRACT

Despite an effective screening programme, 600–700 women are still diagnosed with cervical cancer in the Netherlands each year. In 2009 a prophylactic vaccine against HPV-type 16 and 18 was implemented in the national immunisation programme to decrease the incidence of cervical cancer. There is evidence that infections with several oncogenic HPV types other than the vaccine types 16 and 18 are also prevented by vaccination, also known as cross-protection. Besides cervical cancer, HPV can also cause cancers at other sites such as the oropharynx, vulva, vagina and the anus/anal area. In this study we estimated the maximum health and economic benefits of vaccinating 12-year old girls against infection with HPV, taking cross-protection and non-cervical cancers into account. In the base-case, we found an incremental cost ratio (ICER) of €5815 per quality adjusted life year (QALY). Robustness of this result was examined in sensitivity analysis. The ICER proved to be most sensitive to vaccine price, discounting rates, costs of cervical cancer and to variation in the disutility of cervical cancer.

1. Introduction

Worldwide about 500,000 new cases of cervical cancer occur and 250,000 women die due to this disease every year. Approximately 83% of these cases arise in developing countries [1,2]. Screening programmes in developed countries have significantly reduced the number of deaths caused by cervical cancer [3]. In the Netherlands, women between 30 and 60 years old are invited to attend screening every five years. Despite population-wide screening for abnormal cells, 600–700 women are still diagnosed with cervical cancer in the Netherlands annually. Every year, approximately 200 women die due to cervical cancer [1]. In 2009 the bivalent HPV-vaccine (Cervarix™) was implemented in the Dutch National Immunisation Programme (NIP) for 12-year old girls. This prophylactic vaccine prevents infection with Human Papillomavirus (HPV) types 16 and 18, responsible for about 70% of all cervical cancer cases [4]. Beside cervical cancer, infection with an oncogenic HPV-type can lead to cancer at other sites, such as the vagina, anus, vulva, and oropharynx [3]. There is evidence suggesting that vaccinating women against HPV also prevents non-cervical HPV-related cancers [5]. There is also evidence that the bivalent vaccine may also prevent infection with pylogenetically related types, such as HPV types 31, 33, 45 and 51, next to the initially targeted types 16 and 18 [6]. The aim of this study is to estimate the costs and effects of HPV vaccination for 12-year old girls, including prevention of anal, cervical, oropharyngeal, vaginal and vulvar HPV-cancers, next to cervical cancer. For this purpose, a static model was built to estimate the cost per quality adjusted life year (QALY). The results of this study can be conceived to reflect the maximum benefits on the health and economic burden due to HPV-related cancers, by including both cross-protection and all relevant types of cancer.

2. Methods

2.1. Markov model

To estimate the cost per QALY for the bivalent vaccine, a cohort of 100,000 12-year old girls was simulated over lifetime. During lifetime, these women are at risk of developing one of the following cancers: vulvar cancer, vaginal cancer, oropharyngeal cancer,

* Corresponding author at: University of Groningen, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands. Tel.: +31 50 363 2607; fax: +31 50 363 2772.
E-mail address: m.j.postma@rug.nl (M.J. Postma).

0264-410X/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.vaccine.2013.06.044

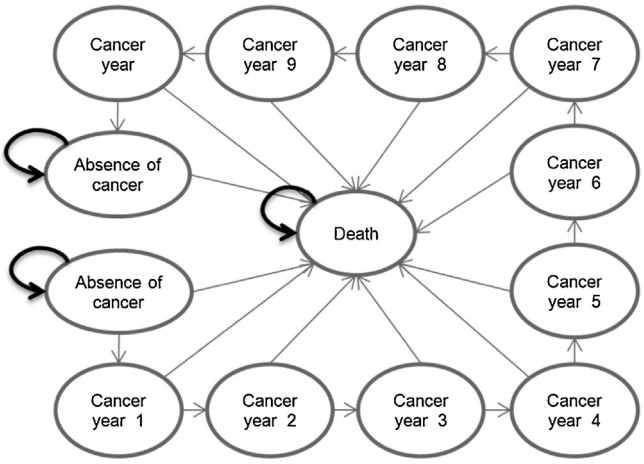

Fig. 1. Schematic representation of the Markov model used in this study.

anal cancer and cervical cancer. The cost–effectiveness analysis was done by running the model with and without the vaccine and subsequently comparing both analyses on relevant outcomes. Data on age-dependent mortality were retrieved from the website of Statistics Netherlands [7] and the data on cancer survival and risk to develop cancer were received from Netherlands Cancer Registry for the respective periods of 1989–2010 and 2005–2009 [8]. Cancer survival was modelled for ten years. Ten years after diagnosis of cancer, "normal" survival was again assumed. Every year after diagnosis of cancer was modelled individually as different survival rates apply for each year. Estimated survival was subsequently linked to cost and quality of life loss estimates in the Markov model (Fig. 1). We applied two 'Absence of cancer'-states, because of a difference in quality of life between women who never had cancer and women cured from cancer [9]. Herd-immunity was not included in this static model and 100% vaccine coverage was assumed.

2.2. HPV prevalence

To estimate the reduction of health and economic burden from HPV-related cancers by the vaccine, the prevalence of HPV-types per cancer was needed. These data were derived from two meta-analyses [10,11] and a systematic review [12] and are summarised in Table 1. In contrast to cervical cancer, not all the cancer cases at other sites are due to HPV. Therefore, a relatively smaller part of the non-cervical cancers can be prevented compared to cervical cancer.

2.3. Vaccine cost and efficacy

Data on the efficacy was obtained from the Summary of Product Characteristics (SPC) [6]. The efficacy of the bivalent vaccine has been estimated for HPV-types 16/18 at 92.9%, for 31 at 76.8%, 33 at 44.8%, 45 at 73.6% and for 51 at 54.4%. In probabilistic sensitivity analysis (PSA), the respective 95% confidence intervals were used to estimate the shape parameters alpha and beta for a beta distribution [13]. The price of a single vaccine dose was set at €120 in the base case, reflecting the Dutch pharmacy price. As we know that in the NIP lower prices apply, we reduced the price to €90, €60 and €30 in sensitivity analysis. Lifelong protection against HPV was assumed.

2.4. Cost of cancer

Data on costs of the cancers included in this analysis are scarce. Yet, some information could be gathered (Table 1). In our study we tried to come up with average cost of cancer, because data from Netherlands Cancer Registry did not provide data on the distribution of FIGO stages. The paper of Rogoza et al. provided the cost per FIGO stage for cervical cancer. Next, with incidence of the different FIGO stages from an Italian study, the average cost of cervical cancer was estimated as the sum of the cost per FIGO stage multiplied by the fraction that these particular stages represent in the total number of cervical cancers [1,14]. The costs of the initial treatment of vaginal and vulvar cancer were based on De Kok et al. [15]. Notably, the costs for the initial treatment of vulvar cancer were estimated at 56 days after surgery, which excludes costs of possible recurring cancers. As costs of the last year of life with cancer were not included in the initial treatment costs, these costs were taken into account separately [16,17]. Anal cancer costs were assumed to be the same as colorectal cancer costs. This assumption is strengthened by the fact that the ICD-9 code for rectal cancer includes anal cancer, although there may be an actual difference in costs between these cancers. By combining the information on FIGO stage distribution, costs of the different FIGO stages and ten-year survival, the average cost of initial treatment was estimated [18–20]. In a study of Wilschut et al. additional costs of colorectal cancer were provided [18]. These costs are specified in costs in the late phase of colorectal cancer and cost of continuous care between the initial phase and the terminal phase. These costs were also presented per FIGO stage and were converted as done for the initial treatment [18–20]. Costs of oropharyngeal cancer were found in a study of van Agthoven et al. [21]. In this study costs were estimated retrospectively taking initial treatment, but also ten-year follow-up explicitly into account. All cost were updated to a 2010 price level.

2.5. Quality of life

To estimate QALYs, quality of life (QoL) was combined with duration in disease states. Literature on QoL of anal, vulvar, vaginal and oropharyngeal cancer is again scarce. To get QoL estimates for every cancer, numbers from Chesson et al. were modified [22]. In their article Chesson et al. provide a distribution of local, regional and distant cancers and a QoL depending on survival. Using these numbers, QoL was calculated for each year after the diagnosis of cancer (Table 1). Data from the American Surveillance, Epidemiology and Results (SEER) program shows a change in distribution of stages of cancer after the age of 50. To model a gradual change a linear transition between the ages of 41 and 49 was used. According to Chesson et al. QoL losses should also be taken into account for women cured from cancer. Long-term survivors of cervical cancers reported a lower quality of life due to sexual functioning problems and reproductive concerns due to potential reduced fertility or even infertility [22,23].

2.6. Probabilistic sensitivity analysis

To gain insight in the level of uncertainty of the base-case value of the incremental cost–effectiveness ratio, a probabilistic sensitivity analysis (PSA) was performed. In Table 1 the ranges of values for the costs of cancers, QoL, vaccine efficacy and type prevalence are presented. Due to a lack of exact data, the range of costs for cervical cancer and anal cancer are constructed taking the cost of FIGO stage I and IV as boundaries. For the other cancers and the quality of life losses the range was chosen such to reflect 50–150% of the base-case parameter values. For the ranges of the costs and QoL uniform probability distributions were assumed. For HPV prevalence and vaccine efficacy the 95% confidence intervals from the literature were used to define beta distributions. The model simulated a thousand repeat drawings for the PSA.

Table 1
Model parameters.

Cancer	HPV prevalence	Type prevalence, (95% CI), Beta[α, β]	Costs (€), in parentheses the range of costs used in PSA	QoL loss first year, age <50, (50–150% value for PSA)	QoL loss first year, age >49, (50–150% value for PSA)	QoL loss second year, age <50, (50–150% value for PSA)	QoL loss second year, age >49, (50–150% value for PSA)	QoL loss third year, age <50, (50–150% value for PSA)	QoL loss third year, age >49, (50–150% value for PSA)	QoL loss fourth year and further, age <50, (50–150% value for PSA)	QoL loss fourth year and further, age >49, (50–150% value for PSA)
Cervical cancer	100%	**16**: 56.6%, (54.5–56.6%), [1009, 774] **18**: 16.0%, (14.0–16.0), [421, 2212] **31**: 3.8%, (3.2–5.6%), [148, 3752] **33**: 4.0%, (3.6–5.6%), [77.5, 1607] **45**: 4.5%, (3.5–5.5%), [74.2, 1576] **51**: 1.0%, (0.5–1.5%), [15.2, 1505]	20,767, (19,827–27,518)	0.24, (0.12–0.36)	0.29, (0.15–0.44)	0.20, (0.10–0.30)	0.26, (0.13–0.39)	0.20, (0.10–0.30)	0.26, (0.13–0.39)	0.08, (0.04–0.12)	0.09, (0.05–0.13)
Vulvar cancer	40.4%	**16**: 32.2%, (30.0–34.4%), [558, 1174] **18**: 4.4%, (3.4–5.4%), [71.1, 1544] **33**: 4.5%, (3.5–5.5%) [74.2, 1576]	**Initial treatment**: 15,724, (6670–35,587) **Death due to cancer**: 24,964, (12,482–37,446)	0.21, (0.10–0.32)	0.24, (0.12–0.36)	0.16, (0.08–0.24)	0.20, (0.10–0.30)	0.16, (0.08–0.24)	0.20, (0.10–0.30)	0.08, (0.04–0.12)	0.08, (0.04–0.12)
Vaginal cancer	69.9%	**16**: 53.7%, (45.5–61.9%), [76.7, 65.3] **18**: 7.6%, (1.9–13.3%), [6.23, 75.8] **31**: (5.6%, (0.4–10.8%), [4.15, 70.0]	**Initial treatment**: 15,724, (6670–35,587) **Death due to cancer**: 24,964, (12,482–37,446)	0.24, (0.12–0.36)	0.28, (0.14–0.42)	0.20, (0.10–0.30)	0.25, (0.13–0.38)	0.20, (0.10–0.30)	0.25, (0.13–0.38)	0.06, (0.03–0.09)	0.04, (0.02–0.04)
Anal cancer	84.3%	**16**: 73.4%, (70.7–76.1%), [754, 273] **18**: 5.2%, (3.6–6.8%), [38.4, 700] **33**: 4.8%, (3.3–6.3%), [37.4, 741]	**Initial treatment**: 22,033, (15,753–29,288) **Late stage care**: 26,756, (3435–10,305) **Death due to cancer**: 40,463, (10,400–31,200) **Continuous care**: 368, (184–553)	0.25, (0.13–0.38)	0.25, (0.13–0.38)	0.22, (0.11–0.33)	0.21, (0.10–0.32)	0.22, (0.11–0.33)	0.21, (0.10–0.32)	0.08, (0.04–0.12)	0.09, (0.05–0.13)
Oropharyngeal cancer	35.6%	**16**: 30.9%, (28.0–33.8%), [301, 673] **33**: 1.1%, (0.6–2.1%), [4.59, 463] **18**: 1.0%, (0.9–1.9%), [4.69, 463]	43,120, (21,560–64,680)	0.35, (0.18–0.53)	0.34, (0.17–0.51)	0.34, (0.17–0.51)	0.33, (0.17–0.50)	0.34, (0.17–0.51)	0.33, (0.17–0.50)	0.10, (0.05–0.15)	0.10, (0.05–0.15)

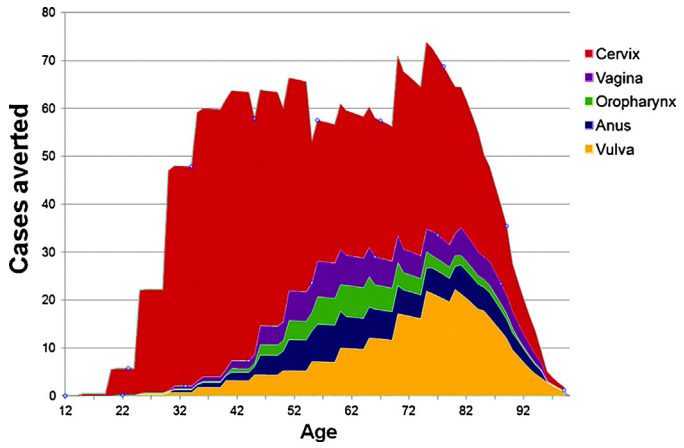

Fig. 2. Total cancers averted in the base-case by vaccination for each year. Overall cases averted are subdivided by cancer site.

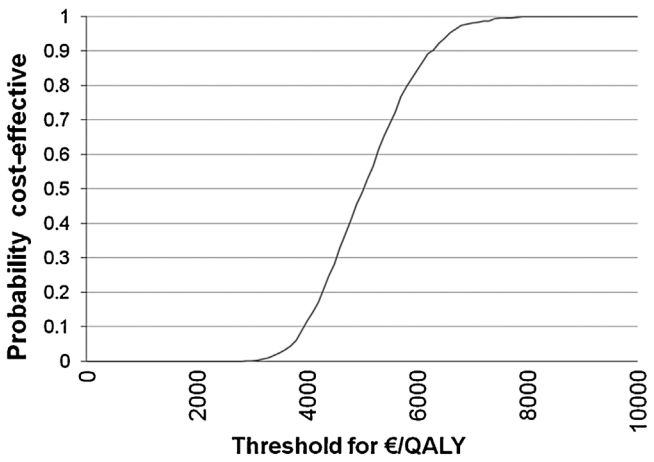

Fig. 3. Cost–effectiveness acceptability curve showing the portion of simulations falling below the willingness-to-pay threshold for a QALY.

2.7. Deterministic sensitivity and scenario analyses

As it is common knowledge that the actual vaccine price after tendering lies far below our base-case price, lowering of the vaccine prices with 25%, 50% and 75% was investigated in a sensitivity analysis. Different discounting rates for costs and health gains as used in the Netherlands are not generally accepted. To make the results useful for other countries, a sensitivity analysis was performed on the discount rate using equal rates for money and health. Furthermore, the impact of varying cost- and QoL-parameters was analysed in a sensitivity analysis over a ±25% range. Finally, a scenario analysis was performed for the vaccine being only effective against infections with HPV16 and 18; i.e. excluding cross-protection and varying the inclusion of the different HPV-cancers.

3. Results

3.1. Base-case and PSA

In Fig. 2 the total number of cancer cases averted at every age in the model are presented, categorised by cancer site. Of all cancers cases averted, prevention of cervical cancer contributes most, followed by the prevention of vulvar cancer. The figure illustrates that the specific health gains are time dependent. Cervical cancer incidence is relative high earlier in life compared with, for example, vulvar cancer which has the highest incidence later in life. To calculate the ICER, the discounted costs for the vaccinated cohort were compared with the costs in the non-vaccinated cohort, and subsequently divided by the difference in QALYs. This calculation led to a base-case ICER of €5815/QALY, see Table 2. The uncertainty of this value was investigated in the PSA, as reflected in Fig. 3. This cost–effectiveness acceptability curve shows the probability of being cost-effective for various threshold values. The median ICER is €5028/QALY, the 95% percentile €6581/QALY and 100% is below €8700/QALY. The full range of simulations fell between €2800 and €8700/QALY.

Table 2
The cost–effectiveness of multiple scenarios in which effect of the HPV on the different cancers was varied. The scenarios were also calculated with and without cross-protection.

	ICER protection against HPV 16/18 (€/QALY)	ICER including cross-protection (€/QALY)
Cervix only	11,431	9547
Cervix, anus	10,078	8458
Cervix, vulva, vagina	8985	7364
Cervix, vulva, vagina, anus	7881	6471
Cervix, vulva, vagina, anus, oropharynx (base-case)	7142	5815

3.2. Sensitivity and scenario analysis

Table 2 shows the impact on the ICER when not all HPV-cancers are taken into account. Beside this variation the ICER was also calculated without the contribution of cross-protection. Without cross-protection the ICER of the vaccine against cervical cancer was found to be €11,431/QALY. One-way deterministic sensitivity and scenario analyses were performed to evaluate the effect of varying parameters on the ICER. First the vaccine price was changed over a 25–75% range. Obviously, cost–effectiveness is sensitive to changes in the vaccine price. At a price of €90 per vaccine dose the ICER drops to €2680/QALY. For vaccine prices of €30 and €60 per dose each, the bivalent vaccine becomes cost saving. Table 3 shows the sensitivity of the ICER to variation in discount rates. Since 2005 differential discounting is preferred in the Netherlands. This is in contrast with other countries, such as the UK (3.5% equal discounting). The discount rate has a major influence on the ICER of the HPV-vaccine. The base-case value is almost tripled when a 4% discount rate is applied for both money and health. However, for a 3% equal discount rate the ICER is already almost identical to the base-case value (€5738 and €5815/QALY, respectively). A one-way sensitivity analysis was done by varying the cost and the QoL ±25%. The impact on varying these parameters is shown graphically in Fig. 4. As can be seen in the figure varying the cost or the QoL of cervical cancer have the greatest impact on the ICER. The HPV vaccine was designed to prevent infections with HPV types 16 and 18, which are responsible for about 70% of cervical cancers. We assumed cross-protection against other types as mentioned previously. In a scenario analysis taking only efficacy against 16 and 18 into account, an ICER of €7142/QALY was found.

4. Discussion

Taking cross-protection and effects on non-cervical cancers explicitly into account, the cost–effectiveness ratio estimated for the bivalent vaccine lies far below the lowest Dutch willingness-to-pay threshold even mentioned (€20,000/QALY) [24]. Decrease of the vaccine price lowers the ICER even further, which is a realistic scenario in a large-scale vaccination programme [1]. Therefore the bivalent vaccine can be considered highly cost-effective in the Netherlands or even cost saving. In the PSA, for some parameters

Table 3
Results of varying the discount rates of cost and health gain on the incremental cost–effectiveness ratio. Base-case values are 4% for cost and 1.5% for health gain.

Discount % QALY	Discount % cost (€)					
	0%	1.5%	3%	3.5%	4%	5%
0.0%	−10,609	−2409	1356	2118	2726	3612
0.5%	−13,769	−3126	1759	2748	3538	4687
1.0%	−17,724	−4024	2265	3538	4554	6033
1.5%	−22,631	−5138	2892	4518	5815	7704
2.0%	−28,664	−6507	3663	5722	7365	9758
2.5%	−36,019	−8177	4602	7190	9255	12,261
3.0%	−44,909	−10,195	5738	8965	11,539	15,288
3.5%	−55,567	−12,615	7100	11,092	14,278	18,916
4.0%	−68,246	−15,493	8720	13,623	17,536	23,232
4.5%	−83,217	−18,892	10,633	16,612	21,382	28,328
5.0%	−100,770	−22,877	12,876	20,115	25,892	34,303

a broad range of ±50% was chosen, resulting in a broad range of uncertainty for the base-case value. Yet, 100% of the thousand simulations fell below €8700/QALY, again illustrating highly favourable cost–effectiveness. We assumed lifetime protection of the vaccine. Yet, long term protection against HPV infection has still to be established. The vaccine is only recently developed, while major health gains can only be expected in the distant future. If vaccine waning occurs, there might be need for a booster vaccination. While this needs further investigation, it likely does not push the ICER over the Dutch €20,000/QALY threshold. Actual implementation of a booster might be a challenge as vaccination of adult women is not common in the Netherlands except for travels and specific risk groups for influenza. Therefore, boostering might have only limited coverage and cost–effectiveness might be worsened due to this. This illustrates the general importance of relatively long duration of protection of the HPV-vaccine. This is obviously uncertain, but follow-up of clinical trials and immunological studies are promising. Cross-protection against types that are phylogenetically related to HPV 16 and 18 is already proven for the bivalent vaccine [7]. However cross-protection is only estimated over a period of 44 months and there is a chance that the protection against non-vaccine types is not as lasting as protection against the vaccine types [25]. Yet, even if cross-protection is assumed not to occur, the ICER only increases about 25% to just over €7000/QALY, still remaining far below any Dutch willingness-to-pay threshold.

The almost similar ICER for the 3% discounting for cost as for health gains and the 4%/1.5% combination may surprise. However, the 4%/1.5% discounting combination lowers the savings in the ICER-formula but not the vaccination costs and increases the QALYs in the denominator, as compared to the 3%/3% combination. Of course uncertainty exists with respect to the efficacy of the vaccine against the non-cervical HPV-related cancers as elaborated here. Further evidence strengthening this assumption is required. Stronger evidence will probably come forward in the coming decades as vaccinated women reach the ages at which they are at a significant risk of developing HPV-related cancers. Notably, Kjaer et al. already showed a reduction of precancerous lesions of the vagina and the vulva, for the quadrivalent vaccine [5]. This supports the idea that not only cervical cancers are prevented by vaccinating against HPV, but also other HPV-related cancers are potentially prevented. Notably, in the absence of exact data, assumptions on the costs of anal cancer, vulvar and vaginal cancer had to be made. The cost of vaginal and vulvar cancer might be underestimated, because in these costs only the initial treatment and the costs of the last year of life year could be included; i.e. costs of follow-up and treatment of reoccurring cancers are lacking. Our analysis is limited in its inclusion of cost categories. Notably, we could not include costs for pre-stages of the cancers considered in the absence of reliable estimates for most of these pre-stages. Furthermore, given the static nature of our model, indirect effects of herd protection could not be included. Notably, if coverage is relevantly below 100% major options exist to indirectly protect unvaccinated women through reduced transmission in the population. Generally, our exclusion of these cost categories, reflects a conservative approach and leads to an underestimation of the benefits of vaccination. Our study showed that the HPV-vaccine is cost-effective even when cross-protection or protection against non-cervical HPV-cancers are not taken into account. This is in contrast with the findings of De Kok et al. [26]. In their study a cost–effectiveness ratio of €53,500 per QALY was found. De Kok et al. use in their study a discount percentage of 3% for both cost and health gain. Beside this difference De Kok et al. use lower values for the quality of life loss for cervical cancer in comparison to our study. Due to these lower values, the health gain per cancer case averted is also lower. This makes the denominator of the ICER smaller, resulting in high cost per QALY. Notably, our study and De Kok et al. have used different sources to base estimates for QoL in cervical cancer on. It is currently impossible to determine which source is the better one. The advantage of our estimate is that the estimate for cervical cancer is part of a full integrative approach to determine cancer QoL losses, and therefore potentially better for the purpose of this study. Further research into such QoL in cancer values is obviously needed. In the one-way sensitivity analysis the influences of these assumptions on the ICER were investigated. Varying cervical cancer costs and quality of life appeared to have a major influence on the ICER, whereas the cost and quality of life of the other cancers barely influence the ICER. This is partly due to the greater number of cervical cancers, but also due to the relatively late emergence of the other cancers. Discounting reduces the effects and savings in

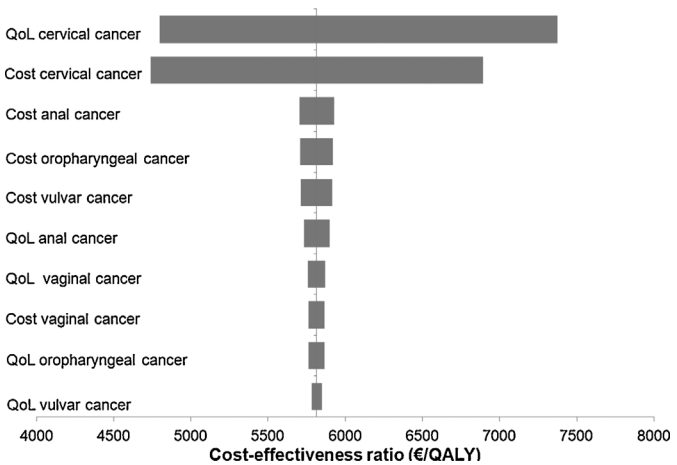

Fig. 4. Tornado diagram showing the impact on the cost–effectiveness ratio of varying cost or QoL of the cancers on the cost–effectiveness ratio.

the ICER as the cancers occur later in life. Further research on the costs of cancer treatment in the Netherlands is required. These data not only help to gain insight in the cost–effectiveness of HPV vaccines, but are also useful in comparing the (often expensive) new treatments of cancers with the treatments currently used.

5. Conclusion

Evidence on cross-protection and protection against precancerous lesions of the vulva and the vagina supports the idea that health and economic benefits of vaccinating against HPV goes beyond cervical (pre-)cancer (states for types 16 and 18 only). In this study an ICER of €5815/QALY was estimated taking cross-protection and other cancers into account, inclusive assumed effects on anal and oropharynx cancers. The ICER showed to be sensitive to vaccine price, discounting rates, cost of cervical cancer and to variation in the disutility of cervical cancer. The ICER was less sensitive to the inclusion of cross-protection. Over the full range of sensitivity and scenario analyses, favourable cost–effectiveness remained. Notably, the inclusion of other non-cervical cancers in health-economic models seems to have the potential to make the HPV-vaccines highly cost-effective, if not cost-saving at reduced vaccine prices.

Acknowledgements

The authors thank the registration teams of the Comprehensive Cancer Centers for the collection of data for the Netherlands Cancer Registry and the scientific staff of the Netherlands Cancer Registry for their help.

References

[1] Rogoza RM, Westra TA, Ferko N, Tamminga JJ, Drummond MF, Daemen T, et al. Cost–effectiveness of prophylactic vaccination against human papillomavirus 16/18 for the prevention of cervical cancer: adaptation of an existing cohort model to the situation in the Netherlands. Vaccine 2009;27(July (35)):4776–83.
[2] Parkin DM, Bray F. Chapter 2: the burden of HPV-related cancers. Vaccine 2006;24(August (Suppl. 3)):S11–25.
[3] Lowy DR, Schiller JT. Reducing HPV-associated cancer globally. Cancer Prev Res (Phila) 2012;5(January (1)):18–23.
[4] Kim JJ, Goldie SJ. Health and economic implications of HPV vaccination in the United States. N Engl J Med 2008;359(August (8)):821–32.
[5] Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, Perez G, et al. A pooled analysis of continued prophylactic efficacy of quadrivalent human papillomavirus (Types 6/11/16/18) vaccine against high-grade cervical and external genital lesions. Cancer Prev Res (Phila) 2009;2(October (10)):868–78.
[6] GlaxoSmithKline. Cervarix summary of product characteristics. Available from: http://www.medicines.org.uk/emc/medicine/20204/SPC/cervarix/
[7] Causes of death; main primary causes of death, sex, age. Available from: www.statline.cbs.nl
[8] Dutch cancer Figures. Available from: http://cijfersoverkanker.nl/?language=en
[9] Chesson HW, Ekwueme DU, Saraiya M, Dunne EF, Markowitz LE. The cost–effectiveness of male HPV vaccination in the United States. Vaccine 2011;29(October (46)):8443–50.
[10] De Vuyst H, Clifford GM, Nascimento MC, Madeleine MM, Franceschi S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. Int J Cancer 2009;1(April (7)):1626–36.
[11] Li N, Franceschi S, Howell-Jones R, Snijders PJ, Clifford GM. Human papillomavirus type distribution in 30,848 invasive cervical cancers worldwide: variation by geographical region, histological type and year of publication. Int J Cancer 2011;15(February (4)):927–35.
[12] Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. Cancer Epidemiol Biomarkers Prev 2005;14(February (2)): 467–75.
[13] Brigg A, Claxton K, Sculpher M. Decision modelling for health economic evaluation. New York: Oxford University Press; 2006.
[14] Ricciardi A, Largeron N, Giorgi Rossi P, Raffaele M, Cohet C, Federici A, et al. Incidence of invasive cervical cancer and direct costs associated with its management in Italy. Tumori 2009;95(April (2)):146–52.
[15] De Kok IM, Habbema JD, van Rosmalen J, van Ballegooijen M. Would the effect of HPV vaccination on non-cervical HPV-positive cancers make the difference for its cost–effectiveness. Eur J Cancer 2011;47(February (3)): 428–35.
[16] Uyl-De Groot CA, Hartog JG, Derksen JG, Symons EA, Buijt I, van der Velden J, et al. Cost–effectiveness and quality of life of granulocyte-colony stimulating factor (filgrastim) after radical vulvectomy and bilateral inguino-femoral lymphadenectomy: results of a randomized clinical trial. Eur J Obstet Gynecol Reprod Biol 2004;114(May (1)):77–82.
[17] Polder JJ, Barendregt JJ, van Oers H. Health care costs in the last year of life—the Dutch experience. Soc Sci Med 2006;63(October (7)):1720–31.
[18] Wilschut JA, Hol L, Dekker E, Jansen JB, Van Leerdam ME, Lansdorp-Vogelaar I, et al. Cost–effectiveness analysis of a quantitative immunochemical test for colorectal cancer screening. Gastroenterology 2011;141(November (5)), 1648–55.e1.
[19] Elferink MA, Pukkala E, Klaase JM, Siesling S. Spatial variation in stage distribution in colorectal cancer in the Netherlands. Eur J Cancer 2012;48(May (8)):1119–25.
[20] Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG, Habbema JD, Kuipers EJ. Effect of rising chemotherapy costs on the cost savings of colorectal cancer screening. J Natl Cancer Inst 2009;101(October (20)):1412–22.
[21] van Agthoven M, van Ineveld BM, de Boer MF, Leemans CR, Knegt PP, Snow GB, et al. The costs of head and neck oncology: primary tumours, recurrent tumours and long-term follow-up. Eur J Cancer 2001;37(November (17)):2204–11.
[22] Chesson HW, Ekwueme DU, Saraiya M, Markowitz LE. Cost–effectiveness of human papillomavirus vaccination in the United States. Emerg Infect Dis 2008;14(February (2)):244–51.
[23] Sun CC, Frumovitz M, Bodurka DC. Quality of life and gynecologic malignancies. Curr Oncol Rep 2005;7(November (6)):459–65.
[24] Bogaards JA, Coupe VM, Meijer CJ, Berkhof J. The clinical benefit and cost–effectiveness of human papillomavirus vaccination for adult women in the Netherlands. Vaccine 2011;29(November (48)):8929–36.
[25] Harper DM, Vierthaler SL. Next generation cancer protection: the bivalent HPV vaccine for females. ISRN Obstet Gynecol 2011;(July).
[26] De Kok IM, van Ballegooijen M, Habbema JD. Cost–effectiveness analysis of human papillomavirus vaccination in the Netherlands. J Natl Cancer Inst 2009;101(August (15)):1083–92.