# The Economic Case for Expanding Vaccination Coverage of Children*

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**Abstract**

While childhood vaccination programs, such as WHO's Expanded Program on Immunization, have had a dramatic impact on child morbidity and mortality worldwide, lack of coverage with several existing vaccines is responsible for large numbers of child deaths each year, mostly in developing countries. According to WHO estimates, increased coverage of three vaccines alone – pneumococcal conjugate vaccine (PCV), rotavirus vaccine (Rota), and *Haemophilus influenzae* type b (Hib) vaccine – could have prevented one and a half million deaths in children under five years in 2002. In deciding whether to implement interventions to expand vaccination coverage policy makers often consider economic evaluations. Past evaluations, however, have usually ignored both important vaccination benefits and potentially large cost reductions in vaccination delivery. We demonstrate for the example of benefit-cost analysis (BCA) of the Hib vaccination that past studies have mostly taken narrow evaluation perspectives, focusing on health gains, health care cost savings, and reductions in the time costs that parents incur when taking care of sick children, while ignoring other benefits, in particular, outcome-related productivity gains (Hib vaccination can prevent permanent mental and physical disabilities) behavior-related productivity gains (reductions in child mortality due to Hib can trigger changes in fertility which in turn may stimulate economic growth) and community externalities (Hib vaccination can prevent the development of antibiotic resistance and reduce the risk of Hib infections in unvaccinated persons). We further show that the costs of Hib vaccine delivery can be reduced if the monovalent Hib vaccine is replaced by combination vaccines. Such cost reductions have usually been ignored in CBA of Hib. Our analysis thus suggests that past BCAs are likely to have substantially underestimated the value of Hib vaccination, even though most have found it to be cost-beneficial. Unless future BCAs of childhood vaccinations take full account of benefits and costs, policy makers may lack sufficient information to make the right decisions on vaccination interventions.

## Recent history of childhood vaccination

Childhood vaccination programs have had a dramatic impact on child morbidity and mortality worldwide. A universal effort to extend vaccination coverage to all children began in 1974, when the World Health Organization (WHO) founded the Expanded Program on Immunization (EPI). This initiative helped countries establish the infrastructure needed to deliver a standard vaccination package (original EPI in Table 1), which in 1974 included the vaccine against diphtheria-tetanus-pertussis (DTP), measles-containing vaccine (MCV), polio vaccine (Pol), and Bacillus Calmette-Guérin (BCG) vaccine. Over time, additional vaccines have been added to national EPI packages in some countries (later-stage EPI in Table 1), including those against *Haemophilus influenzae* type b (Hib) infection, yellow fever, and hepatitis B (Halsey & Galazka, 1985).

Despite the longstanding availability of EPI vaccines and national health policies aiming at universal or near universal coverage (WHO, 1974), actual coverage is widely incomplete. For instance, Lim et al. (2008) estimated that, in 2006, 26% of children younger than one year of age worldwide had not received the third dose of the DTP vaccination series (DTP3) (Lim, Stein, Charrow, & Murray, 2008). DTP3 is commonly used as an indicator to assess the performance of national vaccination systems because it captures a system's capacity to repeatedly vaccinate the same individual and to record vaccination doses and because DTP is included in most routine vaccination schedules worldwide. The lack of DTP3 coverage thus suggests that vaccination systems are not reaching millions of children (Lim et al., 2008).

Incomplete vaccination coverage, in turn, leads to large numbers of avoidable child deaths. Currently, the three vaccine-preventable diseases responsible for the highest mortality burdens in children are pneumococcal disease, rotavirus infection, and Hib infection, which in 2002 were responsible, respectively, for 716,000, 402,000, and 386,000 deaths in children under five years of age (WHO, 2003). Those children who do not die from vaccine-preventable diseases may

suffer debilitating sequelae. For example, Hib infection and pneumococcal disease can cause bacterial meningitis, which may lead to severe neurological conditions such as deafness, blindness, or intellectual impairment. Rotavirus infection can lead to malnutrition in early childhood, potentially resulting in stunted height. Vaccination against these diseases, therefore, can avert both death and impairment.

## Table 1: Vaccination data summary

| | Vaccine* | Vaccination coverage† (1999) (WHO, 2008b) | Vaccination coverage† (2007) (WHO, 2008b) | Number of deaths worldwide in children under five years due to vaccine-preventable diseases |
|---|---|---|---|---|
| **Original EPI** | Diphtheria-tetanus-pertussis vaccine (DTP3) | 72% | 81% | 5,000 diphtheria (2002) (WHO, 2009a)<br>294,000 pertussis, (2002) (WHO, 2009b)<br>18,000 non-neonatal tetanus (2002) (WHO, 2009b) |
| | Measles-containing vaccine (MCV) | 71% | 82% | 217,000 (2006) (WHO, 2008b) |
| | Polio vaccine (Polio3) | 73% | 82% | |
| | Bacillus Calmette-Guérin vaccine (BCG) | 79% | 89% | |
| **Later-stage EPI** | *Haemophilus influenzae* type b vaccine (Hib3) | 8% | 26% | 386,000 (2002) (WHO, 2009b) |
| | Yellow fever vaccine (YF) | 21% | 51% | 15,000 (2002) (WHO, 2008b) |
| | Hepatitis B vaccine (HepB3) | 18% | 65% | |
| **New vaccines** | Rotavirus vaccine (Rota2, Rota3) | Not yet introduced in most developing countries | | 402,000 (2002) (WHO, 2008b) |
| | Pneumococcal conjugate vaccine (PCV3) | Not yet introduced in most developing countries | | 716,000 (2002) (WHO, 2009b) |

*In this column, we show the name of each vaccine and the abbreviation used to denote the last dose of the vaccine in the full vaccination series (excluding booster doses), i.e. DTP3 = third dose of diphtheria-tetanus-pertussis vaccine, MCV = first dose of measles-containing vaccine, Polio3 = third dose of polio vaccine, BCG = first dose of Bacillus Calmette-Guérin vaccine, Hib3 = third dose of *Haemophilus influenzae* type b vaccine, YF = first dose of yellow fever vaccine, HepB3 = third dose of hepatitis B vaccine, Rota2 = second dose of rotavirus vaccine (Rotarix®), Rota3 = third dose of rotavirus vaccine (RotaTeq®), PCV 3 = third dose of pneumococcal conjugate vaccine.

†Vaccination coverage is the average coverage with the last dose of the full vaccination series across the WHO Member States. It is expressed as a percentage of the target population. While the "target population varies depending on the countries' policies", in "most instances the target population is the number of children surviving their first year of life" (WHO, 2008b).

In deciding whether to finance a health care intervention, decision makers commonly consider not only the effects of the intervention but also the costs. Cost-effectiveness analyses (CEA) and benefit-cost analyses (BCAs) are the most common approaches to systematically compare the costs and effects of health care interventions. CEA evaluates the health effectiveness of an intervention (measured in a common unit, e.g., life-years or quality-adjusted life-years) relative to the costs (measured in monetary units), while BCA compares monetary measures of intervention benefits to costs. Below, we argue that economic evaluations of vaccination have traditionally adopted a *narrow perspective*, considering only some categories of vaccination effects, while disregarding others, and have failed to take into account changes in vaccine costs that can be achieved by combining several vaccines into a single delivery system.

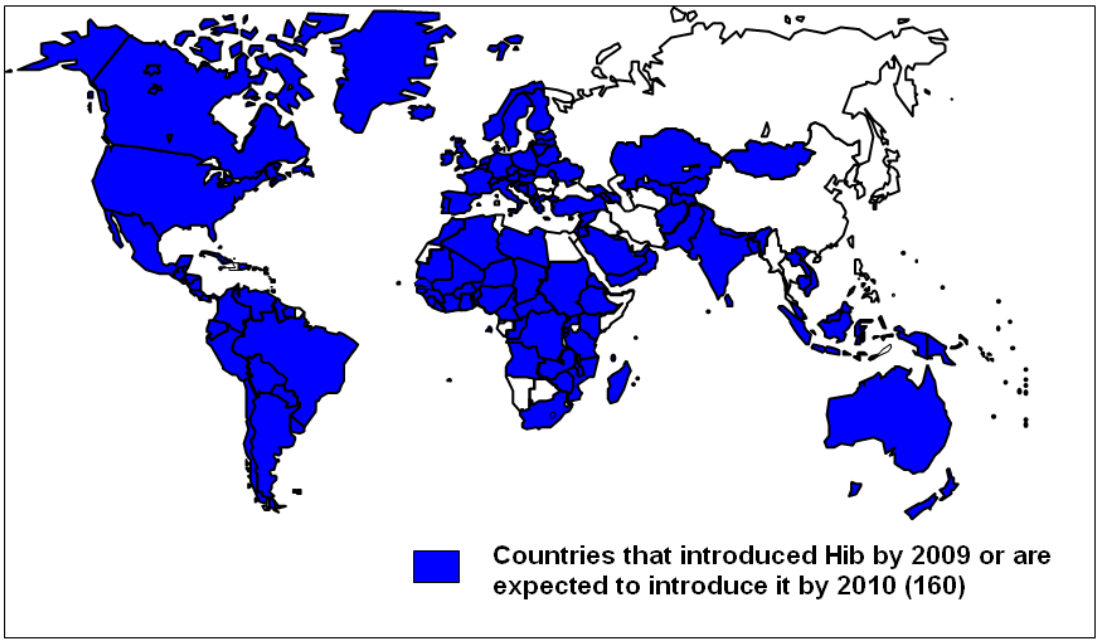
Such a narrow perspective can lead to an underestimation of the benefits of a vaccination and to an overestimation of its costs, resulting in wrong decisions on vaccination roll-out. A broad perspective in BCA, CEA, or other types of economic evaluation of vaccinations should thus replace the narrow perspective. We have chosen the Hib vaccine as an example to make this case. While the Hib vaccination has been introduced into national schedules in most countries worldwide, with a global coverage of merely 26%, it has the lowest coverage of those vaccinations that are commonly included in EPI (Table 1) (WHO, 2008b). It is also among the vaccinations that could prevent the largest number of deaths in children under five years of age. Unlike the two other vaccines that could, on their own, prevent even larger numbers of deaths in children in this age group – the vaccine against pneumococcal disease (which could prevent 716,000 deaths annually) or rotavirus infection (which could prevent 402,000 deaths annually) – Hib vaccine can be combined with the DTP vaccine and delivered as a multivalent formulation in a single injection (DTP-Hib). Vaccination with DTP-Hib could prevent 703,000 deaths annually, i.e., more deaths than the rotavirus

vaccination and approximately the same number of deaths as the pneumococcal vaccination.

### The *Haemophilus influenza*e type b vaccine

Infection with Hib can give rise to different diseases and disease sequelae. Non-invasive Hib infection occurs when the bacteria enter a non-sterile liquid, e.g., the lungs or the nasal passages. Such infections can cause pneumonia, particularly in infants and children. Invasive disease involves penetration by the bacteria of a sterile liquid such as the blood or cerebrospinal fluid, which can lead to bacteremia or acute bacterial meningitis, respectively. The highest rates of Hib-related morbidity and mortality are associated with invasive Hib disease. In 1985, a polysaccharide vaccine against Hib was licensed in the United States. However, the vaccine displayed limited immunogenicity among children under two years of age and was not effective in reducing the incidence of infection. It was later removed from the market. In 1987, the United States licensed a protein-conjugated Hib vaccine with high efficacy among children under two years of age (WHO, 2008a). One-hundred and sixty countries either introduced the Hib vaccine by 2009 or are expected to introduce it by 2010 (Figure 1) (Anonymous, 2009b).

**Figure 1: Countries offering Hib vaccine through national vaccination programs**




Source: (Anonymous, 2009b)

Many studies have demonstrated the success of the Hib conjugate vaccine in reducing child morbidity and mortality. For instance, following routine use of the Hib conjugate vaccine in the US since 1990, the national incidence of invasive Hib disease decreased from pre-vaccination levels of 41 per 100,000 per year (in 1987) to approximately 1 case per 100,000 children per year (in 1997) (Anonymous, 1998). A 2006 study in Kenya showed that the vaccination reduced the incidence of Hib disease by 88% within three years and prevented approximately 3,370 Kenyan children from being hospitalized in 2005 (Cowgill, Ndiritu, Nyiro, Slack, Chiphatsi, Ismail et al., 2006). A 2007 study in Bangladesh found that routine Hib vaccination of infants could prevent over one third of Hib pneumonia cases and approximately 90% of meningitis cases (Baqui, El Arifeen, Saha, Persson, Zaman, Gessner et al., 2007). A 2008 study in Uganda estimated that within four years of introduction of the Hib vaccine into the national vaccination program, the incidence of Hib meningitis declined by 85%. By the fifth year after introduction the number of cases had fallen to nearly zero (Lee,

Lewis, Makumbi, Kekitiinwa, Ediamu, Bazibu et al., 2008). These studies suggest that the Hib vaccine is highly effective at reducing Hib-related morbidity and mortality in a variety of settings.

**Benefit-cost analysis of Hib vaccination**

We performed a comprehensive literature review of BCAs of Hib vaccination in order to assess which benefits and costs have been taken into account in past studies. We chose to review the literature on BCA rather than CEA because our argument that economic evaluations of vaccination have traditionally accounted for too narrow a set of benefits focuses on both health and non-health benefits. Non-health benefits of vaccinations can be easily incorporated in BCA since all benefits are measured in monetary units. CEA of vaccinations, on the other hand, measure the health benefits (or effects) in natural units, so that non-health benefits cannot be added to the benefits side of the analysis. Thus, BCA is the more natural evaluation framework to demonstrate one of our main points. Nevertheless, it is theoretically possible to account for those non-health benefits that have often been neglected in economic evaluations of vaccinations in a CEA by expressing them as cost savings and incorporating these savings into the cost side of the analysis.

We searched medical, economic, and general literature databases (EconLit (Anonymous, 2009a), PubMed (Anonymous, 2009d), Science Citation Index Expanded (Anonymous, 2009e), and JSTOR (Anonymous, 2009c)) in order to identify BCAs that evaluate Hib vaccination at the national or subnational level. In our search, we found 62 distinct economic evaluation studies of Hib vaccination published from January 1985 through March 2009. After excluding all studies that did not use BCA as an evaluation approach or reported only regional results, 11 studies remained in our final selection for review (see below).

## Rethinking the benefits of vaccination

BCAs of vaccination programs have usually focused on gains in health, health care costs, and the time costs of parents taking care of their sick children. However, a new understanding of the linkages between health and wealth, and of vaccine-related externalities, suggests that this understanding of vaccine-related benefits is incomplete and neglects a number of long-term individual- and population-level gains. Approaching BCA of vaccination from a broad perspective that accounts for these additional gains invites a new and more comprehensive conceptualization of the benefits of vaccination. Table 2 outlines this approach and illustrates its application for Hib vaccination.

## Table 2: Types of benefits in economic evaluations of vaccinations

| Perspective | | Benefit categories | Definition | Hib-specific examples |
|---|---|---|---|---|
| Broad | Narrow | Health gains | Reduction in mortality through vaccination[2] | Hundreds of thousands of children die each year from Hib disease (WHO, 2009b). |
| | | Health care cost savings | Savings of medical expenditures because vaccination prevents illness episodes | Hib diseases lead to substantial health care costs (Akumu, 2007; Gessner, 2008; F. Zhou, Jeanne Santoli, Mark L. Messonnier, Hussain R. Yusuf, Abigail Shefer, Susan Y. Chu, Lance Rodewald, Rafael Harpaz, 2005). |
| | | Care-related productivity gains | Savings of parents' productive time because vaccination avoids the need for taking care of a sick child | Parental care of children suffering from Hib disease can contribute to the overall cost of the disease (Ginsberg, Kassis, & Dagan, 1993). |
| | | Outcome-related productivity gains | Increased productivity because vaccination improves cognition, physical strength, and school attainment | Hib meningitis is relatively common (WHO, 2008a), and Hib meningitis "leaves 15 to 35% of survivors with permanent disabilities such as mental retardation or deafness", severely reducing cognition (WHO, 2005). |
| | | Behavior-related productivity gains | Benefits accruing because vaccination improves child health and survival and thereby changes household behavior | Hundreds of thousands of children die each year from Hib disease (WHO, 2008a). |
| | | Community externalities | Benefits accruing because vaccination improves outcomes in unvaccinated community members | Hib infections are treated with antibiotics, leading to the development of resistance (Elbasha, 2003).<br>Hib vaccinations can protect unvaccinated individuals through herd effects (Stephens, 2008). |

Source: (Bärnighausen et al., 2008)

[2] The denominator of the cost-effectiveness ratio in CEA is either a measure of mortality (e.g. number of life-years saved), morbidity (e.g. cases of meningitis averted) or mortality and morbidity (e.g. number of disability-adjusted life-years saved). Thus, for CEA the benefits considered in the narrow-perspective category "health gains" should be defined as "reduction in mortality or morbidity through vaccination" (Bärnighausen, Bloom, Canning, & O'Brien, 2008). Outcome-related productivity gains due to reductions in morbidity could be incorporated separately in the denominator of the cost-effectiveness ratio, but are commonly ignored. In contrast, in BCAs "health gains" in terms of the value of saved life-years are commonly considered (for example, in 9 out of 11 studies in Table 3), while morbidity reductions are rarely included in the valuation (for example, in only 1 out of the 11 studies in Table 3). If morbidity reductions are included in BCA, they are usually valued as outcome-related productivity gains. Since the focus of this paper is on BCA, we assign mortality reductions, but not morbidity reductions, to the category "health gains".

Categories of vaccination benefits that are usually ignored in economic evaluation studies of vaccinations, such as Hib vaccination, include outcome-related productivity gains, behavior-related productivity gains, and community externalities (see Table 2 for definitions of these types of benefits). Below, we describe examples in these three benefit categories for Hib vaccination.

*Outcome-related productivity gains*

Childhood vaccinations may result in outcome-related productivity gains (Bärnighausen et al., 2008) because they protect children's physical health and ability to achieve their full cognitive potential. Children who are physically and cognitively healthy are more likely to attend school and to attain high education levels; adults who are physically healthy and well educated can work more and more productively (see Bloom and Canning (2009) for a review of the literature on the relationships between health, cognitive development, education, and labor productivity (D. E. Bloom & Canning, 2009)). Hib vaccination can avert long-term neurological sequelae of Hib infection, such as blindness, deafness, mental retardation, epilepsy, and paralysis (WHO, 2005). Such sequelae can severely affect a child's ability to attend school and to learn. For example, a longitudinal study in Australia comparing outcomes in adolescents who survived a bout of bacterial meningitis, such as Hib meningitis, to outcomes in controls who did not suffer from meningitis revealed "substantial excess risk of intellectual, cognitive, and auditory impairment" and "[c]ontinuing developmental problems of higher order language, organisation, problem solving, and central auditory function" in the meningitis survivors, resulting in lower educational achievement and higher risk of behavior disorders (Grimwood, Anderson, Anderson, Tan, & Nolan, 2000). As cognitive ability and educational achievements are related to labor productivity and income (Colclough, Kingdon, & Patrinos, 2008; Psacharopoulos & Patrinos, 2004), these findings suggest that the roll-out of a vaccination that protects against common causes of meningitis, such as Hib, can increase a country's

economic growth – a benefit that can potentially be measured and should be taken into account in BCA of vaccinations against Hib and other infections.

*Behavior-related productivity gains*

Broad-perspective economic analyses also account for gains in productivity that come about when vaccination effects change behavior. For instance, in areas with high child mortality rates, couples may choose to have more children in order to ensure the survival of a sufficient number of children who can work to support the family. As Hib vaccination can reduce child mortality, mothers of vaccinated children can achieve their target family size through fewer births. Having fewer children allows parents to invest more resources in each child, improving its nutrition, health, and educational attainment. These improvements, in turn, will increase a child's labor productivity as an adult.

At the population level, reductions in fertility rates will decrease the number of youth dependents relative to the size of the adult labor force, because fewer children are born and more women can participate in the labor market. A larger share of working-age individuals supporting a smaller number of children can lead to increased savings. The additional savings can be used to invest in physical and human capital, stimulating economic growth. Research suggests that this phenomenon of rising shares of working-age people leading to increases in the rate of economic growth (the so-called demographic dividend (D. Bloom, Canning, & Sevilla, 2003)) contributed substantially to economic development in the Republic of Ireland (D. Bloom & Canning, 2003) and several East Asian nations during the 1990s (D. Bloom, Canning, & Malaney, 2000; D. Bloom & Williamson, 1998).

*Community externalities*

In addition to outcome- and behavior-related productivity gains, community externalities are also typically overlooked in economic analyses of vaccination. In the case of Hib vaccination, these include herd effects and reductions in antibiotic resistance. Herd effects refer to the reduction in an unvaccinated

person's risk of contracting a disease due to the vaccination of another person. For instance, a study of Navajo Indians in the US found that children under two years of age who lived in communities where 20-39% and 40-59% had received at least one dose of Hib vaccine had, respectively, a 56.5% and 73.2% lower risk of invasive Hib disease than their peers who lived in communities with 0-19% Hib vaccination coverage, independent of their own Hib vaccination status (Moulton, Chung, Croll, Reid, Weatherholtz, & Santosham, 2000). Herd effects will be especially significant in countries where large proportions of the unvaccinated population are at increased risk of contracting a vaccine-preventable infection and developing severe forms of the disease, for instance, because of old age or HIV infection.

Vaccinations can lead to another type of community externality by avoiding the development of antibiotic resistance. Many bacterial infections, including Hib infection, are treated using antibiotics. The probability of antibiotic resistance increases with the number of patients treated with an antibiotic. In the case of Hib, infections with strains that are resistant to first-line antibiotics can be treated with second- and third-line antibiotics. However, these later-stage drugs may not be available in some settings and are far more costly than their first-line counterparts (Saha, Darmstadt, Baqui, Islam, Qazi, Islam et al., 2008). According to a recent study by Saha et al. (Saha et al., 2008), the proportion of cases of infection with Hib that are resistant to the first-line antibiotics ampicillin and chloramphenicol has risen to roughly 50%. Hib vaccination can prevent disease and thus obviate the need for antibiotic use, reducing the prevalence of antibiotic-resistant strains. This benefit is shared by communities, governments, and medical institutions, which might otherwise have to shoulder the morbidity burden, costs, and work load associated with treating antibiotic-resistant strains.

*Broadening the perspective on benefits in benefit-cost analysis of Hib vaccination*

Of the 11 studies we identified in our review as reporting results from BCA of Hib vaccination (Table 3), nine found a benefit-cost ratio (BCR) greater than one (or

positive net benefits). Two studies, one in South Korea (Shin, Shin, & Ki, 2008) and the other one in Chile (Lagos, Levine, Avendano, Horwitz, & Levine, 1998), found BCRs that were smaller than one. Overall, BCRs ranged from 0.12 to 8.39. These results seem to suggest that in some countries introducing the Hib vaccination into national vaccination schedules may not be cost-beneficial. Such a conclusion, however, may be wrong because none of the 11 reviewed studies included all broad-perspective benefits in the evaluation. In fact, while all 11 studies included the benefit category health care cost savings, nine the category health gains, and eight the category care-related productivity gains, only one study (Shin et al., 2008) took a broad-perspective benefit category into account in the analysis (outcome-related productivity gains). Thus, BCA that account for broad-perspective benefits in addition to those included under a narrow perspective (Table 2) would be expected to find BCR that are (even) more favorable than those shown in Table 3. For example, Levine et al. (1998) demonstrated in an analysis of infant vaccination with Hib in developing countries that the estimated health-related benefits of the vaccination increase when herd effects are taken into account (by 38%, measured in DALYS) (Levine, Schwartz, Pierce, & Kane, 1998).

Studies by Bloom, Canning, and Weston also used BCA to account for a wide array of vaccine-mediated benefits (D. Bloom, Canning, & Weston, 2005). Their investigation of the impact of the Global Alliance for Vaccines and Immunization (GAVI) program to expand coverage of new and underused vaccines, including Hib vaccine, used life tables to measure the contributions to countries' gross national products of children who, by virtue of vaccination, survive and enter the labor force as healthy workers. They estimated that the vaccination program would have a return on investment (ROI) of 18% by 2020.[3] In another analysis, Bloom, Canning, and Weston examined the ROI of a vaccination program (that

[3] Education – considered by many to be one of the most important means of economic development – has ROIs of similar magnitude (ranging from 19% for primary education to 11% for tertiary education) (Psacharopoulos & Patrinos, 2004).

did not include Hib vaccine) using cognitive testing data from the Philippines' Cebu Longitudinal Health and Nutritional Survey. Translating cognitive gains among vaccinated children into income values as adults, the ROI was 21%. These studies suggest that a proper accounting of the impact of vaccination requires an understanding of the broad scope of vaccine-mediated benefits. Ignoring the broad-perspective benefits of vaccination may lead to wrong decisions on vaccination roll-outs.

## Table 3: Cost-benefit analyses of Hib vaccination

| Study | Country | BCR or net benefits[†] | Assumed vaccination coverage | Types of benefits considered | Types of Hib diseases accounted for | Number of vaccine doses | Valency of vaccine formulation |
|---|---|---|---|---|---|---|---|
| (Asensi, Otero, Perez-Tamarit, Miranda, Pico, & Nieto, 1995) | Spain[††] | 2.4 - 5.1* | 100% | 1, 2 | Invasive disease | 3 | monovalent |
| (Garpenholt, Silfverdal, & Levin, 1998) | Sweden | Net benefits per child: 160 SEK | 99% | 1, 2, 3 | All | 3 | monovalent |
| (Ginsberg et al., 1993) | Israel | 1.45 | 88% | 1, 2, 3 | All | 4 | monovalent |
| (Jimenez, Guallar-Castillon, Rubio Terres, & Guallar, 1999) | Spain | 1.49 | 90% | 1, 2, 3 | Invasive disease | 4 | monovalent |
| (Lagos et al., 1998) | Chile | 0.12-1.10 | 100% | 2 | All | 3 | monovalent |
| (Levine, Ortiz, Contreras, Lagos, Vial, Misraji et al., 1993) | Chile[†††] | 1.66 | 87% | 2 | Invasive disease | 3 | monovalent |
| (Limcangco, Armour, Salole, & Taylor, 2001) | Philippines | 8.39* | 85% | 1, 2, 3 | Meningitis | 3 | monovalent |
| (Shin et al., 2008) | Korea | 0.77 | 90% | 1, 2, 3, 4 | All | 3 | monovalent |
| (Trollfors, 1994) | Sweden | 1.6 | 100% | 1, 2, 3 | Meningitis and acute epiglottis | 3 | monovalent |
| (Pokorn, Kopac, Neubauer, & Cizman, 2001) | Slovenia | 1.38 | 95% | 1, 2, 3 | Invasive disease | 3 | monovalent |
| (F. Zhou, Bisgard, Yusuf, Deuson, Bath, & Murphy, 2002) | USA | 5.4 | 93% | 1, 2, 3 | Invasive disease | 3, 4 | monovalent and multivalent |

1 = health gains, 2 = health care cost savings, 3 = care-related productivity gains, 4 = outcome-related productivity gains (see Table 2 for definitions of these types of benefits). BCR = Benefit-cost ratio.

*BCR was calculated using data provided in the publication. †When several BCRs were provided in the publication for different sets of benefits, we selected the BCR estimated for the largest set of benefits. If the BCR could not be calculated using data shown in the publication, we selected the net benefits as a summary measure of the BCA result. ††Analysis was conducted at a subnational level (Valencia). †††Analysis was conducted at a subnational level (Santiago). SEK = Swedish Kronor.

## Rethinking the costs of Hib vaccination

While narrow-perspective BCA of vaccination programs may underestimate the benefits of Hib vaccination, they may also overstate its costs by failing to account for savings that can occur when vaccines are combined and delivered in a single vial. Many of the vaccination costs commonly included in BCA – the costs of the vaccine serum, syringes, cold storage, and health worker time of administering the vaccination – can be reduced when, instead of delivering a vaccine in single, monovalent form, it is added to an existing vaccine formulation in a multivalent solution. The resulting reduction in cost can be particularly large if the vaccination antigen is added to a vial that contains DTP, which typically has the broadest coverage within the existing vaccination network.

For instance, the Hib vaccine can not only be delivered in monovalent form but also in combination with the trivalent DTP or the tetravalent DTP-HepB vaccine (i.e. as tetravalent DTP-Hib or pentavalent DTP-Hep-Hib vaccine, respectively). The pentavalent DTP-HepB-Hib vaccine is already being used in several countries and recommended for use by UNICEF, GAVI, and WHO (UNICEF, 2008; UNICEF & WHO, 2009). With one exception, all BCAs of the Hib vaccine identified in our review estimate the value of adding the monovalent vaccine to current national vaccination schedules (Table 3). However, the costs of adding the Hib vaccine in multivalent formulations to vaccines that are already delivered in the schedules will be lower than those of adding the monovalent formulation. Using the cheapest price estimates of DTP in the UNICEF/WHO 2009 *Immunization Summary* (UNICEF & WHO, 2009) and the cheapest price estimates of Hib, DTP-Hib, and DTP-HepB-Hib in the UNICEF *Vaccine Projections for 2009* (UNICEF, 2009), an added dose of monovalent Hib will cost US$ 3.4, while the addition of Hib in the tetravalent formulation DTP-Hib will cost

US$3.1, and the addition of Hib in the pentavalent DTP-Hep-Hib will cost US$ 2.8.[4]

Comparing the costs of phasing in a monovalent Hib vaccine with those of replacing DTP with a tetravalent or a pentavalent vaccine further requires consideration of the amount of hazardous waste generated, the volume of storage required, and differences in the time required to administer the vaccines. Disposing of biohazardous waste is very expensive, often requiring costly incinerators, which can be particularly burdensome for developing countries. However, the costs of improperly disposing of the syringes and vials used in vaccinations – which include the costs of infections, environmental degradation, and social opposition to vaccination – may be even larger.[5] Adding the Hib vaccination through use of the tetravalent or the pentavalent vaccination implies that no syringes would need to be used in addition to those already in use for the DTP or the DTP-HepB three-shot vaccination series (Agrawal, Singh, & Mahesh, 2004).

Nearly all vaccines must be transported and stored in temperature-controlled conditions known as the cold-chain storage network. This network constitutes a major implementation cost for all countries. Cold storage costs increase with vaccination volume. When using the lowest volume-per-dose estimate of Hib, DTP, DTP-Hib, and DTP-HepB-Hib listed in the WHO *Vaccine Volume Calculator* (WHO, 2009c), the addition of one dose of monovalent Hib requires storage room for 3.3 cubic centimeters ($cm^3$), while the addition of Hib in the tetravalent DTP-

[4] The price estimates are weighted average prices across countries eligible for funding through GAVI (UNICEF, 2009).

[5] For instance, WHO estimates for 2000 identify contaminated syringes and needles as the cause of 32% of all new hepatitis B infections, 40% of all new hepatitis C infections, and 5% of all new HIV infections, resulting in significant morbidity, mortality, and monetary costs for individuals and society. This is a particular issue in developing countries as few have established systems for managing sharps waste. In remote and rural areas of developing countries, the combination of poor road conditions and personnel reluctant to transport the unwieldy and hazardous waste contributes to inappropriate and unsafe disposal, often through shallow burial or open burning. Urban areas face similar problems because primary health clinics rarely have access to hospitals' incinerators and thus dispose of sharps in public waste sites—where rag pickers may come across them—or through open burning, which is often toxic (Program for Appropriate Technology in Health (PATH), 2006).

Hib requires no additional storage room and the addition of Hib in DTP-HepB-Hib requires storage room for 0.6 $cm^3$, i.e. the increase in cold chain costs will be substantially higher for monovalent Hib than for the addition of Hib in its multivalent formulations.

Finally, it is immediately apparent that health worker time to administer vaccinations will be shorter if fewer injections are required. Adding Hib in a multivalent formulation will thus be less time-consuming than adding it in its monovalent form.

A study of Ethiopia's national vaccination services shows the size of the savings that can be achieved by combining vaccines into a single vial. The study found that cold chain storage costs alone accounted for over 75% of all system costs per fully vaccinated child, with a cost of US$0.03 per additional $cm^3$ of cold storage (Griffiths, Korczak, Ayalew, & Yigzaw, 2009). As the added volume required for storing the tetravalent DTP-Hib or the pentavalent DTP-HepB-Hib vaccines is less than that required for the monovalent Hib vaccine, using the pentavalent vaccine would be expected to significantly reduce system costs associated with cold chain storage relative to the use of the monovalent vaccine.

*Broadening the perspective on costs in benefit-cost analysis of Hib vaccination*

None of the studies in our review of BCA of Hib vaccination estimated the BCR when exclusively using pentavalent Hib formulations (Table 3); only one (Shin et al., 2008) of the 11 studies indentified considered cost reductions due to replacing the monovalent Hib vaccine with a combination vaccine. At baseline, the study estimated the BCR of Hib vaccination using the actual distribution of monovalent and multivalent Hib vaccines in the USA in 2000 (yielding a BCR of 5.4). In sensitivity analysis the study then recalculated the BCR assuming that all Hib vaccinations were performed either with the monovalent formulation (yielding a BCR of 5.0) or with a HepB-Hib combination vaccine (BCR of 7.5), demonstrating the increase in the estimate of vaccination value if multivalent

formulations are used in evaluation as opposed to monovalent vaccines. It is likely that all studies listed in Table 3 would have found substantially higher BCRs had they evaluated the tetravalent DTP-Hib or the pentavalent DTP-HepB-Hib vaccine instead of the monovalent Hib form.

## Discussion

Policy makers often consider economic evaluations in deciding whether to introduce a vaccine into national vaccination schedules or to implement campaigns to improve vaccination coverage (Fuguitt & Wilcox, 1999). Past economic evaluations of vaccinations, however, have usually ignored both important benefits and potentially large cost reductions and may thus have substantially underestimated the value of vaccinations. We demonstrate, for the example of the Hib vaccine, that BCAs have taken narrow evaluation perspectives, focusing on health gains, health care cost savings, and care-related productivity gains, while ignoring other benefits, in particular, outcome-related productivity gains (Hib vaccine can prevent permanent mental and physical disabilities), behavior-related productivity gains (reductions in child mortality due to Hib can trigger changes in fertility which in turn may stimulate economic growth), and community externalities (Hib vaccination can prevent the development of antibiotic resistance and reduce the risk of Hib infection in unvaccinated persons).

Similarly, economic evaluations of vaccinations have usually ignored savings that can be achieved if economies of scope in vaccination delivery are fully exploited. We show for the example of the Hib vaccine that substantial cost reductions are likely to occur if a monovalent Hib formulation is replaced by a combination vaccine in the evaluation, because adding the Hib vaccine to a vaccination schedule in a multivalent form reduces serum cost, waste, storage volume, and health worker time. Theoretically, combination vaccines may have a few disadvantages. For instance, if only combination vaccines are available in a country, some children may unnecessarily forgo the opportunity to receive some

vaccinations because they have a medical contraindication against one specific vaccine included in the combination. This potential problem, however, may not affect a large number of children and can be avoided by using combination vaccines in routine situations but offering children with vaccine-specific contraindications those vaccines they can safely receive in monovalent forms. Our analysis thus suggests that past BCAs of Hib vaccination have underestimated the value of the vaccination, even though most have found it to be cost-beneficial. One hundred sixty countries either introduced the Hib vaccine by 2009 or are expected to introduce it by 2010. Nevertheless, Hib vaccination coverage remains low (26% in 2007). Our results should encourage researchers to conduct BCA of Hib vaccination that take into account broad sets of benefits and cost. According to our findings, the results of such research are likely to strengthen the case for interventions to increase Hib vaccination coverage.

It is important to keep in mind that the different benefits and costs included in broad-perspective economic evaluations of vaccinations accrue at different times relative to the date of vaccination. For instance, the timing of health gains will depend on the disease avoided by the vaccination – some diseases, such as measles, will mostly affect children, while others, such as hepatitis B, may afflict both children and adults and thus lead to health gains throughout the life course. Outcome-related productivity gains will usually start accruing only once the vaccinated children have become adults and enter the labor market. Behavior-related productivity gains may materialize only after a long lag times because changes in child health and survival may first need to be observed in children already born before they can change future fertility decisions. Cost reductions due to changes in vaccine formulation, on the other hand, will be realized immediately at the time of the vaccination. Because the broad-perspective evaluation expands the sets of benefits and costs included in the analysis, the relative timing of benefit and cost realization will more complex than in narrow-perspective studies. Broader evaluation perspectives may thus require more complex evaluation methodologies. The increased demand on the skill of the

evaluator, however, should not distract from the fact that broad-perspective evaluations will improve the validity of evaluation results and should thus be routinely undertaken.

Understanding the complex links between vaccination programs, health, education, and labor productivity has implications for all vaccines, not just the Hib vaccine. In particular, the broad-perspective approach to economic evaluation should be applied to new vaccines, such as PCV and Rota, that are more expensive than the vaccines currently included in most EPI. A broadening of evaluation perspective that is not considered above relates to the possibility that the children who would be vaccinated if vaccination coverage were to be expanded in a country stand to benefit more from vaccination than children who were vaccinated in the past. A number of studies suggest that children who reside farther away from clinics, who come from lower economic status households or larger families, or whose mothers have fewer years of education or less knowledge about health and health care, are less likely to receive vaccinations (Bondy, Thind, Koval, & Speechley, 2009; Cui & Gofin, 2007; Ndirangu, Bärnighausen, Tanser, Khin, & Newell, 2009; Ndiritu, Cowgill, Ismail, Chiphatsi, Kamau, Fegan et al., 2006; Waters, Dougherty, Tegang, Tran, Wiysonge, Long et al., 2004). Children with these characteristics are more likely to suffer if they contract a vaccine-preventable disease than children who live in more privileged circumstances, because they will be less likely to have access to health care and to support systems that can reduce the effect of disease sequelae on their lives. At the same time, it is likely that the marginal costs of extending vaccination coverage to additional children are increasing. Past economic evaluations have usually assumed that the vaccination benefits and costs observed in vaccinated children are valid for those children who are currently unvaccinated. Future BCAs of Hib and other vaccinations should take into account that both the costs and benefits of a vaccination may change as coverage increases, possibly changing overall estimates of the vaccination BCR.

As vaccinations could save the lives of large numbers of children – PCV and Rota together have the potential to save the lives of more than one million children under the age of five – expanding vaccination coverage can clearly contribute to the progress towards the fourth Millennium Development Goal (MDG) of reducing child mortality. Broad-perspective economic evaluation can draw attention to the non-health benefits of vaccination, including effects on educational attainment (which are relevant for the second MDG of achieving universal primary education) and labor productivity (which is relevant for the first MDG of eradicating extreme poverty and hunger). Only when all benefits of vaccinations for health, education, and the economy of a country are considered simultaneously with the cost of vaccine delivery will policy makers have sufficient information to make optimal decisions on vaccination roll-out.

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