The economic case for expanding vaccination coverage of children

Till Bärnighausen, University of KwaZulu-Natal

David E. Bloom, Harvard School of Public Health

David Canning, Harvard School of Public Health

Abigail Friedman, Harvard School of Public Health

Orin Levine, Johns Hopkins Bloomberg School of Public Health

Jennifer O'Brien, Harvard School of Public Health

Lois Privor-Dumm, Johns Hopkins Bloomberg School of Public Health

Damian Walker, Johns Hopkins Bloomberg School of Public Health

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 introduce and deliver a standard vaccine 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 [1].

Despite the longstanding availability of EPI vaccines and national health policies aiming at universal or near universal coverage [2], actual coverage is widely incomplete. For instance, Lim et al. (2008) estimate that in 2006 26% of children younger than one year of age worldwide had not received DTP3 [3]. DTP3 is commonly used as an indicator vaccination to assess the performance of national vaccination systems, because it is the multi-dose vaccination that is included in most routine vaccination schedules worldwide and coverage of multi-dose vaccinations, unlike coverage of single-dose vaccinations, depends on the capacity of vaccination systems to recorded vaccination doses and to repeatedly vaccinate the same individual [3]. The lack of DTP3 coverage thus suggests that vaccination systems are not reaching substantial numbers of children worldwide.

Incomplete coverage of vaccinations, 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 [4]. 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. Vaccines against these diseases, therefore, can avert both death and impairment.

In deciding whether to finance a health care intervention, decision makers commonly consider not only the effects of the intervention but also the costs. Table 1 shows the cost per dose of those vaccines included in the original and the later-stage EPI packages and of newer vaccines that are not yet included in EPI. Cost-effectiveness analyses (CEA) and benefit-cost analyses (BCA) 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 money units), while BCA compares money measures of intervention benefits to costs. Below, we will argue that economic evaluations of vaccination, such as CEA and BCA, have traditionally taken a *narrow perspective*, considering only some categories of vaccine 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 the costs and thus to wrong decisions on vaccination roll-out.

Table 1: Vaccine data summary

	Vaccine	Vaccine coverage* (1999) [5]	Vaccine coverage* (2007) [5]	Number of deaths worldwide in children under five years due to vaccine-preventable diseases	Cost per dose of vaccine in US$ [6]
Original EPI	Diphtheria-tetanus-pertussis vaccine (DTP3)	72%	81%	5,000 diphtheria (2002) [7]; 294,000 pertussis, (2002) [8]; 18,000 non-neonatal tetanus (2002) [8]	13.25[1]; 13.75[2]; 13.75[3]
	Measles-containing vaccine (MCV)	71%	82%	217,000 (2006) [5]	
	Polio vaccine (Polio3)	73%	82%		11.51[4]
	Bacillus Calmette-Guérin vaccine (BCG)	79%	89%		
Later-stage EPI	*Haemophilus influenzae* type B vaccine (Hib3)	8%	26%	386,000 (2002) [8]	8.66[6]; 11.29[5]
	Yellow fever vaccine	21%	51%	15,000 (2002) [5]	
	Hepatitis B vaccine (HepB3)	18%	65%		9.75[7]; 10.00[8]
New vaccines	Rotavirus vaccine (Rota)	Not yet introduced		402,000 (2002) [5]	57.20[9]; 83.25[10]
	Heptavalent pneumococcal conjugate vaccine (PCV7)	Not yet introduced		716,000 (2002) [8]	71.04[11]

DTP3 = third dose of diphtheria-tetanus-pertussis vaccine, Polio3 = third dose of polio vaccine, Hib3 = third dose of *Haemophilus influenzae* type b vaccine, HepB3 = third dose of hepatitis B vaccine.

*The vaccination coverages are averages across the WHO Member States. Vaccine coverage 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" [5].

[1]Tripedia (Sanofi Pasteur, 10 pack, 1 dose vials); [2]DAPTACEL (Sanofi Pasteur; 10 pack, 1 dose vials); [3]Infanrix (GlaxoSmithKline, 10 pack, 1 dose vials; or 5 pack, 1 dose syringes); [4]IPOL (Sanofi Pasteur, 10 dose vials; or 10 pack, 1 dose syringes, no needle); [5]ActHIB (Sanofi Pasteur, 5 pack, 1 dose vials); [6]PedvaxHIB (Merck, 10 pack, 1 dose vials); [7]ENGERIX B (GlaxoSmithKline, 10 pack, 1 dose vials; or 5 pack, 1 dose syringes, no

needle); [8]Recombivax HB (Merck, 10 pack, 1 dose vials); [9]RotaTeq (Merck, 10 pack, 1 dose tubes); [10]Rotarix (GlaxoSmithKline, 10 pack, 1 dose vials); [11]Prevnar (Wyeth/Lederle, 10 pack, 1 dose syringes, no needle)

A broad perspective in BCA, CEA, or other types of economic evaluation of vaccinations should thus replace the previous narrow perspective. As an example to make this case, we have chosen the Hib vaccine. While the Hib vaccine has been introduced into national vaccination schedules in most countries worldwide, with a global coverage of merely 26% it has the lowest coverage of all EPI vaccines (Table 1) [5]. Hib vaccine is among the vaccines that could prevent the largest number of deaths in children under five years of age. Unlike the only two other vaccines that on their own could prevent even larger numbers of deaths in children in this age group – the vaccines 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. The multivalent DTP and Hib vaccination 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 infection incidence. 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 [9]. 160 countries have either introduced the Hib vaccine by 2009 or are expected to introduce it by 2010 (Figure 1) [10].

Figure 1: Countries offering Hib vaccine through national vaccination programs

Source: [10]

Many studies have demonstrated the success of the Hib conjugate vaccine at 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) [11]. 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 [12]. 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 [13]. 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 fell to nearly zero [14]. These studies suggest that the Hib is highly effective at reducing Hib-related morbidity and mortality in a variety of settings.

Benefit-cost analysis of Hib vaccination

We performed a literature review of BCA of Hib vaccination in order to assess which benefits and costs have been taken into account in past such 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 money 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 the benefits that have usually been neglected in economic evaluations of vaccinations in CEA by expressing them as cost savings and incorporating these savings on the cost side of the analysis.

We searched medical, economic, and general literature databases (EconLit [15], PubMed [16], Science Citation Index Expanded [17], and JSTOR [18]) in order to identify CBAs of Hib vaccination. In our search, we found 62 distinct economic evaluation studies of Hib vaccination published from January 1985 through March 2009, 11 of which included a BCA of Hib vaccination (see Table 3).

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[1]	Hundreds of thousands of children die each year from Hib disease [8].
		Health care cost savings	Savings of medical expenditures because vaccination prevents illness episodes	Hib diseases lead to substantial health care costs [20-22].
		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 [23].
		Outcome-related productivity gains	Increased productivity because vaccination improves cognition, physical strength, and school attainment	Hib meningitis is relatively common [9], and Hib meningitis "leaves 15 to 35% of survivors with permanent disabilities such as mental retardation or deafness", severely reducing cognition [24].
		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 [9].
		Community externalities	Benefits accruing because vaccination improves outcomes in unvaccinated community members	Hib infections are treated with antibiotics, leading to the development of resistance [25]. Hib vaccinations can protect unvaccinated individuals through herd effects [26].

Source: [19]

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 will describe examples in these three benefit categories for Hib vaccination.

[1] 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" [19]. 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 BCA, "health gains" in terms the value of saved life-years are commonly considered (for example, in 9 out of 11 studies in Table 2), while morbidity reductions are rarely included in the valuation (for example, in only 1 out of the 11 studies in Table 2). 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".

Outcome-related productivity gains
Childhood vaccination may result in outcome-related productivity gains [19] 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 [27]). Hib vaccination can avert long-term neurological sequelae of Hib infection, such as blindness, deafness, mental retardation, epilepsy, and paralysis [24]. 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 [28]. As cognitive ability and educational achievements are related to labor productivity and income [29, 30], these findings suggests 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 [31]), contributed substantially to the economic development in the Republic of Ireland [32] and several East Asian nations during the 1990s [33, 34].

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 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 [35]. 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 in avoiding 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 [36]. According to a recent study by Saha et al. [36], 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 eleven studies reporting results from CBA of Hib vaccination we identified in our review (Table 3), nine found benefit-cost ratio (BCR) greater than one (or positive net benefits). Two studies, one in South Korea [37] and the other one in Chile [38], 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 eleven reviewed studies included all broad-perspective benefits in the evaluation. In fact, while all eleven 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 [37] took a broad-perspective benefit category into account in the analysis (outcome-related productivity gains). Thus, BCAs 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) [39].

Studies by Bloom, Canning, and Weston have also used BCA to account for a wide array of vaccine-mediated benefits [40]. 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 will have a return on investment (ROI) of 18% by 2020.[2] In another analysis, Bloom, Canning, and Weston examined the ROI of a vaccination program (that did not

[2] 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) [29].

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, 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 et al., 1995 [41]	Spain	2.4 - 5.1*	100%	1, 2	Invasive disease	3	monovalent
Garpenholt et al., 1998 [42]	Sweden	Net benefits per child: 160 SEK	99%	1, 2, 3	All	3	monovalent
Ginsberg, Kassis and Dagan, 1993 [23]	Israel	1.45	88%	1, 2, 3	All	4	monovalent
Jiménez et al., 1999 [43]	Spain	1.49	90%	1, 2, 3	Invasive disease	4	monovalent
Lagos et al., 1998 [38]	Chile	0.12-1.10	100%	2	All	3	monovalent
Levine et al., 1993 [44]	Chile	1.66	87%	2	Invasive disease	3	monovalent
Limcangco et al., 2001 [45]	Philippines	8.39*	85%	1, 2, 3	Meningitis	3	monovalent
Shin et al., 2008 [37]	Korea	0.77	90%	1, 2, 3, 4	All	3	monovalent
Trollfors, 1994 [46]	Sweden	1.6	100%	1, 2, 3	Meningitis and acute epiglottis	3	monovalent
Pokorn et al., 2001 [47]	Slovenia	1.38	95%	1, 2, 3	Invasive disease	3	monovalent
Zhou et al. 2002 [48]	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. SEK = Swedish Kronor.

Rethinking the costs of Hib vaccination

While narrow-perspective BCAs 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, yielding a multivalent solution. The resulting reduction in cost can be particularly large if the 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 tetravalent DTP-HepB vaccine. The resulting pentavalent DTP-HepB-Hib vaccine is already being used in several countries and recommended for use by UNICEF, GAVI, and WHO [49, 50]. Comparing the costs of phasing in a monovalent Hib vaccine with those of replacing DTP with a pentavalent vaccine requires consideration of the price of the vaccine serum, the volume of storage required, the amount of hazardous waste generated, and differences in the time required for health worker training and vaccine distribution. The pentavalent vaccine serum is less costly than the monovalent Hib serum (Table 4), requires less storage area (Table 5), generates less hazardous waste, and would be expected to require less time for training and vaccine distribution. According to data from the 2009 edition of the UNICEF and WHO's *Immunization Summary: A statistical reference containing data through 2007*, "the pentavalent vaccine costs significantly less than all other combinations" [50], i.e., three-fifths the price of the next cheapest option (see Table 4). Other costs, including spending on needles and vials, would also be expected to decrease with increasing vaccine valency (see Table 5).

Table 4: Cost of full three-dose infant vaccination series

Vaccines	Costs in US$
Trivalent DTP[3] + monovalent Hib + monovalent HepB	11.17
Tetravalent DTP-Hib + monovalent HepB	10.77
Tetravalent DTP-HepB + monovalent Hib	12.33
Pentavalent DTP-HepB-Hib	5.70

Source: [50]

[3] DTP is available in various numbers of doses per vial. This calculation is based on the 20-dose per vial DTP presentation, which has the lowest volume per dose.

Table 5: Incremental costs, number of syringes and volume due to introduction of Hib vaccination

Vaccine	Incremental costs in US$	Incremental number of syringes	Incremental volume in cm^3
Pentavalent DTP-HepB-Hib[4]	5.30	0	5.58
Monovalent Hib	10.20	3	7.50

cm^3 = cubic centimeter
Source: [50]

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 against vaccination – may be even larger.[5] Considering the number of syringes required to administer the complete vaccinations against diphtheria, tetanus, pertussis, hepatitis B and Hib infection, the pentavalent DTP-HepB-Hib vaccine requires the fewest syringes. Adding the Hib vaccination through use of the pentavalent vaccination implies that no syringes would need to be used in addition to those already in use for the DTP three-shot vaccination series [52].

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. Considering the lowest volume-per-dose form of each vaccine as listed in the WHO Vaccine Volume Calculator [53], it is clear that the pentavalent combination yields the lowest packed volume per three-dose series covering the DTP, HepB, and Hib vaccines. In particular, the pentavalent combination requires less than half the volume required by the combination of the trivalent DTP with the monovalent Hib and HepB vaccines (see Table 5).

Broadening the perspective on costs in benefit-cost analysis of Hib vaccination
Delivering the Hib vaccine in pentavalent form may significantly reduce a series of implementation costs relative to those required for monovalent Hib vaccination. None of the studies in our review of BCA of Hib vaccination estimated the CBR when exclusively using pentavalent Hib formulations (Table 3); only one [37] of the eleven studies

[4] As it is highly unlikely that Hib would be adopted before DTP, a country phasing in the pentavalent DTP-HepB-Hib vaccine would already be devoting resources to pay for the cost of trivalent DTP and to provide the required syringes and storage space. The incremental costs (or syringes or volume) of adding Hib in the pentavalent formulation are thus the total costs (or syringes or volume) of the pentavalent formulation minus the costs (or syringes or volume) of the trivalent DTP.

[5] 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 percent 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 sharp 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 [51].

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 CBR assuming that all Hib vaccinations were performed either with the monovalent formulation (yielding a BCR of 5.0) or with the HepB-Hib combination vaccine (CBR of 7.5).

A study of Ethiopia's national vaccination services further demonstrates the reductions in cost that result from 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 cubic centimeter of cold storage [54]. As the added volume required for storing the pentavalent vaccine (above the volume already required for DTP storage) 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 a monovalent vaccine. These finding suggests that studies in Table 3 would have found substantially higher BCR had they evaluated the pentavalent DTP-HepB-Hib vaccine instead of the monovalent vaccine.

Conclusion

Policymakers often consider economic evaluations in deciding whether to introduce a vaccine into national vaccination schedules or to implement campaigns to improve vaccination coverage. 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 Hib infection in unvaccinated persons as well as the development of antibiotic resistance.

Similarly, economic evaluations of vaccinations commonly ignore 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 that substantial cost reductions are likely to occur if the monovalent Hib vaccine is replaced by combination vaccines. 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. 160 countries have 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 CBAs of Hib vaccination that take into account broad sets of benefits and cost; it should encourage policy makers to consider interventions to increase Hib vaccination coverage.

Understanding the 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 PCV7 and Rota, that are more expensive than the vaccines currently included in EPI. Our list of benefits that should be taken into account in BCA of vaccinations, but are commonly ignored, is not completely exhaustive. For instance, we have not considered 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 [55-59]. Children with these characteristics are also 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. Economic evaluations usually extrapolate benefits and costs observed in children who were vaccinated in the past to currently unvaccinated children of the same age. Future BCAs of Hib and other vaccinations could take into account that children who currently lack vaccination coverage may benefit more from vaccination than those children who are already vaccinated – another broadening of evaluation perspective that may improve the BCR of the vaccinations.

As vaccinations could save the lives of large numbers of children – PCV7 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 the health, education, and economy of a country are considered simultaneously with the cost of vaccine delivery will policy makers have sufficient information to take the right decisions on vaccination roll-out.

Acknowledgments

We thank Larry Rosenberg and Marija Ozolins for valuable comments and research support.

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