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Economic evaluations of massive HPV vaccination: Within-study and between study variations in incremental cost per QALY gained

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ABSTRACT

Objective. We describe the heterogeneity of the estimates of the incremental cost per quality-adjusted year of life (QALY) within and between cost-utility studies of the *human papillomavirus* (HPV) vaccine.

Method. We searched for articles in English published in peer-reviewed journals that perform cost-utility analyses to evaluate the addition of HPV vaccine to 12-year-old girls to existing cervical cancer screening practices. Fifteen studies were selected according to our inclusion and exclusion criteria.

Results. There are large within-study variations in estimates of the cost per QALY gained. The most influential source of uncertainty is the duration of the vaccine protection. Between-study variations are mainly due to three causes: methodological differences, assumptions, and local conditions in the application area. We find large variations between studies for a given country.

Discussion. Economic evaluation models are increasingly sophisticated, but scientific treatment of epidemiological and market uncertainty does not compensate for the lack of basic information.

Conclusions. The large disparities in cost per QALY estimates of massive vaccination programs around the world may be attributed to several critical sources (unavoidable and avoidable) of uncertainty. An asset of economic evaluation is the ability to highlight the areas of research that could be undertaken to reduce uncertainty.

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Introduction

By July 2008, Merck quadrivalent *human papillomavirus* (HPV) vaccine had been approved in 100 countries worldwide, and GSK bivalent vaccine in about 27 countries. Vaccination is recommended in the official vaccine calendar of most European countries, Australia, US and Canada (Koulova et al., 2008; King et al., 2008). Preadolescent girls are vaccinated once (three doses) at ages that vary from country to country, between 9 and 13. In addition, most developed countries recommend temporary catch-up programs up to ages ranging from 18 (Department of Health, 2008) to 26 (Markowitz et al., 2007; NAC, 2007).

The launching of the HPV vaccine in 2006 carried a sequence of decisions concerning its use, in the context of both pressure from the population—induced by the pharmaceutical industry—and uncertainty on long term vaccine efficacy and cost effectiveness. Although some developed countries have based their public recommendations on cost-effectiveness studies (Koulova et al., 2008), external pressures interfered in the working environment of the committees. This was the case in Australia, a pioneering country in applying economic evaluation for funding new drugs. The Pharmaceutical Benefits Advisory Committee (PBAC) had to deal with public outcry and

interferences from consumers, health professionals and politicians. Finally it changed its recommendation from exclude to include vaccination, after securing a lower price (Roughhead et al., 2008). In the Netherlands, the HPV vaccine was the first case of a product denied for the Reimbursement System based on the health economics report (Boot et al., 2007). However, later on a re-assessment was made, based on a new positive opinion on the health economics report, and reimbursement was finally approved. Universal vaccination will start in 2009 (Boeke, 2008).

This short paper describes from a public policy perspective the heterogeneity of the estimates of the incremental cost per quality-adjusted year of life (QALY) within and between HPV vaccine cost-utility studies, and identifies the main sources of parameter uncertainties that are responsible for those disparities.

Methods

We searched in PUBMED, NHS EED and HTA, from the Centre for Reviews and Dissemination (University of York) for English language articles published in peer-reviewed journals from January 2002 to October 2008 that provide cost-utility analyses of the vaccine. Specifically, those studies that compare as base-case alternatives the current cervical cancer screening practices to the combination of screening plus 12-year-old girl vaccination. We have excluded cost-

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utility studies that do not use health utilities in the base-case, those that do not report detailed figures for sensitivity analysis results, and those that do not include cervical cancer among HPV health-related outcomes. We have checked for and excluded double publications.

Fifteen studies were selected according to our inclusion and exclusion criteria. Several surveys of cost-effectiveness analysis of HPV vaccines have been published recently (Barnabas and Kulasingham, 2007; Newall et al., 2007; Techakehakij and Feldman, 2008; Ferko et al., 2008), but they provide limited coverage of the literature. Only five published cost-utility studies were included in the most comprehensive of those surveys (Techakehakij and Feldman, 2008; Ferko et al., 2008). This paper is unique in providing a comprehensive and updated international survey of the cost per QALY gained by adding HPV vaccine in 12-year-old girls to current screening practices.

We looked at how the parameter uncertainty was handled: what values were given to unknown parameters and what distributions were assumed in sensitivity analysis.

By parameter uncertainty we mean that which concerns the true values of the input parameters. Model uncertainty, which involves the way these parameters are modelled (Goldie et al., 2006; Ferko et al., 2008) is not considered in this paper. As proposed in the literature (Drummond et al., 2007; Ferko et al., 2008; Suárez et al., 2008), we selected some specific parameters related to screening, vaccination and costs that are particularly affected by uncertainty, and therefore they could cause large variations in cost per QALY gained. Those parameters are screening compliance, vaccine efficacy, vaccine coverage, duration of the vaccine protection, health outcomes considered, herd immunity, health utilities, discount rates for QALYs and costs, included costs, vaccine cost per series, and cost per case of cervical cancer.

Since the primary usefulness of economic evaluations for health policy is to decide the optimal mix of vaccination and screening, we reviewed the full text of the studies looking for variations, within and between studies, concerning Incremental cost per QALY gained (the cost to gain a QALY with HPV vaccination of 12-year-old girls vs. the cost to gain a QALY with the HPV current screening practices). We define within-study variations as those reported in sensitivity analysis. They depend on the distance between unknown or uncertain parameters in the base-case scenario and those considered in alternative scenarios. Between-study variations are defined as variations among base-case scenario results from different studies.

Results

Within-study variations

Table 1 reports the sensitivity of the results of each study, in terms of cost per QALY, to assumptions on vaccine efficacy, duration and cost of the vaccine. We report also the sensitivity of the results to the discount rates that the authors applied to effects, costs and QALYs.

One of the key sources of uncertainty is the duration of the vaccine protection. For instance, in the US, vaccination of 12-year-old girls cost \$43,600 per QALY in the base-case (lifelong immunity), but it would rise to \$144,100 if the immunity lasted 10 years (Kim and Goldie, 2008). In two studies vaccination is dominated by current screening when it assumed a limited duration of the protection instead of longlife immunity (Elbasha et al., 2007; Insinga et al., 2007). In this context, “dominated” means that vaccination is not worth it, in terms of opportunity costs (a strategy is dominated if a more effective strategy is relatively less costly). In other five out of seven studies, when a limited duration of protection is assumed in sensitivity analysis, the cost per QALY more than double the cost in the base case, and in four of the latter more than triple.

Discount rates are set by the authors in order to discount the costs and the health outcomes of the programs. Except in one of the studies, published years before the vaccine was launched, the cost per QALY when no discount or a small rate is applied is ten or more times lower than the cost per QALY when a high rate is applied. Although the results of cost-effectiveness analysis of programs with long time horizons like vaccination are extremely sensitive to the discount rate, there is some international consensus in using rates around 3%, and that is what most of the surveyed studies do as in their case-base.

Between-study variations

Between-study variations in cost per QALY gained estimates are mainly due to three causes: 1) methodological differences, 2) assumptions, and 3) local conditions in the application area.

Methodological differences

Studies differ in the alternatives they consider (for instance, target population; screening frequency and type), as well as in discount rate

Table 1
Within-study variability of incremental cost per QALY

Authors (year)	Base-case cost per QALY	Monetary units (year)	Cost per QALY sensitivity to vaccine efficacy ^a	Cost per QALY sensitivity to vaccine duration ^a	Cost per QALY sensitivity to vaccine cost per series ^a	Cost per QALY sensitivity to discount rates ^a
Sanders and Taira (2003)	\$22,755	US\$ (2001)	\$52,398 (2.3)	\$12,682/\$45,599 (2.0)	n.a.	\$9286/\$37,552 (1.7)
Goldie et al. (2004) ^b	\$24,300	US\$ (2002)	\$20,600/\$33,700 (1.4)	n.a.	n.a.	n.a.
Taira et al. (2004)	\$14,583	US\$ (2001)	n.a.	n.a.	n.a.	n.a.
Brisson et al. (2007) ^b	\$20,512–\$31,600	CAN\$ (2005)	n.a.	\$36,981/\$114,846 (3.6)	n.a.	n.a.
Elbasha et al. (2007) ^b	\$2964	US\$ (2005)	\$2094/\$3116 (1.1)	Weakly dominated by current screening ^c	\$997/\$2964 (1.0)	n.a.
Ginsberg et al. (2007)	\$81,404	I\$ (2007)	n.a.	\$272,010 (3.3)	<0/\$81,404 (1.0)	n.a.
Insinga et al. (2007) ^b	\$2719	US\$ (2005)	n.a.	Dominated by no vaccination	n.a.	n.a.
Kulasingham et al. (2007)	\$18,735	AUS\$ (2005)	\$21,098 (1.1)	\$24,988/\$52,600 (2.8)	\$15,606/\$26,038 (1.4)	\$8419 (0.5)
Bergeron et al. (2008) ^{b,d}	€8409	€ (2005)	€10,444 (1.2)	€14,935/€37,228 (4.4)	n.a.	€2019/€35,652 (4.2)
Chesson et al. (2008)	\$3906–\$14,723	US\$ (2005)	\$8374/\$11,710 (0.8)	n.a.	\$4237/\$20,009 (1.4)	<0/\$24,901 (1.7)
Dasbach et al. (2008) ^b	£5890	UK£ (2006)	£12,627 (2.1)	n.a.	£14,828 (2.5)	£2532 (0.4)
Jit et al. (2008)	£22,474	UK£ (2006–7)	n.a.	£15,094/£33,868 (1.5)	n.a.	£2238/£22,474 (1.0)
Kim and Goldie (2008)	\$34,900–\$43,600	US\$ (2006)	n.a.	\$83,300/\$144,100 (3.3)	n.a.	n.a.
Kulasingham et al. (2008) ^b	£21,059	UK£ (2005)	£25,081 (1.2)	£26,782/£68,417 (3.2)	£19,450/£22,668 (1.1)	£3123/£36,618 (1.7)
Szucs et al. (2008) ^b	CHF26,005	CHF (2007 ^e)	CHF24,800/27,400 (1.1)	CHF45,400 (1.7)	n.a.	CHF7900/105,145 (4.0)

n.a. = not available. Cost per QALY sensitivity to vaccine parameters is represented by the value or the range (lowest and highest) of the ICER reported in the sensitivity analysis.

^a In brackets the ratio between the maximum value in sensitivity analysis over the base-case cost per QALY.

^b Some funding received from the producer of the evaluated vaccine.

^c A strategy is weakly dominated if there is another more effective program that has a lower incremental cost effectiveness ratio.

^d The reference target population in this study is 14-year-old girls.

^e Year not reported in the paper. We assumed that it was the year before it was accepted for publication.

Table 2
Between-study variability (I): main study characteristics and base-case cost per QALY gained in I\$ (2007)

Authors (year of publication)	Country	Target of the vaccine	Perspective	Time horizon	Model	Cost per QALY in I\$ (2007)
Sanders and Taira (2003)	United States	HPV 16/18	Not mentioned	Lifetime	Markov model	I\$26,641
Goldie et al. (2004) ^a	United States	HPV 16/18	Societal	Lifetime	Markov model	I\$28,007
Taira et al. (2004)	United States	HPV 16/18	Not mentioned	Lifetime	Deterministic dynamic transmission model	I\$17,073
Brisson et al. (2007) ^a	Canada	HPV 6/11/16/18	Ministry of Health	Lifetime	Compartmental deterministic model	I\$17,906–I\$27,585
Elbasha et al. (2007) ^a	United States	HPV 6/11/16/18	Healthcare system	100 years	Dynamic transmission model	I\$3,147
Ginsberg et al. (2007)	Israel	HPV 6/11/16/18	Ministry of Health	100 years	Dynamic transmission model	I\$81,404
Insinga et al. (2007) ^a	Mexico	HPV 6/11/16/18	Healthcare system	100 years	Dynamic transmission model	I\$2,887
Kulasingam et al. (2007)	Australia	HPV 16/18	Government	12–85 years	Markov model	I\$14,137
Bergeron et al. (2008) ^a	France	HPV 6/11/16/18	Healthcare system	14–85 years	Markov model	I\$9,594
Chesson et al. (2008)	United States	HPV 6/11/16/18	Societal	12–99 years	Cohort model	I\$4,147/I\$15,631
Dasbach et al. (2008) ^a	United Kingdom	HPV 6/11/16/18	Healthcare system	100 years	Dynamic transmission model	I\$9,052
Jit et al. (2008)	United Kingdom	HPV 6/11/16/18	Health care provider	100 years	Dynamic transmission model	I\$33,745
Kim and Goldie (2008)	United States	HPV 6/11/16/18	Societal	Lifetime	Dynamic transmission model	I\$35,894/I\$44,842
Kulasingam et al. (2008) ^a	United Kingdom	HPV 6/11/16/18	National Health System	Lifetime	Markov model	I\$33,106
Szucs et al. (2008) ^a	Switzerland	HPV 6/11/16/18	Health care system	Lifetime	Markov model	I\$15,761

CI = 95% confidence interval.

^a Some funding received from the producer of the evaluated vaccine.

and time horizon, which largely influence the results, because present vaccination would prevent occurrence of the disease in the distant future. Studies also differ in model design and other technical issues.

Assumptions

This is the fundamental unavoidable source of uncertainty. The only way for validating many of the assumptions of the studies is allowing the passage of time. Assumptions concern biological issues related to the natural history of the disease, coverage of the vaccination programs, percent of efficacy, disease scope (cervical cancer, genital warts, and others). The assumptions are also related to human behavior: sexual practices, adherence to screening schedules. Screening practices of vaccinated women are likely to vary after vaccination, therefore assumptions are counterfactual (what would happen if), and they cannot be checked with real data.

In Table 2 we provide the main characteristics of the studies, and their base-case cost per QALY gained, in international 2007 dollars so that they can be compared. First we deflated to 2007 prices the original study's figures using the Consumer Price Index for the country, and then we applied the PPP converter to calculate I\$ (2007). Table 3 compare key parameters related to screening, vaccination and costs in base-case scenarios.

In Table 3 we find large variations in the cost per QALY for a given country. For instance, the cost per QALY in the US ranges from I\$3147 (Elbasha et al., 2007) to I\$44,842 (Kim and Goldie, 2008). The studies authored by academic or neutral organizations used to report results less favorable to massive vaccination than studies authored by the firms sponsoring the vaccines. Some of the latter conclude that vaccination is cost-effective even for boys and men.

Local conditions

Local conditions vary among areas, particularly the actual screening programs and their cost, the burden of disease and incidence of genital warts and cervical cancer, sexual behavior of the population, costs of screening and cancer treatment, and the price of the vaccine (Table 3).

Discussion

Economic evaluation models are increasingly sophisticated. They fit all relevant epidemiologic and economic data into a set of up to dozens of thousands of plausible scenarios (Jit et al., 2008). But omn-comprehension of those alternative worlds created by the modeler in order to give thorough scientific treatment to epidemiological and market uncertainty does not compensate for the lack of basic

information. Those models are useful for policy purposes only to the extent they can reduce uncertainty.

The search for an optimal mix of vaccination and screening is complex because vaccination reduces gradually the marginal effectiveness of screening. Some studies conclude that massive vaccination would be more cost-effective if the frequency of screening were reduced and the starting age were postponed (Haug, 2008). Both the cost of a QALY and the optimal combination of vaccine and screening are time-varying (Goldhaber-Fiebert et al., 2008; Kiviat et al., 2008), and individual preferences should be accounted for (Stout et al., 2008). If prevalence of infection is to be dramatically reduced thanks to vaccination, how many cytology tests will have to be done in 2050 to avoid one single case of cervical cancer?

Many developing countries, particularly in Sub-Saharan Africa and Latin America (Clifford et al., 2005), have high prevalence of infection caused by any high-risk HPV type, and high incidence of cervical cancer. Screening programs are either inefficient or do not exist, and the optimum duopolistic price of the vaccine is much lower than in the developed world. Consequently, it would be cost-effective to vaccinate massively preadolescent girls even in the poorest countries of the world at a cost of I\$10 per vaccinated girl (Diaz et al., 2008). The poorest countries should be the first candidates to massive vaccination programs in a worldwide cost-effectiveness ranking. Massive vaccination would probably prove cost-effective in those countries where screening is badly practiced or not at all. In some sense, screening and vaccination are competitive. It is crucial then that cost-effectiveness studies define properly the comparison alternatives. Cost-effectiveness should achieve the optimal combination of vaccine and screening. From the economic evaluation perspective, HPV vaccine complicated even more the difficult problem of identifying the most cost-effective approach to cervical cancer screening (Kiviat et al., 2008).

Prices are important sources of variation in the cost per QALY between studies. For instance, the price of the vaccine ranges from \$2 per dose in studies for developing countries (Diaz et al., 2008; Goldie et al., 2008) to \$120–\$150 in USA and UK (Chesson et al., 2008; Dasbach et al., 2008; Goldhaber-Fiebert et al., 2008; Goldie et al., 2004; Jit et al., 2008; Kim and Goldie, 2008).

We can therefore look at the local price as endogenous, in the sense that it could be set to such a level as to make the vaccine cost-effective, given local conditions and social ability to pay for a QALY (local ICER threshold). There is an underlying price bargaining process, in free market countries as well as in price regulating countries, and the Australian case is a good example (Roughead et al., 2008). In fact, price setting is a key point, often veiled, in the recommendation debate.

Table 3
Between-study variability (II): key parameters related to screening, vaccination and costs in base-case scenarios

Authors (year)	Screening compliance	Vaccine efficacy against incident HPV (%)	Vaccine coverage	Duration of vaccine protection	Health outcomes considered	Herd immunity	Health utilities for cervical cancer	Discount rate (%)	Included Costs	Vaccine cost per series (without administration costs) in US\$ (2007)	Cost per case of cervical cancer in US\$ (2007)
Sanders and Taira (2003)	71% every 2 years	75	70%	10 years	Cervical cancer	Not	0.62/0.79	3	Direct medical costs	US\$351	US\$17,537/US\$28,103
Goldie et al. (2004) ^a	5.2% never screened	90	100%	Lifetime	Cervical cancer	Not	0.48/0.65	3	Direct medical costs and patient time	US\$435	US\$24,818/US\$42,543
Taira et al. (2004)	71% every 2 years	90	70%	10 years	Cervical cancer	Yes	0.62/0.79	3	Direct medical costs	US\$351	US\$17,537/US\$28,103
Brisson et al. (2007) ^a	Not reported	95	Not reported	Lifetime	Cervical cancer; CIN 1/2/3; genital warts	Not	0.51/0.68	3	Direct medical costs	US\$349	US\$8,729/US\$18,870
Elbasha et al. (2007) ^a	5% never screened	90	From 14% in year 1 to 70% in year 5	Lifetime	Cervical cancer; CIN 1/2/3; genital warts	Yes	0.48/0.76	3	Direct medical costs	US\$382	US\$28,104/US\$48,177
Ginsberg et al. (2007)	Not reported	94.3	95%	Lifetime	Cervical cancer; genital warts	No	0.88/0.91	3	Direct medical costs	US\$360	Not reported
Insinga et al. (2007) ^a	12% never screened	90	From 20% in year 1 to 70% in year 5	Lifetime	Cervical cancer; CIN 1/2/3; genital warts	Yes	0.48/0.76	3	Direct medical costs	US\$255	US\$7,417/US\$8,206
Kulasingam et al. (2007)	5%–30% not screened	100	80%	Lifetime	Cervical cancer; CIN 1/2/3	Yes	0.67/0.76	5	Direct medical costs	US\$87	US\$8,012/US\$11,871
Bergeron et al. (2008) ^a	55%	100	80%	Lifetime	Cervical cancer; CIN 1/2/3; genital warts	No	0.67/0.75	3.5 ^b	Direct medical costs	US\$533	US\$10,456/US\$30,676
Chesson et al. (2008)	Not reported	100	From 20% in year 1 to 70% in year 5	Lifetime	Cervical cancer; CIN 1/2/3; genital warts; anal, vaginal, vulvar and selected esophageal cancers	Yes	Not reported	3	Direct medical costs	US\$382	US\$33,041
Dasbach et al. (2008) ^a	4% never screened	90	80%	Lifetime	Cervical cancer; CIN 1/2/3; genital warts	Yes	0.48/0.76	3.50	Direct medical costs	US\$346	US\$20,771/US\$35,197
Jit et al. (2008)	Not reported	100	80%	20 years	Cervical cancer; CIN 1/2/3; anogenital warts	Yes	Not reported	3.50	Direct medical costs	US\$270/US\$363	Not reported
Kim and Goldie (2008)	5% never screened	100	75%	Lifetime	Cervical cancer; CIN 1/2/3; genital warts; vulvar, vaginal, anal, oral and oropharyngeal cancer; juvenile-onset recurrent respiratory papillomatosis	Yes	0.48/0.76	3	Direct medical and non-medical costs	US\$370	US\$27,296/US\$46,837
Kulasingam et al. (2008) ^a	74%/84%	98	85%	Lifetime	Cervical cancer; CIN 1/2/3; genital warts	No	0.67/0.76	3.50	Direct medical costs	US\$354	US\$19,088/US\$36,790
Szucs et al. (2008) ^a	Not reported	95	80%	Lifetime	Cervical cancer; CIN 1/2/3; genital warts	No	0.67/0.76	3 ^b	Direct medical costs	US\$431	US\$12,121

^a Some funding received from the producer of the evaluated vaccine.

^b QALYs discount rate = 1.50%.

Launching of the second vaccine to the market in 2007 put some pressure downwards on prices worldwide.

Within-study variations depend also strongly on the alternatives under evaluation (not showed in Table 1). For instance, the recommended practice in the US (massive vaccination of girls at 12 plus temporary catch up from 13 to 26-year-old women, costs from \$152,700 per QALY (lifelong immunization) to \$233,500 (ten years immunization). Those figures multiply by 3.5 and 1.6 respectively the costs of the vaccination to 12 year-old-girls without catch-up, reported in Table 1 (Kim and Goldie, 2008).

Conclusions

Policy usefulness of available cost per QALY estimates depends heavily on the reliability of the economic evidence. The descriptive information reported in this short paper (Tables 1–3) highlights large variations in cost per QALY estimates of massive vaccination programs around the world. Those disparities may be attributed to several critical sources (unavoidable and avoidable) of uncertainty in the estimation of the opportunity cost of massive HPV vaccination. The wider the confidence interval resulting from a study, the weaker the confidence of the preventive health policies in its cost-effectiveness results. An asset of economic evaluation is the ability to highlight the areas of research that could be undertaken to reduce uncertainty.

Conflict of interest statement

The authors have received in the past funding from the Research Centre for Economics and Health of the University Pompeu Fabra (CRES-UPF) stemming from unrestricted academic grants of the US Merck Foundation. That funding was not related to either this study or HPV. Jaume Puig-Junoy has received funds, in the past and without any relation with this study or with HPV, from GSK.

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