Possible Role of Cost-Effectiveness of HPV Vaccination within the Decision Context on Inclusion of HPV in the Country-Specific National Immunization Programs

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Abstract: *Background*: Vaccination against HPV presents a new primary prevention strategy against cervical cancer and is now being introduced in countries all over Europe. Health-economic modelling plays an increasingly important role in the decision making process when introducing new health-care technologies into national programmes. This study compares the economic evaluations used by European countries in the decision making process about the introduction of HPV vaccination in European countries and evaluate the role of these evaluations in this decision making process.

Method: Publicly available reports from official government advisory and regulatory bodies were obtained and analysed in terms of their perspective, discount rate, time horizon, type of mathematical model, assumptions made regarding the vaccine and the current screening practice, sensitivity analysis, and outcome.

Results: Health-economic studies were found for nine European countries. All analysed in the base-case analysis the cost-effectiveness of vaccination of girls around the age of 12 year in addition to a cervical carcinoma screening program. Both static and dynamic models were used and especially assumptions regarding cost data varied widely among included studies. Estimated incremental cost-effectiveness ratios varied from €11, 400 to €64, 000 per life-year gained in the base cases. Results were most sensitive to the choice of discount rate, vaccine costs and duration of protection after vaccination.

Conclusion: We show that cost-effectiveness results cannot be transferred among European countries due to large variations in parameter assumptions. In those countries that undertook an economic evaluation health-economic analyses seem to have played an important role in the decision-making process surrounding the potential introduction of HPV vaccination.

Keywords: Human papillomavirus, vaccination, reimbursement, health economics, decision making.

INTRODUCTION

Cervical cancer is a major cause of cancer morbidity and mortality among European women [1]. Human papillomavirus (HPV) types 16 and 18 are responsible for about 70% of all cases of cervical cancer while HPV types 6 and 11 cause about 90% of all genital warts [2]. The incidence of cervical cancer has been largely reduced since the introduction of secondary prevention programmes by performing regular Pap-smear tests, however still more than 5% of all cancer cases worldwide is related to HPV infections [3, 4]. In 2006 a quadrivalent vaccine (Gardasil®) against HPV types 16, 18, 6 and 11 became available, and in 2007 a bivalent vaccine (Cervarix®) protecting against HPV 16 and 18 was approved by the European Medicines Evaluation Agency (EMEA) for the EU market.

Now that this new technology for the prevention of cervical cancer has become available, individual countries need to make a decision on whether to reimburse/recommend these vaccines. In European countries the introduction of a new vaccine into national immunization programs commonly occurs in two steps, first a recommendation is made by a national vaccine advisory body and secondly an official decision is taken by the national health authorities [5]. While in the past, decisions about new technologies were primarily based on data on clinical efficacy, safety and effectiveness, there is now an increasing focus on economic aspects, in particular cost-effectiveness ratios. In many European countries health economic analysis is now required for introduction of new health care technologies into national programmes. Because of the large differences in health care systems, budgets, screening programmes and vaccination policies, results from economic evaluations from one country are often not transferable to other countries. The European Centre for Disease Prevention and Control (ECDC) has issued guidelines for the introduction of HPV vaccination in EU countries, and advises that "an effort should be made by each country to perform such an (economic) evaluation before making a decision about the best strategy to prevent cervical cancer" [6].

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The aim of this paper is to compare the economic evaluations used by European countries in the decision making process about the introduction of HPV vaccination in these countries in terms of their methods, assumptions, preconditions and results and to evaluate the role of these evaluation in the decision making process.

MATERIALS AND METHODOLOGY

Publicly available reports from official government or semi-government advisory and regulatory bodies were obtained from the respective websites, or, where applicable, from peer reviewed publications. Included were those western European countries with a report on the cost-effectiveness of HPV vaccination that was publicly available. Also, we limited ourselves to those countries with reports written in either English, Dutch, German, or French, given the language expertise of the research team. To compare cost-effectiveness studies, official reports that included an economic analysis were used.

Obtained reports were analysed in terms of their type of economic analysis, comparator, target population, type of mathematical model that was used (static or dynamic), time horizon, discounting rates, perspective, included costs, assumptions that were made on cervical-cancer screening and vaccination coverages, vaccine efficacy, duration of protection, quality adjusted life years (QALY) estimates and factors included in sensitivity analysis and outcome.

Non-€ currencies were converted to €'s with exchange rates from August-September 2008 [7]. Because reports all dated from 2007 or 2008, incremental cost-effectiveness ratios (ICERs) and costs were used as reported and not corrected for inflation.

RESULTS

Selected Studies and Type of Economic Analysis

Health economic studies were found for Austria, Belgium, Denmark, France, Ireland, the Netherlands, Norway, Switzerland and the United Kingdom. Table **1** summarizes the investigated studies. It shows authorship, type of economic analysis, time frame, discount rates, type of model, perspective, total cost per vaccination, vaccine efficacy and coverage, requirement for a booster dose, cervicval screening characteristics, performed type of sensitivity analysis, cost-effectiveness thresholds and obtained ICERs. Note that for the Netherlands two separate health-economic studies were performed [8, 9]. Spain and Sweden did not carry out an economic analysis themselves, but instead reviewed existing literature and health economic analyses carried out by other countries [10, 11]. In Germany a HTA is currently being carried out [12], while the vaccine has already been recommended and is reimbursed by health care insurances since 2007 [13]. Note that in Germany it is generally the normal procedure to analyse health economics only after reimbursement. Of the included studies, four performed a cost-effectiveness analysis in which cost per life-year (LY) gained was the main outcome parameter used. The remaining six performed a cost-utility analysis of which four also reported the ICER per LY gained.

Comparator

Since vaccinated women will still be at risk of cervical cancer by HPV types that are not covered by the vaccine, vaccination cannot replace the current screening programmes, even for vaccinated women.

While almost all European countries have some kind of cervical cancer screening programme, there are large differences in the way women are targeted, the coverage, the intervals between the screening periods and the level of organisation of the screening programme. For example, in the Dutch models it was assumed that 85% of the women between the age of 30 and 60 will be screened every five year based on actual attendance rate for this country [14]. In contrast to Ireland, where a national population-based cervical screening program was not implemented yet at the time of analysis [15]. However, in the model screening was assumed for women between the ages 25 and 60 using a coverage rate of 80% as screening was assumed to be introduced in 2008. The UK study reported that cervical cancer screening is currently carried out using Pap-smear, although this is being replaced by liquid-based cytology and used midpoint prices and wide ranges for the specificity and sensitivity to encompass possible improvements. Most models assumed screening routinely started around 25 years and was continued up to approximately 65 years of age. Two studies assumed the start of screening below the age of 20 years [16, 17].

Differences in assumptions regarding screening can be explained by organisational levels of screening. For example, in some countries (e.g. the Netherlands and Finland) cervical cancer screening is highly organized, with every woman in the target group receiving a personal invitation to take part in the screening programme. In most countries, women who have not had a Pap-smear within the recommended period of time are personally invited (e.g. Norway, Sweden and the UK) while in others (e.g. Germany and Luxembourg), screening is entirely opportunistic, that is to say screening takes place when women report to the gynaecologist for other reasons, or on their own initiative. When screening and vaccination are both entirely opportunistic, it is likely that a part of the population will be reached by neither programme, and the effectiveness of added vaccination might be relatively low. Many countries report that while a part of the population is not reached by screening programmes (usually between 20-40% of the population) at all, the part of the population that takes part in the programmes is being "overscreened", i.e. women are screened much more frequently than is recommended according to their national guidelines (e.g. Belgium [18] and France [19]). Overscreening is undesirable because it increases the costs of cervical cancer screening programmes without added effectiveness. See Anttila *et al.* [20] for a detailed overview of cervical cancer screening programmes in European countries.

Target Population

Both Cervarix® and Gardasil® have proven efficacy against disease caused by the HPV types for which subjects

Table 1. Methods, Assumptions, Preconditions and Results of Health-Economic Analyses Carried out by Nine European Countries

Country and Ref.	Austria [17]	Belgium [18]	Denmark [35]	France [19]	Ireland [15]	Netherland [8]	Netherlands [9]	Norway [33]	Switzerland [16]	UK [29]
Type of Economic Analysis	CEA	CUA	CEA	CEA	CEA	CUA	CUA	CUA	CUA	CUA
Time Frame (Years)	52	lifelong	62	70	70	lifelong[a]	88	52	lifelong	100
Discount Rates Costs/Health Effects (%)	5 / 5	3 / 1.5	3 / 3	3 / 3	3.5 / 3.5	4 / 1.5	4 / 1.5	4 / 4	3 / 1.5	3.5 / 3.5
Type of Model	dynamic	static	dynamic	static	dynamic	static	static	dynamic	static	dynamic
Perspective	HCP SOC	HCP	HCP SOC	HCP	HCP	SOC[b]	HCP	HCP SOC	HCP	HCP
Total Cost Per Vaccination (€)	120	115	139	136	130	139	139	118	174	93[c]
Vaccination Coverage	65%	84%	70%	60%	80%	85%	85%	90%	80%	80%
Booster Included (After)	10 years	10 years	no booster	no booster	no booster	no booster	no booster	10 years	no booster	no booster[d]
Vaccine Efficacy (Against)	90% (infection)	46% (CIN2+) 60%(cancer)[e]	70% (CIN/ cancer)[f]	95% (CIN/ cancer)[g]	95%[h]	90%[i]	95% (CIN)	90%[h]	95% (CIN)[j]	100% (infection)
Age of Screening	9 -90[k]	25-64	23-59	25-65[l]	25-60	30-60	30-60	26-69	18-69	25-647
Cervical Screening Coverage	47%/ 3 year	79%/ 3 years	70%/ 3 years	55%/ 3 years	80%/ 3-5 years[m]	79% / 5 years[n]	79% / 5 years[n]	76%-80% / 3 years	65.2%/ 2 years[p]	79.5% / 5 years[q]
Age of Target Population	12	12	12	14	12	12	12	12	11	12
Type of Sensitivity Analyses	U	U, P	U	U	U	U	U	U	U	U, P[r]
Cost-Effectiveness Threshold	no fixed point	not specified	not specified	not specified	€45, 000 /QALY	€20, 000 /QALY	€20, 000 /QALY	NOK425, 000 /QALY[s]	no officially accepted threshold	£20,000 – 30,000 /QALY[t]
€/LY HCP	64, 000	51, 300	11, 400	45, 200	17, 400	-	-	59, 700	27, 800	-
€/QALY HCP	-	32, 700	-	-	-		19.500[u]	49, 900	17, 150	28, 500
I€/LY SOC	50, 000	-	1, 500	-	-	33, 000		17, 600	-	-
€/QALY SOC	-	-	-	-	-	30, 000		14, 800	-	-

Results provided refer to the main target group for vaccination of teenage girls and do not include catch-up vaccination of other age groups. CUA: Cost-utility analysis, CEA: Cost-effectiveness analysis, LY: Life Year, QALY: Quality Adjusted Life Year, ICER: Incremental Cost Effectiveness Ratio, HCP: Health Care Payer perspective, SOC: Societal perspective. P: probabilistic sensitivity analysis, U: univariate sensitivity analysis.

[a]Not explicitly stated, although as the vaccine was estimated to protect lifelong the time frame can also be expected to be lifelong.

[b]Although in the study it is stated that the analysis was performed form the societal perspective no details regarding productivity losses are given.

[c]Averaged vaccination costs (costs were inserted in the model as a distribution).

[d]An average duration of protection 20 years was assumed in the base-case analysis.

[e]Efficacy against infection HPV 16 and 18 is not explicitly mentioned. In the report a 46% efficacy against CIN2+ lesions is assumed and a 60% efficacy against all cervical cancers is assumed. If 70% of cervical cancers are caused by HPV 16 and 18, this presumes a 85% efficacy of the vaccines against these types.

[f]If 70% of cervical cancers are caused by HPV 16 and 18, this presumes a 100% efficacy of the vaccines against these types.

[g]Not clearly stated.

[h]Probably the efficacy was against HPV infection, although not clearly stated.

[i]Not clear, but it was stated that a 90% efficacy was assumed against high-risk HPV types.

[j]Including an efficacy of 95% resulted in a reduction of approximately 33% for CIN1, 52% for CIN2/3, 71% for cervical cancer and 86% for genital warts.

[k]In the report a table is given with different age groups and percentages of women who underwent a Pap-smear screening. It is, however, not stated which age groups are included for routine screening program in the model.

[l]Not reported in the economic evaluation itself but obtained from the main report.

[m]Women will be screened every three years between the ages of 25 and 44 years, and then every five years up to sixty years of age.

[n]Not reported in the economic evaluation but obtained from [14].

[o]Not clear which coverage is used.

[p]Obtained from [61] as referred in [16].

[q]Obtained from [62] as referred in [29].

[r]Parameters in the base-case analysis were included as distributions.

[s]In Norwegian Crones, approximating €50, 000.

[t]From the NICE-guidelines [63], approximating €25, 000 – 38, 000.

[u]Note that in the main report [14] an ICER of approximately €21, 000 per QALY is mentioned.

were not HPV DNA positive previously to infection (see below). There is no evidence of protection from disease caused by HPV types for which subjects were positive at study entry [21, 22]. Therefore, most countries make recommendations to define a primary vaccination target population of young girls before the average age of sexual debut. Except for two studies, all included studies modelled the impact of the vaccination of 12 year old girls. The Swiss study assumed that 11 year old would be vaccinated while the French study assumed girls would be vaccinated at the age of 14 [16, 19].

Modelling Strategies

Models used to estimate the impact of vaccination programmes can be classified as dynamic or static models. In a static model the risk of infection is a constant, while a dynamic model takes the effects of vaccination on the transmission of the disease into account and is able to predict herd-protection effects [23, 24]. Herd protection is the protection of non-vaccinated individuals due to a reduction in the transmission of infection in the population. Often dynamic models show more favourable results of vaccination compared to static models, although this not always the case depending on the infectious agent and the vaccination coverage [25]. In contrast to the positive herd effects in non-vaccinated individuals there might also be serotype replacement. If oncogenic vaccine strains are effectively suppressed by vaccination there might be a selective pressure on the remaining HPV strains resulting in an increase of other oncogenic serotypes [26].

Of all studies included, more than half used dynamic models (see Table **1**). Those countries that made use of a dynamic model often adapted models that were initially developed for other countries and populations. Norway adapted the model originally developed for the UK [27] to reflect the Norwegian health-care system and using Norwegian data on sexual activity and health-care use. Austria in turn made use of the Norwegian model and adapted it to the Austrian health-care system, but using Norwegian and UK data on sexual behaviour due to lack of Austrian data [17]. Denmark developed a dynamic model based on a network model originally developed in the UK [28]. The Danish model was later adapted by Ireland and used in the Irish HTA [15]. For the UK a new model was developed which was the first according these authors to include the incidence adenocarcinomas not assuming these carcinomas would behave the same way as squamous cell carcinomas [29].

Belgium, France, the Netherlands and Switzerland used all static models [8, 9, 18, 19]. The authors from the Belgium paper validly argue that although dynamic models are in theory superior to static models in practice they need to rely on more assumptions than static models [18]. Detailed information regarding the level of sexual activity and mixing paters within and across age groups are necessary in order to develop a dynamic HPV model. Both the studies from the Netherlands and Belgium stated that it was not feasible to develop a dynamic model due to lack of availability of such data for the population in question [14, 18]. Switzerland considered the possibility of underestimating the benefits of vaccination by using a static model in their discussion [16, 30]. None of the models included the potential impact of serotype replacement.

Time Horizon and Discounting

The time horizon of an economic analysis should be long enough to capture all the differential effects of the interventions compared [31]. Particularly, in the case of a primary prevention strategy, the costs occur immediately, while the benefits of the intervention are only reaped in the future. This is especially true in the case of vaccination against HPV, as it takes 15-25 years from the time of infection to the development of invasive cancer [32]. Of all studies, four reported a time horizon which can definitely be labelled as sufficient applying lifelong horizons or a period of 100 years [14, 16, 18, 29]. All remaining studies used timeframes of 50 years and more. Nevertheless, the time frame used by Austria and Norway might still be considered too short at 52 years, as beyond this period still LY and QALYs are gained due to averted mortality and morbidity by vaccination [17, 33].

Comparable to the time horizon also discount rates have a great impact on the cost-effectiveness ratio. Discounting adjusts future costs and benefits for decreasing marginal utility, time preference and the opportunity costs of capital [34]. With the postponed health effects of vaccination especially the discount rate for health effects will influence the cost-effectiveness ratio largely. In all included reports, both costs and outcomes were discounted in the base-case analysis at rates between 3-5% (costs) and 1.5-5% (outcomes). Most analyses used the same discount rate for health and money [15, 17, 19, 29, 33, 35] of which three applied the same discount rates to costs and outcomes in all scenarios, including the sensitivity analyses [15, 17, 35]. The remaining countries [8, 9, 16, 18] applied a lower discount rate of 1.5% to health outcomes. Except for France and Norway, all countries included a scenario in which neither costs not effects were discounted.

Costs and Perspective

Costs included into health-economic analyses can be divided into direct and indirect cost. Direct healthcare costs are defined as all economic consequences directly related to the use of the intervention, in general these include primarily medical costs. Of the nine countries that published an economic analysis as part of or along with the official recommendation, six models only considered the costs that were paid by the health-care payer (note that for the Netherlands two analyses were performed of which one states that it was conducted from the societal perspective while the other was performed from the health-care perspective) [8, 15, 16, 18, 19, 29]. France made a distinction between the direct medical costs, and the costs that are covered by the health care provider, since vaccination costs are only partly reimbursed. Four studies explicitly stated that they were (also) conducted from a more societal perspective [8, 17, 33, 35]. When a societal perspective is adopted all relevant costs and consequences for society should be considered, including productivity losses. Indirect medical costs, which involve costs that occur in LYs gained, were not included by any of the analist.

Cost of Vaccination

In sensitivity analysis (see also below), most studies showed that the most important costing parameter was the cost of vaccination. Vaccination costs can be split into the actual cost of the vaccine and other costs such as administration and invitation costs. For example, the total cost of one vaccination was estimated in both Dutch studies at €138.50 per dose including program cost per invitation and administration cost at €7.50 and €6.00 respectively. Administration costs vary depending on the vaccination delivery system. Vaccination can be organised by governmental public health organizations which administer vaccines through school based programmes (e.g. in the UK), or at public health clinics (e.g. in the Netherlands) while in systems with limited input from government institutions vaccines are administered by physicians (e.g. Austria). With the exception of Switzerland and the UK the cost of vaccination per dose varied between the €115 and €140. The average cost of vaccination in the UK was well below this range at €93 while Swiss study assumed the highest cost per vaccination at €174. Partly these differences can be explained by the assumed administration cost at €28 per dose (GP and gynaecologist fees) for Switzerland and at €5 for the UK (school based). Other factors attributable to variations between countries are assumed discounts at buy in bulk and exclusions of VAT [18].

Other Direct Costs

In the sensitivity analyses of the included studies it was shown that the impact of treatment cost was limited (see also below), therefore these will only be discussed briefly. Large variations are observed between studies regarding for the treatment costs of precancerous lesions. For example, in Norway and Denmark treatment cost for CIN1 are relatively low (€71 and €33) if compared to those Ireland and the Netherlands (€317 and €825- €1, 325). On the other hand cost of cervical cancer treatment was high in Denmark at €25, 000 compared to other countries such as Switzerland and Austria at €12, 345 and €13, 720, respectively. Furthermore, none of the studies seem to have included the initial implementation/starting-up costs of the vaccination program although the Dutch studies did include program costs per invitation.

Indirect Costs

Four studies explicitly state that the analyses was conducted from the societal perspective (Table **1**), however one of these does not provide any details regarding the indirect costs included [8]. The remaining 3 studies explicitly considered effects on production and valued these using the human capital method [31]. This method is however subject of debate, due to the inherent assumption in the human capital approach that work days lost are not compensated. Especially with long periods of absenteeism, this approach may give a substantial overestimation of the benefits of an intervention [31, 36]. For Denmark and Norway the amount of production loss was taken into account by taking the average wage and employment rates for women of the corresponding age group [33, 35]. For Austria, on the other hand, it was argued that due to differences in employment rates and wages between men and women, the use of sex-specific values for production loss is undesirable, as this would systematically reduce the benefits of any health-care intervention specifically aimed at women [17]. Therefore, the Austrian study used average wages and employment rates for the whole population to calculate the amount of production loss. Norway, as the only country, also included travel costs and time losses related to treatment of cervical cancer [33]. The impact on the ICER of inclusion of these costs is discusses below.

Coverage

Vaccination policies vary between European countries. While almost all countries make recommendations about which vaccines should be administered at what age, there are large differences between countries when it comes to the degree to which immunization against infectious diseases is organized. In general, vaccination systems can be divided into two groups: centralized and decentralized [37]. In centralized systems (e.g. in the UK and the Netherlands) vaccination is organized by governmental public health organizations, who actively invite parents to take part in the vaccination programme. In decentralized systems (e.g. France, Germany and Austria) there are no publicly organized vaccination programmes and vaccinations take place with limited input from government institutions. While centralized systems usually achieve a higher rate of coverage, they are more expensive to set up initially. In centrally organized systems it is easy to keep track of the level of coverage of childhood vaccination programmes, which makes it easier to estimate the expected level of coverage when modelling the effects of a newly introduced vaccine, such as the HPV vaccine.

Assumptions on vaccination coverage varied between 60% [19] and 90% [33]. This percentage was usually based on coverage rates of other vaccinations at a similar target age, although some countries expected a lower coverage due to the requirement of three consecutive injections. For example, the measles-mumps-rubella coverage was used as a proxy in the Belgium study while in Ireland the coverage achieved for the Meningitis C catch-up program was used [15, 18]. Most countries considered uncertainties about the coverage rates by including variations of this factor in the sensitivity analysis.

In the absence of indirect effects in static models, the vaccine coverage can only be of influence on the ICERs in studies using dynamic models. Jit *et al.* showed that the ICER was practically insensitive to the vaccine coverage in girls over a range of 70%-90% as there is an approximately linear relation between coverage and the reduction in disease as well as a linear relation between coverage and the costs of the programme [29]. The Norwegian study showed a larger impact, a decrease in the coverage of 10% (from 90% to 80%) increased the ICER approximately 50% when a societal perspective was adopted and 15% when a health-care payer perspective was adopted. The study does not explain the large impact of the 10% change in coverage nor the large difference between the perspectives when the coverage is changed. Surprisingly at first glance, the three remaining studies which modelled the impact of HPV vaccination dynamically predicted higher cost-effectiveness ratios when coverage increased or lower ratios when vaccination coverage decreased [15, 17, 35]. Of note, the

studies performed for Denmark and Ireland (both based on the same model, see above) predicted eradication of HPV types 16 and 18 after 33 and 50 years, respectively. This difference is likely to occur to the differences in assumed coverage between both countries [15, 35]. However, these model predictions are based on a closed population model, in reality eradication is also dependent upon neighbouring countries [35].

Vaccine Efficacy and Number of Doses

The effectiveness of an HPV vaccination program is dependent on the serotype coverage of the vaccine, the efficacy of the vaccine against these serotypes and the number of doses given. For Gardasil® a vaccine efficacy of 98.8% (95%CI; 93.3%-100%) against HPV16/18-related CIN2/3 or AIS (adenocarcinoma in situ) was observed for girls who received all three doses of the vaccine and were previously not infected with HPV-16 or HPV-18 [21]. For Cervarix® the most recent result shows an efficacy of 92.9% (96.1%CI; 79.9%-98.3%) against CIN2+ lesions associated with HPV-16 and 18 for girls previously not infected with relevant HPV-types and received all three doses of the vaccine [22]. Similar efficacy estimates were observed for these same groups against persistent infections [22, 38]. So both vaccines are highly effective against the prevention of persistent infection and against HPV16/18-related CIN2/3 or AIS in HPV naive girls.

Studies included into our review modelled the effect of vaccination using different approaches. The Belgian, the Danish and one Dutch study explicitly stated that an overall efficacy against all CIN lesions was used, while the Swiss study used different efficacy estimates against CIN1, CIN2/3, cervical cancer and genital warts based on the proportion attributable to vaccine serotypes [9, 18, 35]. Most of the studies which used a dynamic model seem to use an efficacy against HPV infection [15, 17, 29, 33]. Seven studies did not include a booster dose in the base-case analysis. Of these all but one assumed lifelong protection. Jit *et al.* assumed that the immunity against HPV infection in vaccinated individuals would wane exponentially with an average duration of protection of 20 years in the base-case analysis [29]. Of those not included a booster in the base-case analysis five did investigate the impact of a booster dose in the sensitivity analysis [8, 9, 15, 16, 35].

QALY Estimates

All studies (except for Belgium) which included utilities into their analyses (indirectly) refer to the two published peer reviewed papers [39, 40] and one unpublished abstract presented at a conference that exist on the topic [41]. For example, the Norwegian study included QALY estimates for cervical cancer as reported in the study of Goldie *et al.* based on the mid-points of the ranges for quality weights after treatment for invasive cancer [33, 39]. Most other studies implicitly or explicitly used a combination of one of the above mentioned studies to estimate the utility losses [8, 9, 16, 29].

The UK study showed that regarding utilitiy estimates, especially assumptions for CIN2 and CIN3 and the duration of a genital warts episode influenced the ICER the most. This is probably due to much higher incidence of precancerous lesion and genital warts than to the actual incidence of cervical cancers. Except for Norway all studies included utility detriments due to positive CIN2+ Pap-smear results. Estimations of utility losses due to precancerous varied among these studies. The Belgium study applied a utility loss of 0.19 due to CIN2 compared to a utility detriment of 0.065 to 0.13 in the other studies [18]. One of the Dutch studies also included utility losses due to the injection of the vaccine and due to Pap-smear invitations [8]. This same study also used the highest utility (lowest utility detriment) for women diagnosed with invasive cancer state FIGO2+ at 0.82 compared to 0.67 used in the Swiss and 0.56 in the UK study. Of the two studies which included a utility detriment due to genital warts the overall detriment in QALYs was 0.020 in the Swiss study and 0.0056 in the UK study (based on own calculations).

Estimated ICERs

From the health-care perspective, ICERs in the base case varied from €11, 400/LY for Denmark [35] to €64, 000/LY for Austria [17]. If the societal perspective was taken, the ICER for Austria was reduced to €50, 000/LY and that in Norway improved to about one-third of its value in the health-care perspective. For corresponding results per QALY, we refer to Table **1**. Only the UK differentiate between the two available vaccines (Gardasil® and Cervarix®) and concluded that due to the absence of additionally preventing anogenital warts, the price of the bivalent vaccine would have to be £13-21 (€16-26) lower than that of the quadrivalent vaccine to achieve the same cost-effectiveness ratio [29]. In the French study, the cost-effectiveness of the existing opportunistic screening programme was explicitly factored into the analysis, and it was concluded that this was still the most cost-effective component in the prevention of cervical cancer.

Sensitivity Analyses

All countries that carried out an economic analysis also carried out some type of sensitivity analysis. Most studies only performed a so-called univariate or one-way sensitivity analysis in which the impact of a single parameter is explored while keeping all other variables constant. In most studies the choice of discount rate turned out to be the most sensitive factor. Since the benefits of the vaccination against cervical cancer are only expected 15-25 years after the costs, a higher discount rate for effects will greatly reduce the current value of these effects. Other factors that greatly influenced cost-effectiveness ratios are the price of the vaccine, the vaccine efficacy and protection period after three doses (with the potential requirement of a booster injection). Variations of treatment costs had only a slight effect on the cost-effectiveness of vaccination [15-17].

Only the Belgian and UK studies included probabilistic sensitivity analyses [18, 29]. In a probabilistic-sensitivity analysis distributions are incorporated for key parameters of which random samples are generated and subsequently taken into the analysis.

Additional Scenarios Analysed

Most countries included alternative scenarios of catch-up vaccinations of older age groups, next to the initial target population of young teenagers. These scenarios are currently not explcitly reviewed in detail by us here. The majority of

reports did not include vaccination of boys into their analysis. The three countries that did include vaccination of boys [17, 29, 35] found that it greatly increased costs and rendered only little added health gains. In the Austrian analysis, inclusion of boys increased the ICER from approximately €55, 000 - €64, 000/LY to €299, 000 - €311, 000/LY, and in the Danish analysis the ICER rose from €11, 400 to €31, 200/LY. In the UK-analysis, inclusion of boys increased the ICER between three- and thirty fold, depending on the duration of protection.

DISCUSSION AND CONCLUSION

Methodological Issues

It was surprising to see that there are large variations in the model frameworks and model assumptions between the country-specific studies. For example, more than half of the included studies used a dynamic model while all remaining studies used a static model. When an infectious disease is modelled preferably a dynamic model should be used although this is not always feasible if not enough data regarding transmission dynamics are available. Those studies which used a static model (except for France) used a relatively high coverage rate. At very high or very low coverages, herd protection may only have a limited influence on the results of economic evaluations [42]. It is in between these extremes that major impacts on herd protection may be achieved. The dynamic models included in this review showed different effects when the coverage was increased or decreased. Three studies showed an increase of the ICER when coverages increased [15, 17, 35]. This is probably due to the fact that at lower coverages (although still higher than 50%) the relative impact of herd protection is larger [42]. This same effect was also shown in two recent studies focussing on developing countries [43, 44].

The studies using a dynamic model did not produce lower ICERs than the static models. This can partly be explained by the limited effects of herd protection as discussed above and by the choice of the discount rates. The studies using dynamic models generally used higher discount rates for effects (3-5%) than the static models (1.5-3%), which is of course not inherent to the dynamic modelling but merely to the country-specific guidelines for health-economic research.

Furthermore, it was surprising to see that the analysis performed for the Netherlands, which stated that is was performed from a societal perspective [8], rendered more unfavourable ICERs than the study which adopted a health-care perspective for this same country [9]. Possibly no indirect costs were explicitly included into the former analysis as the overall total costs associated with cancer seem to be higher in the study which adopted the health-care payer perspective. Also, the larger utility decrements associated with disease states in this latter study or the utility losses due to vaccination in the study performed from the societal perspective could partly explain the more favourable ICERs obtained.

Inspection of the sensitivity analyses showed that in almost all cases, the choice of the discount rates for cost and effects, along with vaccine price and the duration of protection, had the greatest influence on the cost-effectiveness ratios for HPV vaccination. This is not surprising since the effects of HPV vaccinations occur decades after the costs of vaccination. There is much discussion about whether or not to discount health outcomes at different rates than monetary costs, especially in the case of preventive interventions such as vaccinations [34]. Studies analysed did all use the discount rates as specified in the country-specific guidelines. Variations in health-care costs and exact epidemiological conditions seemed to have little effect on cost-effectiveness ratios. In particular, the differences in results between the countries might be better explained by the specific choices of individual assumptions, rather than differences in the population and health-care systems. Therefore, one could suggest the development of one common model for all European countries that can be adapted to meet the national preferences in terms of discount rates, vaccination coverage, and other factors.

Role of Health Economics and Current Vaccination Policies

Economic evaluations provide an important tool for policy-makers to allow rational decision making when allocating resources. In the recently published VENICE (Vaccine European New Integrated Collaboration Effort) survey, favourable cost-effectiveness ratios have been reported as one of the main drivers in the decision making process to introduce HPV vaccination in those countries which had taken the decision to introduce HPV vaccination or anticipated taking such a decision in the future [5]. Nevertheless, also the potential impact of external pressure - both from the population and the pharmaceutical industries - cannot be ruled out. In particular, as HPV vaccination seems to be less cost-effective compared with other vaccines which are not yet implemented in the Netherlands, such as Hepatitis B and possibly varicella [25, 45]. However, of those countries included into the analysis it seems that health-economic analyses did play a role in recommendations of the national advisory bodies, obviously next to various other aspects inclusive safety and implementation issues. For example, in the Netherlands, the quadrivalent HPV vaccine was denied inclusion into the Dutch Drugs Reimbursement System in 2007 for girls aged 13-26 years after the economic report provided by the manufacturer was deemed insufficient due to methodological issues [46, 47]. However, after carrying out two independent health-economic studies, the Dutch Health Council has recommended to introduce HPV vaccination into the National Immunization Programme for girls aged 12 years combined with a catch up to only 16 years of age [47]. The Dutch Minister of Health has now decided to introduce HPV vaccination into the National Immunization Programme under the condition that the vaccine price is lowered to meet the accepted cost-effectiveness threshold [48]. In November 2008 the decision to introduce vaccination with Cervarix® in September 2009 was taken [49]. This illustrates the important role that economics have played in the decision making processes, in this case in the Netherlands.

In august 2008 the Irish Minister of Health and Children announced the intention to introduce HPV vaccination starting in September 2009, "based on the implementation of a plan that can be shown to be cost-effective, in terms of delivery costs and uptake rates" [50]. However, in November

this decision was renounced due to the current economic situation and the need to introduce a cervical cancer screening programme in Ireland [51]. Denmark has started vaccinating against HPV in October 2008 [51, 52], and in Norway the government has proposed to introduce HPV vaccination from September 2009 [53]. Switzerland has started a vaccination programme free of charge for girls between 11 and 19 years [54]. In Belgium and France the vaccine is recommended for young girls and is partly reimbursed. Yet, the influence of the health economic analysis for Belgium was probably limited, as the vaccine was approved before the country's health technology evaluation committee had finished deliberating [55]. Austria has recommended the vaccine for both girls and boys, but does not reimburse the costs of vaccine [56]. The Austrian Ministry of Health has announced that it does not plan to introduce HPV vaccination into the National Childhood Vaccination Programme in the near future due to budgetary constraints, but mentioned at the same time that the further proceeding of the ministry will eventually depend on whether or not the vaccine manufacturers are prepared to reduce the costs of vaccination which in addition will also make the vaccination more cost-effective [57, 58]. In June 2008 the UK Department of Health announced the decision to introduce the bivalent rather than the quadrivalent vaccine [59]. At the price differential that is given in the UK analysis, this choice would be equivalent to a saving in vaccine costs of £11.5 as compared to £18.6 million for the quadrivalent vaccine [60]. It has been suggested that this choice represents a debatable preference for lower costs of vaccination at the expense of not preventing the disease burden associated with anogenital warts [60].

CONCLUSION

We conclude that health economic evaluations seem to have played an important role in the decision-making process surrounding the potential introduction of HPV vaccination for those countries that have undertaken an economic evaluation [5]. Nevertheless, not all countries included into this review have undertaken such an evaluation possibly due to the lack of financial resources or the belief that similar studies performed by other countries were sufficient [5]. However, cost-effectiveness result cannot simply be transferred between different countries as there are large differences between models and parameters included into the country specific models which result in a wide range of ICERs. To increase the amount of countries which base their decisions on cost-effectiveness result a common model at European level could be developed which can be adapted to meet specific preferences. This will reduce the costs associated with the development of an economic model and increase the transparency and consistency of the models used.

CONFLICTS OF INTEREST

Professor M.J. Postma has received research grants from both the manufacturers of the HPV vaccines.

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