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Review

Present challenges in cervical cancer prevention: Answers from cost-effectiveness analyses

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ABSTRACT

Simulation models are commonly used to address important health policy issues that cannot be explored through experimental studies. These models are especially useful to determine a set of strategies that result in a good value for money (cost-effectiveness). Several mathematical models simulating the natural history of HPV and related diseases, especially cervical cancer, have been developed to calculate a relative effectiveness and cost-effectiveness of HPV vaccination and cervical cancer screening interventions. Virtually all cost-effectiveness analyses identify HPV vaccination programmes for preadolescent girls to be cost-effective, even for relatively low vaccination coverage rates. Routine vaccination of preadolescent girls is the primary target population for HPV vaccination as it shows to provide the greatest health impact. Cost-effectiveness analyses assessing other vaccine target groups are less conclusive. Adding additional age-cohorts would accelerate health benefits in some years, although cost-effectiveness becomes less favourable as age at vaccination increases. Including men in HPV vaccination programmes may be a less efficient strategy if done at the expense of female vaccination coverage for reducing the burden of HPV in the population. However, as the HPV vaccine price decreases, the cost-effectiveness of universal vaccination improves, becoming equally as efficient as female-only vaccination. Vaccine price is a decisive factor in the cost-effectiveness analyses. The lower the price, the greater the likelihood that vaccination groups other than the primary target would be considered cost-effective.

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1. Background

Health economic evaluations, particularly cost-effectiveness analyses (CEA), have become more prevalent in recent years and are increasingly used to inform decisions on which new products to include in the common services portfolios of the national health care systems.[1,2] At present, several health technology assessment (HTA) agencies, such as the National Institute for Health and Care Excellence (NICE, UK), the Pharmaceutical Benefits Advisory Committee (PBAC, Australia) and the Canadian Agency for Drugs and Technologies in Health (CADTH), use cost-effectiveness as the most influential factor in the HTA decision-making process.[3] Together with the effectiveness, safety and quality, cost-effectiveness evaluation is one of the four cornerstones for the identification of best value and resource allocation decision-making. That said, decision-makers must also consider issues of equity, acceptability, accessibility and affordability when drawing their conclusions.

Over the past two decades, mathematical models simulating the natural history of human papillomavirus (HPV) and related diseases, especially cervical cancer, have been developed to assess health policy issues related to prevention strategies. These models are commonly used to simulate a relative effectiveness and cost, and then to calculate the cost-effectiveness of HPV vaccination and cervical screening interventions in relation to different parameters. Doing so via experimental studies is virtually impossible for a number of reasons: first, the interest lies in the mid- to long-term impact of these interventions; second, they target a group of diseases with relatively low incidence which, moreover, can take a very long time to manifest as precancerous lesions after infection; and third, the parameter combinations possible for each intervention are numerous and varied, and include the synergy between primary and secondary prevention strategies.[4]

2. Cost-effectiveness analysis methodology

The primary goal of the CEA is the optimal allocation of typically constrained resources to obtain the greatest gain in population health.[5] This approach provides a systematic and theoretical framework by which to compare the relative costs and health effects of different interventions and decide which of them represent good value for money.[6] The incremental cost-effectiveness ratio (ICER) is the most common summary measure used in this regard, defined as the difference in cost between two interventions (e.g. A and B) divided by the difference in health effects: $\text{ICER} = (\text{Cost}_A - \text{Cost}_B)/(\text{Effect}_A - \text{Effect}_B)$, where said change in health effects is usually measured in terms of the number of life years (LYs) saved or the number of quality-adjusted life years (QALYs) gained. As such, the ICER is frequently expressed as the cost per LY saved or QALY gained.

In order to draw conclusions about which strategies are cost-effective, the ICERs must be compared to a pre-determined reference value or threshold below which an intervention would be considered cost-effective. This threshold serves to signpost policy-makers to which of the possible interventions offer an efficient use of resources. It can also be understood as the upper limit of what society is willing to pay for an additional unit of health effect (e.g. QALY).[7] There is no consensus as to a universal ICER threshold, with different HTA agencies defining country-specific benchmarks to aid the decision-making process. The most extensive discussion on the use of these values can be found in the UK, where NICE has defined a range of £20,000–£30,000/QALY gained.[8] In the rest of Europe it ranges from country to country, from €20,000/QALY gained in Spain to the €50,000/QALY gained reported in studies in Denmark and Germany.[9–11] In the USA interventions that cost less than $50,000/QALY gained or, occasionally, between $50,000 and $100,000/QALY gained, are considered to be good value for the resources invested.[12] The most universal threshold was used by the World Health Organisation's Commission on Macroeconomics and Health in its 2002 report on investing in health for economic development. This heuristic recommends that an intervention be considered highly cost-effective if the ICER is less than the country's per capita gross domestic product (GDP) and cost-effective if the ICER is less than three times the per capita GDP.[13]

3. HPV vaccination in preadolescent girls

The WHO-recommended primary target population is preadolescent girls aged 9–14 prior to becoming sexually active. To date, numerous simulation models have been developed to address the health and economic impact of introducing HPV vaccination programmes for preadolescent girls. Despite the diversity of the approaches, the different complexities of the models parameters and assumptions, almost all economic evaluations found such HPV vaccination programmes to be cost-effective, even for relatively low vaccination coverage rates.[14] Over the last ten years, prophylactic vaccination against HPV in preadolescent girls has been introduced in many countries, especially in high- and upper-middle-income countries (Fig. 1).[15]

By 2014, around 47 million women worldwide had received the full course of three doses and 59 million had received at least one dose. In the more developed countries, these figures represent a 33.6% and 43.3% coverage of female population aged 10–20 years, respectively, while in less developed countries this rate stands for 2.7% and 3.0%. The impact of HPV vaccination has become increasingly evident in women and heterosexual men, with reduced population prevalence for targeted HPV genotypes, e.g. genital warts and low- and high-grade cervical lesions, especially among women vaccinated before HPV exposure in countries with high vaccine uptake.[16] Pressure from international public health authorities and HPV vaccine deals in 2013 mean that some non-profit making non-governmental organisations can now purchase HPV vaccines at around US$ 4.50 per dose, allowing a growing number of girls to be protected in low and lower-middle-income countries.[17] It is estimated that 30 million girls will be vaccinated in these countries by 2020 with international assistance at different levels.

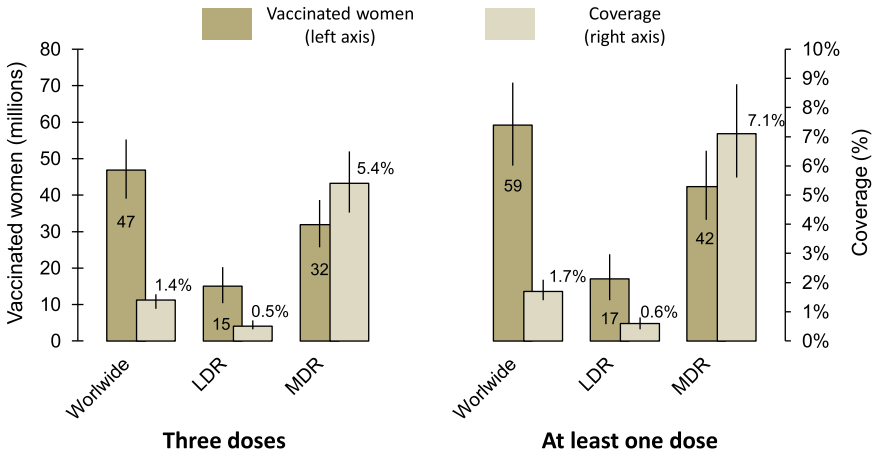

Fig. 1 – Total number of vaccinated women and coverage as a percentage of the total female population, worldwide and by level of development.
Data extracted from Bruni et al., 2016.[15]

Massive HPV vaccination of all preadolescent girls would prevent millions of women dying from avertable cervical and other HPV-related cancers, also protecting heterosexual men through herd protection.

4. HPV vaccination in adolescent to postadolescent girls and adult women

Postadolescent girls (15–26 years) and adult women (>26) are considered by WHO as a secondary target population for HPV vaccination, recommended only where this is feasible, affordable, cost-effective and does not divert resources from vaccination of the primary target population or from effective cervical cancer screening programmes.[18] Simulation models for several developed countries have weighed up the costs and health benefits of adding catch-up vaccine for postadolescent and older women to the vaccination of the primary target.[19–36] These studies tend to conclude that the effectiveness and cost-effectiveness of HPV vaccination decrease as age at vaccination increases.

In terms of their effectiveness, some models do report health benefits for the vaccination of women aged 15 and over. For instance, 34% of deaths from invasive cervical cancer can be avoided by vaccinating women at age 40 (compared to 85% if vaccinated at age 12).[29] In another study, cervical cancer cases were shown to drop by half if women are vaccinated at age 25.[28] The lifetime risk of cervical cancer is estimated at 0.5% under current screening programmes with no vaccination, 0.14% when girls are vaccinated at age 17, and 0.4% when women are vaccinated at age 25.[30] An interesting finding in some models is that a temporary catch-up campaign for older girls and younger women speeds up the reduction of cervical cancer incidence by several years compared to baseline vaccination.[19,21,22,25,26,30,31,33,34] In the Netherlands, extending the vaccination age range from 12–16 to 12–29 years could bring forward a 5% reduction in cervical cancer cases by three years.[30] In terms of HPV 16/18 prevalence, a one-year catch-up campaign targeting young women from just a few birth cohorts could bring forward a 50% reduction by as much as five years depending on the country (Fig. 2).[33,34]

In terms of cost-effectiveness, temporary catch-up vaccination campaigns were found to be less favourable at older ages, although the upper age limit varied widely from country to country from 16 to 40 years old.[19–23,25–32] These reported differences may be due to a combination of multiple factors, such as the characteristics of the models and other country-specific variables. Only one such model looked specifically at the effect of HPV vaccination in women aged 30 or over, concluding that the likelihood of vaccination being cost-effective for women aged 35 to 45 in the USA was 0% with annual or biennial screening and less than 5% with triennial screening, at thresholds considered good value for money.[24]

However, most of the studies referenced above have been rendered somewhat outdated due to rapid breakthroughs in various aspects related to the HPV vaccine and HPV screening. For example, all models assume vaccination followed by intensive screening, usually with intervals of 1–5 years, and most of this screening is cytology-based, whether conventional or liquid. However, the dramatically-reduced baseline risk in vaccinated women observed, together with the transition from a cytology-based screening to one based on HPV DNA testing, would allow the starting age for screening to be raising and the screening intervals to be extended. Another critical issue is that the baseline vaccine prices in these earlier studies ranged from €225 to €400 for the three doses. Today, the price has dropped by as much as 75% since the vaccine was first licenced, especially when subjected to tender procedures. Yet, although several studies demonstrate the sensitivity of ICERs to vaccine price, only two studies from the Netherlands specifically present results at near current tender prices. One of these studies concludes that vaccination at €45 per dose would remain cost-effective up to age 30.[28] Fig. 3 shows how the ICER varies with vaccine price at different vaccination ages.[30] At all ages, we observe a remarkable reduction in the cost-effectiveness ratio when the vaccine price is reduced from 125€ to 35€ (72% decline),

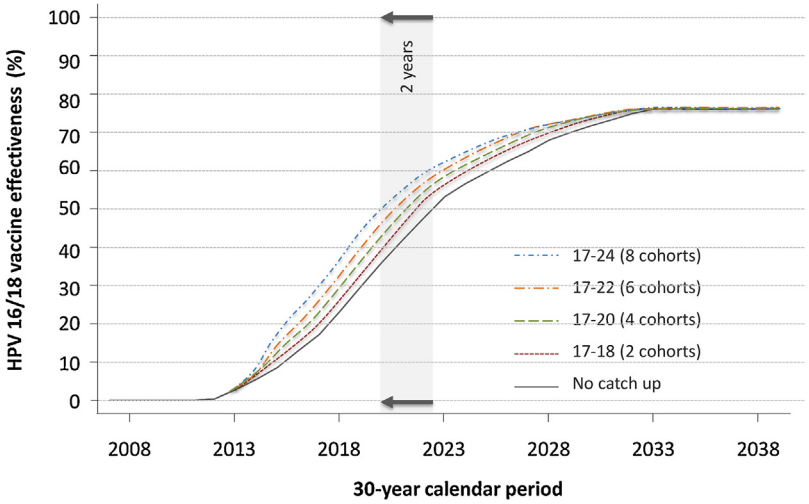

Fig. 2 – Effect of increasing the number of age cohorts vaccinated against HPV16/18 on time to reduction in the prevalence of HPV infection in Italy.
Figure adapted from Bosch et al.[38]

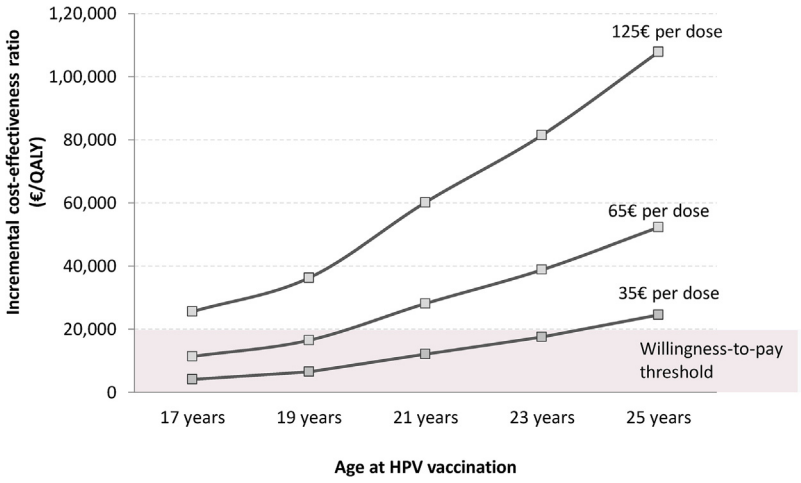

Fig. 3 – Incremental cost-effectiveness ratios at different HPV vaccination ages and vaccine prices.
Data extracted from Bogaards et al., 2016.[30]

making vaccination very cost-effective at almost all ages analysed.

The latest results reporting high efficacy of vaccination in older women,[37] together with the reduction in vaccine price; the arrival of vaccines targeting more HPV types, the ability to reduce the number of doses, and the consolidation of HPV DNA testing as the primary screening method presents a new cervical cancer screening scenario,[38] making vaccination of postadolescent and adult women an attractive means of HPV prevention.[39,40]

5. HPV vaccination in men

Women are at higher risk of presenting with HPV-related cancers than men, although the proportion of these cancers in men is increasing. Worldwide, it is estimated that around 60,000 HPV-attributable cancers are diagnosed in men each year, along with a non-estimated but substantial number of preventable cases of genital warts.[41] As of now, gender-neutral vaccination has been recommended in at least 21 countries: Antigua and Barbuda, Argentina, Australia, Austria, Bahamas, Barbados, Bermuda, Brazil, Canada, Croatia, Czech Republic, Israel, Italy, Liechtenstein, New Zealand, Norway, Panama, Serbia, Switzerland, the United States of America and Turkmenistan. Other than penile cancer, men are particularly at risk of head and neck cancers caused by HPV, accounting for 80% of all cases. Anal cancer is disproportionately high in men who have sex with men (MSM), especially in those who are HIV-positive.[41,42] HPV vaccination in men can provide additional health benefits, decreasing male risk of contracting genital warts and developing HPV-related cancers, contributing to reduce HPV transmission in general, and ensuring equity in protection from HPV-associated diseases in both men and women. However, certain reservations emerge when assessing whether

a universal HPV vaccination represents good value for money.

To date, 21 studies starting in 2004 have examinated the cost-effectiveness of universal vaccination, of which 12 have been published in the last four years.[10,11,23,27,35,43–58] The general view is that increasing female coverage is a more efficient strategy for reducing the burden of HPV in the population than extending vaccination to males. However, models are very sensitive to certain parameters, such as the inclusion of some health outcomes, the duration of vaccine protection, female coverage rates and the cost of the vaccine. Several studies agree that vaccinating males could be cost-effective where female coverage is low or if the vaccine cost is substantially reduced. As mentioned in previous sections, HPV vaccination has undergone significant changes in recent years, which is reflected in the parameters used in cost-effectiveness studies, with less optimistic coverage rates in females, prices well below the original market values, and a greater range of potential health benefits. Fig. 4 shows a summary of the ICERs from studies evaluating universal vaccination versus female-only vaccination. For enhanced comparability, all ICERs were converted to the same currency (euro, €) using the exchange rates from the corresponding indexed year. Panel A charts the size of the ICERs (bubbles) against cost per vaccinated individual (vertical axis) and female coverage (horizontal axis). By tracing an imaginary boundary at the €200 mark and another at 60% coverage, we group the ICERs into three quadrants. The highest ICERs are found in the upper right quadrant, where both cost and coverage are also among the highest. These correspond to some of the oldest studies; only 4 out of the 14 studies in this quadrant were post-2013. In the other two quadrants, where the ICERs either consider lower coverages or lower vaccine costs, the size of the ICER is more homogeneous. Panel B gives a box plot depicting the variation in the ICERs in the three quadrants. The highest mean (€156,206/QALY gained) and median (€68,923/QALY) scores are obtained for coverages greater than 60% and costs per vaccinated individual of over €200, followed by the scores obtained when costs per vaccinated person fall below 200€ (mean €39,480/QALY gained and median €33,219/QALY) and coverages fall below 60% (mean €36,740/QALY gained and median €34,634/QALY).

As the HPV vaccine price decreases, the cost-effectiveness of universal vaccination is more evident, becoming equally as efficient as female-only vaccination. Some authors identify the cost from which universal vaccination would be cost-effective. For instance, a study in New Zealand found that extending vaccination to boys, based on a three-dose schedule, would only be cost-effective when the price was below NZ$ 125 per dose (approximately €71 as in 2011).[51] Another recent study from the Netherlands found that vaccination of boys based on a two-dose regime, would be considered cost-effective when vaccination cost was below €65 per person, which was the actual cost in this country from 2012 to 2014.[58] An increase in the cost per vaccinated individual from €65 to €350 would enhance the ICERs by 7.35. This study also reports that universal vaccination is only slightly less efficient than increasing coverage among girls.

6. HPV vaccination in MSM

The number of MSM that develop anal cancer as a result of HPV infection has increased in all Western countries over the last decades, especially among HIV-positive men.[59] According to the Centres for Disease Control and Prevention (CDC), men who have sex with men are about 17 times more likely to develop anal cancer than men who only have sex with women (MSW).[60] HPV 16 and 18 are responsible for approximately 87% of anal cancers, while the relative contribution of the 9-valent vaccine types is 96%.[41] It is estimated that 15% of MSW are positive for HPV, compared to 60% of HIV-negative MSM and 90% of HIV-positive MSM.[61,62]

High vaccine coverage in the female population benefits heterosexual males through herd immunity, where a substantial decrease in the disease burden is related to genital warts.[63] However, even if all females were immunised, HPV transmission in men would remain through MSM. Therefore, the MSM population may be an additional target for routine HPV vaccination. The immunogenicity of HPV vaccination in MSM aged 16–23 has already been proved in a randomised clinical trial.[64]

The first model to explore the potential effectiveness and cost-effectiveness of the HPV vaccination of MSM was that of Kim et al. in 2010.[65] Their model assessed a healthy cohort of MSM starting at age 12 years who were at risk of anal cancer and genital warts during their lifetimes. Under different scenarios of age at vaccination, duration of vaccine protection, HPV and HIV exposure and anal cancer incidence, cost-effectiveness ratios remained lower than the aforementioned thresholds of $50,000 and $100,000/QALY gained. Assuming 50% coverage, HPV vaccination of MSM at age 12 years had a cost-effectiveness ratio of $15,290/QALY gained as compared to no vaccination; $19,160/QALY gained if MSM were vaccinated at age 26 and assuming 10% exposure to HPV 16, 18, 6 and 11; and $37,830/QALY gained assuming 50% exposure. Using a dynamic model, Lin et al. evaluated the impact of offering vaccination to MSM who visited genitourinary medicine clinics (GUM).[66] Substantial declines in anogenital warts and male HPV-related cancer incidence were estimated by offering HPV vaccination to MSM aged 16–40 who attended GUM clinics. Specifically, anogenital warts incidence was lowered by 35% within five years (by 15% where only HIV-positive MSM were vaccinated) and HPV-related cancer incidence dropped by 55% within 100 years (40% where only HIV-positive MSM were vaccinated). The authors also indicated that HPV vaccination of this group could be cost-effective if all MSM up to age 40 were vaccinated at a cost of £48 per dose or if only HIV-positive MSM were vaccinated at maximum cost of £96.50 per dose. However, an analysis with a compartmental model for Australia concluded that the greatest health benefits for MSM would only be achieved by targeting all boys, and that a vaccination programme for young MSM aged 15–26 years in addition to the boys programme would only be cost-effective if implemented immediately.[67]

HPV vaccination as a secondary strategy for the prevention of recurrent high-grade anal intraepithelial lesions and invasive anal cancer was assessed for both HIV-negative and HIV-positive men aged 27 and above.[68–70] For both, the risk of

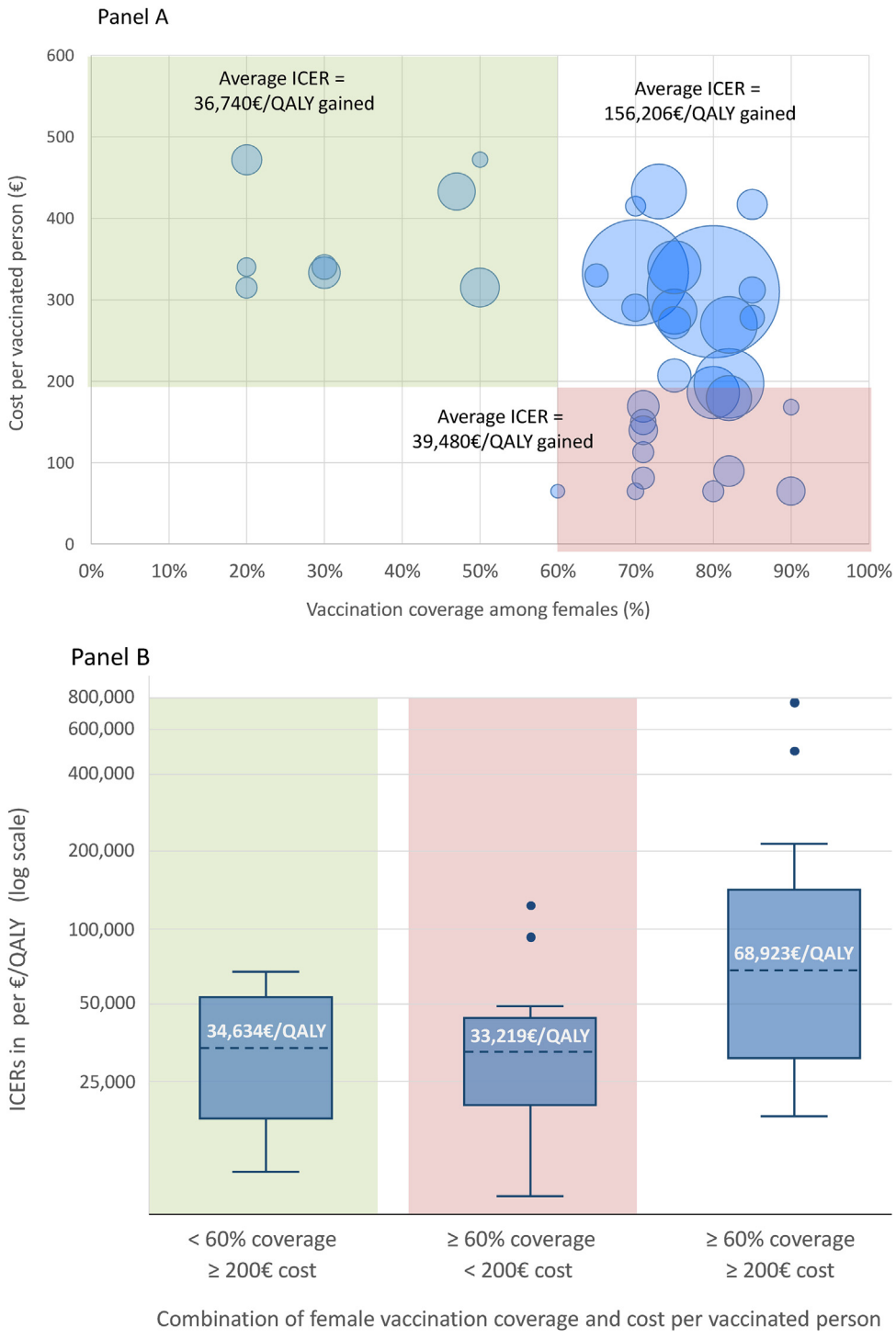

Fig. 4 – Summary of ICERs from studies including universal vaccination versus female-only vaccination. Panel A: Bubble diagram of ICERs (bubble) plotted against cost per vaccinated individual and female vaccination coverage. Panel B: Box-plot of ICERs in three groups combining female vaccination coverage and cost per vaccinated individual. All studies report figures in euros per QALY gained, except one where they are given in euros per life-year gained.

recurrence and subsequent progression to invasive anal cancer decreased by around 60% as compared to no vaccination. Such intervention would be cost-effective for HIV-negative men and cost-saving for HIV-positive men.

7. HPV vaccination in childhood

Although HPV infection predominantly affects adults, HPV-related diseases in the oropharyngeal and anogenital mucosa of infants and children have also been widely reported. However, the prevalence of and progression to HPV-related lesions is unclear. HPV has been shown to be transmitted in several modes including perinatal transmission, auto- and hetero-inoculation, sexual abuse and indirect transmission via fomites.[71]

Irrespective of the HPV burden in infants and children, HPV vaccination in childhood might be considered a significant step forward for the overall reduction of HPV-related diseases and essential for achieving global immunisation.[72,73] It is estimated that coadministration of HPV vaccine with other vaccines such as diphtheria, tetanus, pertussis, meningococcal conjugate, and influenza vaccine could increase HPV vaccine coverage for the first dose to 90%.[74] It has been demonstrated to be safe and effective in children as young as 9, but no clinical trials are available for younger age groups, nor are there any models specifically evaluating the effectiveness and cost-effectiveness of vaccination in childhood. Only one study from 2004, before vaccines became licensed and primarily focusing on vaccination in children aged 12, considered the vaccination of infants as a possible strategy.[43] The number of lifetime cervical cancer cases was estimated to be the same when vaccinating infants as when vaccinating 12-year-olds, because it was held that most infections occur after age 12. Assuming 70% coverage and a booster dose after 10 years, the model suggests that a vaccination programme focusing on 12-year-olds would be more cost-effective than one focusing on infants.

8. Other future directions in HPV vaccination

Besides identifying which target groups are more favourable for vaccination, other issues have a critical impact on cost-effectiveness, such as the dosing schedule, the new generation of vaccines against more HPV types and protection against HPV-associated diseases other than cervical cancer.

Some studies suggest that two doses of the HPV vaccine (sometimes even one dose) may be as protective as three doses.[75,76] The most important factor influencing cost-effectiveness in this scenario is the lower cost of HPV vaccination, which will cut total health expenditure. Lower doses would improve uptake, increase competition rates and likely lead to fewer adverse events. Some models have evaluated the impact of different dosing schedules for the three vaccines.[11,36,50,77–79] The results from a model for Canada show that two doses of the bivalent (2-valent: HPV 16 and 18) vaccination administered to preadolescent girls as compared to no vaccination would be cost-effective if vaccine protection lasted over 10 years.[50] The third dose would not be cost-effective if protection lasted over 30 years for the 2-valent vaccine and over 20 years for the nonavalent (9-valent: HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58) vaccine.[50,80] These findings are very consistent with results from the UK, which concluded that a third dose of the quadrivalent (4-valent: HPV 6, 11, 16, and 18) vaccine would need to be priced substantially lower to be cost-effective if two doses provided the same protection as three doses for over 20 years.[36] In 2014, the WHO recommended a 2-dose schedule when vaccination series started at <15 years and many countries are now using this schedule for this age group.[18]

The 9-valent vaccine was approved by the US Food and Drug Administration in December 2014 and by the European Medicine Agency in June 2015. Two doses of this vaccine protect against some 90% of all HPV-positive cancers, over 80% of high-grade precancerous lesions and 90% of genital wart and recurrent respiratory papillomatosis cases caused by HPV types 6/11.[41,81] Economic evaluations in the USA, Italy and Germany comparing the 9-valent with the 4-valent HPV vaccine suggest that the 9-valent could reduce the health burden from cervical cancer and HPV-related diseases to a greater extent than the 4-valent, which would make it highly cost-effective and even cost-saving in some cases.[56,57,82] However, to provide three doses of the 9-valent vaccine to females aged 13–18 who had previously completed a course of the 4-valent vaccine exceeded the upper limit of the USA threshold ($100,000/QALY).[83]

Generally available economic evaluations take different health outcomes into account, from cervical cancer to the entire range of HPV-related diseases. Cost-effectiveness ratios can underestimate the potential of HPV vaccination if not all HPV-related diseases are included. Several articles have quantified these differences, progressively including more health outcomes in the model. A recent study assessing the influence of non-cervical HPV-associated diseases on the ICERs calculated for HPV vaccination concluded that the mean ICERs were 2.85 times more favourable for female-only vaccination and 3.89 times more favourable for universal vaccination when other HPV-related diseases are included.[84] One study in Canada evaluated the potential cost-effectiveness of HPV vaccination for boys aged 12 in relation to the prevention of oropharyngeal cancer.[85] The authors concluded that 4-valent HPV vaccination in males for the prevention of HPV-related oropharyngeal cancer could result in QALY gains and cost savings as compared to no vaccination.

9. Conclusions

Based on the above analysis, HPV vaccination of preadolescent girls emerges as a very cost-effective strategy to reduce the health and economic burden of HPV-related diseases. The greatest impact would be obtained by routinely vaccinating preadolescent girls prior to their becoming sexually active, where high coverage is necessary to achieve substantial herd effects. The vaccination of catch-up cohorts would accelerate the observed health benefits, although cost-effectiveness becomes less favourable as age at vaccination increases. However, coverage of female-only vaccination has been suboptimal in many settings. Good female coverage

provides protective effects to heterosexual men. Thus, including men in HPV vaccination programmes would ensure equity in protection from HPV-associated disease both for men and women, and would extend the benefits to MSM who do not benefit from the herd effects of female-only vaccination. This would make MSM population a potential additional target for routine HPV vaccination, given that this has been proven cost-effective. However, the feasibility of this strategy is questionable, since early identification of this specific population is difficult. Therefore, universal vaccination might be the only way to protect all men, rather than relying on the benefits of herd protection.

However, the cost-effectiveness of most of these strategies depends on vaccine cost and other vaccine and model assumptions. Vaccine price is the most decisive factor. Indeed, the lower the price, the greater the likelihood that vaccinating groups other than the primary target would be considered cost-effective in relation to alternative uses of healthcare resources. Based on the simulation models, the inclusion of all HPV-related outcomes, reduced dosing schedules and the new generation of HPV vaccines into the current vaccination scenario, as well as lower vaccine prices, is expected to boost cost-effectiveness, which may contribute to greater financial support for massive universal HPV vaccination programmes by governments.

Mathematical models will continue to be used in the future to address important health policy issues that cannot be to explored through experimental studies. These models are especially useful to determine which of a set of strategies is good value for money. The model-building process is important and labour-intensive. Modellers should make the structure and content of the model transparent to researchers and health decision-makers, as well as test the assumptions using sensitivity analyses and model validation. As in all research, simulation models can sometimes produce inaccurate results and can need to be repeated as and when more data becomes available. However, rigorous and reliable results can undoubtedly help make informed decisions about healthcare practices and resource allocation.

Conflict of interest

MD, SdS, FXB, and LB declare no competing personal or financial interests in relation to this manuscript. SdS and FXB (Personal support): Travel grants to conferences, symposia and/or meetings were occasionally granted by GlaxoSmithKline, Sanofi Pasteur MSD or Qiagen. MD and LB (Institutional support): HPV vaccine trials and epidemiological studies were sponsored by GlaxoSmithKline (GSK), Merck, Roche and Sanofi Pasteur MSD.

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