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Abstract

Economic evaluations of health interventions, such as vaccinations, are important tools for informing health policy. Approaching the analysis from the appropriate perspective is critical to ensuring the validity of evaluation results for particular policy decisions. Using the example of benefit-cost analysis (BCA) of *Haemophilus influenzae* type b (Hib) vaccination, we demonstrate that past economic evaluations have mostly adopted narrow evaluation perspectives, focusing primarily on health gains, health care cost savings, and reductions in the time costs of caring, while ignoring other important benefits including outcome-related productivity gains (prevention of mental and physical disabilities), behavior-related productivity gains (economic growth due to fertility reductions as vaccination improves child survival), and community externalities (prevention of antibiotic resistance and herd immunity). We further show that the potential cost reductions that could be attained through changes in the delivery of the Hib vaccine have also usually been ignored in economic evaluations. Future economic evaluations of childhood vaccinations should take full account of benefits and costs, so that policy makers have sufficient information to make well-informed decisions on vaccination implementation.

1. Introduction

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 diphtheria-tetanus-pertussis (DTP) vaccine, 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) 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) [3]. DTP3 is commonly used as an indicator to assess the performance of national vaccination systems because DTP3 captures a system's capacity to repeatedly vaccinate the same individual and to record vaccination doses. The deficits in DTP3 coverage discussed by Lim et al. suggest that millions of children are not receiving the full course of recommended vaccines [3].

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

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children under five years of age [4]. 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.

Table 1: Vaccination data summary

	Vaccine*	Global vaccination coverage† (1999) [5]	Global vaccination coverage† (2007) [5]	Annual 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) [6] 294,000 pertussis, (2002) 18,000 non-neonatal tetanus (2002) [7]
	Measles-containing vaccine (MCV)	71%	82%	217,000 (2006) [5]
	Polio vaccine (Pol3)	73%	82%	
	Bacillus Calmette-Guérin vaccine (BCG)	79%	89%	
Later-stage EPI	*Haemophilus influenzae* type b vaccine (Hib3)	8%	26%	386,000 (2002) [7]
	Yellow fever vaccine (YF)	21%	51%	15,000 (2002) [5]
	Hepatitis B vaccine (HepB3)	18%	65%	
New vaccines	Rotavirus vaccine (Rota2, Rota3)	Not yet introduced in most developing countries		402,000 (2002) [5]
	Pneumococcal conjugate vaccine (PCV3)	Not yet introduced in most developing countries		716,000 (2002) [7]

*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, Pol3 = 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.

†The vaccination coverage data are WHO/UNICEF estimates. The denominator used to estimate coverage differs by vaccination. With the exception of YF and Hib3, the denominator is the "target populations" across all WHO Member States "expected to report" data on the particular vaccination coverage to WHO because they have introduced the vaccination into their routine vaccination schedules. The number of WHO Member States "expected to report" coverage data to WHO was 193 (for DTP3, MCV, Pol3), 161 (for BCG), and 171 (for HepB3). In the case of YF and Hib3, the

denominators are the "countries at risk" for Hib and yellow fever. While the "target population varies depending on the countries' policies, the specific vaccine, and the dose for which coverage is being calculated", in "most instances the target population is the number of children surviving their first year of life". In the case of BCG, the "target population" is the "national annual number of births" [5].

In deciding whether to finance a health care intervention, decision makers should consider not only the effects of the intervention, but also the costs. Cost-effectiveness analysis (CEA) and benefit-cost analysis (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., cases of disease, life-years, or quality-adjusted life-years) relative to the costs (measured in monetary units), while BCA compares monetary measures of intervention benefits to its 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 adoption. 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. In 2007, the Hib vaccination had been introduced into national routine vaccination schedules in 115 WHO Member States. Hib3 coverage across countries "at risk" of Hib disease, however, was estimated at merely 26% in 2007(Table 1) [5]. Hib is 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

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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 the HepB vaccine to be delivered as a multivalent formulation in a single injection (DTP-Hib or DTP-Hib-HepB). 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.

2. 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 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 [8].

In 1987, the United States licensed a protein-conjugated Hib vaccine [8]. Many studies have demonstrated the success of the conjugate vaccine in reducing child morbidity and mortality. Following routine use of the conjugate Hib 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)

[9].[1] 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 [10]. 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 [11]. 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 [12]. These studies suggest that the Hib vaccine is highly effective at reducing Hib-related morbidity and mortality in a variety of settings. Nevertheless, worldwide Hib vaccination coverage stood at only 26% in 2007 (see Table 1).

3. 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 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

[1] In the following text, the terms "Hib vaccine" and "Hib vaccination" refer to the conjugate Hib vaccine and the administration of the conjugate Hib vaccine, respectively.

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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 [13], PubMed [14], Science Citation Index Expanded [15], and JSTOR [16]) 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). Note that we classified any study as BCA that compared costs and benefits measured in monetary terms, including those studies that compared the cost of a vaccination to only one single benefit, such as health care cost savings. A recent systematic review of CEA of Hib vaccine in both high-income and low- and middle-income countries can be found elsewhere [17].

4. 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 [17-18]. 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 [19]. 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.

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.

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 [7].
		Health care cost savings	Savings of medical expenditures because vaccination prevents illness episodes	Hib diseases lead to substantial health care costs [21-23].
		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 [24].
		Outcome-related productivity gains	Increased productivity because vaccination improves cognition, physical strength, and school attainment	Hib meningitis is relatively common , and Hib meningitis "leaves 15 to 35% of survivors with permanent disabilities such as mental retardation or deafness", severely reducing cognition [25].
		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 [8].
		Community externalities	Benefits accruing because vaccination improves outcomes in unvaccinated community members	Hib infections are treated with antibiotics, leading to the development of resistance [26]. Hib vaccinations can protect unvaccinated individuals through herd effects [27].

Source: [19]

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[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 and/or morbidity through vaccination" [19]. 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). The value of a life year in BCA usually incorporates pure longevity effects, the productivity gains due to an additional year of life, as well as the value of leisure and joy [20]. In contrast, morbidity reductions are rarely included in BCA (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".

4.1. Outcome-related productivity gains

Childhood vaccinations 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 [28]). Hib vaccination can avert long-term neurological sequelae of Hib infection, such as blindness, deafness, mental retardation, epilepsy, and paralysis [25]. 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, organization, problem solving, and central auditory function" in the meningitis survivors, resulting in lower educational achievement and higher risk of behavior disorders [29]. As cognitive ability and educational achievements are related to labor productivity and income [30-31], 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 taken into account in BCA of vaccinations against Hib and other infections.

4.2. 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 [32]) contributed substantially to economic development in the Republic of Ireland [33] and several East Asian nations during the 1990s [34-35].

4.3. 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 [36]. 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 [37]. According to a recent study by Saha et al. [37], 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.

4.4. Broadening the perspective on benefits in benefit-cost analysis of Hib vaccination
All 11 studies identified by our review as reporting results from BCA of Hib vaccination included the benefit category 'health care cost savings' (Table 3). Eight included the category 'health gains', and eight included the category 'care-related productivity gains'; however, only one study [38] took a broad-perspective benefit category into account in the

analysis ('outcome-related productivity gains'). Nine of the 11 studies found a benefit-cost

ratio (BCR) greater than one (or positive net benefits). Only two studies, one in South Korea

[38] and the other one in Santiago, Chile [39], found BCRs that were smaller than one.

Overall, BCRs ranged from 0.12 to 8.39. In general, we would expect studies that take a

broader range of benefits into account to find BCR that are more favorable than those using

narrower ranges of benefits. 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) [40].

It may thus seem surprising that the only study in our review that included a broad-

perspective benefit is one of the two studies that found the Hib vaccine not to be cost-

beneficial [41]. However, as Griffith, Edmond and Haijeh have pointed out, the study used

an inflated estimate of the cost of Hib vaccine (a public-sector price of US$ 20 per dose, at a

time when the vaccine was available for US$ 9-11 per dose in the United States and for US$

8 per dose in Australia). At the same time a slightly lower cost estimate (US$ 16 per dose)

would have rendered the vaccine cost-beneficial in the study [42].

The Hib vaccination serves as a good example of an intervention which has not been

evaluated from a broad perspective – many BCAs exist, but only one takes into account a

broad-perspective benefit. However, since only two BCAs did not find the vaccination to be

cost-beneficial (one of which found the vaccination to be cost-beneficial in some scenarios

[39] while the other made questionable assumptions [41]) the inclusion of additional

broad-perspective benefits would have only changed the size of the net benefits of the

vaccination but not the qualitative conclusion that benefits exceed costs.

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Studies by Bloom, Canning, and Weston used BCA to account for a wide array of vaccine-mediated benefits [43]. Their investigation of the impact of the GAVI Alliance (formerly 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 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.

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[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) [30].

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 [44]	Spain[††]	2.4 - 5.1*	100%	2	Invasive disease	3	monovalent
Garpenholt et al. 1998 [45]	Sweden	Net benefits per child: 160 SEK	99%	1, 2, 3	All	3	monovalent
Ginsberg, Kassis and Dagan 1993 [24]	Israel	1.45	88%	1, 2, 3	All	4	monovalent
Jimenez et al. 1999 [46]	Spain	1.49	90%	1, 2, 3	Invasive disease	4	monovalent
Lagos et al. 1998 [39]	Chile	0.12-1.10	100%	2	All	3	monovalent
Levine et al. 1993 [47]	Chile[†††]	1.66	87%	2	Invasive disease	3	monovalent
Limcangco et al. 2001 [48]	Philippines	8.39*	85%	1, 2, 3	Meningitis	3	monovalent
Shin, Shin and Ki 2008 [38]	Korea	0.77	90%	1, 2, 3, 4	All	3	monovalent
Trollfors 1994 [49]	Sweden	1.6	100%	1, 2, 3	Meningitis and acute epiglottis	3	monovalent
Pokorn et al. 2001 [50]	Slovenia	1.38	95%	1, 2, 3	Invasive disease	3	monovalent
Zhou et al. 2002 [51]	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.

5. 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.

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-HepB-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 [52-53]. 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* [52] and the cheapest price estimates of Hib, DTP-Hib, and DTP-HepB-Hib in the UNICEF *Vaccine Projections for 2009* [54], 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 expensive, often requiring costly incinerators,[5] 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.[6] 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 [56].

Nearly all vaccines must be transported and stored in temperature-controlled conditions known as the cold-chain storage network. This network constitutes a major

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[4] The price estimates are weighted average prices across countries eligible for funding through GAVI [54].
[5] Of course, the fixed costs of incinerators and other infrastructure to dispose of biohazardous waste need to be allocated across all products that are disposed using this infrastructure. The fraction of total fixed costs allocated to the Hib vaccine is likely to be small.
[6] 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 [55].

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* [57], 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-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. Administering Hib in a multivalent formulation will thus be less time-consuming than administering 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 [58]. 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.

5.1. 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 [38] 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.

6. Discussion

Past economic evaluations of vaccinations 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. For example, severe immunodeficiencies are contraindications for live attenuated vaccines, such as MCV, but not for toxoid vaccines, such as DTP [59]. 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, globally 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.

Our arguments are of course only relevant insofar as economic evaluations of health interventions influence policy-making decisions. While some early evidence suggests that economic evaluations are rarely used systematically in health policy-making [60], more

recent research suggests a somewhat more optimistic picture, e.g. that "[d]ecision makers generally recognized the usefulness and necessity of published economic evaluations in informing their decision-making processes" [61]. In some countries, economic evaluations are systematically included in the decision-making on inclusion and exclusion of health interventions in the public-sector health care system. For instance, the UK National Institute for Health and Clinical Excellence (NICE), which provides "guidance on the use of new and existing medicines, treatments and procedures within the NHS [the UK National Health Service]" [62], systematically incorporates evidence from economic evaluations of health interventions in producing guidance for health policy, including guidance on the adoption of new vaccination into the national vaccination schedule [63].

In addition, it is plausible that the results of economic evaluation enter the policy-making process indirectly, as they contribute to a general understanding – conveyed formally by policy advisors or informally in meetings and discussions between policy-makers, scientists, and advocates – whether an intervention is "good value" for government budget money. It is important that obstacles to the use of economic evaluation in policy-making are better understood and, where possible, removed, such as through improved methods, better generalizability of results [61], or clearer presentation of relevant findings [64].

A number of caveats are important to keep in mind when considering our approach of expanding the perspective of economic evaluation of vaccination. For one, the different benefits and costs included in broad-perspective 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 individuals vaccinated as children 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 be

more complex than in narrow-perspective studies.

Broader evaluation perspectives may require more complicated methodologies, or more

extensive data collection, than narrower perspectives. For instance, in order to estimate the

vaccination benefits of herd immunity, it may be necessary to build complex models of the

transmission dynamics of a vaccine-preventable disease. The analysis of the economic

effects of vaccination on antibiotic resistance will require information that may not be

currently available, such as data on the speed of resistance development at different levels

of vaccination coverage, disease incidence, and costs and effectiveness of second-line

antibiotics. However, the increased demand on the skill of the evaluator in conducting the

analysis and the possible necessity to collect new data 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 health interventions, health outcomes, education,

and labor productivity has implications for all types of interventions, not only childhood

vaccinations. However, two limitations are important to consider. Firstly, evidence on the

"broad" benefits of many health interventions is largely lacking. For instance, we know only little about the link between specific childhood vaccinations and educational attainment. Future research must seek to fill these knowledge gaps in order to improve the specificity of recommendations to include certain types of "broad" benefits in the economic evaluation of individual health interventions. Secondly, research itself has benefits and costs – in some situations, the expected marginal benefits of broadening the evaluation perspective may not exceed the marginal costs of funding such research. Consider, for instance, a health intervention that has been found to be highly cost-beneficial in narrow-perspective evaluations. If we know based on theoretical considerations that a broadening of the evaluation perspective could only further increase the difference between benefits and costs of the intervention, the value of the additional information to be gained in broad-perspective evaluation may not exceed the costs of the exercise.

One type of 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 [65-69]. 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.

Note, however, that the newest cost and benefit estimates may not always be the preferable ones. For instance, subsidized prices should not be used to estimate the costs of vaccines in most types of evaluations. From a societal perspective, subsidized prices will underestimate the true market costs of producing the vaccines and should thus be replaced with a "shadow prices" that adequately represent the social opportunity costs of producing vaccines [70]. From the perspective of a Ministry of Health, a subsidized price may be relevant for short-term planning purposes, but planners must consider that subsidies are usually temporary and prices will revert back to their true market values after some time.

As vaccinations could save the lives of millions of children – vaccines protecting against pneumocoocal disease and rotavirus together have the potential to save the lives of more than one million children under the age of five per year – 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 known and considered simultaneously with the cost of

vaccine delivery will policy makers have sufficient information to make optimal decisions on vaccination roll-out.

References

1.   Halsey N and Galazka A. The efficacy of DPT and oral poliomyelitis immunization schedules initiated from birth to 12 weeks of age. Bull World Health Organ, 1985; 63(6): 1151-69.
2.   WHO. Handbook of resolutions and decisions of the World Health Assembly and the executive board. Geneva: WHO, 1974.
3.   Lim SS, Stein DB, Charrow A and Murray CJ. Tracking progress towards universal childhood immunisation and the impact of global initiatives: a systematic analysis of three-dose diphtheria, tetanus, and pertussis immunisation coverage. Lancet, 2008; 372(9655): 2031-46.
4.   WHO. Global strategy for infant and young child feeding. Geneva: WHO, 2003.
5.   WHO. WHO vaccine-preventable diseases: monitoring system. Geneva: WHO, 2008.
6.   WHO. Diphtheria. Available at: http://www.who.int/immunization_monitoring/diseases/diphteria/en/index.html. Webpage last accessed May 2009.
7.   WHO. Global immunization data. Available at: http://www.who.int/immunization/newsroom/GID_english.pdf. Webpage last accessed March 2010.
8.   WHO. Hepatitis B -- key facts. Available at: http://www.who.int/mediacentre/factsheets/fs204/en/. Webpage last accessed 22 March 2009.
9.   Anonymous. Progress toward eliminating Haemophilus influenzae type b disease among infants and children--United States, 1987-1997. MMWR Morb Mortal Wkly Rep, 1998; 47(46): 993-8.
10.   Cowgill KD, et al. Effectiveness of Haemophilus influenzae type b Conjugate vaccine introduction into routine childhood immunization in Kenya. JAMA, 2006; 296(6): 671-8.
11.   Baqui AH, et al. Effectiveness of Haemophilus influenzae type b conjugate vaccine on prevention of pneumonia and meningitis in Bangladeshi children: a case-control study. Pediatr Infect Dis J, 2007; 26(7): 565-71.
12.   Lee EH, et al. Haemophilus influenzae type b conjugate vaccine is highly effective in the Ugandan routine immunization program: a case-control study. Trop Med Int Health, 2008; 13(4): 495-502.
13.   Anonymous. EconLit. Available at: http://www.aeaweb.org/econlit/index.php. Webpage last accessed June 2009.
14.   Anonymous. PubMed. Available at: http://www.ncbi.nlm.nih.gov/pubmed/. Webpage last accessed June 2009.
15.   Anonymous. Science Citation Index Expanded. Available at: http://nihlibrary.nih.gov/Features/scibackfiles.htm. Webpage last accessed June 2009.
16.   Anonymous. JSTOR. Available at: http://www.jstor.org/. Webpage last accessed June 2009.

17. Griffiths UK and Miners A. Economic evaluations of Haemophilus influenzae type b vaccine: systematic review of the literature. Expert Rev Pharmacoecon Outcomes Res, 2009; 9(4): 333-46.

18. Brinsmead R, Hill S and Walker D. Are economic evaluations of vaccines useful to decision-makers? Case study of Haemophilus influenzae type b vaccines. Pediatr Infect Dis J, 2004; 23(1): 32-7.

19. Bärnighausen T, Bloom DE, Canning D and O'Brien J. Accounting for the full benefits of childhood vaccination in South Africa. S Afr Med J, 2008; 98(11): 842, 844-6.

20. Commission on Macroeconomics and Health. Macroeconomics and health: investing in health for economic development. Geneva: World Health Organization, 2001.

21. Gessner BD, Endang R. Sedyaningsih, Ulla K. Griffiths, Agustinus Sutanto, Mary Linehan, Dave Mercer, Edward Kim Mulholland, Damian G. Walker, Mark Steinhoff, Mardiati Nadjib. Vaccine-Preventable Haemophilus influenza Type B Disease Burden and Cost-Effectiveness of Infant Vaccination in Indonesia. The Pediatric Infectious Disease Journal, 2008; 27(5).

22. Zhou F, Jeanne Santoli, Mark L. Messonnier, Hussain R. Yusuf, Abigail Shefer, Susan Y. Chu, Lance Rodewald, Rafael Harpaz. Economic Evaluation of the 7-Vaccine Routine Childhood Immunization Schedule in the United States, 2001. Archives of Pediatrics & Adolescent Medicine, 2005; 159: 1136-1144.

23. Akumu AO, Mike English, J Anthony G Scott, Ulla K Griffiths. Economic evaluation of delivering Haemophilus influenzae type b vaccine in routine immunization services in Kenya. Bulletin of the World Health Organization 2007; 85 (7): 511-518.

24. Ginsberg GM, Kassis I and Dagan R. Cost benefit analysis of Haemophilus influenzae type b vaccination programme in Israel. J Epidemiol Community Health, 1993; 47(6): 485-90.

25. WHO. Haemophilus influenzae type B (HiB). Available at: http://www.who.int/mediacentre/factsheets/fs294/en/. Webpage last accessed March 2009.

26. Elbasha EH. Deadweight loss of bacterial resistance due to overtreatment. Health Economics, 2003; 12: 125-138.

27. Stephens DS. Vaccines for the unvaccinated: protecting the herd. J Infect Dis, 2008; 197(5): 643-5.

28. Zielinski A, Christy B. Kwon, Joanna Tomaszunas-Blaszczyk, Wieslaw Magdzik, John V. Bennett. Risk of Haemophilus influenzae Type B Meningitis in Polish Children Varies Directly with Number of Siblings: Possible Implications for Vaccination Strategies. European Journal of Epidemiology, 2003; 18(9): 917-922.

29. Grimwood K, Anderson P, Anderson V, Tan L and Nolan T. Twelve year outcomes following bacterial meningitis: further evidence for persisting effects. Arch Dis Child, 2000; 83(2): 111-6.

30. Psacharopoulos G and Patrinos HG. Returns on investment in education: a further update. Education economics, 2004; 12(2): 111-134.

31. Colclough C, Kingdon G and Patrinos HA, The pattern of returns to education and its implications, in Policy Brief. 2008, Research Consortium on Educational Outcomes & Poverty: Cambridge, UK.
32. Bloom D, Canning D and Sevilla J, The demographic dividend: a new perspective on the economic consequences of population change. 2003, RAND: Santa Monica, USA.
33. Bloom D and Canning D. Contraception and the Celtic Tiger. Economic and Social Review,, 2003; 34(3): 229-247.
34. Bloom D and Williamson J. Demographic transitions and economic miracles in emerging Asia. World Bank Economic Review, 1998; 12(3): 419-455.
35. Bloom D, Canning D and Malaney P. Demographic change and economic growth in Asia. Supplement to Population and Development Review, 2000; 26: 257-290.
36. Moulton L, Chung S, Croll J, Reid R, Weatherholtz R and Santosham M. Estimation of the indirect effect of Haemophilus influenzae type b conjugate vaccine in an American Indian population. International Journal of Epidemiology 2000; 29: 753-756.
37. Saha SK, et al. Direct detection of the multidrug resistance genome of Haemophilus influenzae in cerebrospinal fluid of children: implications for treatment of meningitis. Pediatr Infect Dis J, 2008; 27(1): 49-53.
38. Shin S, Shin YJ and Ki M. Cost-benefit analysis of haemophilus influenzae type B immunization in Korea. J Korean Med Sci, 2008; 23(2): 176-84.
39. Lagos R, Levine OS, Avendano A, Horwitz I and Levine MM. The introduction of routine Haemophilus influenzae type b conjugate vaccine in Chile: a framework for evaluating new vaccines in newly industrializing countries. Pediatr Infect Dis J, 1998; 17(9 Suppl): S139-48.
40. Levine OS, Schwartz B, Pierce N and Kane M. Development, evaluation and implementation of Haemophilus influenzae type b vaccines for young children in developing countries: current status and priority actions. Pediatr Infect Dis J, 1998; 17(9 Suppl): S95-113.
41. Shin S, Young-jeon Shin, Moran Ki. Cost-Benefit Analysis of Haemophilus Influenzae Type B Immunization in Korea. Journal of Korean Medical Science, 2008; 23: 176-84.
42. Griffiths UK, Edmond K and Hajjeh R. Is Hib vaccine of economic value in South Korea? J Korean Med Sci, 2009; 24(1): 187; author reply 188.
43. Bloom D, Canning D and Weston M. The value of vaccination. World Economics, 2005; 6(3): 15-39.
44. Asensi F, Otero MC, Perez-Tamarit D, Miranda J, Pico L and Nieto A. Economic aspects of a general vaccination against invasive disease caused by Haemophilus influenzae type b (Hib) via the experience of the Children's Hospital La Fe, Valencia, Spain. Vaccine, 1995; 13(16): 1563-6.
45. Garpenholt O, Silfverdal SA and Levin LA. Economic evaluation of general childhood vaccination against Haemophilus influenzae type b in Sweden. Scand J Infect Dis, 1998; 30(1): 5-10.

46. Jimenez FJ, Guallar-Castillon P, Rubio Terres C and Guallar E. Cost-benefit analysis of Haemophilus influenzae type b vaccination in children in Spain. Pharmacoeconomics, 1999; 15(1): 75-83.
47. Levine OS, et al. Cost-benefit analysis for the use of Haemophilus influenzae type b conjugate vaccine in Santiago, Chile. Am J Epidemiol, 1993; 137(11): 1221-8.
48. Limcangco MR, Armour CL, Salole EG and Taylor SJ. Cost-benefit analysis of a Haemophilus influenzae type b meningitis prevention programme in The Philippines. Pharmacoeconomics, 2001; 19(4): 391-400.
49. Trollfors B. Cost-benefit analysis of general vaccination against Haemophilus influenzae type b in Sweden. Scand J Infect Dis, 1994; 26(5): 611-4.
50. Pokorn M, Kopac S, Neubauer D and Cizman M. Economic evaluation of Haemophilus influenzae type b vaccination in Slovenia. Vaccine, 2001; 19(25-26): 3600-5.
51. Zhou F, Bisgard KM, Yusuf HR, Deuson RR, Bath SK and Murphy TV. Impact of universal Haemophilus influenzae type b vaccination starting at 2 months of age in the United States: an economic analysis. Pediatrics, 2002; 110(4): 653-61.
52. UNICEF and WHO. Immunization summary: a statistical reference containing data through 2007. New York: UNICEF, 2009.
53. UNICEF (2008) Project menu for vaccines supplied by UNICEF for the Global Alliance for Vaccines and Immunization (GAVI).
54. UNICEF. Vaccine projections -- projections for 2009. Available at: http://www.unicef.org/supply/index_7991.html. Webpage last accessed June 2009.
55. Program for Appropriate Technology in Health (PATH), Achieving effective sharps waste management in GAVI host countries: a proposed approach with estimates of costs. 2006, The Bill & Melinda Gates Foundation.
56. Agrawal A, Singh R and Mahesh P, Disposing immunisation waste in India, in Policy paper. 2004, Toxics Link.
57. WHO. Vaccine volume calculator. Available at: http://www.who.int/immunization_delivery/systems_policy/logistics/en/index4.html. Webpage last accessed June 2009.
58. Griffiths UK, Korczak VS, Ayalew D and Yigzaw A. Incremental system costs of introducing combined DTwP-hepatitis B-Hib vaccine into national immunization services in Ethiopia. Vaccine, 2009; 27(9): 1426-32.
59. Centres for Disease Control and Prevention. Contraindications to vaccines chart. Available at: http://www.cdc.gov/vaccines/recs/vac-admin/contraindications-vacc.htm. Webpage last accessed 20 January 2010.
60. Ross J. The use of economic evaluation in health care: Australian decision makers' perceptions. Health Policy, 1995; 31(2): 103-10.
61. Hoffmann C, Stoykova BA, Nixon J, Glanville JM, Misso K and Drummond MF. Do health-care decision makers find economic evaluations useful? The findings of focus group research in UK health authorities. Value Health, 2002; 5(2): 71-8.

62. NHS National Institute for Health and Clinical Excellence. About NICE. Available at: http://www.nice.org.uk/aboutnice/. Webpage last accessed 5 March 2010.
63. Martin A, Batty A, Roberts JA and Standaert B. Cost-effectiveness of infant vaccination with RIX4414 (Rotarix) in the UK. Vaccine, 2009; 27(33): 4520-8.
64. Williams I, McIver S, Moore D and Bryan S. The use of economic evaluations in NHS decision-making: a review and empirical investigation. Health Technol Assess, 2008; 12(7): iii, ix-x, 1-175.
65. Bondy JN, Thind A, Koval JJ and Speechley KN. Identifying the determinants of childhood immunization in the Philippines. Vaccine, 2009; 27(1): 169-75.
66. Cui F and Gofin R. Immunization coverage and its determinants in children aged 12-23 months in Gansu, China. Vaccine 2007; 25(4): 664-671.
67. Ndiritu M, et al. Immunization coverage and risk factors for failure to immunize within the Expanded Programme on Immunization in Kenya after introduction of new Haemophilus influenzae type b and hepatitis b virus antigens. BMC Public Health, 2006; 6(132).
68. Waters HR, et al. Coverage and costs of childhood immunizations in Cameroon. Bull World Health Organ, 2004; 82(9): 668-75.
69. Ndirangu J, Barnighausen T, Tanser F, Tint K and Newell ML. Levels of childhood vaccination coverage and the impact of maternal HIV status on child vaccination status in rural KwaZulu-Natal, South Africa*. Trop Med Int Health, 2009; 14(11): 1383-93.
70. Drèze J and Stern N. Shadow prices and markets: policy reform, shadow prices and market prices, In: R Layard and S Glaister, editors. Cost-benefit analysis,Cambridge University Press: Cambridge, 1994.