Economic evaluation of vaccination: capturing the full benefits, with an application to human papillomavirus

T. Bärnighausen1,2, D. E. Bloom1, E. T. Cafiero1 and J. C. O’Brien1
1) Department of Global Health and Population, Harvard School of Public Health, Boston, MA, USA and 2) Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Mtubatuba, South Africa

Abstract

Vaccination has been among the greatest contributors to the past century’s dramatic improvements in health and life expectancy. Recent advances in vaccinology have resulted in new vaccines that will likely lead to substantial future health gains. However, the high cost of these new vaccines, such as the human papillomavirus (HPV) vaccine, poses an obstacle to their widespread adoption in many countries. Economic evaluation can help to determine if investment in vaccine introduction is worthwhile. However, existing economic evaluations usually focus on a narrow set of vaccination-mediated benefits—most notably avoided medical-care costs—and fail to account for several categories of potentially important gains. We consider three sources of such benefit and discuss them with respect to HPV vaccination: (i) outcome-related productivity gains, (ii) behaviour-related productivity gains, and (iii) externalities. We also highlight that HPV vaccination protects against more than just cervical cancer and that these other health gains should be taken into account. Failing to account for these broader benefits of HPV vaccination could result in substantial underestimation of the value of HPV vaccination, thereby leading to ill-founded decisions regarding its introduction into national immunization programmes.

Keywords: Benefit–cost analysis, economic evaluation, economics, externalities, human papillomavirus vaccine, vaccination

Introduction

Vaccination has been among the greatest contributors to the past century’s dramatic improvements in health and life expectancy. The start of the World Health Organization’s (WHO) Expanded Programme on Immunization (EPI) in 1974 played a key role in this success. The EPI aimed to improve worldwide vaccination coverage [1,2] and established standard immunization policies and schedules that helped to guide national immunization programmes worldwide [3]. The original EPI schedule contained six vaccines, including diphtheria–tetanus–pertussis vaccine, measles-containing vaccine, polio vaccine and bacillus Calmette–Guérin vaccine. Some countries have since updated their EPI schedules to include vaccines that protect against Haemophilus influenzae type b, yellow fever, hepatitis B and other infectious diseases.

In recent years, a number of new vaccines such as the pneumococcal conjugate vaccine and the human papillomavirus (HPV) vaccine have come onto the market. Compared with the original EPI vaccines, these new vaccines are more costly, partly as the result of their complex, patent-protected technologies, such as recombination techniques, carrier proteins and adjuvants [4,5]. In addition, recent analyses suggest that increased regulatory oversight is another factor driving up the price of new vaccines [6,7]. As Table 1 shows, the per-dose prices of pneumococcal conjugate and HPV vaccines are each more than five times that of diphtheria–tetanus–pertussis.

For today’s policymakers facing tight healthcare budget constraints, economic evaluation could help to determine whether new vaccines should be added to national immunization programmes [10]. Indeed, national policymakers and international organizations commonly use the results of economic evaluation to inform spending decisions on vaccination programmes:
Bärnighausen et al. The full benefits of vaccination

TABLE 1. New vaccines are priced higher than original Expanded Programme on Immunization vaccines: US vaccine prices for 2012

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Year of licensure</th>
<th>Price per dose</th>
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<tbody>
<tr>
<td>DTP vaccine</td>
<td>Mid-1940s</td>
<td>US$ 20.96</td>
</tr>
<tr>
<td>Pneumo vaccine</td>
<td>2000</td>
<td>US$ 120.95</td>
</tr>
<tr>
<td>HPV vaccine</td>
<td>2006</td>
<td>US$ 130.27 (quadrivalent)</td>
</tr>
<tr>
<td>HPV vaccine</td>
<td></td>
<td>US$ 128.75 (bivalent)</td>
</tr>
</tbody>
</table>

DTP, diphtheria-tetanus-pertussis (acellular pertussis vaccine); Pneumo, pneumococcal conjugate; HPV, human papillomavirus. Source: [8,9].

*Prices refer to the private sector price per dose, as reported by manufacturers to the US Centres for Disease Control and Prevention.

- The United States’ Advisory Committee on Immunization Practices (ACIP) offers guidance on vaccine adoption and delivery. Its governing charter states that ‘when considering recommendations for use of a vaccine, ACIP members’ deliberations should include consideration of vaccine efficacy as well as cost:benefit and risk:benefit analyses’ [11].
- The United Kingdom’s National Institute for Health and Clinical Excellence is charged with supporting healthcare-related decisions, including vaccine introduction status, through economic evaluation [12].
- The GAVI Alliance, the international public–private partnership charged with ‘[s]aving children’s lives and protecting people’s health by increasing immunization in poor countries’ [13], uses economic evaluation to inform spending and project-planning activities [14,15].

There are different approaches to economic evaluation and it is essential to understand—both conceptually and in practice—the scope and properties of each, because these could affect results and their interpretation [16]. In this paper, we discuss two important aspects of economic evaluation of vaccination: the breadth and the measurement of the benefits that are accounted for in the analysis. We first introduce a general framework to account for a full range of vaccination benefits. We then apply the general framework to HPV vaccination to argue that economic evaluation of HPV vaccination should include a far broader set of vaccination benefits than is currently standard practice.

**Broadening the Scope of Benefits in Evaluating Vaccines**

Existing economic evaluations of vaccination usually adopt a narrow perspective that incorporates benefits closely linked to the healthcare sector, such as health gains and averted medical spending. Broader vaccination benefits are usually overlooked in these analyses [16,17]. This is a potentially significant oversight insofar as recent studies show that population health affects economic development through a number of pathways. For example, healthier people tend to be physically stronger and so able to work longer and harder [18,19]. Healthier children and young adults are more likely to attend and progress through school [20–22]. Higher levels of education imply higher economic productivity because education improves people’s ability to execute complex tasks effectively and efficiently. In addition, in populations with lower child mortality and longer life expectancy, families tend to have fewer children and invest more in each child’s education, in turn boosting economic productivity when these children enter the labour market [23]. Finally, a healthy workforce also attracts foreign direct investment, which can be used to expand physical capital and infrastructure and introduce technology that enhances economic productivity [24].

How might we structure our thinking on both health and economic benefits in economic evaluations of vaccination? We would suggest a framework that takes a broad perspective and captures benefits that are commonly considered as well as benefits that are commonly neglected in economic evaluations of vaccination (Table 2). The latter category of benefits includes:

- **Outcome-related productivity gains.** These can result because many of the diseases that vaccinations prevent can lead to long-term physical, mental or cognitive changes, including paralysis, deafness or blindness [25]. Insofar as vaccine-preventable diseases can cause physical disability, impair cognitive development and reduce school attendance, they can result in decreased educational attainment and adult earnings [26–28].
- **Behaviour-related productivity gains.** These can result because many of the diseases that vaccinations prevent can lead to behaviours affecting productivity. For example, with increased child survival as a result of avoiding vaccine-preventable disease, a typical family will be able to achieve its desired number of children through fewer births [29–31]. Raising fewer children allows parents to invest more resources in each child, including spending that improves health and educational outcomes—and it enables more women to enter the labour force [31–34].
- **Externalities.** These include vaccination-related herd effects—whereby unvaccinated members of a community incur protection from disease through the vaccination of others [35,36]—and reductions in the development of drug resistance because vaccination prevents cases of a disease that are typically treated (and mistreated) with drugs to which pathogens can develop resistance [16].
Given the framework laid out in Table 2, benefit–cost analysis is a more natural approach to economic evaluation than cost-effectiveness analysis, even though the latter is more commonly used. Unlike cost-effectiveness analysis, which values a single health outcome in natural or composite units (e.g. averted cases or disability-adjusted life-years, respectively), benefit–cost analysis can incorporate multiple outcomes, and those outcomes can be both health-rooted and economically rooted because each is ultimately expressed in monetary units (note: cost-effectiveness analysis sometimes takes account of the economic benefits of an intervention by using them to offset costs). Using monetary units is useful not just for setting spending priorities within the health budget, but also for determining resource allocation across budget categories: by expressing health interventions in monetary terms, they can be compared with interventions in other budget categories (such as education) to rank them with respect to their return on investment.

Insofar as most existing economic evaluations of vaccination focus predominantly on the ‘narrow’ set of benefits identified in Table 2, it is possible that economists have significantly undervalued vaccinations—which may have resulted in ill-founded policy decisions regarding vaccine adoption. This possibility should encourage researchers to rework economic evaluations of vaccination, ensuring that all relevant benefits are taken into account. Revised results on the value of particular vaccinations could lead policymakers to revisit vaccination-related funding decisions.

### Applying the Broadened Framework: Examples

Is there evidence to support the assertion that economic evaluations of vaccination should be expanded beyond just ‘narrow’ benefits and costs?

A recent study examined the literature to identify which types of benefits and costs had been captured in existing benefit–cost analyses of *Haemophilus influenzae* type b vaccination [16]. None of the 11 articles reviewed accounted for behaviour-related productivity gains and only one article considered outcome-related productivity gains and externalities, even though it seems highly plausible that these benefits could be substantial [16].

The following studies by researchers at the Harvard School of Public Health empirically examined the magnitudes of broader benefits of childhood vaccinations.

One set of studies used data from Matlab, Bangladesh to examine the impact of vaccination on school attainment. An analysis exploring the impact of maternal tetanus vaccination on schooling outcomes in children showed that there were significant schooling gains among children whose mothers had been vaccinated relative to children whose mothers had not been vaccinated [27]. Another analysis showed that age-appropriate measles vaccination as a child increased the probability of school enrolment by 9.5% among boys; no such impact was seen for girls [38].

Another study evaluated a preliminary GAVI vaccination programme that aimed to extend the use of new and underused childhood vaccines to 75 low-income countries during 2005–20 [39]. This study accounted for productivity-related effects of vaccinations resulting from improvements in health and estimated the return on investment in the GAVI immunization programme to be 12% by 2005, rising to 18% by 2020. These estimates were conservative, however, insofar as they accounted for outcome-related productivity gains only, and did not take other categories of benefit into account.

Yet another study used data from the Cebu Longitudinal Health and Nutrition Survey in the Philippines to examine the impact of traditional EPI vaccines on cognitive gains, as measured by language, mathematics and intelligence test scores [26,39]. Using international evidence to translate test score gains into earnings gains as adults, an early version of the paper cited in [26] estimated the return on investment in vaccination spending to be 21% [40]. This result was...
conservative in that it reflected only a few of the possible benefits of vaccination—cognitive gains and a subset of outcome-related productivity gains—and did not capture other categories of benefit.

In both the GAVI and Cebu studies, the estimated returns on investment in vaccination programmes compared favourably with estimated returns on investment in primary education [41], which is commonly considered to be one of the most potent instruments of economic development [42].

Applying the Broadened Framework to Human Papillomavirus Vaccination

Human papillomavirus (HPV) is a sexually transmitted virus affecting both women and men [43]. Oncogenic (‘high-risk’) types can cause various cancers. Non-oncogenic (‘low-risk’) types are responsible for genital warts and, rarely, recurrent respiratory papillomatosis (Fig. 1). In 2006, two vaccines that protect against HPV entered the market: Cervarix®, a bivalent vaccine that protects against HPV types 16 and 18; and Gardasil®, a quadrivalent vaccine that protects against types 6, 11, 16 and 18. The vaccines were initially licensed for the prevention of HPV type 16/18-related cervical pre-cancers and cancer only [8]; in addition, Gardasil was also licensed for the prevention of HPV type 6/11-related genital warts. Since then, Gardasil has also been licensed for protection against HPV type 16/18-related anal, vaginal and vulvar pre-cancers and cancers [44,45].

Although <80% of all HPV-related cancer cases occur in the developing world (Table 3) [37,43,46,47], few countries have introduced the HPV vaccine into national immunization programmes, owing, at least in part, to the relatively high price of the vaccine [48]; see Table 1.

Deepening our understanding of the benefits of HPV vaccination would require attention to several key categories of benefit in the conceptual framework.

First, an economic evaluation of HPV vaccination should account for benefit categories that are typically neglected in economic evaluations, such as outcome-related productivity gains. Patients with HPV-related cancers must sometimes withdraw from the workforce temporarily or permanently, resulting in lost productivity and income. For example, in countries like the Congo, age-specific incidence and mortality owing to cervical cancer are greatest at ages when the majority of women are economically active (Fig. 2). This suggests that withdrawal from the workforce could hurt productivity at both the household and national levels. For anal

FIG. 1. Taxonomy of human papillomavirus (HPV) infection. Source: [43].

TABLE 3. Developing countries carry the brunt of human papillomavirus (HPV)-related cancers: global data for 2002*
cancer, 2003 data from the USA show that men and women experience 21.8 and 19.97 years of productive life lost, respectively, for each anal-cancer-related death [49]. The lost productivity associated with these deaths was valued at US$ 580 292 and US$ 333 246 per case, respectively. Economic evaluations of HPV vaccination must therefore account for averted lost income that might otherwise result from HPV-related disease.

Second, given that many HPV-related cancers strike during late adulthood, an economic evaluation of HPV vaccination should account for behaviour-related productivity gains. For example, household-level behaviour changes such as reductions in daily food consumption were reported by patients receiving treatment for cervical cancer in Argentina [52]. In addition, a portion of these households reported a variety of education-related impacts, including school absences and difficulty paying for school. Studies show that health and educational losses as a child tend to diminish productivity and earnings as an adult. Although it is possible that the behavioural effects could be negative as well, for example if HPV vaccination increases high-risk behaviour, this has not been reported in settings where the HPV vaccine has been introduced [53,54].

Third, the framework should account for externalities, including herd effects [35]. Given the sexually transmitted nature of HPV, herd effects could theoretically be realized in two ways: by vaccinating both males and females, who would confer protection directly to their unvaccinated sexual partners; or by vaccinating just females, which would then reduce transmission to their subsequent, unvaccinated male partners [55], and so on. Whereas mathematical models have predicted the impact of herd effects from HPV vaccination [56], recent data from Australia suggest a 44% decline in the incidence of male genital warts as a result of female HPV vaccination [57]. This finding confirms that there could be significant herd effects resulting from HPV vaccination. Acknowledging that the health and economic benefits of HPV vaccination could extend to unvaccinated members of the population should encourage researchers to account for these gains in economic evaluation.

Finally, the framework must account for all economically meaningful clinical endpoints (not to mention side-effects, which should also be taken into account). Whereas many vaccines target a single endpoint, HPV vaccination can protect against multiple endpoints (see Fig. 1). Many existing economic evaluations of HPV vaccination focus solely on averted cases of cervical cancer [48,58,59], and so are likely to underestimate the true value of vaccination. For example, data from the USA show that while cervical cancer is the most costly HPV-related cancer to treat (US$ 146.4 million annually; see Table 4), the costs to treat other HPV-related cancers, which are usually ignored in economic evaluation, are substantial. Anal cancer, of which roughly 90% is caused by HPV (Table 3), is estimated to cost US$ 65.5 million to treat per year. Treating vaginal and vulvar cancers, of which roughly 40% is caused by HPV, costs c. US$ 30 million annually [46,60]. While the percentages and exact types of HPV responsible for each clinical endpoint may vary by country, these data suggest that failing to include clinical endpoints beyond just cervical cancer will result in substantial underestimates of the value of HPV vaccination.

**Conclusion**

Previous economic evaluations of relatively new vaccinations have largely focused on a ‘narrow’ set of benefit categories [61–64]—a practice that has probably led to substantial underestimates of the value of vaccination. Future studies and economic evaluations of HPV vaccination should adopt a perspective that includes outcome-related productivity gains, behaviour-related productivity gains and externalities. In addition, the new perspective should be applied to a com-

**TABLE 4.** HPV-related diseases pose a high fiscal cost: economic burden of HPV-related disease in the USA in 2008

<table>
<thead>
<tr>
<th></th>
<th>Cervical cancer</th>
<th>Anal cancer</th>
<th>Oropharynx cancer</th>
<th>Penile cancer</th>
<th>Vaginal cancer</th>
<th>Vulvar cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>US$ (millions)</td>
<td>146.4</td>
<td>65.5</td>
<td>153.1</td>
<td>4.5</td>
<td>7.9</td>
<td>20.8</td>
</tr>
</tbody>
</table>

Source: [60].
prehensive set of clinical endpoints. In addition to broader benefits, any comprehensive economic evaluation must also account for related costs, including systems and non-systems components, which have been discussed elsewhere [16]. Moreover, some economic evaluations may value vaccination against alternative strategies; in the case of HPV vaccination, for example, economists may look at the benefits and costs of a vaccination programme relative to maintaining or strengthening an existing cervical cancer screening programme. Given that many countries are struggling to finance the inclusion of HPV vaccine into national immunization programmes, such economic evaluations are urgently needed to ensure that policymakers have information that is sufficiently accurate and relevant to reach well-founded decisions.

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Conflict of interests

The authors declare no conflicts of interest.

References