Ecological validity of cost-effectiveness models of universal HPV vaccination: a systematic literature review.

1. Introduction

The discovery of a causal relationship of human papillomavirus (HPV) to cancers is relatively recent, with the 2008 Nobel Prize in Medicine awarded to Harald zur Hausen [1]. Vaccines against HPV have now been licensed for a decade: a quadrivalent HPV vaccine (four strains of HPV: 6, 11, 16, 18) Gardasil®, has been licensed for prevention of cervical cancer within the USA and Europe since 2006 by the US Food and Drug Administration, and European Medicines Agency, respectively [2,3], and a bivalent vaccine (two strains: 16, 18) Cervarix®, has been licensed in Europe since 2007 and the USA since 2009 [4,5]. A more recent development, the nonavalent HPV vaccine (nine strains: 6, 11, 16, 18, 31, 33, 45, 52, 58) has been licensed in the USA since 2014 and Europe since 2015 [6,7].

With the availability of new prophylactic HPV vaccines, policy makers have been asked to make choices regarding the most cost-effective immunisation strategies to reduce HPV infection and associated burden of disease [8]. The question of whether males should be vaccinated stems from the recognition that male HPV infection significantly contributes to the burden of HPV-induced diseases [9].

Epidemiological and economic models have been used to inform this decision making. Increasing demand for modelling resulted in the development and publication of numerous complex statistical models looking at the efficacy and cost-

effectiveness of the available HPV vaccines and screening programmes deployed in immunisation strategies [10].

The prevailing policy option resulting from this sophisticated approach has been the selective vaccination of pubertal girls [11]. The protective effect of selective immunisation can be described as the probability (function of the vaccination coverage) that one of the two partners involved in intercourse is successfully immunised, hence preventing the other from infection [12]. This “herd immunity” effect depends on vaccination coverage and vaccine efficacy [10]. Assuming lifelong protection from vaccination, the annual selective immunisation of 80% of 12-year-old school girls would result in the elimination of HPV vaccine types [13]. For herd immunity to be assured, a truly representative “risk of exposure” (i.e. all the ways in which the infection can be transmitted) should be established and use in scenario modelling. Case controlled studies have demonstrated that men’s sexual behaviour affects women’s risk for HPV-induced malignancies, even when controlling for female sexual activity [14-17]. Although previously published systematic reviews [10,18,19] showed that most cost-effectiveness studies in the extant literature have demonstrated the cost-effectiveness of selective high coverage (>80%) of 12-year-old girls, an increasing number of medical associations advocate the need for universal vaccination against HPV. The American Society of Clinical Oncology (ASCO) recognises the long latent period of HPV infection prior to the development of invasive cancers means many years of follow-up are required to demonstrate a significant reduction in HPV-related cancers; it recommends, along with the US Centre for Disease Control (CDC) that all boys and girls are vaccinated at 11 or 12 years old, prior to possible HPV exposure through consensual sexual activity [20].

Despite this clinical advice, public health policy makers in most European Countries (except Austria, Sweden and some regions of Italy) have, to date, largely accepted the published cost-effectiveness modelling based on the protective effect of herd immunity, and have implemented girls-only vaccination programmes [21].

The epidemiological and economic models used to inform public health decisions should include all known dynamics of transmission of infection along with the populations affected. HPV is primarily transmitted via penetrative sexual intercourse, although there is evidence of other modes of transmission, including transmission from hands to genitals or genitals to hands [22]. Hence cost-effectiveness valuations of HPV vaccination strategies should include consideration of sexual behaviours and population mixing. Behaviours must be provided for in any economic modelling for the outcome to demonstrate ecological validity, whereby the scenarios modelled remain faithful to the real-life social and cultural context [23].

Ecological validity is of clear importance when informing a public healthcare decision, and modelling should therefore have a generalised relationship to the natural behaviours of the affected population; in the case of HPV vaccination, this should be based on the inclusion of the representative individuals within the population and the sexual behaviours they undertake. The primary aim of this review is therefore to test the ecological validity of the universal HPV vaccination cost-effectiveness modelling available in the published literature; each model will be defined by the number of representative characteristics and behaviours taken into consideration.

2. Methods

The research protocol related to this systematic review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42016034145), available online at: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016034145.

A full description of the research methodology has been published [24].

Inclusion criteria for the literature included in the review were for (a) studies reporting the incremental cost effectiveness ratio (ICER) per quality-adjusted year gained (QALY) of adding males to a female-only HPV vaccination; (b) health outcomes not limited to cervical cancer and genital warts, but including additional HPV-induced diseases such as vulval cancer, vaginal cancer, anal cancer, penile cancer, oro-pharyngeal cancer, recurrent respiratory papillomatosis (RRP); (c) HPV universal vaccination compared to cervical cancer screening and vaccination of females only; (d) studies reporting a full disclosure of the inputs chosen to inform the economic model; (e) economic models that were individual, static, transmission dynamic or hybrid models.

Health outcomes limited to the valuation of cervical cancer and genital warts, and studies not published in the English language, were excluded.

2.1 Search Strategy

The literature search is outlined in the PRISMA flow diagram [25] reported in Figure 1.

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Two Graduate Research Associates (GRAs) independently identified relevant literature through database searching, and then screened and assessed for eligibility to include in the review. Opinion of one of the reviewers (authors) was sought to arrive at a consensus in the case of disagreement. Nine bibliographic databases were searched for literature: MEDLINE (via PubMed); Scopus; Science Direct; EMBASE via OVID SP, Web of Science, DARE, NHS EED and HTA (via CRD); CINHAL Plus. An additional search for grey literature was conducted on GoogleScholar and OpenGrey, and search results were screened and assessed for eligibility of inclusion according to the PRISMA 2009 process [25]. To reduce the risk of missing original articles, reviews were included, the PubMed "related articles" search feature was used, and references of the included studies were also searched in order to identify any additional missed relevant studies. The search terms used in the search strategy are included as Appendix A. A pilot of the study selection process was conducted before initiating the systematic search of relevant articles.

Two external experts (a health economist and a clinical oncologist) independently assessed the risk of bias for each of the studies included in the review. The critical appraisal of the included economic evaluations was carried out in two subsequent stages:

- A preliminary stage, aimed to assess the risk of bias in the estimates of treatment effect (e.g. vaccine efficacy) used as data inputs in the economic evaluation. Although the efficacy of HPV immunisation has been preliminarily confirmed by small-sample cohort studies (n=29), the choice of the Cochrane Risk of Bias tool [26] was based on the premise that the body of primary studies

informing the estimates of relative treatment effect in cost-effectiveness models is still represented by the randomised clinical trials that supported the regulatory approval of the HPV vaccines currently available [27]. The Cochrane Risk of Bias tool is reported in Appendix B.

- A main stage, aimed to identify additional risks of bias and, ultimately, to assess the validity of the included studies. The risk assessment will follow the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) approach [28]. The CHEERS statement is reported in Appendix C.

The main findings were summarised according to the PRISMA checklist for assessing susceptibility to bias in health economic valuation [25], reported in Appendix D.

2.2 Data extraction

Data were extracted and recorded independently by two additional Graduate Research Associates (GRAs) from the studies included in the review, according to a predefined data extraction table. Data extracted were clustered and prioritised: the main outcomes report the inputs to the demographic and epidemiological model, while additional outcomes refer to basic inputs to the cost-effectiveness valuation. The ecological validity of each model was defined by the representative population and behaviours taken into consideration within the modelling.

Population characteristics and behaviours were defined according to the extant literature [29,30]. In relation to the population modelled: (a) the number of susceptible individuals (population size and growth); (b) gender; (c) age; (d) ethnicity; (e) self-defined sexual identity. In relation to sexual behaviours: (a) sexual activity, defined as the rate of change of sexual partners; (b) concurrent sexual

partnerships; (c) at least one sexual partner from outside the UK; (d) paid-for sex; (e) the frequency of unprotected (without condom) sex. Sexual behaviours data refer to men only, since women are actively protected by the selective vaccination against HPV in all the cost-effectiveness models included in the systematic review (see inclusion criteria a).

Monetary values were converted into US dollars (where required) using purchasing power parities (PPPs), and further adjusted to 2015 US dollar value using the US Consumer Price Index (CPI).

2.3 Data synthesis

Each study included in the review was scored by the number of representative population characteristics and behaviours considered. The individual study's scores were plotted on a 2x2 matrix plotting sexual behaviours on the x axis, and characteristics of participants on the y axis, a modified structure from Hogarth (2005) [31]. Studies included in the upper right quadrant can therefore be defined as ecologically valid through high levels of consideration of population characteristics and behaviours; it is these studies that provide more representative scenarios to inform economic recommendations on public health policies.

3. Results

3.1 Search results

The database search identified 525 publications, and an additional 46 were discovered through open sources; this consisted of 173 studies after duplicate records were removed (Figure 1). Following exclusion of models that did not account for incremental cost-effectiveness ratio (ICER) associated with male HPV vaccination, 21 individual records remained (16 full text articles and five reviews). Of

these, all the reviews were excluded (following confirmation they did not include any new original articles), and eight published articles were excluded because outcomes did not include all HPV-induced disease. This resulted in eight original studies to be included in the review for data extraction: Elbasha and Dasbach, 2010 [32]; Kim and Goldie, 2009 [33]; Chesson *et al.*, 2011 [34]; Burger *et al.*, 2014 [35]; Laprise *et al.*, 2014 [36]; Pearson *et al.*, 2014 [37]; Olsen and Jørgensen, 2015 [38]; and Haeussler *et al.*, 2015 [39].

The independent assessment for risk of bias identified two main findings. Firstly, three studies to be included in the review (Elbasha and Dasbach, 2010; Pearson *et al.*, 2014; Olsen and Jørgensen, 2015) used unreferenced estimates of vaccine efficacy to inform the cost-effectiveness model [27,32,38]. The efficacy estimates used to inform these models were in the same range (90 to 100% vaccine efficacy) as the outcomes of randomised clinical trials used by all other studies included in the review.

Secondly, the three studies which recommended the cost-effectiveness of universal vaccination (Elbasha and Dasbach, 2010; Olsen and Jørgensen, 2015; and Haeussler *et al.*, 2015) were funded by a research grant from Sanofi Pasteur MSD, a leading supplier of HPV vaccine [32,38,39]. Source of funding and conflict of interest were appropriately reported by the Authors.

These findings would represent a marginal risk of bias for the outcomes of this review, since they are virtually irrelevant to the assessment of the ecological validity of each model, which is the main objective of research. The independent reviewers and the Authors agreed to include in the review the eight studies identified through

the database search. The relative impact of input choices on cost-effectiveness outcomes will be further discussed in the following sections.

3.2 Summary of cost-effectiveness outcomes

Cost-effectiveness studies represents the normative side of health economics, using models to facilitate decision making from the perspective of making the most efficient use of limited resources [40]. The policy recommendations emerging from the extant literature on universal vaccination against HPV have been contradictory, although all the included studies analysed averted direct medical costs only, from a societal or health payer perspective. The universal vaccination against HPV resulted as cost-effective in three studies [32,38,39]; possibly cost-effective in two studies, secondary to increasing immunisation coverage of women [34,35]; and ultimately never cost-effective according to three studies [33,36,37].

The inputs chosen to inform the cost-effectiveness models included in this systematic review are reported in Table 1.

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3.3 Summary of inputs to demographic and epidemiological method.

The inputs to the infection diffusion models (participant characteristics and sexual behaviours) utilised by the cost-effectiveness studies included in the review are reported in Table 2.

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The results of the review for ecological validity demonstrated differences in the modelling of the population and behaviour. None of the studies considered the impact of sexual partners from outside the population (either within the country or

overseas), sex that was paid for, or the frequency of unprotected sex. Only one of the models [36] considered men who have sex with men (MSM) as a self-defined sexual identity, but none of the models considered single or occasional same-sex partnerships, where sexual identity may not be self-defined as MSM or bisexual.

The results were plotted on a 2x2 matrix (sexual behaviours on the x axis, and characteristics of participants on the y axis). Figure 2 demonstrates the outcome.

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None of the studies showed due consideration of the complexities of human sexual behaviour and the impact this may have on the economic modelling; this can be seen by the lack of entries on the right of Figure 2. A study of the cost-effectiveness of HPV universal vaccination with ecological validity would be present in quadrant A of Figure 2. On this basis, all the included models might be affected by a different degree of ecological bias, which implies an inability to reflect the natural demographic and behavioural trends in their outcomes and, consequently, to accurately inform public healthcare policy.

4. Discussion

Our results are consistent with the outcomes of recently published reviews of HPV vaccination modelling approaches [41,42,43]. The heterogeneity of outcomes observed in the reviewed studies results from the high degree of sensitivity to boundary conditions and the choice of inputs [39]. The incremental cost effectiveness ratio (ICER) values increase as a consequence of higher vaccine efficacy, duration of protection, cross-protection, duration of immunisation, and observation period. Conversely, ICER values decrease as a consequence of

including a larger set of HPV-induced diseases (such as recurrent respiratory papillomatosis), lifetime duration of efficacious vaccination (no subsequent “booster” dose), a reduced number of doses needed to complete immunisation (two versus three) and a lower unit price per vial of the vaccine. Funding might also play a role in the choice of the inputs to inform the economic models.

Therefore, the difference between the observed ICER values and the acceptability threshold (usually $50,000 or £30,000) may result as positive (adding boys is not cost-effective) or negative (universal vaccination is cost-effective), simply on the basis of the prevalent effect of the mix of inputs chosen to inform the model on the ICER value. As an illustrative example, the highest ICER (in $2015 values) observed among the studies included in the systematic review was >$200,000 [34]. The reported ICER value was driven by the highest level of immunisation coverage observed in the review (75% of all 12-26 year-old women, a 13-26 year-old women catch-up cohort and 75% of all 12 year-old males), by an elevated (90 to 100%) adherence to a three-dose vaccination schedule, and by a relatively high vaccine price ($128 per vial).

In more general terms, sensitivity analyses showed that the vaccine price per vial is one of the factors most relevant to the determination of the incremental cost-effectiveness ratio, and hence of the cost-effectiveness of universal vaccination (Table 1). All else equal, a vaccine price per vial of $31.47/£22.03/€28.01 would drive all the base-case ICER values reported by the studies included in the review below an acceptability threshold of $50,000 (in $2015 values, using the average 2015 dollar: pound and dollar: euro exchange rates, Bloomberg data). A vaccine price per vial of $26.97/ £18.88/€24.00 would drive all the base case ICER values

below an acceptability threshold of £30,000. Calculations are reported in Appendix E.

The importance of the price per vial values, probably deemed insignificant inputs at the time of the cost-effective analyses, seem quite realistic almost a decade after the first introduction of the HPV vaccines in 2007. In Italy, the price of Cervarix® (GSK) dropped to €28.60 per vial by late 2015 [44], while the lowest price observed for Gardasil® (Sanofi Pasteur MSD) was €33.90 per vial [45].

The volatility implied in the ICER values, a consequence of the large variance observed in the chosen economic inputs over time, suggests the need for an "expiration date" on the validity of the normative outcomes stemming from cost-effectiveness analyses. Economic and demographic inputs, however, are not the only parameters exposed to significant change over time. In the case of HPV vaccination, inputs related to the efficacy of the new vaccines to prevent HPV-induced malignancies have been on the basis of the results of a few large randomised clinical trials submitted for regulatory approval [46-55]. The observed inputs ranged from a minimum of 50% clinical efficacy (specifically to head and neck cancer [39]) to a maximum of 100% [33,35,38].

Over the last decade, the impact of HPV vaccination in real-world settings has become increasingly evident: maximal reductions of ~90% for HPV 6/11/16/18 infection, ~90% for genital warts, ~60% for low-grade cytological cervical abnormalities, and ~90% for high-grade histologically-proven cervical abnormalities have been reported [56]. On the basis of the inputs related to vaccine efficacy, it is probable that six out of the eight studies included in this review have over-estimated

the benefits gained from the selective vaccination of pubertal girls only, consequently making the option to add boys to the HPV immunisation cost-ineffective [33-38].

The primary aim of this review of the cost-effectiveness models of universal HPV vaccination available in the literature was to test their ecological validity, the implicit condition that the characteristics and sexual behaviours of the individuals observed in the models are representative of, and relational to, the natural behaviours of the population. The ecological validity of each model was defined by the number of representative characteristics and behaviours of the population taken into consideration [29]. Table 2 reports the representative characteristics and behaviours taken into consideration by each study included in the systematic review.

The first general consideration is related to the appropriateness of the demographic model used to inform the cost-effectiveness analyses: the prevailing choice is the age structured multiple birth cohorts, adopted by six of the eight studies included in the review. Only two studies [32,36] used a population-based model. Although individual- and cohort-based approaches are generally used in most published healthcare decision models, this choice is rarely discussed by the modellers. In a cohort-based model, a closed group of individuals who have at least one specific dimension in common over a defined period of time (e.g. 12-year-old girls at the time of HPV immunisation) is run through a state transition process (e.g. sexual mating, infection, clearance or development of HPV-induced malignancies). The cohort is generally composed of a pre-defined number of “average” individuals, and the resulting population is considered to be a homogeneous group [57]. The risk of acquiring a sexually transmitted infection depends on individual-level factors as well as the behaviour and infectiousness of others. Consequently, study designs and analysis methods developed for studying risk in individuals or cohorts may not apply

directly [58]. Structured population models address the heterogeneity of population by representing demographic processes in the form of a mathematical function or set of functions relating two or more measurable variables. The primary purpose of modelling is to make possible an approximate representation of reality in its complexity. Contrary to the cohort method, demographic models allow the social and behavioural diversity within the population to be reflected in the outcomes of the cost-effectiveness analysis, a crucial aspect that modellers should consider [57].

In the case of universal HPV immunisation, most of the characteristics of participants and common behaviours representative of their sexual mixing were not included in the reviewed publications, regardless of the demographic model chosen.

Sexual behaviours such as same sex partnership, sex abroad, sex with a partner from a different country, and paid sex were almost completely ignored by the eight models included in the review. Men having sex with men (MSM) was an input included in a single study: a 7% incidence of homosexual males and the relatively high risk of disease among MSM vs. heterosexual males would make a two-dose universal vaccination more cost-effective that a two-does girls-only immunisation [36]. The outcomes of the latest survey of sexual behaviours in the UK show that 8% of males have occasional partners of the same sex [29].

Taking this argument further, if we compare the most common inputs in models with current population characteristics and sexual behaviours within the UK, we see that the models within the review do not match the real environment, which leads to a lack of ecological validity. Table 3 shows large areas of discord.

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If we reflect on the non-modelled behaviours related to sexual mixing, for example with non-UK partners (in the UK or overseas), it is plausible that the models may have produced an over-estimation of the impact of herd immunity [35]. If sexual partners of unvaccinated males enter the population from countries without a vaccination programme, then the vaccination coverage may be significantly lower than assumed, altering assumed herd immunity and the subsequent modelled cost-effectiveness.

Within the UK, the National Surveys of Sexual Attitudes and Lifestyles ("Natsal") show that, of the cohorts aged 16-24 years old and 25-34 years old, 13.2% (11.5-15.2%) and 14.5% (12.8-16.5%), respectively, have had at least one new sexual partner from outside the UK in the past five years [29,30,59]. It is within these age-range cohorts that the HPV vaccination programme has been undertaken, and for whom herd immunity is now assumed. If unvaccinated partners from overseas are entering the modelled population, then the cost-effectiveness outcomes could be challenged.

With this consideration, we re-examined the results of the study closest to ecological validity in Figure 2 [36] to appraise possible impact. The study estimates the ICER of a 2-dose vaccine protection for 30 years in 14 different scenarios. The 95% confidence interval of the mean ICER value was ± 0.21 (i.e. there is 95% certainty that the true population mean falls within 21% of the mean value). The impact of herd immunity on the percentage reduction in HPV-induced health outcomes predicted by cost-effectiveness model can be as large as 50%, as tested in the sensitivity analyses of one study included in the review [34]. When we tested a

credible hypothesis of 5% to 20% overestimation of QALYs gained in the selective immunisation (2-dose girls-only) scenarios, most of the universal ICER values (2-dose girls + boys) dropped below the acceptability threshold (Table 4). This finding was confirmed by another study included in the review [35], where a reduction of >15% of the herd immunity benefits lowered the ICER of universal immunisation below the $50,000 acceptability threshold.

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The results modelled here demonstrate the limitations of the cost-effectiveness studies for HPV vaccination, and highlight the concern that public healthcare policy might have been built upon incomplete studies. The impact of herd immunity and the decision to vaccinate girls and boys, or girls only, must be further defined by additional studies that are built upon inputs that are ecologically valid as they are truly reflective of the population and its behaviours. The use of a cohort-based approach to economic modelling versus a population-based approach (fixed population with no further entry, versus one that allows future incident patients to enter the population, respectively) has been discussed elsewhere [57], and the findings in this systematic review would suggest that the methodological choice of individual or cohort-based model is likely to over-estimate the benefits of herd effects on the unvaccinated population. A population-based approach to modelling would better serve economic decisions attached to HPV vaccination strategies.

Our findings indicate that the selective immunisation of pre-pubertal girls is likely to fail to achieve the expected level of herd immunity at population level. A relatively small (15 to 20%) over-estimation of QALY-gained with selective immunisation programmes could induce a significant error in the estimate of the cost-effectiveness

of universal immunisation, making the option of vaccinating boys cost-ineffective. To minimise potential ecological bias, population characteristics and sexual behaviours of the modelled population should be aligned more closely to real-life scenarios. This would confer ecological validity to the outcomes, it would better inform any resulting policy decisions made by public healthcare providers and, ultimately, it would ensure the population is best protected against the risk of contracting HPV-induced diseases.

Original publication

The review is original work and it has not been submitted for publication elsewhere.

Conflicts of interest statement

Giampiero Favato was part of the BEST Research Group, which received unrestricted research grants from Sanofi Pasteur MSD for the BEST study (Favato *et al. Med Care* 2012; 50(12):1076-85.) and BESTII study, the latter included as part of this systematic review (Haeussler *et al*., 2015 [39]). All authors declare that they are aware of no potential conflicts.

Statement of funding:

This study did not receive any funding.

Ethics statement

This is a review of extant literature using publicly available secondary sources only. No specific ethical review was obtained for this study.

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