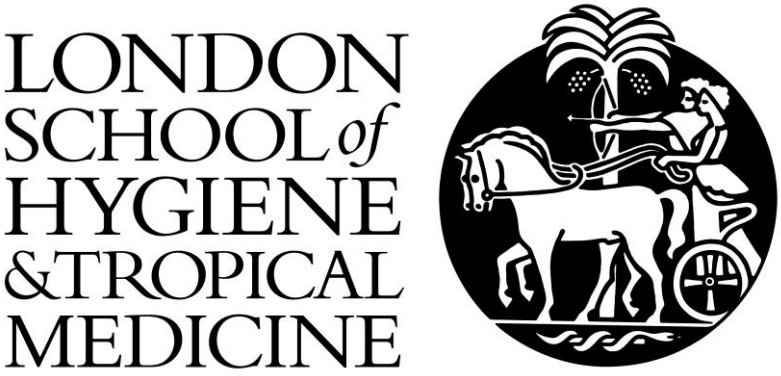

Haemophilus influenzae type b vaccine in low- and middle-income countries:
Impact, costs and incremental cost-utility

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Faculty of Public Health and Policy

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To my father Carl Erik Kou

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ABSTRACT

Haemophilus influenzae type b (Hib) is an infectious bacterium transmitted from person to person through close contact. Hib can cause meningitis, pneumonia and a number of rarer forms of disease, primarily in children less than five years. Hib conjugate vaccines became available during the early 1990s and high-income countries quickly introduced this vaccine into their routine programmes and have now achieved a near disappearance of Hib disease. However, relatively high vaccine prices and uncertainties about Hib disease burden led to a slow uptake in low- and middle-income countries.

The aim of this PhD is to fill gaps in knowledge about the value of Hib vaccination, in terms of whether or not it is a cost-effective intervention in low- and middle-income countries. Moreover, since economic evaluation involves gathering evidence about numerous criteria that may be considered in isolation by policy makers, such as vaccine efficacy, disease burden, meningitis sequelae prevalence and cold chain expansion costs, specific objectives are also to address some of the unanswered questions about key inputs and determinants of cost-effectiveness.

The framework of the PhD is shaped around a decision-analytic model designed to estimate the cost-utility of Hib vaccination. The methodology, collection and analysis of data inputs needed to populate the model represent a number of sub-studies, which are all contributions to new evidence. These include a meta-analysis of Hib vaccine efficacy, calculation of Disability Adjusted Life Years due to Hib disease, estimation of treatment costs of Hib disease, assessment of productivity costs due to meningitis sequelae, and calculation of systems costs of introducing Hib vaccine. Case studies from two countries are included in the sub-studies; productivity costs of meningitis sequelae are investigated in Senegal and systems costs of Hib vaccine introduction are estimated in Ethiopia. Cost-utility results generated from the decision-analytic model are presented for two low-income countries; India and Uzbekistan, and one middle-income country; Belarus.

This PhD thesis is the first attempt to combine evidence on disease burden, costs and impact of Hib vaccine across multiple countries using a consistent framework and comparable input parameters. As a result, new insights into the relative cost-utility in countries with different economic and epidemiological circumstances are obtained.

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ACKNOWLEDGEMENTS

This PhD builds on work I did for the Hib Initiative during 2006 – 2009. I am grateful to all my former colleagues in the Hib Initiative for exceptionally enjoyable collaboration. It really was an inspiring initiative! I particularly want to thank our former director, Rana Hajjeh, for always being encouraging, supportive and open to my ideas.

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Karen Edmond and Andy Clark have been with me all the way on this amazing Hib vaccine journey. I don't know where to start when thanking them. We really make a great team and working with you is both creative and productive, but most of all fun. I will miss Karen now that she has left us for the other side of the world, but thankfully I can still enjoy working closely with Andy.

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Since my thesis is a so-called "staff PhD", writing was mostly done at home during evenings and weekends. I am therefore grateful to the four au-pairs we have had while I worked on this thesis. Thanks to Sara (dark haired), Sarah (blond haired), Ronja and Anne for their amazing help with child caring, cleaning, cooking and tea making. It is a mystery to me how anyone can complete a PhD without an au-pair.

I have dedicated this thesis to my late father. Education and knowledge were the driving forces in his life and he would have been tremendously proud of having a daughter with a PhD. It is to his credit that I have continued to educate myself and I will be forever grateful for his endless support to my schooling. From I was a small girl no expense was spared when it came to buying learning books, language lessons and degree courses abroad.

My dear mum has always been immensely supportive and I am thankful for everything she has done for me. This is by no means small things! When she was around while I worked on the thesis, she helped in her usual way by looking after everything else and only interrupted to bring me drinks and snacks. She really is the best mum in the world.

I also want to thank my lovely cousin, Mette, for being who she is and for being genuinely concerned about me finishing this thesis. It gave me extra incentive.

The greatest credit must be given to John, Johan and Serena for putting up with me always being on the computer with no end in sight. Thanks to John for even taking the kids away on holiday and leaving me at home to get on with it. You are the best. I have not yet managed to convince you to read even one page of my thesis, but I am confident that you understand the importance of it ☺. Johan and Serena are now old enough to know what a PhD is and I could not have done without their encouragement during the last few months: "No, mummy, you should not do that. You need to work on your PhD"!

ABBREVIATIONS

ALRI	Acute lower respiratory infection
BMGF	Bill and Melinda Gates Foundation
CBA	Cost benefit analysis
CCTR	Cochrane Clinical Trial Registry
CE	Cost-effectiveness
CFR	Case fatality rate
CHOICE	Choosing Interventions that are Cost-Effective
CSF	Cerebrospinal fluid
CUA	Cost utility analysis
DALY	Disability Adjusted Life Year
DTwP	Diphteria-tetanus-wholecell pertussis combined vaccine
EPI	Expanded Programme on Immunization
EURO	WHO European Regional Office
FVC	Fully vaccinated child
GBD	Global Burden of Disease
GNI	Gross National Income
GSK	Glaxo Smith Kline
HI	*Haemophilus influenzae*
Hib	*Haemophilus influenzae* type b
IBIS	Invasive Bacterial Infections Surveillance
ICER	Incremental cost-effectiveness ratio
IM	Intramuscular
IPV	Injectable polio vaccine
IV	Intravenous
MCCIDH	Minsk City Children's Infectious Disease Hospital
MMR	Measles-mumps-rubella combined vaccine

NGO	Non Governmental Organisation
NICE	National Institute of Health and Clinical Excellence
NHS	National Health Service
NPNM	Non-pneumonia, non-meningitis
NTAGI	National Technical Advisory Group on Immunization
PATH	Programme for Appropriate Technologies for Health
PIE	Post introduction evaluation
PNG	Papua New Guinea
PSA	Probabilistic Sensitivity Analysis
PV	Present Value
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
RFP	Request for proposal
RR	Relative risk
SEARO	WHO South East Asia Regional Office
SII	Serum Institute of India
SNNPR	Southern Nations Nationalities and People's Region
UNICEF	United Nations Children's Fund
YLD	Years of life with disability
YLL	Years of life lost
WCC	White cell count
WHO	World Health Organization

STATEMENT OF WORK

Publications arising from this thesis:

1. Griffiths UK, Korczak V, Ayalew D, Yigzaw A, Incremental system costs of introducing combined DTwP-Hepatitis B-Hib vaccine into National Immunization Services in Ethiopia, *Vaccine*. 2009 Feb 25; 27(9)

2. Griffiths UK, Miners A, Cost-effectiveness of *Haemophilus influenza* type b vaccine: A systematic review of the literature, *Expert Review of Pharmacoeconomics and Outcome Research*, 2009 August (4):333-46

3. Griffiths UK, Clark A, Shimanovich V, Glinskaya I, Tursonova,Kim L, Mosina L, Hajjeh, R, Edmond K, Comparative economic evaluation of *Haemophilus influenzae* type b vaccine in Belarus and Uzbekistan, *PLoS One*. 2011;6(6)

4. Griffiths UK, Clark A , Gessner B, Miners A, Sanderson C, Sedyaningsih ER, Mulholland K, Efficacy of *Haemophilus influenzae* type b conjugate vaccines: Systematic review and meta-analysis, *Epidemiol Infect*. 2012 May 14:1-13. [Epub ahead of print]

5. Griffiths UK, Dieye, Y, Fleming J, Hajjeh, R, Edmond K, Costs of meningitis sequelae in Dakar, Senegal, *Pediatr Infect Dis J.* 2012 Jun 4. [Epub ahead of print]

I certify being the lead author on the above publications, designing the methods, conducting analysis and writing the manuscripts. Fellow authors had inputs relating to data collection, analysis and reviewing the manuscripts.

The studies are used as a basis for the results of the thesis, although they have been modified in content and structure to adapt to the specific thesis aims and objectives.

Ulla Griffiths

As part of my thesis preparations, I have been a co-author on the following papers, which are being referred to in the thesis:

1. Ayieko P, Akumu AO, **Griffiths UK**, English M., The economic burden of inpatient paediatric care in Kenya: household and provider costs for treatment of pneumonia, malaria and meningitis, *Cost Eff Resour Alloc*. 2009 Jan 22;7:3.

2. Edmond K, Clark A, Korczak V, Sanderson C, **Griffiths UK**, Rudan I. Global and regional risks of disabling sequelae from bacterial meningitis. *Lancet Infect Dis*. 2010 May;10(5):317-28.

3. Edmond K, Dieye Y, **Griffiths UK**, Fleming J, Ba O, Diallo N, Mulholland K, Prospective Cohort Study of Disabling Sequelae and Quality of Life in Children With Bacterial Meningitis in Urban Senegal, *Pediatr Infect Dis J*. 2010 Nov;29(11):1023-9

4. Ojo LR, O'Loughlin RE, Cohen AL, Edmond KM, Shetty SS, Bear AP, Loo JD, Privor-Dumm L, **Griffiths UK**, Zuber PLF, Mayers GF,Hajjeh RA, Global Use of *Haemophilus influenzae* type b conjugate vaccine, *Vaccine*. 2010 Oct 8;28(43):7117-22

5. Hajjeh RA, Privor-Dumm L, Edmond K, O'Loughlin R, Shetty S, **Griffiths UK**, Bear AP, Cohen AL, Chandran A, Schuchat A, Mulholland EK, Santosham M, Supporting new vaccine introduction decisions: lessons learned from the Hib Initiative experience. *Vaccine.* 2010 Oct 8;28(43):7123-9.

6. Temple B, **Griffiths UK**, Mulholland EK, RatunFT, Tikoduadua L, Russell FM, The cost of outpatient pneumonia in children less than five years of age in Fiji, *Trop Med & Int Health*, 2011 Oct 18 [Epub ahead of print]

7. Sinha A, Kim S, Ginsberg G, Franklin H, Kohberger R, Strutton D, Madhi SA, **Griffiths UK**, Klugman KP, Economic burden of acute lower respiratory infection among children in South Africa, *Paediatr Int Child Health,* 2012;32(2):65-73

8. Burchett HE, Mounier-Jack S, **Griffiths UK**, Mills AJ, National decision-making on adopting new vaccines: a systematic review, *Health Policy Plan.* 2012 May;27 Suppl 2:ii5-16

9. Burchett HE, Mounier-Jack S, **Griffiths, UK**, Biellik R, Chavez E, Haribondhu S, Jasim U., Konate M, Kitaw Y, Molla M, Ongolo-Zogo P, Wakasiaka S, Gilson L, Mills A, New Vaccine Adoption: Qualitative Study of National Decision-Making Processes in Seven Low- and Middle-Income Countries, *Health Policy Plan.* 2012 May;27 Suppl 2:ii5-16.

1 INTRODUCTION

The overall objective of this PhD is to assess the cost-effectiveness of Hib vaccine in low- and middle-income countries, in order to help policy makers determine whether it is good value for money to include the vaccine in routine childhood vaccination programmes. It is anticipated that this information will be useful not only to policy makers who are yet to introduce Hib vaccines, but also for countries with GAVI Alliance assisted provision that is due to cease in 2015. When these governments are required to take over financing of the vaccine, cost-effectiveness evidence is likely to be vital for ensuring that appropriate levels of funding are made available.

This thesis builds on work I undertook as Director of Cost-effectiveness for the Hib Initiative during 2006-2009. The Hib Initiative was a four-year project initiated and funded by the GAVI Alliance with the main objective of accelerating evidence-based decisions for Hib vaccine introduction in low-income countries [1]. The Initiative was a consortium of Johns Hopkins Bloomberg School of Public Health, LSHTM, the WHO, and the US Centers for Disease Control (CDC). The Director of the initiative was Dr. Rana Hajjeh, who was based partly at Johns Hopkins and at CDC during the project period. At LSHTM we were six staff working for the project; Professor Kim Mulholland, who was also a member of the Hib Initiative Steering Committee, Dr. Karen Edmond (senior lecturer in epidemiology), Mr. Andrew Clark (research fellow in mathematical modelling), Ms. Viola Korzcak (research assistant), Fiona Marquet (administrator), and myself (lecturer in health economics). The work of the Hib Initiative focused on three topics believed to be critical to overcome the barriers for vaccine introduction: (i) communications and advocacy, (ii) research and surveillance, and (iii) coordination of programmatic activities, such as finance, supply and vaccine logistics. My area of responsibility was cost-effectiveness analysis of the vaccine, which was integrated within the research and surveillance component. Several country-specific analyses, which were part of the technical assistance delivered by the Hib Initiative, are presented in this thesis. Country studies were either conducted in response to a request by the Ministry of Health or commenced by the Hib Initiative with the aim of answering specific research questions.

The thesis is divided into 13 chapters. Chapters 2 and 3 are introductory chapters providing a background to Hib disease and Hib vaccine, respectively. In Chapter 4 the purpose of economic evaluation is described. Chapter 5 presents two literature reviews; one of economic evaluations of Hib vaccine and one of treatment cost studies of Hib

disease in low- and middle-income coutries. Based on identified limitations with the existing evidence base, the thesis aims, objectives and conceptual framework are outlined in Chapter 6. The decision-analytic model used for the economic evaluation is presented in Chapter 7. Subsequent chapters consist of studies aimed at generating the required input parameters for the model. A meta-analysis of Hib vaccine efficacy estimates is presented in Chapter 8, health related quality of life from Hib disease is the topic of Chapter 9, and treatment and productivity costs of Hib disease are presented in Chapter 10, including a case study from Senegal on the costs of meningitis sequelae. Costs of Hib vaccine introduction are analysed in Chapter 11, exemplified with a study on incremental systems costs from Ethiopia. Hib vaccine cost-utility results from three countries, Belarus, India and Uzbekistan, are presented in Chapter 12. The final chapter contains thesis conclusions and considerations on the usefulness of economic evaluation for decision making in low- and middle-income countries. A number of reflections on the challenges of undertaking health economic studies in resource poor settings are also given in this chapter.

2 BACKGROUND TO *HAEMOPHILUS INFLUENZAE* TYPE B DISEASE

This introductory chapter contains background information on *Haemophilus influenzae* type b (Hib) disease. The issues described in this chapter are crucial for understanding the reasoning behind the methods used when developing the decision-analytic model and for recognizing the overall importance of the topic. The chapter is divided into six sections. In the first two sections the Hib bacterium and how it causes infection and disease are described. The different types of Hib diseases are summarized in section 2.3, followed by an overview of treatment practices. In section 2.5 an account of the difficulties regarding diagnostic procedures for detecting Hib are given. The epidemiology of Hib disease is described in section 2.6.

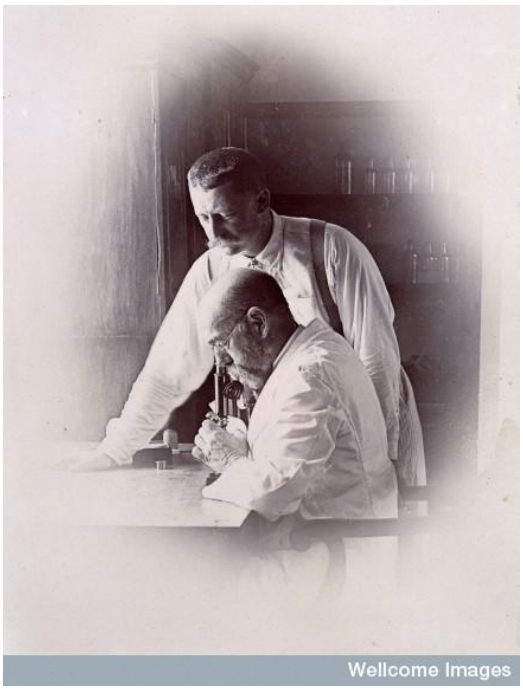
2.1 THE *HAEMOPHILUS INFLUENZAE* BACTERIUM

Haemophilus Influenzae (HI) is a gram negative bacterium that resides in the noses and throats of humans. HI was first discovered in 1892 by the German scientist Robert Pfeiffer who worked with Robert Koch. Robert Koch was the first scientist to devise a series of postulates used to verify the "germ theory of disease", which proposes that microorganisms are the cause of many diseases [2]. Robert Pfeiffer isolated HI from the lung and sputum of patients during the 1889-1892 global influenza pandemic and proposed that HI was the cause of influenza [3]. The organism was thus initially known as the "Pfeiffer influenza bacillus". However, during the 1918 influenza pandemic, which spread to nearly every part of the world and is commonly referred to as the Spanish flu, the etiological role of HI as a cause of influenza was rejected. In 1920 the Society of American Bacteriologists renamed the organism *Haemophilus influenza*e to acknowledge the historic association with influenza and to reflect the requirement for blood when growing the organism [3]. The word "*haemophilus"* is Greek and means "blood-loving". When the influenza virus was discovered by Smith *et al*. in 1933 any remaining confusion about the erroneous association between HI and influenza was finally dismissed [3].

In the 1930s Margaret Pittman, who worked at the Rockefeller Institute in New York, isolated six HI serotypes as well as "non-typable" HI. Pittman designated the six distinct serotypes as a, b, c, d, e and f, and she discovered that most isolates from cerebrospinal fluid and blood of patients were type b, indicating that mainly this type causes serious disease [4]. This was groundbreaking work, which eventually paved the way for development of a vaccine. A culture plate growing HI is seen in Figure 2.2. The surface of

HI is composed of a cell wall and polysaccharide capsule. Polysaccharide capsules are common cell-surface components of bacterial pathogens that cause systemic disease [5].

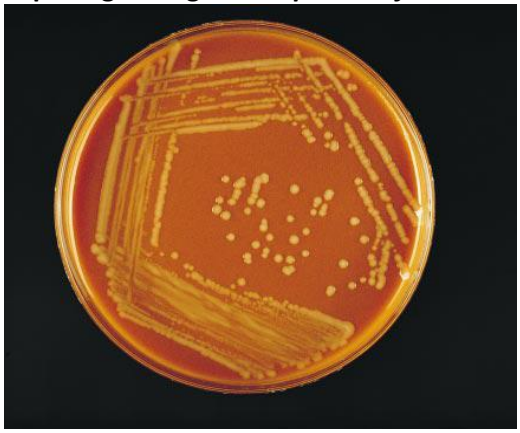
Figure 2.1: The discoverers of *Haemophilus influenzae* type b



Professors Koch and Pfeiffer investigating the plague in Bombay
(Photograph attributed to Captain C. Moss, 1897)

Margaret Pittman (1901-1995)

Figure 2.2:
A culture plate growing *Haemophilus Influenzae* bacteria

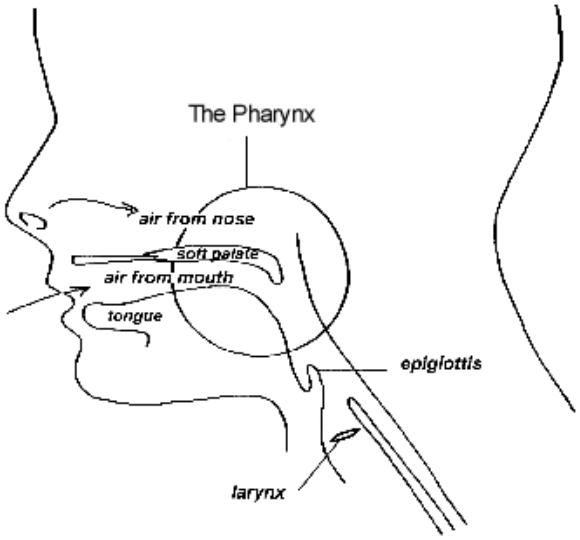


Source: WHO laboratory manual [6]

2.2 *HAEMOPHILUS INFLUENZAE* CARRIAGE AND TRANSMISSION

Humans are the only natural hosts of HI [7]. The bacterium is carried in the moist mucosa of the human nasopharynx (Figure 2.3) and transmitted from person to person via respiratory droplets or by direct contact with respiratory secretions [3]. Similar to other encapsulated bacteria, such as *Neisseria meningitides* and *Streptococcus pneumoniae*, HI is not particularly contagious; it requires close contact for transmission. The spread thus mainly occurs within families and day-care institutions. From the nasopharynx, HI can spread and cause both local and systemic disease [5], as the polysaccharide capsule mentioned above enables HI to evade the immune system in young children. Invasion occurs when there is dissemination of bacteria from the nasopharynx mucosa to the bloodstream and elsewhere in the body [3]. The time between infection and the appearance of symptoms is thought to be between two and ten days [5].

Figure 2.3: The nasopharynx



The relationship between carriage and subsequent development of disease is however not well understood. Only a very small fraction of those acquiring carriage of HI will develop disease. HI may pass from a patient with disease through many people who remain asymptomatic carriers before it again causes illness in a susceptible person. Hence, the incubation period and the pattern of transmission is difficult to determine [3]. Spread of infection has been documented in places with low carriage rates while no evident disease has been reported from areas with high carrier rates [8]. Three factors have been identified to have the potential to increase the risk of disease; lack of antibody levels, the size of the bacterial inoculum [9] and the presence of a concomitant viral infection [10].

HI carriage studies aim to determine the proportion of a defined population who are HI carriers, classified as persons with HI colonization in the nasopharynx mucosa. Many such studies, which are undertaken by collecting nasopharyngeal swabs from a sample of the population, have been conducted around the world [11, 12, 13, 14]. However, due to the low prevalence of HI carriage, relatively large sample sizes are needed for accurate estimates. Most studies in developed countries have found Hib carriage prevalence rates between 1% and 5% in young children, but most unimmunized children become colonized with Hib at some point during their first 2-5 years of life [7]. A modelling study from the UK has estimated the duration of carriage to be approximately five months [10]. HI carriage can be considerably higher in crowded areas, such as day-care centres, and carriage rates increase with the number of siblings in a family [15, 16]. For these reasons, HI carriage is generally higher in low-income than in high-income countries. In a study from Massachusetts, USA, before Hib vaccine introduction, samples were taken from 832 children less than 14 years attending day-care centres. It was found that 15.1% were colonized with Hib and 49% with other HI strains than type b [16]. A recent study in Northern India found a Hib carriage rate in children less than two years of 10% in rural areas, 7% in slum areas and 3% in urban areas [13]. In a study from Turkey, Hib carriage in children less than two years was found to be 7.2%, and there was no significant difference between children who had received Hib vaccine (6.8%) and those who had not (8.4%) [14]. While other studies have found substantial decreases in Hib carriage rate following Hib vaccine introduction [17, 18], there have been large variations among studies, and the specific interactions that explain how the vaccine limit Hib colonization are poorly understood [8].

2.3 *HAEMOPHILUS INFLUENZAE* DISEASES

HI can infect many parts of the body. Tissues most usually infected are summarized in Table 2.1. Common to all of these diseases are that they can be caused by many other pathogens than HI, with the exception of epiglottitis, which is only due to HI [19]. As a result, accurate laboratory diagnosis is crucial for determining both appropriate treatment and also whether HI should be considered a problem in the respective population.

In epidemiological studies, HI disease is generally divided into two categories; invasive disease and non-invasive disease. While approximately 95% of invasive HI diseases are due to type b, most non-invasive diseases are caused by nontypable HI strains [3]. Invasive HI disease is commonly defined as the *isolation of HI from a sterile site such as the blood stream, synovial fluid or cerebrospinal fluid* [20]. On the other hand, the term non-invasive disease is used when HI has been isolated from a non-sterile site, such as an external ear

Table 2.1: Types of *Haemophilus influenzae* diseases

HI disease	Infected tissue	Common clinical presentation
Invasive diseases:		
Meningitis	Lining of the brain	Fever, lethargy and poor feeding for infants. Headache, fever and stiff neck for older children
Epiglottitis	Epiglottis	Fever, sore throat, toxicity and upper airway obstruction
Septicemia	Blood	Fever without any apparent focus of infection which may lead to septic shock
Pneumonia	Lungs	Fever, cough and fast breathing
Cellulitis	Skin	Fever, skin swelling and redness, most commonly periorbital. Often associated with septicaemia
Septic arthritis	Joints	Fever, swelling and pain in large joints, such as knee, hip, ankle and elbow. Usually only one joint at a time
Osteomyelitis	Bones	Fever and bone swelling and tenderness
Pericarditis	Lining of the heart	Fever and respiratory distress
Non-invasive diseases:		
Otitis media	Middle ear	Fever and ear pain
Sinusitis	Sinuses	Fever and painful nasal passages

Source: Crawford and Daum (2004) [21]

or throat swab. Invasive diseases can be life threatening while non-invasive diseases are not fatal. The definitions can however coincide and are sometimes a cause of confusion. This is particularly the case for Hib pneumonia. Pneumonia is in the large majority of cases non-bacteraemic (meaning that the bacterium cannot be detected in blood) and therefore sometimes not classified as an invasive disease in epidemiological studies. However, since lung tissue can be classified as usually sterile, pneumonia is technically an invasive disease, but lung taps are rarely done. In many ways, the classifications are dependent on what can be detected in the laboratory, as explained in section 2.5 below.

One of the most severe forms of Hib disease is bacterial meningitis, which is characterized as an inflammation of the membranes that cover the brain and the spinal cord. If left untreated meningitis will in almost all cases lead to death [22]. Moreover, survivors of Hib meningitis can suffer from lifelong disabilities, such as deafness and a range of neurological problems that can be severe [23]. Other severe forms of Hib disease are epiglottitis, septicemia and pneumonia. Epiglottitis is a swelling and inflammation of the epiglottis and surrounding structures. The disease is considered a medical emergency because of the risk of sudden death from acute airways obstruction [21]. Septicemia

occurs when an organism such as Hib enters the blood stream. It may cause no symptoms and resolve without treatment, but it can also be a serious, life-threatening infection. If left untreated, Hib septicemia develop to meningitis in approximately 25% of cases [21]. Pneumonia is an inflammatory illness of the lung, usually caused by infection. While a large proportion of pneumonia cases are relatively mild and can be treated without hospitalization, pneumonia can also develop into a severe and critical form. Pneumonia is classified as community- and hospital-acquired pneumonia, in order to differentiate those cases that occur in hospitalized patients, usually due to bacteria circulating in the hospital, and those who are infected in the community. Hib is one of many causes of community-acquired pneumonia.

Rarer forms of invasive HI diseases are osteomyelitis, septic arthritis and pericarditis, which are infections of the bones, joints and lining of the heart, respectively. However, these are predominantly caused by microbial agents other than HI. When HI infects the middle ear and the sinuses it causes otitis media and sinusitis. While these non-invasive diseases are less severe, they are widespread. Otitis media is the most common infection of childhood [21]. However, most HI isolates causing otitis media and sinusitis are non-typable and therefore not preventable by Hib vaccine [21]. One of the largest studies ever undertaken on otitis media is an American study published in 1983. This study found that out of 2,625 cases of HI otitis media, approximately 6.3% were due to type b [24].

Many country-specific studies on Hib epidemiology have analysed the distribution of different invasive Hib diseases. These were all undertaken as sentinel surveillance in hospitals with contemporary laboratory facilities. Examples from the Czech Republic, England, Gambia and Thailand are seen in Table 2.2.

Meningitis was the most common type of invasive Hib disease detected in all four settings, comprising between 52% and 78% of all confirmed invasive Hib cases. However, the

Table 2.2: Distribution of different types of invasive Hib diseases in Czech Republic, Thailand, England and the Gambia

First author [ref.]	Country	Study sample size	Meningitis	Septicemia	Septic arthritis	Epiglottitis	Pneumonia	Cellulites
Lebedova [25]	Czech Republic	94	52%	5%	2%	33%	7%	0%
Likitnukul [26]	Thailand	79	56%	15%	1%	0%	25%	3%
Williams [27]	England	200	71%	3%	6%	12%	3%	6%
Adegbola [28]	Gambia	180	78%	2%	2%	0%	17%	1%

remaining distribution of different types of Hib diseases was quite different. Most importantly, while epiglottitis comprised 33% and 12% in the Czech Republic and England, respectively, this disease was not diagnosed at all in the Gambia and Thailand. Low rates of epiglottitis have also been observed in other developing countries and in indigenous populations in developed countries such as Australian Aboriginals [7, 29]. The reason for this geographic and population specific difference is unclear, but may relate to age exposure [30]. Epilottitis is most often seen in children above two years of age, so if Hib disease mainly occurs in children younger than two years, the incidence of epiglottitis is likely to be low.

Pneumonia constituted 7% of Hib diseases in the Czech Republic, 3% in England, 17% in the Gambia and 25% in Thailand. Pneumonia is one of the most common childhood illnesses and is believed to be the most frequent form of Hib disease globally [31]. It is estimated that pneumonia caused approximately 18% of global deaths in children under the age of five in 2008 [32] and Hib vaccines are seen as an important tool to reduce this mortality. However, the true incidence of Hib pneumonia in children is unknown because the signs and symptoms of Hib pneumonia cannot be differentiated from those of pneumonia caused by many other microorganisms and only a proportion of Hib pneumonia is bacteraemic. Invasive lung tap procedures are required to obtain cultures that can prove the proportion of Hib pneumonia and these are seldom performed. It is thus possible that the prevalence of Hib pneumonia is under-estimated in the four studies referred to above. The uncertainty about the proportion of total pneumonia episodes and deaths caused by Hib is a major topic of this thesis, as it is pivotal for determining the cost-effectiveness of the vaccine. No cases of osteomyelitis and pericarditis were identified in the four example studies, confirming that these are rare Hib diseases.

2.4 RECOMMENDED TREATMENT

Antibiotics kill or damage bacteria and are today among the most frequently prescribed medications in the world. All Hib diseases are treated in largely the same way; through an intensive and sustained course of antibiotics [3]. Antibiotics are classified according to their chemical structure, which determines their effectiveness, toxicity, and allergic potential. Most antibiotics were discovered during the 1940s and 1950s, but new agents within the same class are continually being developed. The main reason for development of new agents is antibiotic resistance, which has become a growing problem since the 1970s. When bacteria are exposed to the same antibiotics repeatedly, they can change and no longer be affected by the drug. This mounting problem is caused by the widespread use of antibiotics both inside and outside the medical system. Within the medical system the

biggest problem is inappropriate and over-prescribing of antibiotics, which apply selective pressure to potentially pathogenic bacteria that are carried by children with minor, usually viral illnesses. When the bacteria are found or suspected to be resistant to first generation antibiotics, treatment has to be switched to second- or third-generation drugs, which are generally considerably more expensive and sometimes more toxic. In low-income countries the high cost of such replacement drugs is prohibitive, with the result that some diseases, particularly meningitis, can no longer be treated in areas where resistance to first-line drugs is widespread. Hib vaccine thus has the added advantage of potentially reducing the demand for antibiotics, thereby slowing the spread of antibiotic resistance.

Penicillin became available after the Second World War and was initially active against Hib, but resistance soon developed. Chloramphenicol was the first broad spectrum antibiotic, first licensed in 1950, and ampicillin/amoxicillin became available in the 1970s. The 3rd generation cephalosporins, the first of which was cefotaxime, was licensed in 1983 and have become the standard for treatment of invasive Hib disease and meningitis in general.

Since all Hib diseases are treated through an intensive and sustained course of antibiotics, this is the most important type of drug to include in treatment cost estimates. However, total treatment costs vary according to setting and mode of drugs delivery. Antibiotics can be administered intravenously (IV), intramuscularly (IM) or orally. While hospital admission is generally needed for IV and IM administration, oral delivery can take place in outpatient settings and at home.

WHO recommended treatment procedures for Hib diseases are outlined in Annex 1. The purpose of these standard recommendations is first of all to reduce mortality, but also to support the rational use of antibiotics [33]. Treatment of meningitis routinely requires hospitalisation with IV antibiotics, and the course of antibiotics should last for a total of three weeks. Similarly, for treatment of epiglottitis, cellulitis, septic arthritis, serticemia and osteomyelitis hospitalisation with IV or IM antibiotics is necessary. The appropriate treatment of pneumonia varies according to severity. While very severe and severe pneumonia require hospitalisation with IV or IM antibiotics, children with non-severe pneumonia should receive antibiotics as outpatients.

The WHO recommendations on the different types of antibiotics to be used, as specified in Annex 1, are guided by known antibiotic resistance patterns and global market prices of the drug. Examples of prices of antibiotics recommended by the WHO for treatment of

bacterial meningitis and pneumonia are summarised in Table 2.3. These were compiled from the International Drug Price Indicator; a comparative guide of drug prices from pharmaceutical suppliers, international development organizations, and government agencies published by the Management Sciences for Health and the WHO (http://erc.msh.org). The procurement prices quoted for International Mission Hospitals were chosen for this example. It is seen that the most expensive IM compound, ceftriaxone, is five times as expensive as IM ampicillin. While the WHO recommends both drugs for treatment of meningitis, Hib is now resistant to ampicillin in many settings [34].

Table 2.3: Unit prices of selected antibiotic compounds used for treatment of Hib disease procured by International Mission Hospitals (2009)

Generic name	Strength	Dosage form	Route of admin.	Package	Package price (US$)	Unit price (US$)
Sulfamethoxazole + Trimethoprim	200+40mg/5ml	Liquid	Oral	1 bottle (100 ml)	0.39	0.0039/ml
Amoxicillin	250 mg/5 ml	Liquid	Oral	1 bottle (100 ml)	0.56	0.0056/ml
Ampicillin	500 mg	Vial	IM	50 vials	5.30	0.106/vial
Cefotaxime	500 mg	Vial	IM	1 vial	0.16	0.1556 /vial
Penicillin	2.4 mu	Powder	IM	50 vials	10.87	0.2174/vial
Chloramphenicol	1 g	Vial	IM	50 vials	12.44	0.2488/vial
Ceftriaxone	500 mg	Vial	IM	1 vial	0.53	0.5300/vial

Source: (http://erc.msh.org/mainpage.cfm?file=1.0.htm&module=DMP&language=english)
IM: Intramuscularly

2.5 LABORATORY DIAGNOSIS

Laboratory diagnosis of Hib disease is essential for two reasons. At the hospital, accurate diagnosis is necessary for the clinician to be able to administer the most effective treatment to the patient. This is particularly important in settings with antibiotic resistance. Another fundamental purpose of laboratory diagnosis is to be able to determine the overall burden of Hib disease. All the Hib diseases described in section 2.3, apart from epiglottitis, are also frequently caused by other organisms, including other bacteria, such as *Streptococcus pneumoniae* and *Neisseria meningitidis,* as well as viruses and parasites, and it is therefore only possible to determine whether Hib is the source if the bacterium is identified in a laboratory from a sterile site.

Meningitis is the most studied type of Hib disease for three key reasons: (i) it is the most severe form of Hib disease, (ii) it has a relatively straightforward clinical diagnosis, and (iii) it is the type of Hib disease that can be most easily diagnosed in a laboratory. The

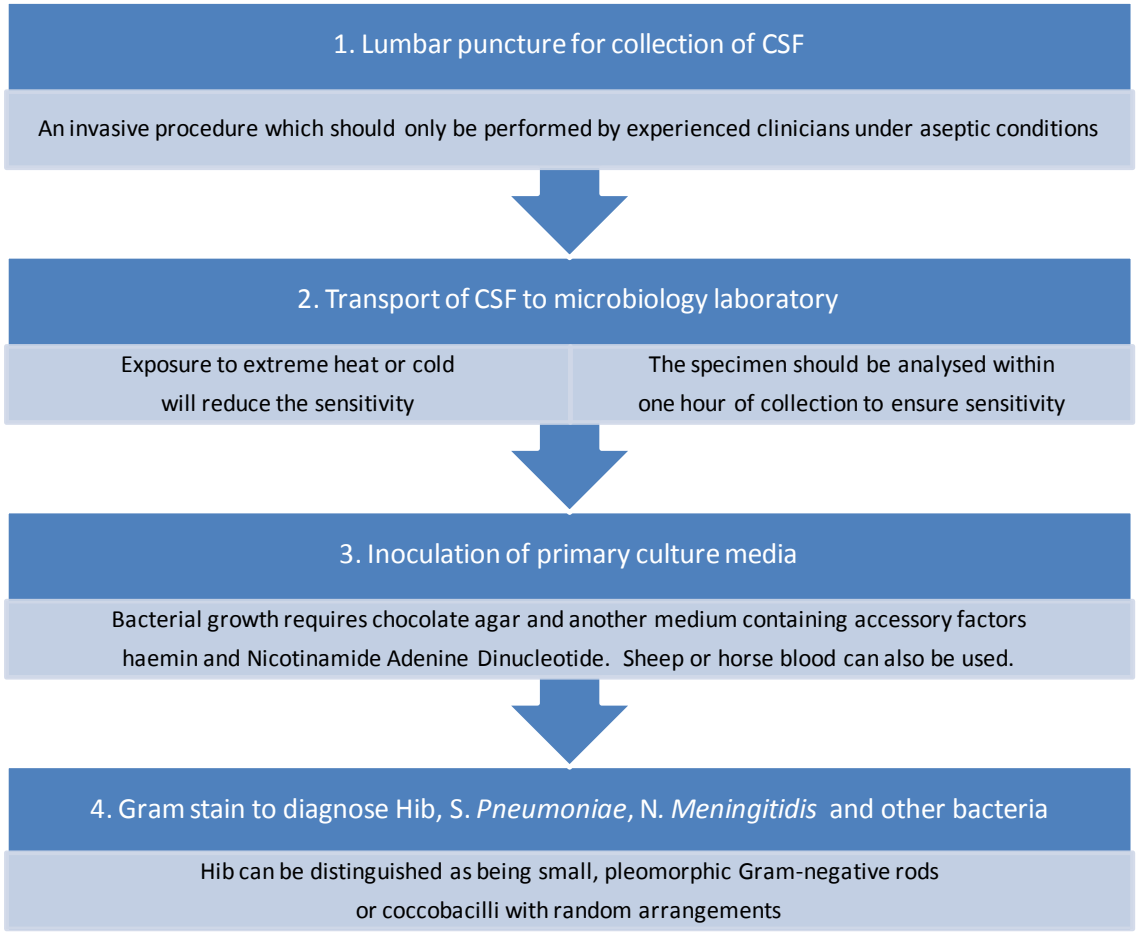
bacterial agents of meningitis can be identified by culture of cerebrospinal fluid (CSF) from patients with clinical symptoms of meningitis [35]. Moreover, because severe meningitis in children is always caused by bacterial agents, the yield from CSF cultures of these patients is greater than from blood cultures of patients with most other Hib syndromes. Pneumonia can for instance occur due to many different types of viruses and parasites as well as bacteria, so an extraordinary large sample of patients would be needed to demonstrate disease burden due to Hib. Since only a relatively small proportion of pneumonia is bacteraemic, the best way to establish the etiology of pneumonia is by lung puncture or open lung biopsy. However, the risks of these procedures are relatively high, so they are used only in special clinical circumstances [36].

Recommended procedures for diagnosing Hib meningitis are outlined in Figure 2.4. In low-income countries with relatively limited laboratory capacities, it can be intrinsically difficult to grow Hib from CSF and/or blood. Hib is demanding in its growth requirements, so the process summarized in Figure 2.4 only needs to be sub-optimal in one small area and Hib will not be detected in the culture, leading to underestimates of Hib disease prevalence. Moreover, use of antibiotics before the CSF is taken reduces the sensitivity of the culture considerably [20].

A common problem seen in laboratories in low-income countries is the use of discarded human blood instead of sheep blood, horse blood, or commercially available chocolate agar for primary isolation [37]. In low-income country hospitals it is thus common that Hib has never been diagnosed from any CSF. This was for instance the case after a review of seven hospital laboratories in Uzbekistan in 2002 [38]. Similarly, in Latvia in 1993, it was reported that out of 291 cases of bacterial meningitis, a definite bacterial aetiology was only established in 50% of cases, and these were mainly S*teptococcus pneumonia* and *Neisseria meningitidis* while none were Hib. After an evaluation of the reagents used in the laboratory, it was shown that with the addition of agar supplements, it was possible to grow Hib [39].

Due to the laboratory constraints it is thus not straight forward to demonstrate whether Hib is a problem or not in low-income settings. The problems arising with regard to assessing the true burden of Hib disease and subsequently the cost-effectiveness of the vaccine are explained in detail within this thesis.

Figure 2.4: Step-by-step procedures for laboratory diagnosis of Hib meningitis

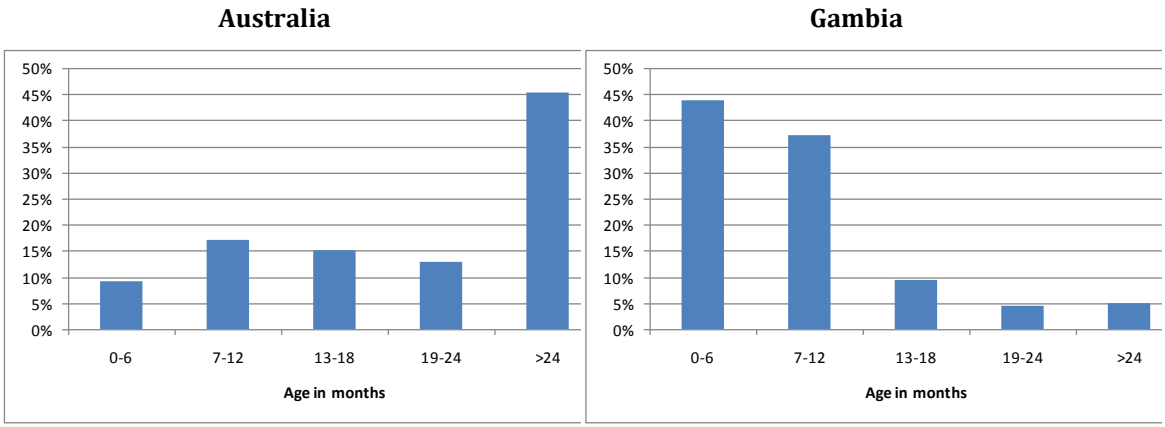


Source: WHO laboratory manual for bacterial meningitis (1999) [6]

2.6 HIB EPIDEMIOLOGY

Hib disease is mainly seen in children less than two years of age and rarely in children above five years or adults [7]. While the incidence of Hib disease is relatively low during the first few months of life, the risk increases as maternal immunity wanes. The highest risk period is usually between six and 18 months, although in high-risk African countries more than half of all cases are in children less than six months of age. By the age of five years the incidence of Hib disease is universally low and remains low throughout adulthood with only a small increase in the incidence in the very elderly [5]. Figure 2.5 shows the age distribution of Hib meningitis in Australia and the Gambia before Hib vaccine introduction. A general difference that has been observed between low- and high-income countries is seen. While studies from developed countries demonstrate a peak in the incidence around two years, the majority of cases in developing countries occur during the first year of life [30].

Figure 2.5: Age distribution of Hib meningitis cases in Australia and the Gambia



Source: McIntyre *et al*. (1991) [40] and Adegbola *et al*. (1996) [28]

Establishment of Hib disease incidence in children less than five years in different countries and regions of the world has been the subject of much research and some controversy. Since invasive Hib disease is not reliably reported, population based epidemiological studies are needed to determine the incidence. The WHO has developed guidelines for population based surveillance of Hib disease [35] and several studies following these recommendations have been undertaken during the past two decades [41, 42, 43, 44]. Hib meningitis incidences per 100,000 children less than five years for a selection of settings are summarized in Table 2.4.

A comparison of study results shows considerable variability between countries, and many authors have tried to explain this difference [22]. It can probably be concluded that while some of the differences are due to the laboratory and epidemiological methods used, there is also a real difference among populations. One of the most debated topics has been the disease incidence in Asia [45, 46, 47]. Some population based studies in this region have shown incidence rates one tenth of those observed in North America and Europe, and there is still not enough knowledge to conclude whether these results reflect a true low disease burden, or whether they are due to problems in detection, such as widespread use of antibiotics before hospitalization and/or suboptimal microbiologic methods for culturing Hib. Use of antibiotics before clinical assessment has two distinct effects: It can treat the child during the bacteraemic phase, thus preventing meningitis, or it simply suppresses the culture positivity.

Table 2.4: Hib meningitis disease incidence before Hib vaccine introduction in selected countries

	Incidence per 100,000 children < 5 years	Source
Africa:		
Senegal	36	Cadez (1981) [48]
Gambia	60	Bijlmer (1990) [49]
Niger	51	Campagne (1999) [50]
America:		
USA	22	Wenger (1998) [51]
Asia:		
Thailand	4	Rerks-Ngarm (2004)[45]
Hong Kong	2	Lau (1995) [52]
Vietnam	12	Anh (2006) [53]
Europe:		
France	13	Reinert (1993) [54]
England	24	Tudor-Williams (1989) [55]

Not all individuals within a population are at equal risk of Hib disease and a number of factors associated with an increased risk have been identified [5]. In the United States, Hib disease has been noted to be 1.2-1.5 times higher in boys than in girls and to be 2-4 times higher for black than for white children less than five years old [51]. Indigenous populations, such as Aboriginals in Australia, Alaskan Eskimos and Apache and Navajo Indians have been shown to have the greatest known risk of invasive Hib disease with rates as high as 400 per 100,000 children [56]. The reasons for these very high rates are likely to be a combination of genetic and environmental interactions [5].

During 2004-2009 particular efforts were made to generate country-specific Hib disease incidence and case fatality rates for all WHO member states for the year 2000. The "Global Burden of Disease (GBD) of Hib and pneumococcal diseases project" was undertaken as collaboration between the WHO, the Hib Initiative and the Pneumococcal Vaccines Accelerated Development and Introduction Plan (PnemoADIP) project. The methods and results of this project were published in the Lancet in 2009 [31, 57, 58]. The paper by Watt *et al*. provides a table with estimates of Hib cases, deaths, incidence rates and case fatality rates according to WHO regions [31]. The mortality table is replicated in Table 2.5, showing that a total of 370,200 deaths were estimated in 2000, with 49% occurring in Sub-Saharan Africa. 79% of Hib deaths were estimated to be caused by pneumonia.

Country specific estimates are only available in letters sent by the WHO to Ministries of Health of all member states informing them about the estimates and inviting them to provide additional information. Countries with no population-based Hib surveillance data available could use these numbers for illustrating impact and cost-effectiveness of the vaccine. As will be seen in Chapter 7, the decision-analytic model developed for this thesis has been designed so that the GBD estimates can be easily used as input data.

Table 2.5: Global estimated deaths due to Hib disease in year 2000

Type of Hib disease	Africa	Americas	Eastern Mediter-ranean	Europe	South East Asia	Western Pacific	Total
Pneumonia	146,000	4,900	41,600	6,500	75,300	17,600	**291,900**
Meningitis	34,600	3,500	6,800	2,000	21,800	9,500	**78,200**
NPNM	100	<100	<100	<100	<100	<100	**100**
Total	***180,700***	***8,400***	***48,400***	***8,500***	***97,100***	***27,100***	***370,200***

Source: Watt *et al.* (2009) [31]
NPNM: Non-pneumonia, non-meningitis

3 BACKGROUND TO *HAEMOPHILUS INFLUENZAE* TYPE B VACCINES

3.1 AVAILABLE HIB VACCINES

The first vaccine developed against Hib was produced in the early 1970s and was composed of purified Hib capsular polysaccharide. This vaccine was however only effective in adults and children above two years of age, as young children have poor immune responses to T-cell-independent antigens such as polysaccharides [59]. Subsequently, more immunogenic vaccines were developed by conjugating capsular polysaccharides to protein carriers. The first conjugated Hib vaccine was licensed in 1987 in the USA. Four different Hib conjugate vaccines that differ in the carrier protein, the structure and lengths of the polysaccharide, polyribosol-ribitol phosphate (PRP) element and the method of conjugation, have been developed [20]. The four vaccines are known as PRP-D, PRP-OMP, HbOC and PRP-T (Table 3.1).

The PRP-D vaccine was licensed following a successful trial in Finnish children [60]. However, the vaccine was the least immunogenic of the four vaccines, and when it subsequently proved ineffective in preventing Hib disease in Alaskan children [61], it was taken out of production [7]. The three currently available vaccines are produced by different companies and it should be noted that the PRP-T has never been patented. The immune response of the different vaccines varies. As shown in Figure 3.1, the PRP-OMP elicits a greater response after the first dose, but the geometric mean titres elicited after three doses are higher for the other vaccine types, although this does not mean greater effectiveness. Consequently, the PRP-OMP is seen as the vaccine of clinical choice

Table 3.1: Conjugate Hib vaccines that underwent clinical trials or controlled intervention studies during the 1980s and early 1990s

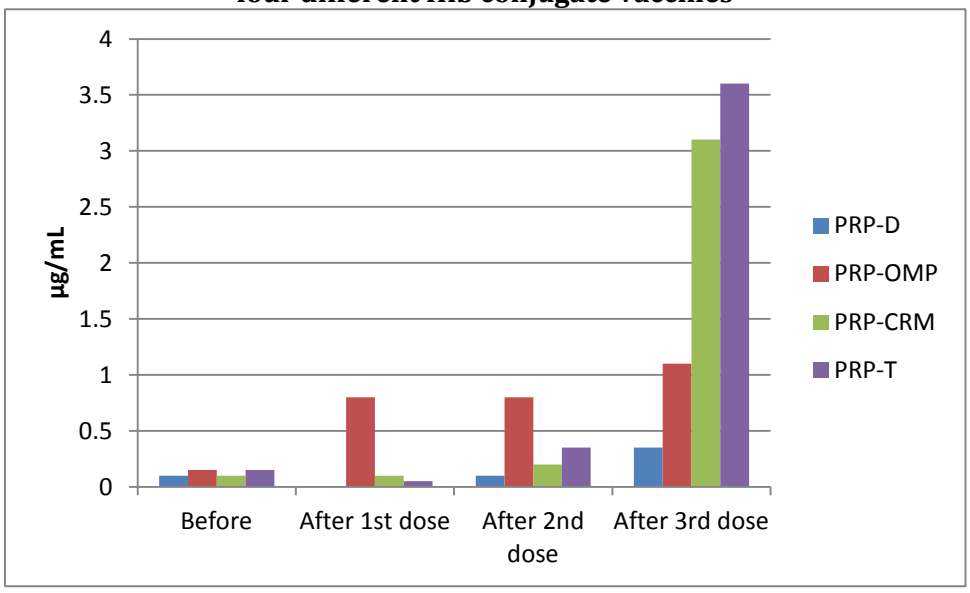
Product type	Carrier protein	Original manufacturer	Year licensed in the USA	Status
PRP-D	Diphteria toxoid	Connaught	1987	Not available
PRP-OMP	*Neisseria meningitidis* group B outer membrane protein complex	Merck	1990	Available
HbOC	Mutant non-toxic diphteria toxoid	Praxis Biologics	1991	Available
PRP-T	Tetanus toxoid	Pasteur Merieux	1993	Available

Source: Chandran *et al*. (2008) [30]

in populations with high Hib disease incidence in very young children where a good response is needed after the first dose. In other populations, the PRP-T or the HbOC vaccines are likely to be the best options. It should however be noted that the HbOC seems to need two months between the doses to provide adequate immunity whereas PRP-T does not, so HbOC may not be suitable for all schedules. Vaccine efficacy of the different vaccines has been evaluated in a meta-analysis as part of this thesis, which is presented in Chapter 8.

There are numerous different types of Hib vaccine presentations available, such as monovalent vaccine or as a combination vaccine with several other vaccines. Since Hib vaccine can be delivered at the same time as diphtheria-tetanus-pertussis (DTP) vaccine, combination vaccines are widely used as these are generally preferred by both health care workers and parents because the number of injections needed is reduced. The different vaccine presentations are reviewed in conjunction with Hib vaccine prices in Chapter 11.

Figure 3.1: Comparison of antibody response to four different Hib conjugate vaccines



Source: Watt *et al.* (2003) [20]

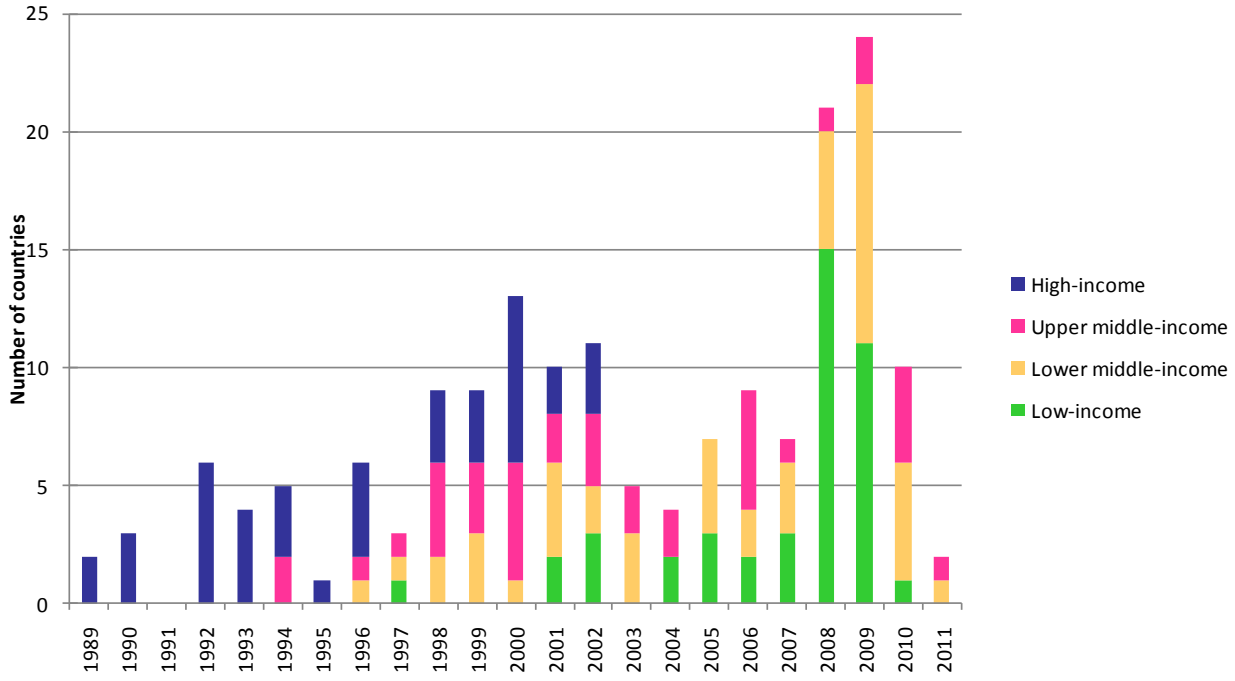
3.2 TRENDS IN HIB VACCINE UPTAKE

During the 1980s, substantial investments were made in routine vaccination programmes around the world, with global vaccination coverage of the third dose of DTP vaccine reaching 75% in 1990 compared to 20% in 1980 [62]. These efforts were led by WHO and Unicef through the Universal Child Immunization Initiative [63]. Hence, during the early 1990s, most programmes had become sufficiently mature to manage the introduction of a new vaccine. High-income countries relatively quickly introduced Hib vaccine into their routine schedules. However, as was the case with hepatitis B vaccine, uptake of Hib

vaccine was slow in low- and middle-income countries. As seen in Figure 3.2, the first time Hib vaccine was introduced into a low-income country was in 1997. This country was the Gambia where the only African Hib vaccine trial took place and Hib vaccine introduction was made possible through a donation from the vaccine manufacturer that had supplied vaccine for the trial. In 2001, Kenya and Ghana were the first two low-income countries to introduce the vaccine with GAVI Alliance support.

The uptake of Hib vaccine has recently increased substantially. As of July 2011, 172 of the world's 196 countries (88%) have adopted the vaccine into their routine programmes, but 50% of these have only done so only during the past eight years (Figure 3.2). Most low- and lower-middle income countries have introduced the vaccine with support from the GAVI Alliance, amounting to 37% of the 172 countries that have introduced. The international attention GAVI has given to Hib vaccine may also have influenced upper-middle-income countries, as their uptake has also increased during the past few years. During 2010, four upper middle-income countries (Botswana, Bulgaria, Gabon and Seychelles) adopted the vaccine. The two countries that introduced in 2011 were Azerbaijan and Vanuatu.

Figure 3.2: Number of countries introducing Hib vaccine 1989-2011 according to 2010 World Bank income groups



Source: The Hib Initiative, the WHO and the GAVI Alliance

3.3 GAVI ALLIANCE POLICY ON HIB VACCINE

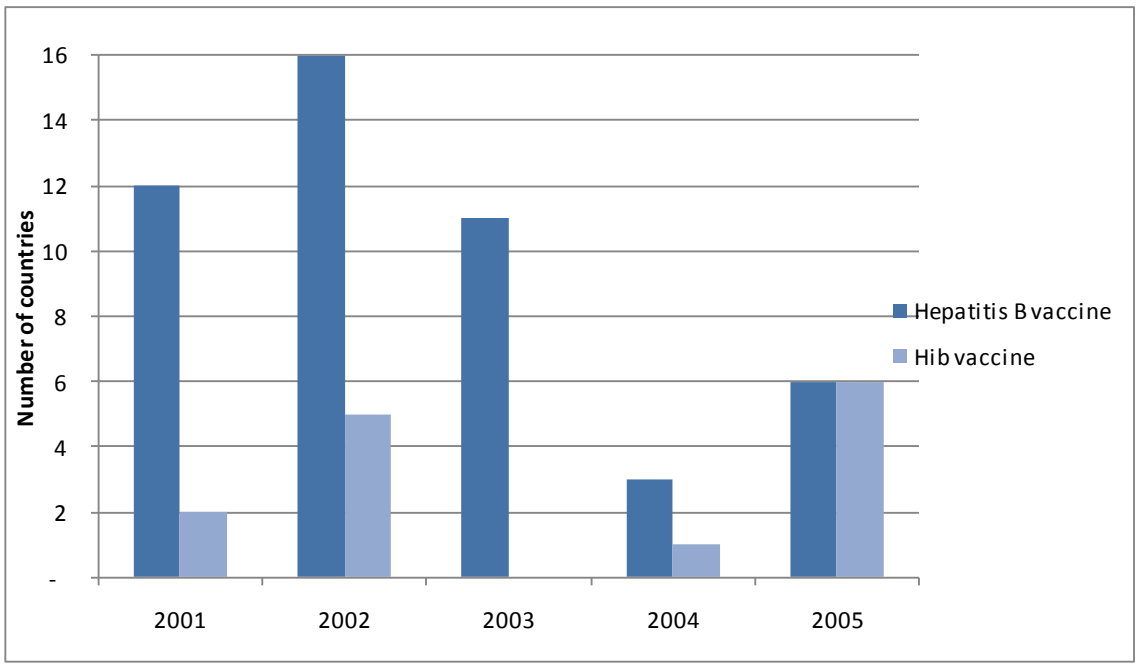
Since 2000, the GAVI Alliance has provided financial support for Hib vaccine to the poorest countries in the world. During GAVI's first phase (2000–2005), eligibility was determined by 1998 Gross National Income (GNI) per capita of less than US$ 1,000, making 77 countries eligible for support [64]. For the second phase (2006 – 2010) the criteria was adjusted to 2003 per capita GNI of less than US$ 1,000, which led to 72 eligible countries. The current eligibility threshold, established in 2011, is per capita GNI of less than US$ 1,500 and this threshold will be adjusted annually for inflation to remain constant in real terms. Of the 72 countries eligible in the second phase, 16 now have per capita GNI levels in excess of US$ 1,500 per annum and the assistance to these countries will therefore end when their current support terminates in 2015 [64]. The graduating countries are: Angola, Armenia, Azerbaijan, Bhutan, Bolivia, Congo, Cuba, Georgia, Honduras, Indonesia, Kiribati, Moldova, Mongolia, Sri Lanka, Timor-Leste and Ukraine.

In addition to the GNI criteria, it is also a condition that countries must have DTP vaccination coverage rates above 50% to be eligible to apply for new vaccine support [65]. The rationale for this condition is that programmes need to be relatively strong to be able to effectively introduce a new vaccine, and DTP vaccine coverage is considered a valid approximation for measuring programme strength.

Despite the availability of financial support since year 2000, the introduction of Hib vaccine remained uncommon among the GAVI eligible countries during the first phase. Figure 3.3 shows that while 48 countries introduced hepatitis B vaccine between 2000 and 2005, only 14 chose to apply for Hib vaccine. In response, in June 2005, the GAVI Alliance established the Hib Initiative with the aim of accelerating the use of evidence-informed decision-making about Hib vaccine in GAVI-eligible countries. As mentioned in the introduction, the consortium's members were Johns Hopkins Bloomberg School of Public Health, the WHO, the US Centers for Disease Control and Prevention and the LSHTM. The Hib Initiative's strategy focused on communication, research and coordination with various partners, especially the WHO regional offices [66].

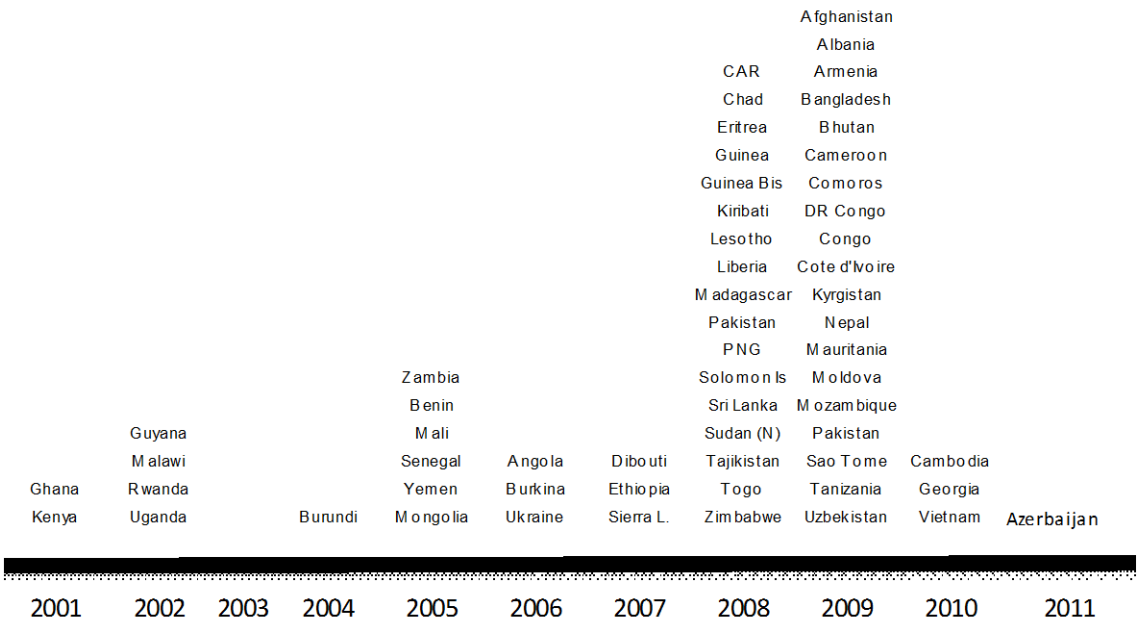
Between 2004 and 2008, uptake among GAVI-eligible countries increased by 56% and out of the 77 initially GAVI eligible countries, 65 had introduced the vaccine by 2011 (Figure 3.4). Honduras, Nicaragua, Turkmenistan and Ukraine were GAVI eligible in the first two

Figure 3.3: Hepatitis B and Hib vaccine introduction in GAVI eligible countries 2000-2005



Source: GAVI Alliance secretariat

Figure 3.4: Hib vaccine introduction supported by the GAVI Alliance 2000-2011



Source: GAVI Alliance Secretariat

phases, but these countries had either already introduced the vaccine when GAVI was established or they chose to introduce it using government funds; they have thus not taken advantage of GAVI support for Hib vaccine.

The remaining initially GAVI eligible countries which in early 2012 have still not introduced the vaccine at a national level are China, DPR Korea, Haiti, India, Indonesia, Myanmar, Nigeria, Somalia, South Sudan and Timor Leste. All of these countries are regarded as "special cases", either because of internal political issues or because of their GAVI eligibility status. China was only eligible in phase one and did not apply for Hib vaccine at that time. Somalia, Nigeria and Haiti have until recently reported DTP vaccine coverage rates less than 50% and have thus not been able to apply to GAVI for new vaccines, including Hib vaccine. However, reported coverage has been above 50% during the past few years in all three countries and they all applied, and were approved, for Hib vaccine in May 2011. Hence, introduction should happen during 2012. DPR Korea and Timor Leste were also approved for Hib vaccine support in May 2011. The population sizes of India and Indonesia have been too large for GAVI to be able to grant these countries full support. Although these limitations have recently been loosened and India and Indonesia have now applied for Hib vaccine support, the assistance has not yet been fully granted due to several challenging issues. The case of India is explained in this thesis. Myanmar and South Sudan are thus the only GAVI eligible countries that have not yet applied for the vaccine.

During the first phase of GAVI, 100% of the costs of the new vaccines and injection supplies were granted to countries, normally for a five-year period. In GAVI phase II, it was decided to introduce co-financing for new vaccines. This policy and its implications for recipient countries are explored with the Indian and Uzbekistan case studies in Chapter 12.

4 BACKGROUND TO ECONOMIC EVALUATION

This chapter provides a brief introduction to the field of economic evaluation. In section 4.1 and 4.2, the objectives and the basic principles of economic evaluation are explained. Analytical frameworks are summarized in section 4.3, discounting in section 4.4, the incremental cost-effectiveness ratio is explained in section 4.5, and issues specifically related to economic evaluation of vaccines are discussed in section 4.6.

4.1 OBJECTIVES OF ECONOMIC EVALUATION

The foundation of economics is a scarcity of resources. Scarcity has two sides; the infinite nature of human wants and the finite or limited nature of resources available to produce goods and services. Health care in our time is marked by infinite demands partly due to an increase in real income, a growing proportion of elderly in the population, development of new drugs and medical technologies, and new emerging diseases, such as HIV, type 2 diabetes and obesity. Resources, including staff, health facilities, medical technologies and knowledge, however remain limited. Economic evaluation is one of the most applied branches of health economics, as it provides researchers with a set of methodologies to estimate how to optimise the use of scarce resources with respect to maximising health gain.

Economic evaluation can be defined as a "comparative analysis of alternative courses of action in terms of both their costs and their consequence"[67], and it attempts to identify ways in which scarce resources can be employed efficiently so that healthcare resources are being used to obtain the best "value for money". Adopting the criterion of value for money or "efficiency" implies that society makes choices that maximize the health outcomes gained from the resources allocated to health care. Inefficiency exists when resources could be reallocated in a way which would increase the health outcomes produced [68]. There are three types of efficiency; technical, economic and allocative. Technical efficiency refers to the physical relation between resources and outcomes and addresses the issue of using given resources to maximum advantage. Economic efficiency refers to the maximization of outcomes for given costs and is thus about choosing different combinations of resources to achieve the maximum health benefit or given level of output at least cost [68]. The concept of allocative efficiency takes into account not only economic efficiency with which healthcare resources are used to produce health outcomes, but also that the generated goods and services are in accordance with societal preferences [69]. Economic evaluation can be viewed as a method of assessing these notions of efficiency.

4.2 BASIC PRINCIPLES OF ECONOMIC EVALUATION

An economic evaluation consists of a comparison between two or more alternative courses of action. The alternative that produces the most health effects is often also the most costly and we are therefore looking at the *incremental* costs of achieving *incremental* health effects. If the analysis shows that the least costly alternative also produces the most health effects, this is said to dominate the other alternatives [67].

The perspective of an analysis refers to the types of costs included and this need to be determined from the outset. There are generally two perspectives to consider; the health sector and society. When using a health sector perspective, only the costs incurred by the health service provider are included, while costs such as medicines bought by patients and patients' travel costs are excluded. In the societal perspective all costs are included irrespective of who pays. Time costs, also referred to as productivity or indirect costs, can also be included in this perspective. Three types of cost data are relevant for an economic evaluation of a vaccine: (i) costs of vaccine delivery, (ii) disease treatment costs and (iii) productivity losses. Vaccine delivery costs include the costs of the vaccine, injection supplies and items such as vaccine storage and transport. Treatment costs for the disease in question are comprised of outpatient visits and hospitalizations during the acute disease period and any long-term costs due to disability. Productivity loss from disease could be included if a societal perspective is taken. For example, for childhood diseases the time loss of parents while looking after a sick child can be incorporated.

Economic evaluations can be divided into three different types, which vary according to the chosen outcome measure. While costs are always expressed in monetary values, there are a number of options for measuring and valuing effects (Table 4.1). In a cost-effectiveness analysis, the health effect is measured in natural units, such as numbers of infections or life years. However, the usefulness of this analysis may be limited because the outcomes measures are not comparable to those used for measuring the impact of other interventions. The costs per life years gained are for instance only comparable to analyses of other interventions where premature deaths are prevented and cannot be compared to interventions that solely prevent or treat morbidity. Moreover, some of the outcome

Table 4.1: Three types of economic evaluation methods

Type	Cost measurement	Effect measurement
Cost-effectiveness analysis	$	Natural units (cases, life years)
Cost-utility analysis	$	Healthy years (QALYs/DALYs)
Cost-benefit analysis	$	$

measures used in cost-effectiveness analysis, such as costs per child vaccinated or costs per infection prevented, are intermediate instead of final outcome measures and are therefore often not adequate as a guide for overall resource allocation decision making because they are difficult to interpret and ignore longer term costs and consequences.

The main limitations of cost-effectiveness analysis are usually addressed in cost-utility analysis where the outcome measure is expressed in terms of morbidity and mortality, combined in a single measure. The two most commonly used measures are Quality Adjusted Life Years (QALYs) and Disability Adjusted Life Years (DALYs). QALYs are derived by weighting time spent in a particular health state with a corresponding preference score. The preference scores are collected from both the general population ("community preferences") and from patients in different health states using validated tools. However, in many cost-utility analyses from low-income countries, DALYs are used instead, as preference scores are rarely collected in these countries. For DALYs, generic, disease-specific disability weights are used, which do not involve country-specific data collection. The differences between DALYs and QALYs with respect to health related quality of life due to Hib disease are explored in Chapter 9.

Cost-benefit analysis (CBA) is the original type of economic evaluation, dating back to around 1820 when the British economist Alfred Marshall devised the formal concepts of the approach. In CBA, all costs and benefits of a particular project are compared in monetary terms; if benefits exceed the costs, the project is considered worthwhile. Today the method is widely used in many sectors and businesses, such as for evaluating water dams or motorways. Within the transport sector, a common method for determining the monetary value of traffic fatalities is the "value of a statistical life" approach [70].

In a CBA of a health intervention, such as Hib vaccine, the costs of disease in terms of treatment costs and lost productivity due to mortality and morbidity are compared against the costs of delivering the intervention. The estimates are combined in a benefit-cost ratio and if the ratio exceeds one, the intervention is considered advantageous, as the benefits are greater than its costs. The two most common methods for determining a monetary value of health are the human capital and the willingness to pay approaches [67]. In the human capital approach a market wage is used to place a monetary weight on healthy time, while in the willingness to pay approach the value is either directly assessed by survey or inferred from decisions actually made that involve trade-offs between health and money [67]. Since only the willingness to pay approach assesses the actual value people place on a life, it is usually considered the stronger method of the two [67].

4.3 ANALYTICAL FRAMEWORKS

Broadly speaking, three main frameworks are commonly used to undertake an economic evaluation; alongside a controlled clinical trial, using a decision-analytic model or a mixture of the two. The advantage of conducting economic evaluations alongside a clinical trial is the relatively easy availability of patient-specific data on both costs and outcomes. Moreover, given the large costs of conducting a clinical trial, the marginal costs of adding economic data collection to the study may be modest. There is however broad consensus that a purely trial-based study poses several problems [67]. One issue is that the comparison therapy might not be the most relevant for economic analysis. Secondly, clinical trials frequently make use of surrogate instead of final health outcomes and thirdly, since clinical trials have limited follow-up time, long-term effects remain unknown in a purely trial-based economic evaluation. Hence, decision-analytic models, which are able to predict final health impacts, are generally considered to be unavoidable when undertaking an economic evaluation [71].

Decision analysis is defined as "a systematic approach to decision making under conditions of imperfect knowledge"[72]. It entails the use of a model representing the alternative courses of action, the identification of possible costs and outcomes related to these options, and the assignment of probabilities to each of these. Hence, decision analysis facilitates the handling of situations where a decision is required despite uncertainty in some of the aspects that determine final outcome. The events could for instance be provision of vaccines and treatment, and the outcomes could be the impact on people's health. Since the model must depict the natural history of the disease and the sequence in which the events take place, it can be simple or more sophisticated, depending on the disease epidemiology and the relevant decision problem. Decision-analytic models for Hib disease are reviewed in Chapters 5 and 7.

The impact on the result (or the decision) of parameter and structural uncertainties should be assessed in sensitivity analysis. Deterministic sensitivity analysis is performed by changing one or more parameter estimates at a time and re-running the evaluation. Probabilistic sensitivity analysis (PSA) is undertaken by specifying parameters as distributions rather than point estimates and simultaneously varying all parameter estimates in a Monte-Carlo simulation. Thus, PSA based analyses not only provide estimates of mean expected costs and effects, but also accompanying uncertainty ranges, typically expressed as cost-effectiveness acceptability curves or frontiers [67].

4.4 DISCOUNTING FUTURE VALUES

Evidence suggests that society has a positive rate of time preference; that is, a preference for benefits today rather than in the future and prefer to postpone costs [67]. Hence, a key element in economic evaluation is to ensure that all values are appropriately adjusted for differential timing, so that sensible comparison can be made between interventions where costs and effects occur at different time points. To do this, future values are discounted to reflect the fact that these have less weight than money spent or health effects gained today. The present value, PV, is typically calculated as:

$$PV = 1/(1 + r)^t$$

where r is the discount rate and t is the number of years after year zero.

For costs the rationale for discounting is warranted by returns to investment in the market place and the choice of discount rate should therefore reflect the real rate of return, which can be approximated by, for instance, the real market interest rate. Jurisdictions in many countries advise on the discount rate analysts should use, which is most commonly between 3% and 5% per year [73]. Discounting of health effects has to do with the strength of preferences for consumption now rather than later, which is more difficult to measure empirically [67].

The mainstream practice is to discount effects at the same rate as costs, but the principle of discounting effects is an ongoing methodological debate. Some analysts maintain that costs and effects should be discounted by the same rate, others argue that effects should be discounted at a lesser rate than costs, and a third group makes the case that effects should not be discounted at all [74, 75]. Arguments against discounting of health effects include that this give less weight to future generations compared to the present one and that empirical evidence shows that individuals discount future health at a lesser rate than monetary benefits. One of the key arguments for discounting costs and effects at a similar rate is that this insures consistency in reasoning by treating health care projects in a similar way to those in other sectors of the economy. However, Nord has recently shown that these arguments are logically flawed [74]. He argues that "discounting of future health effects is less a matter of pure logic and more a matter of empirical research and societal values than what has been suggested by leading health economists for decades" [74]. The debate is still ongoing, so even though most guidelines currently specify that an equal discount rate should be used for costs and effects this could change in the future. As an example, initially, the UK's National Institute for Health and Clinical Excellence (NICE) required that costs be discounted at 6% per year and effects at 1.5%. However, NICE

amended its discounting guidance in 2004 and required that both costs and effects should be discounted at 3.5% per year [76].

Since there is always a time lag between when a vaccine is delivered and when health effects can be seen, discounting is an important issue in economic evaluations of vaccines. For childhood diseases like measles, pertussis, varicella, polio and Hib, the health impact is normally seen within about five years, so discounting may not be a major issue, although the time lag does need to be accounted for. However, for vaccines such as human pappiloma virus and hepatitis B discounting is a critical factor, as the health effects are realised much later than when the costs of vaccine provision are incurred.

4.5 THE INCREMENTAL COST-EFFECTIVENESS RATIO

Cost-effectiveness is traditionally expressed in terms of the incremental cost-effectiveness ratio (ICER). Depending on the effect measure, the ICER could for instance be "incremental costs per life years gained" or "incremental costs per QALY gained". The definition of the ICER is:

$$ICER = \frac{(cost\ intervention\ A) - (cost\ intervention\ B)}{(outcome\ intervention\ A) - (outcome\ intervention\ B)}$$

If the intervention evaluated turns out to be cost-saving and clinically superior, the conclusion should be to implement the intervention and the ICER should not be used in this case because negative ICERs have little meaning. However, since the more effective interventions are most often also more costly, appropriate interpretation of the ICER is crucial. Two overall approaches are currently recommended. First, one can compare the ICER against ICERs of other interventions that have been studied with the aim of determining which of these interventions should be prioritised. A problem with this approach is however that relatively few studies are normally available to compare with, and if there are studies, different methodologies may have been used. The second option is to apply an explicit threshold where any intervention with an ICER below the threshold is considered cost-effective [77]. NICE is one of the few reimbursement agencies that have formally published a cost-effectiveness threshold. According to NICE, if the cost per QALY gained is shown to be below £20,000, the decision to recommend the use of the technology is normally based on this result. If the cost-effectiveness estimate is between £20,000 and £30,000 per QALY gained, judgements take into account factors such as the degree of certainty of the estimate and the innovative nature of the technology. If the cost per QALY gained is above £30,000 the technology is unlikely to be adopted without considerable debate [78].

The WHO has established the following cost-effectiveness threshold values using DALYs [79]:

- Cost per discounted DALY averted < GDP per capita: The intervention is very cost-effective
- Costs per discounted DALY averted 1-3 x GDP per capita: The intervention can be considered cost-effective
- Costs per discounted DALY averted > 3 x GDP per capita: The intervention cannot be considered cost-effective.

In 2010, the United Kingdom GDP per capita was approximately £ 23,500. Hence, the basic principle of considering those interventions that cost less than GDP per capita for each health related quality of life year gained for cost-effective is a common feature of the NICE policy and the WHO recommendations.

The use of cost-effectiveness analysis for decision making is discussed in Chapter 13 of this thesis.

4.6 GUIDELINES FOR ECONOMIC EVALUATION OF VACCINES

There are numerous guidelines available on economic evaluation and for designing decision-analytic models [67, 69, 80, 81]. Economic evaluations of vaccines should follow the broad principles of these guidelines, which in many ways can be considered as standard procedures with step-by-step approaches. However, certain features are specific to vaccines and it has been suggested that economic evaluation of these should be undertaken with special considerations compared to analysis of other health care interventions [82, 83, 84, 85].

The most critical attribute that distinguishes vaccines from analysis of other interventions is that most vaccine preventable diseases are infectious. The effect of vaccination against an infectious disease is two-fold. First, a vaccine induces individual protection against a disease for the vaccinated person and secondly, vaccination reduces the susceptibility of an individual so that there is a reduced chance of transmitting the infection to others [86]. Hence, vaccination not only protects those who are vaccinated, but also the unvaccinated because of a decrease in the circulation of the pathogen. This latter effect is known as herd immunity. To accurately account for herd immunity, a dynamic infectious disease model is required [87]. In such as model, the probability of an individual acquiring an infection is dependent on the contact patterns of that individual, the transmissibility of the infection, and the distribution of the infection within the population over time [82]. Differences

between static and dynamic models with a focus on Hib vaccination and disease are addressed in Chapter 7.

In 2008, the WHO published guidelines for standardization of economic evaluation of immunization programmes [88]. The primary target audiences for the guidelines are economists and health service researchers who conduct and critically appraise economic evaluations of immunization programmes at national, regional and global levels. The guidelines provide recommendations on framing the analysis, how to assess the costs and effects of a vaccination programme, modelling, discounting and how to present and interpret cost-effectiveness data. A checklist for appraising the quality of economic evaluation of immunization programmes is also included [88].

In a paper published in 2008 by Kim and Goldie, recommendations for modelling approaches in cost-effectiveness analysis of vaccination programmes were given [89]. The authors emphasized that there is a need for improving modelling methods for economic evaluation of vaccines, specifically model choice, construction, assessment and validation. A framework for classifying models according to three main attributes was proposed:

i. Static or dynamic
ii. Stochastic or deterministic
iii. Aggregate or individual

This framework is explained further in Chapter 7 and the decision-analytic model developed for this thesis is described and categorised accordingly.

5 ECONOMIC EVALUATIONS OF HIB VACCINE AND HIB DISEASE TREATMENT COST STUDIES: REVIEWS OF THE LITERATURE[1]

Two literature reviews are presented in this chapter. First, a systematic review of economic evaluations of Hib vaccine was undertaken with three overall objectives: (i) to ascertain the quantity of published papers, in particular for low- and middle-income countries, (ii) to evaluate the methods used in the published studies and (iii) to determine the main limitations with the existing evaluations and then identify knowledge gaps which should be addressed. The second literature review is on Hib disease treatment cost studies. The objectives of this review were to establish in which low- and middle-income countries such research has been undertaken, to compare methods and results of the studies, and to make broad conclusions about the costs of treating Hib disease. Further more, in the context of the PhD, objectives were to identify which cost components are important to include in an economic evaluation and to assess if it would be suitable to use any of the study results in the present analysis.

5.1 LITERATURE REVIEW OF ECONOMIC EVALUATIONS OF HIB VACCINE

5.1.1 METHODS

5.1.1.1 Search strategy

Papers were identified from PubMed using the search terms "*Haemophilus influenzae* type b" and "vaccine" and "cost". Two health economic evaluation databases were also searched; the National Health Service Economic Evaluation Database [90] and the Health Economic Evaluation Database [91]. References in the retrieved articles were reviewed for relevant papers. There was no time limit on older papers and the search ended in February 2009. All languages were included. The criteria for inclusion was that a study should assess both the incremental costs and health consequences of Hib conjugate vaccine compared to a situation without the vaccine in the routine childhood immunization schedule. Reported cost data were converted to 2010 US$ values based on local consumer price indices and average annual exchange rates [92].

[1] A modified version of this chapter has been published as: Griffiths UK, Miners A, Cost-effectiveness of Hib vaccine: A systematic review of the literature, *Expert Review of Pharmacoeconomics and Outcome Research*, 2009 August (4):333-46

5.1.1.2 Assessment of study quality

Several comprehensive checklists, which to a large extent are overlapping, have been developed to guide quality assessments of economic evaluations [67, 93]. Quality scoring systems have also been devised, but since these are subjective they are not considered to be sufficiently valid and consistent as a method of quality assessment [93]. The quality and relevance of each identified study was evaluated by using the standard checklists coupled with criteria that were *a priori* considered to be important for Hib vaccine economic evaluations. In particular, the following issues were evaluated:

Study design:

1. Were details of any decision-analytic model given?
2. Was herd immunity included in the impact estimates?

Data collection:

3. Were the Hib disease syndromes clearly stated and did the disease incidence estimates have a reliable source?
4. Was Hib pneumonia included in the impact estimates?
5. Was there a clear explanation of the methods used to value health states and other benefits of vaccination?
6. Were both acute illness in young children and life-long sequelae for a proportion of meningitis cases included in the outcome measures?
7. Were treatment cost data transparently presented and disaggregated into quantities and unit costs?
8. Were treatment costs of sequelae from meningitis included?
9. Were vaccine delivery costs included?

Interpretation of results:

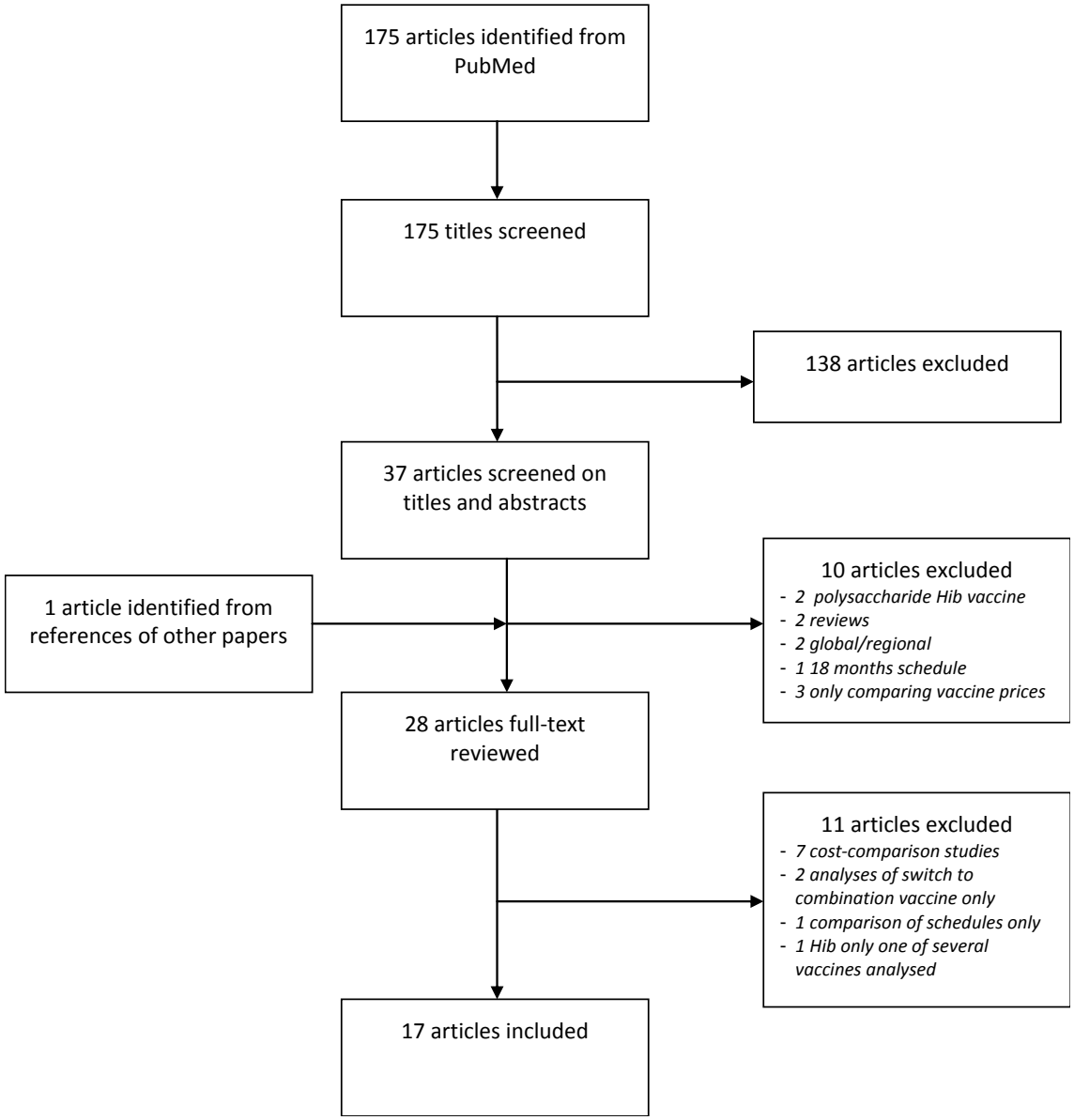
10. If productivity costs due to mortality and morbidity were included, were these reported separately and was the relevance of these to the overall result discussed?
11. Was sensitivity analysis undertaken?

5.1.2 RESULTS

5.1.2.1 Study selection

The search identified a total of 175 papers (Figure 5.1). After reviewing titles and abstracts, 28 of these were considered potentially relevant. One paper was in Spanish [94], one in Italian [95], one in Dutch [96] and the remaining in the English language. Eleven papers were excluded before the data abstraction process; the Italian paper was excluded because it compared different Hib vaccination schedules only, a paper from the USA evaluated Hib vaccine along with several other vaccines without separately presenting the

Figure 5.1 Study selection for literature review



Hib specific cost-effectiveness results [97], two papers analysed only the cost implications of switching from monovalent Hib vaccine to a combination vaccine [98, 99] and seven papers were excluded because they were cost comparison studies only [96, 100, 101, 102, 103, 104, 105]. In these seven studies the costs of vaccination were compared directly against the costs of treating prevented Hib disease without placing a value on the health effects of the vaccine. As this type of partial evaluation implies that we should only implement programmes that are cost saving, it is not as useful to decision makers as a full economic evaluation that also values health effects [67]. Three of the cost comparison studies were incorrectly labelled as cost-benefit analysis (CBA) [101, 104, 105] and one as a cost-effectiveness analysis [102]. As mentioned in Chapter 4, the definition of a CBA is

that a monetary value is assigned to health outcomes [67], but this was not done in the papers. A total of 17 articles were included in the review.

Two other reviews of economic evaluations of Hib vaccine were identified: one by Clements from 1994 [100] and one by Brinsmead and colleagues ten years later [106]. When Clements published his review only six economic studies had been published and two of these were for the polysaccharide Hib vaccine [107, 108]. In the review by Brinsmead *et al*., 18 studies were included. Their inclusion criterion was broader than in the present review, as both cost comparisons studies and international economic analyses were included alongside country-specific economic evaluations. Another difference is the methods used to assess methodology and quality of the studies. While Brinsmead *et al*. evaluated the overall methods used in the studies, a direct comparison of key parameter values was not presented and their review did not assess the methodological differences between studies conducted in high- versus low- and middle-income countries.

5.1.2.2 Study settings

The 17 papers included in the review cover a total of 14 countries (Table 5.1). According to 2010 World Bank classifications [109], seven of the countries are high-income (GNI per capita of US$ 12,276 or more) two are upper middle-income (GNI between US$ 3,976 - US$ 12,275 per capita), three are lower middle-income (GNI between US$ 1,006 - US$ 3,975 per capita) and two are low-income countries (GNI below US$ 1,005 per capita). Most of the studies from high-income countries are from the early 1990s when these countries were making decisions about Hib vaccine. The earliest paper is an Israeli study from 1993 [110]. The US study by Zhou *et al*. was undertaken nine years after Hib vaccine introduction, making it possible to use Hib disease surveillance data from before and after the vaccine introduction to assess health impact [111]. All the studies from low- and middle-income countries except the one from South Africa [112] are subsequent to year 2000, reflecting that most of these countries have only relatively recently started the decision-making process regarding Hib vaccine introduction.

5.1.2.3 Study quality and comparison of methods and parameter values

In Table 5.1, the 17 studies are assessed according to the selected quality factors. The more crosses a study has, the higher the quality. It is seen that none of the papers fulfil all quality factors. Three studies (from Papua New Guinea (PNG) [113], Colombia [94] and the Philippines [114]) fulfilled none, one or only two of the indicators and are thus of very low quality. The weakest aspect of all the papers was the methods used for calculating and reporting treatment costs. Only six papers did this in a transparent way.

Table 5.1: Assessment of key quality indicators of Hib economic evaluation studies included in the review ("x" indicates that study comply with criteria)

Country income group and first author [ref.]	Country (year)	Use of decision analytic model	Hib disease incidence rates clearly reported with reliable data source	Hib pneumonia included in effectiveness measure	Full disease impact included in outcome measure	Treatment costs reported in transparent and reliable way	Treatment costs of sequelae included	Vaccine delivery costs included	Productivity changes reported transparently	Sensitivity analysis undertaken
High income										
Ginsberg [110]	Israel (1993)		X		X		X	X	X	X
McIntyre [115]	Australia(1994)	X					X	X	NA	X
Harris [116]	Australia (1994)	X	X				X	X	NA	X
Trollfors [117]	Sweden (1994)				X		X		X	
Garpenholt [118]	Sweden (1998)	X	X		X	X	X	X		X
Livartowski [119]	France (1996)	X	X				X			X
Pokorn [120]	Slovenia (2001)	X	X	X	X		X	X	X	X
Zhou [111]	USA (2002)	X	X	X	X		X	X		X
Shin [121]	South Korea (2008)	X	X	X	X		X	X		X
Middle income										
Hussey [112]	South Africa (1995)			X	X			X	X	X
Platonov [122]	Russia (2006)	X	X		X	X	X		NA	X
Limcangco [114]	Philippines (2001)	X			X					X
Guzmán [94]	Colombia (2006)			X				X		X
Broughton [123]	Indonesia (2007)	X	X	X	X		X		NA	X
Gessner [124]	Indonesia (2008)	X	X	X	X	X			NA	X
Low income										
Duke [113]	PNG (2002)								NA	
Akumu [125]	Kenya (2007)	X	X	X	X	X			NA	X

NA: Non applicable as productivity costs were not included in the analysis

Modelling methods

A decision-analytic model was presented in 12 of the 17 studies. Most of the models were designed in a decision tree structure with branches representing the different types of Hib disease included in the analysis. However, in five of the studies (the Swedish paper by Trollfors and the papers from PNG, Colombia, South Africa and Israel) no model was presented and insufficient detail was provided on how the health and cost impacts were estimated and combined, indicating that fairly simplistic approaches were used.

None of the studies attempted to model the transmission dynamics of Hib disease when estimating vaccine impact. Instead, static models that follow fixed size cohorts over time and predict Hib disease using constant rates of infection were used. Only Akumu *et al*. in the Kenyan paper mentioned the potential impact of herd immunity and performed a crude sensitivity analysis by assuming elimination of Hib disease in the long run [125].

Hib disease syndromes

The papers incorporated different types of Hib disease syndromes, although all included Hib meningitis (Table 5.2). Eight of the 17 papers included pneumonia, but the reliability of the evidence provided for this disease burden varied considerably. For instance, the South Korean paper [121] used data from the USA, which is unlikely to be valid for Asia due to different risk factors in the two populations. The Indonesian papers presented the most reliable Hib pneumonia burden estimates, as these were based on results from a Hib vaccine probe study [123, 124].

Table 5.2: Hib disease syndromes included in the economic evaluation studies

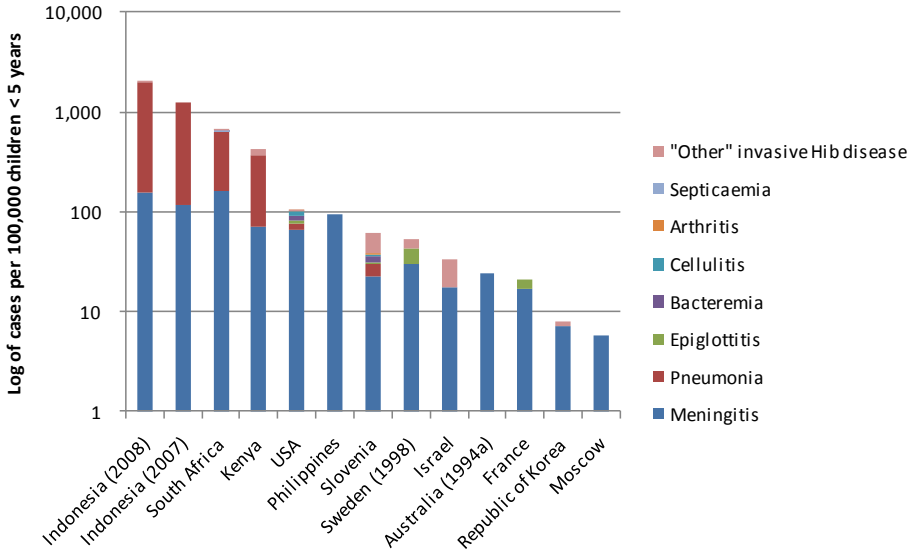
Syndromes	No. of papers	Reference
Meningitis only	3	[113, 114, 122]
Meningitis, epiglottitis and "other" Hib disease	3	[115, 116, 118]
Meningitis, pneumonia and "other" Hib disease	2	[121, 123]
Meningitis, bacteraemia and pneumonia	2	[112, 125]
Meningitis and pneumonia	2	[94, 124]
Meningitis and epiglottitis	1	[117]
Meningitis and "other" Hib disease	1	[110]
Hib invasive disease	1	[105]
Meningitis, epiglottitis and septicaemia	1	[119]
Meningitis, epiglottitis, arthritis, cellulitis, bacteraemia and pneumonia	1	[120]
Meningitis, epiglottitis, arthritis, cellulitis, pneumonia, septicaemia and other Hib disease	1	[111]

Hib disease incidence rates

Hib disease incidence rates per 100,000 children less than five years varied considerably between the studies. Since the difference between the highest and lowest disease

incidence was as much as 1,982 cases per 100,000 children, a logarithmic scale has been used to show this in Figure 5.2. The Hib meningitis incidence rate ranged from six in the Russian study [122] to 158 in the Indonesian study [124]. Hib pneumonia incidence was assumed to be 1,825 per 100,000 children less than five years in the Indonesia study by Gessner *et al*. [124], but most other studies did not even include pneumonia. While most researchers agree that Hib disease incidence rates differ between geographic regions, the range of estimates seen in the studies also reflects different methods. For example, in the Kenyan study and in one of the Indonesian studies [124, 125], hospital derived incidence rates were adjusted upwards to account for limited access to hospital care, but this adjustment was not made in other countries where this might be an issue, such as the Philippines and Colombia.

Figure 5.2: Logarithmic scale of Hib disease incidence per 100,000 children less than 5 years used in the economic evaluation studies



Methods used to value health states

The choice of health outcome measure is a key difference between the studies. Of the 17 papers reviewed, eight are cost-benefit analysis, seven are cost-utility analysis and two are cost-effectiveness analysis using "costs per life saved" as the outcome measure (Table 5.3).

In a Hib vaccine cost-benefit study, a monetary value can be placed on premature death and on the loss of productivity due to meningitis sequelae. The willingness to pay approach was used in the two Swedish studies while the human capital approach was used in the remaining six studies; four of these used the average wage rate [111, 112, 114, 121] and two studies used GDP per capita to approximate the value of a life (Israel and Slovenia) [110, 120]. There were wide differences in the results reflecting the distinct income levels between countries. It is moreover apparent that the Swedish willingness to

Table 5.3: Costs of Hib disease used in the studies (2010 US$)

First author [ref.]	Country	Monetary value of a life	Lifetime productivity loss due to meningitis sequelae	Average length of stay in hospital of a meningitis case (days)	Average treatment costs of a meningitis case	Discounted lifetime treatment costs of a meningitis sequelae case
Cost-benefit studies						
Garpenholt [118]	Sweden	2,279,525	2,279,525	12.0	10,490	2,569,295
Trollfors [117]	Sweden	2,388,630	NI	NS	NS	1,821,627
Ginsberg [110]	Israel	380,029	NI	11.8	13,043	610,748
Hussey [112]	South Africa	167,158	167,158	14.6	1,702	448
Limcangco [114]	Philippines	NS	NS	NS	NS	NS
Pokorn [120]	Slovenia	565,210	NI	18.9	8,366	924,314
Shin [121]	South Korea	536,984	536,984	NS	3,509	215,436
Zhou [111]	USA	NS	NS	7.2	12,881	NS
Cost-utility studies						
Akumu [125]	Kenya	NI	NI	11.7	332	NI
Broughton [123]	Indonesia	NI	NI	13.0	1,353	6,580
Gessner [124]	Indonesia	NI	NI	8.1	292	NI
Harris [116]	Australia	NI	NI	NS	16,650	827,724
Livartowski [119]	France	NI	NI	NS	11,570	NS
McIntyre [115]	Australia	NI	NI	NS	9,886	722,008
Platonov [122]	Russia	NI	157,132	30.0	5,616	56,229
Cost-effectiveness studies						
Duke [113]	Papua New Guinea	NI	NI	NS	51	NI
Guzmán [94]	Columbia	NI	NI	NS	1,800	NI

NI: The parameter is not included in the analysis
NS: The parameter is included in the analysis, but the value is not stated

pay approach resulted in considerably higher values than the human capital approach (Table 5.3).

There are seven cost-utility studies: three from high-income countries that use QALYs as the outcome measure [115, 116, 119] and four from low- and middle-income countries where outcomes are expressed in DALYs [122, 123, 124, 125]. In the three QALY papers, only the impact of mortality and life-long meningitis sequelae were included in the QALY estimate while Hib disease episodes due to meningitis, epiglottitis, pneumonia, etc., were excluded. When attaching a preference score to life-long meningitis sequelae, widely different values were used in the three papers. In the French paper, preference scores were based on experts' opinion and found to be 0.371 for severe sequelae, 0.84 for moderate sequelae and 0.977 for isolated auditory sequelae [119]. Harris *et al*. used a preference score of 0.8 for mild disability and 0.6 for severe disability [116] and McIntyre *et al*. used -0.12 for severe disability, 0.80 for less severe disability, 0.86 for hearing aid and 0.91 for less severe hearing loss [115]. The methods used to determine these preference scores were not explained in any of the Australian papers.

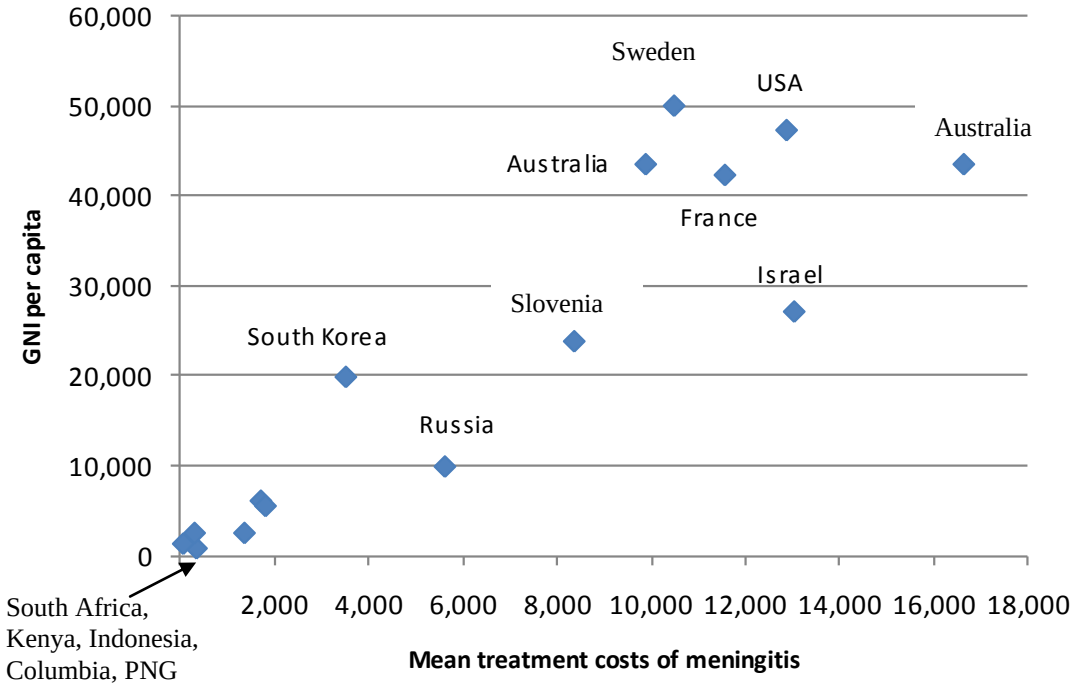
In the four DALY papers the formula and disability weights developed by Murray and Lopez for the 1996 GBD study were referenced [126], except in one of the Indonesian papers where the specific disability weights used were not specified or referenced [123]. The three other papers used the standard GBD disability weights for bacterial meningitis and pneumonia, but different assumptions about types and proportions of disabilities were used when calculating DALYs due to meningitis sequelae [122, 124, 125].

Treatment costs

Most studies included treatment costs of the same syndromes as included in the effect estimates. Hence, all studies except two (Philippines and Sweden) [114, 117] reported the average costs of treating a meningitis case. This was usually estimated by multiplying the average length of stay in hospital for each syndrome by the cost per bed day. However, the majority of studies provided inadequate details on the methods used for the treatment costs estimates. For example, only five studies reported disease specific costs of drugs and diagnostics [94, 110, 111, 124, 125]. Of the studies from low- and middle-income countries, arguably the study by Gessner *et al.* provided the most reliable treatment cost estimates, as patient specific treatment costs were collected by reviewing patient records and undertaking exit interviews alongside a Hib vaccine probe study. Hence, standard deviations around a mean value were given for many of the cost items [124].

As seen in Table 5.3, considerably higher meningitis treatments costs were reported in high-income than low-income countries, ranging from US$ 51 in PNG to US$ 16,650 in Australia. There is a clear correlation between GNI per capita and treatment costs of an acute meningitis case (Figure 5.3).

Figure 5.3: Correlation between GNI per capita and treatment costs of an acute meningitis case (2010 US$)



The inconsistencies are that the South Korean estimate is noticeably less than those for the other high-income countries, one of the Australian estimates are twice as high as the other, one of the Indonesian papers reports a value five times higher than the other paper from Indonesia, and the estimate from PNG is five times less than in Kenya, the other low-income country. While the reason for the South Korean divergence is not clear, the source for the hospital bed day costs in the Indonesian paper by Broughton were reportedly an Indonesian travel guide suggesting that private sector prices were used [123], and in the PNG study it seems as if drugs were the only cost item included [113].

Treatment costs of meningitis sequelae were included in all but four studies (Table 5.3). The studies from Kenya, Indonesia, PNG and Colombia did not include these costs, most likely because treatment of disabilities are limited in these countries and these data are thus scarce. The highest lifetime treatment costs of meningitis sequelae were reported in the two Swedish studies (Table 5.3).

Hib vaccine assumptions

Assumptions on Hib vaccine efficacy against Hib meningitis varied between 90%-100% among the studies (Table 5.4). All except three of the studies [94, 112, 120] provided a source for this estimate, which was generally referenced to a single randomized controlled trial of Hib vaccine. None of the studies performed a meta-analysis on vaccine efficacy evidence. In the studies from the USA and Indonesia it was not necessary to include an efficacy assumption as the Hib vaccine impact was generated from surveillance data and a vaccine probe study, respectively [111, 124]. Three studies evaluated a four-dose Hib vaccine schedule, two analysed both three and four doses and the remaining 12 used three doses only (Table 5.4). The large majority of studies assumed use of monovalent Hib vaccine. This is partly because combination vaccines were not yet available when many of the studies were undertaken, but probably also because vaccine costs are simpler to estimate when a monovalent vaccine is assumed. The studies from Indonesia and Kenya assumed use of the combined DTP-Hepatitis B-Hib vaccine, also known as the "pentavalent" vaccine, which is the vaccine of choice in most GAVI Alliance supported countries. The costs of Hib vaccine was estimated as the difference between pentavalent and DTP-hepatitis B vaccine. The range of vaccine prices is consistent with the different bargaining powers of countries. Kenya and Indonesia are eligible for procurement through UNICEF, which can obtain cheaper prices due to bulk procurement. Similarly, the public price in the USA is likely to be less than in other high-income countries because of the larger quantities procured. Nine of the studies included costs of vaccine delivery in addition to the vaccine costs while the remaining eight studies excluded this cost. Of the low- and middle- income country studies only the South African study included this. None of the studies provided much detail on the source of these cost estimates.

5.1.2.4 Study results

Comparison of some of the study results is not straight forward due to the different methods used for valuing health states. As seen in Table 5.5, five of the cost-benefit studies presented a positive benefit-cost ratio while it was negative in South Korea [121]. However, contrary to standard guidelines, in three of the cost-benefit studies a ratio was not calculated. Instead, the difference between the annual costs of Hib vaccination and Hib disease were presented, illustrating cost savings in both settings (Sweden and the Philippines).

The two Australian studies presented results in terms of costs per QALY gained and these values are in a comparable range. The costs per QALY gained were higher in the French study, probably due to the lower disease incidence (Figure 5.2) and higher vaccine prices

Table 5.4: Hib vaccine assumptions used in the studies

First author [ref]	Type of Hib vaccine	Vaccine efficacy against Hib meningitis	Number of Hib vaccine doses	Hib vaccine price per dose (2010 US$)	Vaccine delivery costs per dose (2010 US$)
High income					
Ginsberg [110]	Hib monovalent	100%	3 and 4	15.72	1.35
McIntyre [115]	Hib monovalent	90%	3	16.07	4.02
Harris [116]	Hib monovalent	95%	3	8.93	0.63
Trollfors [117]	Hib monovalent	90%	3	25.30	NI
Garpenholt [118]	Hib monovalent	95%	3	25.11	1.55
Livartowski [119]	DTP-Hib	100%	4	26.82	NI
Pokorn [120]	Hib monovalent	95%	3	12.24	0.76
Zhou [111]	Hib monovalent and others	NI	3 and 4	6.96	7.70
Shin [121]	Hib monovalent	99%	3	24.93	5.71
Middle income					
Hussey [112]	Hib monovalent	100%	4	22.67	0.53
Platonov [122]	Hib monovalent	95%	4	15.15	NI
Limcangco [114]	Hib monovalent	90%	3	6.60	NI
Guzmán [94]	Hib monovalent	90%	3	4.87	NI
Broughton [123]	DTP-HepB-Hib	95%	3	3.70	NI
Gessner [124]	DTP-HepB-Hib	NI	3	3.79	NI
Low income					NI
Duke [113]	NS	NS	3	NS	NI
Akumu [125]	DTP-HepB-Hib	NS	3	3.70	NI

NI: Parameter value not included in the study
NS: Parameter value included, but value not stated
DTP: Diphteria-tetanus-pertussis vaccine
HepB: Hepatitis B vaccine

(Table 5.5). The Russia study estimated considerably higher costs per DALY averted than the studies from Kenya and Indonesia. Again, this is arguably due to a combination of a higher vaccine price and a lower Hib disease incidence rate used in this analysis.

The two cost-effectiveness studies from PNG and Colombia produced widely different results. However, none of these estimates can be considered reliable. The overall quality of the study from PNG is weak and many of the parameter assumptions do not seem trustworthy. As an example, it was assumed that meningitis causes 13% of all child deaths; such a high figure is implausible. While the parameter assumptions in the Colombia study can be considered valid, the cost-effectiveness results are reported in a confusing and incorrect way. It is for instance stated that the "costs per life saved is US$ 2.38 with vaccination and US$ 3.81 without vaccination" [94], which most likely reflects the use of average cost-effectiveness ratios of the two alternatives instead of only the incremental cost-effectiveness ratio.

Table 5.5: Base case results reported in the studies (2010 US$)

Country [ref.]	**Result measure**	
Cost-benefit	Benefit-cost ratio with productivity costs included	Benefit-cost ratio without productivity costs
Israel [110]	1.45	1.26
South Africa [112]	1.43	Will be < 1
Slovenia [120]	1.39	0.99
South Korea [121]	0.77	NI
USA [97]	5.40	3.40
Cost-benefit	Annual cost savings with productivity costs included	Annual cost savings without productivity costs
Sweden [118]	16,999,651	NI
Philippines [114]	24,629,930	11,215,415
Sweden [117]	5,464,880	1,821,627
Cost-utility	Costs per discounted QALY gained	Costs per discounted DALY averted
Kenya [125]	NI	96
Indonesia [123]	NI	117
Indonesia [124]	NI	90
Russia [122]	NI	38,536
Australia [116]	1,816	NI
Australia [115]	1,649	NI
France [119]	8,418	NI
Cost-effectiveness	Costs per life year saved	
Papua New Guinea [113]	2,056	
Columbia [94]	20	

NI: Result measure not included in the analysis

All papers except those from South Korea and Russia concluded that Hib vaccine was good value for money and recommended introduction of the vaccine into the routine vaccination schedule. The main reason for negative conclusions in South Korea and Russia are the assumptions about relatively low Hib disease burden, as was shown in Figure 5.2.

5.1.2.5 Sensitivity analysis

In all the studies except two (PNG and Sweden) [113, 117] sensitivity analyses of the most uncertain variables were presented. While most of the studies used one-way sensitivity analysis, four studies included probabilistic sensitivity analysis by assigning a statistical distribution to uncertain parameters and running Monte Carlo simulations [122, 123, 124, 125]. This analysis enabled the authors to present cost-effectiveness ratios around an uncertainty range. In the majority of studies the one-way sensitivity analysis was comprehensive. One study varied as many as 19 parameters [119]. The most common parameters to vary were vaccine price and Hib disease incidence, which almost all the authors referred to as the most important determinants of the result. Other parameter values varied included discount rates, vaccine coverage and the proportion of meningitis cases suffering from sequelae.

5.1.3 DISCUSSION

The aim of the review was to assess the quality of existing economic evaluations of Hib vaccine with a particular focus on papers from low- and middle-income countries. Only five of the studies were considered to be of high quality according to the different criteria assessed. In particular, the studies from Kenya and Indonesia showed good examples of how results from epidemiological studies can become much more policy relevant when used in conjunction with economic decision-analytic models. The overall finding of the review is, however, that there are important limitations with the existing literature, both in terms of methodological quality and general level of reporting. Eight studies from low- and middle-income countries were included in the review, but three of these (PNG, Philippines and Columbia) [94, 113, 114] were of such poor quality with respect to data inputs and presentation of results that their results are either unlikely to be useful for decision-making purposes or could lead to erroneous policy decisions.

Some of the most important limitations of the papers were unreliable disease burden estimates and non-transparent methods used for treatment cost calculations. In addition, the model descriptions were inadequate, reliable sources were not given for quality of life estimates, in particular for meningitis sequelae, and none of the studies from low-income countries included treatment and productivity costs of meningitis sequelae. Moreover, the differences between studies with regard to Hib disease syndromes included have

contributed to confusion about the health impact of the vaccine. In particular, the impact on pneumonia has not been satisfactorily addressed.

Evidence on the cost-effectiveness of Hib vaccine is not yet available from certain geographical areas, as there are no studies from central Asia and the Middle East. Central Asia is a region where there is considerable uncertainty about Hib disease burden and where policy makers are consequently not fully convinced about the value of the vaccine. While it cannot be recommended to undertake cost-effectiveness studies of Hib vaccine in all countries of the world, it is widely known within the vaccine field that policy makers are reluctant to utilize evidence from other countries than their own [127, 128]. It is thus essential that methodologically robust studies at least are available from countries that account for a relatively large proportion of the global Hib disease burden, such as India.

5.2 REVIEW OF HIB DISEASE TREATMENT COST STUDIES IN LOW- AND MIDDLE-INCOME COUNTRIES

Prediction of treatment costs averted is an important component of any economic evaluation of a vaccine. Treatment costs of Hib disease are comprised of costs to the health sector as a result of delivering care and to households as a result of requiring care. As explained in Chapter 4, the types of treatment costs included in the analysis depend on the perspective taken. If a government health sector perspective is considered, costs are limited to resources financed by the public health sector while with a societal perspective costs incurred by households should also be included. In low-income countries, household costs are generally comprised of user fees paid for consultations and hospitalizations, expenses for drugs and diagnostic tests, transport costs to get to and from the health facility and other costs, such as food purchased while receiving treatment. The objectives of this review were to compare methods and results of studies in which treatment costs of childhood meningitis and pneumonia have been estimated, to identify which cost components are important to include in a Hib vaccine economic evaluation, and to assess the feasibility of using any of the study results for the economic evaluation.

5.2.1 METHODS

5.2.1.1 Study selection

Only studies with the overall aim of estimating costs of treating childhood pneumonia and meningitis in low- and middle-income countries were reviewed; estimates provided within cost-effectiveness studies were not included. No systematic search was undertaken to identify the studies. Instead, the papers were gathered gradually during the course of preparing this thesis. I have been directly involved in a number of the treatment cost

studies and this has lead to identification of other studies for comparison of our study results. Since I have a relatively large network of colleagues working within the field who I communicate with frequently, it is unlikely that any important studies have been missed in the review.

5.2.1.2 Data analysis

To facilitate quality assessment of the studies, recommended methods for estimating treatment costs in low-income settings were established. These are summarized in Texbox 5.1 and further details given in Annex 2.

For each study, the following methodological issues were reviewed:

i. The type of health facility where data were collected.
ii. Methods used for estimating bed-day and/or visit costs.
iii. The sample size used for collecting patient specific cost data.
iv. Whether household out-of-pocket costs were included in the study.

Costs were converted to 2010 US$ values using consumer price indices (imf.org/external/data.htm) and average annual exchange rates (oanda.com/currency/historical-rates/).

5.2.2 RESULTS

5.2.2.1 Comparison of study methods

The eleven identified studies are summarised in Table 5.6. Treatment costs of pneumonia were included in all eleven papers and meningitis in five. Patient specific resource utilization items, such as drugs, supplies and diagnostic tests, were determined either by retrospectively reviewing patient records or by collecting data prospectively. Sample sizes for estimating patient specific costs ranged from 56 patients in one of the two Indian studies to 980 patients in the study from Vietnam. In six of the studies caregivers were interviewed about their out-of-pocket costs, such as user fees and transport costs. A government health sector perspective was taken in the remaining five studies, in which no household cost data were collected.

Seven of the studies used micro-costing methods of varying intensity for calculating the costs per hospital bed-day. In the studies by Guzman *et al*. and Constenla insufficient details were however given for the reader to understand the methods used for collecting these data. In the studies by Krishnan *et al*., Hussain *et al.*, Chola *et al.*, Madsen *et al.* and Sinha *et al.*, data on the annual costs of repairs, maintenance, electricity, consumables, institutional overheads, staff, capital costs, etc. were collected and analysed in close

Textbox 5.1: Overview of recommended methods for estimating treatment costs

Estimating costs from the perspective of a government health facility:

Costs should be divided into two components:

(a) Hospital bed-day costs / out-patient visit costs

(b) Patient specific costs

(a) Bed-day and visit costs:

- All cost items shared between patients admitted to a hospital or receiving an outpatient consultation are included. These are the building, kitchen services, laundry services, cleaning, maintenance, administration, etc.
- Even though clinical personnel strictly speaking is a patient specific cost item because some patients take up more staff time than others, all personnel costs are generally included in bed-day/visit costs due to the difficulty in measuring precisely how much time is spent with an individual patient.
- Since health facilities in low-income settings rarely have computerised accountancy systems, it can be a substantial task to determine bed-day and visit costs.

(b) Patient specific costs:

- These are resources that vary between patients, such as drugs, medical supplies and diagnostic tests.
- Primary data collection on resource utilisation from a sample of patients is needed to determine the costs accurately, with data sources either being patient records or specially designed data collection forms.
- Resource items are multiplied by their respective unit costs to generate total costs per patient.
- In low-income settings, unit costs are often difficult to establish due to inadequate cost-accounting systems, numerous procurement mechanisms and donations in kind.

Estimating costs from the household perspective:

A sample of patients or caregivers should be interviewed about their out-of-pocket costs using data collection forms designed for the purpose.

collaboration with the accountancy departments of the health facilities, and the estimated costs per bed-day were reported in these studies.

In the studies by Ayieko *et al.* (Kenya) and Temple *et al.* (Fiji), detailed patient-specific cost data were collected by reviewing patient records and conducting caregiver interviews, but hospital bed-day and outpatient visit costs were not estimated for the participating facilities. Ayieko used a published study from Kenya to approximate bed-day costs, but Temple excluded outpatient visit costs, except for personnel expenses. In the Vietnamese study by Anh, a so called "ratio of costs to charges method" was used, giving reference to

Table 5.6: Overview of studies estimating the costs of pneumonia and meningitis treatment in children less than five years in low- and middle-income countries

First author [ref]	Country	Year	Types of diseases included	Facilities included	No. of inpatient records reviewed*	Method used for bed-day costs	Method used for outpatient visit costs	Number of patient interviews for household costs*
Krishnan [129]	India	2001	Pneumonia, meningitis and diarrhoea < 5 years	2 primary, 4 secondary and 2 tertiary hospitals	372	Micro-costing	Micro-costing	355
Guzman [130]	Columbia	2005	Pneumonia in children < 2 years	3 tertiary hospitals	128	Micro-costing	Micro-costing	Not included
Hussain [131]	Pakistan	2006	Pneumonia and meningitis in children < 5 years	2 primary, 2 secondary and 1 tertiary hospital	589	Micro-costing	Micro-costing	Not included
Constenla [132]	Brazil, Chile and Uruguay	2007	Pneumonia and meningitis in children < 5 years	33 hospitals and 10 outpatient centres	753	Micro-costing	Micro-costing	Not included
Hussain [133]	Pakistan	2008	Pneumonia, severe pneumonia and very severe febrile disease in children < 5 years	15 hospitals and clinics	NA	NA	NA	112
Chola [134]	Zambia	2009	Pneumonia and diarrhoea in children < 5 years	1 primary hospital	829	Micro-costing	Micro-costing	Not included
Ayieko [133]	Kenya	2009	Pneumonia, malaria and meningitis in children < 5 years	3 primary, 3 secondary and 1 tertiary hospital	307	Other Kenyan study	NA	205

First author [ref]	Country	Year	Types of diseases included	Facilities included	No. of inpatient records reviewed*	Method used for bed-day costs	Method used for outpatient visit costs	Number of patient interviews for household costs*
Madsen [135]	India	2009	Severe pneumonia in children < 3 years	1 secondary and 1 tertiary hospital	56	Micro-costing	NA	56
Anh [136]	Vietnam	2010	Pneumonia, meningitis and sepsis in children < 5 years	1 tertiary hospital	980	Ratio of costs to charges	NA	Not included
Temple [137]	Fiji	2011	Outpatient pneumonia in children < 5 years	2 tertiary hospital outpatient departments	400	NA	Not included	400
Sinha [138]	South Africa	2012	Pneumonia in children < 5 years	1 tertiary hospital	745	Micro-costing	NA	325

*Count only for pneumonia and meningitis patients. If other diseases were included in the study, these patients were excluded from the count.

NA: Non-applicable.

an approach from the USA. Hussain *et al* only took a household perspective in their 2008 study from Pakistan, so it was not relevant to include bed-day or outpatient visit costs

5.2.2.2 Comparison of results

The mean costs of meningitis treatment per patient varied from US$ 211 in Vietnam to US$ 5,855 in Chile (Table 5.7). According to the author, the costs in Chile were considerably higher than even in the two other South American countries of the same study because of higher hospitalisation costs. However, the underlying reasons for these higher hospitalisation costs were not explained and unit costs and quantities of resource items were not presented in the paper [132]. The mean meningitis treatment costs in Pakistan were significantly higher than in the three other low-income countries (Kenya, India and Vietnam). A likely reason for this is that the study facility in Pakistan was owned by an NGO while government facilities were evaluated in the other countries.

The mean costs per case of outpatient pneumonia ranged from US$ 3.4 in India to US$ 56 in Zambia (Table 5.8). One reason why the Indian and Fiji estimates are relatively low is that not all visit cost components, such as the building and utilities are included in these studies.

The costs of inpatient pneumonia treatment varied from US$ 36 in Vietnam for non-severe pneumonia to US$ 4,502 in Chile for severe pneumonia (Table 5.9). The South American study by Constenla showed a considerable cost difference between confirmed pneumococcal pneumonia compared to pneumonia from other causes (Table 5.9) [132]. Hib pneumonia would most likely not have been among the other causes because the three countries had used Hib vaccine routinely for several years prior to the study. Since Hib pneumonia is also bacterial, treatment costs of pneumococcal and Hib pneumonia are likely to be in a comparable range.

Table 5.7: Mean meningitis treatment costs per case in tertiary hospitals (2010 US$)

Country	Type of meningitis	Mean costs (SD)	Ref.
Vietnam	Bacterial	211 (172)	[136]
Kenya	All-cause	434 (365)	[139]
India	All-cause	750	[129]
Brazil	Pneumococcal	1,474	[132]
Pakistan	All-cause	2,758	[131]
Uruguay	Pneumococcal	4,203	[132]
Chile	Pneumococcal	5,855	[132]

Table 5.8: Mean outpatient pneumonia treatment costs per case (2010 US$)

Country	Types of hospital	Mean costs (95% CI)	Ref.
India	Public secondary	3.2	[129]
Fiji	Public tertiary	7 (6 .16 - 7.23)	[137]
Pakistan	Public secondary and NGO	18	[133]
South Africa	Public tertiary	19	[138]
Zambia	Public secondary	56	[134]

Table 5.9: Mean inpatient pneumonia treatment costs per case (2010 US$)

Country	Type of pneumonia	Type of hospital	Mean costs (SD or 95% CI)	Ref.
Vietnam	Non-severe	Tertiary	36 (33)	[136]
Vietnam	Severe	Tertiary	42 (47)	[136]
Uruguay	All-cause	Tertiary	80	[132]
Vietnam	Very severe	Tertiary	89 (85)	[136]
India	All-cause	Secondary	93 (72-114)	[135]
India	All-cause	Secondary	94	[129]
Kenya	All-cause	Secondary	95	[139]
Pakistan	Non-severe	Secondary	96	[131]
Brazil	All-cause	Tertiary	127	[132]
Zambia	All-cause	Primary	252	[134]
India	All-cause	Tertiary	162 (133-191)	[135]
Kenya	All-cause	Tertiary	270 (316)	[139]
Chile	All-cause	Tertiary	284	[132]
Pakistan	Severe	Secondary	317	[131]
India	All-cause	Tertiary	319	[129]
Brazil	Pneumococcal	Tertiary	628	[132]
South Africa	Severe	Primary	651 (607-694)	[138]
South Africa	Severe	Secondary	849 (793-906)	[138]
Columbia	Bacterial	Tertiary	1,063 (914-1,211)	[130]
South Africa	Severe	Tertiary	1,160 (1,083-1,237)	[138]
Uruguay	Pneumococcal	Tertiary	2,052	[132]
Chile	Pneumococcal	Tertiary	4,502	[132]

Household out-of-pocket costs of pneumonia treatment were determined from patient interviews in Fiji, India, Kenya, Pakistan and South Africa (Table 5.10). While the study from Fiji only included outpatient treatment, the remaining studies evaluated the costs of a severe episode where both inpatient and outpatient treatment were received. The highest cost was in the Indian NGO tertiary hospital where households on average paid US$ 149 (95% CI US$ 115, 183) per episode. In this study, out-of-pocket expenses were comprised of user fees (47%), drugs (19%), diagnostic tests (17%), transport (8%) and other expenses, such as food, phone calls, soap, etc. (9%) [135].

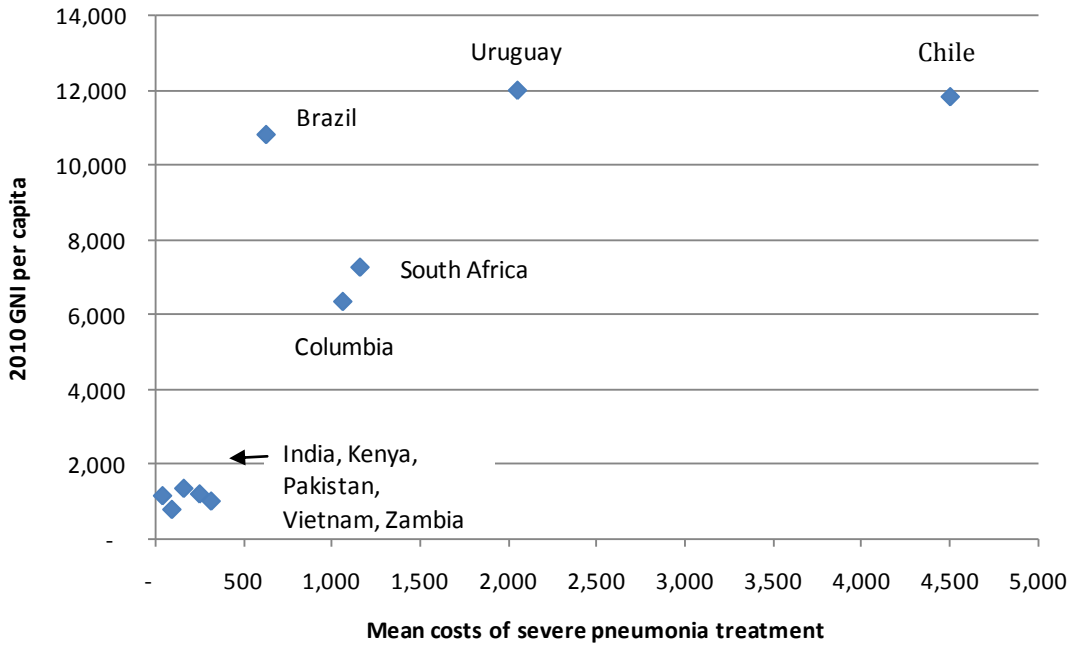
As shown for meningitis in the previous literature review, there was correlation between GNI per capita and the costs of treating severe pneumonia (Figure 5.4). In the five low-income countries, the mean costs per case ranged between US$ 42 in Vietnam and US$ 317 in Pakistan while in the middle-income countries, the mean costs were between US$ 628 and US$ 4,502. Brazil and Chile are outliers with relatively low and high costs per case, respectively, compared to their GNI per capita. As already mentioned, it is unfortunately not possible to understand the underlying reasons for the cost differences between the three South American countries in the paper by Constenla.

Only six of the studies (from Columbia, Kenya, Vietnam, Fiji, India and South Africa) presented descriptive statistics around the mean cost estimates, such as standard deviation or a 95% confidence interval (Tables 5.7 – 5.10). All of these showed great variation in costs between patients, with some of the standard deviations exceeding the mean costs. This confirms a standard tendency of treatment costs (see Annex 2).

Table 5.10: Mean household out-of-pocket costs of pneumonia treatment (2010 US$)

Country	Type of hospital	Mean costs (95% CI)	Ref.
Fiji	Public tertiary outpatient	2.82 (2.28, 3.46)	[137]
Pakistan	Secondary and NGO (non-severe)	5	[133]
South Africa	Public tertiary	21 (12, 34)	[138]
Kenya	Public primary	22	[139]
India	NGO secondary	46 (36, 55)	[135]
Kenya	Public secondary	46	[139]
Pakistan	Secondary and (severe)	55	[133]
Kenya	NGO secondary	97	[139]
Kenya	Public tertiary	98	[139]
India	NGO tertiary	149 (115, 183)	[135]

Figure 5.4: Correlation between GNI per capita and costs of treating severe pneumonia (2010 US$)



5.2.3 DISCUSSION

This is the first time the literature on the costs of treating childhood pneumonia and meningitis in low- and middle-income countries has been reviewed and results compared across settings. Treatment cost studies are available from five low-income countries; Fiji, India, Kenya, Pakistan, Vietnam and Zambia, and from five middle-income countries; Columbia, Chile, Brazil, South Africa and Uruguay.

In the seven studies where both meningitis and pneumonia treatment costs were estimated, it was found that the costs of treating meningitis is between two and eight times higher than pneumonia treatment costs, depending on setting and type of hospital. It was also found that the costs of treating pneumonia in a tertiary hospital were between 1.3 and 2.8 times higher than treatment in a secondary hospital in the same country. Inpatient pneumonia treatment in a secondary hospital was five times more expensive than outpatient treatment in Zambia and Pakistan, 30 times higher in India and 34 times higher in South Africa. The differences between countries are especially large with regard to outpatient costs and it is likely that this is explained by methodological study variation. In the Indian study, several cost components were for instance not included in the outpatient cost estimate, but they were included in the inpatient bed-day cost figures [129].

In all of the five studies where treatment costs were estimated from the perspective of households, it was concluded that out-of-pocket expenses comprised a relatively large proportion of household income and were unaffordable for a large share of the population. In the study from Pakistan it was found that the average household costs of one episode of hospitalised pneumonia was considerably higher than total annual health expenditure per capita. Similarly, in the Fiji study it was concluded that household costs of outpatient pneumonia treatment accounted for a quarter of the annual per capita outpatient expenditures. In the Kenya study the authors showed that costs of pneumonia hospital treatment were equivalent to approximately one month of total household expenses and that user fees comprised around 40% of total treatment costs in the tertiary government hospital.

As explained in Annex 2, estimation of hospital treatment costs in low- and middle-income countries is typically a relatively large undertaking. Since cost-accounting systems are seldom computerised and costs not tracked systematically and routinely, investigators need to collect resource quantities and unit costs from several different sources and this can be a time consuming task. For the studies included in the review, it took on average five years from data collection was started until the study was published, ranging from one year for the Indian study by Madsen *et al*., and ten years for the South African study by Sinha *et al*.

The methodological quality varied between the studies. It is postive that all the studies included patient specific cost data from a sample of patients, but it is a shortcoming that only six of the eleven studies presented descriptive statistics of these data. The majority of studies estimated costs per hospital bed-day using micro-costing methods, but unfortunately the quality of reporting was inadequate in several papers with insufficient details provided on methods and only a few, selected unit costs shown.

An important limitation of these types of studies is that it is uncertain to what extent data from one or two health facilities can reliably be extrapolated to a national level, which is needed for economic evaluation of Hib vaccine. Since health facilities within a country differ in management systems, capacity, size and efficiency, the mean costs per patient differ between facilities. It is particularly important not to use results from a tertiary university teaching hospital for estimating treatment costs in a whole country as costs in this type of facility are considerably higher than lower level facilities, as was shown in some of the studies. However, while the problem of extrapolation from a few facilities to the national level is important to bear in mind there are no immediate solutions in sight.

Resources for undertaking these types of studies are limited, so it is not realistic to collect data from more than a relatively small selection of facilities within a study. Until countries invest in systems for routine monitoring of costs, it will not be possible to establish precise national level estimates and to make robust conclusions about how costs vary according to facility level and type.

Even though considerable variations in mean treatment costs between countries and between facilities within a country were shown in the studies, it is possible to make some broad conclusions about the costs of treating meningitis and pneumonia in low- and middle-income countries. It is clear that mean costs are positively correlated with GNI per capita and that the costs of meningitis treatment are considerably higher than pneumonia treatment. In the South American study it was moreover found that bacterial pneumonia was substantially more costly to treat than pneumonia due to other causes. In low-income countries, the mean costs of treating childhood pneumonia in a hospital were in the range of US$ 36 - US$ 96 per case and the costs of treating meningitis were between US$ 211 - US$ 434 per case.

5.3 CONCLUSION

Two complementary literature reviews were presented in this chapter. Seventeen country specific economic evaluations of Hib vaccine were assessed with regard to modelling methods, input parameter values and overall results. In 15 of the studies it was concluded that Hib vaccine can be considered a cost-effectiveness intervention, but in the studies from South Korea and Russia it was argued that the vaccine should not be regarded as a priority compared to other health interventions. Only two studies were available from low-income countries; the study from Kenya was of relatively high quality, but the study from PNG was of extremely low quality.

A total of eleven studies were identified in the review on treatment cost studies of childhood pneumonia and meningitis in low- and middle-income countries. From this review, it can be concluded that it is crucial to integrate health care seeking behaviour within the economic evaluation. Costs per patient treated varied considerably according to facility ownership, levels of care and between inpatient and outpatient treatment, so it is imperative to determine what proportion of patients seeks treatment where when estimating the costs at a national level. Even though costs are considerably higher at tertiary level, focus on estimating these costs precisely are only justified if a considerable proportion of the population receive care at thi level.

The study results from the treatment cost review provide a relatively robust basis for comparison with the estimates generated as part of this PhD. Moreover, two studies were identified from India, which is one of the study countries. In Chapter 10 it is explained how these studies are used in the economic evaluation.

Based on the findings of the literature reviews, the intention of this PhD is to undertake a detailed and complete economic evaluation of Hib vaccine in a selection of low- and middle-income countries. The current literature on this topic is limited for these countries and the studies undertaken in high-income countries have used fairly simplistic methods. All the inadequacies identified in the current economic evaluations are addressed in this thesis.

6 THESIS AIMS, OBJECTIVES AND CONCEPTUAL FRAMEWORK

The overall aim of this thesis is to estimate the health and economic impact of Hib vaccine in low- and middle-income countries. A decision-analytic model is used to estimate the cost-utility of Hib vaccine. Input parameters used in the model are derived from a thorough and critical review of the Hib disease burden literature, meta-analysis of Hib vaccine trials, and from collection of primary data in the study countries. This PhD thesis is the first attempt to combine evidence on disease burden, costs and cost-utility of Hib vaccine across multiple countries using a consistent framework and comparable input parameters. As a result, useful insights into the relative cost-utility in countries with different economic and epidemiological circumstances are generated.

The research has eight objectives, which are all sub-components of the overall aim:

1. Development of Hib vaccine decision-analytic model.
2. Generation of Hib vaccine efficacy estimates from a meta-analysis.
3. Estimation of change in health related quality of life due to actute Hib disease and Hib meningitis sequelae.
4. Estimation of the costs of treating Hib disease in a selection of low- and middle-income countries.
5. Assessment of the household costs of meningitis sequelae.
6. Estimation of system costs of Hib vaccine introduction.
7. Comparison of the incremental cost-utility of Hib vaccine in three countries; Belarus, India, and Uzbekistan.
8. Use of the findings and the decision-analytic model to address relevant policy questions for Hib vaccine priority setting in low- and middle-income countries:
    - Can Hib vaccine be considered cost-effective? Does the conclusion vary according country income groups and epidemiological setting?
    - In what ways can the economic evaluation be used to enhance sustainability of Hib vaccine in GAVI supported countries?

In addition to these overall objectives, there are specific needs for the economic evaluation in the three study countries. These countries were chosen because they requested the analysis from the Hib Initiative during 2005-2009, but since they have distinct Hib vaccine policy issues, they also provide excellent examples on how economic evaluation can be used for decision making. They are moreover representatives of different country income groups and Hib epidemiology.

In this thesis, the Belarus analysis is representative for middle-income countries that are not eligible for GAVI support. It is apparent that policy making on new vaccine introduction is considerably different in these countries compared to countries that can apply to GAVI for new vaccines [140, 141]. As was shown in Chapter 3, most of the Hib vaccine introductions in middle-income countries have only taken place in recent years and several countries in this income bracket have not yet introduced the vaccine. In Belarus, the local government of Minsk city introduced Hib vaccination in 2008, covering around one-fifth of the birth cohort. The national government has since considered whether to expand the programme to the rest of the country and the economic evaluation was requested by the manager of the national immunization programme to help guide this decision.

India is an example of a GAVI eligible country where policy makers are in doubt about the value of the vaccine and concerned about financial sustainability when GAVI support comes to an end. This scepticism has been seen in several South East Asian and Western Pacific countries because of continuing uncertainty about Hib disease burden. Due to India's large birth cohort, the GAVI Alliance has placed an upper limit on its support to the country so the whole country can only be covered for 1-2 years of vaccine use. The Indian government decided to introduce the vaccine in 2008, but some groups have questioned the strength of the evidence, and the level of priority Hib vaccine should be given. In December 2009, a high court petition was filed by seven public health figures in India, including a former Health Secretary and a former advisor to the Finance Ministry. This petition was filed in the public interest to highlight "how irrational vaccines are being introduced in the public health system by the government, under the influence of vaccine manufacturers and international agencies" [142]. Specifically, the petitioners argue that new vaccines against Hepatitis B and Hib are being introduced without proper epidemiological and medical studies, while at the same time, basic more affordable vaccines such as DTP and measles are not being made available to approximately half the children of India. Hib vaccine was introduced with GAVI support in two of the 28 Indian states (Karala and Tamil Nadu) in December 2011, but expansion to the rest of the country has not yet been decided upon. The economic evaluation presented in this thesis is thus crucial for Indian decision makers as it shows to what extent the vaccine is good value for money. While the study was not directly requested by the Ministry of Health and Family Welfare, it was undertaken in close collaboration with Indian partners who also worked with the Hib Initiative on epidemiological studies.

Uzbekistan is representative of a more typical GAVI eligible country compared to India. As many other GAVI countries, Uzbekistan introduced hepatitis B vaccine shortly after this was offered by GAVI, and when GAVI stopped supporting monovalent hepatitis B vaccine after five years, the country switched to pentavalent vaccine. Uzbekistan introduced hepatitits B vaccine in 2001. However, the Uzbek government had initially serious doubts about the value of Hib vaccine and they expressed scepticism about GAVI's co-financing requirements. The application process therefore took several years and Hib vaccine was not introduced until 2009. The country has since been in default to GAVI on co-financing because the Ministry of Health has problems receiving these funds from the Ministry of Finance. The economic evaluation was requested by the manager of the Uzbekistan Expanded Programme on Immunization (EPI) who considers it crucial evidence for ensuring future financial sustainability of the vaccine.

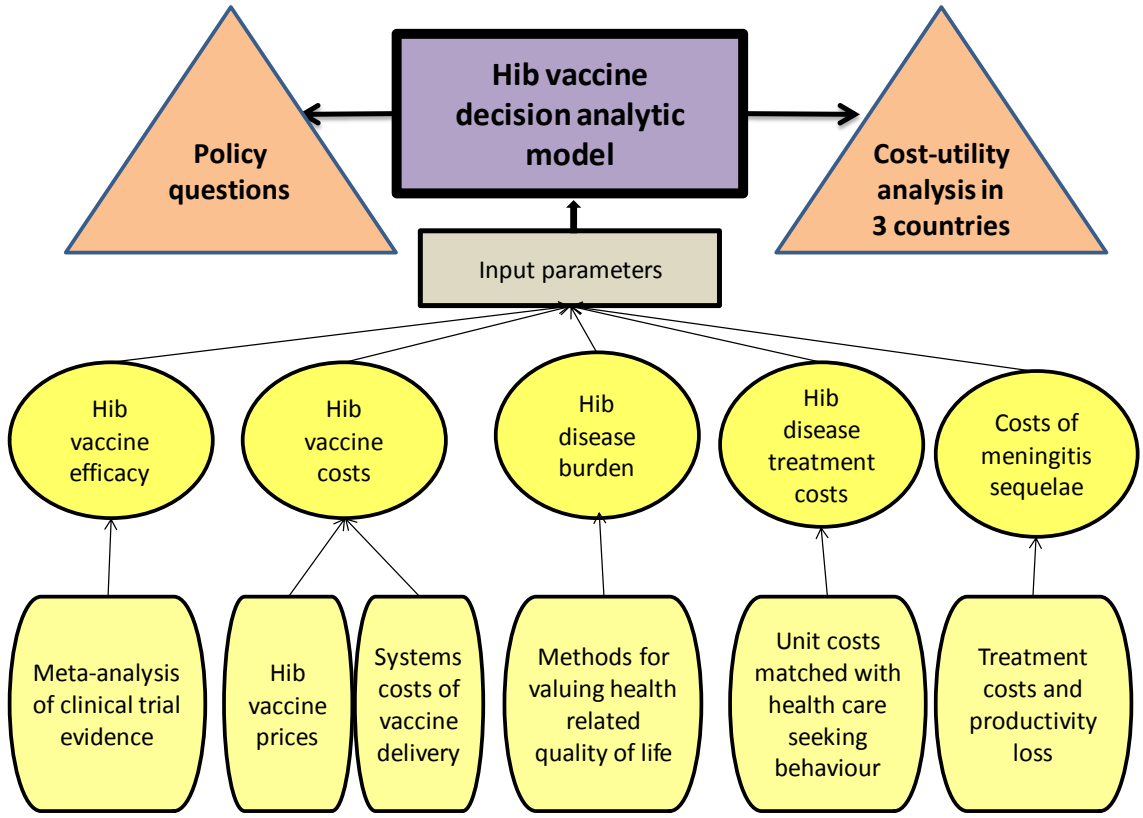
In addition to the three main study countries, the thesis includes sub-studies from Senegal and Ethiopia. Household costs of meningitis sequelae were investigated in Senegal and system costs of Hib vaccine introduction were evaluated in Ethiopia. These studies were undertaken in response to research priorities identified by the Hib Initiative. Of all the sub-studies included in this thesis, research ethics approval was only necessary for the study in Senegal and this was obtained accordingly.

6.1 CONCEPTUAL FRAMEWORK

The conceptual framework of the thesis is shown in Figure 6.1. The decision-analytic model is used to address policy questions regarding Hib vaccine in low- and middle-income countries. This is done with case studies from Belarus, India and Uzbekistan. The input parameters needed for the model are each an individual subject within the thesis. The broad subject areas are vaccine efficacy, vaccine costs, disease burden, treatment costs of acute Hib disease and meningitis sequelae, as shown by the circles in Figure 6.1.

Different types of research questions and study methodologies were used to address these broad topics, as shown by the quadrilateral shapes at the bottom of the figure. A meta-analysis of clinical trial evidence was undertaken to determine Hib vaccine efficacy. Vaccine delivery costs were split into vaccine costs and systems costs, including data from a case study in Ethiopia. On the subject of disease burden, a focus was placed on methods for valuing health related quality of life using Disability Adjusted Life Years. When estimating treatment costs, it was investigated to what extent health care seeking behaviour and access to health services impacts the overall result. The costs of meningitis sequelae were estimated by a case study from Senegal where the opportunity costs of parents' time due to the burden of caring for a disabled child were quantified.

Figure 6.1: Conceptual framework for assessment of impact, costs and incremental cost-utility of Hib vaccine in low- and middle-income countries



7 DECISION-ANALYTIC MODEL

The aims of this chapter are to describe the overall structure of the decision-analytic model, discuss the considerations that were taken into account when choosing its design, and to sign post in which subsequent chapters particular input parameters are addressed. To understand the model considerations that were made, the differences between static and dynamic models are explained in section 7.1 and published dynamic models of Hib disease are reviewed in section 7.2. The decision-analytic model is presented in section 7.3.

The decision-analytic model was developed in close collaboration with Mr. Andrew Clark, research fellow at LSHTM. When I joined the Hib Initiative in May 2006 as Director of Cost-effectiveness, I initiated development of a decision-analytic model for use in GAVI eligible countries. In 2007, Mr. Clark began to work with me on this. The division of our work on the model is explained at the end of this chapter.

7.1 THE CHOICE OF STATIC VERSUS DYNAMIC HIB DISEASE MODEL

In the systematic literature review of Chapter 5 it was found that all the published economic evaluation studies evaluated the impact of Hib vaccination on a single birth cohort over time. These models are "static" as the risk of infection is independent of time and the impact of herd immunity ignored. Most vaccines prevent not only disease outcomes in the infected individual, but also prevent acquisition of the pathogen from other infectious individuals. In a dynamic transmission model the force of infection (the probability that a susceptible person acquires infection per unit of time) changes over time. Hence, as more children are vaccinated and the vaccine prevents transmission of the pathogen from infectious to susceptible persons, the proportion of infectious people in the population will decrease. Consequently, the force of infection acting on the remaining susceptible declines as well. A dynamic model takes this into account by cyclically recalculating the force of infection from the proportion of susceptible and infectious people at each point in time [88]. A key parameter in a dynamic model is the basic reproduction number, often denoted as R_0. This is the mean number of secondary cases a typical single infected case will cause in a fully susceptible population, i.e. a population with no immunity to the disease in the absence of interventions to control the infection [143]. This metric is useful because it helps determine whether or not an infectious disease will spread through a population. When $R_0 < 1$, the infection will die out in the long run, but if $R_0 > 1$, the infection will be able to spread in a population. R_0 is affected by

several factors, including the duration of infectivity of affected patients, the infectiousness of the organism, and the number of susceptible people the infectious carrier is in contact with. The proportion of the population that needs to be vaccinated to provide herd immunity and prevent sustained spread of the infection is given by $1 - 1/R_0$ [143].

Use of a dynamic model in economic evaluation of Hib vaccine is likely to generate more precise results as it allows for assessment of change in cost-effectiveness over time in line with changes in herd immunity. In most instances, the vaccination effect will be underestimated when using a static model, as herd immunity is not included. However, for certain vaccines negative dynamic effects also need to be accounted for. This is for instance the case with rubella vaccine where it is important to accurately predict the impact of shifts in the average age of infection, as rubella infection in pregnant women is considerably more damaging to health than infection during childhood [144].

Dynamic models thus take into account changes in the risk of infection over time and they can be used to estimate elimination thresholds, defined as the level of vaccination coverage which results in elimination of the pathogen. This is not the case for static models. However, in reality R_0 will differ according to geography, patterns of travel and socioeconomic status and dynamic models are thus inherently more complicated and require data that can be difficult to gather, such as carriage rates and population mixing [87]. The data needed for static models are simpler to generate and these models are also less complicated to develop. Hence, static models are overwhelmingly the most common models used for economic evaluation of vaccination programmes, despite their limitations, and known biases [82]. Researchers need to assess whether the additional benefits of a dynamic model outweigh the additional costs and efforts needed to build it. In low- and middle-income countries, there is increasing emphasis on building the capacity of Ministries of Health to conduct their own economic evaluations. In this context, static models are easier to explain, and may be more suited to the limited data available in many countries.

Kim and Goldie reviewed modelling approaches for cost-effectiveness studies of vaccination programmes published between 1976 and 2007 [89]. They categorized models for economic evaluation of vaccines into six different types, as shown in Table 7.1, and recommended that model developers clearly describe which type their model belongs to. According to the framework, models are either (i) dynamic or static, (ii) changes to the model occur at random (stochastic) or are fixed (deterministic), (iii) the model aggregates the behaviour of populations (aggregate) or track's individuals (individual-level), (iv)

events occur in discrete or continuous time, (v) individuals can enter or leave the populations (open) or not (closed), and (vi) the model's equations are linear or non-linear functions of parameters. Kim and Goldie found that out of 276 studies, only 23 (8.3%) used a dynamic transmission model while 66.7% used a static model (Table 7.2). In 13.1% of the papers the model description was not clear enough to be classified [89].

Table 7.1: Classification of mathematical models for economic evaluation of vaccines

Type 1: Deterministic aggregate-level static model 1.1 Decision trees 1.2 State-transition model (e.g. Markov model) 1.3 Hybrid model (e.g. a decision tree embedded with Markov models)	**Type 2: Deterministic aggregate-level (compartmental) dynamic model** 2.1 Discrete difference equation model 2.2 Ordinary difference equation model (continuous time) 2.3 Partial differential equation model (continuous time) 2.4 Other types of models that allow for interaction
Type 3: Stochastic aggregate-level static model • Monte Carlo simulation of a decision tree or a state-transition model	**Type 4: Stochastic aggregate-level dynamic model** • Individual sampling of compartmental dynamic model
Type 5: Static individual level micro simulation model • Monte Carlo micro simulation of a decision tree or a state-transition model	**Type 6: Dynamic individual-level micro simulation model** 6.1 Monte Carlo simulation of a Markov model with interaction 6.2 Discrete-event simulation model 6.3 Agent-based model

Source: Kim and Goldie (2008) [89]

Table 7.2: Model types identified in systematic literature review of vaccine economic evaluations

Model type	No. of studies	Percent
Static	184	66.7%
Dynamic	23	8.3%
Empirical	18	6.5%
Monte Carlo simulation	1	0.4%
Other	14	5.1%
Unclear	36	13.1%
Total	**276**	**100%**

Source: Kim and Goldie (2008) [89]

7.2 REVIEW OF DYNAMIC HIB DISEASE MODELS

While none of the published economic evaluations of Hib vaccine used a dynamic model, these types of models have been constructed to answer other types of research questions. A summary of Hib disease modelling studies identified from a non-systematic review of the published literature is seen in Table 7.3. These models belong either to types 2, 4 or 6 in the framework of Kim and Goldie.

Dynamic modelling of Hib disease has been undertaken by three research groups; a team in Finland and two different groups in the UK. As seen in Table 7.3, the Finnish group has published the largest amount of papers. Auranen, Leino and others have developed four different models to analyse various questions about Hib disease. The first model published

Table 7.3: Published dynamic Hib disease models

Author [ref]	Year	Type of model	Objective of analysis
Studies from Finland:			
Auranen *et al.* [145]	1996	Susceptible-Carriage-Susceptible model with Markov process	To predict prevalence and incidence of Hib carriage as a function of family size and age structure
Auranen *et al.* [146]	1999	Hierarchical Bayesian regression model	To predict the duration of immunity to Hib carriage and invasive Hib disease as a function of concentration of serum antibodies to capsular polysaccharide of Hib
Auranen [147]	2000	Baysian non-parametric intensity model	Back-calculating the age-specific incidence of recurrent Hib carriage
Leino *et al.* [148]	2000	Hierarchical Bayesian regression model	To estimate the duration of natural immunity to Hib under different forces of infection
Leino *et al.* [149]	2002	Hierarchical Bayesian regression model	To compare two different populations before the implementation of Hib vaccine
Makala *et al.* [150]	2003	Hierarchical Bayesian regression model	To predict antibody persistence after initial response to Hib vaccine
Auranen *et al.* [151]	2004	Individual based stochastic simulation model	To model transmission, immunity and disease of Hib in a structured population
Leino *et al.* [152]	2004	Individual based stochastic simulation model	To study factors determining the magnitude of indirect protection in Hib vaccination and determine the indirect and direct vaccination effects on carriage and disease
Studies from the UK:			
Coen *et al.* [153]	1998	Susceptible-infected-recovered model	To explore the relationship between Hib carriage and disease
Coen *et al.* [154]	1999	Susceptible-infected-recovered model	Validation of model by comparing Hib vaccine impact results to surveillance data
McVernon *et al.* [155]	2008	Age-structured deterministic model.	To understand interacting factors that contributed to a rise in Hib infections in the UK during the late 1990s

in 1996 simulated the individual risk of acquiring carriage as a function of historical events, e.g. whether an individual gets married, has children, takes their child to a day-care centre, etc. The objective was to predict prevalence of Hib carriage in families as a function of family size and age structure [145].

The next two models were developed in a Bayesian structure with data and parameters specified as a joint probability distribution [147, 148, 149, 150]. These were used to estimate age specific Hib carriage incidence rates [147], the duration of natural immunity to Hib under different forces of infection [148], and the relationships between Hib and cross-reactive antigens [149]. The final model was a stochastic, individual based transmission model where carriage was transmitted from person to person in three different contact sites: Family, day-care centre, and school class [150]. This model was used to study factors determining the magnitude of herd immunity from Hib vaccine [152]. In all of the papers, Finnish population and carriage data were used, supplemented by UK data in the 2002 paper by Leino *et al*. [149].

Two models have been published by researchers in the UK. Coen *et al*. used differential equations to represent the flows of age-structured groups between states over time as susceptible → infectious carrier → susceptible [153]. The authors used this model to analyse the impact of Hib vaccine on disease incidence in the Oxford region [154]. The objective of McVernon and colleagues' analysis from 2008 was to understand the reasons for a resurgence of Hib disease observed in the UK during the late 1990s. It was concluded that a key factor was over-reliance on immunological memory from vaccination, which was the reason for not having introduced a booster dose [155].

When reviewing the published models, it appears that the model presented by Coen *et al*. would be the most suitable for use in an economic evaluation, as this is the only model that was developed with the objective of analyzing vaccine impact on disease incidence. This model is therefore reviewed in more detail below.

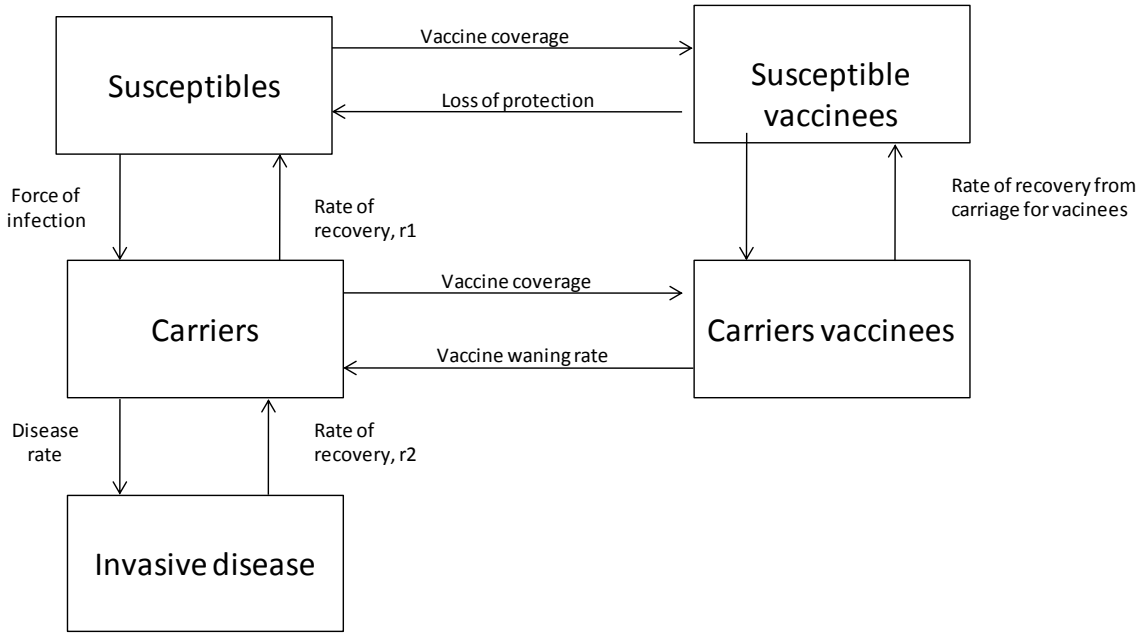
7.2.1 Dynamic Hib disease model developed by Coen and colleagues

Coen *et al*. developed a mathematical model describing asymptomatic carriage and Hib disease, based on a review of UK data on the prevalence of carriage and the incidence of disease by age. In a subsequent paper, the model was extended to include the impact of vaccination, and the model was validated by comparing the results to surveillance data from the Oxford region [154]. The model, which is represented by partial differential equations, is seen in Figure 7.1.

The force of infection and the disease rate are age-dependent parameters and the force of infection also depends on the rate at which susceptibles interact with Hib carriers across all ages. Coen *et al*. divided the population into five age groups and determined the interaction by means of "Who Acquires Infection From Whom (WAIFW) matrices; a standard method used in infectious disease models for depicting population mixing patterns [143].

The model was used to generate an estimate of the duration of carriage of 5 months, age-specific force of infection between 0.02 and 0.12, R_0 for Hib as 3.275, and a rate of age-specific Hib disease per carrier per year between 0.0001 and 0.1 [153]. Hib invasive disease cases captured from the surveillance system in Oxford were compared with the numbers predicted by the model for a variety of assumptions to gain insights about the behavior of the vaccine [154]. The main conclusions from the analysis were that Hib vaccine seems to block the acquisition of carriage and that other factors than experience of Hib carriage are likely to generate acquired immunity to Hib disease prior to vaccine introduction. Based on this, Coen *et al*. concluded that a booster dose would provide very little additional benefit in the UK. However, the UK saw a resurgence of Hib disease one year after the paper was published and a booster dose was consequently introduced in 2003 [156].

Figure 7.1: Schematic of Hib disease model by Coen *et al*.



Source: Coen *et al*. (1999)[154]

7.3 HIB VACCINE DECISION-ANALYTIC MODEL

7.3.1 MODEL DEVELOPMENT CONSIDERATIONS

Andrew Clark and I spent a substantial amount of time considering the model structure to be used. We were initially keen on developing a dynamic model, but after discussions with the Hib Initiative Steering Committee, it was decided to restrict the analysis to a static model. The main argument of the Steering Committee against a dynamic model was that since Hib carriage in a population is not an accurate determinant for Hib disease, it would be difficult to generate meaningful disease burden estimates from a model dependent on carriage rates. Moreover, reliable carriage data are only available from few developing countries.

Other arguments in favour of a static model were:

1. The model was developed to be used in all GAVI eligible countries. For a multi-country model, a transmission dynamic framework becomes less appropriate given the need to populate each individual country with good quality, local estimates on age-specific carriage and disease and reliable age-structured mixing patterns.
2. It was considered important to keep the model relatively simple, as the methods needed to be communicated to a number of different stakeholders with various backgrounds. Transmission dynamic models can be difficult to explain to policy makers due to their inherent complexity while transparent, static models can be more easily demonstrated.
3. If a static model can demonstrate that Hib vaccine is considered to be cost-effective, there is no need from a policy perspective to include transmission dynamics, as the static model estimate is conservative [87]. Hence, in this case there may be limited benefit in investing time and energy in accurately estimating the herd immunity benefits for the unvaccinated population.

The decision to limit the analysis to a static model was discussed extensively during my PhD upgrading, and the upgrading committee, which consisted of Professor John Edmunds and Dr. Rosa Legood, also came to the conclusion that a static model was the preferable approach.

The GBD project mentioned in Chapter 2 was being finalized during the time when we developed the decision-analytic model. Since it was apparent that country-specific Hib disease incidence and case fatality estimates generated by the GBD project would be key input parameters in the model for several countries, it was essential to develop a

framework that was compatible with these figures, and we therefore decided to structure the model in a comparable way to the GBD estimates.

The first activity of the GBD project was to conduct a comprehensive literature review to determine the availability and quality of country-specific disease burden data. Based on this literature review, it was decided to divide Hib diseases into three different groups; (i) meningitis, (ii) pneumonia and (iii) invasive non-pneumonia-non-meningitis (NPNM), and different modelling methods were developed for these three syndromes. For pneumonia, disease burden was estimated as an etiologic fraction of all-cause pneumonia cases and deaths. For Hib meningitis, an incidence-based approach was used wherein incidence and case fatality rates were derived from the literature. For Hib NPNM disease syndromes, incidence and case fatality rates were estimated indirectly based on the reported relationship between NPNM and meningitis cases and deaths [58]. We decided to use this division of syndromes when structuring our decision-analytic model and also similar methods for calculating disease cases.

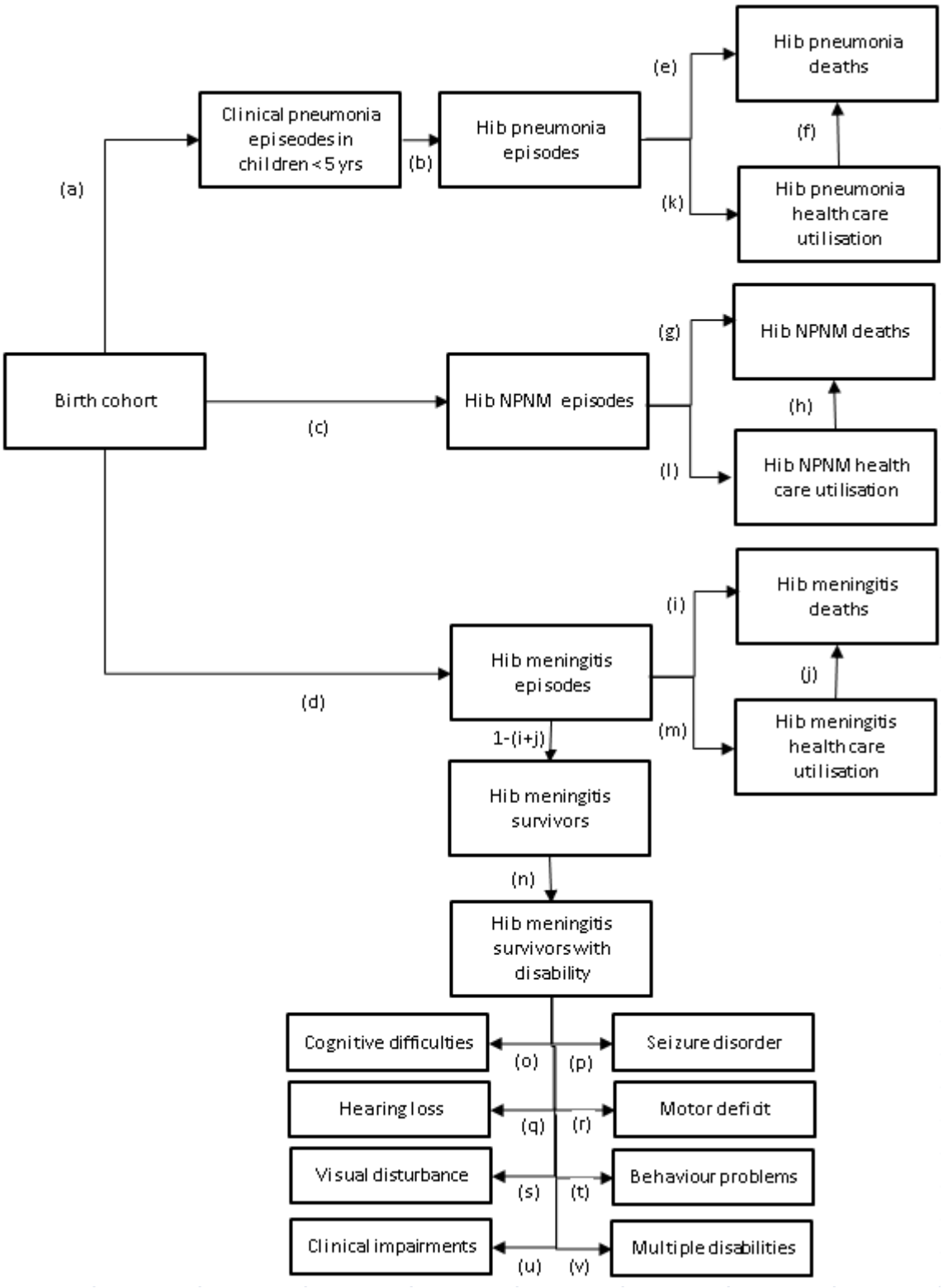
The results of the GBD project, in terms of estimated numbers of Hib disease cases and deaths in year 2000 according to geographical region, were published in the Lancet in September 2009 [31] and the methods were published as a web appendix [58].

7.3.2 DECISION-ANALYTIC MODEL STRUCTURE

The model framework is seen in Figure 7.2. According to the Kim and Goldie proposed framework, the model can be classified as a type 1.1: A deterministic aggregate-level static decision tree model. Projected numbers of person-years lived between 1 and 59 months are multiplied by disease incidence rates to estimate Hib cases in each cohort. The time horizon is until everyone in the cohort has died. An all-cause pneumonia incidence rate is used to calculate total pneumonia cases and it is assumed that a proportion of these are caused by Hib. Hib meningitis and Hib NPNM cases are calculated directly from aetiology specific incidence rates. A proportion of cases are assumed to seek health care and their treatment costs vary according to the type of care received. Hib meningitis, pneumonia and NPNM deaths are estimated from case fatality ratios (CFRs). A risk of permanent disability is applied to all survivors of Hib meningitis and classified according to type. The different sequelae classifications included at the bottom of Figure 7.2 are explained in Chapter 9.

The impact of Hib vaccine is estimated as the difference between scenarios with and without vaccination. In the Hib vaccination scenario, cases are reduced by age-specific vaccination coverage rates and dose-specific vaccine efficacy. Incremental cost-

Figure 7.2: Hib disease model structure

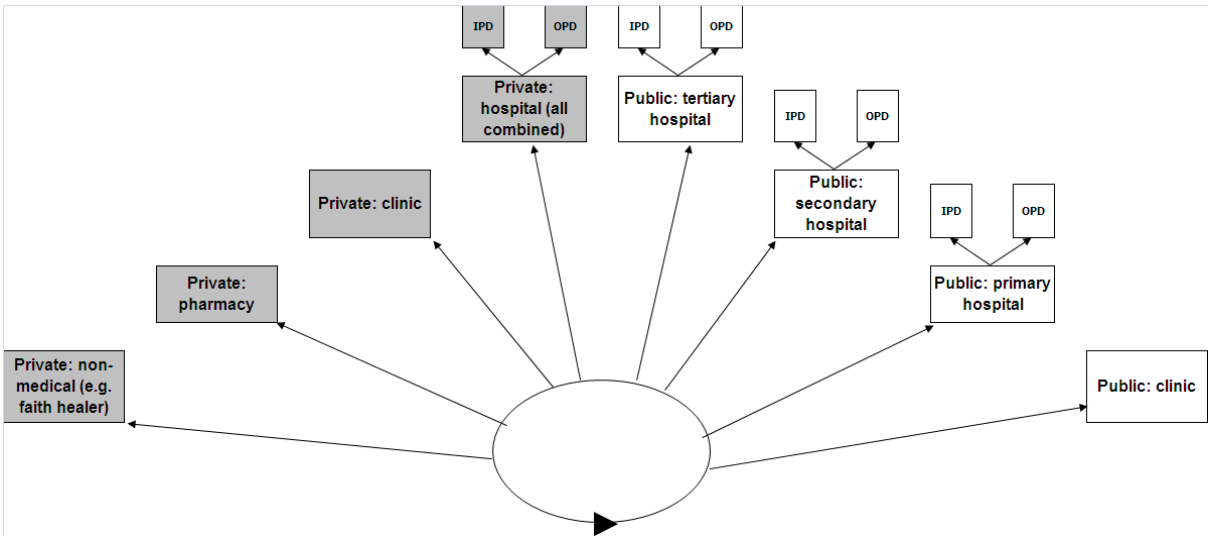


(a) Clinical pneumonia incidence in children < 5 yrs
(b) Percent of clinical pneumonia caused by Hib
(c) Hib NPNM incidence in children < 5 years
(d) Hib meningitis incidence in children < 5 years
(e) Pneumonia CFR without access to care
(f) Pneumonia CFR with access to care
(g) Hib NPNM CFR without access to care
(h) Hib NPNM CFR with access to care
(i) Hib meningitis CFR without access to care
(j) Hib meningitis CFR with access to care
(k) Proportion of Hib pneumonia cases seeking care
(l) Proportion of Hib NPNM cases seeking care
(m) Proportion of Hib meningitis cases seeking care
(n) Proportion of Hib meningitis survivors with disability
(o) Proportion with cognitive difficulties only
(p) Proportion with seizure disorders only
(q) Proportion with hearing loss only
(r) Proportion with motor deficit only
(s) Proportion with visual disturbance only
(t) Proportion with behavioural problems only
(u) Proportion with clinical impairments only
(v) Proportion with multiple disabilities

effectiveness ratios (ICERs) are calculated by subtracting annual treatment costs from annual vaccine delivery costs and dividing by incremental health effects, expressed as cases, deaths and Disability Adjusted Life Years (DALYs) in children less than five years. Future costs and health effects are in the base case scenario discounted by 3% per year, following WHO recommendations [88].

The model allows for a government health sector as well as a societal perspective. These different perspectives are especially important for the treatment cost data. In an analysis with a government perspective, only treatment costs incurred by the public health sector will be included, while out-of-pocket or health insurance expenses in both public and private facilities are also included in a societal perspective. The framework for treatment costs is shown in Figure 7.3. Data on health care seeking behaviour in the country in question is used to determine the proportions seeking care at primary, secondary and tertiary levels, and in the private versus the public health sector. Since treatment cost data from private hospitals are more difficult to access than from public facilities and since private facilities are relatively homogeneous in many countries, private hospitals have been grouped as one, irrespective of level. The circular arrow shows that a patient can seek health care from more than one of the facilities during the same illness episode. A visit to an outpatient clinic is for instance common before hospital admission and so is follow- up visits after discharge. This is accounted for by attaching a number of outpatient visits and hospital admissions per case of Hib disease.

Figure 7.3: Types of health facilities included in the decision-analytic model



IPD: In-patient Department
OPD: Out-patient Department

The model contains a total of 250 parameter values divided into eight main groups: (i) demography, (ii) vaccine coverage, (iii) vaccine efficacy, (iv) vaccine costs, (v) burden of disease, (vi) DALY parameters and discount rate, (vii) health services utilization and (viii) treatment costs. The broad headings of the parameters are summarized in Table 7.4. The next four chapters of this thesis are concerned with reviewing published evidence, data collection and analysis with the objective of obtaining robust parameter values. The respective chapters are listed in the second column of Table 7.4.

Table 7.4: Hib decision-analytic model parameters

Symbol in Figure 7.2	Parameter name	Possible data source or thesis chapter where details of methods and data for the parameter are investigated
	Demography	
	Number of live births per year	UN population division
	Infant mortality rate (per 1000 live births)	UN population division
	% of infant deaths in the neonatal period (<1m)	UN population division
	Under-5 mortality rate (per 1000 live births)	UN population division
	Life expectancy at birth	UN population division
	Vaccination coverage	
	Vaccine coverage of DTP1, DTP2 and DTP3 in base year	WHO/Unicef or local data
	% annual change in DTP1 coverage since year 2000	WHO/Unicef or local data
	% annual change in DTP3 drop-out since year 2000	WHO/Unicef or local data
	Maximum possible future vaccination coverage	Assumption
	Vaccine efficacy	
	Vaccine efficacy following 3 doses:	
	Hib meningitis	Chapter 8
	Hib invasive NPNM	Chapter 8
	Clinical pneumonia	Chapter 8
	Relative efficacy of fewer doses	
	2 doses only (as % of 3 dose efficacy)	Chapter 8
	1 dose only (as % of 3 dose efficacy)	Chapter 8
	Annual decrease in protection (waning immunity)	Chapter 12
	Vaccine costs	
	Vaccine price	Chapter 11
	% decline in vaccine price per year	Chapter 11
	Systems costs of vaccine delivery per child	Chapter 11
	Hib disease burden	
	Ratio of Hib invasive NPNM to Hib meningitis	Chapter 12
	Annual incidence per 100,000 aged 1-59 months:	
(a)	Clinical pneumonia	Chapter 12
(d)	Hib meningitis	Chapter 12
(c)	Hib NPNM	Chapter 12
	% case fatality ratios in ages 1-59 months:	

Symbol in Figure 7.2	Parameter name	Possible data source or thesis chapter where details of methods and data for the parameter are investigated
(e), (f)	Hib pneumonia	Chapter 12
(i), (j)	Hib meningitis	Chapter 12
(g), (h)	Hib NPNM	Chapter 12
(b)	% pneumonia episodes due to Hib	Chapter 12
(n)	% Hib meningitis survivors with permanent sequelae	Chapter 9
(o-v)	**%** with different types of disabilities	Chapter 9
	DALYs and discounting	
	Discount rate	Assumption
	Disability weights	Chapter 9
	Age weighting modulation factor	Chapter 9
	Age weighting parameter	Chapter 9
	Health care utilisation	
	Number of outpatient visits per case	Chapter 10
	Number of hospital admissions per case	Chapter 10
	Distribution of visits according to type of provider	Chapter 10
	Treatment costs	
	Cost per outpatient visit according to type of provider	Chapter 10
	Cost per admission according to type of provider	Chapter 10
	Lifetime treatment costs of sequelae	Chapter 10
	Lifetime productivity costs of sequelae	Chapter 10

7.3.3 SPECIFIC MODEL FEATURES

7.3.3.1 Age specific vaccination coverage rates

The exact age of Hib vaccine administration varies between countries according to their routine schedule, but the vaccine is generally delivered at the same time as DTP, polio and hepatitis B vaccines. The first dose should be given to children at approximately six weeks of age and the interval between doses should be at least one month. Most GAVI-eligible countries follow a schedule of 6, 10 and 14 weeks. When modelling the impact of Hib vaccination, it is assumed that Hib vaccine coverage will be similar to DTP coverage in the respective country. Coverage rates of DTP are routinely collected by the WHO from all member states and they can also be extracted from Demographic Household Surveys (DHS) [157].

The third dose of DTP vaccine (DTP3) is frequently used as an indicator for monitoring coverage trends. However, due to drop-out rates in many low-income countries, DTP3 coverage is often considerably lower than coverage of DTP1 and DTP2. Drop-out rates measure the proportion of children who have received the first dose, but are not taken

back to the health facility for their remaining vaccinations. In some countries, drop-out rates are as high as 30% [158].

Another problem seen in several countries is delayed vaccination until after the recommended age according to the schedule. Clark and Sanderson used DHS data for 45 countries between 1996 and 2005 and generated age-specific coverage data for 217,706 children [159]. They found the median delay in DTP3 coverage to be 6.2 weeks, but there was considerable variation among countries.

The decision-analytic model incorporates the potential negative impact of drop-out rates and delayed vaccination by using age-specific vaccination coverage rates for DTP1, DTP2 and DTP3 in terms of percent of total coverage achieved by 3, 6, 9, 12, 24, 36, 48 and 60 months.

7.3.3.2 Waning immunity

Vaccination failures are called primary when an immune response does not develop and secondary when immunity develops initially, but wanes over time. Since Hib vaccine has been shown to wane with time [156], most high- and upper-middle income countries provide a booster dose to children at around one year of age. However, a booster dose is not provided in GAVI eligible countries, partly due to the increased costs and administrative complexity, but also because Hib disease occurs in younger ages in low-income countries and the need for a booster dose has not yet been demonstrated in these settings. The decision-analytic model incorporates the effect of waning immunity by allowing for an annual percentage decrease in vaccine efficacy.

7.3.3.3 Crude approximation of herd immunity

Since this is a static model, herd immunity is not explicitly integrated into the model. However, a feature has been added to incorporate herd immunity in a crude way to be used only in a sensitivity analysis. The user of the model can choose a percentage point for expressing the additional percentage population protection. The calculation in the model is:

$$\text{Total vaccine effect} = \%\ \text{direct effect} / (1 - \%\ \text{herd effect})$$

If the direct effect for instance is calculated as 70% and 20% herd effect is assumed, the total vaccine effect is 88%. The % herd effect could for instance be derived from estimates generated by Wolfson *et al*. for the Hib GBD study [58]. The authors reviewed six post-vaccination surveillance studies from the US, Israel, Denmark, Gambia, Brazil and Cuba that had estimated population-level impact. By comparing the overall impact to Hib

vaccination coverage rates, a least squares-plural regression line was fitted to the six data points to obtain an equation linking population-level coverage among children less than five years to the reduction in invasive Hib disease. The overall effect on invasive Hib disease was approximately 15-30 percentage points higher than coverage of the third dose, and depended on the level of vaccination coverage. A herd immunity threshold (i.e. elimination) at around 85% coverage of the third dose was suggested [58]. One advantage of the Wolfson *et al*. method is that it is based on real world experience of several countries rather than a modelled estimate. However, as emphasised in a recent paper by Jit and Brisson, there are a number of dangers when approximating herd immunity in static models [87]. One important limitation is that there are inherent differences between populations, such as age structure and the size of risk groups, and this can lead to different vaccine effects between countries. Hence, unless there is good real world evidence of the magnitude of herd immunity from a similar population, the herd immunity feature of the model should not be applied in the base-case analysis, but only used to evaluate different "what-if" scenarios. This is done in Chapter 12.

7.3.4 VERIFICATION OF MODEL STRUCTURE AND PARAMETER ASSUMPTIONS

As mentioned above, the model structure was heavily influenced by the methods used for generating the Hib GBD estimates. The GBD methods were endorsed by an advisory committee in a number of meetings organised by the WHO during 2006-2008 [31, 58, 160]. Subsequent to this, the decision-analytic model structure and parameter assumptions were approved by three advisory groups:

i. Hib Initiative Steering Committee (2007)
ii. Technical staff at the Immunization, Vaccines and Biologicals Department in the WHO, Geneva (2008)
iii. The WHO Quantitative Immunization and Vaccines Related Research (QUIVER) Advisory Committee (2010)

7.3.5 SENSITIVITY ANALYSIS

The model has been designed so that all parameter values can be given a base case value and high and low limits. Vaccine efficacy could for instance be assumed to be 90% in the base case and 95% and 85% in the high and low limits, respectively. In the model, the high and low values can be used for single and multiple univariate sensitivity analysis. In addition, probabilistic uncertainty analysis using Monte Carlo simulation can be undertaken by attaching a distribution to each parameter. In a single univariate analysis, one parameter is varied at a time to assess the impact on the cost-effectiveness ratio.

Relevant parameters could for instance be the vaccine price, case fatality from Hib meningitis, or perhaps the herd immunity factor explained above.

Multiple univariate sensitivity analysis and probabilistic Monte Carlo simulation are used for assessing the sensitivity of results to the uncertainty of several or all parameter values simultaneously. The model has been designed so that a bar chart is easily generated in multiple univariate sensitivity analysis showing the varying effects on the ICER when choosing the higher and lower values of selected parameters. While several parameters should be included simultaneously, it is important to focus only on variables that are known to have considerable uncertainty or are of particular interest. If all 250 model parameters were included, the diagram would become too difficult to interpret.

The challenge of not being able to include all parameter uncertainties simultaneously is dealt with in the probabilistic Monte Carlo simulation. Here, each parameter is attached a statistical distribution and repeated random samples are selected. The outputs of this can be used to for estimating a 95% uncertainty interval around the ICER and for designing cost-effectiveness acceptability curves.

The different approaches to sensitivity analysis are explored in Chapter 12. In addition to parameter uncertainty it is important to evaluate methodological and structural uncertainty of the model, and this is also addressed in Chapter 12.

7.3.6 DISTRIBUTION OF MODELLING WORK

Andy Clark and I designed the overall structure of the model in close collaboration. The initial starting point was a simpler model I had developed when undertaking Hib vaccine cost-effectiveness studies in Russia, Kenya and Indonesia [122, 124, 125]. Andy is a mathematical programmer, so he was responsible for setting up the model in Excel, developing a user friendly interface, and programming several features using Microsoft Visual Basic™. I provided Andy with formulas for estimating incremental vaccine and treatment costs and I quality assured the model during all development steps. This has been an iterative process, which started in 2007 and is still ongoing.

8 HIB VACCINE EFFICACY[2]

One of the important components of any economic evaluation is to establish the effect of the intervention. As described in the previous chapter, dose-specific vaccine efficacy against Hib meningitis, Hib pneumonia and Hib NPNM are input parameters in the decision-analytic model. In this chapter, a meta-analysis of randomised controlled trials (RCTs) of Hib vaccine is undertaken to determine these parameter values. The chapter starts off by explaining the differences between vaccine efficacy and vaccine effectiveness. An overview of basic methods of meta-analysis is given in section 8.2, previous meta-analyses of Hib vaccines are summarised in section 8.3, the new meta-analysis is presented in section 8.4, and section 8.5 is a summary of the efficacy values used in the economic evaluation.

8.1 DEFINITIONS OF VACCINE EFFICACY AND EFFECTIVENESS

Vaccine efficacy is defined as the extent to which the vaccine produces a beneficial result under ideal conditions [161]. Clinical vaccine trials generally proceed as Phases I, II, and III. The aim of phase I trials is to evaluate vaccine safety, tolerability and immunogenicity over different dosages or regimens, and they typically involve between 10 and 100 participants. Phase II trials usually require between 100 and 500 participants and the aim is to characterise safety and immunogenicity in the population in which the vaccine is to be used. Vaccine candidates that are safe and immunogenic in Phase I and II trials can be taken to phase III trials for evaluating efficacy within the population of interest. These trials can involve up to 100,000 people and are usually double-blind and randomized with one arm assigned to the vaccine and the other arm to placebo.

Since phase III clinical trials are undertaken under ideal conditions with the aim of optimizing detection of the chosen endpoint, it is not possible to predict accurately the level of protection that will be achieved in public health practice where the vaccine may be refrigerated inadequately and administered inappropriately or late [162]. Vaccine effectiveness is defined as the extent to which a vaccine does what it is intended to do for a defined population when deployed in the field [161]. This can be evaluated by a screening test study, a cohort study, a case-control study or a phase IV study in which a large community is randomised by area to receive the vaccine or not. The screening test study

[2] A modified version of this chapter has been published in the Journal of Epidemiology and Infection as: Griffiths UK, Clark A, Gessner B, Miners A, Sanderson C, Sedyaningsih ER, Mulholland KE, Dose-specific efficacy of *Haemophilus influenzae* type b conjugate vaccines: Systematic review and meta-analysis, Epidemiol Infect. 2012 May 14:1-13. [Epub ahead of print].

involves comparing vaccine coverage among cases and the general community, without reference to the possibility of confounders. Cohort studies use longitudinal data on the target outcome, such as Hib disease, for a group of vaccinated individuals contrasted with an unvaccinated group. The most common method used for establishing Hib vaccine effectiveness is however the case-control method. In this, a group of cases with the target outcome, most frequently Hib meningitis, is contrasted with a group of controls who did not develop the target outcome [162]. The advantages of a case-control study over clinical trials are that i) they involve relatively few participants, ii) the necessary information can be obtained within a short time, and iii) their results are based on actual field conditions [163]. However, case control studies also have many problems. The most important challenge is to produce convincing evidence that the vaccinated and unvaccinated populations are sufficiently alike in all relevant characteristics other than vaccination to allow a reasonable conclusion that differences between groups are attributable to vaccine effectiveness [163].

Vaccine efficacy estimates from RCTs are used as input parameters in the decision-analytic model and not effectiveness. The reason for this is partly because of the many methodological limitations of observational studies, but also because the decision-analytic model separately includes factors for adjusting vaccine efficacy in line with the situation in the respective country, such as timing of vaccination through age-specific coverage rates and waning protection.

8.2 OVERVIEW OF META-ANALYSIS METHODS

The aim of meta-analysis is to summarize the evidence gathered in several studies on a variable of interest, such as vaccine efficacy from RCTs, or an effect measure generated from observational studies. Summary estimates should however only be calculated if the study specific effects appear to be fairly similar. Hence, trials using Hib pneumonia as an outcome measure can for example not be analysed together with trials that measure vaccine efficacy against Hib meningitis.

There are two main ways to summarise the results of different studies [164]. The first is known as the *fixed effects* approach. With this method the pooled effect is calculated as a simple weighted average of the separate effects. The underlying assumption is that each study measures the same effect, with the weighted average estimating the common effect. The relative weight assigned to each study will vary from method to method, but should reflect the amount of information that each trial contains. One of the most popular

techniques is the Mantel-Haenszel method, in which weights are proportional to the inverse variance of each study, which in turn is closely related to the sample size [165].

The second method is the *random effects* approach, in which effects of the individual studies are assumed to vary around some overall average treatment effect [165]. The studies are viewed as a random sample of a population of studies, in which the true effects in each study are assumed to be normally distributed around a 'global' mean. The most common method for the random effects models is the DerSimonian and Laird approach, which estimates the magnitude of heterogeneity and assigns a greater variability to the estimate of overall treatment effect to account for any heterogeneity [166].

There is no consensus regarding the choice of fixed or random effect models, although they differ only in the presence of heterogeneity, when the random effect model will usually be more conservative [165]. Heterogeneity is defined as the extent to which studies disagree on the magnitude of effects, or perhaps even on the direction of effects. Possible clinical explanations of heterogeneity are that studies use different eligibility criteria for participants, different definitions of disease, different methods of measuring or defining exposure, or different variations of treatment [164]. Statistical heterogeneity could be caused by publication bias whereby those with dramatic results may more often be published or poor methodological quality of some trials. If heterogeneity is detected, the random effects model may be most appropriate as this takes explicit account of variability in the calculations. If there is little heterogeneity across studies the choice of a fixed versus random effects model is not crucial, as the two approaches give very similar results [164]. The random effects model should however not be viewed as a panacea when heterogeneity is large; it would then be important to consider whether a single summary measure is indeed valid [164]. Instead, the reasons for the differences between trial results should be investigated and a pooled estimate not reported.

Heterogeneity can be detected by comparing results of fixed and random effects models. If the two approaches lead to different results, heterogeneity could be a problem. Relatively simple tests of heterogeneity are also available, mostly based on chi-squared or F statistics. The null hypothesis is that there is no significant heterogeneity among study results. Hence, if the test is statistically significant, the between trial variability is more than would be expected by chance alone. A cut-off significance level of 0.10 is normally used. The chi-squared statistics can be supplemented by the I^2 statistics to quantify heterogeneity [167]. The I^2 is the percentage of variation attributable to heterogeneity and lies between 0% and 100%. A value of 0% indicates no observed heterogeneity and larger

values show increasing heterogeneity. Higgins has tentatively suggested that low I^2 values are between 25%-50%, moderate are between 50% and 75%, and high are above 75% [167].

Assessment of risk of bias is a crucial part of meta-analysis, both as an approach to investigating causes of heterogeneity and also for assessing the validity of the pooled estimate. The Cochrane Collaboration has developed a Risk of Bias Tool to assess internal validity of randomized controlled trials [168]. The tool was developed over several years as a way to address concerns about the existing methods of assessing study quality in Cochrane reviews. The Risk of Bias Tool has six domains:

i. Sequence generation
ii. Allocation concealment
iii. Blinding of participants, personnel and outcome assessors
iv. Incomplete outcome data
v. Selective outcome reporting
vi. Other sources of bias

Use of the tool is demonstrated in the new Hib vaccine efficacy meta-analysis in section 8.4.

8.3 PREVIOUS META-ANALYSES OF HIB VACCINE EFFICACY AND EFFECTIVENESS STUDIES

The first meta-analysis of Hib conjugate vaccine efficacy studies was published by Stieb and colleagues in 1990 [169], but at that time only two efficacy trials had been completed; both of the PRP-D vaccine, in Finland and Alaska, respectively. A Cochrane systematic review and meta-analysis of Hib vaccine efficacy was published around the year 2002, but this has since been removed from the Cochrane system due to lack of updates and is no longer available for reference.

A meta-analysis of Hib vaccine efficacy trials was published by Obonyo and Lau in 2006 [170]. Three databases were searched in this review: Medline and EMBASE for the period 1990 to June 2005 and the Cochrane registry of controlled trials from year 2000. The authors included published randomized or quasi-randomized studies that reported the efficacy of Hib vaccination compared to placebo. A total of eight studies were included; one PRP-OMP trial, one HbOC trial, two PRP-D trials and four PRP-T trials [170]. Summary log odds ratios were obtained using a random-effects model. Subgroup analysis was performed to compare the efficacy of vaccination in developing versus developed countries, according to the type of conjugate vaccine, age of children at vaccination, number of doses received, baseline risk, and HIV status. While it is stated in the methods

that the potential for bias in results was evaluated, these issues were not reported in the results section. The protective efficacy of three doses of Hib conjugate vaccine was found to be 84% against invasive Hib disease, 75% against Hib meningitis, and 69% against Hib pneumonia. The efficacy of one and two doses was found to be 72% and 82%, respectively [170]. However, not many details were given about the dose-specific estimates. As will be shown in the new meta-analysis, different trials use different clinical endpoints and not all trials report efficacy according to the number of doses, so there is a need to explain which studies are used for which estimates, and what weight each individual study contributes to the pooled estimate.

Observational studies for assessment of Hib vaccine effectiveness were recently evaluated by O'Loughlin *et al*. in a systematic review and meta-analysis [171]. A total of 25 studies reporting Hib vaccine effectiveness were included. Fourteen of these were case–control studies, three used the surveillance/screening method, two calculated the ratio of observed cases (regardless of vaccination history) to expected cases (based on assumptions made using pre-vaccine surveillance data), and one study used a vaccine probe study design. One of the conclusions from the review was that the effectiveness of Hib vaccine has now been well documented and the need for more case-control studies is minimal [171].

Theodoratou *et al*. undertook a systematic review and meta-analysis of RCTs and observational studies to evaluate the effect of Hib and pneumococcal vaccines on childhood pneumonia incidence, severe morbidity and mortality [172]. It was concluded that no studies were available to determine the effect of Hib vaccine on childhood mortality and that the efficacy against radiological pneumonia was the best approximation to use for severe pneumonia [172].

8.4 EFFICACY OF HIB VACCINES: SYSTEMATIC REVIEW AND META-ANALYSIS

8.4.1 OBJECTIVES

The objectives of the new systematic review and meta-analysis are:

1. To update the literature review of RCTs published by Obonyo and Lau.
2. To use data from identified studies to derive quantitative estimates of dose-specific Hib vaccine efficacy in a way that that can be used be in the decision-analytic model.
3. To determine whether there is heterogeneity in the study results and if so, to examine sources of heterogeneity, including the risk of bias resulting from study design. If appropriate, stratify results based on the findings.

4. To assess whether there are significant differences in efficacy between the different available conjugate vaccines.

The main differences between the current study and the study by Obonyo and Lau are:

- Only Hib conjugate vaccines that are currently available have been included in the present study. The PRP-D Hib vaccine trial studies are excluded.
- The literature review is updated since year 2005 when the search by Obonyo and Lau ended.
- The new review includes supplementary information received directly from trial authors.
- The new study includes more detailed dose-specific analyses.
- A risk-of-bias analysis is performed using the Cochrane Risk of Bias Tool.

8.4.2 METHODS

The meta-analysis was undertaken according to recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [173].

8.4.2.1 Search strategy and study selection

Studies were identified from the Cochrane Controlled Trials Register (CCTR) using the search term "haemophilus vaccine" in March 2011. The CCTR is a bibliographic database of controlled trials systematically identified by the contributors to the Cochrane Collaboration. The researchers have identified CCTR records through a combination of hand- and database searching that include all those indexed as controlled trials in MEDLINE and EMBASE [174]. When looking only for controlled trials there is thus generally no immediate need to also search MEDLINE and EMBASE, as these databases are already included in the CCTR. However, to quality check the search, the CCTR results were compared with a similar search in MEDLINE for 2005. Reference lists in identified papers were checked and experts in the field were contacted to confirm that no studies had been missed.

Studies were eligible for inclusion if they compared a commercially available Hib vaccine with placebo, if clinical endpoints were reported, and if participants had been allocated prospectively using random or quasi-random allocation. To maximise the amount of data available for analysis, quality measures were not used as exclusion criteria. There were no language restrictions.

One author kindly provided primary data from his trial. In the paper by Gessner *et al.*, results were only given by comparing disease incidences per 100,000 child years in the

vaccine versus the placebo group. However, for the vaccine efficacy estimates, the number of Hib disease cases in each group according to syndrome and according to number of vaccine doses received is needed, as well as the total number of children in each group. I received the necessary primary data from Dr. Brad Gessner from Association pour l'Aide a la Medicine Preventive (AMP) in Paris, via email.

The data extracted included setting, type of Hib vaccine, schedule, number of Hib disease cases according to study group, and total numbers of children in both groups.

8.4.2.2 Outcome measures

The choice of primary outcome measure is one of the most critical aspects of a RCT. Vaccines are normally evaluated against disease proven to be due to the pathogen in question [175]. For diseases that can be caused by a variety of different pathogens, which include all Hib diseases except epiglottitis, it is common practice to look for protection against microbiologically proven disease [175]. As explained in Chapter 2, this is in particular feasible for Hib meningitis cases, as Hib can be detected from CSF when optimal laboratory procedures are followed. However, the aetiology of childhood pneumonia is intrinsically difficult to determine [176]. The only method which would reliably determine the aetiology is culture of lung aspirate, but this procedure is invasive and not always ethically feasible in an RCT. Moreover, selection bias will occur if antibiotics are commonly used before seeking health care as this will markedly reduce the sensitivity of the lung aspirate test [177]. Blood culture is only useful when pneumonia is associated with bacteraemia, which is only a fraction of cases. The bacterial yield from blood culture in patients with pneumonia has ranged from 10% to 30% [178]. Hence, since there are currently no validated and specific methods for confirming the pathogen-specific bacterial aetiology of pneumonia, several non-specific pneumonia endpoints were used in the studies.

The following outcomes were included in the meta-analysis: (i) confirmed invasive Hib disease (ii) confirmed Hib meningitis (iii) confirmed Hib pneumonia, (iv) clinical meningitis, (v) radiologically (or chest x-ray) confirmed pneumonia, (vi) hospitalized pneumonia and (vii) clinical pneumonia. In addition, efficacy estimates were calculated according to the number of doses of Hib vaccine received as:

i. Only one dose
ii. Only two doses
iii. Three doses

8.4.2.3 Statistical analysis

Trial results were expressed as vaccine efficacy with 95% confidence intervals. Vaccine efficacy is defined as 100% x (1- relative risk). Relative risks were calculated as:

$$\text{Relative risk } = \frac{\text{risk of event in Hib vaccine group}}{\text{risk of event in placebo group}} = \frac{a/(a+b)}{c/(c+d)}$$

where,

a = disease events in Hib vaccine group

b = no disease events in Hib vaccine group

c = disease events in placebo group

d = no disease events in placebo group

Since Hib disease is a relatively rare event and the vaccine is highly efficacious, some trials report zero events in the vaccine group for certain outcome measures. In these cases, the relative risk ratio is zero and the standard error cannot be estimated. For meta-analysis, this is a problem because the inverse variance is commonly used as the study weight. A standard way to deal with this is to add 0.5 to each cell counts to avoid division by zero errors [165], and this method was use in the analysis.

A random effect model was used. Heterogeneity was assessed using the chi-squared test with a p-value of <0.10 indicating statistical significance. All statistical analyses were performed in STATA (version 11).

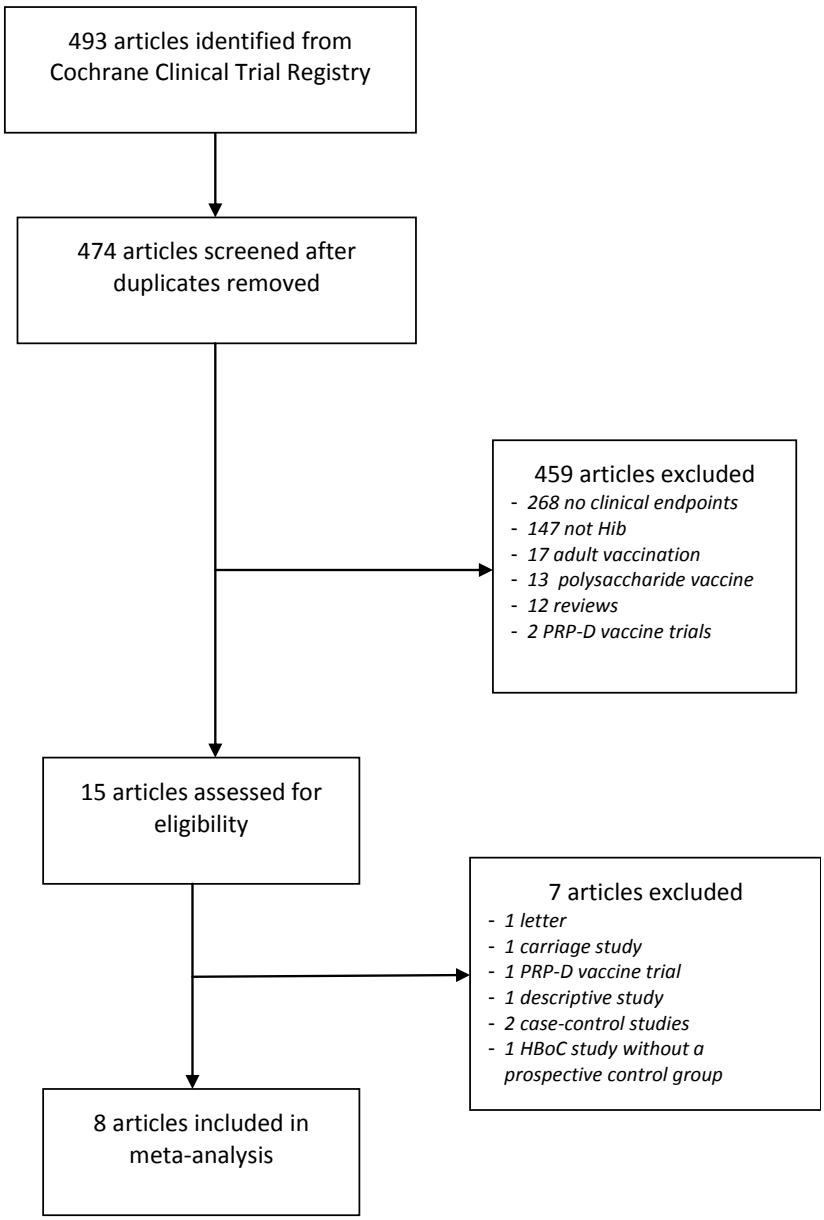
8.4.3 RESULTS

8.4.3.1 Characteristics of eligible trials

The search strategy yielded 493 references (Figure 8.1). After removing duplicates, 474 titles and abstracts were screened and 459 papers excluded. The most common reason for exclusion at this stage was that the study reported only safety and immunogenicity of the vaccine with no clinical endpoints.

Fifteen papers were retrieved for full-text review and seven of these were excluded. One of the excluded studies was a large, Finnish prospective study where children born on even numbered days received HBoC vaccine and those born on uneven numbered days received PRP-D vaccine [179]. Vaccine efficacy was estimated as 87% (95% CI, 69%, 96%) for the PRP-D vaccine and as 95% (95% CI, 76%, 99%) for the HBoC vaccine. These efficacy

Figure 8.1: Study selection for Hib vaccine efficacy meta-analysis



estimates were generated by comparing the number of Hib disease cases during the study period with the number that would have been expected based on historical, routine surveillance data. Hence, the comparison group was not based on prospective data and the study was excluded for this reason.

Characteristics of the eight included studies are seen in Table 8.1. The PRP-T vaccine was evaluated in six of the eight papers, the HbOC vaccine in one study, and the PRP-OMP vaccine in one paper. The studies by Lagos and Levine used data from the same trial. Three of the studies were undertaken in USA and the remaining in England, Chile, Gambia and Indonesia. One of the US studies was conducted in a Navajo Indian reservation, targeting a group with one of the highest Hib disease incidences in the world [180]. In this trial only two doses of Hib vaccine were administered while three doses were evaluated in the seven other studies. In all the studies, follow-up stopped after a specified time period. The study by Booy had the shortest follow-up time and the study by Mulholland the longest, with the oldest children being 18 and 30 months, respectively, when the studies ended.

Two of the eight studies were not included in the meta-analysis by Obonyo and Lau. In their analysis, only the primary Chilean study by Lagos *et al*. was included while no mention was made of the study by Levine *et al*. The objective of Levine's study was to estimate Hib vaccine efficacy on clinical pneumonia and this endpoint was not part of the Obonyo and Lau meta-analysis. The Indonesian study by Gessner *et al*. is the only study published since 2005 when Obonyo and Lau's search ended. This study was a so-called vaccine probe study where a randomized controlled trial design with a vaccine of known efficacy is used to determine the vaccine preventable burden of disease. By comparing vaccinated and non-vaccinated groups of children, Gessner and colleagues aimed to estimate the incidence of vaccine preventable Hib disease in the Indonesian island of Lombok [181]. The study, which was funded by USAID, the Gates Foundation, PATH and Aventis Pasteur, was undertaken as a response to the persisting uncertainty about Hib disease burden in Asia [47].

8.4.3.2 Outcome measures used in the trials

The six different outcome measures used in the trials are summarized in Table 8.2 and the case definitions in Table 8.3. The studies by Booy, Levine and Vadheim did not report vaccine efficacy for less than three vaccine doses.

Table 8.1: Characteristics of studies included in the meta-analysis

First author [ref]	Year recruitment started	Location	Type of Hib vaccine	Vaccine manufacturer	Hib vaccine schedule (weeks)	No. of children enrolled in study	Max age when follow-up ended (months)
Black [182]	1988	California, USA	PRP-HbOC	Praxis Biologics	8, 16, 24	61,080	24
Booy [183]	1991	Oxfordshire, England	PRP-T	Pasteur Merieux	8, 12, 16	27,860	18
Gessner [181]	1998	Lombok, Indonesia	PRP-T	Aventis Pasteur	6, 10, 14	55,073	24
Lagos [184]	1992	Santiago, Chile	PRP-T	Pasteur Merieux	8, 16, 24	76,533	28
Levine [185]	1992	Santiago, Chile	PRP-T	Pasteur Merieux	8, 16, 24	21,420	23
Mulholland [186]	1993	Western region of Gambia	PRP-T	Pasteur Merieux	8, 12, 16	42,848	30
Santosham [180]	1988	Navajo Indian Reservation, USA	PRP-OMP	Merck	6, 12	5,166	23
Vadheim [187]	1989	California, USA	PRP-T	Pasteur Merieux	8, 16, 24	10,317	24

Table 8.2: Outcome measures available in the studies included in the meta-analysis

Author (reference)	Confirmed Hib invasive disease			Confirmed Hib meningitis			Confirmed Hib pneumonia			Clinical meningitis			Radiological pneumonia			Clinical pneumonia			Hospitalised pneumonia		
No. of doses	***1***	***2***	***3***	***1***	***2***	***3***	***1***	***2***	***3***	***1***	***2***	***3***	***1***	***2***	***3***	***1***	***2***	***3***	***1***	***2***	***3***
Black [182]	x	x	x																		
Booy [183]			x																		
Gessner [181]				x	x	x				x	x	x	x	x	x	x	x	x	x	x	x
Levine [185]															x						x
Lagos [184]			x																		
Mulholland [186]	x	x	x	x	x	x	x	x	x						x			x			
Santosham [180]	x	x		x	x		x	x													
Vadheim [187]			x																		
No. of studies	***3***	***3***	***5***	***3***	***3***	***2***	***2***	***2***	***1***	***1***	***1***	***1***	***1***	***1***	***3***	***1***	***1***	***2***	***1***	***1***	***2***

Table 8.3: Hib disease case definitions used in the Hib vaccine RCTs

Outcome measure	Definition
Confirmed Hib invasive disease	Clinical signs of any invasive Hib disease and Hib isolated from CSF, blood or other sterile body fluids
Confirmed Hib meningitis	Clinical signs of meningitis and Hib isolated from CSF, blood or other sterile body fluids
Confirmed Hib pneumonia	Clinical signs of pneumonia and Hib isolated from CSF, blood or other sterile body fluids
Clinical meningitis	Probable: CSF visibly cloudy or a white-blood-cell count > 10 x 10^6/L with >80% neutrophils, glucose <2·22 mmol/L, or protein >1 g/L Possible: CSF white-cell count of >10 x 10^6/L Hospitalised: As determined by the admitting physician, but generally based on the presence of convulsions with fever
Radiological pneumonia	Clinical signs of pneumonia and substantial alveolar consolidation or pleural effusion on chest X-ray
Clinical pneumonia	WHO defined ALRI: Respiratory rate $\geq$ 50 per min for children 2-12 months and $\geq$ 40 per min for those aged 12-24 months
Hospitalised pneumonia	Levine: Five different pneumonia ICD9-codes Gessner: Hospitalised with severe clinical pneumonia diagnosis

ALRI: Acute Lower Respiratory Infection

The outcome measure used by most of the studies was invasive Hib disease, defined as "isolation of Hib from a normally sterile body site". While all types of Hib diseases are included within the invasive disease group, meningitis is likely to be the most frequent type of disease syndrome detected. In the study by Gessner, the only outcome measure that included etiologic confirmation was Hib meningitis. This endpoint could also be extracted from the studies by Mulholland and Santosham because cases were summarized according to disease syndromes in these two papers.

Four different types of pneumonia outcomes were included in the studies. Confirmed Hib pneumonia was reported by Mulholland and Santosham, along with the other types of invasive Hib disease detected (Table 8.2). However, as mentioned above, because only a small proportion of Hib pneumonia is bacteraemic, this outcome measure will only capture a fraction of all Hib pneumonia in a study population.

Clinical, non-specific pneumonia outcome measures were included in the RCTs from Chile, Gambia and Indonesia. As explained in Chapter 2, pneumonia disease incidence is considerably higher in low-income compared to high-income countries, so non-specific pneumonia endpoints were not relevant to include in the RCTs from the USA and England. However, in low-income countries prevention of pneumonia might be the primary argument for introducing Hib vaccine, so it was crucial to try and measure the efficacy against pneumonia in these countries.

Radiological confirmed pneumonia was used in the studies by Gessner, Levine and Mulholland, clinical pneumonia by Gessner and Mulholland, and hospitalized pneumonia by Gessner and Levine. All of these outcome measures pose a number of definition problems leading to risk of heterogeneity among the studies.

Radiological confirmed pneumonia was in all three studies defined as pneumonia with consolidation or pleural effusion on the chest X-ray. The studies in Gambia and Chile were the first studies in the world to use this outcome measure, and their results lead to a WHO working group for using chest radiographs as a benchmark for evaluating the efficacy of Hib and pneumococcal vaccines [188, 189]. Hence, these specific WHO definitions were used in the Indonesia study. However, in spite of a considerable amount of work to standardize the definition, it is still common that radiologists and clinicians, and even radiologists among themselves, disagree on the presence or absence of infiltrates in paediatric chest X-rays [176].

Hospitalised pneumonia was used as an outcome measure in the studies from Chile and Indonesia. In the study from Chile, five different pneumonia ICD-codes were abstracted from patient records while in Indonesia the definition was hospital admission due to severe pneumonia. These endpoints may be subject to bias because pneumonia is not easy to distinguish from other types of Acute Lower Respiratory Infections (ALRIs), such as bronchitis, and lower and upper respiratory infections can also be difficult to differentiate. Hence, the pneumonia diagnosis given by hospital clinicians may not be accurate. Moreover, this endpoint could cause heterogeneity among study sites due to different hospital referral patterns, with some settings admitting children with less severe pneumonia than others.

Clinical pneumonia was evaluated by Gessner and Mulholland, defined according to the WHO definition of ALRI in both studies [190]. While there are also caveats with regard to correct clinical diagnosis for clinical pneumonia, this is likely to be less than for hospitalized pneumonia.

8.4.3.3 Methodological quality of trials

The domains specified in Cochrane's Risk of Bias tool are summarized in Table 8.4. The only individual RCTs among the included studies were the PRP-T trials by Mulholland and Vadheim. However, the Vadheim study ended prematurely due to inclusion of the HbOC vaccine in the US routine vaccination schedule while the Vadheim study was ongoing. Hence, the sample size of this study ended up being too small

Table 8.4: Methodological quality of included trials: Assessment based on Cochrane's risk of bias tool

First author [ref]	Unit of randomisation	Sequence generation	Blinding	Allocation concealment	Outcome reporting
Black [182]	Individual	Placebo group was refusers and children born on the first 5 days of a month.	No, but microbiologists performing tests for Hib were unaware of vaccination status.	NA	Enhanced surveillance to detect all Hib patients treated in the study area.
Booy [183]	Cluster	Hib vaccine districts determined from availability of computer systems	No, but microbiologists performing tests for Hib were unaware of vaccination status.	NA	Enhanced surveillance to detect all Hib patients treated in the study area.
Gessner [181]	Cluster	Random	Double blinding	Vaccine vials identical except four colour codes; two for Hib and two for placebo. Code in a locked vault.	Education for diagnosis and referral. Young women in every village to identify children with pneumonia and get them to hospital. Families reimbursed treatment costs.
Lagos [184]	Cluster	Random	No, but microbiologists performing tests for Hib were unaware of vaccination status.	NA	Active surveillance at 11 hospitals in Santiago. Bacteriology laboratory reports reviewed weekly.
Levine [185]	Cluster	Random	No	NA	Retrospective review of five ICD-9 pneumonia discharge diagnoses.
Mulholland [186]	Individual	Random	Double blinding	Five vaccine vial codes used for Hib and the five others for placebo. Only safety monitoring group knew the code.	Study children presenting to health centres due to any illness referred to study physician.
Santosham [180]	Cluster	Random	Double blinding	Vaccine and placebo vials had similar appearances. Code not known until end of study.	Active and passive surveillance throughout study area.
Vadheim [187]	Individual	Random	Double blinding	No details given on method used.	Active and passive surveillance throughout study area.

for vaccine efficacy estimates to be presented in the paper [187]. The study by Black and colleagues was a controlled, individual trial in which unvaccinated children were either those who had refused to participate or children enrolled in the trial who were born on the first five days of any month [191].

A cluster design was used in three of the trials. In the studies by Gessner and Santosham, vaccine allocation among clusters was randomly and blindly determined. However, in the study by Booy, choice of Hib vaccine clusters was dictated by availability of computer systems needed for planning of a new vaccine schedule [183]. The study from Chile used prospective, selective vaccination where one set of 36 health centres delivered combined PRP-T/DTP vaccine and another set of 35 centres administered only DTP vaccine. The two sets of health centres were assembled so that they were similar in geographic distribution and population size served, and it was randomly decided which of the two sets should receive the PRP-T/DTP vaccine.

From reviewing the five domains, it can be concluded that risks of bias due to randomization, sequence generation and allocation concealment were relatively low in all the studies. Even though two studies were not randomised, it seems unlikely that the results would be biased for this reason. However, four of the studies were not blinded and this leads to risk of bias. In the three studies where confirmed Hib disease was the only endpoint, the risk of bias would most likely be low because the microbiologists undertaking the tests for Hib were not aware of the child's vaccination status. However, in the Levine study, radiological and hospitalised pneumonia were the chosen endpoints and assessments of these were made from hospital records of children with known vaccination status, leading to moderate risk of bias. With regard to inclusion of all randomized participants, all the studies suffer from high risk of bias due to the inherent difficulties of diagnosing Hib. Even in the studies with enhanced surveillance, it is possible that not all Hib cases were detected. The risk of detection bias is especially large in the three studies with non-specific (or all-cause) pneumonia as an outcome.

An additional risk of bias in the studies using non-specific pneumonia outcomes is that estimated Hib vaccine efficacy will vary with the relative proportion of Hib pneumonia occurring during the study period. Since many of the other pathogens that cause pneumonia are known to be seasonal, such as for instance respiratory synical virus (RSV) or influenza, this could be a problem. Hib vaccine efficacy against clinical pneumonia would for instance be less in a year with a RSV pneumonia outbreak than in a year with low RSV incidence [192]. Since all the trials lasted for more than one year, seasonal

fluctuations might have been evened out to some extent, but the risk of this bias is apparent. This is also an important limitation to bear in mind when generalising the efficacy values to other settings where the relative proportion of Hib pneumonia may be different.

The risk of publication bias is an additional factor to assess in any meta-analysis [193]. This relates to the fact that studies giving positive results are more likely to be published than studies in which the intervention has little or no effect. If this is the case, the pooled meta-analysis estimate would give a positively biased result. However, for vaccine trials risk of publication bias must be considered low. These are large trials involving thousands of children and lasting several years and there is strong pressure on investigators and vaccine manufacturers to publish the results. It is thus highly unlikely that any Hib vaccine phase III trial has taken place without being published.

8.4.3.4 Vaccine efficacy compared to placebo

The Hib vaccine efficacy estimates for five different endpoints are seen in Figures 8.2 – 8.4. The pooled efficacy estimate against confirmed, invasive Hib disease following three, two and one dose are 93% (95% CI 83, 97), 92% (95% CI 69, 98) and 59% (95% CI -20, 86), respectively (Figure 8.2). There is no heterogeneity among the studies for three and two doses and only low heterogeneity for one dose (I^2 = 20.7%), which is attributable to the Santosham study of the PRP-OMP vaccine reporting considerably higher efficacy than the three other studies. The pooled estimate of the PRP-T and the HbOC trials, and excluding the PRP-OMP trial, is 47% (95% CI -28, 70) with no heterogeneity (I^2=0.0%).

For confirmed Hib meningitis there is no heterogeneity among any of the dose-specific estimates, but due to the relatively small sample sizes, the confidence intervals are wide for one and two doses (Figure 8.3). Moreover, since the Santosham trial only estimated one and two dose efficacy, the pooled value for three doses (88% (95% CI 46, 97)) is less than for two doses (92%, 95% CI 37, 99). The pooled one-dose estimate is 62% (95% CI -29, 89).

Data on confirmed Hib pneumonia were only available from the Mulholland and Santosham studies, and Santosham did not identify any cases following two doses. The Mulholland midpoint efficacy estimates of both two and three doses were 91% (95% CI -66, 99) and the pooled estimate between Mulholland and Santosham following one dose was 67% (95% CI -44, 93).

Vaccine efficacy against radiological pneumonia with three doses was 22% in both the Levine and Mulholland studies, but the result was negative in the study by Gessner, causing large heterogeneity (I^2=64%) (Figure 8.4). Hence, the pooled estimate has limited validity. The pooled estimate without the Gessner study was 22% (95% CI 6, 35) with no heterogeneity (I^2=0.0%).

Hib vaccine efficacy against hospitalised pneumonia following three doses of vaccine was reported by Gessner and Levine (Figure 8.4). There is however also large heterogeneity between these two studies and the pooled estimate is not meaningful. While Levine found a vaccine efficacy of 26% (95% CI 7, 41), Gessner only estimated it as 2% (95% CI -8, 10).

Clinical pneumonia efficacy after three doses was reported by Gessner and Mulholland and found to be 4% (95% CI 1, 7) in both studies (Figure 8.4). However, due to the larger number of cases detected in Indonesia compared to the Gambia, the weight of the Gessner study in the pooled estimate is as high as 92.3%.

Clinical meningitis was only included in the study by Gessner and three different types were included; probable, possible and hospitalised meningitis (Table 8.5). There were consistently less cases in the vaccinated compared to the placebo group and two of the efficacy estimates were significant at the 95% level. This indicated that, in the Indonesian environment, many cases of Hib meningitis were reaching the health facility, but they either did not have a lumbar puncture or lumbar puncture was done and found to have the microscopic appearance of meningitis, but for reasons of specimen handling or microbiological procedures, Hib was not cultured.

Figure 8.2: Hib vaccine efficacy against confirmed invasive Hib disease

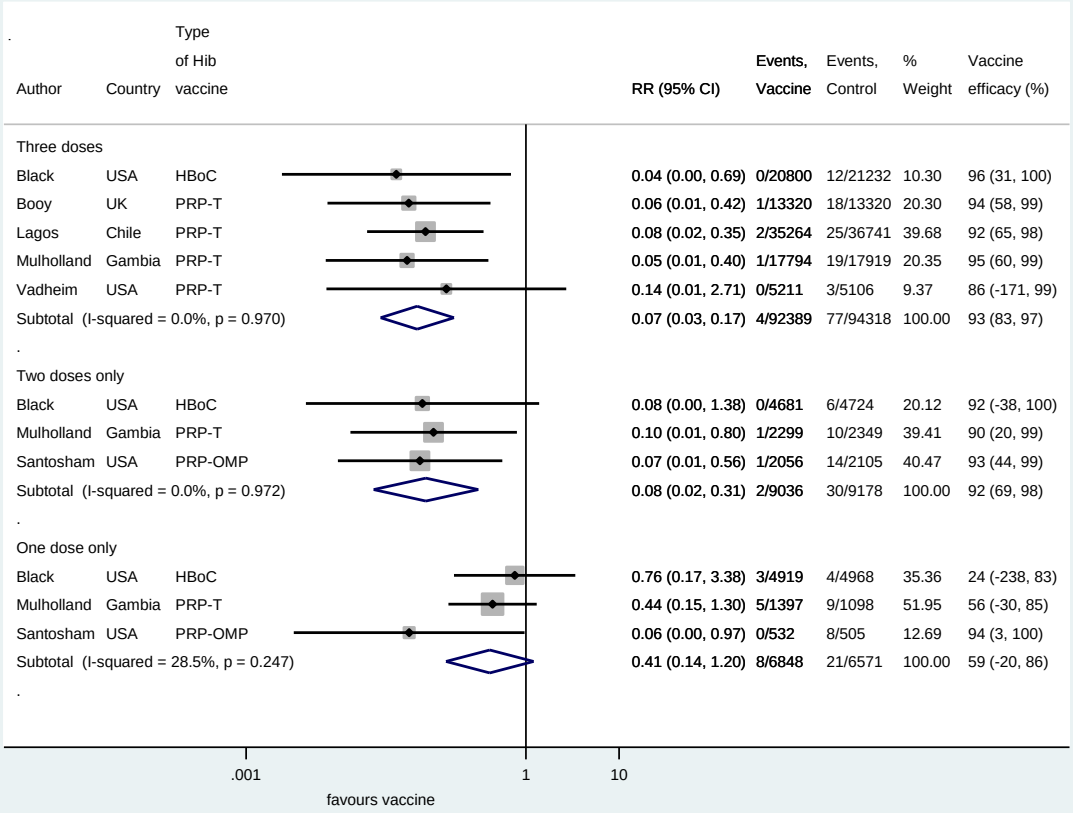


Figure 8.3: Hib vaccine efficacy against confirmed Hib meningitis

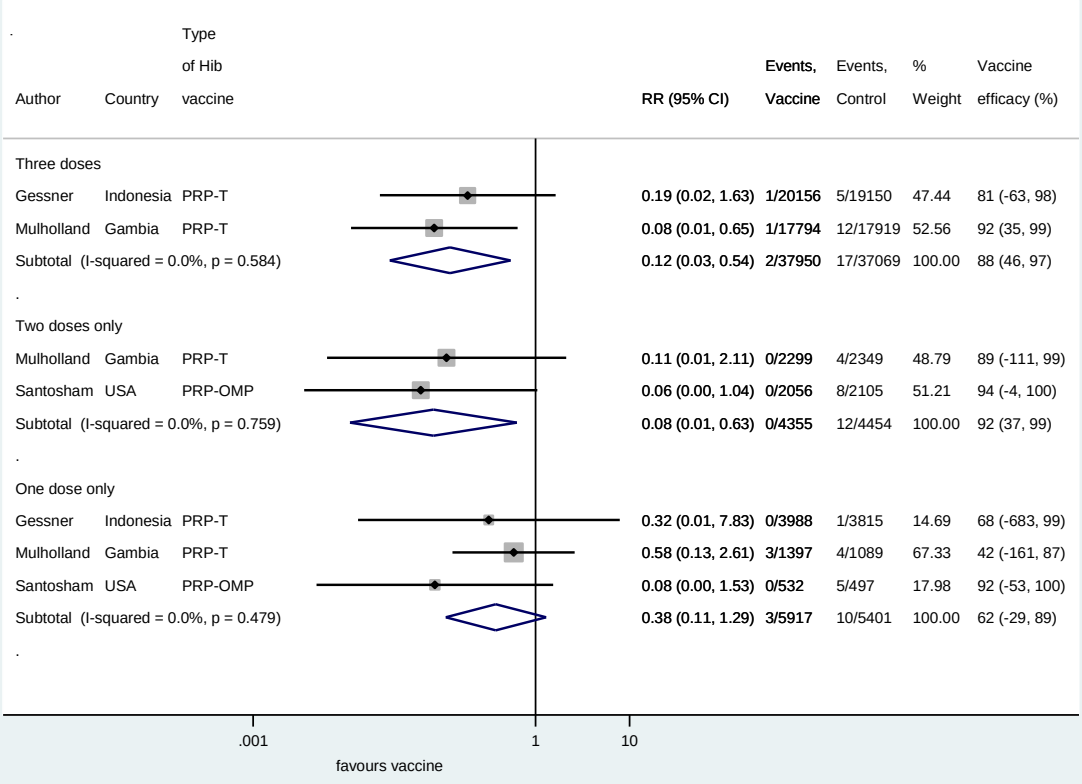


Figure 8.4: Hib vaccine efficacy against non-confirmed pneumonia

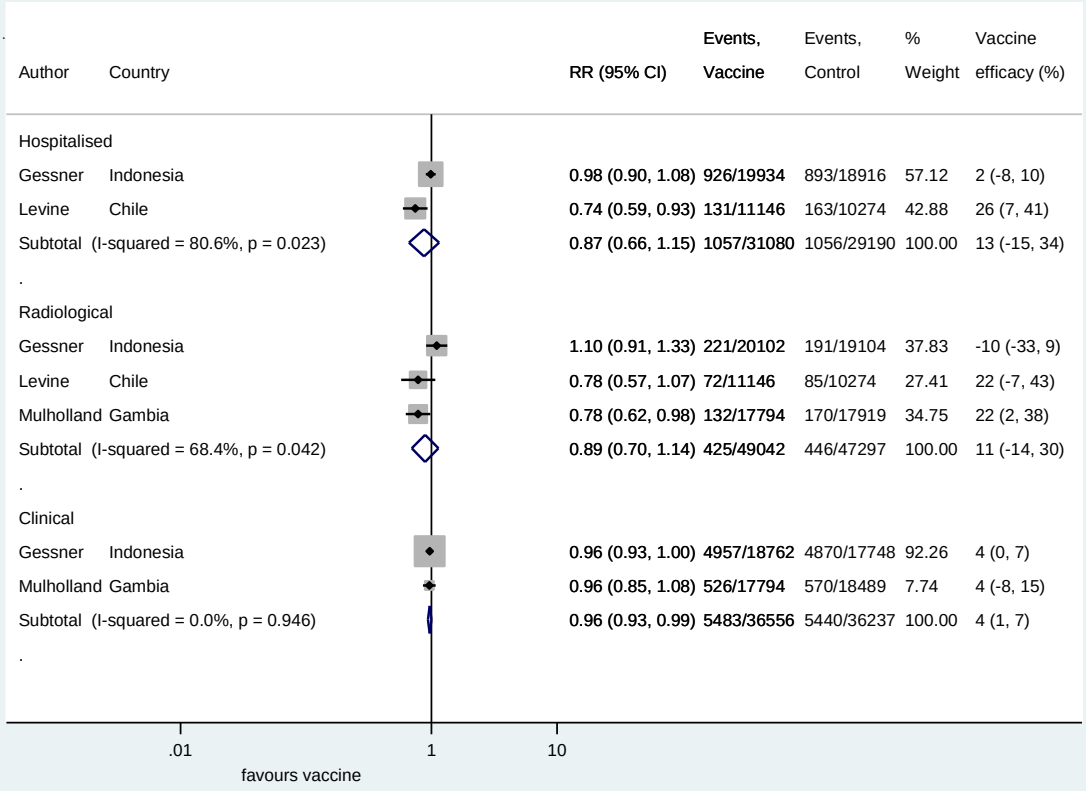


Table 8.5: Vaccine efficacy against clinical meningitis in Lombok, Indonesia

Outcome measure	No. of doses	Cases of Hib disease / no. of children with no event		Vaccine efficacy	95% CI		P-value
		Hib	Placebo		Low	High	
Probable bacterial meningitis	1	1/3989	6/3816	84%	-32%	98%	0.06
	2	5/4006	6/3963	18%	-170%	75%	0.77
	3	9/20152	20/19147	57%	6%	81%	0.04*
Possible bacterial meningitis	1	3/3989	9/3819	68%	-18%	91%	0.09
	2	6/4006	6/3963	1%	-206%	68%	1.00
	3	17/20152	34/19144	53%	15%	73%	0.01*
Hospitalised meningitis	1	21/3993	34/3824	41%	-2%	66%	0.06
	2	33/4010	41/3971	20%	-26%	49%	0.35
	3	118/20144	121/19131	7%	-19%	28%	0.56

*Significant at the 95% level using Fisher's exact t-test.

8.4.4 DISCUSSION

All the studies demonstrated high vaccine efficacy against confirmed invasive Hib disease following two and three doses (93% and 92%), and there was no heterogeneity in the pooled estimate. With one dose, the pooled estimate was 59% (95% CI -20, 86) and there was only low heterogeneity. Hence, the evidence on Hib vaccine efficacy against invasive disease is convincing and robust for all dose regimens. This conclusion is similar to the findings of O'Loughlin and colleagues in their meta-analysis of observational studies [171]. The pooled vaccine effectiveness estimate against invasive Hib disease from three case-control studies was 95% (95% CI 82, 99) after three doses and 92% (95% CI 81, 97) following two doses. In the meta-analysis of RCTs by Obonyo and Lau, vaccine efficacy against invasive Hib disease after three doses was only 84% (95% CI 69, 92). The reason for the higher pooled estimate in the new analysis is partly the exclusion of the PRP-D trials, but also that Obonyo and Lau combined all doses into one analysis, so that children receiving only one dose, only two doses and all three doses were included in the same calculation.

The evidence for confirmed Hib meningitis and confirmed Hib pneumonia is less robust because few studies report on these outcomes, so the pooled estimates are based on small sample sizes, which give wide confidence intervals. As both diseases are contained within the overall group of invasive Hib disease, these efficacy estimates should be used instead of seeking to categorise according to invasive Hib disease type.

As expected, the strength of the evidence of vaccine efficacy against the three, non-specific pneumonia outcomes is less than for confirmed Hib disease. For hospitalised pneumonia the heterogeneity is too large for the efficacy estimate to be meaningful. The large heterogeneity between the Indonesian and Chilean studies may partly be due to different case detection methods. Pneumonia detection in Indonesia was based on individual presentation for medical care, but supported by village health workers whose task was to identify children in the community with possible severe respiratory disease and refer them for treatment. By contrast, cases were retrospectively identified from patient records in Chile. Another possible explanation is differences between the two sites in the distribution of non-Hib pneumonia etiologies. For example, a large burden of RSV infection in one site will lower the measured vaccine efficacy even if the two sites have similar vaccine-preventable Hib disease incidences, as has been described by Gessner [192]. Consequently, for clinical outcomes (rather than microbiologically confirmed), vaccine preventable disease incidence may be a better measure than vaccine efficacy and effectiveness.

The Indonesian trial by Gessner did not detect an impact on radiological pneumonia [181]. The study authors have proposed several possible explanations for why pneumonias with lobar infiltrate or pleural effusion were not preventable with Hib vaccine. First, Hib may not be an important cause of pneumonia in Indonesia; this seems unlikely, since the vaccine preventable disease incidence measured against all severe or clinical pneumonias was as high or higher than in other studies (24). Secondly, some characteristic of children in South East Asia could lead to a different pneumonia presentation; this also seems unlikely since many children presented with a lobar infiltrate meeting the WHO case definition. Lastly, and perhaps most likely, early antibiotic use through self-medication or early identification and intervention could have modified the evolution of Hib pneumonia [192].

The two remaining studies by Mulholland (Gambia) and Levine (Chile) found a remarkably similar result of 22% vaccine efficacy against radiological pneumonia, in spite of different definitions used (the 95% CIs were -7, 41 in the Chilean study and 2, 38 in the Gambian study). In Gambia, standardized radiology readings were used while in Chile radiology reports were searched for key words, such as "alveolar consolidation". The 22% estimate is however less than in three case-control studies from Bangladesh, Dominican Republic and Columbia, which reported effectiveness against radiological pneumonia as 32%, 31% and 55%, respectively [171]. In a study by Theodoratou *et al*., these three studies were combined with the RCTs of Gessner, Levine and Mulholland and a pooled vaccine effectiveness estimate of 18% against radiological pneumonia was generated [194]. There was considerable heterogeneity in the pooled estimate, but this problem was not addressed [194].

It must be emphasised that the radiological pneumonia outcome measure imposes a large risk of bias due to the many definition problems of reading chest x-rays. This was in particular demonstrated in the case-control study from Bangladesh where chest radiographs were taken of 2,679 children with clinical pneumonia [195]. According to per-protocol readings, 17.7% cases were identified as having radiologically confirmed pneumonia. However, when the radiographs were read by a WHO panel, it was concluded that 26.0% were radiologically confirmed. Only 13.2% of cases were radiologically confirmed by both per protocol readings and WHO readings [195]. It is thus difficult to determine which estimate to use, and the choice greatly affects the vaccine effectiveness estimate. When using the per protocol readings, the preventable fraction of radiological confirmed pneumonia was 17% following at least 2 doses of Hib vaccine. When the WHO readings were used, the vaccine was associated with 15% protection, and when the subset

considered positive by both sets of readings was used the vaccine offered 34% protection [195].

The pooled vaccine efficacy estimate against clinical pneumonia appears robust as there is no heterogeneity between the two studies from Gambia and Indonesia. It is noteworthy that the two studies found such comparable results as there is a high risk of bias with this non-specific outcome measure. However, with only two studies the evidence is limited and as discussed earlier, caution should be taken when generalising to other settings due to potential fluctuations in clinical pneumonia aetiology between countries and years.

Vaccine efficacy data against all non-specific outcomes must in general be interpreted cautiously. While vaccine efficacy against microbiologically confirmed outcomes reflects the ability of the vaccine to induce protective immunity against infection and disease, vaccine efficacy against non-specific outcomes reflects vaccine performance in combination with the epidemiological context in which the vaccine is used. For example, vaccine efficacy may change by number of doses based on a different distribution of etiologies at different vaccination ages.

The PRP-T and the HbOC vaccines showed similar dose-specific efficacy values, but the PRP-OMP vaccine, which has different kinetics to the other two vaccines, had larger efficacy following one dose. The PRP-OMP vaccine has shown significantly higher immunogenicity after the first dose than the two others in all studies comparing the vaccines [196]. While all three vaccines are indicated for primary infant immunization, PRP-OMP may afford a marginal advantage in populations with high disease burden and carriage prevalence in young infants. In Alaska, a change from PRP-OMP to HbOC vaccine in 1996 led to an increase in invasive Hib disease incidence in the Alaska Native population from 19.8 to 91.1 cases per 100,000 children < 5 years of age [197]. When the State subsequently switched back to PRP-OMP vaccine, disease incidence decreased to 0 per 100,000 in 2004 [197]. Nevertheless, most countries in Africa have reported a high Hib disease burden in young infants pre-vaccine, and yet have achieved near elimination of Hib disease with PRP-T [198, 199].

There was no significant difference between two and three doses, with efficacy against invasive Hib disease being 92% and 93% following two and three doses, respectively. In theory, then, the routine schedule could be reduced to two instead of three doses. A study evaluating this option found that while PRP-T elicited high immune response after two doses, this was not universally true of PRP-HbOC, with only 87% of infants reaching seroprotective concentrations [200]. The authors concluded that before switching to a

two-dose regimen, additional studies would be needed [200]. These studies have not been conducted, and moreover, additional barriers to a two-dose schedule exist. First, studies would need to confirm vaccine effectiveness against carriage, since indirect protection is a critical component of overall disease reduction and secondly, additional studies would need to confirm long-term immunity and protection against carriage, as well as booster responses with a two-dose schedule. Programmatically, Hib vaccine is now widely introduced in combination with DTP and other vaccines with a primary 3-dose schedule, which has large advantages. For these reasons, it is unlikely that any country would consider a 2-dose primary series without a booster. However, if countries were to switch to a 2+1 schedule for pneumococcal vaccines, our analysis supports the use of the same schedule for Hib vaccine.

Waning immunity and the possible need for a booster dose is another important issue to consider. While all high-income and some middle-income countries recommend a Hib vaccine booster dose at 12 to 15 months, this has not been included in immunization schedules in low-income countries. The reason for not including a booster dose is partly due to the increased cost, but also because the average age of Hib infection is substantially lower in low-income compared to high-income countries [201]. It is however extremely important to closely monitor the impact of Hib vaccine in low-income countries to establish whether a booster dose is also needed in these settings. A recent study indicates that this may be the case in South Africa [202].

While not evaluated in this analysis, choices of vaccine formulations and schedules must also consider the immune status of the population, particularly the effects of human immunodeficiency virus (HIV) infection and malnutrition. For example, HIV infection leads to decreased immunogenicity [203]; however, population impact against Hib disease in HIV endemic areas has varied with South Africa showing reduced impact [204] and Malawi showing high impact [205].

Investigators of large-scale vaccination trials do not routinely report dose-specific outcomes despite their potential importance for the impact and cost-effectiveness of immunization programs. Estimates of dose-specific vaccine efficacy provide a direct way for analysts and decision makers to account for vaccine impact among partially vaccinated children. Models that do not account for partial protection will underestimate overall program effectiveness in populations with high drop-out rates between doses.

8.5 VACCINE EFFICACY ESTIMATES USED IN THE ECONOMIC EVALUATION

Pooled vaccine efficacy estimates for use in the decision-analytic model were generated by the meta-analysis. The numbers used in the economic evaluation are summarized in Table 8.6. None of the studies reported efficacy against NPNM, so the pooled estimate for invasive Hib disease was used. Moreover, as explained in the discussion above, the estimates for confirmed Hib meningitis and Hib pneumonia were not considered robust, so the invasive Hib disease estimates were also used for these syndromes.

The studies included in the pooled estimates of radiological and clinical pneumonia did not report on vaccine efficacy for less than three doses. To derive numbers for one and two doses only, the ratio between one and two doses and between two and three doses of the invasive Hib disease estimates were used for the other two outcome measures.

The 95% confidence values generated in the meta-analysis were used as high and low values in the univariate uncertainty analysis and for fitting a distribution to the data in the probabilistic uncertainty analysis.

Table 8.6: Hib vaccine efficacy estimates used in the economic evaluation

Disease case definition	1 dose only			2 doses only			3 doses		
	Mid	Low	High	Mid	Low	High	Mid	Low	High
Hib meningitis	59%	0%	86%	92%	69%	98%	93%	83%	97%
Hib pneumonia	59%	0%	86%	92%	69%	98%	93%	83%	97%
Hib NPNM	59%	0%	86%	92%	69%	98%	93%	83%	97%
Radiological pneumonia	14%	0%	32%	22%	5%	35%	22%	6%	35%
Clinical pneumonia	2.3%	0%	6%	4%	0.5%	7%	4%	1%	7%

9 DISABILITY ADJUSTED LIFE YEARS DUE TO HIB DISEASE

As described in Chapter 4, QALYs and DALYs are the two main health related quality of life (HR-QOL) measures used in economic evaluation. In spite of recognised limitations of DALYs, these were chosen as the main outcome measure in the economic evaluation. The rationale for this choice and the methods applied for estimating DALYs due to Hib disease are described in this chapter.

The DALY estimate for Hib disease is calculated as the sum of three components:

$$DALY_{Hib} = YLL_{Hib} + YLD_a + YLD_s$$

where,

YLL_{Hib} = Years of life lost due to premature mortality from Hib disease

YLD_a = Years of life with disability from acute Hib disease

YLD_s = Years of life with disability from Hib meningitis sequelae

The overall objective of this chapter is to estimate these three components.

An overview of methodological issues for measuring HR-QOL used in economic evaluation is given in section 9.1, with particular focus on childhood illnesses. A background to DALYs is presented in section 9.2 and estimation of DALYs due to acute Hib disease is explained in section 9.3. In section 9.4, it is demonstrated how evidence on the risk of different types of sequelae from bacterial meningitis were used for determining DALY parameters for this syndrome. The DALY parameter assumptions used in the three case study countries are summarised in section 9.5, and the strengths and limitations of the estimates are discussed in section 9.6.

9.1 OVERVIEW OF METHODS USED FOR VALUING HEALTH RELATED QUALITY OF LIFE

Possible methods for measuring HR-QOL improvements for cost-utility analysis include healthy years equivalent (HYE), QALYs and DALYs. QALYs have gradually become the standard type of outcome measure used in cost-utility analyses in high-income countries [206]. However, in low- and middle-income countries, resources for collection of population preference data and the expertise needed for development of HR-QOL instruments and scoring systems are limited, contributing to the fact that DALYs are usually used instead.

There are four general steps when calculating QALYs or DALYs: (a) describing the health state, (b) development of preference scores or weights for the health state, (c) determining

the time spend in each health state, and (d) combining the information. Development of preference scores or weights for the health state is the most methodologically challenging and this is one area where DALYs and QALYs particularly differ [207].

Preference scores for QALY estimates are generally derived using a multi-attribute approach. With such a system, patients are asked to complete questionnaires about their health status and these data are scored using a multi-attribute scoring function based on community preferences. Two types of preference-scored, multi-attribute health status classification systems are in widespread use: the EuroQol EQ-5D and the Health Utility Index (HUI) [208]. The multi-attribute scoring functions are based on direct preference measurement data from random samples of people in the general population of the respective country. Multi-attribute scoring functions for the EQ-5D system are available for eleven European countries and for Japan, New Zealand, Canada and Zimbabwe (http://www.euroqol.org/eq-5d/population-norms.html)

There are however inherent limitations with preference-based approaches for measuring the health status of children. First, children undergo dramatic changes in growth and function at different rates, so it can be difficult to attribute improvements to health care interventions rather than to normal development [209]. Secondly, children of young ages do not have cognitive ability to comprehend and complete a valuation questionnaire, so some form of proxy must be used for measurement, most likely by administering the instrument to a parent or a clinician [209, 210].

Almost all the original generic instruments used in the multi-attribute approaches have been created for use in adult populations and are generally not suitable for children. The exception to this is the Health Utility Index Mark 2 (HUI2), which was developed for proxy respondents to assess outcomes among survivors of cancer in childhood. Some domains in this tool are thus specific to cancer. The problems with the adult generic instruments are that some questions are not relevant for the lives of children and attributes that might be more relevant for children than for adults, such as autonomy, cognitive skills and family relationships, are not included [209]. However, improvements are underway with several groups working on appropriate tools. A version of the EQ-5D instrument for use in children and adolescents aged 7-12 years is for instance currently in the validation phase [211, 212]. However, no generic tool has yet been developed for children less than five years of age [213].

It is apparent that using QALYs as an outcome measure in cost-utility analysis of Hib vaccine would be problematic. There is first of all no generic instrument available for

measuring HR-QOL preferences in children less than five years and secondly, multi-attribute scoring functions have not been developed for any of the study countries included in the present analysis. Hence, even if HR-QOL preference data were collected, there is no straight forward way of generating QALY values that reflect preferences in the particular countries. For these reasons it was decided to use DALYs as the primary outcome measure in the present study.

9.2 BACKGROUND TO DALYS

DALYs were originally constructed by the World Bank and the WHO as part of the first Global Burden of Disease (GBD) study, which aimed at providing a comprehensive assessment of the disease burden in 1990. The estimates were presented in the World Bank's 1993 World Development report "Investing in Health" [214]. The aim at the time was to objectively quantify and compare the aggregate regional and worldwide health burdens caused by many different diseases. Chris Murray states in the first chapter of the 1996 GBD series that, "a DALY is a health gap measure that combines potential years of life lost due to premature death with years of healthy life lost due to individuals being in states of poor health or disability" [126]. One DALY can be thought of as one lost year of healthy life and the burden of disease in terms of DALYs as a measure of the gap between current health status and an ideal situation where everyone lives into old age free from disease and disability.

In DALYs, preference values are termed "disability weights". These range between 0 and 1, with 0 equal to perfect health and 1 to death. Disability weights for a total of 237 different types of diseases were included in the original GBD of disease study [126]. The values for these weights were derived during a two-day WHO expert meeting in 1995. During this meeting, a group of people were asked to value 22 tracer conditions using the person trade-off approach. After these were completed, they were asked to distribute the severity of the remaining 212 conditions between a number of categories anchored around the results of the 22 tracer conditions [215]. During the most recent GBD update, the same disability weights were used for YLD calculations as in the original study, but the weights are now differently tabulated and the new reference is Annex Table A6 of Mathers *et al*. (2006) [216].

DALYs for a particular disease are calculated as the sum of years of life lost (YLLs) and years of life with disability (YLDs) due to the particular health condition. There are a number of important underlying assumptions of DALYs that differ from the construction of QALYs:

a. DALYs describe specific diseases, rather than health states. One consequence of this is that no distinction is made between severe and non-severe disease.
b. DALYs make no provision for co-morbidities. For example, the HR-QOL of a person who suffers from type 2 diabetes and cardiovascular disease at the same time cannot be easily generated.
c. DALY preference values for diseases have been decided upon by a group of health professionals, rather than from preferences of the population as is often the case for QALYs.
d. Both QALY and DALY preference scores/disability weights are numbers between 0 and 1. However, while a QALY preference score of one represents full health and zero represents death, the opposite is true with DALYs.
e. In DALYs, different value weights are placed on populations based on their age structure with the very young and very old valued less than other age groups. The justification for age weighting is that adults in their productive life are more important for income generation of a country and this group should therefore be valued highest.
f. In the standard DALY recommendations, life expectancy is assumed 82.5 years for women and 80 years for men. These numbers were chosen to represent the longest life expectancy in the world, which is in Japan. However, in country-specific analysis, local life expectancies are frequently used by study investigators.

The GBD study is an ongoing effort that continues to evolve. The study was most recently updated in 2004 and the Bill & Melinda Gates Foundation currently provide funding for a new GBD study scheduled to be published during 2012. This update is led by the Institute for Health Metrics and Evaluation at the University of Washington, with key collaborating institutions including the WHO, Harvard University, Johns Hopkins University and the University of Queensland [217].

9.3 DALYS DUE TO ACUTE HIB DISEASE

9.3.1 YEARS OF LIFE LOST (YLL)

The formulas for YLLs and YLDs with and without discounting are given in Textbox 9.1. r is the discount rate used for adjusting future life years, β is a parameter in the age weighting function and C is a constant. In the original form, r equals 3%, β is 0.04 and C is 0.16243 [126]. Without discounting the formula is simplified.

Textbox 9.1: Formulas for calculating YLLs and YLDs

Discounted YLL:

$$YLL\ (r,K,\beta) = \left(\frac{KCe^{ra}}{(r+\beta)^2}\{e^{-(r+\beta)(L+a)}[-(r+\beta)(L+a)-1)]-e^{-(r+\beta)a}[-(r+\beta)a-1]\} + \left(\frac{(1-K)}{r}\right)(1-e^{-rL})\right)$$

Non-discounted YLL:

$$YLL\ (0,K,\beta) = \left(\frac{KCe^{-\beta a}}{\beta^2}\{e^{-\beta L}[-\beta(L+a)-1)]-[-\beta a-1]\} + (1-K)(L)\right)$$

Where:
K= Age weighing modulation factor
C = Constant
r = Discount rate
a = Age of death
β = Parameter for the age weighing function
L = Life expectancy at age a

Discounted YLD:

$$YLD\ (r,K,\beta) = D\left(\frac{KCe^{ra}}{(r+\beta)^2}\{e^{-(r+\beta)(L+a)}[-(r+\beta)(L+a)-1)]-e^{-(r+\beta)a}[-(r+\beta)a-1]\} + \left(\frac{(1-K)}{r}\right)(1-e^{-rL})\right)$$

Non-discounted YLD:

$$YLD\ (0,K,\beta) = D\left(\frac{KCe^{-\beta a}}{(\beta^2)}\{e^{-\beta L}[-\beta(L+a)-1)]-(\beta a-1)\} + \{(1-K)(L)\}\right)$$

Where:
D = Disability weight
K = Age weighing modulation factor
C = Constant
r = Discount rate
a = Age of disease episode
β = Parameter for the age weighing function
L = Duration of disability

Source: Murray and Lopez (1996) [126]

In the present economic evaluation the life expectancy of the country in question is applied and not the Japanese life expectancy as recommended by the WHO. The rationale is that national life expectancy will make the study most relevant to local decision makers. Hence, for estimation of YLLs, data on the average age of death from Hib disease and life expectancy of the particular country are the only data needed. These data are readily available from either national surveys or from the United Nations Population Fund. YLLs

due to Hib disease in Uzbekistan during 2010 are estimated in Textbox 9.2 as an illustrative example (assumptions about the age distribution of Hib disease are described in section 9.4 below). It is seen that discounting of future values makes a considerable difference to the YLLs, decreasing number of life years lost by 58% compared to no discounting. Age weighting makes less of a difference, increasing the number of life years by 13% compared to no age weighting.

Textbox 9.2: YLL calculations for acute Hib disease in Uzbekistan in 2010* (assuming that Hib vaccine was not introduced)

As shown in Chapter 12, it is estimated that a total of 338 Hib disease deaths would have occurred in Uzbekistan in 2010 without Hib vaccine. Of these deaths, 207 were due to Hib meningitis, 120 due to Hib pneumonia and 11 due to Hib NPNM.

The following parameter values were assumed for the YLLs estimation:

K = 1
C = 0.16243
β = 0.04
r = 3%
L = 68 years
a = The age of a Hib disease death varies between 0.5 and 4.5 years

When inserting the parameter values in the YLLs formula, it is estimated that Hib disease caused **11,197** discounted YLLs, which is on average **33** discounted YLLs per death.

Without discounting, total YLLs are **26,886** (**78** YLLs per deceased case).

Without age weighting (K = 0), total discounted YLLs amount to **9,732** (**29** YLLs per death).

*The 2010 Uzbekistan birth cohort was 558,459 children

9.3.2 YEARS OF LIFE WITH DISABILITY (YLD) DUE TO ACUTE DISEASE

YLDs due to Hib disease must be divided into disability during the acute disease episode and disability from lifelong meningitis sequelae. As described in Chapter 7, acute Hib disease episodes are divided into meningitis, pneumonia and NPNM in the decision-analytic model. Data needed for YLD estimates of these three types of Hib disease are (i) the average age of onset of disease, (ii) duration of the disease episode and (iii) the disability weight. Numerous studies have reported on the average age of Hib disease and the average length of stay in hospital can be used as an approximation for duration of disease episode. The disability weight for children between zero and four years for a meningitis episode is 0.616 and the disability weight for a lower respiratory infection episode is 0.279 [216]. Lower respiratory infection is synonymous to pneumonia, as the resulting infection is pneumonia.

There is however no disability weights available in the GBD study for any of the NPNM diseases, most likely because these are all relatively rare illnesses. In instances of no disability weight available, it is common practice to use a weight for a comparable disease [218]. To be able to determine what disability weight to use, epidemiological studies reporting on NPNM were reviewed. The studies were identified via email contact to collaborators who had worked on the Hib and pneumococcal GBD project, as they had conducted a systematic literature review for determining the incidence of NPNM [219]. The 21 ascertained studies are summarized in Table 9.1. It is seen that epiglottitis was the most common type of NPNM in the majority of the countries, although this disease was not established everywhere. This was followed by cellulites, arthritis and sepsis. When determining the most suitable disability weights for NPNM in the three study countries (Belarus, India and Uzbekistan), only studies from the respective region were used to identify the most common types of NPNM. In Belarus, the meningitis disability weight was used for NPNM because epiglottitis is the most common type of NPNM in Western European countries and the Czech Republic and this illness has comparable severity to meningitis. In India and Uzbekistan, the pneumonia disability weight of 0.28 was used, as there is currently no evidence of epiglottitis in these countries and the remaining NPNM diseases have more comparable severity to pneumonia than to meningitis.

YLD calculations for acute Hib disease episodes in Uzbekistan in 2010 are summarised in Textbox 9.3. Due to the relatively short duration of a disease episode, no more than 5.9 discounted YLDs were estimated. Moreover, since these episodes are predicted to occur within the first five years of the model timeframe, omitting discounting only increases the result marginally, to 6.2 YLDs. When adding the YLLs and the YLDs caused by acute Hib disease in Uzbekistan in 2010, 11,203 discounted DALYs are estimated (11,197 YLLS + 5.9 YLDs).

Table 9.1: Number of cases of different types of Hib disease detected in Hib sentinel surveillance studies that included NPNM syndromes

				Non-pneumonia-non-meningitis (NPNM) Hib diseases										
Author [ref.]	**Country**	**Menin-gitis**	**Pneu-monia**	**Epiglot-titis**	**Sepsis**	**Cellulitis**	**Arthritis**	**Pericar-ditis**	**Endocar-Ditis**	**Osteo-Myelitis**	**Peritoni-tis**	**Cholan-gitis**	**Sinusitis**	**Total**
Torres [220]	Argentina	19	3	1	4	11	4	3			1			46
Asturias [221]	Guatemala	71	24	2	3	6	1							107
Forbes [222]	Jamaica	65	11	1	2		7							86
Takala[223]	Finland	152	11	97	23	21	27							331
Peltola [224]	Finland	492	17	187	25	19	21							761
Booy [225]	UK	289	8	48	15	28	21							409
Williams [27]	UK	142	6	23	5	12	12							200
Reinert [54]	France	177	17	20	15	11	16							256
Martin [226]	Spain	37	4	6		5	6							58
Muhleman[227]	Switzerland	1,270		1,392	62	69	64							2 ,857
Kojouharova[43]	Bulgaria	21	2		1	1								25
Lebedova[25]	Czech Rep.	49	7	31	5		2							94
Dagan [228]	Israel	182	72	1	34	45	2	2	1	2		1	1	344
Madhi [204]	South Africa	26	13		1	2								42
O'Dempsey[229]	Gambia	10	18		1									29
Adegbola [28]	Gambia	141	31		3	1	4							180
Ishiwada[230]	Japan	39	0	3	2		3							47
Likitnukul [26]	Thailand	44	20		12	2	1							79
Anglaret[231]	N. Caledonia	22	3	1	1	1	3		1					32
Gilbert [232]	Australia	84	20	94	14	16	6							234
McIntyre[40]	Australia	143	12	91	5	18	13	1						283
Total		***3,475***	***299***	***1,998***	***233***	***268***	***213***	***6***	***2***	***2***	***1***	***1***	***1***	***6,500***
Percent of total		***53%***	***5%***	***31%***	***4%***	***4%***	***3%***	***0.09%***	***0.03%***	***0.03%***	***0.02%***	***0.02%***	***0.02%***	***100%***

Textbox 9.3: YLD calculations for acute Hib disease in Uzbekistan in 2010

As is shown in Chapter 12, it is estimated that 3,766 Hib disease cases would have occurred in Uzbekistan in 2010 without Hib vaccine. 2,994 of these were Hib pneumonia, 492 were Hib meningitis and 280 were Hib NPNM cases.

The following parameter values were used for the YLDs estimates:

K = 1
C = 0.16243
β = 0.04
r = 3%
L = 9 days for pneumonia and 11 days for meningitis and NPNM (based on average length of stay in hospital as explained in Chapter 10)
D = 0.616 for meningitis, 0.28 for pneumonia, 0.28 for NPNM
a = The age of Hib disease episode varies between 0.5 and 4.5 years

When inserting the parameter values in the YLD formula, it is estimated that acute Hib disease caused **5.9** discounted YLDs, which is **0.002** YLDs per Hib disease case. Without discounting, YLDs amount to **6.2**, and without age weighting discounted YLDs are **32.1**.

9.4 YLD DUE TO MENINGITIS SEQUELAE

9.4.1 BACKGROUND

As described in Chapter 2, survivors of Hib meningitis risk severe, lifelong sequelae. The term "sequelae" refers to any abnormal bodily condition or disease related to or arising from a pre-existing disease. To estimate DALYs due to meningitis sequelae, the proportion of meningitis survivors suffering from disabilities, the average age of onset, and the duration of disability must be determined. Moreover, to be able to decide on the appropriate disability weights, it is necessary to know what specific types of sequelae the survivors suffer from, and what proportions suffer from what types. This is problematic because severity and type of sequelae vary considerably among cases. Complications range from subtle forms of cognitive impairment to devastating neurological handicaps, and it is furthermore common for children to suffer from multiple sequelae. Severe sequelae include sensorineural hearing loss, seizures, motor problems, hydrocephalus and mental retardation, while more subtle outcomes are cognitive, academic and behavioural problems [233]. Important risk factors for neurological sequelae following bacterial meningitis are coma, seizures and prolonged fever for at least seven days [234]. Hence, the risk of sequelae increases with limited access to health care, as patients in these settings would present late for treatment and thus suffer from the above mentioned risk factors.

The four steps that have been undertaken for estimating YLDs due to bacterial meningitis sequelae are:

1. Definition of the different types of sequelae and identification of their disability weights
2. Assessment of the risk of sequelae caused by bacterial meningitis
3. Establishment of the proportion of children suffering from the different types of sequelae
4. Calculation of weighted average disability weights for use in DALYs calculations

To increase the applicability and interpretation of the findings, the three most common types of bacterial meningitis were included in the analysis; Hib, meningococcal and pneumococcal meningitis. The two other types of meningitis serve as useful comparators to Hib meningitis sequelae.

Some of the work described in the following sections was derived from a global, systematic literature review, which I initiated with the aim of more accurately estimating DALYs due to meningitis sequelae. The review was undertaken in collaboration with Hib Initiative colleagues and titled "Global and regional risk of disabling sequelae from bacterial meningitis". The study was published in the Lancet Infectious Diseases during 2010 with Dr. Karen Edmond, my former Hib Initiative colleague, as first author [235]. The objectives of the review were to:

1. Estimate the risks of major and minor sequelae caused by bacterial meningitis
2. Estimate the distribution of the different types of sequelae
3. Compare sequelae risk by region and Gross National Income (GNI).

9.4.2 SEQUELAE CASE DEFINITIONS AND DISABILITY WEIGHTS

In the systematic literature review mentioned above, sequelae types were divided into minor and major forms to facilitate a clear distinction between severe and less severe complications. We also included a multiple impairments category for children suffering from more than one disability type [235]. The case definitions are summarised in Table 9.2. Four of the major sequelae case definitions were taken directly from the 1996 GBD study; cognitive deficit, seizures, hearing loss and motor deficit. These were the only types of meningitis sequelae included in the original GBD study and the associated disability weights can be found under the "Meningococcaemia without meningitis" category in the GBD disability weight list as "mental retardation", "seizure disorder", "deafness" and "motor deficit" [216].

All the minor case definitions and the categories for visionary problems and clinical impairments were developed by Dr. Edmond. Hence, there are no associated meningitis

Table 9.2: Sequelae case definitions and disability weights

	Minor sequelae	Major sequelae	
Type	**Case definition**	**Case definition**	**Disability weight**
Cognitive deficit	Learning difficulties or deficits with IQ > 70 or speech/language impairment	Mental retardation with IQ <70	0.469
Seizures	-	Seizures of any type	0.099
Hearing loss	Unilateral sensorineural hearing loss with audiometric hearing threshold level (averaged over 0.5, 1, 2, 4kHz) of >26dBHL	Bilateral sensorineural hearing loss with audiometric hearing threshold level (averaged over 0.5, 1, 2, 4kHz in the better ear) of >26dBHL	0.223
Motor deficit	Isolated hypotonia, motor delay, ataxia, gait or coordination difficulties	Impairment, spasticity or paresis of one or more limbs	0.388
Visionary problems	Unilateral visual disturbance, diplopia, nystagmus, or cranial nerve dysfunction	Presenting visual acuity in the best eye of less than 6/12 or corresponding visual field loss	0.223
Clinical impairments	Any behavioural disorder attributed to the meningitis episode	Distinct pathologic entity with any impairment to activities of daily living	0.359
Multiple impairments	Distinct pathologic entity with no impairment to activities of daily living: Mild cerebral dilatation	≥1 of above domains	0.627

IQ: Intelligence quotient
Sources: Edmond (2010)[235] for definitions and Mathers (2006) for disability weights [216].

sequelae disability weights for these conditions. As a solution, it was decided not to include the minor types of sequelae in the DALY estimates, and to use approximate disability weights for major visionary problems and major clinical impairments. The exclusion of minor sequelae is justified by the lack of disability weights and also because the diagnoses of these conditions are more difficult to make, leading to large uncertainty in the prevalence. For visionary problems, the "low vision" disability weight with a value of 0.223 from the corneal scar, onchocerciasis and trachoma categories was used. The clinical impairments category was created to depict children with disturbance in the function or structure of an organ. Since the majority of children in this category had

hydrocephalus (a build-up of fluid inside the skull, leading to brain swelling), the GBD disability weight for long term intracranial injury of 0.359 was used for clinical impairments. For multiple sequelae a weight of 0.627 was assumed, which is the highest value in the GBD disability weight list, similar to dementia [216].

9.4.3 RISK OF SEQUELAE FROM BACTERIAL MENINGITIS

One of the objectives of the systematic literature review mentioned above was to estimate the median risk of sequelae from bacterial meningitis according to pathogen and to compare the risk by region and country income groups [235]. The results of the review are summarised below followed by the risk of sequelae estimates assumed for the three case study countries.

9.4.3.1 Risk of sequelae from bacterial meningitis: Results of the systematic literature review

The literature review covered studies published between 1980 and 2008. Medline and WHOLIS databases were searched using the terms "meningitis", "bacterial" AND complications" [235]. A total of 132 papers were included. Of these papers, 87 investigated meningitis sequelae from all causes, 33 focused on Hib meningitis sequelae, 27 on pneumococcal meningitis sequelae, and 35 on meningococcal meningitis sequelae. Overall, 19,272 survivors of acute bacterial meningitis were examined for sequelae in the included studies, with the mean number of children per study being 146. The Hib meningitis sequelae analysis is based on a sample of 7,298 children [235].

Studies reported sequelae at either the time of discharge from hospital or during a follow-up period after discharge. We decided to use the post discharge data, as symptoms from acute meningitis persist until hospital discharge and patient responses to hospital neurological examinations are usually suboptimal [235]. The mean post discharge follow-up time was 37.7 months, with the longest time being 16 years after the meningitis episode, which was reported in two of the studies [236, 237].

The median ages at the time of the meningitis episode and the risk of sequelae according to bacterial pathogen are summarised in Table 9.3. Compared to the two other bacterial pathogens, Hib is seen to infect children at a younger age. While the median age of Hib meningitis was 17 months, it was 36 and 67 months for pneumococcal and meningococcal meningitis, respectively. The median risk of developing major sequelae following Hib meningitis was 9.5%, with an interquartile range between 7% and 15%. The risk following pneumococcal meningitis was 2.6 fold greater with a median value of 24.7%. There were

Table 9.3: Global median values for the risk of sequelae from bacterial meningitis

	All-cause	Hib	Pneumococcal	Meningococcal
Median age of meningitis episode:				
Number of studies	53	15	4	14
Age in months (IQR)	32 (20, 67)	17 (12, 25)	36 (31, 136)	67 (33, 96)
At least one type of any sequelae:				
Number of studies	59	27	20	27
Risk (IQR)	19.9% (12%, 35%)	14.5% (10%, 27%)	34.7% (28%, 45%)	9.5% (5%, 15%)
At least one type of major sequelae:				
Number of studies	58	27	20	26
Risk (IQR)	12.8% (7%, 21%)	9.5% (7%, 15%)	24.7% (16%, 35%)	7.2% (4%, 11%)
At least one type of minor sequelae:				
Number of studies	37	17	10	11
Risk (IQR)	8.6% (4%, 15%)	5.7% (2%, 15%)	18.6% (11%, 23%)	2.3% (1%, 12%)

Source: Edmond (2010)[235]

no statistically significant differences between the risks from meningococcal and Hib meningitis [235]

The interquartile ranges of the risk estimates are relatively wide, reflecting broadly different results in the included studies. We investigated whether geographical region and country income groups could explain the variation among studies, and it was found that the risk of at least one major sequelae following bacterial meningitis was almost three fold greater in the WHO African region (25.1%; 95% CI 18.9, 32.0) and the South East Asian region (21.6%; 95% CI 13.1, 31.5) compared to the European region (9.4%; 95% CI 7.0, 12.3) [235]. There was also a progressively higher risk of sequelae as mortality strata increased; risk of a major sequelae was three times greater in the highest mortality stratum countries (29.1%; 95% CI 20.9, 37.9) than in the lowest stratum (9.1%; 95% CI 7.2, 11.1) [235]. As mentioned above, the primary reason for higher risk in low- income countries is likely to be late presentation to health facilities. There were no clear associations between risk and duration of follow up, type of study design, percentage of isolates with laboratory confirmation, or decade of data collection [235].

The wide variation in sequelae risk across country income groups and mortality strata emphasise the need for using local data in country specific studies, or at least data from a comparable country. Furthermore, due to the significant higher risk of sequelae from

pneumococcal meningitis compared to Hib and meningococcal meningitis, it is desirable to use pathogen-specific estimates and not all-cause bacterial meningitis data, which for Hib and meningococcal meningitis are likely to overestimate the risk and for pneumococcal meningitis would underestimate the risk.

9.4.3.2 Risk of meningitis sequelae in Belarus, India and Uzbekistan

Five Indian papers on the risk of sequelae were identified, but there were no published studies from Belarus and Uzbekistan. The Indian papers are summarised in Table 9.4. Since the papers by Gupta and George did not present pathogen specific data, these were excluded. In the paper by Cherukupally only hearing deficit was assessed during the follow-up tests, so this paper was also excluded. The studies by Chinchankar and Singhi identified a risk of sequelae following Hib meningitis of 46% and 31%, respectively. However, as seen in the footnote of Table 9.4, one of the cases was diagnosed with behavioural problems, which is categorised as minor sequelae according to the classifications in Table 9.1. When excluding this case, a total of nine major sequelae cases were detected among 26 confirmed Hib cases, giving a pooled estimate of 35%, and this value was used in the India analysis. This corresponds well to the risk of the high-mortality strata found in the literature review.

In Belarus, Hib Initiative collaborators conducted Hib meningitis surveillance during 2002-2007 at the Minsk City Children's Infectious Disease Hospital (MCCIDH). All children that had suffered from meningitis were followed up every three months during the first year after discharge and annually for the next two years [238]. The data showed that 12% of children with confirmed Hib meningitis suffered from major disability at six months follow-up, 75% of whom had reduced hearing. A sequelae risk of 12% was therefore used for Belarus.

There were no data available from Uzbekistan or any of its neighbouring countries. The Indian value was used for Uzbekistan, as these two countries have comparable GDP per capita and infant mortality rates. In 2010, GDP per capita were US$ 1,370 in India and US$ 1,380 in Uzbekistan (www.imf.org), and the infant mortality rates were 66 and 36 per 1,000 live births in India and Uzbekistan, respectively (www.unicef.org).

9.4.4 DISTRIBUTION OF TYPES OF SEQUELAE DUE TO BACTERIAL MENINGITIS

The most common type of major sequelae caused by Hib is hearing loss, followed by multiple impairments and motor deficit. Visual disturbance is a rare type of sequelae for all three pathogens, but especially for Hib with only 0.1% of discharged children diagnosed with this (Table 9.5).

Table 9.4: Summary of Indian bacterial meningitis sequelae studies

First author [ref]	Year	Place of study	Number of children followed up	Types of sequelae evaluated	Pathogen confirmation	Number of children with sequelae	Risk of sequelae from Hib meningitis	Risk of sequelae from pneumococcal meningitis	Risk of sequelae from all-cause bacterial meningitis
Gupta [239]	1993	Varanasi, North India	24	Hearing loss	None	5	NA	NA	21%
Chinchankar [240]	2002	Pune, West India	31	All	13 Hib 17 pneumococcal 13 others	6 Hib* 13 pneumococcal 8 others	46%	76%	63%
George [241]	2002	Kerala, South India	100	All	None	40	NA	NA	40%
Cherukupally [242]	2004	Hyderabad, South India	28	Hearing loss	15 Hib 8 pneumococcal 5 tuberculosis	3 Hib 3 pneumococcal 2 tuberculosis	20%	38%	29%
Singhi [243]	2006	Chandigarh, North India	80	All	13 Hib 6 pneumococcal 5 others 56 not specified	4 Hib** 6 pneumococcal 2 others 20 not specified	31%	100%	40%

*The six Hib cases were: Two persistent seizures, three isolated hearing loss and one moderate to severe development delays

**The four Hib cases were described as minor sequelae, which in the study were defined as extra-pyramidal movements, hearing loss, hemiparesis, hyperactivitiy, peripheral facila palsy, mild mental retardation and language delay.

Table 9.5: Percentage breakdown of different types of major sequelae in discharged children due to Hib, pneumococcal and meningococcal meningitis

	Hib		Pneumococcal		Meningococcal	
	No. of studies	**% of children**	**No. of studies**	**% of children**	**No. of studies**	**% of children**
Cognitive difficulties	8	1.0%	7	3.2%	3	0.4%
Seizure disorder	11	1.5%	8	2.5%	5	0.5%
Hearing loss	19	3.2%	15	6.7%	16	2.1%
Motor deficit	14	1.2%	7	3.3%	9	0.8%
Visual disturbance	4	0.1%	5	1.1%	3	2.1%
Clinical impairments	4	0.7%	1	3.4%	1	0.3%
Multiple impairments	24	1.9%	20	4.5%	24	1.0%
Total	***27***	***9.6%***	***20***	***24.7%***	***26***	***7.2%***

Source: Edmond (2010) [235]

9.4.5 WEIGHTED DALY DISABILITY WEIGHTS FOR MENINGITIS SEQUELAE

Weighted average disability weights for Hib, pneumococcal and meningococcal meningitis sequelae were calculated from the disability weights in Table 9.2 and the percentage breakdowns in Table 9.5. The weighted disability weights are 0.291 for Hib, 0.356 for pneumococcal and 0.307 for meningococcal meningitis sequelae (Table 9.6).

YLD calculation for meningitis sequelae in Uzbekistan is summarised in Textbox 9.4. Total annual YLDs due to meningitis sequelae amount to 964. It is seen that discounting makes a considerable difference to the result. With discounting at 3% per year, YLDs per sequelae case amount to 9.6 while without discounting the result is 22.8 YLDs per sequelae case.

Textbox 9.4: YLDs calculation for Hib meningitis sequelae in Uzbekistan 2010

As shown in Chapter 12, it is estimated that 100 Hib meningitis sequelae cases would have occurred in Uzbekistan in 2010 without Hib vaccine.

The following parameter values were used for the estimating YLDs from these cases:

K = 1
C = 0.16243
β = 0.04
r = 3%
L = Lifelong (life expectancy of 68 years)
D = 0.291
a = The age of Hib infection varies between 0.5 and 4.5 years

When inserting the parameter values in the YLD formula, a total of **964** discounted YLDs are estimated. This is **9.6** YLDs per sequelae case. Without discounting, YLDs amount to **2,320**, or **22.8** YLDs per sequelae case.

Table 9.6: Weighted average disability weights due to bacterial meningitis sequelae

Type of sequelae	Disability weight	Percent of cases	Percent distribution	Weighted average disability weight
Hib:				
Cognitive difficulties	0.469	1.0%	10%	0.049
Seizure disorder	0.099	1.5%	16%	0.015
Hearing loss	0.223	3.2%	33%	0.074
Motor deficit	0.388	1.2%	13%	0.049
Visual disturbance	0.223	0.1%	1%	0.002
Clinical impairments	0.359	0.7%	7%	0.026
Multiple impairments	0.627	1.9%	20%	0.124
Total		*9.6%*	*100.0%*	***0.340***
Pneumococcal:				
Cognitive difficulties	0.469	3.1%	13%	0.059
Seizure disorder	0.099	2.5%	10%	0.010
Hearing loss	0.223	6.7%	27%	0.061
Motor deficit	0.388	3.3%	13%	0.052
Visual disturbance	0.223	1.1%	4%	0.010
Clinical impairments	0.359	3.4%	14%	0.050
Multiple impairments	0.627	4.5%	18%	0.115
Total		*24.7%*	*100%*	***0.356***
Meningococcal:				
Cognitive difficulties	0.469	0.4%	6%	0.026
Seizure disorder	0.099	0.5%	7%	0.007
Hearing loss	0.223	2.1%	30%	0.066
Motor deficit	0.388	0.8%	11%	0.044
Visual disturbance	0.223	2.1%	30%	0.066
Clinical impairments	0.359	0.2%	3%	0.050
Multiple impairments	0.627	1.0%	14%	0.088
Total		*7.2%*	*100%*	***0.307***

9.5 SENSITIVITY ANALYSIS

When adding the YLLs and the two types of YLDs, total discounted DALYs for the 2010 Uzbekistan birth cohort are: 11,197 YLLs + 5.9 YLDs + 964 YLDs = 12,166 DALYs. Hence, YLLs account for as much as 92% of the DALY estimate. One reason for this is the relatively short duration of acute Hib disease, which in total only amount to 5.9 YLDs for the cohort. YLDs from sequelae are also considerably less than YLLs because there are three times fewer sequelae cases than deaths and the value of these are reduced by the disability weight of 0.291.

A number of assumptions were made when deciding on parameters for the DALY estimates. To assess the impact of changing these values, one-way sensitivity analysis was undertaken for the Uzbekistan example (Table 9.7). The analysis was done for discounted and age weighted DALYs; the effects of no discounting and no age weighting have already been evaluated in Textboxes 9.1-9.4 above.

It can be seen that changes to the YLD parameter values, such as using the meningitis disability weight instead of the pneumonia disability weight for NPNM, only increases the overall DALY value by 0.0007%. Similarly, reducing the multiple sequelae disability weight from 0.627 to 0.469, which is the disability weight for cognitive difficulties, decreases total DALYs by no more than 0.8%. Since YLLs account for such a large proportion of the DALY estimates, changes to mortality is a key determinant. When decreasing the meningitis CFR from 42% to 20%, total DALYs decrease by 26.5%.

Table 9.7: DALY parameter sensitivity analysis: Uzbekistan 2010 birth cohort

	Discounted YLLs	Discounted YLDs from acute disease	Discounted YLDs from meningitis sequelae	Discounted DALYs	Percentage change from base case
Base case	**11,197**	**5.9**	**964**	**12,166**	**-**
Use meningitis disability weight for NPNM instead of pneumonia disability weight	11,197	6.4	964	12,166	0.0007%
Decrease risk of sequelae from 35% to 12% (use Belarus value instead of India value for Uzbekistan)	11,197	5.9	330	11,532	-5.2%
Reduce multiple sequelae disability weight from 0.627 to 0.469	11,197	5.9	861	12,063	-0.8%
Increase average, weighted sequelae disability weight from 0.340 to 0.600	11,197	5.9	1,987	13,189	8.4%
Reduce meningitis case fatality rate from 42% to 20%*	7,607	5.9	1,329	8,942	-26.5%

*The case fatality rate assumptions are explained in Chapter 12.

9.6 DALY ASSUMPTIONS USED IN THE ECONOMIC EVALUATION

The DALY parameter assumptions used in the three study countries are summarized in Table 9.8 below. Since the age of Hib infection affects both the YLLs and YLDs, relatively narrow age ranges were included in the model. Local data on age distributions were available from Belarus and India, but data from a global literature review were used for Uzbekistan, as specified in the footnote of the table.

Table 9.8: DALY parameters used in the four case studies

Parameter	Belarus	India	Uzbekistan
Age weighting modulation factor (K)	1	1	1
Age weighting parameter (β)	0.04	0.04	0.04
Constant (C)	0.1658	0.1658	0.1658
Life expectancy	70	65	68
Age distributions of Hib invasive disease episodes:*			
<3 months	5.0%	23%	10.6%
3-5 months	5.0%	19%	13.6%
6-8 months	5.0%	20%	17.8%
9-11 months	5.0%	10%	17.8%
12-23 months	23.0%	22%	23.8%
24-35 months	27.0%	2%	5.5%
36-47 months	20.0%	2%	5.5%
48-59 months	10.0%	2%	5.5%
Risk of meningitis sequelae	12%	35%	35%
Disability weights:			
Pneumonia	0.279	0.279	0.279
Meningitis	0.616	0.616	0.616
NPNM	0.616	0.279	0.279
Meningitis sequelae	0.340	0.340	0.340
Duration of acute illness in days:			
Pneumonia	13	10	9
Meningitis	21	11	11
NPNM	21	11	11
Duration of meningitis sequelae	Lifelong	Lifelong	Lifelong

*Sources for age distributions:

- Belarus: Hib meningitis surveillance at Minsk City Children's Infectious Disease Hospital
- India: Invasive Hib disease surveillance at several hospitals by Gupta *et al.* (2011) [244]
- Uzbekistan: Global literature review by Bennett *et al*. (2002) [245]

9.7 DISCUSSION

In this chapter, YLLs from Hib disease mortality, YLDs due to acute Hib meningitis episodes and YLDs caused by Hib meningitis sequelae were estimated. By adding up these numbers, DALYs due to Hib disease were calculated. The example from Uzbekistan demonstrated that discounting of particularly the YLLs makes a large difference to the DALY estimates for Hib disease, emphasising the importance of presenting cost-utility ratios both with and without discounting of future values. For estimating YLDs due to meningitis sequelae, in-depth analysis was undertaken of the risk of sequelae and the proportional types of disabilities. This exercise revealed that it is important to differentiate between high- and low income countries and between Hib and pneumococcal meningitis when deciding on the risk of sequelae assumptions.

Weighted average disability weights were calculated for Hib, pneumococcal and meningococcal meningitis sequelae. Since pneumococcal and meningococcal meningitis are also vaccine preventable, these figures are useful for cost-utility studies of these vaccines. The single weighted, average values represent an important improvement

compared to previous studies where the evidence used for YLDs due to meningitis sequelae has been weak. Four of the studies included in the literature review of Hib vaccine economic evaluation in Chapter 5 used DALYs as the outcome measure [122, 123, 124, 125]. In the Indonesian study by Broughton, the disability weights used were not reported [123]. In the Kenya study, the motor deficit disability weight was assumed for all sequelae cases [125], and in the Russian study the deafness disability weight was used for an estimated proportion suffering from hearing loss and the motor deficit weight for remaining cases [122]. In the second Indonesian study, meningitis sequelae were divided into mental retardation, deafness, blindness, seizure disorder and motor deficit and the respective disability weights were applied to each category. However, the proportions suffering from the different syndromes were not based on a meta-analysis, but on a single study from the Gambia.

Estimation of DALYs due to Hib disease demonstrates several limitations with the measure. First, it is apparent that the approach is not suitable for measuring HR-QOL from a disease marked by many different severities. As mentioned in the beginning of this chapter, one of the differences between QALYs and DALYs is that while QALYs measure health states, DALYs depict specific diseases. Hence, one disability weight is used for each disease and it is not possible to distinguish between severities. This is a limitation for DALY estimates of all diseases, but the Hib example provides a good illustration of the problem. Pneumonia is for instance characterised by three main severities, but only one disability weight is available. This is a problem when evaluating the cost-utility of Hib and pneumococcal vaccines because bacterial pneumonias are more severe than pneumonia caused by for instance viruses [178]. Similarly, a broad range of different severities of meningitis sequelae occur in children, but with only a few, distinct disability weights available, it was necessary to omit minor sequelae from the analysis. Hence, the DALY estimates presented for meningitis sequelae are likely to underestimate the impact on HR-QOL and give conservative cost-utility estimates.

A related second limitation is that DALYs do not account for co-morbidities, as the disability weights represent single diseases. Approximately 20% of Hib meningitis sequelae cases suffer from multiple impairments, but with DALYs there is no standard way of valuing the impact of more than one disease at a time. In the present analysis this was resolved by using the highest available disability weight (which is for dementia) to approximate the impact of multiple sequelae on HR-QOL, but this was a fairly random decision, which is open for questioning. However, as shown in the Uzbekistan example, changing these values makes hardly any difference to the DALY estimates.

Thirdly, the DALY estimates of Hib diseases were constrained by a lack of disability weights for several of the syndromes. There were no weights for any of the NPNM diseases, so these were approximated by using either the meningitis or pneumonia weights, and since there are no disability weights for low vision and clinical impairments caused by meningitis sequelae, these were approximated from other disease categories. Again, the rationales for these best guesses are not founded on evidence and can be challenged.

The Hib YLD calculations presented in this chapter were evidently complicated by the amount of data required and their quality. However, the results of the analysis suggest that YLD contribute only a marginal part of the overall DALY estimate. For example, the Uzbekistan example showed that the YLLs entirely dominate the DALY estimate, with YLDs only accounting for 7% of the total value. Hence, in high mortality countries YLDs are only of marginal importance to the overall result and it therefore seems unnecessary to go into great efforts to accurately measure these, as it is not likely to make any difference to the cost-effectiveness conclusion. YLDs could be of relatively greater importance in countries where the large majority of Hib cases survive. However, as was also shown in the Uzbekistan example, discounting of YLDs decreases the value considerably and it is questionable whether the choice between using one particular disability weight instead of another would make any difference to the overall cost-effectiveness result. These issues are evaluated in uncertainty analysis of the cost-utility estimates presented in Chapter 12.

It is apparent that calculation of DALYs for Hib diseases was based on a number of assumptions, which were not easy to justify, such as determining disability weights for diseases not included in the GBD list. This piecemeal approach to HR-QOL valuation must be regarded as one of the greatest limitations of using DALYs. When estimated according to standard guidelines, there is little doubt that the QALY approach is considerably more evidence based than DALYs. Preference scores for QALY estimates are usually based on data collected from the general public as well as patients, so there is less need for making explicit assumptions when calculating the values.

A distinct advantage of QALYs is also that they value health states instead of individual diseases, so different severities and co-morbidities are implied in the values. However, as mentioned in the beginning of the chapter, the work on developing generic, validated instruments and QALY scoring systems for use in low-income countries is still only in its early beginning, so DALYs can probably be expected to be the standard measurement used for many years to come.

A revision of the DALY methods is in progress and expected to be released during 2012. The revision, which is being completed by the several different research groups, involves updated global burden of disease estimates for all the previous and a number of new diseases and sequelae. These estimates are largely based on systematic literature reviews. The DALY disability weights will also be revisited and this time they will be based on population preference surveys instead of expert opinion [246]. However, details of the work are not yet open to the public, so it is not possible to judge the extent of the changes and what it means for future analyses. Many of the limitations observed over the years by several researchers would most likely have been dealt with in the new methods, so large improvements are hoped for.

10 COSTS OF HIB DISEASE

The costs of treating disease should it occur is an important component of any economic evaluation, as are costs associated with longer term health outcomes. The decision-analytic model is structured so that up to five different types of Hib disease costs can be included:

i. Treatment costs of Hib meningitis
ii. Treatment costs of Hib pneumonia
iii. Treatment costs of Hib NPNM
iv. Lifetime treatment costs of Hib meningitis sequelae
v. Lifetime productivity costs due to Hib meningitis sequelae

If a government health sector perspective is taken, only costs incurred by the public health sector should be included while with a societal perspective, household costs in the form of out-of-pocket payments for public as well as private treatment are also incorporated. Lifetime productivity costs due to meningitis sequelae can be included if a societal perspective is taken.

As was shown in the literature review of treatment cost studies in Chapter 5, it is important to integrate access to health care and treatment utilization behaviours into the analysis. This is essential because treatment costs are potentially reduced if a proportion of the population have limited or no access to health care and mean costs per case vary between levels of care and between public and private health facilities.

In this chapter, treatment costs of i) meningitis, ii) pneumonia and iii) NPNM are estimated for the three study countries; Belarus, India and Uzbekistan. This is followed by a case study from Senegal on iv) lifetime treatment costs of meningitis sequelae, and v) lifetime productivity costs of caregivers due to meningitis sequelae.

10.1 TREATMENT COST ESTIMATES FOR BELARUS, INDIA AND UZBEKISTAN

10.1.1 STUDY OBJECTIVES AND PERSPECTIVES

The aim was to estimate total annual costs of treating Hib meningitis, Hib pneumonia and Hib NPNM in children less than five years in Belarus, India and Uzbekistan. Secondary objectives were:

1. To determine the proportion of the population accessing health care.
2. To establish health care utilization behaviours of those with access to care.

3. To estimate the mean costs per patient of treating meningitis, pneumonia and NPNM, according to type and level of health care provider.
4. To determine the proportion of total costs financed by the government versus households.

Fundamental aspects of the health systems in the three countries are described in Annex 3. In India, approximately 70% of all health spending occur in the private sector, which is one of the highest proportions in the world. Out-of-pocket payments for health services are a considerable burden for poor households in India, and it is estimated that more than 40% of people have to borrow money or sell assets to cover hospital expenses [247]. While the government was the sole provider of health care in Belarus and Uzbekistan during Soviet times, private health expenditures has increased rapidly since independence, largely due to a widespread problem of informal out-of-pocket payments for public services [248]. During 2008, private expenditures comprised around 50% and 25% of total health sector expenditures in Uzbekistan and Belarus, respectively [249].

It was decided to restrict the Belarus analysis to the government health sector perspective. While it is likely that a proportion of treatment costs for Hib diseases are financed by households as unofficial out-of-pocket costs, there is no legitimate information on this. Belarus is still ruled by a socialist dictatorship and data collection on household health expenditures is not politically feasible. In Uzbekistan and India, societal perspectives were taken with treatment costs separated into government and household expenses.

10.1.2 METHODS

Data were collected from a mixture of primary and secondary sources in the three countries. I visited India in November 2007 and July 2008, Uzbekistan in November 2008, and Belarus in December 2008 and June 2009. During these visits I established a working relationship with the country collaborators, conducted interviews with key stakeholders, determined the need for primary data collection, and trained the collaborators in collecting the data.

10.1.2.1 Access to care and health care utilization

Penchansky and Thomas define access as a concept that incorporates features of "fit" between the patient and the health care system, i.e. the dimensions span over both the supply and demand sides. Three main factors influence access [250]:

1. Affordability: The ability to pay and the impact on livelihoods of households

2. Availability: The relationship between the volume and type of relevant health care workers, facilities and services on the one hand and the volume and type of patient needs on the other. It covers factors such as location of services, availability of transport, opening hours and waiting time.
3. Acceptability: The patient's attitudes to the characteristics of the providers and the attitudes of providers towards patients. This is about how well social and cultural aspects of the health system reflect those of communities.

In the decision-analytic model, assumptions about access to care are expressed in terms of number of outpatient visits and hospital admissions per case. According to the WHO treatment recommendations for Hib diseases, all Hib syndromes except non-severe pneumonia require hospitalisation (see Annex 1). Hence, if all children in a country have access to appropriate health care services, each case of meningitis, severe pneumonia and NPNM would lead to at least one hospitalisation and most likely also at least one outpatient visit, as hospitalisations are generally referred during an outpatient consultation. The number of outpatient visits per case would exceed one in places with high access to care as clinical follow-up is commonly recommended after hospital discharge. If access to health care is limited, the number of outpatient visits and hospitalisations per Hib disease case would be less than one.

For each of the three countries, health sector appraisals, household surveys and published literature were reviewed to establish the most reliable assumptions for access to care and health care utilization patterns. Routine meningitis and pneumonia surveillance data were also used to establish the proportion of cases being treated at the different levels of care.

10.1.2.2 Estimation of mean treatment costs per case

In Belarus and Uzbekistan a selection of hospitals were visited for treatment cost data collection. In Belarus, the hospitals were the MCCIDH, Minsk Regional Hospital and Stolbtsy District Hospital. In Uzbekistan the Infectious Disease Hospital #1, the Paediatrics Research Institute, the Children's Hospital #5 of Yunusobod District, and the Uchtepa District Children's Hospital were visited. A description of the facilities is given in Annex 4. Hospital administrators were interviewed through an interpreter. Questions were asked about standard treatment procedures for childhood pneumonia and meningitis, the average length of stay in hospital of these patients, and the estimated costs per bed day of the facility. This information was supplemented by a retrospective review of approximately ten pneumonia and ten meningitis patient records at the national referral hospitals in each country (the MCCIDH in Belarus and the Infectious Disease Hospital #1 in

Uzbekistan), with the purpose of collecting data on common diagnostic tests and drug utilization. Unit costs of drugs were gathered from the hospital pharmacies. My study collaborators completed this work using a data collection spreadsheet I developed for the purpose.

Since there is no information available on the average costs of an outpatient visit in Belarus and Uzbekistan, data from WHO CHOICE were used (see Annex 2). The values were US$ 9.31 per visit in Belarus and US$ 1.53 per visit in Uzbekistan [251]. It was assumed that meningitis treatment costs were 20% less at secondary than at the tertiary hospitals where the meningitis treatment cost data were collected.

In India, a number of meetings were held with researchers who had worked on treatment cost analysis. Health services in India vary considerably between states, so efforts were made to identify studies that could be considered nationally representative. After many discussions it was decided to estimate household costs from the sixtieth round of the Government of India National Sample Survey Organisation (NSSO) socio-economic survey, which in 2004 for the first time incorporated questions on morbidity and health [252]. In this survey, detailed information was collected from households on medical expenditures according to type of disease episode, with data on outpatient treatments and hospitalisations collected for the last 15 and 365 days preceding the interview, respectively. Household out-of-pocket costs were categorised in a specified manner according to medicines, user fees, lodging, transport, etc. The NSSO questionnaire is included in Annex 5. Results of the survey on "respiratory ailments" in children less than five years old were used for approximating household costs of pneumonia treatment. For this disease category, the nationwide sample sizes were 644 outpatient episodes and 238 inpatient admissions. For meningitis treatment, the respiratory ailments costs were adjusted upwards in accordance with the additional lengths of stay in hospital for meningitis compared to pneumonia. Hospital length of stay for pneumonia and meningitis patients less than five years old were collected from a Hib Initiative supported multi-centre surveillance study [253].

Treatment costs from the Indian government perspective were derived from the study by Krishnan and colleagues from the All India Institute of Medical Sciences in New Delhi [129, 254, 255]. This study was included in the literature review in Chapter 5. A meeting was held with Dr. Krishnan to inform him about the Hib economic evaluation, discuss the methods he had used in his study, and determine to what extent his results can be assumed representative of other government facilities in India. The study by Krishnan *et*

al. was undertaken in the state of Haryana in North India with the aim of estimating outpatient and inpatient treatment costs of meningitis, pneumonia and diarrhoea in children less than five years. Data were collected from six government hospitals and two private hospitals. Both urban and rural areas were included and all three levels of health care (primary, secondary and tertiary) were represented [129]. Micro-costing methods were used for estimating costs per bed-day and a sample of patient records was reviewed for determining patient specific costs. The methods of the Krishnan study and how the data have been used for the present analysis are explained in more detail in Annex 4.

In all three countries, treatment costs of NPNM were assumed similar to hospitalised pneumonia as it was not possible to locate costs of these relatively rare diseases.

In Uzbekistan, only household expenses on drugs were included while in India information on other expenses, such as transport to the facility, was available from the NSSO survey. Productivity costs of caregivers due to time spent when taking children for treatment were excluded in all three analyses. Key informants in all three countries were asked whether data or studies on the costs of treating meningitis sequelae were available, but nothing was obtainable. This is the topic of the next section in this chapter.

Costs were estimated in 2010 US$ using exchange rates of 2,793 Belarusian rubles, 45.7 Indian rupees and 1,464 Uzbek som to one US$ (www.oanda.com/convert/fxhistory). Cost data prior to 2010 were adjusted using the average consumer price index (www.imf.org).

10.1.3 RESULTS

10.1.3.1 Access to care

There is substantial evidence that access to health care is higher in Belarus than in the two other countries. In a quantitative, cross-sectional survey assessing health care seeking behaviour in eight former Soviet Union countries by Balabanova *et al*., Belarus consistently came on top of the list [256]. For example, the probability of seeing a health professional in the previous year was found to be 67% in Belarus while it was 24% in Georgia, the probability of seeking care when it seemed justified was 91% in Belarus, but only 51% in Georgia, and in Belarus 56% of adults responded yes when asked whether they would consult a health professional in the case of fever for more than three days, while only 16% would do so in Armenia [256]. Another indication of relatively high functional access is that Belarus has the largest number of doctors and nurses per 1,000 population in Central and Eastern Europe [257]. Children's health is particularly monitored closely with every

newborn seen by their primary care doctor three times during their first month and at least once a month up to the age of one year, and every child is supposed to have a general check-up by all main specialists annually until they are 18 years [257].

In Uzbekistan and India, a relatively large proportion of the population has limited access to health care. A study on access to care in rural parts of Ferghana Oblast in Uzbekistan found that of individuals who reported an illness in the previous 30 days, around 45% self-treated with drugs before deciding whether to seek care and only about 50% went on to seek care, including visits to traditional healers [258]. Low-income individuals were significantly less likely to seek care than those with higher income. The study concluded that 21% of people reporting a health problem did not seek health care because they did not have enough money and of those who did seek care, 86% paid at least some money out of pocket [258]. A comparable conclusion was made in the 2006 Uzbekistan Multiple Indicator Cluster Survey (MICS) where data were collected from a representative sample of 10,505 households [259]. The data showed that of children aged 0–59 months with suspected pneumonia during the two weeks preceding the survey (defined as children who had an illness with a cough accompanied by rapid or difficult breathing), 35% of those living in rural areas and 26% of urban children were not taken to an appropriate health care provider. The national average of children without access to care was 32% [259].

In India, selective, fragmented strategies and lack of resources have made the health system disconnected to public health goals and it fails to provide financial risk protection to the poor [247]. While there are substantial differences between the 28 states, access to health care is generally severely constrained due to geographic locations, bad roads, unreliable functioning of health facilities and transport costs [260]. One of the most important data sources on access to care is the Indian National Family Health Survey (NFHS). The third survey (NFHS-3) was conducted in 2005-2006 and had an interview sample of 230,000 people between 15 and 54 years [261]. Similar to the Uzbekistan MICS survey, it was asked whether children less than five years had been ill with a cough accompanied by short, rapid breathing in the two weeks preceding the survey and if so, if he/she had been taken to a health care provider. It was found that 29% of children with Acute Respiratory Infections (ARI) symptoms did not have access to health services, with a range between 11% and 79% across the states [261].

Access to care assumptions for the three countries are summarised in Table 10.1. Based on the evidence of high access to care in Belarus, it was assumed that all severe Hib disease

cases were hospitalised at least once. In this country it is moreover required that children who have suffered from meningitis should be re-hospitalised for follow-up one month and again six months after the initial discharge. As part of the present study, collaborators at MCCIDH reviewed hospital records of 18 meningitis cases admitted during 2007 and 2008 and found that two of these children were re-admitted three times, seven two times and nine once as part of their follow-up. Based on these data, it was assumed that all children with meningitis were re-hospitalised 1.6 times in Belarus. Hence, the total number of hospitalisations was 2.6 per meningitis case. Three outpatient visits per pneumonia and NPNM episode and seven outpatient visits per meningitis episode were assumed based on the evidence of frequent consultations [257].

In India and Uzbekistan, 0.71 and 0.68 hospital admissions per severe case were assumed, based on the findings from the NFHS-3 and MICS surveys, respectively. Two outpatient visits were assumed for each admission of severe pneumonia, meningitis and NPNM, following common treatment procedures of one outpatient visit before admission, where the referral is made, and one follow-up visit after hospital discharge. For non-severe pneumonia, access to outpatient health care was assumed similar to inpatient access for severe diseases.

Table 10.1: Numbers of hospital admissions and outpatient visits per Hib disease case

	Belarus	India	Uzbekistan
Number of admissions per case:			
Severe Hib pneumonia	1.0	0.71	0.68
Hib meningitis	2.6	0.71	0.68
Hib invasive NPNM	1.0	0.71	0.68
Number of outpatient visits per case:			
Severe Hib pneumonia	3.0	1.42	1.36
Hib meningitis	7.0	1.42	1.36
Hib invasive NPNM	3.0	1.42	1.36
Non-severe Hib pneumonia	1.0	0.71	0.68

Sources: Belarus: 2008 health systems review [257], India: 2005-06 NFHS-3 [261], Uzbekistan: 2006 MICS survey [259].

10.1.3.2 Health care utilization

Assumptions about levels of hospital admissions are seen in Table 10.2. Private facilities were excluded from the Belarus and Uzbekistan analyses because private health care is only available in urban areas and only used by a marginal proportion of the population [257, 262]. Based on the Belarus population distribution, it was assumed that 80% of meningitis cases were admitted to secondary hospitals and the remaining 20% to the specialised, tertiary hospitals in Minsk. 2008 national pneumonia surveillance data from

Belarus showed that 76% of pneumonia admissions were at primary hospitals and 24% at secondary or tertiary hospitals.

According to 2008 surveillance data from Uzbekistan, 4% of clinical meningitis cases were admitted to tertiary hospitals, 32% to secondary hospitals, and 64% to primary hospitals, and these figures were only slightly different for pneumonia (Table 10.2).

In India, the NFHS-3 data reported that 41% of children with ARI were admitted to private hospitals, 27% to government primary hospitals and 32% to government secondary/tertiary hospitals. For the latter category, it was assumed that tertiary-level care accounted for 2% of admissions. Similar assumptions were made for meningitis.

In Belarus and Uzbekistan, it was assumed that all outpatient consultations take place at government polyclinics. In India, the NFHS-3 data on outpatient consultations for ARI in children less than five years showed that 61% were taken to private clinics, 5% to private hospital outpatient departments, 10% purchased drugs in private pharmacies, 9% sought treatment from a traditional healer, and only 16% of children were taken to government outpatient providers [261].

Table 10.2: Assumptions about distribution of hospital admissions for children less than five years with access to care

	Belarus	India	Uzbekistan
Hib meningitis:			
Government primary hospital	0%	27%	64%
Government secondary hospital	80%	30%	32%
Government tertiary hospital	20%	2%	4%
Private hospital	0%	41%	0%
Hib pneumonia and NPNM:			
Government primary hospital	76%	27%	66%
Government secondary hospital	20%	30%	31%
Government tertiary hospital	4%	2%	3%
Private hospital	0%	41%	0%

Sources: Belarus and Uzbekistan: MOH surveillance data gathered for the present study , India: 2005-06 NFHS-3 [261]

10.1.3.3 Mean treatment costs per case

The mean length of stay in hospital was longer in Belarus than in the two other countries (Table 10.3). During re-hospitalisation for meningitis in Belarus the mean length of stay was nine days, compared to 21 days during the acute episode.

Table 10.3: Mean length of stay in hospital (days)

	Belarus	India	Uzbekistan
Pneumonia	13	6	9
Meningitis	21	10	11

Details of the resource items and their respective unit costs from the different facilities are included in Annex 4. In Belarus, the mean costs per bed-day were US$ 40 at MCCIDH and US$ 23 at Stolbtsy District Hospital. Staff costs comprised 59% and 83% of total bed-day costs in the two hospitals, respectively. When multiplying by mean length of stay, including the days in hospital during re-hospitalisation, and adding patient-specific items, such as drugs and diagnostic tests, average meningitis treatment costs amounted to US$ 1,959 per episode at tertiary level (Table 10.4). Mean pneumonia treatment costs were US$ 413, US$ 448 and US$ 542 for primary, secondary and tertiary levels, respectively.

In Uzbekistan, costs per hospital bed-day in the Infectious Disease Hospital #1 amounted to US$ 9.10. Mean costs of treating meningitis were US$ 238, US$ 257 and US$ 276 in primary, secondary and tertiary hospitals, respectively. For a very severe case less than one year old, drug costs comprised 46%, bed-day costs 40%, diagnostic tests 12% and food 2% of total costs The mean costs of pneumonia treatment were approximately 20% less than the costs of treating meningitis in primary and secondary hospitals, but only 3% less at tertiary level. Approximately 33% and 11% of costs were covered by households as out-of-pocket payments for drugs, for meningitis and pneumonia, respectively (Table 10.4).

In India, costs per bed-day were estimated as US$ 18 in a government secondary hospital and US$ 39 in a tertiary hospital. For primary and secondary government facilities total costs were almost similar to those estimated for Uzbekistan, but for meningitis treatment at tertiary level, costs were 40% higher in India than in Uzbekistan. According to the NSSO survey data, 35% of household expenditures at government facilities were for drugs. Other expenditure categories were oxygen, diagnostic tests, transport and food and lodging. In private facilities user fees were the biggest cost item, comprising 57% of total household costs [252]. Further details on this are given in Annex 4.

Table 10.4: Mean inpatient treatment costs per acute case (2010 US$)

Provider type	**Belarus**	**Uzbekistan**			**India**		
Hib meningitis	**Government**	**Government**	**Households**	***Total***	**Government**	**Households**	***Total***
Primary hospital	*NA*	169	86	*238*	164	81	*245*
Secondary hospital	*1,567*	188	86	*257*	172	81	*253*
Tertiary hospital	*1,959*	242	86	*276*	380	81	*461*
Private hospital	*NA*	NA	NA	*NA*	NA	241	*241*
Hib pneumonia/NPNM							
Primary hospital	*413*	152	26	*195*	97	50	*141*
Secondary hospital	*448*	171	26	*214*	101	50	*151*
Tertiary hospital	*542*	190	26	*268*	224	50	*274*
Private hospital	*NA*	NA	NA	*NA*	NA	149	*149*

Table 10.5: Mean outpatient treatment costs per visit (2010 US$)

Provider type	**Belarus**	**Uzbekistan**			**India**		
	Government	**Government**	**Households**	***Total***	**Government**	**Households**	***Total***
Public clinic	*9.31*	1.53	5.00	*6.53*	2.88	12.30	*15.18*
Private clinic	NA	NA	NA	NA	NA	10.70	*10.70*
Private hospital outpatient department	NA	NA	NA	NA	NA	10.70	*10.70*
Traditional healer	NA	NA	NA	NA	NA	6.20	*6.20*
Pharmacy	NA	NA	NA	NA	NA	0.90	*0.90*

10.1.4 DISCUSSION

In this section, access to care, health care utilization behaviours and the mean treatment costs per case of Hib meningitis, Hib pneumonia and Hib NPNM according to different levels and providers of care were determined for the three study countries. In Chapter 12, these parameter values are combined with disease incidence estimates to generate total treatment costs for 2010 birth cohorts, with and without Hib vaccine introduction.

A finding from the literature review in Chapter 5 was that treatment costs were closely related to GNI per capita, with higher mean treatment costs per case in wealthier countries. This tendency was confirmed in this chapter as the treatment costs per case in Belarus were more than double compared to the two other countries. The 2010 GNI per capita were US$ 6,130 in Belarus, US$ 1,340 in India and US$1,280 in Uzbekistan [109]. The estimates for the three countries are in a similar range as the comparable study results shown in Chapter 5. The costs of treating meningitis at tertiary level in Belarus (US$ 1,959) are comparable with the costs in Brazil (US$ 1,474), and the India (US$ 461) and Uzbekistan (US$ 276) estimates are in a comparable range to those in Kenya (US$ 434) and Vietnam (US$ 211).

There are important strengths and limitations of the methods used for estimating mean treatment costs per case. A micro-costing exercise involving collection of resource utilization data and associated unit costs from a sample of patients, as done in the studies reviewed in Chapter 5, was not undertaken as part of this thesis. Instead, a more pragmatic approach of using the best available published data supplemented by information collected relatively rapidly was employed. While there is no doubt that the estimates would have been more precise if a micro-costing exercise had been undertaken, this was not feasible within the timeframe of the studies. It is moreover unlikely that such an approach would have been possible in Belarus due to the political climate.

An alternative to collecting data relatively rapidly in Belarus and Uzbekistan could have been to extrapolate from the results of the more rigorous studies in Chapter 5. However, when working in countries during the time of the Hib Initiative it was repeatedly found that local researchers and policy makers rarely accept the use of data from other countries than their own [66]. Even when data underpinning local estimates are of less quality than those from other countries, local estimates are generally preferred. I have moreover observed that the interest in the study of policy makers and the general trustworthiness of the analysis are substantially enhanced when stakeholders recognize the health facilities where data have been collected. An additional advantage was that when visiting health

facilities for treatment cost data collection, the opportunity was taken to inform about the study and about Hib vaccine in general. This was extremely important for building local ownership of the analyses and for fostering collaboration with local researchers. Health economics is a relatively new concept in both Belarus and Uzbekistan and the present study represent some of the first treatment cost estimates ever generated in these countries.

In India the treatment cost estimates were derived from published sources and limited primary data collection was undertaken. This approach was justified because transparent and detailed studies already exist in this country. Government health sector costs were derived from a high quality micro-costing study by Krishnan *et al.* and household costs were based on NSSO survey data. Both of these sources obtained estimates from large sample sizes and in the NSSO survey, households from all 28 states were included. It would not have been possible within the normal time and budget constraints of a research study to collect data of comparable high quality.

All the parameter estimates presented in this section are surrounded by uncertainty. It is therefore crucial to assess the importance of the treatment cost estimates to the overall cost-utility results and this is done in the sensitivity analysis in Chapter 12. Furthermore, in the probabilistic uncertainty analysis, all the treatment cost parameters are attached a gamma distribution and Monte Carlo analysis is undertaken to generate an uncertainty range around the cost-utility estimate, thus taking the uncertainty of parameter values into account.

10.2 COSTS OF TREATING MENINGITIS AND LIFETIME COSTS OF MENINGITIS SEQUELAE IN SENEGAL[3]

10.2.1 INTRODUCTION

A major gap in the literature is information about the societal costs of meningitis sequelae in low-income countries. These costs consist of three components: (i) treatment costs of sequelae, (ii) productivity costs of caregivers due to time spent looking after a disabled child and (iii) future productivity costs because the child will not be able to work in productive activities when he/she grows up.

In all the nine economic evaluations from high-income countries reviewed in Chapter 5, all or parts of these costs were included in the studies, but this was not the case for the low- and middle-income country studies. In the economic evaluations from high-income countries, lifetime treatment costs of meningitis sequelae were based on data collected from education agencies, disability services and medical insurance companies on the costs of hearing aids, special education, rehabilitation and institutional care [110, 115, 116, 118, 119, 120, 121]. However, in low- and middle-income countries with limited access to health care and hardly any special education institutions, these types of assumptions cannot easily be made. Only two of the eight studies from low- and middle-income countries made attempts to include these costs, but the estimates were largely based on assumptions with no or limited primary data. In one of the Indonesian studies, treatment of sequelae was assumed to consist of four annual outpatient visits, but there was no evidence for this and it was not specified for how many years this would occur [123]. In the Russian study, parents of 31 meningitis patients were telephoned one year after hospital discharge and asked about medical expenses due to meningitis sequelae, and it was assumed that these costs would remain the same for the subsequent ten years and be reduced to zero thereafter [122].

Productivity costs due to meningitis sequelae were included in six of the papers reviewed in Chapter 5 and excluded in the remaining 11 studies. In the Swedish study by Garpenholt, 25% productivity costs were attached to parents of a disabled child until the child was 20 years old, and from 20 years onwards 100% productivity costs were included for all persons with severe disability [118]. Productivity costs were determined using a figure from the Swedish Road Administration where a life had been valued using the willingness-to-pay approach. In the studies from the Philippines, Russia, South Africa,

[3] A modified version of this section has been published in the Paediatric Infectious Disease Journal as: Griffiths UK, Dieye, Y, Fleming J, Hajjeh, R, Edmond K, Costs of meningitis sequelae in Dakar, *Pediatr Infect Dis J*. 2012 Jun 4. [Epub ahead of print].

South Korea and the USA, the average wage rate was used to value future lost productivity due to premature mortality and disability [111, 112, 114, 121, 122]. Productivity loss of parents were not included.

In this part of the chapter, a study from Dakar in Senegal on the costs of acute meningitis and meningitis sequelae is presented. Methodological issues for valuing productivity costs are discussed in the next section, study objectives are outlined in section 10.2.3, methods are described in section 10.2.4, results in section 10.2.5, and the study findings are discussed in section 10.2.6.

10.2.2 METHODOLOGICAL ISSUES FOR VALUING PRODUCTIVITY COSTS IN LOW-INCOME SETTINGS

It is widely accepted that forgone production due to illness and mortality represents a cost to society, which should be taken into account when assessing the cost-effectiveness of health interventions [67]. The traditional method for placing a monetary value on time is the human capital approach where productivity costs equals the present value of lost gross wages over the period of illness or from the time of premature death until retirement age [263]. The theoretical foundation of this method is that in a well-functioning labour market, productive output and compensation to the worker are equal, because they represent the same resource. The human capital approach has however been challenged by the proponents of the "friction cost" approach, who argue that in practice, if a worker is absent from work for an extended period of time, lost productivity would only be during the period until an otherwise unemployed replacement worker is found [264]. Hence, the productivity costs should be limited to this frictional period because sufficient unemployment generally exists to replace the ill worker. With the friction cost approach, production losses due to long term disability or death are thus limited to a relatively short period required to replace a worker, which makes a large difference to the estimates compared to the human capital method.

For both approaches it is assumed that the bulk of the working population is oriented towards paid employment and that channels for the exchange of labour market information exist and is widely used. These assumptions do however not hold in low-income countries, which are characterised by fragmented labour markets and a large informal sector. As an example, in Senegal during 2005, only 17% of the labour force was wage earners and 40% of these worked in the informal economy, mostly within household enterprises [265]. With only a relatively small proportion of the adult population being wage earners, application of an average formal sector gross wage for estimating productivity costs as dictated by the human capital approach is likely to overestimate the

real value. Since the period until a new worker can be found is particularly short in the informal sector, use of the friction cost approach would lead to considerably lower productivity cost estimates compared to the human capital approach.

The challenges mentioned above could be one reason why GDP per capita has been used for valuing productivity costs in a number of low-income country studies, such as a recent study on estimating the economic benefits of vaccines in GAVI eligible countries [266]. The purpose of GDP per capita is to quantify the average amount of goods and services available to each person in an economy. It is closely correlated to average income, but since GDP includes all age groups, conceals income inequalities and does not include informal sector activities, it is not analogous to average income and is therefore not an appropriate measure for valuing productivity costs. The use of GDP per capita for valuing productivity costs is not a recommendation included in standard economic evaluation guidelines and it is questionable why this approach has been used in several studies without any explanations or justifications [110, 120, 266].

10.2.3 STUDY OBJECTIVES

Senegal is a low-income country in West Africa with 2010 GNI per capita of US$ 1,090 [109]. With support from the GAVI Alliance, Hib vaccine was introduced in 2005 and pneumococcal vaccine is scheduled for introduction during 2012. The aim of this study was to estimate the lifetime costs of bacterial meningitis sequelae in children less than five years of age in Dakar. Secondary objectives were to:

1. Estimate household treatment costs of an acute bacterial meningitis episode, based on recall information from caregivers.
2. Investigate health care seeking behaviours of caregivers of children suffering from meningitis sequelae.
3. Estimate lifetime household treatment costs of meningitis sequelae.
4. Estimate lifetime productivity costs of caregivers of children with meningitis sequelae.

A “sequela” was defined according to the 2001 Global Burden of Disease project as a health state due to bacterial meningitis, which impairs quality of life or activities of daily living and for which prevalence and average duration can be estimated [216].

The research was part of a prospective cohort study designed to assess disability, quality of life and the economic burden of children with bacterial meningitis sequelae in Dakar. The study was funded by the Hib Initiative and undertaken in collaboration with the

Programme for Appropriate Technologies in Health (PATH) country office in Senegal. Staff at this office were completing a Hib vaccine case-control study when our study began, which was a major advantage because the field investigators already had experience with Hib disease and Hib vaccine [267]. Data collection for the study took place between January and July 2009. The results of the disability and quality of life assessments were published in the Paediatric Infectious Disease Journal in 2010 [268].

The study was approved by the ethics committees of PATH, LSHTM and the Senegal Ministry of Health. A one-year programme of free follow-up care was developed for children recognized with a disability [268].

10.2.4 METHODS

10.2.4.1 Sequelae definitions

A "sequela" was defined according to the 2006 Global Burden of Disease (GBD) project as a health state due to bacterial meningitis, which impairs quality of life or activities of daily living [126]. Minor and major sequelae were also classified according to GBD definitions and a separate category was created for individuals with more than one sequela (multiple impairments) [126, 235]. Children with minor sequelae were defined as those with speech deficits, hearing deficits or behavioural problems. Children with major sequelae were those with multiple sequelae and/or movement problems, vision deficit, cognitive problems or epilepsy.

10.2.4.2 Identification of study children

Children were enrolled from a Paediatric Bacterial Meningitis (PBM) database at the Albert Royer Hospital in Dakar. Since 2001, this hospital has been part of the WHO African Regional Office Laboratory PBM Surveillance Network [269]. PATH provided technical support to the surveillance system between 2006 and 2009 as part of their Hib vaccine case-control study [270].

For logistical reasons, only Dakar residents could be included the study. Additional inclusion criteria were that children should have been less than five years old at the time of the meningitis episode and at least four years old at the time of the study assessments. The latter criterion was included because neurological tests are generally not reliably administered in children younger than four years.

A total of 320 children were included in the Albert Royer Hospital PBM database up to November 2007, when the study protocol was prepared (Table 10.6).

Table 10.6: Bacterial meningitis cases in the PBM database 2002 - 2007 at Albert Royer Hospital

Age on 1st Jan. 2008	Hib	Pneumococcal	Meningococcal	Other bacteria	Total
Less than 1 year	0	5	1	5	11
1-2 years	1	14	0	1	16
2-3 years	14	8	1	10	33
3-4 years	41	14	1	13	69
4-5 years	43	15	2	5	65
5-6 years	28	20	2	9	59
6-7 years	35	12	3	4	54
7-8 years	4	4	0	0	8
8-9 years	0	3	0	1	4
9-10 years	0	0	0	0	0
≥10 years	0	0	1	0	1
Total	**166**	**93**	**11**	**48**	**320**

Hib was the most frequent cause of meningitis, representing 52% of all cases identified during the six year period. Of the 320 children, 191 were at least four years old in January 2008 and 159 of these were Dakar residents. However, residential contact details were only available for about half of the patients, so we aimed to recruit 80 children who had suffered from bacterial meningitis.

10.2.4.3 Data collection

Children were located at their home between January and July 2009 and caregivers were administered a detailed questionnaire by one of two recruited research staff. Questions included whether the child had epilepsy or behavioural, physical, cognitive, verbal, auditory and/or visionary problems. Socio-demographic information about the caregiver's education, occupation, religion and socio-economic status was also collected. The socio-demographic questionnaire is included in Annex 6. If the child had died, families were interviewed using a verbal autopsy questionnaire.

The economic questionnaire was divided into four parts:

1. Costs related to the acute meningitis episode.
2. Costs of subsequent hospital admissions due to meningitis sequelae.
3. Costs of outpatient visits due to meningitis sequelae.
4. Costs of caring for a disabled child, including estimated productivity costs of caregivers.

The economic questionnaire is included in Annex 7. If receipts of the treatment expenses were available, these were reviewed by the research staff, otherwise, all costs were based on recall. Both questionnaires were translated into French and piloted with two families by myself and the research staff before the study started. The interviews were undertaken in either French or Wolof.

After the interview, all children were invited for clinical evaluations by a neurologist, a psychologist and an audiologist at hospitals and clinics in Dakar. The results of these assessments were published in the 2010 paper by Edmond *et al*. [268]. In-depth interviews were conducted with three families to qualitatively evaluate how it has affected their lives to have a disabled child. I developed an interview guide for this purpose.

10.2.4.4 Estimating lifetime productivity costs of caregivers

Caregivers were asked who looked after the child during the day, whether this was different compared to if the child had not suffered from sequelae, if any household members were unable to work due to the child's disability, how much money any childminder was paid, and the estimated weekly lost earnings of any household member who was not able to work because he/she cared for the child.

Katz reviewed studies on the life expectancy of children with cerebral palsy and mental retardation and concluded that their life span is reduced by certain key disabilities, most importantly decreased cognitive abilities [271]. Life expectancies at five years varied between 12 and 41 years, depending on disability severity, but all the identified studies were from high-income countries [271]. Eyman *et al*. found that in the USA around 1990, five-year old children who are mobile, but not ambulatory and could eat with assistance had a life expectancy of 40.9 years while those who are immobile, not toilet trained but could eat with assistance had a life expectancy of 25.2 years [272]. This is compared to a life expectancy of 71.2 years for five-year old children in the general US population [273]. To account for the lower life expectancy in Senegal (62.9 years for five-year olds in 2009 [273]) and the fact that our study children presented with a wide variety of disabilities, an overall life expectancy of 30 years was assumed. Hence, annual productivity costs were assumed to last for 30 years. While the life expectancy of those with minor sequelae is likely to be relatively similar to the rest of the population, their costs were also predicted for 30 years because they most probably become self-sufficient at some point in their lives.

10.2.4.5 Data analysis

Data were single-entered into a Microsoft Access database and analysis was undertaken in Excel and STATA version 11.1. All past costs were adjusted to 2010 US$ values using the annual consumer price index of Senegal (www.imf.org) and an average exchange rate of 486 CFR to one US$ (www.oanda.com). It was assumed that the costs of caring for a disabled child and young adult would last for a total of 30 years, based on reviewing literature from high-income countries on the life expectancy of disabled children [271, 272, 274, 275, 276] coupled with expert opinion about their life expectancy in Sub-

Saharan Africa. Hence, treatment and productivity costs were extrapolated 30 years into the future. All future values were discounted by 3% per year [88].

Sensitivity analysis was undertaken to assess changes in the result of using official average wage rates instead of perceived productivity loss, assuming only a 20 year average life expectancy, higher outpatient costs to reflect a situation with better access to care, and no discounting of future values.

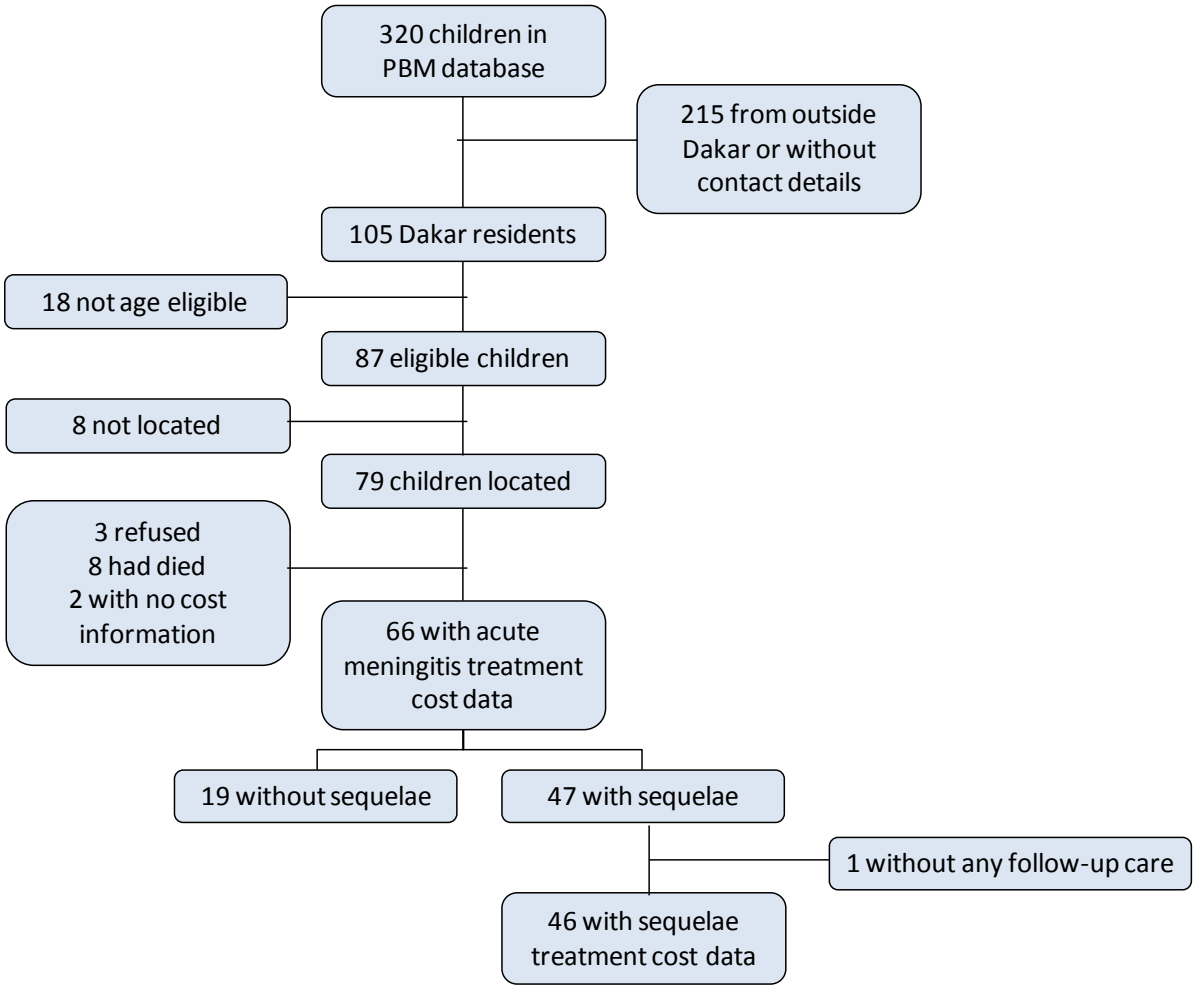
10.2.5 RESULTS

10.2.5.1 Patient recruitment

Efforts made to locate children were highly successful, with 91% of the 87 age eligible Dakar resident children found (Figure 10.1).

Three families refused to participate, eight children had died (case fatality rate of 10%) and two children were excluded from the analysis because the interviewees did not have information about expenses paid for treatment. Hence, 66 children were included in the

Figure 10.1: Identification of study children



cost analysis of acute meningitis. Of these children, 36% had been diagnosed with Hib meningitis, 33% with pneumococcal meningitis, 17% with meningococcal meningitis, and 14% with meningitis caused by another bacterium. Forty seven suffered from sequelae and this sample was used for the sequelae cost analysis.

10.2.5.2 Socio-demographic characteristics of study population

The average age at the time of the interview was six years and eight months, with the youngest child four years and the oldest ten years old. The average age of the meningitis episode was 15 months, with the youngest child three weeks and the oldest four years and eight months. The median time between the interview and when the child was hospitalized with meningitis was five years and five months (IQR 54 – 75 months).

The mother was interviewed in 62% of the visits (Table 10.7). Nine different ethnicities were represented with nearly half of the children being Wolof (Table 10.8). Six percent of the primary caregivers had a university education, 27% had completed secondary school, 26% primary school, 9% Koranic school, and 32% had no education. All households had flush toilets connected to a septic tank and only four did not have electricity (Table 10.9). In 51 (77%) of the households at least one member was earning a cash income, but in seven of these income was solely remittances from emigrated family members and for another six it was pension of one family member only. Occupations included accountant, dressmaker, carpenter, teacher and hair dresser.

The Senegalese live together in large extended families, so in 35% of the households more than ten people slept in the dwelling the night before the interview (Table 10.9). For 17% of the interviewees it was not possible to answer this question because so many people come and go and the number of people sleeping in the dwelling varies day by day.

Table 10.7: Relation to child of the person interviewed

Relation	Number	Percent
Mother	41	62%
Father	8	12%
Grandmother	11	17%
Grandfather	3	5%
Other	3	5%
Total	**66**	**100%**

Table 10.8: Primary caregiver characteristics (n=66)

Characteristics	Number	Percent
Ethnicity:		
Wolof	31	47%
Poular	5	26%
Serere	17	8%
Bambara	4	6%
Diola	1	6%
Soninke	4	3%
Mankagne	2	2%
Naar	1	2%
Lebou	1	2%
Religion:		
Muslim	65	98%
Christian	1	2%
Highest education:		
University	4	6%
Secondary school	18	27%
Primary school	17	26%
School of the Koran	6	9%
No schooling	21	32%

Table 10.9: Household characteristics (n=66)

Characteristics	Percent
Households that own land	6%
Households with at least one person with regular cash income	77%
Households with electricity	94%
Households with flush latrine	100%
Main water source:	
Piped into dwelling	91%
Public tap	6%
Open well	3%
Number of children less than 18 years living in dwelling:	
One	9%
Two	14%
Three	11%
Four	20%
Five	14%
Six or above	27%
Unknown	6%
Number of people sleeping in dwelling the night before the interview:	
Between 3 and 5 people	11%
Between 6 and 10 people	38%
Between 11 and 15 people	21%
Between 16 and 20 people	8%
Between 21 and 35 people	3%
Unknown	17%

10.2.5.3 Meningitis sequelae prevalence

Sequelae prevalence reported by the caregivers and according to the clinical assessments are summarised in Table 10.10. While 49 (74%) of the children were reported to suffer from at least one type of sequelae by the caregivers, the clinical assessments detected sequelae in 53 (77%). The clinical assessments discovered hearing deficits in four children, which the caregivers were unaware of prior to the study. Thirty five percent of all the children and 53% of those with any sequelae suffered from more than one type of disability. As seen in Table 10.11, a total of 21 different combinations of multiple sequelae were identified. Behavioural problems, speech deficits and epilepsy were the most frequent types of sequelae, occurring in 66%, 57% and 34% of children suffering from any type of sequelae, respectively. The most common combination was problems with movement, cognitive deficit, speech deficit, behavioural problems and epilepsy.

Table 10.10: Sequelae prevalence in study children

	Reported by caregivers (n=66)		**Clinical assessments (n=66)**	
	Number	**Percent**	**Number**	**Percent**
No sequelae	19	29%	15	23%
One type of sequelae	12	18%	28	42%
Two types of sequelae	7	11%	10	15%
Three types of sequelae	9	14%	11	17%
Four types of sequelae	2	3%	2	3%
Five types of sequelae	12	18%	0	0%
Six types of sequelae	4	6%	0	0%
Seven types of sequelae	1	2%	0	0%
Total	**66**	**100%**	**66**	**100%**

Source for clinical assessments: Edmond *et al.* (2010)

Table 10.11: Types of sequelae reported by the caregivers

Type of sequelae	Number of children
No sequelae (child is normal)	19
Single sequelae	
Movement problems	5
Hearing deficit	3
Speech deficit	2
Behavioural problems	2
Multiple sequelae (2)	
Cognitive and behavioural problems	2
Speech and hearing deficits	2
Behavioural problems and hearing deficits	2
Vision and hearing deficits	1
Multiple sequelae (3)	
Movement, vision and hearing deficits	1
Movement, hearing deficit and epilepsy	1
Speech, behavioural problems and hearing deficits	2
Movement, speech deficits and behavioural problems	1
Movement, cognitive and speech deficits	1
Movement, cognitive and behavioural problems	1
Cognitive, speech and behavioural problems	1
Cognitive, behavioural problems and hearing deficits	1
Behavioural problems, vision deficit and epilepsy	1
Multiple sequelae (4)	
Cognitive, speech, vision deficits and behavioural problems	1
Cognitive, speech, behavioural and hearing problems	1
Multiple sequelae (5)	
Cognitive, speech, hearing, behavioural problems and epilepsy	1
Movement, cognitive, speech, behavioural problems and epilepsy	9
Movement, cognitive, speech, behavioural and hearing deficits	2
Multiple sequelae (6)	
Movement, cognitive, speech, behavioural problems, hearing deficits and epilepsy	2
Movement, cognitive, speech, behavioural problems, vision deficits and epilepsy	1
Multiple sequelae (7)	
Movement, cognitive, speech, behavioural problems, vision and hearing deficits and epilepsy	1
Total	**66**

10.2.5.4 Household costs of the meningitis episode

During the acute episode, 70% of the children were taken to at least one other health care provider before being admitted to Albert Royer Hospital. Ten families visited two different providers, two sought help at three places and 32 went to one other provider before coming to the hospital. Forty one percent visited a government health post, 24% a traditional healer, 17% a district government hospital and 10% a private health clinic (Figure 10.2). The mean costs of pre-hospitalisation consultation fees and medication were US$ 68 (range US$ 0 – 649).

The mean length of hospital stay was 22 days, but the distribution was positively skewed, with a few patients staying considerably longer than the others; one patient had a stay of 88 days and another 120 days (Figure 10.3).

Figure 10.2: Health providers visited before taking the child to hospital (n=66)

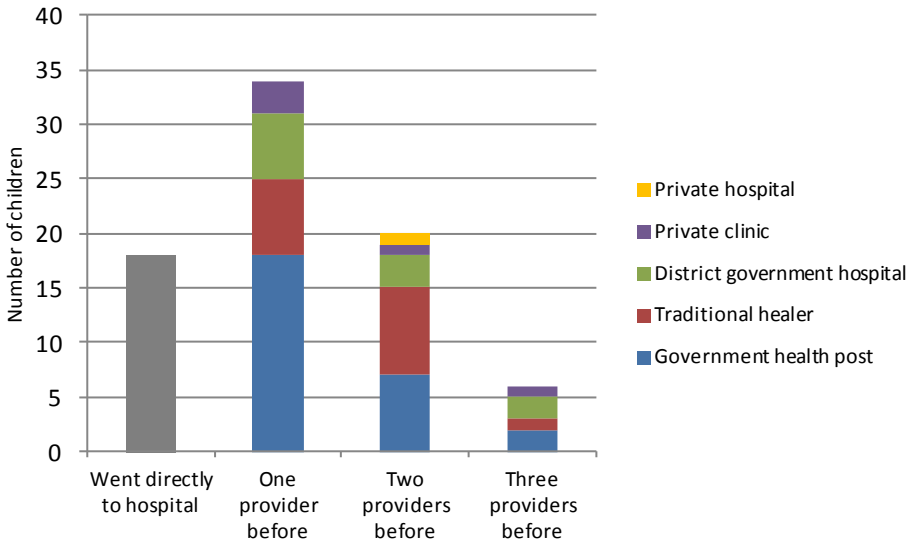
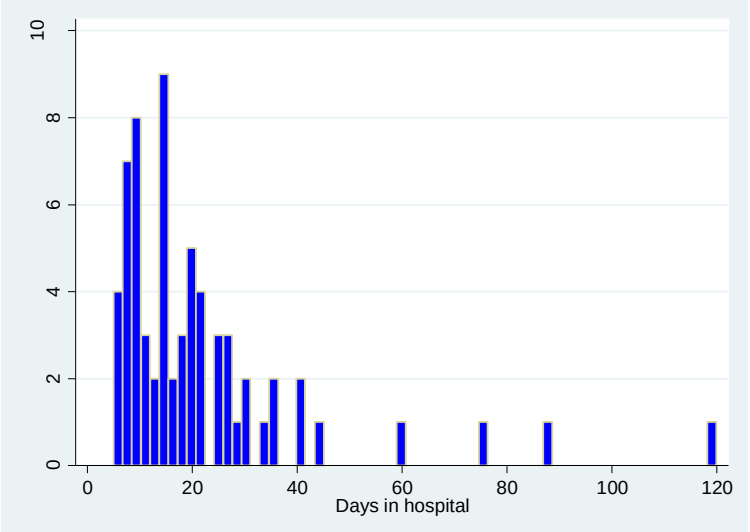


Figure 10.3: Histogram of length of stay in hospital (n=66)



Albert Royer Hospital generates the majority of its income from user fees. During 2011, the charge for one day in the paediatric ward was approximately US$ 27. In addition, patients must pay the full costs of all drugs and diagnostic tests. While social services at the hospital can assist patients who are unable to pay, relatively few families benefit from this due to great administrative complications of applying. Mean household costs of the acute episode were US$ 1,289 per patient (range US$ 207 – 7,076) (Table 10.12 and Figure 10.4). Hospital fees and drugs comprised 71% of total costs, transport 14%, other costs 10% and pre-hospitalization 5%. One child was an outlier with total costs of US$ 7,076. This child was hospitalized with meningitis at the age of 18 months and stayed in hospital for 60 days. Total hospital fees and drugs for treating this child amounted to US$ 5,378, which is over six times more than the mean of US$ 844 for the remaining patients (range US$ 86 – 3,506). Without this child, total mean costs among the children were US$ 1,200 (range US$ 207 – 3,506).

By dividing costs of fees and drugs by the length of stay in hospital, the mean costs per hospitalized day were calculated as US$ 51 (range US$ 1 – 161). Reasons for the large variability in daily treatment costs are that some of the families obtained exemption of their fees through the social service system mentioned above and the purchase of drugs and diagnostic tests varied widely according to disease severity and according to what caregivers could afford to buy.

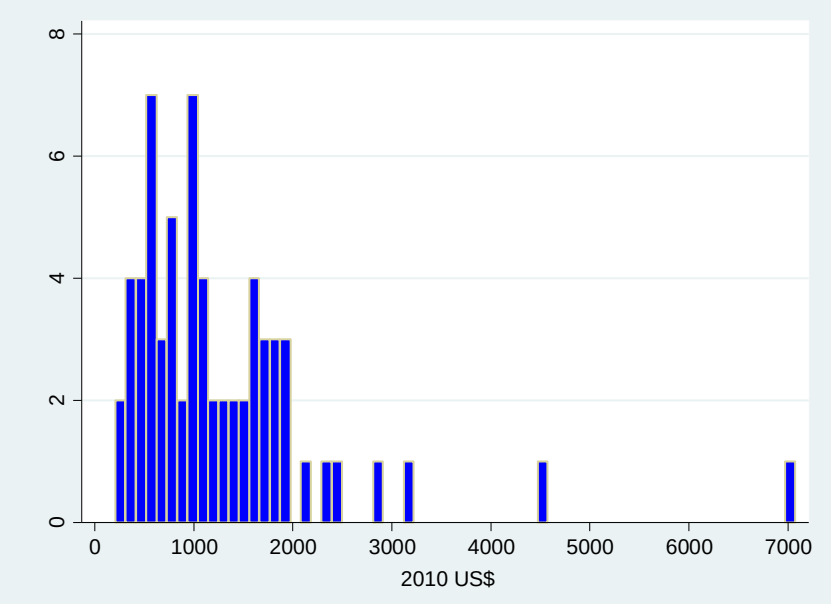
It was apparent from the interviews that the episode had posed an overwhelming financial burden on the families and lack of funds was the primary reason for seeking alternative types of treatment before going to the hospital. Interview quotes on this topic are summarised in Textbox 10.1.

Table 10.12: Household treatment costs of the acute meningitis episode (2010 US$)

Type of expense	No of children	Mean	SD*	95% CI	Minimum cost	Maximum cost
Prior to hospitalisation	66	68	120	0 – 262	0	649
Hospital user fees and drugs	66	913	814	143 – 1,806	86	5,378
Transport costs	66	180	181	23 – 473	0	982
Other costs	66	128	125	16 – 414	0	575
Total costs of acute episode	*66*	*1,289*	*1,047*	*361 – 2,812*	*207*	*7,076*

* SD = standard deviation

Figure 10.4: Histogram of household costs of acute meningitis episode (n=66)



Textbox 10.1: Quotes on the financial burden of direct treatment costs

- "During hospitalization we spent much money because the prescriptions were expensive. The injection was very expensive with the cost of one vial 8,000 CFA (US$ 16). I was obliged to take the heritage of my deceased father, but this was not enough. God assisted us. I borrowed some money from my friend, but I only managed this situation with difficulties because I was unemployed. The hospitalization was a heavy financial charge and now we haven't got the household expenses. I used my only money for the child's treatment".
- "We first thought it was a malaria attack that caused the fracture. We used butter shea in vain during three days for massage. We then brought him to hospital. He spent one month at hospital under drip. He was always sleeping. We bought many medicaments and the prescriptions were very expensive. My parents assisted me to buy the prescriptions and I sold all my possessions".

10.2.5.5 Treatment costs of meningitis sequelae

As described above, 47 of the study children suffered from minor or major sequelae. Ten (21%) of the 47 study children who suffered from sequelae were re-hospitalized after the acute episode. Seven were re-hospitalized once, two children two times and one child three times. Ten of the 14 re-admissions took place at Albert Royer Hospital, three at other public hospitals in Dakar, one at a mission hospital and one at a private hospital. The

average length of stay was 20 days (range 5 - 60 days) and the mean costs per patient amounted to US$ 1,293 (range US$ 105 – 2,572) (Table 10.13).

All the 47 children with sequelae except one had been taken for outpatient consultations. The one child who had not received any follow-up care suffered from hearing, speech, movement, cognitive deficits and behavioural problems. The caregivers reported that they had not taken the child for any consultations because they could not afford the transport expenses. For the remaining 46 children, 88% of the follow-up visits were at specialty outpatient clinics at Albert Royer Hospital. While 21% of these children had attended regular consultations with a physiotherapist or a neurologist during a certain period, all follow-up care had ceased by the time of the interview and only two children had attended an outpatient consultation in the year before the study. The mean number of consultations per child was 2.55 during the same year as the episode, 1.81 one year later, 0.43 two years later, 0.09 three years later, and 0.06 four years later. The mean cost per visit was US$ 27 (range US$ 0 – 72), with transport costs comprising on average 20% (mean transport costs per visit were US$ 7.15 (range US$ 0 - 23)). Mean outpatient costs per child over the study period amounted to US$ 189 (range US$ 5 – US$ 753) among the 46 children receiving consultations (Table 10.13).

Table 10.13: Mean costs of meningitis sequelae among children where expense is reported (2010 US$)

	No of children	Mean	SD*	95% CI	Min	Max
Re-hospitalisation						
Fees of 1st rehospitalisation	10	924	688	70 - 2,271	70	2,271
Fees of 2nd rehospitalisation	3	637	210	401 - 802	401	802
Fees of 3rd rehospitalisation	1	412	-	-	-	-
Re-hospitalisation transport costs	9	152	137	7 - 412	7	412
Total rehospitalisation costs	*10*	*1,293*	*794*	*105 - 2,572*	*105*	*2,572*
Outpatient consultations						
User fees and drug expenses	46	151	141	5 - 115	0	198
Transport costs	46	38	43	14 - 343	0	717
Total outpatient costs	*46*	*189*	*164*	*36 - 503*	*5*	*753*
Childcare and productivity						
Annual childcare costs	12	631	335	226 - 1,073	49	1,480
Annual productivity costs	34	2,206	1,210	173 - 4,934	173	4,934
Total childcare and productivity costs	*38*	*2,173*	*1,375*	*475 - 4,934*	*247*	*5,674*

* SD = standard deviation

10.2.5.6 Unaffordable treatment costs

Thirty nine (83%) of the caregivers of children with meningitis sequelae reported that they knew of treatments which could benefit their child, but they were not accessing these due to inability to pay. These included hearing devices, physiotherapy and speech therapy, but the exact costs were not known by the majority of caregivers. Some responses to this question are summarized in Textbox 10.2.

Textbox 10.2: Information collected about unaffordable treatment costs for meningitis sequelae

- The mother had to stop taking the child for treatment because she could no longer afford paying the consultation fee.
- It happens sometimes that the appointments for treatment are not respected due to financial reasons.
- The mother had to stop visits to Albert Royer Hospital as she no longer had the means. In addition, the mother could not receive the records of the child because she had a debt to the hospital.
- The child needs a thorough examination of the right eye and the right ear, but the mother does not know the costs.
- The child was scheduled for an ear operation because the child has a profound hearing loss, but this operation was not done because it is prohibitively expensive, in the order of millions CFR.
- The grandmother had to stop visiting the physiotherapist because the cost of transport (4,000 CFR (US$ 8)) is very expensive and also very many visits. This means they do not follow the treatment.
- The parents had to stop the appointment at Albert Royer Hospital, as unable to cope with the costs of consultation and transport.
- The child has teething problems, high fever and the hearing is very deficient. The mother cannot estimate the costs.
- They want to buy a device for the ears to obtain a relatively normal hearing, but this costs 815,000 CFR (US$ 1,631).

10.2.5.7 Childcare costs and productivity costs of caregivers

Thirty four percent of the children with sequelae went to school or preschool and the remaining 66% were cared for at home (Table 10.14). For 19 (61%) of the children who did not attend school, parents reported that this was due to meningitis sequelae. Twelve families paid someone to look after the child parts of the day while they were working. Among these families, the costs of childcare per month varied between US$ 4 and US$ 123, with mean monthly costs of US$ 53 (Table 10.13 above).

Thirty four (81%) of the 47 families stated that there was someone in the household who was not able to work because he/she had to care for the child. The reported monthly productivity cost (amount of foregone income) ranged between US$ 14 and US$ 411, with a mean of US$ 184 (Table 10.13). Selected interview responses concerning this issue are included in Textbox 10.3.

Table 10.14: Types of day care of the children with sequelae

Type of day care	Number of children	Percent of all children
School	14	30%
Mother	16	34%
Grandmother	8	17%
Other relative	4	9%
Grandfather	1	2%
Numerous family members	1	2%
Preschool	2	4%
Father	1	2%
Total	**47**	**100%**

Textbox 10.3: Statements made about productivity costs

- If the mother did not look after the child, she would sell at the market.
- The mother would have gone to work and earn a living if she did not have to look after the child.
- His mother would have worked if the child had not been disabled and his father would have worked more.
- If the child had not had meningitis, she could go to school like her brothers. She has language disorders. She has aggressive behaviour if she does not take her medication. Has she not had meningitis, she could have her washed herself.
- We would not have brought the grandmother to take care of the child if she had not had meningitis.
- The child does not speak, does not walk, he cannot even sit down. At the age of eight years he cannot do anything, but is totally dependent. Since the attack of meningitis he is no longer at school.
- If the child was not disabled we would not have to pay someone to look after him and we would save money.

10.2.5.8 Lifetime costs per case of meningitis sequelae

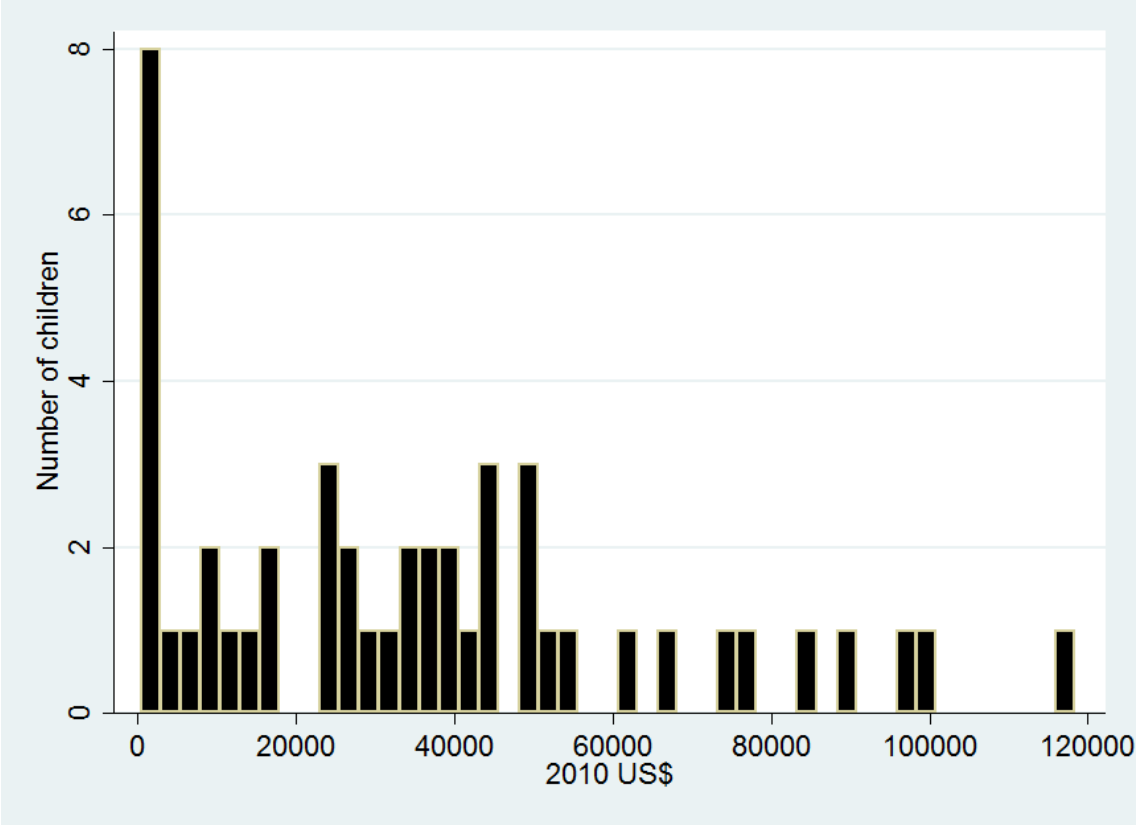
Since none of the children received regular rehabilitation and treatment at the time of the follow-up, no predictions were made for these costs in the base case estimates. When assuming that the costs of childcare and productivity loss last for 30 years, mean discounted lifetime sequelae costs amounted to US$ 34,895 (range US$ 49 – 111,380). Productivity costs comprised 90% of total costs. As seen in the histogram in Figure 10.5, there is high variability in costs between the children, explained by different levels of sequelae severities and socio-economic status of the households. When including costs of the episode, total lifetime costs were US$ 36,336 (Table 10.15).

Table 10.15: Mean discounted lifetime costs per child among all study children with meningitis sequelae (2010 US$)

	No. of children	Mean	SD*	95% CI	Min	Max
Meningitis episode costs	*47*	*1,441*	*1,158*	*435 - 3,165*	*392*	*7,076*
Sequelae costs:						
Re-hospitalization	47	275	640	0 – 1,809	0	2,572
Lifetime outpatient visits	47	185	164	16 – 503	0	753
Lifetime childcare	47	3,158	6,326	0 – 14,506	0	29,012
Lifetime productivity costs	47	31,276	28,033	0 – 96,709	0	96,709
Subtotal: Lifetime sequelae costs	*47*	*34,895*	*29,589*	*67 – 96,755*	*49*	*111,380*
Total lifetime costs	**47**	**36,336**	**30,030**	**775 – 97,387**	**477**	**99,528**

* SD = standard deviation

Figure 10.5: Mean lifetime costs of meningitis sequelae per patient* (n=47)



*Lifetime costs include treatment costs, childcare costs and productivity costs of caregivers

10.2.5.9 In-depth interviews

The transcripts of the three in-depth interviews are included in Annex 9. It is clear from the interviews that the meningitis sequelae have affected the families in an extremely severe way. Their lives with a disabled child are tremendously difficult, both financially and emotionally. It is also apparent that care was sought too late during the acute meningitis episode, increasing the risk of severe sequelae. The main reason for delaying going to the hospital was the expected costs. All three families say that they cannot afford rehabilitation and special schooling for their child.

10.2.6 DISCUSSION

In urban Senegal, the average total lifetime, discounted costs of meningitis sequelae was approximately US$ 35,000 per child. Productivity and childcare costs comprised the majority (98%) of the costs while re-hospitalizations and outpatient consultations accounted for only 2%. Many study families could not afford to seek treatment and no child was receiving any follow-up health care by the time the study was conducted.

The mean cost of an acute meningitis episode of US$ 1,289 (95% CI US$ 361, 2,812) is higher than the results from other low-income countries, but comparable to costs in middle-income countries. As was shown in the literature review in Chapter 5, meningitis treatment costs have been estimated as US$ 211 in Vietnam [136], US$ 434 in Kenya [139], US$ 1,474 in Brazil [132], US$ 4,203 in Uruguay [132] and US$ 5,855 in Chile [132]. While the study from Kenya included household out-of-pocket expenses, the other studies only included government costs, collected retrospectively at hospitals.

According to a 2006 survey of wage rates in Senegal, the average monthly salaries were US$ 457 in the public sector, US$ 419 in the formal sector, and US$ 76 in the informal sector [265]. Only approximately 17% of the labour force is wage earners and 40% of these work in the informal sector [265]. The costs of an acute meningitis episode exceeded the annual income of an informal sector worker by 41% and the mean costs of one outpatient consultation was equivalent to 36% of the monthly salary in the informal sector. The large disparities between disposable income and treatment costs were apparent from the interviews where all caregivers expressed that it had been extremely difficult to pay for the treatment.

In spite of the great financial struggles experienced, the socio-economic indicators of the study households revealed that they on average belonged to the higher economic quintiles in Senegal. According to the 2005 Demographic and Health Survey, 65% of all Senegalese women between 30 and 34 years have no education and for people above six years of age

living in urban and rural areas, 41% and 75% have no schooling, respectively. In Dakar, 1% of adults have an university degree and 2% has secondary school education [277]. In our household sample, only 32% of the primary caregivers had no education, 27% had completed secondary school and 6% had a university degree. Similarly, while 66% of households in all urban areas of Senegal had a septic tank toilet and 80% had electricity [277], the figures for our households were 100% and 94%, respectively. It is highly likely that care received by meningitis patients living in lower socio-economic strata are considerably less than reported in our study population.

According to caregiver responses, 71% of study children suffered from minor or major sequelae. This prevalence is considerably higher than reported by other studies. According to the global meta-analysis on pooled data from 132 follow-up studies of children with bacterial meningitis, the median risk of at least one major or minor sequelea after hospital discharge was 20% (IQR 12 – 35) [235]. However, we also found that the risk varies considerably among geographic regions and country income strata. In the WHO African region the risk was found to be 25.1% with an inter-quartile range of 18.9% - 32.0%. There are several explanations for the higher prevalence rates found in the Senegal study. First, an all-inclusive definition of sequelae was used; focus was not only one type of sequelae, and both minor and major sequelae were included. Secondly, the study had relatively low loss to follow-up of only 9%. Thirdly, because children were identified from a tertiary university teaching hospital, there may be selection bias towards more severe patients, as they would be referred to this hospital rather than treated at lower level facilities. Lastly, and perhaps most importantly, there was substantial evidence that families delayed seeking treatment for financial reasons, which lead to an increased risk of developing sequelae [234].

The study has a number of limitations. First, there is risk of recall bias for the acute episode cost estimates because these were solely based on historical information collected from caregiver interviews. It was however striking that most of the families clearly remembered the costs of treatment, even though the episode had happened on average five years and five months earlier. During the interviews it became clear that the costs of treatment had been a major financial burden and most families were therefore able to specify the costs in detail. In several cases receipts from the hospital had been kept, which were shown to the research staff during the interview. A second limitation is that productivity costs were estimated according to what caregivers envisioned they would be able to earn if they did not have to care for the child, but it is not possible to know to what extent this amount reflects reality. The uncertainty with this estimate is exposed by a

relatively wide range of answers among the 34 respondents, varying from US$ 14 to US$ 411 per month, with a mean of US$ 184. This amount is more than twice the 2006 average monthly salary in the informal sector [265]. Lastly, as with all predictions, the lifetime cost estimates are surrounded by considerable uncertainty. It was assumed that disabled children have an average life expectancy of 30 years, but this is a tentative assumption and it is similarly uncertain to what extent costs stay constant in future years.

This is the first study from a low-income country on the costs of treating and caring for children with disabilities. Productivity costs were calculated by collecting data directly from families on estimated income forgone. This is a relevant alternative to the human capital or the friction cost approach, which are the traditional methods used for placing a monetary value on time in high-income countries with well-functioning labour markets [263]. The study has important implications for future economic evaluations of interventions for prevention and treatment of disability in children. Other vaccines protecting against life-long disabilities are polio, rubella, pneumococcal and meningococcal vaccines. It was shown that the lifetime costs of meningitis sequelae are approximately 26 times higher than the mean cost of treating an acute meningitis episode, so economic evaluations of vaccines against bacterial meningitis underestimate the cost-effectiveness substantially if only treatment costs of the acute episode are included. However, more research is needed on the most appropriate methods for determining productivity costs in societies with a large informal labour market.

10.3 Conclusion

This chapter was divided into two parts. In the first part, access to care, health care utilization and mean treatment costs of Hib disease were estimated for Belarus, India and Uzbekistan. It was shown that a considerable proportion of children in India and Uzbekistan have no access to health care, emphasising the importance of including this parameter in the decision-analytic model. Moreover, since a relatively large proportion of health expenditures are financed directly by households in India and Uzbekistan, it is crucial to divide treatment costs into government and household perspectives.

The study from Senegal is the first in which household costs of meningitis sequelae has been quantified for a low-income country. The study demonstrated that these costs are substantial and therefore important to include in economic evaluations of vaccines that prevent bacterial meningitis. However, since children have limited access to health care and there is a large informal economic sector in low-income countries, the methods for valuing costs of meningitis sequelae are not straight forward and the study showed large variability in costs between households with disabled children.

The type of data collected in the study from Senegal is not available in any of the three study countries and it is not known how well the results from Senegal reflect the realities in Belarus, India and Uzbekistan. Due to the lack of data, the costs of sequelae are excluded from the base case in the economic evaluations presented in Chapter 12. However, the Senegal results, in terms of mean lifetime costs per meningitis sequelae case, are used in sensitivity analysis for all three countries.

Parameter values estimated in the present chapter for use in the economic evaluation are summarised in Table 10.16.

Table 10.16: Parameter values for health care utilization and treatment costs used in the economic evaluation

Parameter	Belarus	India	Uzbekistan
No. of outpatient visits per case			
Severe Hib pneumonia	3.0	1.42	1.36
Non-severe Hib pneumonia	1.0	0.71	0.68
Hib meningitis	7.0	1.42	1.36
Hib NPNM	3.0	1.42	1.36
No. of inpatient admissions per case			
Hib pneumonia	1.0	0.71	0.68
Hib meningitis	2.6	0.71	0.68
Hib NPNM	1.0	0.71	0.68
Distribution of outpatient visits (%)			
Government clinic	100%	16%	100%
Private clinic	0%	61%	0%
Private outpatient department	0%	5%	0%
Traditional healer	0%	9%	0%
Pharmacy	0%	10%	0%
Distribution of inpatient admissions (%)			
Pneumonia/NPNM			
Primary government hospital	76%	27%	66%
Secondary government hospital	20%	30%	31%
Tertiary government hospital	4%	2%	3%
Private hospital	0%	41%	0%
Meningitis			
Primary government hospital	0%	27%	64%
Secondary government hospital	80%	30%	32%
Tertiary government hospital	20%	2%	4%
Private hospital	0%	41%	0%
Government costs per outpatient visit (US$)	9.31	1.53	2.88
Household costs per outpatient visit (US$)			
Government clinic	NA	12	5
Private clinic	NA	11	NA
Private outpatient department	NA	11	NA
Traditional healer	NA	6	NA
Pharmacy	NA	1	NA

Parameter	Belarus	India	Uzbekistan
Government costs per inpatient admission (US$)			
Pneumonia/NPNM:			
Primary government hospital	413	97	152
Secondary government hospital	448	101	171
Tertiary government hospital	542	224	190
Meningitis:			
Primary government hospital	NA	164	169
Secondary government hospital	1,567	172	188
Tertiary government hospital	1,959	380	242
Household costs per inpatient admission (US$)			
Pneumonia/NPNM:			
Primary government hospital	NA	50	26
Secondary government hospital	NA	50	26
Tertiary government hospital	NA	50	26
Private hospital	NA	149	NA
Meningitis:			
Primary government hospital	NA	81	50
Secondary government hospital	NA	81	50
Tertiary government hospital	NA	81	50
Private hospital	NA	241	NA
Discounted lifetime meningitis sequelae costs*	38,344	38,344	38,344

*Only used in uncertainty analysis as this is the estimate from Senegal

11 COSTS OF HIB VACCINE INTRODUCTION

In this chapter, issues concerning Hib vaccine prices as well as systems costs of introducing the vaccine are addressed. As mentioned in Chapter 3, the relatively high price of Hib vaccine has been one of the main reasons for slow introduction of the vaccine in low- and middle-income countries. Hence, any economic analysis of the vaccine must address the important issue of price. While almost all GAVI eligible countries have now introduced the vaccine, the price is a cause of concern for ensuring financial sustainability when GAVI's support comes to an end [278, 279].

Other resource items than the vaccine, such as training, social mobilisation and cold chain expansion, must also be accounted for when estimating the costs of Hib vaccine introduction. These non-vaccine costs are often referred to as "system costs" [280]. During the early years of GAVI Alliance support, beginning in the year 2000, countries received a one-off "vaccine introduction grant" of US$ 100,000 to cover system costs related to new vaccine introduction [281]. The sum of US$ 100,000 was not based on an objective measurement of these costs and it was later acknowledged to be an insufficient amount for larger countries and to have caused inequities between countries with different sized birth cohorts [282]. During GAVI phase II (2006-2015) the support was changed to a minimum of US$ 100,000 or up to a maximum of US$ 0.30 per infant in the birth cohort of the year of introduction [283]. The amount of US$ 0.30 was based on an estimate of the median funding per infant in the countries that had received the vaccine introduction grant of US$100,000 during GAVI phase I [282]. Hence, the sum was not based on an estimate of the actual costs related to new vaccine introduction, but was guided by the original grant of US$ 100,000. During 2012 GAVI is re-assessing the size of the introduction grant and as is referred to in this chapter, the work I have done as part of this thesis is being used to guide this policy change.

The chapter is divided into four sections. Determinants of Hib vaccine prices are discussed in section 11.1, the incremental costs of introducing Hib vaccine in the three study countries are estimated in section 11.2, a case study from Ethiopia on system costs of introducing Hib vaccine is the topic of section 11.3, and conclusions are summarised in section 11.4.

11.1 DETERMINANTS OF HIB VACCINE PRICES

In this section vaccine markets, procurement mechanisms, and Hib vaccine price trends are described. These issues are important for understanding the assumptions made when Hib vaccine introduction costs are estimated for the three study countries in section 11.2.

11.1.1 VACCINE MANUFACTURERS

In market terms the value of vaccines is small in comparison to other pharmaceuticals. In 2010, vaccines represented no more than around 3% of the global pharmaceutical market [284]. However, the market has recently grown rapidly due to developments of new and more expensive vaccines, in particular the pneumococcal and the human papilloma virus vaccines [285]. According to a recent study on vaccine access, research and development (R&D), global vaccine sales were expected to increase from around US$ 20.5 billion in 2008 to US$ 34 billion by 2012 [284]. Sales in low- and middle-income countries were estimated at about $1.6 billion in 2008, or less than 10% of the total.

Vaccine manufacturers are conventionally divided into two groups; the established multinational firms based in the USA and Europe, and the "emerging suppliers" situated in low- and middle-income countries. The multinational firms have over the years become increasingly concentrated due to frequent mergers. The top five multinational firms, GlaxoSmithKline (GSK), Merck, Sanofi-Pasteur, Pfizer and Novartis, accounted for approximately 85% of global vaccine sales in 2008 [286]. Their share of the market is however much lower in volume terms because the emerging suppliers produce large volumes of cheaper vaccines. Important emerging supplies that export vaccines are based in India, Indonesia and Brazil [287]. Traditionally, multinational companies have been responsible for most vaccine innovation. Their business model depends on charging high prices for new vaccines in order to recover R&D costs and return large profits to their investors. The emerging suppliers have traditionally sold older, less complex vaccines in high-volume, low-margin markets [284].

11.1.2 VACCINE PROCUREMENT IN LOW- AND MIDDLE-INCOME COUNTRIES

PAHO and Unicef operate pooled procurement mechanisms for low- and middle-income countries. The objectives are to ensure better and more efficient national planning, to avoid disruptions in vaccine supply, to allow purchase of vaccines in local currencies, to obtain lower prices by consolidating vaccine orders for economies of scale, and to assure vaccine quality [288]. All GAVI supported vaccines are procured either through Unicef's supply division or PAHO's revolving fund.

The Unicef supply division purchases vaccines on behalf of 80-100 countries annually using funds from GAVI, NGOs, foundations, international financial institutions, and the countries themselves [288]. Unicef procures approximately 40% of global vaccine doses, but this only account for approximately 5% of the global market value because vaccines are considerably more expensive in high-income countries [289]. PAHO's revolving fund is similarly a pooled procurement mechanism, but only available for countries in the region of the Americas. The revolving fund played an important role in facilitating early adoption of Hib vaccine in PAHO countries [290].

Unicef and PAHO only procure vaccines that have been prequalified by the WHO. The purpose of the WHO prequalification assessment is to provide assurance that candidate vaccines meet recommendations on quality, safety and efficacy and with regard to operational specifications for packaging and presentation [291]. Unicef procures vaccines from five emerging market countries; Brazil, Cuba, India, Indonesia, and Senegal. During 2006, these together accounted for about 36% of the total procurement value, but India was by far the largest supplying country, representing about 34% of Unicef's total supply in value terms [292].

11.1.3 VACCINE MARKETS AND PRICE SETTING

In high-income countries, vaccine prices are largely determined by profit maximization of the multinational firms. R&D and production costs are generally not taken into account in the price-setting strategies for recently licensed vaccines [284]. However, the marginal costs of production set a floor for the lowest price level and are an important determinant of price in mature, competitive markets. However, production costs vary considerably among classes of vaccines, according to production volume and by site of production. Emerging suppliers have only significant cost advantages for certain vaccine types [291].

Four features of vaccine markets influence prices in low-income countries so that these are not only determined by demand and supply. First, markets for new vaccines tend to be controlled by one or at most two manufacturers for extended periods. This is due to the small number of innovative multinational firms, the large economies of scale in vaccine production and patent protection. This lack of competition gives originating firms substantial freedom to set prices. Secondly, the Unicef and PAHO procurement mechanisms lead to market concentration. Third, "tiered pricing", or market segmentation by country income groups, is increasingly standard. Fourth, the large fixed costs and long lead times required to build new manufacturing plants mean that predictability of demand

is very important to manufacturers, who will offer lower prices in return for long-term commitments [284].

11.1.4 HIB VACCINE FORMULATIONS AND PRICE TRENDS

11.1.4.1 Types of Hib vaccines

There are several different types of Hib vaccine formulations available. Hib can be delivered as a monovalent vaccine or as a combination vaccine with several other antigens. Since Hib vaccine is delivered at the same time as diphtheria-tetanus-pertussis (DTP) vaccine, combination vaccines are widely used as these are normally preferred by both health care workers and parents because they reduce the number of injections needed.

A total of 23 Hib containing vaccines were prequalified by the WHO as of November 2011, as summarised in Table 11.1. Seven of these were monovalent Hib vaccines and another seven were DTwP-Hib combination vaccines. However, only few of the countries procuring through Unicef are using these formulations. As seen in Table 11.2, Unicef only procured around 600,000 doses of monovalent Hib vaccine and 22.2 million doses of DTwP-Hib vaccine between 2001 and 2010. On the other hand, a total of 412.2 million doses of the DTwP-HepB-Hib combined vaccine, also known as the "pentavalent" vaccine, were procured during the same period. The pentavalent vaccine is the product of choice for all GAVI supported countries.

Eleven different formulations of pentavalent vaccines were pre-qualified in November 2011. Six of these were from the Serum Institute of India (SII), two from Biologocal E. in India, two from GSK and one from Crucell. As seen in Table 11.1, the Indian companies only obtained prequalification during 2010 and 2011. The GSK vaccine, which originally was produced by Smith Kline Beecham, was first prequalified in 2000 and was the only available pentavalent vaccine on the market until Crucell obtained prequalification in 2006 [293]. During the early years of GAVI Smith Kline Beecham had monopoly of the pentavalent vaccine, which led to relatively frequent supply shortfalls and also limited the possibility of a price reduction.

The packed volume per dose varies from 2.6 cm^3 for the ten dose SII pentavalent vaccine to 58.7 cm^3 for the lyophilised pentavalent vaccine in a single dose vial produced by Biological E (Table 11.1). The packed volume per dose is an important factor when assessing whether the available cold storage capacity can accommodate introduction of the vaccine, as is shown in the Ethiopian case study later in this chapter.

Table 11.1: WHO prequalified Hib vaccines

Vaccine type	Manufacturer	Country	Date of WHO prequa-lification	Form	Vial size	Packed volume per dose (cm^3)
Hib	Novartis	Italy	Aug 1997	Liquid	10	2.50
Hib	Novartis	Italy	Aug 1997	Liquid	1	13.4
Hib	GlaxoSmithKline	Belgium	Oct 1998	Lyophilised	2	6
Hib	GlaxoSmithKline	Belgium	Oct 1998	Lyophilised	10	2.50
Hib	GlaxoSmithKline	Belgium	Oct 1998	Lyophilised	1	13
Hib	Merck	USA	Feb 2003	Liquid	1	15
Hib	Center for Genetic Engineering and Biotechnology	Cuba	Apr 2010	Liquid	1	5
DTwP-Hib	Novartis	Italy	Jul 2002	Liquid	1	45
DTwP-Hib	Novartis	Italy	Jul 2002	Liquid	10	12
DTwP-Hib	Sanofi Pasteur	France	May 2003	Liquid + lyophilized	10	12.39
DTwP-Hib	Sanofi Pasteur	France	May 2003	Liquid + lyophilized	1	44.72
DTwP-Hib	Serum Institute of India Ltd	India	Jun 2010	Liquid + lyophilized	1	39.2
DTwP-HepB-Hib	Crucell Korea	Republic of Korea	Sep 2006	Liquid	1	12.84
DTwP-HepB-Hib	GlaxoSmithKline	Belgium	May 2000	Liquid + lyophilized	2	11
DTwP-HepB-Hib	GlaxoSmithKline	Belgium	May 2000	Liquid + lyophilized	1	22
DTwP-HepB-Hib	Biological E	India	Aug 2011	Liquid + lyophilized	1	58.7
DTwP-HepB-Hib	Biological E	India	Aug 2011	Liquid + lyophilized	10	7.5
DTwP-HepB-Hib	Serum Institute of India	India	May 2010	Liquid + lyophilized	1	39.2
DTwP-HepB-Hib	Serum Institute of India	India	May 2010	Liquid + lyophilized	2	19.6
DTwP-HepB-Hib	Serum Institute of India	India	May 2010	Liquid + lyophilized	10	5.1
DTwP-HepB-Hib	Serum Institute of India	India	Sep 2010	Liquid	1	26.1
DTwP-HepB-Hib	Serum Institute of India	India	Sep 2010	Liquid	2	13.1
DTwP-HepB-Hib	Serum Institute of India	India	Sep 2010	Liquid	10	4.4

Source: http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html
DTwP: Diphteria-tetanus-wholecell pertussis

Table 11.2: Doses of Hib vaccines bought by Unicef 2001 – 2010 (US$ millions)

Vaccine	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Hib	0.1	0.1	0	0	0	0	0.1	0.1	0.1	0.1
DTP-Hib	0.3	3.9	2.1	0.4	1.4	2.9	2.9	1.9	2.7	3.7
DTP-HepB-Hib	14.5	8.7	16	15	21.1	21.1	39.7	71.7	106.9	97.5

Source: www.unicef.org/supply/files/Table_of_total_Doses_of_Vaccines_bought_1996-2010.pdf

Lyophilized vaccines are freeze-dried powders, which must be mixed with a liquid (called a diluent) in a process known as "reconstitution" before they can be administered. A diluent can either be sterile water or a liquid vaccine, such as DTwP. Since reconstitution is known to cause errors in vaccine preparation, especially in developing countries, a fully liquid formulation is normally considered more convenient to use [294]. Hence, when the fully liquid vaccine produced by Crucell came on the market, several countries requested to switch to this one instead of using the GSK lyophilised pentavalent vaccine. The new liquid SII pentavalent vaccine in a ten dose vial has similarly become popular among GAVI countries because it takes up less space in the cold chain compared to the two- or single dose vial vaccines. At least half of the GAVI supported countries switched to this formulation during 2011/2012.

11.1.4.2 Trends in Unicef pentavalent vaccine prices

When GAVI was established in 1999 and Hib vaccine offered to countries it was expected that the increase in global demand and supply of the vaccine would lead to a price decrease, which would enable countries to pay for the vaccine with their own funds after the initial five years of support [278]. However, as seen in Table 11.3, there was no lasting decrease in the Unicef Hib vaccine price during 2001 – 2009. It was not until 2010 when the SII vaccine was prequalified that GSK and Crucell decided to offer a lower price, and when SII launched the liquid pentavalent vaccine in a ten dose vial in 2011 it was procured by Unicef for only US$ 1.75 per dose. This is a 50% price reduction compared to the previous decade. However, vaccine wastage is higher with larger vial sizes and this need to be factored into the total incremental cost estimates.

Due to the slow price decrease, GAVI's initial five-year support was extended for at least a further five years in most receiving countries [278]. GAVI introduced co-financing in 2007 and all countries are now contributing at least US$ 0.20 per dose of vaccine. GAVI's revised co-financing policy as of November 2011 is outlined in Textbox 11.1.

Table 11.3: Unicef pentavalent vaccine prices per dose (US$)

Formulation	Supplier	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
1 dose liquid	Crucell						3.63	3.75	3.60	3.60	3.20	3.00
1 dose liquid	SII											2.50
2 dose lyophilised	SII										2.25	2.25
2 dose lyophilised	GSK	3.50	3.25	3.10	3.65	3.60	3.60	3.50	3.50	3.50	2.95	2.95
10 dose liquid	SII											1.75

Source: http://www.unicef.org/supply/files/12_01_13_DTP-HepB-Hib.pdf

Textbox 11.1: GAVI's co-financing policy (as of November 2011)

- **Low Income group**: Countries with GNI per capita at or below the World Bank low-income threshold. Co-financing obligation in 2012 and thereafter: US$ 0.20 per dose.
- **Intermediate group**: Countries with GNI per capita above the World Bank low-income threshold, but below the GAVI eligibility threshold of GNI per capita below or equal to US$ 1,520. Co-financing level in 2012: US$ 0.20 per dose, or the amount per dose paid in 2011, whichever is higher. Thereafter, the co-financing amount per dose increases by 15% each year. For any new vaccine adoptions, the co-financing amount would start at US$ 0.20 per dose and increase by 15% annually. When countries transition from low-income to the intermediate group, they would start at US$ 0.20 per dose, followed by 15% annual increases.
- **Graduating group**: Countries with GNI per capita above the GAVI eligibility threshold who are still receiving GAVI support. Co-financing shall increase over four years from rates paid in 2011 in order to reach 100% of the vaccine price in 2016, the year

Source: http://www.gavialliance.org/about/governance/programme-policies/co-financing

11.2 INCREMENTAL COSTS OF HIB VACCINE INTRODUCTION IN BELARUS, INDIA AND UZBEKISTAN

11.2.1 BACKGROUND

Among the three study countries, Hib vaccine has only been introduced nationwide in Uzbekistan as of early 2012. In Belarus, the vaccine is solely offered to children in Minsk city and in India it is only included in the states of Tamil Nadu and Kerala. Hence, when estimating the incremental costs, actual expenditures are calculated for Uzbekistan, but the national estimates for Belarus and India are predictions.

The national vaccination schedules of the three countries vary considerably (Table 11.4). The Indian routine schedule is one of the most basic in the world. The only new vaccine included in the Indian programme in 2011 the last few years. Belarus and Uzbekistan have introduced the MMR vaccine, and Belarus uses IPV as well as OPV, while OPV is solely used in India and Uzbekistan.

The government of Uzbekistan applied to GAVI for pentavalent vaccine in 2007 when the support for hepatitis B vaccine, which Uzbekistan had received since 2001, came to an end. Uzbekistan was approved for pentavalent vaccine in 2007, but due to delays in transfer of the vaccine introduction grant, the vaccine was only introduced in March 2009.

Table 11.4: National vaccination schedules in the three study countries

Vaccine	Belarus	India	Uzbekistan
BCG	3 days	Birth	Birth
OPV	18 and 24 months	Birth, 6, 10 and 14 weeks	3 days, 2, 3 and 4 months , 7 years
Hepatitis B	Birth, 1 and 5 months	Birth, 6, 10 and 14 weeks	Birth
DTwP	3, 4, 5 and 18 months	6, 10, 14 weeks and 16 months	-
DTwP-HepB-Hib	-	-	2, 3 and 4 months
Measles	-	9 months	-
IPV	2, 4 and 5 months	-	-
MMR	1 year	-	1 and 6 years

BCG: Bacille Calmette Guérin vaccine
OPV: Oral polio vaccine
HepB: Hepatitis B vaccine
DTwP: Diphtheria-Tetanus-wholecell pertussis combined vaccine
IPV: Injectable polio vaccine
MMR: Measles-Mumps-Rubella combined vaccine

Uzbekistan uses the Crucell liquid pentavalent vaccine in a single dose vial. Before introduction of pentavalent vaccine, children in Uzbekistan were given four doses of DTwP at 2, 3, 4 and 16 months and three doses of Hepatitis B vaccine at birth, 2 and 6 months. In the new schedule, the hepatitis B birth dose and the DTP booster dose were maintained. The country has been approved for a second period of pentavalent vaccine support, lasting until 2015. The government procures BCG, DTP, OPV, hepatitis B birth dose and MMR vaccines through Unicef with domestic funds.

In Belarus, vaccines for the childhood immunization programme are procured from the national health budget, but Minsk city has chosen to add hepatitis A and Hib vaccines to its schedule using funds from the municipal budget. Hib vaccination was introduced in Minsk city in 2007 for those at 'high risk', i.e. children who are HIV positive, asthmatic or living in orphanages. In 2008 the programme was expanded to include all children in Minsk city, which covers approximately 20% of the population. A ministerial order dictates a four-dose Hib vaccine schedule, following a WHO recommendation of a booster dose in countries where Hib disease frequently occurs in children above 18 months of age [295]. In Minsk City, the schedule is 3, 4, 5 and 18 months, and a combined DTwP-Hib vaccine produced by Sanofi Pasteur in a single dose vial is used.

In India, Hib vaccine was introduced with GAVI support in the states of Tamil Nadu and Kerala during December 2011. These are two high performing states, which cover about 10% of children less than five years in the country. It is anticipated that the vaccine will eventually be expanded to the remaining states, but several challenges have contributed to slow implementation in India. In July 2005, the Hib Initiative started a Hib disease surveillance study, which should lay the groundwork for a large Hib vaccine probe study [253]. However, following the publication of a 2006 WHO position paper recommending global introduction of Hib vaccines "even in countries where local disease burden could not be established"[295], plans for this trial were abandoned due to ethical concerns. In June 2008, the Indian National Technical Advisory Group on Immunization (NTAGI) recommended immediate introduction of Hib vaccination in all states [296]. However, several changes in leadership occurred within the Ministry of Health and Family Welfare and this caused delays. Furthermore, in December 2009, a public interest litigation was filed in Delhi high court by seven public health figures to highlight "how irrational vaccines are being introduced in the public health system by the government, under the influence of vaccine manufacturers and international agencies" [297]. Specifically, the petitioners argued that new vaccines against hepatitis B, Hib and pneumococcal are being introduced without proper epidemiological and clinical studies, while at the same time, basic more

affordable vaccines such as DTP and measles are not being made available to half the children of India [298]. The non-completion of the probe study has inevitably led to uncertainty about the true impact of Hib vaccination in India and doubts about the value of the vaccine are apparent among many stakeholders [299]. The states of Tamil Nadu and Kerala introduced the SII pentavalent vaccine in a 10-dose vial. The Indian government has decided to procure through Unicef instead of buying the vaccine directly from SII.

11.2.2 METHODS

11.2.2.1 Vaccine and injection equipment costs

Incremental vaccine and injection equipment costs were estimated as the difference between the former routine vaccination schedule and a schedule with Hib vaccine. Since all three countries use a Hib combination vaccine, the incremental costs were estimated as the difference between a schedule with the combination vaccine and a schedule without the Hib vaccine component, but the other antigens in the combination vaccine included. Hence, only the Hib vaccine part of the combination vaccine was included in the incremental costs.

Total annual vaccine costs (TC) were estimated according to WHO guidelines as [300]:

$$TC = p \times b \times c \times d \times w$$

where,
p = costs per vaccine dose (including freight expenses)
b = target population
c = predicted vaccination coverage rate of the first dose
d = number of doses per child
w = predicted wastage factor

This formula is also being used in the GAVI application form when countries estimate their annual vaccine needs [301].

Vaccine wastage depends on the number of doses in a vial, whether or not the country in question has an effective open vial policy, the sizes of immunization sessions, any cold chain and distribution failures, and the number of vials discarded due to expiry. The wastage factor is calculated from a percentage wastage rate, r, as [300]:
w = 100 – (100/r).

Since the first dose of Hib vaccine is delivered to children after the neonatal period, the number of surviving infants in each country was used as the target population. These are seen in Table 11.5, along with the vaccine coverage estimates used.

Vaccine and injection equipment prices and wastage rates were collected from vaccine programme managers in the three countries. As seen in Table 11.6, traditional vaccine prices are substantially lower in India than in the two other countries due to the local vaccine manufacturing. In Belarus, Minsk City procures the DTwP-Hib vaccine from Sanofi Pasteur at US$ 4.95 per dose and this price was assumed for the national analysis (Table 11.6). In India and Uzbekistan, Unicef vaccine prices were used. In 2011 Unicef procured the liquid pentavalent vaccine in a single dose and ten dose vials for US$ 3.00 and US$ 1.75 per dose, respectively.

Price per injection syringe were US$ 0.09 in Belarus, US$ 0.06 in India and US$ 0.06 in Uzbekistan. The costs of safety boxes were included in the India and Uzbekistan analysis as these are supplied with GAVI vaccines, but safety boxes were not used in Belarus. The Unicef price was US$ 1.50 per box with capacity of 100 used syringes.

Table 11.5: Target population and coverage rates used for estimating vaccine needs

Parameter	Belarus	India	Uzbekistan
2010 birth cohort	94,200	26,542,850	558,459
Infant mortality per 1,000 live births	9	51	47
Surviving infants	93,352	25,082,993	558,174
2010 DTP1 coverage rate:	97%	83%	98%

Sources: UN Populations Division [302] and WHO/Unicef [303]

11.2.2.2 System costs due to Hib vaccine introduction

In all three countries, vaccine programme staff were interviewed to determine system costs related to introducing the vaccine. In Belarus and Uzbekistan, it was revealed that even though vaccine volume had increased, existing cold chain capacities were sufficient with no additional investments required. Since the ten dose vial is being used in India, there is a reduction in storage volume needed as the volume per dose of this vaccine (4.4 cm^3) is less that the volume needed for the DTP and hepatitis B vaccines previously used (3.0 cm^3 + 4.0 cm^3 = 9.0 cm^3).

In Uzbekistan, a GAVI introduction grant of US$ 100,000 was used for staff training and social mobilization and these costs were included in the analysis. India has negotiated an exceptional agreement with GAVI so that they do not co-finance the usual US$ 0.20 per dose, but in return they did not receive the vaccine introduction grant of US$ 0.30 per child in the birth cohort.

Table 11.6: Vaccine prices and wastage rates in the three study countries

	Belarus			Uzbekistan			India		
Antigen	**Vial size**	**Price per dose (US$)**	**Vaccine wastage rate**	**Vial size**	**Price per dose (US$)**	**Vaccine wastage rate**	**Vial size**	**Price per dose (US$)**	**Vaccine wastage rate**
BCG	10	0.06	62%	10	0.05	50%	10	0.04	61%
Hepatitis B birth dose	1	1.20	0%	1	0.44	33%	-	-	-
Hepatitis B	10	0.63	6%	10	0.34	33%	10	0.11	33%
DTwP	2	0.15	14%	10	0.33	33%	10	0.04	27%
MMR	1	2.68	0%	10	1.36	33%	-	-	-
Measles	-	-	-	-	-	-	5	0.20	35%
OPV	10	0.35	20%	10	0.31	33%	20	0.08	47%
IPV	1	5.10	0%	-	-	-	-	-	-
DTwP-Hib	1	4.95	0%	-	-	-	-	-	-
DTwP-HepB-Hib	-	-	-	1	3.00	5%	10	1.75	27%

11.2.3 RESULTS

The incremental cost estimates are seen in Table 11.7. Without Hib vaccine, costs of vaccines and injection supplies per fully vaccinated child amounted to approximately US$ 23 in Belarus, US$ 8 in Uzbekistan and US$ 2 in India. Introduction of Hib vaccine increased annual vaccine costs by 84% in Belarus, 101% in Uzbekistan and 302% in India, leading to costs per fully vaccinated child of US$ 42, US$ 16 and US$ 9, respectively.

In India and Uzbekistan, injection supply costs decreased by 33% and 29%, respectively, because less syringes and safety boxes were needed for the pentavalent vaccine compared to delivering DTP and hepatitis B vaccines separately. In Belarus, syringe costs increased by 12% because the DTwP-Hib vaccine is lyophilised and therefore needs reconstitution syringes, which is not the case for the DTP vaccine. However, incremental injection supply costs comprised only 1% of total incremental costs in Belarus.

According to the GAVI co-financing policy, India and Uzbekistan should pay US$ 0.20 per dose of pentavalent vaccine. However, as mentioned above India has been exempted from this condition because they requested not to receive the vaccine introduction grant. In Uzbekistan, co-financing payments amounted to US$ 2.9 million in 2010.

11.2.4 DISCUSSION

Hib vaccine is substantially more expensive than the six, traditional vaccines and also the hepatitis B vaccine. Hepatitis B vaccine has experienced marked price reductions since it was first developed in 1981 and Unicef now procures this vaccine for US$ 0.18 per dose [304]. Introduction of Hib vaccine caused approximately a doubling of the vaccine budget in Belarus and Uzbekistan and a quadruple increase in India. The relative increase was less in Belarus and Uzbekistan because these countries already use some new, more expensive vaccines. Both countries have introduced MMR vaccine and IPV is used in Belarus.

Even though the new SII pentavalent vaccine in a ten-dose vial is considerably cheaper than the other pentavalent formulations, the overall budget increase can seem insurmountable in India. However, the main reason for the large budget impact in India is that the vaccine schedule in this country is still only very basic and the traditional vaccines are locally manufactured and therefore procured at a relatively cheap price. The vaccine costs per infant in the birth cohort of the current Indian vaccination schedule is only US$ 1.6, which is a low amount compared to other countries. An analysis of national immunization budgets and financing sources of 50 GAVI eligible countries during 2008-2010 showed that governments on average spend US$ 7.9 per infant in the birth cohort

Table 11.7: Vaccine and syringe costs with and without Hib vaccine (2010 US$)

		Belarus				Uzbekistan				India			
	Antigen	**Doses in schedule**	**Vaccine costs**	**Injection supply costs**	**Total costs**	**Doses in schedule**	**Vaccine costs**	**Injection supply costs**	**Total costs**	**Doses in schedule**	**Vaccine costs**	**Injection supply costs**	**Total costs**
Without Hib vaccine	BCG	1	14,231	9,572	23,802	1	49,928	56,931	106,859	1	2,565,849	2,137,351	4,703,199
	Hepatitis B	3	184,284	26,049	210,333	4	694,253	189,769	884,023	3	9,854,186	3,594,400	13,448,586
	DTP	4	63,945	34,732	98,677	4	588,462	189,769	778,232	3	2,977,936	3,594,400	6,572,336
	MMR	1	245,634	12,060	257,694	1	1,121,184	54,523	1,175,707	0	-	-	-
	Measles	0	-	-	-	0	-	-	-	1	7,603,174	1,467,332	9,070,505
	OPV	2	72,178	-	72,178	5	1,264,578	-	1,264,578	4	8,272,044	-	8,272,044
	IPV	3	1,402,315	26,049	1,428,364	0	-	-	-	0	-	-	-
	Total w/o Hib vaccine		*1,982,586*	*108,462*	*2,091,049*		*3,718,406*	*490,993*	*4,209,399*		*31,273,189*	*10,793,483*	*42,066,671*
	Costs per FVC w/o Hib		*21.85*	*1.20*	*23.04*		*7.05*	*0.93*	*7.98*		*1.63*	*0.56*	*2.19*
With Hib vaccine	Hib containing vaccine*	4	1,814,760	48,239	1,862,999	3	5,345,975	142,327	5,488,302	3	143,600,101	3,594,400	147,194,502
	*Total with Hib vaccine***		*3,733,401*	*121,969*	*3,855,371*		*8,102,345*	*348,666*	*8,451,011*		*162,041,168*	*7,199,083*	*169,240,250*
	Costs per FVC with Hib		*41.14*	*1.34*	*42.48*		*15.36*	*0.66*	*16.02*		*8.44*	*0.37*	*8.81*
	Incremental costs		**1,750,815**	**13,507**	**1,764,322**		**4,383,938**	**- 142,327**	**4,241,611**		**130,767,979**	**-3,594,400**	**127,173,579**

*DTP-Hib in Belarus and DTP-HepB-Hib in Uzbekistan and India.
**In Uzbekistan, hepatitis B vaccine birth dose and booster dose of DTP at 18 months are included.
FVC: Fully vaccinated child (calculated as number of surviving infants multiplied by DTP3 vaccine coverage)

on vaccination, including system costs [278]. In a 2011 study analysing the costs of vaccines and injection supplies in Brazil, India and South Africa, it was shown that the costs per fully vaccinated child is US$ 26 in Brazil, US$ 124 in South Africa, but only US$ 3 in India [305]. The relatively high cost in South Africa is due to recent introductions of pneumococcal, rotavirus and IPV vaccines. It can thus be argued that even though a quadrupling of the Indian vaccine budget is substantial, the baseline budget is low and a resulting cost of US$ 8.81 per fully vaccinated child is still considerably less than what other governments have chosen to spend on vaccines.

11.3 INCREMENTAL SYSTEM COSTS OF PENTAVALENT VACCINE INTRODUCTION IN ETHIOPIA[4]

In this section, the incremental system costs of introducing pentavalent vaccine into vaccination services in Ethiopia are estimated. One of the findings from the literature review of Hib vaccine economic evaluations in Chapter 5 was that only a few studies had included system costs of the new vaccine introduction. These costs were included under "administration costs" or "vaccine programme costs", but they were either extrapolated from case studies on immunization services costs or based on authors' assumptions. While total vaccine and injection supply costs are well established, as these are equal to the amount of funds being granted by the GAVI Alliance, other vaccine introduction costs, such as cold storage and transport expenses, have not been well specified in GAVI supported countries.

System costs vary according to whether the new vaccine is a combination vaccine with one or more of the vaccines already present in the system or whether it is monovalent. If the combination vaccine is procured in the same vial size as before, the new vaccine does not take up more space in the distribution system. If, on the other hand, the new vaccine is monovalent, or if the new combined vaccine is introduced with fewer doses per vial than previously used, or if an extra vial for diluent is required, the vaccine takes up more space in the distribution system and this may necessitate expansion of the cold chain [300]. When pentavalent vaccine was introduced in Ethiopia the switch was from DTwP vaccine in a ten-dose vial to pentavalent vaccine in a single dose vial. Hence, more cold chain space was required.

The study objectives were:

1. To estimate the annual incremental system costs of introducing pentavalent vaccine.
2. To determine financing sources of the incremental system costs.
3. To estimate the share of system costs of total introduction costs.

11.3.1 BACKGROUND

Ethiopia applied to the GAVI Alliance for five-year support of pentavalent vaccine in early 2005 and the application was approved later that year [306]. However, due to a global shortage of pentavalent vaccine, the first shipment did not arrive until December 2006. The switch from DTwP to pentavalent vaccine was officially launched in March 2007. The introduction happened without catch-up for children above 12 months and in such a way

[4] The section has been published in modified form as: Griffiths UK, Korczak V, Ayalew D, Yigzaw A, Incremental system costs of introducing combined DTwP-Hepatitis B-Hib vaccine into National Immunization Services in Ethiopia, *Vaccine*. 2009 Feb 25; 27(9)

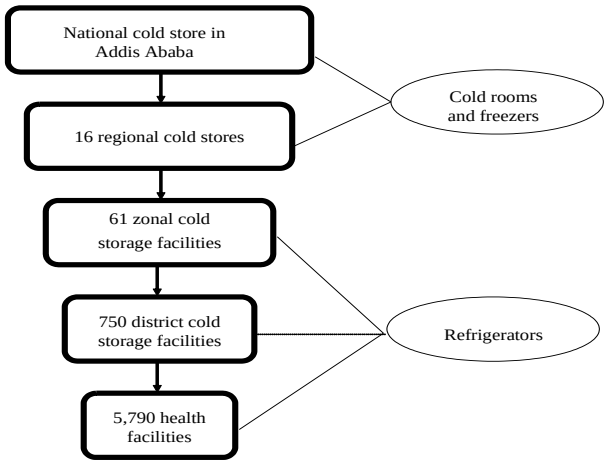
that if a child had started his/her vaccine course with one or two doses of DTwP, he/she would subsequently receive pentavalent vaccine as the second and/or third dose. The pentavalent vaccine gives Ethiopian children protection against two additional diseases, hepatitis B and Hib, compared to the previous schedule which contained only the six traditional antigens: BCG, DTP, measles and OPV. Hepatitis B and Hib vaccines were thus the first new vaccines to be added to the Ethiopian immunisation schedule since the programme was established in 1980.

Ethiopia was one of the first countries in the world to introduce the fully liquid pentavalent vaccine produced by Crucell. This vaccine, marketed under the name Quinvaxem™, came on the market in late 2006 [307]. The vaccine is marketed in a single dose vial only and requires 12.9 cm^3 of cold storage space per dose. The DTwP vaccine in a 10-dose vial requires 3.0 cm^3 per dose.

11.3.1.1 Vaccine distribution system in Ethiopia

As can be seen in Figure 11.1, vaccines are stored at four administrative levels in Ethiopia before they reach the health facilities. Vaccines are delivered quarterly into the country by air and kept in the national cold store in Addis Ababa. From here they are transported to regional, zonal and district cold storage facilities and subsequently to health facilities. At national and regional levels OPV is stored in freezers and the remaining vaccines at refrigerated temperatures, while at the three lower levels all vaccines are stored in refrigerators between 2-8° Celsius.

Figure 11.1: Vaccine cold storage distribution system in Ethiopia



11.3.2 METHODS

The cost analysis was undertaken from a societal perspective. Hence, the full costs of the vaccine introduction whether financed by the government or any other source were estimated. Opportunity costs, such as staff time, were included. Costs were estimated in 2007 US$ with the average 2007 exchange rate of 9.04 birr per one US$ used in all calculations (www.oanda.com). Cost items were divided into capital and recurrent costs. A discount rate of 8%, based on a 2007 inflation rate of 17% minus a 9% interest rate for public lending banks in Ethiopia, was used when annualising capital equipment [308].

11.3.2.1 Data collection

Resource items affected by pentavalent vaccine introduction were identified from interviewing key informants and by reviewing the Ethiopian hepatitis B and Hib vaccines introduction plan [309]. Data collection was undertaken as part of a WHO post-introduction evaluation (PIE) of pentavalent vaccine that took place over a two-week period in November 2007 [310]. Four teams of 2-3 people travelled to four regions (Oromia, Southern Nations Nationalities and People's Region (SNNPR), Somali and Amhara) to interview health sector staff about the programmatic aspects of pentavalent vaccine introduction. The regional health bureaus, zonal health departments, woreda health offices and a minimum of four health facilities were visited per zone. Two teams evaluated two zones each and the remaining two teams evaluated one zone each. The health facilities were selected in consultation with zonal staff based on their vaccine coverage performance. The cold stores at central, regional, zonal and woreda level were evaluated. In the health facilities observations were made during immunization sessions and caregivers were interviewed on exit. Interviews using standard questionnaires and observation sheets were conducted with a total of 50 individuals [310, 311].

I joined the team in Ethiopia and was responsible for conducting a cost analysis alongside the PIE. I developed a cost data collection tool to use at zonal, woreda and health facility levels and trained the field workers in collecting data. The tool is included in Annex 10. I collected all national level data.

Cold storage

Cold storage investments to accommodate the pentavalent vaccine were predominantly part of an overall 2004-2008 cold chain rehabilitation plan [312]. The plan had the following objectives: 1) Expansion of vaccine storage capacity to allow for population growth, introduction of new vaccines, increasing coverage and new health facilities, 2) replacement of cold chain equipment and 3) standardization of vaccine storage facilities.

A two step method was used to allocate a proportion of the cold storage investments to the pentavalent vaccine. First, the percentage increase in overall vaccine volume was estimated using the WHO vaccine volume calculator [313]. Vaccine wastage rates for this calculation were based on long-term vaccine procurement experience by the WHO office in Ethiopia. A 5% wastage rate was predicted for the single dose vial pentavalent vaccine. In the second step, all capital items purchased as part of the rehabilitation plan were assessed and a percentage of the investment allocated to the pentavalent vaccine using partly the result generated by the vaccine volume calculator and partly expert opinion from cold chain logisticians in Ethiopia.

Electricity and kerosene usage according to type of equipment was collected from WHO Product Information Sheets [314] and applied to the capital items purchased as part of the rehabilitation plan. A 2007 unit price of US$ 0.1 per kilowatt per hour and US$ 0.63 per litre of kerosene was used. Annual maintenance costs of cold storage equipment were assumed as 5% of the purchase price, based on average maintenance costs quoted in the rehabilitation plan budget.

Transport

Changes in vaccine transport frequency due to the greater volume were assessed in the four regions taking part in the PIE. Questions included how the vaccines were transported and whether the frequency of transport had changed due to introduction of pentavalent vaccine and if so, by how much. For zonal and district levels, averages from the four regions were extrapolated to the remainder of the country, while for the regional level, estimates from the SNNPR were used for the whole country, as data from the other three regions contained insufficient detail. Since the transport system and the distances are fairly similar in all regions of the country this extrapolation can be considered reasonable.

Training and communication

Costs of training and public communication activities related to the pentavalent vaccine introduction were collected from staff in the WHO and Unicef offices in Addis Ababa, as these organisations had funded these activities.

Vaccine supplies

Incremental, annual vaccine supply costs were calculated as the difference between a schedule with pentavalent and one with DTwP vaccine. A birth cohort of 3.2 million children and the Ministry of Health vaccine coverage predictions for 2007 were applied [306]. Prices of vaccines, syringes and safety boxes were collected from Unicef [315, 316].

Financing of pentavalent vaccine introduction

Information about the financing of pentavalent vaccine introduction was collected from the Ministry of Health, WHO and Unicef offices in Addis Ababa. Ethiopia has traditionally been heavily reliant on external partner support for the immunisation program [317]. During 2007 all vaccines other than the pentavalent were procured by Unicef from a "Protecting Basic Services" fund, supported by the World Bank and other partners.

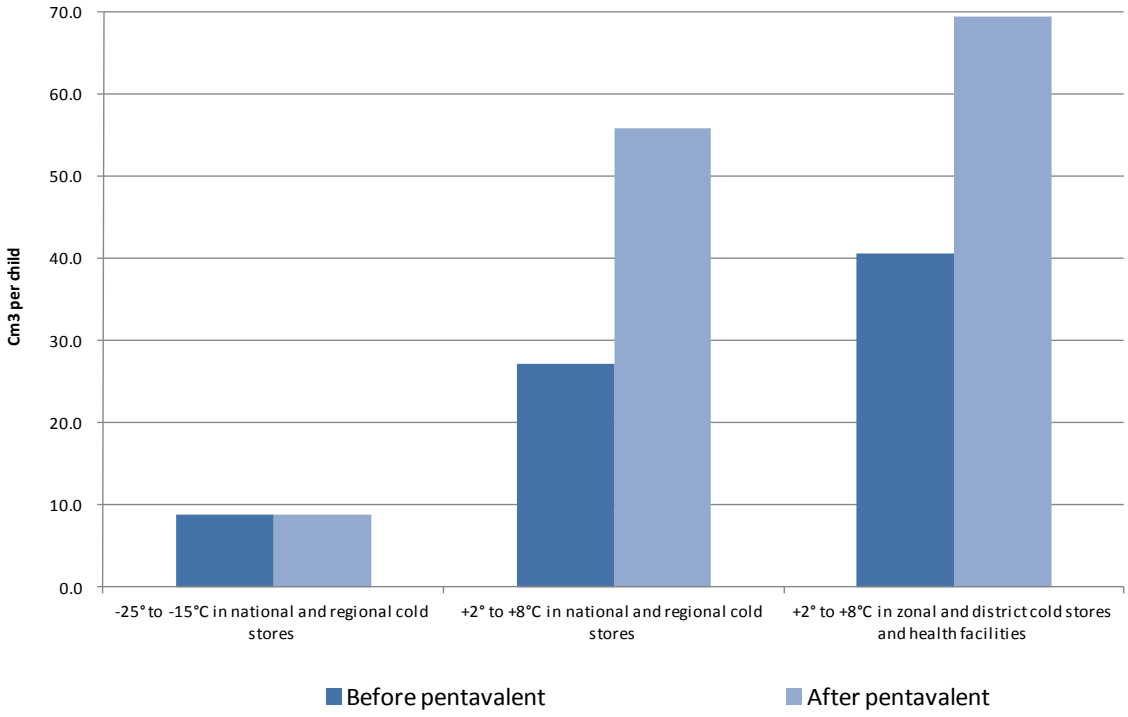
11.3.3 RESULTS

11.3.3.1 Incremental system costs

Cold storage

Packed volume per dose increased by 9.9 cm^3 due to the switch from a 10 dose DTwP vaccine to a single dose pentavalent vaccine. When using three doses and taking vaccine wastage into account, the increase in storage volume per fully vaccinated child was 28.7 cm^3. At national and regional levels, where OPV is stored in freezers and diluents are outside the cold chain, this caused a 106% increase in refrigeration storage volume per fully vaccinated child (from 27.1 cm^3 to 55.8 cm^3). At the three lower levels storage volume increased by 71% per fully vaccinated child (from 40.7 cm^3 to 69.4 cm^3). This is shown in Figure 11.2.

Figure 11.2: Storage volume per fully immunized child before and after pentavalent introduction



At national and regional levels, 15 additional cold rooms were assembled and one building for a cold room was constructed as part of the rehabilitation plan, at a total cost of US$ 638,779. Since these rooms are also used for storage of HIV tests and other vaccines, it was approximated that 70% of these costs can be allocated to the pentavalent vaccine, based on the opinion of the cold store manager (Table 11.8). For zonal and district cold storage facilities and health facilities, refrigerators, cold boxes and vaccine carriers were purchased. Since more than half of these were for equipment to new health facilities, only 40% of this investment was allocated to the pentavalent vaccine, again based on the expert assessment of the cold store manager. Total up-front costs of these cold storage investments amounted to US$ 4.6 million, or US$ 1.44 per child in the 2007 birth cohort and US$ 0.076 per additional cm^3 of storage volume. On an annual basis, incremental costs of cold storage were estimated as US$ 1.9 million, equivalent to US$ 0.87 per fully vaccinated child and US$ 0.03 per cm^3 of storage.

Transport

At all levels of vaccine transport changes were made to accommodate the increase in volume. From central to regional level, vaccines were still collected only four times per year, but instead of using a pick-up vehicle or a four-wheel drive, a truck was used by ten of the 16 regional cold stores. This increased vehicle operating costs by US$ 452 per year and total annual fuel consumption by approximately 3,175 litres. With a fuel price of US$ 0.6 per litre, this amounts to an incremental fuel cost of US$ 2,363 per year.

In SNNPR, staff from 17 zonal cold storage facilities collects vaccines from the regional cold store. The average distance of a round trip from zone to region is 419 km (range 3-530 km) and it takes between 1-3 days to complete this trip. The frequency of zonal vaccine collection has on average doubled from 4 to 8 times per year since pentavalent vaccine has been introduced. When adding up per diems, salary, fuel and vehicle operating costs, it was estimated that transport costs per zone have on average increased from US$ 289 to US$ 577 per year. With 61 zones in Ethiopia, annual incremental costs at this level amount to approximately US$ 17,601.

Interviews with staff at 22 district storage facilities in the four regions revealed that 17 (77%) of these had increased their frequency of vaccine collection. Before pentavalent vaccine introduction, these facilities on average collected vaccines from the zones nine times per year (range of 4 - 18). This has now increased to an average of 17 trips per year (range of 4 – 36). Approximately 85% of district storage facilities use a private vehicle and

Table 11.8: Cold storage investments made during 2005-2007 to accommodate pentavalent vaccine, Ethiopia (2007 US$)

Item	Quantity	Total costs	Useful life years*	Annualised costs	Annual operational costs**	Total annual costs	Percent allocated to pentavalent Vaccine	Costs of pentavalent Vaccine
National cold rooms	2	56,000	15	6,542	6,804	13,346	70%	9,342
Regional cold room building	1	49,090	15	5,735	2,455	8,190	70%	5,733
Regional cold rooms	13	457,600	15	53,461	80,144	133,606	70%	93,524
Generators for regional cold rooms	6	76,089	10	11,339	3,816	15,155	70%	10,609
Refrigerators for zonal storage	13	9,672	10	1,441	23,600	25,042	70%	17,529
Refrigerators for district storage	124	58,280	10	8,685	193,554	202,239	40%	80,896
Refrigerators for health facilities	5,973	8,959,500	10	1,335,230	2,851,518	4,186,748	40%	1,674,699
Cold boxes for health facilities	2,338	1,098,860	20	111,921	-	111,921	40%	44,769
Vaccine carriers for health facilities	12,518	111,161	15	12,987	-	12,987	40%	5,195
Ice pack freezers for health facilities	10	25,000	10	3,726	124	3,850	40%	1,540
TOTAL	*20,998*	10,901,252		*1,551,069*	*3,162,015*	*4,713,084*		*1,943,835*

* Source: Expert opinion based on previous experience in Ethiopia.

** Include spare parts, maintenance, training and monitoring, electricity and kerosene costs. Source: Ethiopia cold storage rehabilitation plan and WHO product information sheets.

the remainder use bus transportation when collecting vaccines. Costs of transport from districts to zones were estimated to have increased by US$ 165,994 per year (Table 11.9).

Substantial differences were seen between health facilities with regard to the frequency of vaccine collection. While eight out of 22 facilities had made no changes and were still collecting vaccines once a month, three facilities had changed from once a month to once a week. The average increase in collection times was from 12 to 26 trips per year; an increase of 121%. Approximately 90% of health facilities used a health sector vehicle when collecting vaccines while the remainder used bus transport. Total incremental transport costs at this level amounted to US$ 273,975 per year (Table 11.9 and 11.10).

Incremental transport costs per fully vaccinated child were estimated as US$ 0.207.

Table 11.9: Vaccine transport costs according to administrative level in Ethiopia (2007 US$)*

Level of vaccine transportation	Before pentavalent	After pentavalent	Difference	Incremental costs per fully vaccinated child**
From central to regions	6,802	9,164	2,362	0.001
From regions to zones	17,601	35,202	17,601	0.008
From zones to districts	177,632	343,626	165,994	0.075
From districts to health facilities	225,909	499,884	273,975	0.123
TOTAL	**427,944**	**887,877**	**459,932**	**0.207**

* The estimate from region to zones is based on data from one region, SNNPR. Estimates for the two lower levels are based on data from four regions in Ethiopia.
** No. of fully vaccinated children are estimated as number of surviving infants (2,849,053) multiplied by 2007 DTP3 coverage (78%).

Training and communication

Training of health staff took place over two days at the regional level and one day in the districts. A total of 6,706 people were trained nationwide. Transport allowance, stationary, refreshments, hall rental and facilitator fees were included in the training costs of US$ 225,760. When assuming a useful life of three years and an 8% discount rate, annualised costs amount to US$ 87,602.

Launching ceremonies were held in Somali, SNNPR and Oromia regions at a total cost of US$ 3,153. A national communication strategy was developed, including printed materials, such as flyers and flipcharts, as well as radio and television spots. Total communication

Table 11.10: Change in transport costs due to pentavalent vaccine introduction: District and health facility levels (Data from four regions in Ethiopia)*

	From zone to district (n=22)			From district to health facility (n=17)		
	Before pentavalent	**After pentavalent**	**Difference**	**Before pentavalent**	**After pentavalent**	**Difference**
Average no. of collection times per year	9	17	8	12	26	14
Costs for facilities using private vehicle:						
Distance travelled per year (km)	448,182	867,000	418,818	680,325	1,505,400	825,075
Annual no. of collection days	5,602	10,838	5,235	6,803	15,054	8,251
Petrol costs (US$)	74,697	144,500	69,803	113,388	250,900	137,513
Vehicle operating costs (US$)	45,364	87,755	42,391	68,860	152,372	83,511
Salary of health care workers and drivers (US$)	26,855	51,950	25,095	32,611	72,162	39,550
Per diem of health care workers and drivers (US$)	79,324	153,451	74,127	96,329	154	116,825
Subtotal (US$)	**163,779**	**316,828**	**153,049**	**216,377**	**478,791**	**262,414**
Costs for facilities using bus service:						
Annual no. of collection days	989	1,913	924	680	1,505	825
Salary of health care workers (US$)	2,916	5,642	2,725	2,007	4,441	2,434
Per diem of health care workers (US$)	7,655	14,809	7,154	5,268	11,657	6,389
Bus tickets (US$)	3,281	6,347	3,066	2,258	4,996	2,738
Subtotal (US$)	**13,853**	**26,798**	**12,945**	**9,533**	**21,093**	**11,561**
TOTAL (US$)	**177,632**	**343,626**	**165,994**	**225,909**	**499,884**	**273,975**

*Unit costs used: One litre of petrol at national level: US$ 0.60, one litre of petrol at regional level: US$ 0.61, daily salary of driver: US$ 1.84, daily salary of health worker:: US$ 2.95, driver per diem: US$ 6.42, health worker per diem: US$ 7.74, operating costs of four wheel drive vehicle per km: US$ 0.03, operating costs of truck per km: US$ 0.05, return bus ticket: US$ 3.32

costs amounted to US$ 51,665. When assuming a useful life of three years and an 8% discount rate, annualised costs of communication were US$ 21,977.

No additional costs were incurred for changing vaccination cards and vaccine schedule posters to include Hib and hepatitis B vaccines. Since these stationary were out of stock at the time of introduction, changes and printing were done without any additional costs.

11.3.3.2 Vaccine supplies

Total costs of vaccine and injection supplies for the Ethiopian immunization schedule increased from US$ 6.1 million to US$ 30.6 million per year; more than a five-fold increase (Table 11.11). The 2007 Unicef price of DTwP vaccine, including freight charges, was US$ 0.23 per dose while the price of pentavalent vaccine was US$ 3.79 per dose.

11.3.3.3 Total incremental costs

Incremental system costs amounted to US$ 2.5 million per year, equivalent to US$ 1.13 per fully vaccinated child (Table 11.12). Non-annualised capital costs, consisting of cold storage equipment, training and communication activities, amounted to US$ 4.8 million, or US$ 1.53 per child in the 2007 birth cohort. Ethiopia received US$100,000 as a vaccine introduction grant from GAVI, amounting to US$ 0.03 per child in the birth cohort. If the country had been approved for pentavalent vaccine during GAVI phase II, it would have been eligible for a vaccine introduction grant of US$ 0.30 per child. With a 2007 birth cohort of 3.2 million children, this is equivalent to US$ 960,000. Hence, the introduction grant would have covered 20% of the capital investments made to facilitate the introduction.

When including vaccine costs, total incremental costs of pentavalent vaccine introduction amounted to US$ 27 million per year, or US$ 12.17 per fully vaccinated child. 91% of these costs were for vaccine and injection supplies and the remaining 9% system costs.

11.3.3.4 Financing of incremental system costs

The government financed vaccine transport, amounting to 18% of the estimated incremental system costs. Cold storage investments, comprising 77% of incremental system costs, were funded by the World Bank, Unicef, USAID and the WHO. Unicef and the WHO also contributed to training and communication activities. In total, the World Bank contributed 60% of system costs, the government 18%, USAID 12%, WHO 6%, Unicef 2%, and GAVI 2% (in the form of the vaccine introduction grant of US$ 100,000, which was used for training of health workers).

Table 11.11: 2007 vaccine and injection supply costs with and without pentavalent vaccine in Ethiopia (US$)

Antigen	Doses per child/ women	Vaccine coverage	Doses per vial	Wastage in percent*	Costs per dose (incl. freight)	Total vaccine costs	Total injection supply costs**	Total Costs	% of total
BCG	1	65%	20	65%	0.09	633,100	92,086	1,125,186	19%
DTwP	3	25%	10	25%	0.23	2,049,935	895,571	2,945,506	48%
Measles	1	30%	10	30%	0.21	607,877	282,309	890,187	15%
OPV	4	10%	10	10%	0.02	166,861	-	166,861	3%
Tetanus toxoid***	2	10%	10	10%	0.09	395,660	552,244	947,904	16%
Total without DTwP-HepB-Hib						**3,853,434**	**2,222,211**	**6,075,645**	100%
DTwP-HepB-Hib	3	78%	1	5%	3.79	26,579,415	895,571	27,474,987	
Total with DTwP-HepB-Hib						**28,382,915**	**2,222,211**	**30,605,125**	
Incremental costs of DTwP-HepB-Hib						***24,529,480***	**-**	***24,529,480***	**80%**

2007 birth cohort: 3,154,398. 2007 surviving infants: 2,849,053 (source: Health and health related indicators, Federal Ministry of Health, Ethiopia)
* Source: WHO, Ethiopia
** Syringes and safety boxes
***2007 women of child-bearing age: 3,162,304. The maximum a pregnant woman can receive is three doses (TT2 4 weeks after TT1 and TT3 6 month after TT2). Two doses are used in the calculation although this is likely to inflate the actual need, as only pregnant women are targeted.

Table 11.12: Incremental system costs of pentavalent introduction in Ethiopia (2007 US$)

	Total capital costs	Annual costs (capital and recurrent)	Annual costs per fully vaccinated child	Annual costs per child in birth cohort	Percent of total annual system costs
Cold storage	4,555,036	1,943,835	0.87	0.62	77%
Transport	0	459,932	0.21	0.15	18%
Training	225,760	87,602	0.04	0.03	3%
Public communication	51,665	21,977	0.01	0.01	1%
Total	**4,832,460**	**2,513,347**	**1.13**	**0.80**	**100%**

* Vaccine wastage included in the estimate

11.3.3.5 Sensitivity analysis

The most important assumption of the analysis was the proportion of cold storage investment allocated to the pentavalent vaccine. The base case scenario assumed 70% at national, regional and zonal level and 40% at district and health facility level. However, since the new vaccine introduction was a prime reason for the cold chain expansion and since the packed volume per child increased by between 71% - 106% according to level, these must be considered minimum allocations. If it is instead assumed that 80% of all additional cold storage investments were allocated to the pentavalent vaccine, incremental cold storage costs were US$ 1.70 per fully vaccinated child instead of US$ 0.87 as in the base case scenario. In this case annual system costs amount to US$ 1.95 per fully vaccinated child. When changing the discount rate from 8% to 3%, incremental system costs decrease from US$ 1.13 to US$ 1.05 per fully vaccinated child.

11.3.4 DISCUSSION

Pentavalent vaccine supplies comprised 91% of the total incremental costs while system costs represented the remaining 9%. However, the study showed that in a resource constrained economy like the Ethiopian, the system costs of facilitating introduction of a new vaccine are substantial. It was estimated that incremental system costs of pentavalent vaccine amounted to US$ 1.13 per fully vaccinated child, or US$ 0.80 per child in the birth cohort. With a public health budget of only around US$ 4 per capita, this is far from insignificant.

The pentavalent vaccine system costs of US$ 1.13 per fully vaccinated child are likely to underestimate the costs of an optimal vaccine introduction scenario. Numerous reports from Ethiopia have concluded that the cold chain system is not functioning optimally and

that additional investments are needed to ensure that vaccines maintain their potency. In this study the costs of the actual changes made to facilitate pentavalent vaccine introduction were estimated and not the costs of an optimal vaccine delivery situation with a greater cold storage expansion and less frequent vaccine transport.

The GAVI vaccine introduction grant of US$0.30 per child in the birth cohort would only cover a fraction of the costs and other partners will therefore most often have to contribute as well, as was the case in Ethiopia. The increase in vaccine storage and transport costs due to the pentavalent vaccine occurred due to the switch from DTwP in a ten-dose vial to pentavalent vaccine in a single dose vial. Only a relatively small proportion of GAVI eligible countries have changed vaccines in this way. Instead, most have opted to first introduce hepatitis B vaccine, frequently combined with DtwP, and then subsequently changed to pentavalent vaccine. However, for countries that have used DTwP-HepB vaccine in a ten-dose vial, the system cost implications will be similar to those in Ethiopia, as the packed volume per vial of this vaccine is similar to the ten-dose DTwP vaccine. The new, Indian manufactured pentavalent vaccine in a ten-dose vial, which was pre-qualified by the WHO in 2010, has a packed volume per dose of 4.4 cm^3, compared to the 12.9 cm^3 per dose of the Crucell pentavalent vaccine. Hence, there is either limited or no need for expansion of the cold chain with this vaccine.

The study has a number of limitations. Regional transport costs were extrapolated to the whole country from one region only. Secondly, cold storage costs were likely to be underestimated as only new equipment was included and the opportunity costs of using the existing equipment were not accounted for. To do this, data on existing cold chain equipment at all facilities would be needed, which is only possible if an extensive cold chain assessment is available.

11.4 Conclusion

This chapter started off by investigating determinants of Hib vaccine prices. Low-income countries eligible for pooled procurement through Unicef and PAHO are able to obtain considerably lower prices than middle- and high-income countries that procure independently. However, during 2000-2010 the Unicef pentavalent vaccine price was still considerably higher than prices of the traditional vaccines, contributing to slow uptake of Hib vaccine. Since the SII pentavalent vaccine became pre-qualified in 2011 a 50% price decrease has been obtained and this has greatly improved the prospects for financial sustainability in low-income countries. However, so far middle-income countries,

including Belarus, have not benefited from price decreases and 17 of the world's middle-income countries have not yet introduced the vaccine.

Incremental costs of introducing Hib vaccine were estimated for Belarus, Uzbekistan and India, and the incremental costs of introducing Hib and hepatitis B vaccines as part of pentavalent vaccine introduction, were estimated for Ethiopia. Incremental costs amounted to US$ 19, US$ 8 and US$ 7 per fully vaccinated child in Belarus, Uzbekistan and India, respectively. In Ethiopia, the incremental costs of Hib and hepatitis B vaccine introduction were US$ 12 per fully vaccinated child, with system costs comprising 9% of total costs. Vaccine costs were the most important cost components in Ethiopia, confirming the fact that the relatively high pentavalent vaccine price is one of the key reasons for slow uptake in low- and middle-income countries. However, even though the amount is relatively low, system costs are important to estimate for budgeting reasons and for precise cost-effectiveness estimates. In a resource constrained country like Ethiopia these costs represented a substantial proportion of total government health care expenditures and they are therefore crucial to quantify.

As mentioned above, the new SII pentavalent vaccine in a ten-dose vial has markedly changed the Hib vaccine landscape. When countries switch from DTP vaccine in a ten-dose vial to pentavalent vaccine in a similar vial size, there is no need for cold chain expansion and system costs are therefore relatively low, mainly comprising of social mobilisation and training. During 2011, the majority of GAVI countries requested to switch from single or two dose pentavalent presentations to the ten-dose SII vaccine. As an example, 20 out of 24 countries in West Africa have now changed to the SII formulation (personal communication with Unicef in Dakar, Senegal). The main reason for wanting to free up cold chain space by switching to the ten-dose presentation is to prepare for pneumococcal and rotavirus vaccine introductions. Both of these vaccines take up considerable space in the cold chain; the packed volume per dose is 12 cm^3 for the pneumococcal vaccine and 17 cm^3 for the rotavirus vaccine.

In preparation for rotavirus and pneumococcal expansions, the GAVI Alliance and the Bill and Melinda Gates Foundation (BMGF) have started to assess to what extent the current vaccine introduction grant accurately represent the system costs of new vaccine introduction. Since the Ethiopia study presented in this chapter is presently the only in-depth analysis available on systems costs, this study has been widely quoted and referred to during these discussions. Based on the evidence from Ethiopia, the GAVI Secretariat is now proposing to increase the vaccine introduction grant. The GAVI Board will make a

decision on this during its meeting in June 2012. In addition, the BMGF issued a request for proposals (RFP) in February 2012 for "analysis of the costs and financing of routine immunization programs and new vaccine introduction". The Ethiopia paper is quoted in this RFP and it is stated that they wish to replicate the study in other settings and evaluate the feasibility of collecting cost data alongside PIEs, as I did in the Ethiopia study.

12 COST-UTILITY OF HIB VACCINE[5]

In this chapter, the incremental cost-effectiveness and cost-utility of Hib vaccine are estimated for the three study countries, using the parameter values generated in the previous chapters. The outcome measures used are Hib disease cases, premature deaths and DALYs. Hib disease burden estimates are crucial for the overall results and these are described in section 12.1. The methods and assumptions used in the sensitivity analyses are described in section 12.2, the results are presented in section 12.3, and the findings are discussed in section 12.4.

12.1 ESTIMATION OF HIB DISEASE BURDEN IN THE THREE STUDY COUNTRIES

As explained in Chapter 7, incidence rates and case fatality rates of Hib meningitis, Hib NPNM and all-cause pneumonia in children less than five years are needed as input parameters in the decision-analytic model. Hib pneumonia incidence is estimated as a fixed proportion of all-cause pneumonia incidence. The methods used for arriving at the best available disease burden estimates are described below.

12.1.1 HIB DISEASE INCIDENCE RATES

12.1.1.1 Hib meningitis incidence

Belarus

In Belarus, population-based childhood bacterial meningitis surveillance was in place at Minsk City Children's Infectious Disease Hospital (MCCIDH) during 2002-2007 [238, 318]. Conditions for successful population-based meningitis surveillance are [319]:

- The surveillance population should be geographically well defined.
- Age-specific population data should be available so that age-specific rates of disease can be calculated.
- All health facilities that diagnose and treat childhood meningitis in the surveillance population should be included in the surveillance system.
- Residence of the surveillance population should have a high level of health care utilization.
- The standard of care should include lumbar puncture in the routine evaluation of children who present with symptoms of meningitis.

[5] Griffiths UK, Clark A, Shimanovich V, Glinskaya I, Tursunova D, Kim L, Mosina L, Hajjeh R, Edmond K. Comparative economic evaluation of *Haemophilus influenzae* type b vaccination in Belarus and Uzbekistan. PLoS One. 2011;6(6)

It is believed that the Minsk city surveillance largely adhered to all these conditions. Since the MCCIDH is the only infectious disease hospital in Minsk city, all children with symptoms of meningitis are referred to this facility and it is unlikely that any cases have been missed by the surveillance. A number of children with residency outside Minsk city were identified in the surveillance, but these were not included in the incidence rate calculations. It is however likely that there is under-ascertainment of cases of bacterial meningitis at the MCCIDH. A review of the hospital laboratory highlighted several sub-optimal methods [320]. In particular, human blood was used instead of sterile animal blood for preparing blood and chocolate agar plates and CSFs were not cultured immediately. For these reasons, the confirmed bacterial meningitis incidence rate is likely to be an underestimate.

During the six-year period, 175 purulent meningitis cases were detected in children less than five years, giving an average bacterial meningitis incidence rate of 31.28 per 100,000 children less than five years. A bacterial pathogen was identified in 87 of the purulent cases (Table 12.1). Thirty of the cases were confirmed as Hib, generating an incidence of 5.4 per 100,000 children, with annual rates between 1.2 and 9.0. However, since 88 of the purulent cases had no confirmed pathogen, this is likely to be an underestimate of the true number. According to WHO guidelines [321] and following methods used in other bacterial meningitis aetiology studies [322], culture negative cases should be allocated to

Table 12.1: Reported purulent* meningitis cases in children less than 5 years in Minsk city, Belarus

Year	Number of confirmed Neisseria meningitis cases	Number of confirmed Hib cases	Number of confirmed Streptococcus pneumoniae cases	Number of confirmed other bacteria	Number of culture negative cases	Total number of purulent cases*	Bacterial meningitis incidence per 100,000 children < 5 years**
2002	3	2	1	0	12	18	24.94
2003	7	6	1	0	11	25	33.57
2004	10	5	1	0	12	28	36.54
2005	9	7	3	0	14	33	42.13
2006	7	1	3	1	25	37	45.69
2007	6	5	1	1	6	19	22.27
2008	3	4	0	0	8	15	16.37
TOTAL	**45**	**30**	**10**	**2**	**88**	**175**	**31.28**

*Purulent meningitis is defined as visibly turbid or cloudy CSF OR white cell count > 100
** Incidence rates are calculated from the following under-five population in Minsk city: 2002: 72,168, 2003: 74,469, 2004: 76,623, 2005: 78,323, 2006: 80,985, 2007: 85,335, 2008: 91,623.

bacterial pathogens according to their proportion of confirmed cases. Hence, 34% of the non-confirmed cases were apportioned to Hib and an *adjusted* Hib meningitis incidence rate of **10.9** per 100,000 children less than five years, with an annual range between 7.4 and 15.1 was estimated (Table 12.2).

It should be noted that Hib vaccination was in place in Minsk city during 2007 (high risk groups) and 2008 (routine use), but data from the 'post-vaccine' era were not excluded since it may take some time before the impact is demonstrated, particularly in countries with a relatively high average age of Hib disease. In addition, the surveillance figures for 2007-2008 were broadly consistent with the previous years. There was a fairly even spread of cases across the first four years of life, with fewer cases in the fifth year of life (Table 12.3). There were two cases in the 5-14 year age group.

Table 12.2: Estimated Hib meningitis incidence in Minsk city 2002-2008

Year	Number of confirmed Hib cases in children < 5 years	*Adjusted* number of confirmed Hib cases in children < 5 years*	Number of children < 5 years in Minsk city	Confirmed Hib meningitis incidence	*Adjusted* Hib meningitis incidence *
2002	2	6	72,168	2.8	*8.5*
2003	6	10	74,469	8.1	*13.2*
2004	5	9	76,623	6.5	*11.9*
2005	7	12	78,323	9.0	*15.1*
2006	1	10	80,985	1.2	*11.9*
2007	5	7	85,335	5.9	*8.3*
2008	4	7	91,623	4.3	*7.4*
TOTAL	**30**	**60**	**559,526**	**5.4**	***10.9***

*Adjusted cases are calculated by adding the fraction of culture negative cases believed to be Hib (using % of confirmed cases that are Hib)

Table 12.3: Age distribution of hospitalized Hib meningitis cases <5yrs in Minsk, 2002-2008

Age	<12m	12-23m	24-35m	36-47m	48-59m	Total
Number	6	7	8	6	3	30
%	20%	23%	27%	20%	10%	100%

India

In the state of Tamil Nadu a population based prospective meningitis surveillance study comparable to the one in Belarus was in place during 1997-1999 [44]. Four hospitals in the district of Vellore participated in the study. The number of meningitis cases detected during the two-year period is seen in Table 12.4. A confirmed Hib meningitis incidence rate of 7.1 per 100,000 children less than five years was estimated by the study authors. For the present analysis, a similar adjustment as used in Belarus was done. Since Hib was the cause of 44% of all confirmed bacterial meningitis, 44% of the culture negative cases

Table 12.4: Estimation of Hib meningitis incidence in India

Area	Estimated children < 5 years	Number of purulent meningitis cases during two years	Annual incidence of purulent meningitis*	Number of confirmed bacterial meningitis cases during two years	Annual bacterial meningitis incidence per 100,000 children < 5 years	Number of confirmed Hib meningitis cases during two years	Annual confirmed Hib meningitis incidence	Number of culture negative cases with CSF>100 WCC during two years	*Adjusted* number of Hib cases** during two years	*Adjusted* Hib meningitis incidence per 100,000 children < 5 years
Vellore, urban	16,407	18	55	8	24.38	3	9.1	10	7.44	*22.69*
Vellore, rural	13,041	7	27	1	3.83	1	3.8	6	3.67	*14.06*
Kaniyambadi, rural	8,677	9	52	2	11.52	2	11.5	7	5.11	*29.45*
Katpadi, rural	7,524	3	20	1	6.65	-	-	2	0.89	*5.91*
Anaicut, rural	10,504	5	24	6	28.56	2	9.5	-1	1.56	*7.40*
TOTAL	**56,153**	**42**	**37**	**18**	**16.03**	**8**	**7.1**	**24**	**18.67**	***16.62***

*Purulent meningitis is defined as visibly turbid or cloudy CSF OR white cell count > 100.
** Adjusted cases are calculated by adding the fraction of culture negative cases believed to be Hib (using % of confirmed cases that are Hib).
Source: Minz *et al*. (2008) [44]

were assumed to be Hib and an *adjusted* Hib meningitis incidence rate of *16.62* per 100,000 children less than five years was estimated

There was moreover evidence that not all children were captured by the surveillance due to limited access to care. The study authors identified all deaths during 1998 and 1999 in a subpopulation of 19,181 children in the two rural study areas with the least access to health care and families were interviewed using a verbal autopsy method. This survey identified 327 deaths over the two years and eight of these had suffered from meningitis symptoms, but had not had a lumbar puncture or died in one of the study hospitals. It was thus concluded that since not all children with meningitis symptoms in the study population had been taken to formal health care facilities, the calculated incidence rate would be an underestimate [44]. For the present study, the rate was therefore adjusted upwards by 23%, which is the estimated proportion of children with ARI in Vellore that are not taken to formal medical care [261]. Hence, the *final adjusted* Hib meningitis incidence rate was *20.44* per 100,000 children < 5 years.

Uzbekistan

Since no population based Hib surveillance studies have been conducted in Uzbekistan, routine surveillance data were used for the estimates. Morbidity and mortality data for pneumonia and meningitis in children less than five years are routinely collected by the Ministry of Health. Meningococcal meningitis is a notifiable disease and therefore reported separately while other types of meningitis are not distinguished according to pathogen. The view that meningococcal meningitis is a very severe disease drives the emphasis on all children with bacterial meningitis being referred to infectious disease hospitals [38].

There are however two important limitations of using routine surveillance data for estimating meningitis incidence rates. First, these data are usually gathered from hospital medical records and are based on the physician's clinical discharge diagnosis, which can vary markedly amongst treating physicians. In many hospitals, a clinical discharge diagnosis of meningitis is usually made on the basis of clinical signs and symptoms of meningococcemia (i.e. purpuric rash and fever or neck stiffness or bulging fontanelle). Children with more subtle signs of septicaemia and vomiting or headache may not be classified as meningitis and may be missed by some doctors. Secondly, all data sources for all children with these diseases must be accessed. Data must thus be obtained from all hospitals that admit children with meningitis and from hospitals that treat children who develop meningitis later in their illness (for example, children who are admitted with

septicaemia, but develop meningitis the following day). Hence, surveillance data are likely to be an underestimate of the true number of cases.

234 hospitals reported 5,245 clinical meningitis cases in children less than five years in 2007, giving an incidence of 166 per 100,000 children. This estimate was adjusted upwards by 32% to account for limited access to care [259], arriving at 219 all-cause meningitis cases per 100,000 children. The proportion of meningitis caused by Hib was approximated from a study conducted by the Uzbek Ministry of Health and the US Naval Medical Research Unit no. 3, based in Egypt [323]. 165 CSF samples from children with clinical meningitis admitted to hospitals in Tashkent and Samarkand during 2002-2004 were tested using Polymerase Chain Reaction and 61 were found to be purulent with nine of them confirmed as Hib [323]. The *adjusted* number is 14 cases, equivalent to 8.5% of all the cases tested. An adjusted Hib meningitis incidence of *18.7* per 100,000 children < 5 years (8.5% of 219) was thus estimated.

12.1.1.2 Hib NPNM incidence

There are no data on Hib NPNM disease incidence rates in any of the three countries. Following the methodology of the GBD study, the NPNM disease incidence was estimated as a proportion of the meningitis incidence rate [58]. For Belarus and Uzbekistan, studies from Bulgaria and the Czech Republic assessing all types of Hib diseases were used to determine the relationship between meningitis and NPNM cases [25, 43]. The pooled average from these two studies is 0.57 NPNM cases diagnosed for each meningitis case. The most important type was epiglottitis, accounting for 78% of cases. Hib NPNM incidence rates of *6.15* and *10.65* per 100,000 children less than five years in Belarus and Uzbekistan, respectively, were estimated.

In India, data published by the Invasive Bacterial Infections Surveillance (IBIS) project in Tamil Nadu showed that for each meningitis case, there were 0.18 confirmed NPNM Hib disease cases [324]. Hence, an incidence rate of *3.72* NPNM cases per 100,000 children less than five years was assumed.

12.1.1.3 All-cause pneumonia incidence

In Belarus and Uzbekistan, all-cause pneumonia incidence was determined from routine surveillance systems of the Ministries of Health. In Belarus, 10,402 pneumonia cases in children less than five years were reported during 2008, giving an annual incidence of *2,302* per 100,000 children, based on an under-five population of 451,960 [325]. 84% of cases were reported from hospitals and the remaining from outpatient clinics.

In Uzbekistan, 20,014 pneumonia cases were reported in 2007, giving an incidence of 633 per 100,000 children less than five years (under-five population is 3,162,151 [326]). 230,201 acute respiratory infections (ARI) cases were reported the same year. The distinction between ARI and pneumonia can be problematic, as it is common to find a lack of consistency when classifying these diseases at health facility level [327]. When hospitalised ARI cases are included, the incidence rate increases to 1,724 per 100,000. After adjusting for limited access to care, the *adjusted* incidence is *2,277* per 100,000 children less than five years.

Various studies of clinical pneumonia incidence have been conducted among children aged less than five years at the community-level in India. However, many of these estimates were reported more than ten, sometimes twenty years ago, and there are great variations among the study results. The incidence per child per year was reported to be 0.54 in Haryana (1987) [328], 0.29 in Pune (1990) [329], 0.86 in Rajasthan (1990) [330], 0.31 in Delhi (1993) [331], 0.07 in Maharastra (1996) [332], 0.10 in Lucknow (1997) [333], 0.4 in Tripura (1998) [334], 0.67 in Delhi (1999) [335] and 0.53 in Karnataka (2003) [336]. The inter-quartile range from the above estimates was 0.29– 0.54 episodes per child per year, or 29,000 – 54,000 cases per 100,000 children less than five years. The mean value is *41,500* cases per 100,000 children less than five years. There is great variation among the study estimates and the values are considerably higher than found in Belarus and Uzbekistan. In light of the greater under-five mortality rate in India than in the two other countries, this is expected, but the differences can seem disproportionally large. This underlines the great difficulties in establishing the true burden of pneumonia.

Hib Initiative funded multi-center surveillance for pneumonia at three different settings found an incidence of severe, clinical hospitalized pneumonia of 2,717 in Chandigarh, 7,890 in Kolkata and 2,887 in Vellore in children less than two years [253]. The average between the three sites is a rate of 4,561. When adjusting to children less than five years of age, the incidence rate of severe all-cause pneumonia is approximately *3,280*. It was decided to use this value in the base case analysis and use a relatively wide range for pneumonia incidence in the uncertainty analysis, as described below.

12.1.1.4 Hib pneumonia incidence

Since the signs and symptoms of Hib pneumonia cannot be differentiated from those of pneumonia caused by other microorganisms, the incidence of Hib pneumonia can best be approximated from Hib vaccine trials [176]. In the meta-analysis presented in Chapter 8, two trials demonstrated Hib vaccine efficacy against all cause, clinical pneumonia and the

pooled estimate was 4% (95% CI 1, 7), with no heterogeneity between the two studies. It was thus assumed that vaccine preventable Hib disease is the cause of 4% of all clinical pneumonia. This assumption is similar to what was used by the Hib GBD project [31]. Hib pneumonia incidence rates of *114* and *115* per 100,000 children less than five years were estimated for Belarus and Uzbekistan, respectively.

Since the Indian all-cause pneumonia estimate is for severe pneumonia only other trial evidence than the clinical pneumonia was used. The Gambian and Chilean Hib vaccine trials showed that Hib pneumonia is the cause of approximately 22% of severe pneumonia (defined as radiological pneumonia in the trials) [185, 186]. A Hib vaccine incidence rate of *722* per 100,000 children less than five years was thus assumed for India (3,280 x 22%).

12.1.2 HIB DISEASE CASE FATALITY RATES

Belarus

In the Minsk city meningitis surveillance project, one of the 30 children with confirmed Hib meningitis died, giving a case fatality ratio (CFR) of 3.2%. This is comparable to CFRs reported in Western European countries, such as 5% in the United Kingdom [27, 225] and 4% in France [54]. Only six and five pneumonia deaths in children less than five years were reported in Belarus during 2007 and 2008, respectively. This is equivalent to around 2% of all deaths in children and a CFR of 0.3% for all-cause pneumonia. The studies from Bulgaria and Czech Republic showed that approximately 78% of NPNM were epiglottitis, which is of similar severity to meningitis. For this proportion, a similar CFR to meningitis was assumed and zero CFR was assumed for the remaining NPNM cases.

India

Hospital bacterial meningitis CFRs have been reported in three Indian studies. In the Invasive Bacterial Infections Surveillance (IBIS) study, a CFR of 18.7% was reported [324], in a study by Minz *et al.* the CFR was 12.5% [44], and in a study by Gupta *et al*. it was 19.7% [253]. The average figure of 17% was used. For children not accessing care meningitis CFR was assumed to be 100% [124, 125]. The overall rate was thus 41%.

In the study by Gupta *et al*., hospital CFRs for severe clinical pneumonia was 1.31% in Chandigarh, 3.32% in Kolkata and 0.89% in Vellore [253]. The average of 1.85% was used for hospitalised cases and 10% was assumed for the 29% with no access to care [125], giving an overall CFR of 4.21%. A similar CFR was assumed for NPNM.

Uzbekistan

In Uzbekistan, 22 children less than five years were reported to have died from meningitis in 2007, giving a CFR of 0.42%. For Hib meningitis, this figure is however unrealistically low. Instead, the 17% hospital CFR from the Indian studies was used and a CFR of 100% was assumed for the estimated 32% of children that do not reach formal health care [125]. The overall meningitis CFR was thus 44%.

According to Uzbek hospital surveillance data, a total of 214 pneumonia deaths occurred in 2007, generating an all-cause hospital pneumonia CFR of 1.07%. For those without access to health care, a CFR of 10% was assumed, giving a weighted mean CFR of 4%. Again, NPNM CFRs were assumed similar to those of pneumonia.

The base case parameter values for the three countries are summarised in Table 12.5.

Table 12.5: Hib disease burden parameters used in the base case analyses

Parameter	Belarus	India	Uzbekistan
2010 live births	94,200	26,542,850	558,459
Under-five mortality rate	6	63	5
2010 life expectancy at birth (years)	70	65	68
Incidence per 100,000 children < 5 yrs:			
All-cause clinical pneumonia	2,302	NA	2,277
All-cause severe pneumonia	NA	3,280	NA
Hib NPNM	6.15	3.72	10.65
Hib meningitis	10.10	20.44	18.70
Proportion of clinical pneumonia due to Hib	4%	NA	4%
Proportion of severe pneumonia due to Hib	NA	22%	NA
Hib pneumonia incidence	115	722	114
Case fatality ratios:			
Hib pneumonia w/o access to care	NA	10%	10%
Hib pneumonia with access to care	0.3%	2%	1.07%
Hib NPNM w/o access to care	NA	10%	10%
Hib NPNM with access to care	2.5%	2%	1.07%
Hib meningitis w/o access to care	NA	100%	100%
Hib meningitis with access to care	3.2%	17%	17%
Treatment utilization:			
Percent of Hib cases accessing care	100%	71%	68%

12.2 METHODS USED FOR UNCERTAINTY ANALYSES

Uncertainty analysis was done according to methods recommended in a recent paper by Bilcke and colleagues on "accounting for methodological, structural and parameter uncertainty in decision-analytic models" [337]. Two types of analyses were carried out; univariate uncertainty analysis and probabilistic uncertainty analysis.

12.2.1 UNIVARIATE UNCERTAINTY ANALYSIS

The aim of the univariate uncertainty analysis was to investigate the impact of changes in methodological choices and selected parameter values. The sources of uncertainty and the assumptions made for this analysis are summarised in Table 12.6. Methodological choices were the perspective taken, the discount rate, inclusion of meningitis sequelae costs and age weighting of DALYs. Two structural model uncertainties were assessed; the herd immunity feature explained in Chapter 7 was set to 20% and waning immunity was set to 5% per year.

Model parameters that have been in particular focus in some of the previous chapters were included to demonstrate the sensitivity to a change in these values. These parameters were meningitis sequelae DALY disability weight, treatment costs, Hib vaccine price, Hib disease incidence rates and Hib disease CFRs.

Hib disease incidence rates assumed in the univariate analysis were those estimated by the Hib GBD project [58]. Using all published studies from the respective regions, the GBD project estimated a Hib meningitis incidence rate of 16 per 100,000 children less than five years for the WHO European region (EURO) (uncertainty range 12-22) and a rate of 27 (range 11-38) for the South East Asian region (SEARO) [31]. The WHO EURO estimate was used for Belarus and Uzbekistan and the WHO SEARO estimate for India (Table 12.6)

The GBD Hib pneumonia incidence rates for the WHO EURO region were 283 (range 259-463) per 100,000 children less than five years and 1,790 (range 1,635 – 2,925) for the WHO SEARO region [31]. Hence, for all three countries the GBD estimates were approximately twice as high as those estimated as part of this thesis. The pneumonia incidence estimates are thus likely to be the most uncertain parameters in the analysis. Due to the inherent problems of defining pneumonia accurately, studies on pneumonia incidence rates are rare and data are often conflicting [338]. As recently argued by Rudan and colleagues, further research on childhood pneumonia burden and pneumonia risk factors are urgently needed [339].

Table 12.6: Univariate uncertainty analysis assumptions

	Base case assumption	Assumption used in uncertainty analysis
Uncertain methodological choices:		
Economic perspective	Societal	Government
Discount rate	3%	0%
Age weighting of DALY estimates	Yes	No
Inclusion of lifetime costs of meningitis sequelae	No	Yes
Uncertain structural aspects:		
Herd immunity	None	20% additional vaccine effectiveness
Waning immunity	None	5% decrease in vaccine efficacy per year
Parameter uncertainty:		
Meningitis sequelae disability weight	0.291	0.616
Inpatient treatment costs	As specified in Table 10.10	Increase by 50%
Outpatient treatment costs	As specified in Chapter 10	Increase by 50%
Price per dose of Hib containing vaccine	US$ 4.95 in Belarus, US$ 1.75 in India, US$ 3.00 in Uzbekistan	US$ 1.50 in all three countries
Hib meningitis incidence per 100,000 children less than five years	Belarus: 10.10 India: 20.44 Uzbekistan: 18.70	Belarus: 16 India: 27 Uzbekistan: 16
Hib pneumonia incidence rate per 100,000 children less than five years	Belarus: 114 India: 722 Uzbekistan: 115	Belarus: 283 India: 1,790 Uzbekistan: 283
Hib disease CFRs	As specified in Table 12.5	Decrease by 20%

The GBD project estimated CFRs in EURO as 27%, 5%, and 1% for Hib meningitis, pneumonia and NPNM, respectively, and 44%, 2%, and 1% for the SEARO region [31]. Since these estimates are averages across diverse settings in terms of income and access to health services, they are not applicable to the country specific analysis. In the uncertainty analyses, the base case CFRs were instead decreased by 20% to investigate the impact a change in these has on the overall result.

12.2.2 PROBABILISTIC UNCERTAINTY ANALYSIS

Probabilistic uncertainty analysis was undertaken to simultaneously assess the uncertainty around all parameter values and generate 95% confidence intervals around the costs per DALY averted. This analysis was only done for Uzbekistan to demonstrate the principle.

Statistical distributions were fitted to all uncertain parameters that were not methodological or structural. Parameters with fixed values that were not considered uncertain, such as vaccine and syringe prices and the 2010 birth cohort, were not varied either. Distributional parameters, such as the proportion of cases accessing different types of care, were not attached a distribution either because these need to add to 100% for the model to run correctly. All parameters and distributions used are summarized in Table 12.7.

Distributions were fitted to parameters according to recommendations by Briggs and colleagues [340]. The beta distribution was used for probability parameters with values between 0 and 1, such as case fatality rates and the risk of meningitis sequelae. The lognormal distribution is frequently used to fit relative risks and this was used for the vaccine efficacy parameters; the 95% confidence intervals estimated in Chapter 8 were used for fitting the distribution. As explained in Annex 2, treatment costs are often highly skewed and the gamma distribution was used to fit these data. Since the Uzbekistan treatment costs were not derived from patient-level data, assumptions had to be made about the standard deviation to be able to fit the gamma distribution. The standard deviation was assumed similar to the mean value of all cost estimates, reflecting the findings of most of the treatment cost studies reviewed in Chapter 5. The gamma distribution was also used to fit the disease incidence parameters. This was considered an appropriate distribution because the GBD estimate for Hib pneumonia is twice as high as used in the base case, indicating a right hand skewed distribution when taking uncertainty into account. The GBD values were used as 95% confidence limits when fitting the incidence rates to the gamma distribution.

10,000 Monte Carlo simulations were run using Oracle Crystal Ball© software and the simulation data were analysed in STATA version 11.0. The importance of individual parameters to uncertainty in the result was assessed by analysis of covariance (ANCOVA), which summarises the proportion of the variance in the ICER explained by variation in the different input parameters [340].

Table 12.7: Assumptions used in probabilistic uncertainty analysis for Uzbekistan

Parameter	Base case value	Statistical distribution (parameters used to fit distribution)
Discount rate and DALY parameters		
Discount rate for disease impact	3%	NA
Discount rate for costs	3%	NA
DALY age weighting modulation factor (K)	1	NA
DALY age weighting parameter (β):	0.04	NA
DALY constant (C):	0.1658	NA
Demography		
2010 live births	558,459	NA
Infant mortality per 1000 live births	47	NA
Under five mortality per 1000 live births	57	NA
Life expectancy at birth (years):	68	NA
% of infant deaths in the neonatal period (<1m):	55%	NA
Hib disease burden		
Incidence rates per 100,000 children < 5 years		
Hib pneumonia	114	Gamma (95% CI: 283)
Hib meningitis	18.70	Gamma (95% CI: 20)
Hib NPNM	11	Gamma (95% CI: 16)
% case fatality ratios in ages 1-59m:		
Hib pneumonia	4%	Beta (100, 96)
Hib meningitis	42%	Beta (42, 58)
Hib NPNM	4%	Beta (100, 96)
Hib meningitis survivors with major sequelae	35%	Beta (35, 65)
DALY disability weights:		
Hib pneumonia	0.279	Beta (27.9, 72.1)
Hib meningitis	0.616	Beta (61.6, 38.4)
Hib NPNM	0.279	Beta (27.9, 72.1)
Meningitis sequelae	0.291	Beta (29.1, 70.9)
Mean duration of illness (in days):		
Hib pneumonia	9	Gamma (4, 2.25)
Hib meningitis	11	Gamma (4, 2.75)
Hib NPNM	9	Gamma (4, 2.25)
Age distribution of disease cases and deaths		
<3m:	10.6%	NA
3-5m	13.6%	NA
6-8m	17.8%	NA
9-11m	17.8%	NA
12-23m	23.8%	NA
24-35m	5.5%	NA
36-47m	5.5%	NA
48-59m	5.5%	NA
Hib vaccination coverage		
Coverage of 1st dose	98%	Beta (98,2)
Coverage of 2nd dose	98%	Beta (98,2)
Coverage of 3rd dose	98%	Beta (98,2)
Vaccine efficacy		
1 dose	59%	Lognormal (95% CI: 86%)
2 doses	92%	Lognormal (95% CI: 98%)
3 doses	93%	Lognormal (95% CI: 97%)
Vaccination impact assumptions		
% decrease in dose efficacy / yr	0.0%	NA
% contribution of herd effect in <5yrs	0.0%	NA
Vaccination costs		

Parameter	Base case value	Statistical distribution (parameters used to fit distribution)
Pentavelent vaccine		
Pentavalent price per dose	$3.00	NA
Percentage UNICEF handling charge	5%	NA
Percentage vaccine wastage	5%	Beta (5, 95)
Safety boxes:		
Price per box	$1.08	NA
Percentage handling:	25%	NA
Percentage wastage	5%	Beta (5, 95)
Number of syringes per safety box	100	NA
Systems costs per dose	US$ 0.06	NA
Syringes:		
Price per syringe	$0.06	NA
Percentage handling:	25%	NA
Percentage wastage	5%	Beta (5, 95)
Existing DTP vaccine		
Price per dose	$0.18	NA
Percentage handling charge	5%	NA
Percentage wastage	33.0%	Beta (33, 67)
Existing HepB vaccine		
Price per dose	$0.21	NA
Percentage handling charge	5.0%	NA
Percentage wastage	33.0%	Beta (33, 67)
Health care utilization		
Number of outpatient visits per case:		
Hib pneumonia	1.36	Gamma (1, 0.5)
Hib meningitis	1.36	Gamma (1, 0.5)
Hib NPNM	1.36	Gamma (1, 0.5)
Number of inpatient admissions per case:		
Hib pneumonia	0.68	Beta (2, 3)
Hib meningitis	0.68	Beta (2, 3)
Hib NPNM	0.68	Beta (2, 3)
Distribution of outpatient visits (%):		
Government outpatient clinic	100%	NA
Distribution of inpatient admissions (%):		
Pneumonia/NPNM:		
Primary hospital	66%	NA
Secondary hospital	31%	NA
Tertiary hospital	3%	NA
Hib meningitis:		
Primary hospital	64%	NA
Secondary hospital	32%	NA
Tertiary hospital	4%	NA
Treatment costs		
Household cost per outpatient clinic visit	$5.00	Gamma (1, 5)
Government cost per outpatient clinic visit	$1.53	Gamma (1, 1.53)
Household cost per inpatient admission:		
Hib pneumonia and NPNM:		
Primary hospital	$26.00	Gamma (1, 26)
Secondary hospital	$26.00	Gamma (1, 26)
Tertiary hospital	$26.00	Gamma (1, 26)
Hib meningitis:		
Primary hospital	$86.00	Gamma (1, 86)
Secondary hospital	$86.00	Gamma (1, 86)
Tertiary hospital	$86.00	Gamma (1, 86)

Parameter	Base case value	Statistical distribution (parameters used to fit distribution)
Government cost per inpatient admission:		
Hib pneumonia and NPNM:		
Primary hospital	$169.00	Gamma (1, 169)
Secondary hospital	$188.00	Gamma (1, 188)
Tertiary hospital	$242.00	Gamma (1, 242)
Hib meningitis:		
Primary hospital	$152.00	Gamma (1, 152)
Secondary hospital	$171.00	Gamma (1, 171)
Tertiary hospital	$190.00	Gamma (1, 190)
Lifetime sequelae costs	$0.0	NA

12.3 BASE CASE RESULTS

12.3.1 DISEASE IMPACTS

It was estimated that the vaccine annually prevents 505 Hib disease cases and three deaths in children less than five years in Belarus. In India, 615,805 cases and 32,152 deaths are averted, and in Uzbekistan 3,246 cases and 291 deaths are averted annually (Table 12.8). Deaths averted represent approximately 0.29%, 1.6% and 0.92% of total 2010 under-five mortality in Belarus, India and Uzbekistan, respectively. Discounted annual DALYs averted amounted to 155 in Belarus, 1,082,471 in India and 10,496 in Uzbekistan. For India, 97% of the DALY estimates were comprised of YLLs while YLDs were only 3%. For Belarus and Uzbekistan, YLLs encompassed 70% and 92% of the DALYs, respectively.

12.3.2 TREATMENT COST SAVINGS

Annual treatment costs with and without Hib vaccine from the societal perspective are also summarised in Table 12.8. Pneumonia hospital admission costs were the most important type of treatment costs in all three countries, comprising 49%, 89% and 73% of total treatment costs averted in Belarus, India and Uzbekistan, respectively. Outpatient costs comprised 4%, 6% and 6% of total treatment costs averted in Belarus, India and Uzbekistan, respectively.

Incremental vaccine costs exceeded total treatment cost savings in all three countries, as depicted in Figure 12.1. Hence, in the base case analysis, Hib vaccination is not predicted to be cost saving in any of the countries. In India, the government health sector finances 20% of Hib disease treatment costs and the remaining 80% are covered by households. In Uzbekistan, the proportions are reversed with households covering 20% and the government health sector 80% of total costs (Table 12.9).

12.3.3 COST-EFFECTIVENESS AND COST-UTILITY ESTIMATES

Four different ICERs are seen in Table 12.9; incremental costs per sequelae case averted, per discounted premature death averted, per discounted life year gained and per discounted DALY averted. Incremental costs per discounted DALY averted amounted to US$ 8,911 in Belarus, US$ 51 in India and US$ 357 in Uzbekistan. The ICER is lower in India compared to the two other countries mainly due to the lower Hib vaccine price and the higher Hib pneumonia incidence rate.

As explained in Chapter 4, the WHO has established cost-effectiveness thresholds that can be used as a guide to determine whether an intervention is cost-effective. If costs per

Table 12.8: Hib disease cases and treatment costs with and without Hib vaccine for the 2010 birth cohort (societal perspective)

	Belarus			India			Uzbekistan		
	No vaccine	**Vaccine**	**Prevented**	**No vaccine**	**Vaccine**	**Prevented**	**No vaccine**	**Vaccine**	**Prevented**
Cases:									
Hib pneumonia	504	61	443	908,593	312,728	595,866	2,994	414	2,581
Hib meningitis	44	5	39	25,723	8,853	16,869	492	68	424
Hib NPNM	27	3	24	4,681	1,611	3,070	280	39	241
Meningitis sequelae	5	1	4	5,312	1,823	3,489	100	14	86
TOTAL	**575**	**70**	**505**	**938,997**	**323,192**	**615,805**	**3,766**	**520**	**3,246**
Premature deaths:									
Hib pneumonia	1	0	1	38,284	13,177	25,107	120	17	103
Hib meningitis	1	0	1	10,546	3,630	6,916	207	29	178
Hib NPNM	1	0	1	197	68	129	11	2	10
TOTAL	**3**	**0**	**3**	**49,027**	**16,875**	**32,152**	**338**	**47**	**291**
Discounted DALYs	177	21	155	1,648,595	566,124	1,082,471	12,166	1,671	10,496
No. of outpatient visits	1,903	232	1,672	688,275	236,896	451,378	5,122	707	4,415
No. of hospital admissions	647	79	568	666,688	229,466	437,222	2,561	354	2,207
Outpatient visit costs (US$):									
Hib pneumonia	14,082	1,713	12,369	6,471,527	2,227,427	4,244,101	26,592	3,673	22,920
Hib meningitis	2,883	351	2,533	366,421	126,118	240,303	4,368	603	3,765
Hib NPNM	752	92	661	66,687	22,953	43,734	2,488	344	2,144
TOTAL	**17,718**	**2,155**	**15,563**	**6,904,635**	**2,376,497**	**4,528,138**	**33,448**	**4,620**	**28,828**
Inpatient admission costs (US$):									
Hib pneumonia	214,366	26,077	188,289	97,771,551	33,651,863	64,119,688	413,507	57,112	356,395
Hib meningitis	190,085	23,123	166,961	4,567,206	1,571,981	2,995,225	82,140	11,345	70,795
Hib NPNM	11,454	1,393	10,061	503,754	173,386	330,367	38,681	5,343	33,339
TOTAL	**415,905**	**50,594**	**365,311**	**102,842,510**	**35,397,230**	**67,445,280**	**534,328**	**73,800**	**460,528**
TOTAL TREATMENT COSTS	**433,623**	**52,749**	**380,874**	**109,747,145**	**37,773,727**	**71,973,418**	**567,776**	**78,420**	**489,356**

Figure 12.1: Comparison of annual incremental vaccine costs and treatment costs averted for the base case analysis (2010 US$)

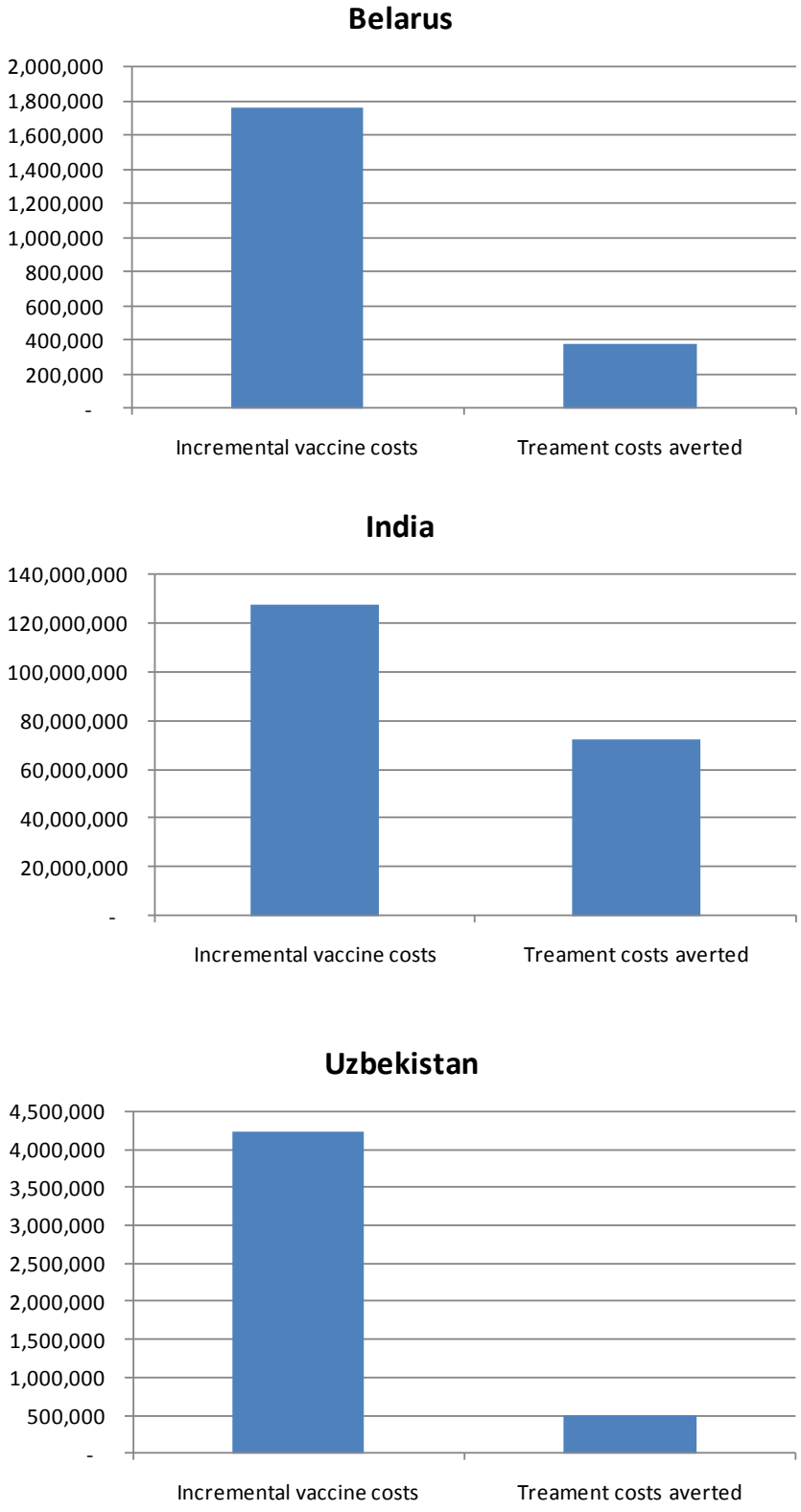


Table 12.9: Incremental cost-effectiveness of Hib vaccine for the 2010 birth cohorts in Belarus, India and Uzbekistan: Base case analysis

	Belarus	India	Uzbekistan
Annual incremental vaccine costs (US$)	1,764,322	127,173,579	4,241,611
Annual government treatment costs averted (US$)	380,874	14,366,948	392,597
Annual household treatment costs averted (US$)	NA	57,606,470	96,760
Total annual treatment costs averted (US$)	380,874	71,973,418	489,357
Annual net costs (US$) (vaccine costs – treatment costs averted)	1,383,448	55,200,161	3,742,337
Hib cases averted	505	615,805	3,246
Hib meningitis sequelae cases averted	4	3,489	86
Premature Hib deaths averted	3	32,152	291
Discounted DALYs averted	155	1,082,471	10,496
Incremental costs per discounted premature death averted (US$)	437,282	1,717	12,863
Incremental costs per meningitis sequelae case averted (US$)	390,302	15,822	43,437
Incremental costs per discounted life year gained (US$)	12,797	53	387
Incremental costs per discounted DALY averted (US$)	8,497	51	352

DALY averted are less than GDP per capita, the intervention is regarded highly cost-effective; if costs per DALY averted are between one and three times GDP per capita the intervention is considered cost-effective; and if costs per DALY averted are more than three times GDP per capita, it is not deemed cost-effective [341]. When using these thresholds, Hib vaccine is considered highly cost-effective in India and Uzbekistan and cost-effective in Belarus (2010 GDP per capita was US$ 5,950 in Belarus, US$ 1,330 in India and US$ 1,280 in Uzbekistan).

12.4 UNCERTAINTY ANALYSES

12.4.1 UNIVARIATE UNCERTAINTY ANALYSIS

The univariate uncertainty analyses are seen in Figures 12.2 – 12.4. In Belarus, increases in the Hib disease treatment costs only make a marginal difference to the ICER. While the vaccine does of course become more cost-effective when treatment costs are increased by 50% and when meningitis sequelae costs are included, the difference compared to the base case is relatively small. A decrease in the DTP-Hib vaccine price to US$ 1.50 per dose would make the vaccine highly cost-effective. However, such a large price reduction is unrealistic. When using the GBD pneumonia incidence rate, cost-effectiveness improves substantially, with the ICER below GDP per capita.

In India, Hib vaccine is estimated to be cost saving from a societal perspective when using the GBD pneumonia incidence rate and when including the lifetime costs of sequelae. Annual cost savings amount to US$ 46 million when using the GBD pneumonia incidence rate and to US$ 83 million when including sequelae costs. Since the Indian Government only finances about 20% of total treatment costs, the vaccine is still not cost saving from a government perspective in these scenarios.

In Uzbekistan, the vaccine does not become cost saving in any of the scenarios, but when including lifetime costs of meningitis sequelae and when using the GBD pneumonia incidence rate, the ICERs are low; US$ 30 and US$ 107 per discounted DALY averted, respectively.

Since life years gained represent as much as 76%, 97% and 92% of the total DALYs caused by Hib disease in Belarus, India and Uzbekistan, respectively, discounting makes a considerable difference to the ICER. Without discounting future values, the results are US$ 3,908, US$ 21 and US$ 148 in Belarus, India and Uzbekistan, respectively. In India and Uzbekistan, the result is also very sensitive to decreases in the case fatality rates. Consequently, if a greater proportion of children accessed health care facilities and

Figure 12.2: Univariate sensitivity analysis for Belarus. Cost per discounted DALY averted (2010 US$)

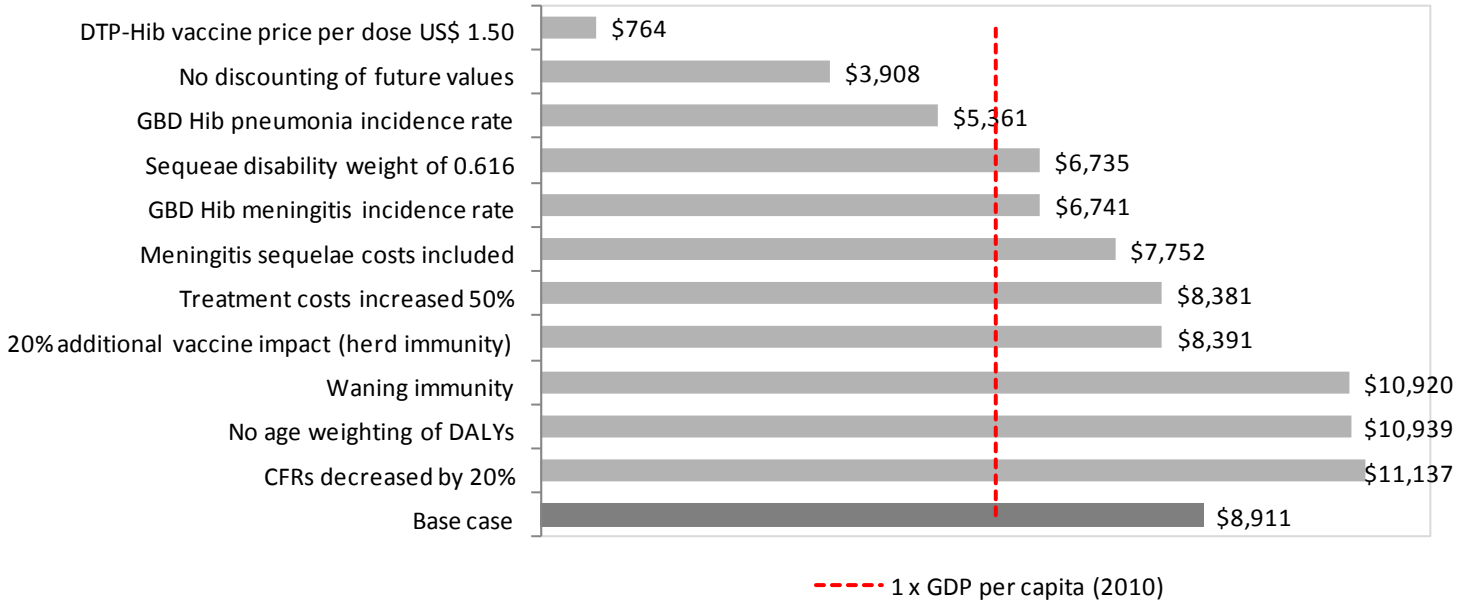


Figure 12.3: Univariate sensitivity analysis for India. Cost per discounted DALY averted (2010 US$)

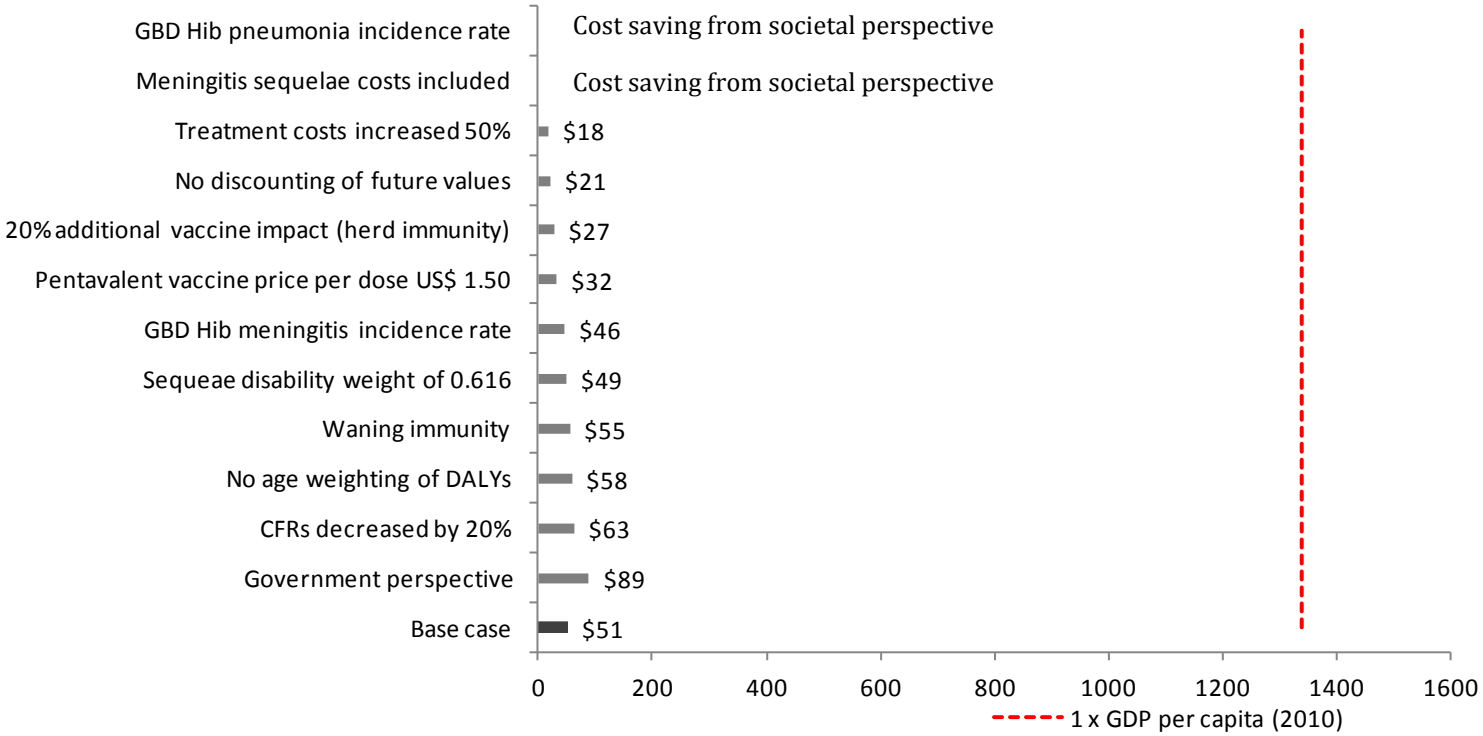
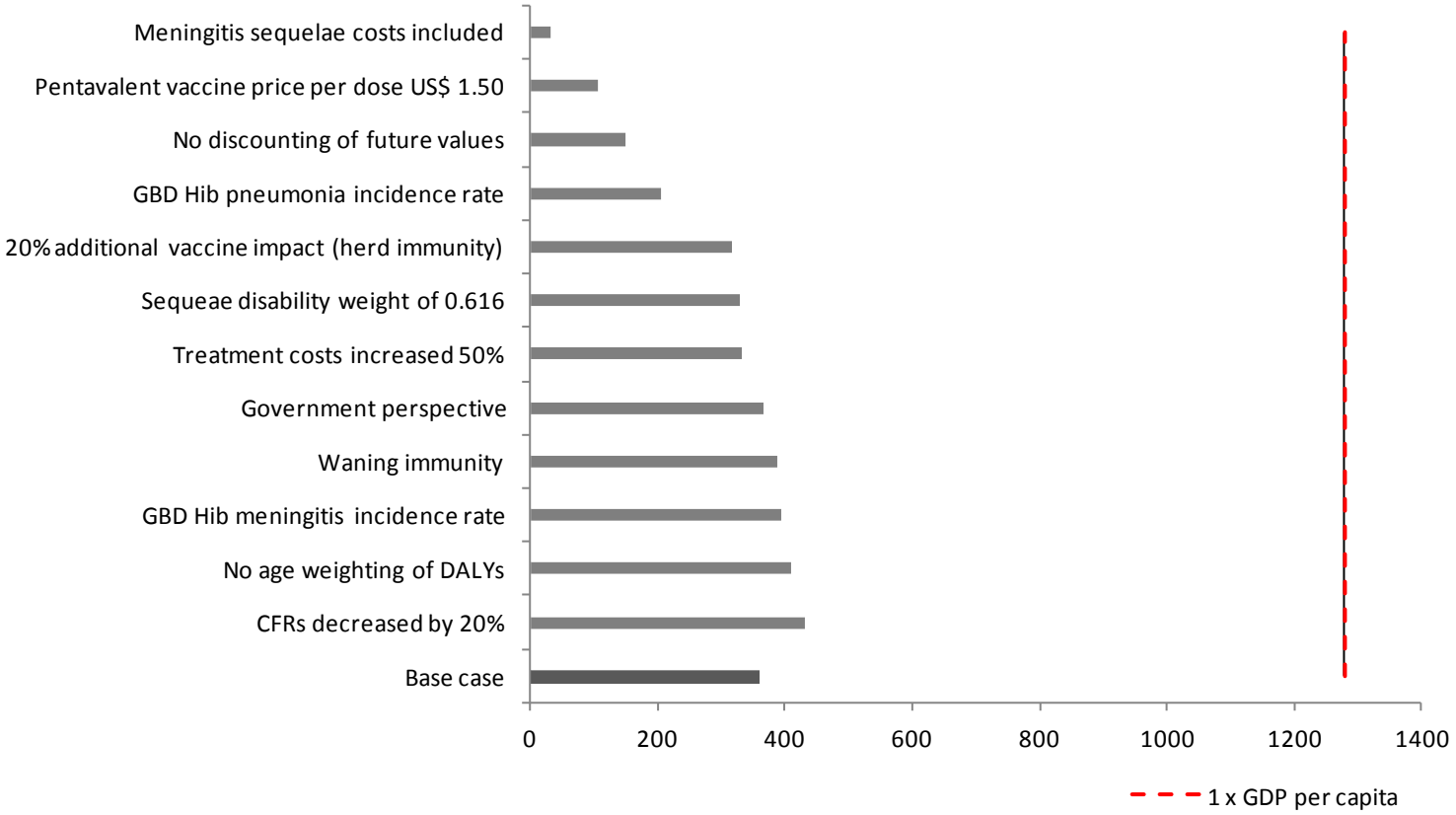


Figure 12.4: Univariate sensitivity analysis for Uzbekistan. Cost per discounted DALY averted (2010 US$)



received appropriate, life saving treatment, the ICER increases, implying that the vaccine becomes less cost-effective. While an increase in the meningitis sequelae disability weight makes a noteworthy difference to the Belarus result, the impact is negligible in India and Uzbekistan due to the higher meningitis case fatality rates in these two settings. When using the Uzbekistan GAVI co-financing amount of US$ 0.20 per dose instead of the vaccine price, Hib vaccine is cost saving for the government. Each year, the Uzbek government saves approximately US$ 7.44 million; 6.21 million for vaccines and syringes donated by GAVI and 1.23 million in treatment costs averted.

PROBABILISTIC UNCERTAINTY ANALYSIS FOR UZBEKISTAN

In the probabilistic uncertainty analysis mean costs per discounted DALY averted amounted to US$ 257 (95% CI 136, 312) from the societal perspective and US$ 379 (95% CI 161, 332) from the government perspective (Table 12.10). The probabilistic distribution is seen in Figure 12.5. From the societal perspective, the maximum value of the Monte Carlo simulation was US$ 342 per discounted DALY averted, which is still considerably below the GDP per capita threshold of US$ 1,280. Hence, when using this decision making criteria there is zero probability that the vaccine is not cost-effective in Uzbekistan. This is also seen in the cost-effectiveness acceptability curves in Figure 12.6.

The importance of the individual uncertain parameters for the result is seen in the ANCOVA analysis in Figure 12.7. As was also seen in the univariate sensitivity analysis, the incidence of Hib pneumonia is by far the most important contributor to uncertainty in the result. This parameter value explains as much as 93% of the uncertainty in the probabilistic analysis. The second and third most important parameters are vaccine efficacy against Hib meningitis and Hib pneumonia, respectively.

Table 12.10: Probabilistic uncertainty analysis (2010 US$)

Variable	Societal perspective	Government perspective
Costs per DALY averted in base case	357	366
Simulation results:		
Mean costs per discounted DALY averted	257	279
Median costs per discounted DALY averted	277	299
Minimum	-106	-55
Maximum	342	362
5% percentile	135	161
95% percentile	312	332

Figure 12.5: Probability distribution of simulation results (societal perspective)

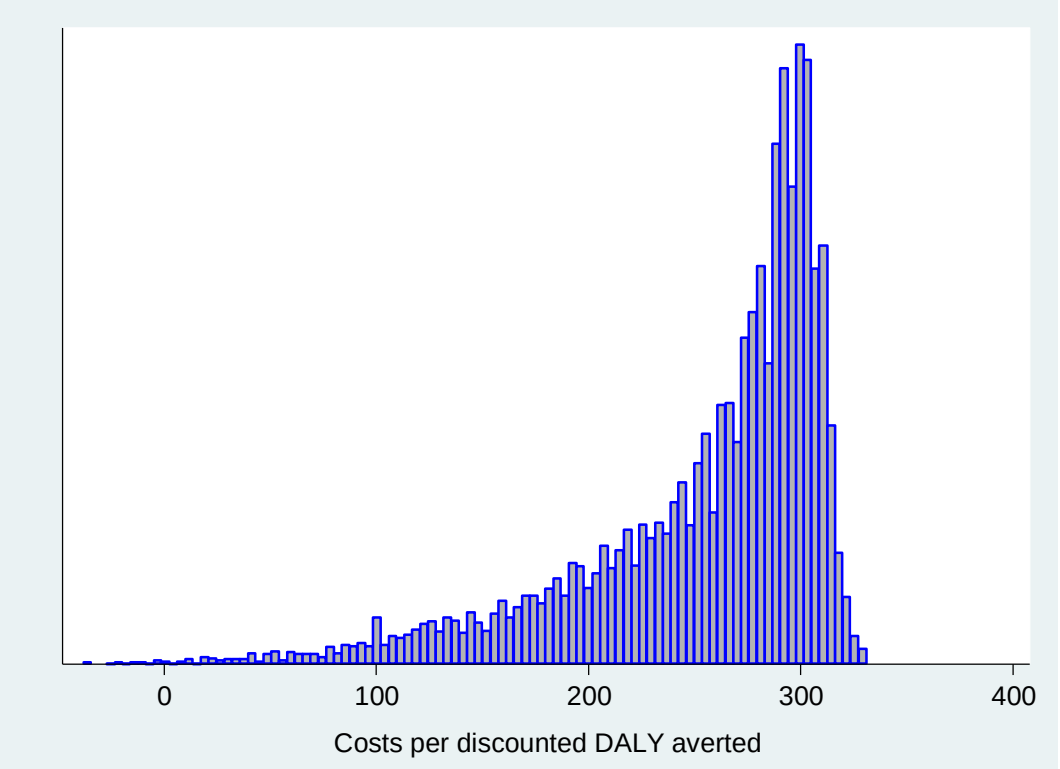


Figure 12.6: Cost-effectiveness acceptability curves for Hib vaccine in Uzbekistan
Costs per discounted DALY averted

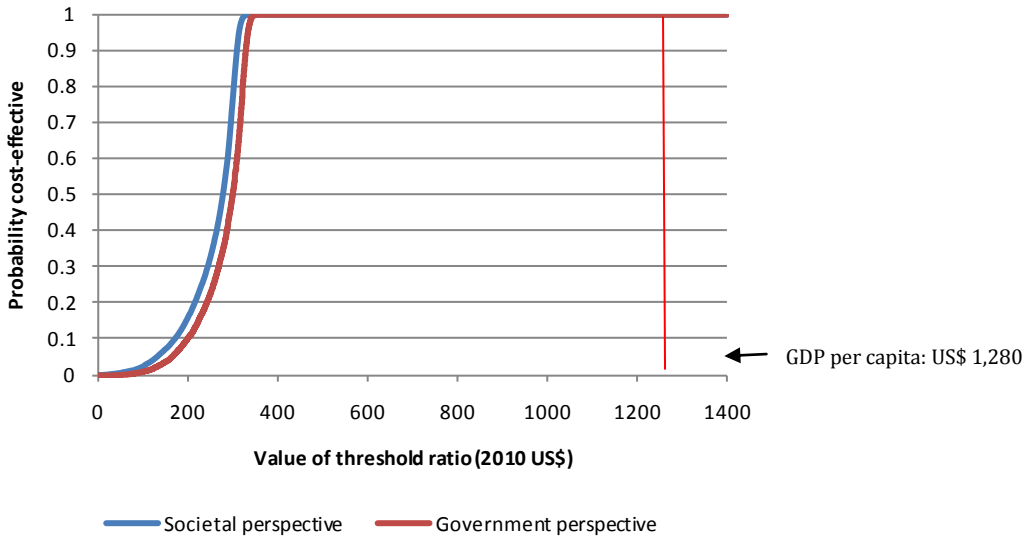
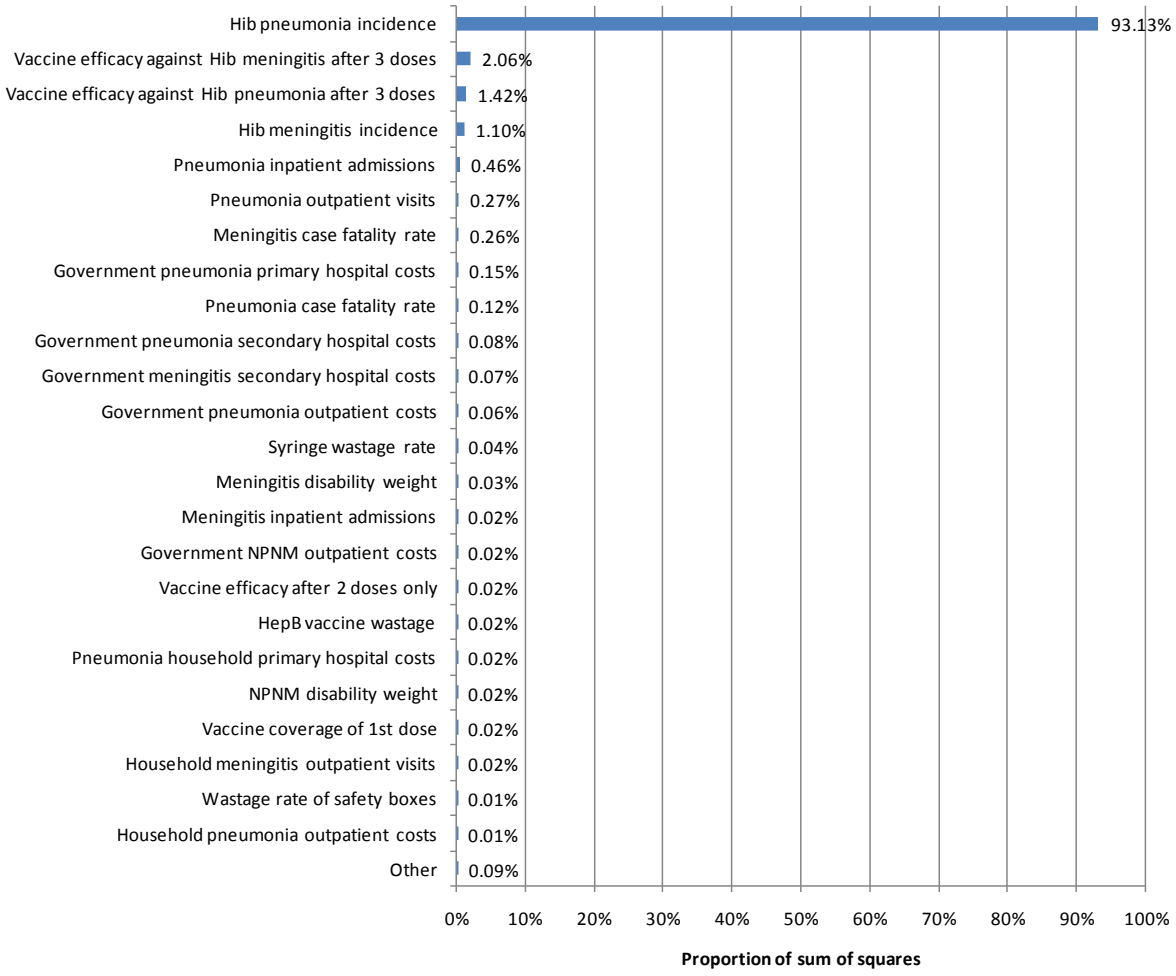


Figure 12.7: Importance of uncertainty of individual parameters (ANCOVA analysis)



12.5 DISCUSSION

The analysis demonstrated that the ICERs are considerably less in India and Uzbekistan than in Belarus. One of the important reasons for this difference is that the baseline Hib mortality burden, expressed as case fatality rates, is higher in India and Uzbekistan than in Belarus, leading to more deaths averted per child vaccinated. The under-five mortality rates are 17 times higher in India and Uzbekistan than in Belarus [32] and the proportion of under five mortality due to pneumonia is approximately 16% and 21% in India and Uzbekistan [32, 342], respectively, while only 4% in Belarus [32]. Hence, Hib vaccine will prevent proportionally more deaths in India and Uzbekistan than in Belarus and since mortality is the most important driver of DALYs, the ICER becomes more favourable in the two low-income countries.

Another critical explanation for the ICER difference is that the vaccine price is higher in Belarus than in the two other countries and that Belarus uses a four-dose schedule while only three doses are used in India and Uzbekistan. Incremental vaccine costs per child are consequently US$ 21.17 in Belarus and only US$ 6.6 and US$ 7.0 in India and Uzbekistan, respectively. A booster dose is recommended in countries where Hib disease is a substantial problem in children above 12 months [295]. In the Minsk city meningitis surveillance it was found that as many as 80% of Hib cases were above 12 months; confirming the need for a booster dose. The requirement for a booster dose might be less in India and Uzbekistan. In a review of Hib disease age distributions, Bennett *et al*. found that while 60% of cases were above 12 months in the WHO European region, the average was only 20% in the WHO South East Asian region [22]. It is thus possible that a similar impact is achieved in India and Uzbekistan with three doses as with four doses in Belarus, but this hypothesis can only be confirmed by undertaking intensive Hib disease surveillance to assess if there is waning immunity.

When deciding whether Hib vaccine is a good use of scarce resources, the ICER values need to be viewed in relation to ability and willingness to pay for health care. The 2010 GDP per capita was US$ 5,950 in Belarus, US$ 1,330 in India and US$ 1,280 in Uzbekistan [109]. Hence, in relative terms, the Belarus government is able to pay considerably more per DALY averted than the two other governments. According to the WHO cost-effective thresholds, Hib vaccine can be considered highly cost-effective in India and Uzbekistan and cost-effective in Belarus. Economic evaluations of rotavirus vaccine have been undertaken in India and Uzbekistan [343, 344]. At a rotavirus vaccine price of US$ 5 per course, it was estimated that the costs per discounted DALY averted amounted to between US$ 75 and US$ 242 in Uzbekistan [345]. In the India analysis, a vaccine price of US$ 1.00

per dose was used, which resulted in costs per discounted DALY averted of US$ 21.41 [343]. Hence, these values are comparable to the findings for Hib vaccine.

To increase the strength of analysis, it was prioritised to use data from national surveillance systems, even if more reliable values might be available from large-scale epidemiological studies in other countries. The analysis is thus an example of how to undertake an economic evaluation with data gathered from routine data sources while using results from other countries only as a quality marker. Undertaking the analysis for three countries simultaneously brings several advantages as useful comparisons can be made on both parameter values and the overall results. Moreover, a key limitation frequently stated regarding economic evaluation studies is that they cannot easily be compared because of differences in methodologies. This study facilitated such a comparison by using the same decision-analytic model for the three countries.

One of the most important advantages of the decision-analytic model is that it integrates numerous types of information on Hib disease into one analysis. Hospital surveillance sentinel site studies on Hib disease have been undertaken in Belarus and India, but on their own these surveillance data are often inadequate for decision making on vaccine introduction. When using the data in the model for prediction of disease burden and vaccine impact on a population level the information becomes much more useful for decision makers. Hib pneumonia incidence was by far the most uncertain parameter in the analysis and the robustness of the result will be greatly improved if more evidence was available on pneumonia incidence, treatment seeking behaviour and case fatality rates. Routine pneumonia surveillance data is problematic to use due to the difficulties of making accurate diagnosis and because not all children receive care. However, when I presented the analysis to the Ministry of Health in Belarus and specifically asked to what extent the pneumonia surveillance data can be considered reliable, the response was that the surveillance data reflect reality and are not believed to underestimate the real burden. Hence, even though international studies conclude that pneumonia is the greatest contributor to under-five mortality [32], it is difficult to use these findings when local data say otherwise.

While data on Hib pneumonia disease burden from Eastern Europe and Asia remain scarce, it was shown that the vaccine can be considered cost-effective despite conservative assumptions about incidence and mortality. However, international cost-effectiveness thresholds say nothing about affordability, and with increases in total vaccine costs of 84% (Belarus), 101% (Uzbekistan) and 302% (India), the governments must carefully

consider the long-term financial sustainability. The GAVI Alliance is currently increasing its support for pneumococcal and rotavirus vaccine introductions and it is likely that its support to Hib vaccine will stop when the current five year commitments come to an end. In countries with relatively high under-five mortality, such as India and Uzbekistan, Hib vaccine is a highly cost-effective intervention and it is therefore vital that future financial sustainability of the vaccine is secured.

13 CONCLUSIONS AND REFLECTIONS

Each chapter in this thesis addressed a separate topic with individual findings. In this final chapter, the main conclusions from the chapters are briefly summarised and the overall conclusion synthesised. Challenges encountered when undertaking health economic research in low- and middle-income countries are first of all reflected upon. This is followed by a summary of thesis conclusions and discussion on the applicability of the results, especially to what extent cost-effectiveness evidence on vaccines is being used for decision making in resource poor settings.

13.1 CHALLENGES OF WORKING IN RESOURCE POOR SETTINGS

It is generally highly rewarding to conduct health economic research in resource poor countries, but there are also a number of challenges specific to these settings. I now reflect upon three types of difficulties; data limitations, problems with ensuring capacity building, and complexities of working in the midst of poverty.

1. Data limitations

One of the things that distinguish health economic research in low-income compared to high-income countries is the many data limitations faced during all aspects of the study. Since very few routine data collection systems are in place, it is often necessary to collect all data from scratch. When undertaking an economic evaluation it is therefore a key advantage to work alongside an epidemiological study which aims to evaluate the impact of the intervention in question as data needed for the effect estimates are then collected by colleagues with the appropriate expertise. For all cost estimates primary data collection will however have to be established. As was explained in this thesis, treatment cost estimates involve substantial primary data collection of both resource utilisation and unit costs and such studies can take years to complete.

2. Health economics capacity building

One issue that demands considerable investment and is more difficult than one might expect is to identify skilled collaborators and ensure that health economic capacity building is integrated into the research project. Skilled health economists are rare in low-income countries and the few that are present are often overcommitted. A common error is to underestimate the time it takes to train relatively inexperienced researchers in health economic principles and to expect that he/she can be responsible for data collection and analysis without close supervision. In my experience, substantial time, patience and

resources are needed to fully ensure that the collaborator takes ownership of the study. In reality, the project is often under time pressure and to guarantee that the work gets done it is often easier to take over and complete the work yourself, but this defeats capacity building. The underlying problem is that all types of skilled human resources are scarce in low-income settings and this is exacerbated by the fact that the field of health economics is still relatively new and training opportunities scarce. Health economics is rarely recognised as an independent discipline, so research collaborators normally come from many other backgrounds and it therefore becomes necessary to train these people in basic principles while they work on the study. On the African continent a health economics degree can only be obtained from universities in South Africa.

3. Undertaking a study in the midst of poverty

Sources of funding for most research studies originate from high-income countries and the principal investigator is often from one of these countries. As a consequence, there are generally considerable differences in salary levels between local collaborators and the international team. This can be a source of friction and it is challenging to ensure some kind of equity between team members. A second difficulty is that it is often a perception that the study is better resourced than it actually is. When working in settings where most people struggle to make a livelihood, many individuals would like to benefit financially from the study. It is thus imperative that strict control is held with the budget as numerous extra-budgetary expenses are likely to appear, often with inflated prices. This happens because people try to take advantage of the study by adding extra activities and as foreigners it can be difficult to know what is really needed and to judge what level of remuneration is reasonable. A third challenge related to this is that several people can be paid by the project on a short-term basis, such as for instance data collectors. It is not easy to realise that the livelihood of entire families sometimes depend on this sole salary and when the project ends the prospects of finding another source of income are limited. It is difficult not to feel a sense of responsibility for these people, but with a time limited research project there is little one can do. A fourth challenge is when extreme poverty is encountered during data collection. As an example, some of the families interviewed for the Senegal study were in dire need and two mothers asked me directly for financial assistance. In as much as one would like to help, it is extremely difficult to get involved because the need is so great and when faced with the situation it is hard to judge what is best to do.

13.2 SUMMARY OF THESIS CONCLUSIONS

The most important conclusion from Chapter 2, which gave a background on Hib disease, was the inherent difficulties in detecting Hib, especially in resource poor settings with limited laboratory capacities. Even though the term "*haemophilus*" means "blood-loving" in Greek, the sensitivity of blood tests for Hib are low and CSF is needed to increase detection rates. However, strict laboratory procedures must be followed to successfully identify Hib from CSF.

In Chapter 3, the global uptake of Hib vaccine in routine vaccination programmes was described. A key message from this chapter was that it is very unlikely that the vaccine would have been introduced into low-income countries if the GAVI Alliance had not been established and started to offer the vaccine free of charge. As of early 2012, 172 countries in the world had introduced the vaccine, but 24 countries have not done so.

A brief background to economic evaluation was given in Chapter 4. It is important to know that a critical attribute of vaccines, which distinguishes their analysis from that of other interventions, is that vaccination decreases circulation of the pathogen causing herd immunity. When this indirect effect is omitted from an economic evaluation, the result is likely to be an underestimate of the full health impact.

In the systematic literature review of Chapter 5, a total of 17 economic evaluations of Hib vaccine were identified; eight were from low- and middle-income countries. However, several of the studies had flaws. The most important deficiencies were sub-optimal modelling approaches, unreliable sources used for health outcome measurement, omission of Hib pneumonia in disease impact predictions, and non-transparent methods used for treatment cost calculations.

Following description of the thesis aims and objectives in Chapter 6, the decision-analytic model was presented in Chapter 7. The model is a deterministic aggregate-level static decision tree model depicting Hib disease progression for a specified cohort. The improvement in model structure compared to other Hib vaccine decision-analytic models includes incorporation of all Hib disease types, separation of meningitis sequelae into different syndromes, and integration of access to health care and health care utilisation within the model structure, enabling treatment costs and CFRs to be linked to these parameter values. In addition, the model offers a higher level of transparency than most of the published Hib vaccine economic evaluations.

A meta-analysis of Hib vaccine efficacy was the topic of Chapter 8. This is the first dose-specific Hib vaccine efficacy analysis and the first time that all available outcome measures have been presented in a common analysis. The pooled vaccine efficacies against invasive Hib disease after two and three doses were 92% and 93%, respectively. Vaccine efficacy after one dose was 59%. There was large heterogeneity between studies that estimated vaccine efficacy against hospitalised and radiological pneumonia, so no firm conclusion could be made about efficacy against these outcomes. Two studies documented 4% efficacy against clinical pneumonia, but one of the key messages of the chapter was that caution must be taken when extrapolating vaccine efficacy values against non-specific outcome measures to other settings.

In Chapter 9, DALYs were calculated for acute Hib diseases and for meningitis sequelae. Numerous limitations with the DALY approach became apparent. It was shown that the measure is problematic to use when the disease in question has a wide range of severities and/or numerous different syndromes, such as for instance meningitis sequelae. It was also concluded that for diseases causing relatively high premature mortality, as is the case for Hib disease in low-income settings, the YLL proportion of the DALY equation dominates the overall result and the YLD fraction is only of marginal importance.

Hib disease treatment costs for acute diseases and for meningitis sequelae were presented in Chapter 10. One of the findings from the Senegal meningitis sequealae study was that children with disabilities have no access to rehabilitation services. In societies like Senegal, services are severely limited largely because the health system grants no financial risk protection to families with disabled children. For this reason, mean direct treatment costs of meningitis sequealae amounted only to 2% of what was spent by households during the acute episode. However, the opportunity costs of looking after a disabled child were a substantial financial burden to the families. This is the first study to estimate the household costs of caring for a child with disabilities in a low-income country.

One of the key messages of Chapter 11 was that the Hib vaccine price has decreased more slowly than was expected by the global community when GAVI was established twelve years ago. For this reason it has been necessary to extend the period of support to ensure that the vaccine is kept in programmes in low-income countries. In Belarus and Uzbekistan, Hib vaccine introduction caused approximately a doubling of the vaccine budget and in India it lead to a quadrupling. The main conclusion from the Ethiopian study on incremental systems costs of pentavalent vaccine introduction was that the cold chain

system could not accommodate a switch to a smaller vial size without a relatively large investment in storage capacity and increased recurrent transport costs.

The overall findings of the thesis were embedded in the cost-utility estimates of Hib vaccine in Belarus, India and Uzbekistan presented in Chapter 12. In this analysis, many of the parameter values generated in the previous chapters were used. It was concluded that Hib vaccine can be considered a cost-effective intervention in all three settings and especially so in India and Uzbekistan. The lower ICERs in these countries compared to Belarus were largely explained by higher case fatality rates of Hib disease cases, leading to a relatively greater number of premature deaths averted, and lower Hib vaccine prices. When costs of sequelae are included in the analysis, the vaccine becomes even more cost-effective and possibly cost saving in some settings, including in India. The probabilistic analysis showed that uncertainty surrounding the Hib pneumonia incidence rate is by far the largest contributor to uncertainty in the cost-effectiveness estimate. This is not a surprising result; the problem of defining the true burden of Hib pneumonia has always been the greatest challenge for determining the value of Hib vaccine [175, 176, 178, 346].

In this thesis, the epidemiology and costs of Hib disease and the efficacy and costs of Hib vaccine were investigated in depth. A decision-analytic model was used to bring all the new information together. This is the first time that the cost-effectiveness of Hib vaccine has been analysed for different settings within a common framework. The overall conclusion of the thesis is that Hib disease has been an unrecognized problem in most settings and as a consequence the value of Hib vaccine has been underappreciated. The most important reasons for under acknowledgement of Hib disease as a problem are the enduring difficulties with determining the overall burden of pneumonia in children and assigning what proportion of this burden is due bacterial infections, including Hib. While the problems of determining the burden of Hib pneumonia were addressed in this thesis, the issue was by no means resolved. Substantial epidemiological and health systems research is needed to make progress in this area, as recently argued by Rudan and colleagues [339]. The main contribution of the thesis in terms of Hib pneumonia was to show that even though lack of knowledge about pneumonia disease burden is the biggest reason for uncertainty when determining the impact of Hib vaccine, the vaccine can be considered cost-effective across the whole range of plausible pneumonia incidence rates.

A second principal reason for under appreciation of the vaccine is limited understanding about the total costs of meningitis sequelae. Lack of data has meant that this parameter has until now not been incorporated into the decision-making process for Hib vaccine in

low- and middle-income countries. This thesis has made a major contribution in this area by demonstrating the household costs of meningitis sequelae in Senegal. It is hoped that the Senegal study will lead to greater awareness about meningitis sequelae disease burden and its associated costs, and that it will guide the way for more research in this field.

I believe that a third reason for ambiguities with regard to appreciating the value of Hib vaccine has been a lack of transparency in research studies. As was shown in the literature review of Hib vaccine economic evaluations, many previous studies did not incorporate all types of Hib diseases and the assumptions made for estimating health impacts and treatment costs, and the methods used when combining the data in a decision-analytic model, were not clearly explained. These non-transparent studies have added to the mystification about the true value of Hib vaccine. When a claim of cost-effectiveness of the vaccine is based on methods and assumptions that are not well justified, there is a danger that stakeholders view the study more as an advocacy exercise than as research demonstrating the true impact. In this thesis efforts were made to clearly explain and justify all assumptions, sources and methods used to generate the estimates and it is hoped that this will increase the confidence in the result.

13.3 APPLICATION OF FINDINGS

Economic evaluation of new and underused vaccines are generally undertaken to provide evidence for decision-makers when they consider whether or not to introduce the vaccine into the routine immunization schedule. The target audience is most often policy makers within the Ministry of Health. However, since only few low- and lower middle-income countries finance Hib vaccine from their government budgets, the present analysis was also targeted to international donors, such as the GAVI Alliance.

In a recent study on decision making factors for new vaccine introduction, two criteria were highlighted as being considerably more important than others; disease burden and political issues [140]. The qualitative study was undertaken in five GAVI eligible countries (Bangladesh, Mali, Ethiopia, Kenya and Cameroon) and in two middle-income countries (Guatemala and South Africa). The study showed that in all of the countries decisions to adopt a new vaccine were largely political, and that in the GAVI eligible countries, availability of GAVI funding was the main driver for introduction [140]. In the two non-GAVI eligible countries, the decision to adopt new vaccines was dominated by politics. In both Guatemala and South Africa, the Minister of Health largely made the decision unitarily without consulting technical experts. Cost-effectiveness evidence and financial considerations were not one of the most important factors in any of the seven case study

countries. However, the issue was appreciated in Kenya where it was felt that the evidence of Hib vaccine impact and cost-effectiveness generated by long-standing research at the Kenya Medical Research Institute [125, 198] increased the confidence of policy makers to believe that it was a right decision to introduce the vaccine.

It is not a new finding that the use of economic evaluations on health care decision making is limited. During the 1990s this was also shown in studies from Australia and the UK, with some of the reasons for limited use found to be poor generalisability of results, narrowness of research questions, and lack of methodological rigor in many published studies [347, 348]. However, during the past decade this has gradually changed as cost-effectiveness evidence has become a requirement for introduction of new health technologies within national health services in several high-income countries [349, 350, 351]. It is however a fact that several other aspects than demonstrated cost-effectiveness generally drives the decision to adopt a new health technology, most importantly probably political pressures. There are certain facets about vaccines that could make them even more political than other health interventions, especially in low-income countries. First, since vaccines prevent disease in a broad spectrum of the population, introduction is generally regarded positively by the public, so from a political viewpoint introduction of a new vaccine can be seen as an "easy win". Secondly, in many low-income countries, vaccines are one of the only health interventions available free of charge to a large proportion of the population, so new vaccine introduction is one of the most equitable health interventions available to a politician. Lastly, the intervention is relatively simple to deliver and integrate into the health system, so to a politician a new vaccine can seem as a relatively straightforward way of doing something concrete to improve the health of the population.

The usefulness of the present analysis differs between the three study countries. With regard to Hib vaccine adoption, Uzbekistan is a relatively typical GAVI eligible country; Hib vaccine was introduced when GAVI support for hepatitis B vaccine came to an end and it is unlikely that the vaccine would have been adopted without GAVI funding. The present economic evaluation has thus not been used as a decision-making factor in Uzbekistan. However, the analysis was requested by the EPI manager in preparation for the time when GAVI support comes to an end. It is thus possible that the study will be referred to by Uzbek decision makers in 2015.

India is in many ways a special case with regard to adoption of new vaccines. Even though the country has a striving vaccine industry that supplies vaccines to a large proportion of

the world's population, the Indian vaccine schedule is one of the most basic in the world and vaccination coverage is as low as 20% in some states. Hib vaccine has only been introduced into two of the 28 states and this only happened in late 2011. A campaign against Hib vaccine by a selection of Indian medical professionals has delayed introduction [299]. As was stated by one of the members of India's National Technical Advisory Group on Immunization (NTAGI) in 2010, "Concrete steps to introduce the pentavalent vaccine into the immunisation programme are still not visible. India's anti-vaccine lobby appears to have succeeded in influencing the health bureaucracy". Lack of evidence on the impact and cost-effectiveness of Hib vaccine is the key argument of the India anti Hib vaccine lobby. They have for instance stated that "the incidence of Hib appears low; immunisation against Hib would be a waste of scarce public resources" and that "the vaccine against DTP costs less than three rupees; the pentavalent vaccine could cost 300 rupees" [299]. The problems with transparently defining the burden of Hib pneumonia is also at the forefront of the debate. A leading anti Hib vaccine activist has for instance stated that "The Indonesian study showed more cases of pneumonia among vaccinated children, and the Bangladesh study showed no significant efficacy in radiologically confirmed pneumonia or meningitis. But these studies have been used to promote the vaccine" [299]. When the economic evaluation for India as part of this thesis is published it is likely to be a key factor in the future decision making for the vaccine.

The Balarus analysis was requested by the EPI manager who intended to use the study in support for national Hib vaccine introduction. However, Belarus is a country with many political difficulties and in spite of much effort from the EPI manager, the Ministry of Health has not yet decided to introduce the vaccine. The present analysis represents one of the first economic evaluations ever done in this country, so there is still no experience with using this type of evidence. A lack of experience in using economic evidence for decision making is prevalent in most former Soviet Union countries.

The Senegal and Ethiopian studies included in this thesis provided new knowledge which had not been researched before. Both of these studies are likely to have impact on policy making. As already mentioned, the Ethiopia study on systems costs of pentavalent vaccine introduction is currently being used as the sole piece of evidence to revise the size of the GAVI vaccine introduction grant upwards. The exact amount of US$ 0.80 per child in the birth cohort found in the Ethiopia study is being proposed to the GAVI Board in June 2012. Lack of evidence on the costs of meningitis sequelae in low-income settings has frequently been mentioned as a hindrance for determining the true value of Hib, pneumococcal and meningococcal vaccines; GAVI, among other organisations, has been requesting these data.

Hence, the Senegal study is likely to be a prime source for assessing the importance of averting meningitis in children.

The decision-analytic model has been used in several other settings than in the three countries presented in this thesis. It must be concluded that a static, transparent model has been adequate for this usage. Since the model is user-friendly, collaborators without any background in Hib disease or modelling have been able to understand and use it. It is likely that a dynamic model would have been much more difficult to use in the countries in question. Moreover, development and parameterization of the static model took three years to complete and is still an ongoing effort, so it is likely that a dynamic model could not have been developed within the timeframe of the Hib Initiative.

14 ANNEXES

ANNEX 1: RECOMMENDED TREATMENT OF HIB DISEASES

Disease	Standard WHO recommended treatment
Meningitis	Hospitalisation. Ampicillin and gentamicin or a third generation cephalosporin, such as ceftriaxone (50 mg/kg every 12 hours) or cefotaxime (50 mg/kg every 6 hours) for 3 weeks. Alternative antibiotics are penicillin and gentamicin. Chloramphenicol is an alternative. but should not be used in premature/low weight neonates. If signs of hypoxaemia, give oxygen.
Very severe pneumonia	Hospitalisation. Ampicillin (50 mg/kg IM every 6 hours) and gentamicin (7.5 mg/kg IM once a day) for 5 days. If child responds well, complete treatment at home or in hospital with oral amoxicillin (15 mg/kg 3 times a day) plus IM gentamicin once daily for a further 5 days. Alternatively, give chloramphenicol (25 mg/kg IM or IV every 8 hours) until child has improved. Then continue orally 4 times a day for a total course of 10 days. Or use ceftriaxone (80 mg/kg IM or IV once daily). If child does not improve within 48 hours, switch to gentamicin (7.5 mg/kg IM once a day) and cloxacillin (50 mg/kg IM or IV every 6 hours). When the child improves, continue cloxacillin (or dicloxacillin) orally 4 times a day for a total course of 3 weeks. Give oxygen to all children with very severe pneumonia
Severe pneumonia	Hospitalisation. Benzylpenicillin (50,000 units/kg IM or IV every 6 hours) for at least 3 days. When the child improves, switch to oral amoxicillin (25 mg/kg 2 times a day). The total course of treatment is 5 days. If child does not improve within 48 hours, or deteriorates, look for complications and treat accordingly as for very severe pneumonia. If there are no apparent complications, switch to chloramphenicol (25 mg/kg every 8 hours IM or IV) until the child has improved. Then continue orally for a total course of 10 days. Give oxygen to any child with severe lower chest wall indrawing or a respiratory rate of ≥70/minute.
Pneumonia	Treat child as an outpatient. Oral cotrimoxazole (4 mg/kg trimethoprim / 20 mg/kg sulfamethoxazole twice a day) for 3 days or amoxicillin (25 mg/kg 2 times a day) for 3 days. Give the first dose at the clinic and teach the mother how to give the other doses at home.
Epiglottitis	Hospitalisation. An airway must be established promptly with an endotracheal tube or by tracheostomy. IV antibiotic therapy for 7-10 days.
Cellulitis	Hospitalisation. IM antibiotic therapy for seven days.
Septic arthritis	Hospitalisation. IV antibiotic therapy for 5-7 days followed by oral antibiotics for two weeks.
Septicemia	Hospitalisation and IV antibiotic therapy.
Osteomyelitis	Hospitalisation. IV antibiotic therapy for 5-7 days followed by oral antibiotics for two weeks.

Source: WHO pocket guide for hospital care in children (2005) [190]

Pneumonia definitions: Very severe pneumonia is characterized by acute respiratory distress where the child is not able to drink, severe pneumonia is distinguished by chest indrawing, and non-severe pneumonia is diagnosed by measuring fast breathing [190].

ANNEX 2: RECOMMENDED METHODS FOR ESTIMATING TREATMENT COSTS IN LOW-INCOME SETTINGS

In this annex, basic methods for undertaking a treatment cost study in a low-income setting are summarised. Since there are no good guidelines available on the topic, the proposed methods are based on my previous experiences with these types of analyses. I have been involved in treatment cost studies in Kenya, Russia, Indonesia, Fiji, Oman, South Africa and Zambia [122, 124, 125, 138, 139, 352, 353].

The preferred method for estimating mean treatment costs per case is calculation of patient-specific costs from a sample of patients. Since severity of disease varies between cases and because circumstances of people differ, treatment costs per case for a particular syndrome can vary widely. It is thus common to see significantly higher costs incurred for a few patients compared to the majority, either due to more severe disease or unusual treatment seeking behaviour. Hence, because there is a relatively small number of patients with high treatment costs and there is absence of negative costs, the distribution of cost data is typically truncated and positively skewed [354]. For this reason, the median value may be more appropriate for descriptive purposes, but this measure does not allow for determining the costs of treating all patients, which is needed as the basis for healthcare policy decisions. It is therefore standard practice to present the mean in treatment cost studies [355]. By multiplying the estimated number of patients by the mean costs per case, total treatment costs can be derived.

Treatment costs should be divided into two components; (a) Bed-day costs in hospitals and visit costs for out-patient consultations, and (b) patient specific costs. These two components are described below.

a) Bed-day and visit costs

Bed-day and visit costs include all cost items shared between patients admitted to a hospital or receiving an outpatient consultation. These include the building, kitchen services, laundry services, cleaning, maintenance, administration, etc. Even though clinical personnel strictly speaking is a patient specific cost item because some patients take up more staff time than others, all personnel costs are generally included in bed-day and visit costs due to the difficulty in measuring precisely how much time is spent with an individual patient.

Hospital bed-day costs should be split into overall hospital bed-day costs and ward-specific bed-day costs. Overall bed-day costs contain all resources needed for the general

running of the hospital, while the ward-specific bed day costs are the costs of running a particular ward, such as the paediatric ward or the infectious disease ward. It is of particular importance to generate a specific estimate for the intensive care unit, as this ward is often considerably more expensive to operate than other wards. Bed-day costs are estimated by dividing total annual costs by the annual number of patient bed-days, for the hospital as a whole and the respective wards. By multiplying the costs per bed-day by the length of stay, total bed-day costs for a particular patient are estimated.

The detail of analysis in a hospital costing study can vary considerably and is largely dependent upon the expertise, time and resources available for data collection. Since most hospitals and clinics in low- and middle-income countries do not have routine cost-accounting systems in place, it is a major undertaking to estimate the costs per hospital bed-day and visit costs. In guidelines for estimating the costs of diarrhoeal disease, which I was the lead author of, we proposed three different approaches for estimating hospital bed-day costs [356]:

1. Standardized WHO-CHOICE estimates. As a part of its WHO-CHOICE project, the WHO has developed estimates of hospital bed-day costs in different settings. Data from hospital cost studies in 49 countries were used in a regression model to predict the costs per bed-day in countries for which these data were not available [357]. In the regression model, country estimates are a function of GDP, ownership (public/private), level of the facility (primary, secondary and tertiary), and the level of capacity utilization. Estimates in international dollars and local currency are given for all WHO member states and can be downloaded from the WHO-CHOICE website: www.who.int/choice/
2. Existing estimates of hospital bed-day costs. In some countries, estimates of the cost per hospital bed-day may be available for some facilities. These may be have been derived from routine cost-accounting systems in hospitals with strong administration or from previous micro-costing studies. In order for the estimates to be used in a new study, it must be ensured that all relevant cost components are included and that the facility can be considered representative for other facilities.
3. Full micro-costing study. This final approach was described above and is the most detailed and resource intensive. The method uses detailed cost and health care utilization data from the hospital. The costs of all activities are estimated individually and all resource items are divided into capital and recurrent costs. The costs of outpatient and inpatient services are estimated separately to ensure that the costs per bed-day and cost per visit can be estimated.

Use of WHO-CHOICE estimates is undoubtedly the less resource-intensive approach. However, while these estimates have been available for downloading from the WHO website since 2003, there is still insufficient detail given on the primary data used for conducting the original regression analysis. It is stated in the 2003 methodological paper that data "from 49 countries, for various years during the period 1973–2000 were part of the initial dataset" [357]. However, it is not specified what these countries were, which hospitals within the countries provided the data, and what type of data collection protocol was used. It would for instance be useful to see examples of the raw data. While I worked at the WHO during 1999-2005, I tried to get this information from the authors numerous times, but I was unsuccessful. It must therefore be emphasised that the validity of the WHO-CHOICE data is uncertain and it is not possible to know how well it reflects actual hospital bed-day costs in a particular country.

b) Patient specific costs

Patient specific cost items are resources that vary between patients, such as drugs, medical supplies and diagnostic tests. Primary data collection on resource utilisation from a sample of patients is needed to determine these accurately. Data sources are either patient records or specially designed data collection forms. Furthermore, depending on study objectives and the perspective taken, patients or caregivers can be interviewed about their out-of-pocket expenses.

Patient-specific resource utilisation data must be multiplied by their respective unit costs to generate total costs. Unit costs are often difficult to establish due to inadequate cost-accounting systems, numerous procurement mechanisms and donations in kind. Unit costs of laboratory and X-ray services can be particularly difficult to establish. To arrive at a mean cost estimate for these services, total annual costs of running the particular diagnostic department should be estimated, including appropriate annualisation of capital equipment. If the capital costs of diagnostic equipment vary considerably, it might be necessary to undertake the analysis separately for the different types of equipment. By dividing total annual costs by the annual number of tests performed, an approximate estimate of costs per test can be arrived at. It is however common to see that facilities do not routinely collect data on the annual number of tests performed. It is for instance likely that the radiology department does not keep a record on how many X-rays are taken each year by each type of machine.

A micro-costing exercise, where resource utilization data and associated unit costs are collected from a sample of patients, is a substantial task to undertake. Since most hospitals

in resource limited settings do not have computerised information systems for patient records and financial accounts, all data need to be manually collected. Studies that include detailed costing of diagnostic services are for instance rarely done. Instead, the costs of a laboratory test or a chest X-ray in a public hospital are often approximated by the fees charged in the private sector for these services. Moreover, since it is common practice in low-income countries that patients pay a relatively large proportion of costs, it is often necessary to interview patients or caregivers about their expenses if a societal perspective is taken. In my experience, a micro-costing study that also includes patient interviews takes between two and three years to complete.

ANNEX 3: DESCRIPTION OF HEALTH SYSTEMS IN THE THREE STUDY COUNTRIES

In this annex, the health systems of Belarus, India and Uzbekistan is briefly described. This is useful background information for understanding the assumptions behind the treatment cost estimates, the Hib vaccine introduction costs, and the Hib disease burden estimates.

Belarus and Uzbekistan

Belarus and Uzbekistan are both former Soviet Union states with health systems originating from the Soviet Semashko model. This was a tax-based, labour intensive system with highly centralized planning of resources and personnel [257, 262]. During Soviet times, the government was almost the sole provider of care and accounted for most health spending. In 1987, Soviet government spending for health represented 5% of the national budget [358]. The Soviet system sought to achieve universal, free access to basic health services, which was centrally planned according to strict norms. It was a goal to deliver services of uniform quality in all parts of the country, but this was never fully achieved and when the Soviet Union collapsed there were great differences in health care access among the 15 republics [256].

Health services have become increasingly fragile in all former Soviet Union states since independence. The economic collapse caused that revenues were no longer able to sustain services, which often had to be stopped. Unofficial out-of-pocket payments for public services are the now norm in most of the countries and unregulated private providers are emerging [248]. The most common informal payment is for medicines [359, 360]. In Uzbekistan, such payments are more widespread in tertiary than primary and secondary facilities and in urban compared to rural areas [262]. The growing private sector largely consists of pharmacists and physicians [262].

In Belarus, the health delivery system is divided into three levels: Highly specialized tertiary hospitals funded directly by the Ministry of Health and secondary and primary care with funding channelled through the six administrative regions: Brest, Gomel, Grodno, Mogilev, Vitebsk and Minsk region without Minsk city, which has the status of an independent administrative entity. The health system is still mainly focused on inpatient treatment while primary health care is relatively weak [257]. In 2008, total health expenditures amounted to 6% of GDP and government health expenditures comprised 75% of total expenditures [361].

In Uzbekistan, there are 12 regions, one autonomous republic (Karakalpakstan) and one administrative city, the capital of Tashkent. There are three types of hospitals in urban areas; regional hospitals, specialized hospitals such as for tuberculosis and sexual transmitted diseases, and tertiary hospitals linked to medical schools. In rural areas there are two types; Rayon (district) hospitals and Central Rayon hospitals [362]. In 2008, total health expenditures amounted to 5% of GDP and government health expenditures comprised 51% of total expenditures [361].

India

India is divided into 28 provincial states. Constitutionally, health care delivery is largely the responsibility of the states with the central government in charge of defining policies and providing a national strategic framework, financial resources, and medical education [363]. However, over time the states have struggled to maintain and administer health care facilities, and they have become dependent on the central government for financial and programmatic assistance [364]. For example, although states account for 75% - 90% of public spending on health, most of these funds go to salaries and wages, making them dependent on the central government for funding drugs, equipment and disease control programmes [364]. In 2008, total health expenditures amounted to 4% of GDP and government expenditure 1% of GDP [249]. Out-of-pocket health expenditures comprise approximately 71% of total health expenditures, which is one of the highest proportions on the world, and one of the leading causes of direct debt and poverty in India [365]

Public health infrastructure in rural areas consists of a three-tier system: A sub centre for every 5,000 population with a male and female worker, a primary health care centre for every 30,000 population with a medical doctor and other paramedical staff, and a community health centre for every 100,000 population with 30 beds and basic specialists. In urban areas, it is a two tier system with a health centre for every 100,000 population followed by general hospitals. However, many government institutions are not functional due to staff shortage and non-availability of drugs, consumables and essential equipment. There are moreover large differences in capacity between states and between rural and urban areas. The numbers of health workers per 10,000 population range from 23.2 in Chandigarh to 2.5 in Meghalaya and the number is four times higher in urban areas than in rural areas.

Curative services are mainly provided in the private sector and evidence from household surveys shows that the private sector in the previous two decades has become the main provider of inpatient care [365]. Seventy percent of health workers in India are employed

in the private sector [366]. The rapid development of the private sector in urban areas has resulted in an unplanned and unequal geographical distribution of services.

Multiple forces have driven an increased privatisation of health services in India since independence. First, the private sector was already dominant at the time of independence and it was allowed to grow in an uncoordinated and unregulated manner, gradually making it the default option for care. The growth of the private sector has outpaced the government capacity to implement the necessary regulatory processes. Secondly, there has been lack of political commitment for public health services shown by consistently low investment and inadequate implementation of programmes. However, to address the challenges of limited access to care, the National Rural Health Mission (NRHM) was launched in 2005, to be completed in a time frame of seven years. This programme aims at providing accessible, affordable, effective, accountable, and reliable healthcare to all citizens and in particular to the poorer and vulnerable sections of the population. Strategies to achieve the goal includes decentralized village and district level health planning, strengthening of public health service delivery infrastructure, improved management capacity to organize health systems and promoting the non-profit sector to increase social participation and community empowerment [367].

ANNEX 4: TREATMENT COST CALCULATIONS IN THE THREE STUDY COUNTRIES

Belarus

Treatment cost data were collected during a visit to Minsk in December 2008. Data on the costs of treating meningitis were collected from the Minsk City Children Infectious Diseases Hospital (MCCIDH) and pneumonia treatment costs were collected at three different facilities; MCCIDH, the Minsk Regional Children's Clinical Hospital and Stolbtsy District Hospital. While the two facilities in Minsk are tertiary hospitals, Stolbtsy Hospital is a secondary facility. Details about the three facilities are summarized in Table A1.

One of the main determinants of treatment costs is the length of stay in hospital. At MCCIDH the average length of stay for a meningitis and pneumonia case is 21 and 12 days, respectively. At Minsk Regional Children's Hospital and at Stolbtsy District Hospital, the average length of stay for pneumonia patients is 14 days. The standard treatment for pneumonia is to give the child antibiotics for the first seven days and daily physiotherapy during the remaining time in hospital.

Table A1: Description of facilities where treatment cost data were collected in Belarus

Minsk City Children Infectious Diseases Hospital	Minsk Regional Children's Clinical Hospital	Stolbtsy District Hospital
• The only infectious disease hospital in Minsk city and Minsk region • Admits children between 0 and 18 years of age • 620 beds, distributed on 14 wards and in one pediatric intensive care unit • Isolation of Hib started during the 1990s for meningitis and epiglottis • Admits approximately 40 cases of suspected bacterial meningitis each year, of which 4-5 are due to Hib • Acute respiratory infections the most common cause of admission • Approximately 15% of all admissions are due to pneumonia	• Founded in 1975, but modernized and reconstructed with new building in 2002 • 615 beds, distributed on numerous specialized departments • Between 75,000-80,000 children less than five years in the catchment area • During 2007, the oblast reported a total of 2,938 pneumonia cases, of which 1,527 (52%) were less than 5 years of age. 118 (4%) of these were admitted to this hospital	• One of 22 District Hospitals in Belarus • 285 beds. Children's department has 40 beds. • Approximately 9,000 children in the catchment area • Children with co-infections are referred to hospitals in Minsk • A total of 105 pneumonia cases were admitted during 2007. This was 14% of all admissions for children between 0-18 years. • In 2007, 8% of pneumonia were between 0-1 years, 30% were between 1-5 years and 62% were between 5-18 years of age. • No deaths due to pneumonia has occurred in the hospital in recent years

All of the three hospitals have well functioning cost accounting systems in place, so it was possible to obtain an estimate for bed-day costs. These estimates had been prepared for us in advance of the visit at the request of my study collaborators. However, it was only possible to receive a detailed breakdown of the bed-day costs from MCCIDH and Stolbtsy Hospital. In spite of repeated attempts, it was not possible to obtain this information from Minsk Regional Children's Clinical Hospital. Costs per patient bed-day and mean patient specific costs for the two hospitals are summarized in Tables A2 and A3, respectively. Total estimated treatment costs of pneumonia and meningitis treatment at the three different hospitals are seen in Table A4.

The mean costs of treating a meningitis case in MCCIDH are estimated as US$ 1,114. Due to shorter stay in hospital and less drug costs, the costs of treating a pneumonia case in the same hospital are approximately half of this amount. The costs of treating pneumonia in Minsk regional hospital and Stolbtsy hospital are 17% and 31% less than in the MCCIDH, respectively.

Table A2: Costs per hospital bed-day (2010 US$)

Cost item	MCCIDH	Stolbtsy hospital
Staff costs:		
Wages	17.3	14.1
Wages taxes	6.0	4.9
Subtotal	*23.3*	*19.0*
Overhead costs:		
Stationary	0.5	0.1
Transport	0.5	0.3
Communal services	9.5	2.3
Heating	2.0	0.1
Electricity	0.4	0.1
Equipment repair	0.6	0.1
Building repair	0.8	0.2
Equipment procurement	0.2	0.1
Other costs	1.6	0.7
Subtotal	*16.3*	*3.9*
Total	***39.6***	***22.9***

Data on 18 children hospitalised with meningitis at MCCIDH showed that two of these were admitted three times after discharge, seven were admitted two times and nine were hospitalised one time after discharge (Irina Glinskay, personal information). The mean length of stay in hospital during re-hospitalisation was nine days. The costs per meningitis episode at tertiary level when including re-hospitalisation costs amounted to US$ 1,960 (Table A5).

Table A3: Patient specific costs in Belarus (2010 US$)

Cost item	MCCIDH		Stolbtsy hospital
	Meningitis	Pneumonia	Pneumonia
Drugs	10.3	2.4	4.6
Medical supplies	0.4	0.4	0.1
Meals	2.7	2.7	2.1
Total	***13.5***	***5.6***	***6.8***

Table A4: Mean treatment costs per pneumonia and meningitis case in Belarus (2010 US$)

	MCCIDH		Minsk Regional Children's Clinical Hospital	Stolbtsy District Hospital
	Meningitis	Pneumonia	Pneumonia	Pneumonia
Length of stay in days	21	12	14	14
Total bed-day costs	1,114	542	448	413
Patient specific costs	13.5	5.6	5.6	6.8
Total costs	***1,128***	***548***	***454***	***420***

Table A5: Calculation of costs per meningitis case including re-hospitalisation costs at MCCIDH

	Length of stay	Probability
Primary admission	21	100%
Re-admission 1	9	50%
Re-admission 2	9	39%
Re-admission 3	9	11%
Mean length of stay per admission	14	
Costs per bed day	53	
Drug costs	13.5	
Costs per admission	751	
Number of admissions	2.61	
Total costs per case	***1,960***	

Uzbekistan

Four hospitals in Tashkent and neighbouring districts were visited in November 2008 with the objective of collecting data to estimate the costs of treating meningitis and pneumonia; the City Infectious Disease Hospital #1, the Paediatrics Research Institute, the Children's City Hospital #5 of Yunusobod District, and the Children's Hospital of Uchtepa District. A brief description of the facilities is given in Table A6. Since all meningitis patients in Tashkent should be referred to the Infectious Disease Hospital #1, treatment costs of this disease were collected from this hospital only. Pneumonia is treated at all lower levels of the referral system, so these treatment costs were collected from the remaining three facilities.

Table A6: Description of facilities where treatment cost data were collected in Uzbekistan

Infectious Disease Hospital #1	The Paediatrics Research Institute	The Children's City Hospital #5 of Yunusobod District	The Children's Hospital of Uchtepa District
• Oldest infectious disease hospital in country • 150 beds • Admits approximately 6,000 patients per year. • Referral hospital for meningitis, respiratory and intestinal diseases. • Between 50% and 60% of admitted patients are children. • Most common cause of admission varies from year to year, depending on infectious disease epidemics. • Average length of stay for meningitis is between 10 and 12 days. • No PCR facilities, so the aetiology of most meningitis cases is unknown. • Some pneumonia cases get admitted, but only few of these are children.	• Roughly 30% of all admissions are due to pneumonia. • In 2007, there were 1,856 cases of pneumonia and 790 of these were children under five years. • Of these there were 14 fatalities, so the case fatality rate for pneumonia in children under five years was 1.7%. • Average length of stay for pneumonia is 10 days. • Meningitis cases are referred to the Infectious Disease Hospital # 1.	• 430 beds in addition to a treatment unit, a pharmacy and a 20-bed intensive care unit. • Three wards which are split according to age; children under 1 month, 2 to 3 years, and 4 to 14 years. • Approximately 15,500 children are admitted per year of which about 5,000 are due to ARI (32%). • Pneumonia is the main cause of inpatient admission followed by neurological disorders. • Average length of stay for pneumonia is 8.1 days. • About 20% of patients arrive from outside the hospital's catchment area.	• 296 beds • Admits between 11,800 and 13,200 patients per year. • Approximately 35% to 40% of children are admitted with pneumonia, of which around 4% have severe pneumonia.

The cost-accounting systems of all four facilities were relatively rudimentary. None of the systems were computerised and only the Infectious Disease Hospital # 1 had a separate accountancy department. The admistration of the Infectious Disease Hospital # 1 was considerably stronger than the other three hospitals. However, with substantial help from the hospital administrators my study collaborators collected as much information as possible.

The costs of drugs and diagnostics were estimated by combining quantities and unit costs of the most common treatment practices. This information was partly based on a review of patient records in the Infectious Disease Hospital #1. It is common practice that the hospital only provides drugs free of charge during the first day of admission while the

parents should purchase drugs from commercial pharmacies for the subsequent days of treatment. Drugs are approximately 40% more expensive in commercial pharmacies than when procured by the government hospitals. To allow for this variation, treatment costs were divided into a government and a household perspective.

Meningitis

The average length of stay of a meningitis case in the Infectious Disease Hospital #1 was 11 days and costs per bed-day were estimated as US$ 9.18. Hence, mean bed-day costs per patient amounted US$ 101. Unit costs of diagnostics are seen in Table A7. Drug costs varied depending on the age of the child and according to the severity of disease, as seen in Table A8. Total average costs of treating a meningitis case is seen in Table A9.

Assuming 50% of cases are less than one year and that only 10% of cases are very severe, the average weighted meningitis treatment costs at the Infectious Disease Hospital #1 is estimated as US$ 276 per case. The government pays on average US$ 190 per case and households US$ 86.

Table A7: Unit costs of diagnostic tests used for meningitis patient in the Infectious Disease Hospital (2010 US$)

Diagnostic tests	US$ per test
General blood test	3.42
Biochemical test of blood	6.83
Coagulogram	5.46
Bacteriological inoculation of liquor	5.12
Bacteriological Inoculation of blood	2.39
Inoculation of nasopharyngeal mucus	5.33
TOTAL	**29.00**

Table A9: Mean costs of treating acute meningitis in Uzbekistan (2010 US$)

	Severe		Very severe	
	< 1 year	**> 1 year**	**< 1 year**	**> 1 year**
Government costs:				
Bed-day costs	101	101	101	101
Diagnostic tests	29	29	29	29
Drugs	10	100	10	100
Food	5.52	5.52	5.52	5.52
Subtotal	***145***	***235***	***145***	***235***
Household drug costs	*18*	*47*	*105*	*1,032*
TOTAL	**164**	**281**	**250**	**1,266**

Table A8: Mean costs of drugs for meningitis treatment in the Infectious Disease Hospital (2010 US$)

Type of drug	Unit	Amount prescribed per day for children < 1 year	Amount prescribed per day for children > 1 year	No of days prescribed for children < 1 year	No of days prescribed for children > 1 year	US$ per unit	US$ per day for children < 1 year	US$ per day for children < 1 year
Cephalosporins	Gr	1	4	10	10	0.68	0.68	2.73
Mannitol*	Ml	70	800	7	5	0.03	2.05	23.42
Furosemide*	Mg	50	500	7	10	0.00	0.16	0.01
Dexamethasone	Mg	20	24	5	5	0.08	1.50	1.80
Magnesium sulphate*	Ml	2	20	10	10	0.07	0.15	1.47
Aktovegin*	Ml	1	10	10	10	3.42	3.42	34.15
Glucose 10% solution	Ml	100	800	10	10	0.00	0.02	0.14
Heparin*	Ml	0.1	1	5	5	6.83	0.68	6.83
Aminophylline*	Ml	1	20	10	10	1.37	1.37	27.32
Ascorbic acid	Mg	350	350	10	3	0.00	0.09	0.00
Na Oxibutirat*	Ml	5	5	10	10	0.03	0.14	0.14

*Prescribed only when disease is very severe

Pneumonia

The average length of stay for a pneumonia patient varied between 7 and 19 days depending on the hospital and the severity of the disease (Table A10). Unit costs of diagnostic tests, bed-day costs and drugs commonly used for pneumonia patients are seen in Tables A10, A11 and A12, respectively.

Assuming 50% of cases are less than one year old and 10% are severe, an average weighted pneumonia treatment costs in hospital is estimated at US$ 168, of which the Government pays on average US$ 143 per case and households US$ 26 per case.

Table A10: Costs of diagnostic tests of pneumonia patients in Uzbekistan

Type of test	US$ per test
General blood test	3.42
Biochemical test of blood	6.83
Bacteriological inoculation of sputum	5.12
Bacteriological inoculation of blood	2.39
Inoculation of nasopharyngeal mucus	5.33
General urine test	2.05
General stool test	2.05
TOTAL	**27.19**

Table A11: Costs per bed per day in the three Uzbek hospitals

	Severe pneumonia			Very severe pneumonia
	Paediatric Research Institute	Children's city hospital # 5	Children's hospital of Uchtepa district	Children's hospital of Uchtepa district
Mean length of stay (days)	7	8	14	19
Costs per bed day	14.44	9.87	14.34	14.34
Mean bed-day costs per patient	101	80	201	273

Table A13: Total costs of pneumonia treatment per patient in Uzbekistan

	Severe		Very severe	
	< 1 year	**> 1 year**	**< 1 year**	**> 1 year**
Government costs:				
Bed-day costs	93	93	236	236
Diagnostic tests	27	27	27	27
Drugs	2	3	3	7
Food	5	5	10	10
Sub total	***127***	***128***	***275***	***279***
Household drug costs	*16*	*30*	*26*	*74*
TOTAL	**143**	**158**	**301**	**353**

Table A12: Unit costs of drugs used for pneumonia treatment in Uzbekistan

Type of drug	Unit	Amount prescribed per day for children < 1 year	Amount prescribed per day for children > 1 year	No of days prescribed for children < 1 year	No of days prescribed for children > 1 year	US$ per unit	US$ per day for children < 1 year	US$ per day for children > 1 year
Penicillin	mln IU	6	18	10	10	0.07	0.57	1.71
Cephalosporins	Gr	0	4	10	10	0.68	-	2.73
Aminophylline	Ml	0	1	10	10	1.37	-	1.37
Mucolytic agent	ml	5	5	5	5	0.27	1.37	1.37
Prednisolone	mg	0	600	5	3	0.01	-	8.20
Dexamethasone	mg	0	24	5	5	0.08	-	1.80
Glucose 10% solution	ml	0	800	10	10	0.001	-	0.14
Ascorbic acid	mg/ml	350	20	10	10	0.005	0.09	0.09

India

Length of hospital stay

The length of stay in hospital was derived from a Hib Initiative funded pneumonia and meningitis surveillance study in three different Indian states [253]. Across the three tertiary hospitals, the mean length of stay in hospital was 5.7 days for pneumonia patients and 9.7 days for meningitis patients (Table A14).

Table A14: Length of stay in hospital in three India hospitals

	Pneumonia		Meningitis	
Surveillance site	**N**	**Mean no. of days**	**N**	**Mean no. of days**
Chandigarh	227	7.4	164	11.9
Kolkota	231	4.1	72	9.2
Vellore	131	5.7	89	8.1
Mean		**5.7**		**9.7**

Source: Personal communication with John Hopkins' University

Household costs

Household costs were estimated from the NSSO socio-economic survey on respiratory ailments in children less than five years. The questionnaire is included in Annex 5. Meningitis costs were calculated by adjusting the respiratory ailment costs upwards in accordance with the additional length of stay. The ratio between meningitis and pneumonia length of stay in hospital is 1.6, as seen in Table A14 above.

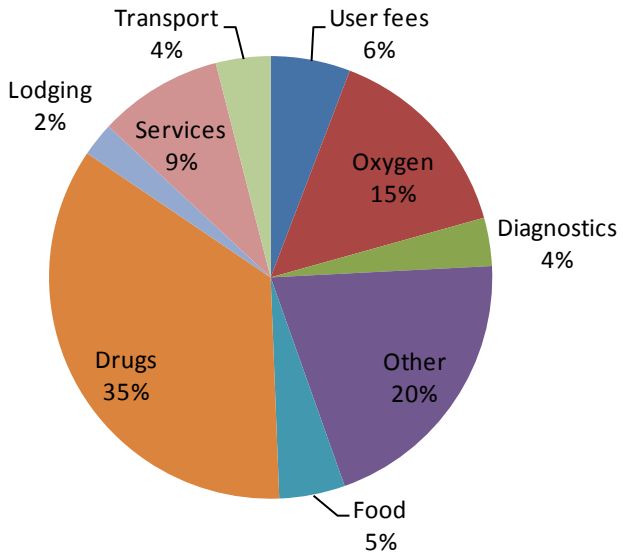
The nationwide NSSO sample survey sizes for respiratory illnesses in children less than five years were 644 outpatient episodes and 238 inpatient admissions. Costs per patient varied widely between states, as seen in Table A15. The national average is used in the economic evaluation. The breakdown of expenditures according to item is seen in Figures A1 and A2 for government and private hospitals, respectively.

Table A15: Mean household costs per case in India according to geographic region (2010 US$)

Region	Outpatient costs per visit		Cost per pneumonia admission		Inpatient cost per meningitis admission	
	Govt	**Private**	**Govt**	**Private**	**Govt**	**Private**
North	12	11	106	126	171	204
Central	3	9	210	213	341	345
East	10	5	32	141	53	229
Northeast	7	5	26	289	42	468
West	1	6	42	298	68	483
South	2	7	22	119	36	193
All India	***6***	***7***	***50***	***149***	***81***	***241***

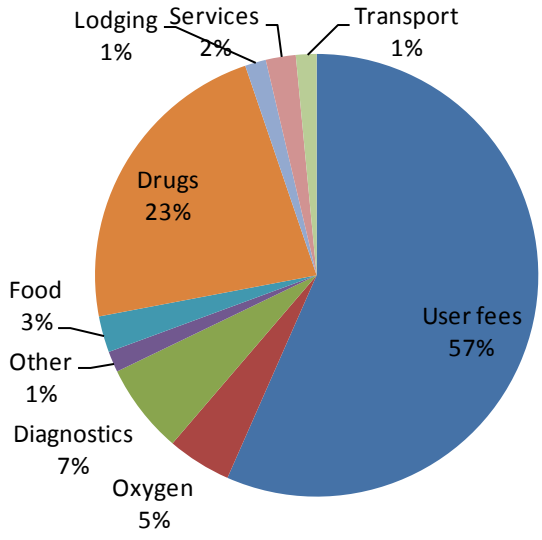
Source: NSSO 2007 [252]

Figure A1: Break-down of household expenses for respiratory illnesses in government hospitals in India



Source: NSSO 2007 [252]

Figure A3: Break-down of household expenses for respiratory illnesses in private hospitals in India



Source: NSSO 2007 [252]

Data source for government costs

Data from a micro-costing study by Dr. Anand Krishnan and colleagues undertaken in New Delhi and in the state of Haryana, North India were used as source for the government treatment cost estimates [129]. Six government facilities were included in the study; three primary facilities were in Dayalpur, Kurali and Palwal, two secondary facilities in

Ballabgarh (the Civil Hospital and the Badshah Khan Hospital), and the tertiary hospital was the All India Institute of Medical Sciences (AIIMS) in New Delhi. Descriptions of the secondary and tertiary hospitals are seen in Table A16.

Table A16: Description of secondary and tertiary government hospitals included in the study by Krishnan

	Civil Hospital Ballabgarh	Badshah Khan Hospital	AIIMS
Number of beds	54	200	801
Paediatric admissions per year	488	2,235	4,233
Average length of stay (days)	3	3	5
Bed occupancy rate	54%	65%	100%
Paediatric case fatality rate	9.2	4.2	5
Paediatric outpatients per year	16,518	22,673	49,937

Source: Krishnan 2001 [129]

Inpatient costs

Hospital bed-day costs were estimated by adding annual capital costs, electricity, water, personnel and other overhead costs. Overhead costs for the paediatric ward were determined by allocating a proportion of total costs in accordance with the share of paediatric admissions out of total admissions. Personnel costs included all allowances. Bed-day costs for the secondary and tertiary hospitals are summarised in Table A17.

Drug costs were estimated by multiplying the amount prescribed by the respective unit costs. Costs of diagnostic tests were estimated by calculating capital costs, personnel, etc for each type of investigation. In all of the hospitals, patients paid for the majority of drugs and investigations, in addition to consultation fees. However, these costs were not

Table A17: Hospital bed-day costs (2010 US$)

Cost item	Civil hospital, Blaabgarh	AIIMS
Capital costs	1.6	2.1
Overhead costs	3.8	5.6
Physician costs	3.4	18.8
Other staff costs	6.9	7.4
Administration	1.6	4.2
Maintenance	0.4	0.9
TOTAL	**17.6**	**39.0**

Source: Krishan 2001 [129]

separated according to whether they were paid for by the public health facility or patients. Since costs of drugs and investigations were already included in the household expenditure data from the NSSO survey, the estimates given in Krishnan's study were not included to avoid double counting. Inpatient costs according to facility level are summarised in the Table A18.

Table A18: Government costs per patient of pneumonia and meningitis treatment

	Pneumonia		Meningitis	
	Secondary level	**Tertiary level**	**Secondary level**	**Tertiary level**
Length of stay	5.7	5.7	9.7	9.7
Costs per bed-day	17.6	39	17.6	39
Total	**101**	**172**	**224**	**380**

Source: Gupta 2011 [253] and Krishnan 2001 [129]

Outpatient costs

Outpatient visit costs were collected from the three primary facilities and also from the outpatient departments at the secondary and tertiary hospitals. The estimates are seen in Table A20. As with the hospital estimates, the costs of drugs and investigations were excluded to avoid double counting as these costs are largely paid by household and captured in the NSSO survey.

Table A19: Outpatient pneumonia costs according to facility level (2010 US$)

	Primary	**Secondary**	**Tertiary**
Physician cost	0.32	0.24	0.77
Other costs	0.53	0.37	0.66
Subtotal	*0.85*	*0.61*	*1.42*
Pneumonia investigations	0.13	0.09	1.40
Pneumonia drugs	2.03	2.51	3.36
TOTAL	***2.88***	***3.12***	***4.78***

Source: Krishan 2001 [129]

ANNEX 5: INDIA NSSO QUESTIONNAIRE FOR HOUSEHOLD MEDICAL EXPENSES

GOVERNMENT OF INDIA
NATIONAL SAMPLE SURVEY ORGANISATION
SOCIO-ECONOMIC SURVEY
SIXTIETH ROUND: JANUARY – JUNE, 2004

SCHEDULE 25.0: MORBIDITY AND HEALTH CARE

srl. no.	name of member	relation to head (code)	(male -1, female -2)	age (years)	marital status (code)	general educational level (code)	usual activity status (code)	during last 365 days		whether ailing		report-ting of columns 11 & 12 (self - 1, proxy – 2)
								whether hospitalised (yes-1, no-2)	if 1 in col. 9, no. of times hospitalised	anytime during last 15 days (yes-1, no-2)	on the day before the date of survey (yes -1, no -2)	
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)

1.	sr1. no. of the hospitalisation case	1	2	3	4	5
2.	srl. no. of member (as in col. 1, block 4/5) hospitalised					
3.	age (years) (as in col. 5, block 4 / col. 4, block 5)					
4.	type of hospital (code)					
5.	nature of ailment (code)					
6.	type of ward (free - 1, paying general - 2, paying special - 3)					
7.	when admitted (code)					
8.	when discharged (code)					
9.	duration of stay in hospital (days)					
10.	loss of household income, if any, due to hospitalisation (Rs)					
details of medical services received (not received - 1; received: free - 2, partly free - 3, on payment - 4)						
	11. surgery					
	12. medicine					
	13. X-ray/ECG/EEG/Scan					

14. other diagnostic tests						
15. whether treatment availed before hospitalisation (yes - 1, no - 2)						
if 1 in item 15	16. source of treatment (code)					
	17. duration of treatment (days)					
18. whether treatment continued after discharge from hospital						
if 1 in item 18	19. source of treatment (code)					
	20. duration of treatment (days)					

[8] expenses incurred for treatment of members treated as inpatient of hospital during the last 365 days and source of finance

srl. no. of the hospitalisation case (as in item 1, block 7)		1	2	3	4	5
srl. no. of member hospitalised (as in item 2, block 7)						
age (years) (as in item 3, block 7)						
whether any medical service provided free by employer (yes: Govt. - 1, pvt . - 2; no – 3, not applicable – 4)						
medical expenditure for treatment during stay at hospital (Rs)						
doctor's / surgeon's fee	5. hospital staff					
	6. other specialists					
medicines	7. from hospital					
	8. from outside					
9. diagnostic tests						
10. bed charges						
11. attendant charges						
12. physiotherapy						
13. personal medical appliances						
others	14. food and other materials					
	15. blood, oxygen cylinder, etc.					
	16. services (ambulance, etc.)					
17. expenditure not elsewhere reported						
18. total (items 5 to 17)						
other expenses incurred by the household (Rs) (not included in item 18)						
19. transport (other than ambulance)						

20. lodging charges of escort(s)						
21. others						
22. total (items 19 to 21)						
23. total expenditure incurred by the household (sum of items 18 & 22 for all cases of hospitalisation taken together)						
expenses in item 23 by source of finance (Rs)						
24. household income/savings						
25. borrrowings						
26. contributions from friends and relatives						
27. other sources (incl. sale of ornaments and other physical assets, draught animals, etc.)						
28. total (items 24 to 27)						
29. amount of reimbursement (Rs)						
31. private						
32. medical insurance companies						
33. other agencies						

[9] particulars of spells of ailment of household members during the last 15 days (including hospitalisation)						
1. srl. no. of spell of ailment		1	2	3	4	5
2. srl. no. of member reporting ailment (as in col. 1 of block 4/5)						
3. age (years) (as in col. 5, block 4 / col. 4, block 5)						
number of days within the reference period	4. ill					
	5. on restricted activity					
	6. confined to bed					
7. nature of ailment (code)						
8. status of ailment (code)						
9. total duration of ailment (days)						
10. whether treatment taken on medical advice (yes - 1, no - 2)						
if 1 in item 10	11. whether any treatment received from govt. sources (yes - 1, no - 2)					
	12. if 2 in item 11, reason (code)					
if 2 in item 10	13. reason for no treatment (code)					
	14. whether any other measure taken for recovery/relief (yes - 1,no - 2)					

	if 1 in item 14	15. whom consulted (code)					
		16. expenditure incurred (Rs)					
17. loss of household income, if any, due to ailment (Rs)							

[10] expenses incurred during the last 15 days for treatment of members (not as inpatient of hospital) and source of finance					
1. srl. no. of ailing member (as in item 2, block 9)					
2. age (years) (as in item 3, block 9)					
3. whether any medical service provided free by employer (yes: Govt. -1, pvt. - 2; no - 3, not applicable - 4)					
Details of medical services received (not received - 1; received: free - 2, partly free - 3, on payment - 4)					
4. surgery					
5. medicine received					
6. X-ray/ECG/EEG/Scan					
7. other diagnostic tests					
medical expenditure for treatment (Rs)					
doctor's / surgeon's fee — 8. hospital staff					
doctor's / surgeon's fee — 9. other specialists					
medicines — 10. from hospital					
medicines — 11. from outside					
12. diagnostic tests					
13. attendant charges					
14. physiotherapy					
15. personal medical appliances					
others — 16. food and other materials					
others — 17. blood, oxygen cylinder, etc.					
others — 18. services (ambulance, etc.)					
19. expenditure not elsewhere reported					
20. total medical expenditure (items 8 to 19)					
expenditure reported in item 20 from — 21. Govt. Sources					
expenditure reported in item 20 from — 22. other sources					

other expenses incurred by the household (Rs) (not included in item 20)					
23. transport charges (other than ambulance)					
24. lodging charges of ailing person and escort(s)					
25. others					
26. total (items 23 to 25)					
27. total expenditure incurred by the household (sum of items 20 & 26 for all persons taken together)					
source of finance for meeting the expenses in item 27 (Rs)					
28. household income/savings					
29. borrrowings					
30. contributions from friends and relatives					
31. other sources (incl. sale of ornaments and other physical assets, draught animals, etc.)					
32. total (items 28 to 31)					
33. total amount of reimbursement (Rs)					

(ii) NATURE OF AILMENT (item 5, block 7 & item 7, block 9)

Ailment	code	ailment	code
Gastro-intestinal		*Diabetes mellitus*	22
Diarrhoea/ dysentery	01	*Under-nutrition*	23
Gastritis/gastric or peptic ulcer	02	*Anaemia*	24
Worm infestation	03	*Sexually transmitted diseases*	25
Amoebiosis	04	Febrile illnesses	
Hepatitis/Jaundice	05	*Malaria*	26
Cardiovascular Diseases		*Eruptive*	27
Heart disease	06	*Mumps*	28
Hypertension	07	*Diphtheria*	29
		Whooping cough	30
Respiratory including ear/nose/throat ailments	08	*Fever of unknown origin*	31
Tuberculosis	09		
Bronchial asthma	10	*Tetanus*	32
Disorders of joints and bones	11	*Filariasis/Elephantiasis*	33
Diseases of kidney/urinary system	12		
Prostatic disorders	13	Disabilities	
Gynaecological disorders	14	*Locomotor*	34
Neurological disorders	15	*Visual including blindness (excluding cataract)*	35
Psychiatric disorders	16	*Speech*	36
		Hearing	37
Eye ailments		*Diseases of Mouth/Teeth/Gum*	38
Conjunctivitis	17	*Accidents/Injuries/Burns/*	
Glaucoma	18	Fractures/Poisoning	39
Cataract	19	Cancer and other tumours	40
Diseases of skin	20	*Other diagnosed ailments*	41
Goitre	21	*Other undiagnosed ailments*	99

ANNEX 6: SOCIO DEMOGRAPHIC QUESTIONNAIRE USED IN THE SENEGAL STUDY

PATH AND LSHTM

MENINGITIS DISABILITY PROJECT

QUESTIONNAIRE ABOUT SOCIO-DEMOGRAPHIC STATUS

ALL THESE QUESTIONS SHOULD BE ASKED OF THE MOTHER OR PRIMARY CAREGIVER OF THE CHILD. THE MOTHER IS THE PREFERED RESPONDENT.

1. BACKGROUND and ID

2.

1.1. Is the child a case or control?	1. Case/Exposed	2. Control/unexposed

1.2 Child's ID: | | | |

1.3 Child's name:

1.4 Date of interview: …….. | | | | | | |

1.5 Staff code: …… | | |

1.6 What is the relationship of the primary caregiver to the child?

11. Mother	12. Father	13. Aunt	14. Uncle
15. Grandmother	16. Grandfather	17. Other relative PLEASE SPECIFY	18. Friend
19. Government official	20. Other. PLEASE SPECIFY	////////////////// //////////////	////////////////// //////////////

INFORMATION ABOUT THE CHILD

2 SEX and AGE

2.1 What sex is the child?	1. Male	2. Female

2.2 In what year was the child born? [88 = NK]…….. | **2** | **0** | | |

2.3 In what month was the child born? [88 = NK]…… | | |

3. BIRTH DETAILS

3.1 What was the child's birth weight? (in kilograms ; 888 = not known, no record).. PLEASE CHECK CHILD HEALTH RECORDS IF AVAILABLE

	.		

3.2. Did this child's pregnancy end early, on time, or late?

1. Early	2. On time	3. Late	8. Not known

3.3 How many weeks pregnant was the mother with this child at delivery (what was the gestational age of the baby)? (40 = term, 88 = NK)……

3.4 How many babies were born at the same time as this child? eg singleton = 1, twins = 2, triplets = 3, quadruplets = 4 ……..

4. PAST IMMUNISATIONS:

4.1. Has the child received Hib (monovalent or pentavalent) vaccination?

If yes, then please specifiy dates (888888 =NK, 999999=not received)

					d	d	m	m	y	y
Hib 1……..	1. Yes	2. No	8.NK	If yes……..						
Hib 2……..	1. Yes	2. No	8.NK	If yes……..						
Hib 3…….	1. Yes	2. No	8.NK	If yes……..						

4.2. Has the child received measles or MMR vaccination?

If yes, then please specify dates (888888 =NK, 999999=not received)

					d	d	m	m	y	y
Measles or MMR 1	1. Yes	2. No	8.NK	If yes……..						
Measles or MMR 2	1. Yes	2. No	8.NK	If yes……..						

5. PAST MEDICAL HISTORY

5.1. Now we want to ask about any hospitalisations where the child has stayed over night in hospital.

					Year		Month		Duration of hospitalisation in days		
Any hospitalisations for bacterial meningitis?	1.Yes	2. No	8. NK	If yes							
Any other hospitalisations 1?(Specify_____)	1.Yes	2. No	8. NK	If yes							
Any other hospitalisations 2?(Specify_____)	1.Yes	2. No	8. NK	If yes							
Any other hospitalisations 3?(Specify_____)	1.Yes	2. No	8. NK	If yes							

5.2 Did the child have any serious problems at birth?	1. Yes	2.No	8. Not known
5.3. If yes please specify these problems (number 1.2.3 etc)			

6. CURRENT DISABILITIES

6.1. Now we want to ask about the <u>current</u> disabilities that the child has. Has the child had any of the following?

Problems with moving	1.Yes	2. No	8. NK
Problems with thinking	1.Yes	2. No	8. NK
Problems with speaking	1.Yes	2. No	8. NK
Behaviour problems	1.Yes	2. No	8. NK

Problems with seeing	1.Yes	2. No	8. NK
Problems with hearing	1.Yes	2. No	8. NK
Epilepsy	1.Yes	2. No	8. NK

INFORMATION ABOUT THE HOUSEHOLD

7 DEMOGRAPHICS

7.1. What was the mother's/primary caregiver's highest educational level reached?

1. None	2. Primary school	3. Secondary school
4. University	5. Other. Specify	8. Not known

7.2 Number of years completed at the highest level reached? [88 = NK, 99= NA/None]……..

7.3. What is the mother's/primary caregiver's religion?

1. Christian	2. Muslim	3. Traditional African	4. Other (SPECIFY):

7.4. What ethnic group does the mother / primary caregiver belong to?	11. Wolof	12. Serere	13. Poular	14. Bambara
	15. Mankagne	16. Diola	17. Soninke	
	18. Other. Please specify.			

7.5. Does anyone in the household own any land?.....

1. Yes	2. No

7.6. What is grown on your land?

1. Food items, mainly for home consumption	2. Food items, mainly for sale on the market	3. Cash crops: peanut, mil, cassava, maize, tomatoes, yam, tobacco etc.	9. NA, no farm

7.7. Does anyone in the household have a regular cash income/ salaried worker?.....

1. Yes	2. No

7.8. If yes, please write the title/name/description of the employment/jobs

7.9. Does your household have electricity?.....

1. Yes	2. No

7.10. What is the main source of drinking water for members of your household?

11. Piped into dwelling/yard/plot	12. Public tap	13. Handpump / closed bore hole	14. Closed well	15. Open well
16. Stream / river	17. Lake / dam /pond	18. Water trucks	19.Rain water	20. Other

7.11. How long does it take for you to go there, get water and come back?

1. Less than 15 minutes	2. 15 minutes- less than 30 minutes	3. 30 minutes – less than 60 minutes
4. 60 minutes or more	9. NA / drinking water source is in compound	

7.12. What kind of toilet facility does your household have?

1. Flush latrine / WC	2. Ventilated improved pit /VIP /KVIP	3. Other pit latrine	4. Open fields
5. Defaecate in house, faeces transferred elsewhere / bucket latrine		6. Other:	

7.13. What are the total number of rooms in the household used for sleeping? ……

7.14. What are the total number of people that slept in the household last night? 88 = NK……

7.15. How many children less than 18 years live in the household?.....

7.16 What materials are used for the construction of the house in which you live?

Floor of sleeping room	1. Cement	2. Mud/clay	3. Other:	8. NK
Roofing	1. Metal/asbestos	2. Thatch/mud	3. Other:	
Wall	1. Cement	2. Mud	3. Other:	

END OF SOCIO-DEMOGRAPHIC QUESTIONNAIRE

ANNEX 7: ECONOMIC QUESTIONNAIRE USED IN THE SENEGAL STUDY

PATH AND LSHTM

MENINGITIS DISABILITY PROJECT

ECONOMIC QUESTIONNAIRE

1. IDENTITY:

1.1 Child's ID..... | | | |

1.2 Child's name: | |

1.3 Date of interview..:..... | | | | | | |

1.3 Interview start time _____ Interview finish time _____

1.4 Staff code: ..... | | |

2. RELATIONSHIP OF THE PRIMARY CAREGIVER TO THE CHILD

1. Mother	2. Father	3. Sister	4. Brother
5. Grandmother	6. Grandfather	7. Other relative	8. Friend

3. MENINGITIS HISTORY

3.1 In what year did the child suffer from meningitis? [88 = NK]…… | **2** | **0** | | |

3.2 In what month did the child suffer from meningitis? [88 = NK]…….. | | |

3.3 What type of health facilities was the child taken to when he/she fell ill with meningitis?

1. Public health centre	2. Traditional healer	3. District Hospital (public)
4. District hospital (private)	5. Tertiary hospital (public)	6. Tertiary hospital (private)
7. Other (SPECIFY)		

YOU MAY CIRCLE MORE THAN ONE RESPONSE

3.4 How many days did the child stay in hospital when admitted for meningitis?..... | | |

3.5 Approximately how much money did you spend on the meningitis episode?

a) Before the child was admitted to hospital ……	CFA						
b) Hospital fees ……	CFA						
c) Transport during the hospital stay …	CFA						
d) Other costs ……	CFA						

Please note down the details of the cost estimates (i.e. costs per day in hospital)

4.1 Since the meningitis episode, has the child been admitted to hospital due to disability from the meningitis episode??

1. Yes	2. No

4.1 If yes, please list where the admission was, the dates, and how many days the child stayed in hospital

	Name of hospital	**Month**		**Year**		**No. days**
Hospitalisation 1:……						
Hospitalisation 2:……						
Hospitalisation 3:……						
Hospitalisation 4:……						
Hospitalisation 5:……						
Hospitalisation 6:……						
Hospitalisation 7:……						
Hospitalisation 8:……						

4.2 Please state the approximate costs in terms of hospital fees of these admissions

Hospitalisation 1:……	CFA						
Hospitalisation 2:……	CFA						
Hospitalisation 3:……	CFA						
Hospitalisation 4:……	CFA						
Hospitalisation 5:……	CFA						
Hospitalisation 6:……	CFA						

Hospitalisation 7:……	CFA						
Hospitalisation 8:……	CFA						

4.2 On average, how much did it cost in transport costs each time the child was admitted to hospital? ……..	CFA						

Please note down the details of the cost estimates (i.e. costs per day in hospital)

5 COSTS OF OUTPATIENT VISITS DUE TO DISABILITY FROM MENINGITIS

5.1 Since the meningitis episode, has the child attended outpatient services due to disability from the meningitis episode?	1. Yes	2. No

5.2 If yes, please list where the visits were and the dates

	Name of facility	**Month**		**Year**	
Visit 1:……					
Visit 2:……					
Visit 3:……					
Visit 4:……					
Visit 5:……					
Visit 6:……					
Visit 7:……					
Visit 8:……					
Visit 9:……					
Visit 10……					

5.3 Please state the approximate costs of each visit

Visit 1:……	CFA						
Visit 2:……	CFA						
Visit 3:……	CFA						
Visit 4:……	CFA						
Visit 5:……	CFA						
Visit 6:……	CFA						
Visit 7:……	CFA						
Visit 8:……	CFA						
Visit 9:……	CFA						
Visit 10:……	CFA						

5.4 On average, how much did it cost in transport costs each time the child has had an outpatient visit?

CFA						

Please note down the details of the cost estimates (i.e. costs per consultation)

6. UN-AFFORDABLE COSTS

6.1 Is there any treatment that you know the child would benefit from , but he/she is not receiving it because you can not afford it ?

1. Yes	2. No

6.2 If yes, explain what this is and the approximate cots (either daily, weekly, monthly or annually)

7. COSTS OF LOOKING AFTER THE CHILD

7.1 Who looks after the child during the day?

1. Mother	2. Father	3. Sister	4. Brother
5. Grandmother	6. Grandfather	7. Other relative	8. Friends
9. Goes to school	10. Attends day care	11. Other (please state)	

YOU MAY CIRCLE MORE THAN ONE RESPONSE

7.2 Is this any different than if the child had not suffered from meningitis?.....	1. Yes	2. No
If yes, explain how		

7.3 Do you pay somebody to look after the child?.....				1. Yes		2. No	
7.4 If yes, how much per month?.....	CFA						

7.5 Are any of your household members unable to work as much as they could/would like to due to the disability of the child?	1. Yes	2. No

7.6 If yes, how much does the household loose in earnings per month?	CFA						

END OF ECONOMIC QUESTIONNAIRE

ANNEX 8: PHOTOS FROM THE SENEGAL STUDY

Picture 1: The child with meningitis sequelae is the boy in the middle.

Picture 2: This healthy boy recovered from the meningitis without sequelae.

Picture 3: The boy has meningitis sequelae

Picture 4: The boy has meningitis sequelae

ANNEX 9: INTERVIEWS WITH FAMILIES AFFECTED BY MENINGITIS SEQUELAE IN SENEGAL

FAMILY OF CHILD 1

The father:
At the beginning the child was healthy before meningitis attack. I was one day at Touba and the child was healthy. When I got back, I saw that the body of the child was hot and had fever. So I told to his mother to bring him at Albert Royer hospital. And then meningitis is diagnosed and the child hospitalized. I thought that the child had tooth problem or malaria attack.

I didn't know well meningitis, but I heard it was a dangerous disease which conducts to death and paralysis. He wasn't fully vaccinated because he felt ill very soon. I spent all my savings. The disease cost us expensive. The child was ten months old when he fell sick. In the house the others children are healthy and there are who are younger than Bara Pouye. My older boy was hospitalized for digestive disease.

The mother:
When Bara had fever my first reaction was to bring him at Albert Royer because his big sister was ill and I bring her to Phillipe Senghor hospital. They prescribed her medicines in vain and unfortunately she died. The daughter just spent 24 hours at hospital. They haven't done an analysis so we don't know the real disease cause. Since then, when a member of the family falls ill I systematically bring him to hospital and no in a health post. The death of her sister had terrified me so much that I haven't confidence to the health post. Bara had a bugle fontanel. When I brought him at Albert Royer they diagnosed meningitis. I called his father to him that the child would be hospitalized. He answered that the disease is not serious and that he should not be hospitalized. Then his father came and the doctor explained to him.

During hospitalization we spent much money because the prescriptions were expensive. The injection was very expensive the cost of one vial was 8000 CFA. The child had diarrhea, he trembled his legs and the fingers were inert. I knew meningitis because my brother had it before.

The prescriptions and the hospitalization were expensive. For spending I was obliged to take the heritage of my deceased father. I called sometime his father when my money finished

The father:
The money of her father's heritage was not enough so I did add money to complete. Indeed the vial costs 8,000 CFA at hospital but it's 10,000 CFA out of hospital. God assisted us. I borrowed some money from my friend for paying hospitalization. I manage this situation with more difficulties because I was unemployed. I just consulted the modern medicine not the traditional healers and marabous because of the death of my daughter. Because of her death my first resort when someone fall sick is the hospital. My daughter got to hospital with delay.

After hospitalization they prescribe to Bara a scanner and they noticed sequelae. His body was awful and his legs were immobile. The right side was paralyzed. And so the appointments began. We didn't respect the appointments because of lack of money. I tried the physiotherapy at home. The child is easily angry and it's the only change I notice in him. He plays with children of same age but he's sometimes rough. He hasn't neurologic, vision and hearing problems. He hasn't fits. His only problem is his leg and arm paralysis and his speech disorders. Bara is smaller than children of the same age. He has growth retardation and speech disorder.

He doesn't react in front of a foreigner. The hospitalization was a heavy financial charge. I haven't got the household expenses the mother needed. I used my only money for the child's treatment. Now he's not going to school because of his speech disorders. The neighbours are kind to him. After his discharge from hospital Bara have often malaria, rhinitis and diarrhea without seriousness.

The mother:
After his meningitis, I wanted to bring him at Talibou Dabo center for his physiotherapy and just your project arrived and assisted us. I paid 1,000 CFA for his consultation

The father:
Your project has assisted us. We are seeing a real improvement. I pray for the recover of the child. I have a big hope. Your project has financially lightened us and I hope that the child will be completely recovered and will be able to go to school.

The disease of Bara reinforced the relationship between me and his mother. She financially supported me. The disease united us increasingly. The lesson learned is hospital must be the first resort and not the traditional healer. At the beginning I thought he had only tooth problem or simple malaria attack.

The mother:
When I am alone, I am sad to see the disabilities of my son but I keep on hoping like a Muslim and agree with God. Nevertheless, we notice an improvement and thank you a lot. When children of the same age hit him and he cries, I feel sad. Sometimes I wonder if he will ever recover. Before he felt often sick, but know he's better. He fights with the children of same age. For this we are deeply thanking you for your important support. You do your work without cheating and you are faithful

The father:
I know that meningitis is dangerous and without the project it would be worse for us. The lesson learned is when a child has fever you must bring him to a doctor. I thank your project for the financial, medical and moral support. If others projects do like it will be excellent. Thank you, again. When Cheikh called me the first day, I was daily worker at the sea port of Dakar. I gave my consent and said to my wife to answer all the questions. I infinitely think you. If in all the disease people had this kind of support, I think families will be lightened. I pray that god assist you. Thank you very much again.

FAMILY OF CHILD 2

The mother:
Before the meningitis attack, the child was well. When I was pregnant, I took my vaccines, but not all. He has a sister and brother who feel healthy in the household.
Six years ago, he felt down in playing, we first thought it was a malaria attack that caused the fracture. We used butter shea in vain during three days for massage. After these three days, we brought him at hospital, where he was hospitalized. He was always sleeping. We bought many medicaments. He spent one month at hospital under drip. The prescriptions were very expensive. My parents assisted me to buy the prescriptions. I wasn't sleeping. Mbar is very attached to me. When I was at hospital, I was always thinking of the children in the village. I was worried. He wants to go to school, but when I bring him they tell to me he can't learn because of his deafness and his speech disorder. Nowadays the child must go to school, but he can't hear nor speak. During discharge, I was happy because the fits disappeared and he ate. His uncle also assisted me. I never went to consult traditional healers. He's living a long ordeal, he must go to school but he can't. I always think that he need assistance, he needs me. I am always asking myself if I die what will be the future of this child. It hurts me terribly. Some of my neighbors feel pity for me, but others make fun of me in a gazed way. For such a child only his mother can support him. Some people think that I have a responsibility in the disease of Mbar. The children of the same age make fun of him. Mbar prefers to be with older people because children of same age laugh at him. And yet I hope for his recovery and that he will go to school, marry a woman and work. Apart from my parents nobody assisted me.

The uncle:
The mother has told it all to you. The disease is terrible. Some people think that the mother of the child has nothing done in the household, it's awful. Others say that the disease come from God. We consulted traditional healers in vain. Fortunately there are organizations which assist them. At the beginning we consulted a traditional healer but afterwards we decided that we must go to hospital to see a doctor. We can't bring him to the disability school because we have no money for this. The mother had sold all her possessions. The child is very clever. The doctor tells us he has recovered. He is very smart. We lack means; this is why we can't bring him to a specialized school. He is amusing. Between the mother and the others members of family the relationship are reinforced.

The mother:
At the beginning I didn't know meningitis. It's when my child had a meningitis attack that I knew it. The sign of meningitis is when a child falls suddenly down. At first we thought to malaria and the fracture, sprain, luxation. Now I can understand the signs of meningitis. When I see a child drop I systematically think to meningitis. It's a dreadful disease which destroys individuals. I hope and I pray that one day my child be recovered and work properly. What hurts me, is that my child want go to school but he has hear impair and can't speak. I haven't got the means to bring him in a specialized school.
In conclusion, I say that the disease is very dreadful and expensive. I ask assistance, I want my son to recover fast. It's very difficult for me. I need assistance for the success of Mbar

The father:
Dreadful and dangerous disease is meningitis. When he goes out I am afraid because of road accident. When he returns he can't hear when you speak or call him. The mother understands the disease, so she will take care of the children's vaccinations.

The mother:
Modern medicine is more efficient. We consulted the traditional healer because we thought of the devil. We hear about many things about this disease. We hope with your project that meningitis will disappear. We ask assistance.

The father:

I wish success to your project. Meningitis is a real social plague.

FAMILY OF CHILD 3

The father:
Before meningitis the child wasn't vaccinated. He has one older brother and sisters who are healthy. He was nine months old when he had meningitis. At the beginning he was crying, his body was hot and he had a stiff neck. I went to Parcelles Assainies health center, but when we came back the situation was worse. The same day we went to Albert Royer, but they gave us nothing. The day after, we went again to Albert Royer because the disease worsened. We consulted a traditional healer woman.

The mother:
I thank you for your visit. The child was healthy before meningitis. Mohamed was recovered. He fell sick at about 10 months old. It was a Friday, I come back the afternoon, I found his body hot, at dusk. I asked to my sister who looked after him if the child felt down. He began to vomit and I brought him to the nearest health center. I paid for the doctor's consultation, but not for the nurse's consultation. They prescribed him antimalaria medicines and vogalene. In the night the situation worsened. I asked my husband to bring the child to hospital Albert Royer, but he said to me that I am stubborn. I took the children and went to hospital and my husband met up with me on the road. The doctor told us to go back home with the antimalaria treatment and give an appointment in three days. The day after the fever continued. Another friend of my husband reassured us and added Oracefal. In the night I wasn't calm because I thought of meningitis and I brought again the child and asked them to do the lumbar puncture. So they did the lumbar puncture and they diagnosed meningitis and hospitalized him during 17 days. The hospitalization was awful for me; all my activities were stopped and I envisaged with anxiousness the sequelae at discharge, the child couldn't sit down. I asked the doctor, what are the risks of sequelae? The doctors comforted me.

During the hospitalization I was under contract with the Ministry of Health so I didn't have a problem with payment. But I couldn't do my activities. The child was followed up in opthalmolgy. I assured the following up with Dr Moustapha Ndiaye until he stopped the appointment. At this moment I was worried. I noticed that he had a hearing impair and I

was disappointed. A friend advised me to see Dr Tendeng. I consulted Dr Tendeng who prescribed me a hearing device which was very expensive. The cost was 500 000 XOF in the optical shop. It was very expensive for me. He proposed me also a cochlear implant. So I wrote a letter to the social service of the Ministry of Health and they found a hearing device. The social service gave me a device but it wasn't adaptable because of the low power. Docteur Tendeng proposed an audiogram and recommended me to Dr Chauvin. Dr Chauvin performed an audiogram and an Evoked Potential Auditive. And then Dr Tendeng propose me a cochlear implant at Bordeaux which costs 2000 Euros (1 300 000 XOF at this moment), without the follow up and the flight ticket for me and the child. I hadn't money for all this to continue. I opened an account in a bank but I hadn't enough money. The bill included the feasibility evaluation of the cochlear implant. And if it's feasible the total will be around 20,000,000 XOF without the follow-up. I hadn't this money and with the assistance of my director I opened an account in a bank. I received some money but it's not enough yet. So I failed twice the appointment in Bordeaux. Nevertheless I keep hoping.

Everyday that my child falls ill, I go to hospital and marabous are secondary. My work is disturbed because the child is often ill. I am often out of my office. My husband always buys the prescriptions.

The neighbors have pity on the child. At the beginning, the children mocked him and named him the deaf-mute. And it hurts me. But now things are changed. I believe in God, but sometimes I have indignation to see the situation of my child. Concerning the future, I pray for success in medical research. I wish that the cochlear implant will be a success for Mohamed. I am always questioning if the cochlear implant will be feasible. Between my husband and me the climate is very convivial. The child isn't source of conflict. The child is going now to verbo-tonal center for his education.

I hail the authorities to better do concerning the control of meningitis. Certainly the vaccination against meningitis is in the EPI but it's too late. Meningitis has done many damages. The government must introduce all vaccines against meningitis in the EPI. The month when my child had meningitis I did not have a job and the vaccine cost 6000 FCFA. Now the HIb vaccine is free and meningitis reduced. The child is now at verbal-tonal center. The mothers must bring all the children for vaccinations every day. It's very important because meningitis cause damages.

I thank you, for the interest toward my child and pray for your success. If many projects did like you many health problems would be eradicated. I thank you again.

ANNEX 10: ETHIOPIA SYSTEM COSTS DATA COLLECTION FORM

ETHIOPIA POST INTRODUCTION EVALUATION DATA COLLECTION FORM:

INFORMATION FOR THE ECONOMIC ANALYSIS

Name of town/area: _____

Date of data collection:_____

Name and contact details of person interviewed:_____

_____

_____

DEMOGRAPHICS FOR THE LAST YEAR WHERE DATA IS AVAILABLE

Year:_____

	Regional state	**Zone**	**Wereda**	**Kebele**
Name of area				
Total population				
Births				
Crude birth rate (birth per 1000 population)				
Infant mortality rate (per 1000 children)				
Notes				

DTP/PENTAVALENT VACCINE DATA

	May 06	**June 06**	**July 06**	**Aug 06**	**Sep 06**	**May 07**	**June 07**	**July 07**	**Aug 07**	**Sep 07**

Vaccine coverage rate											
Reserve stock (no. of vials)											
#of doses administered											
#of doses issued[6] [7]											

WASTE MANAGEMENT OF USED VIALS AND SYRINGES

Question	Feedback
Do you use safety boxes for used syringes?	
If so, what is their capacity? (how many syringes per safety box?)	
How long does it on average take to fill a safety box?	
What do you do with used vials and syringes?	
Do you have staff specifically employed to manage medical waste?	
If so, how many and what is the monthly salary of these staff?	
What type of equipment do you have to deal with waste management? Please list (examples include incinerators, needle cutters, etc).	
If you have an incinerator, how much fuel do you use per month (in litres)?	
Do you spend resources on maintenance of equipment for waste management?	
If so, how much do you spend on	

[6] All doses given to facility for use, including those that are wasted, missing etc.
[7] Vaccine usage rate= # of doses administered/ number of doses issued x 100.
Wastage rate= 100-vaccine usage rate.

maintenance per month?	
Notes	

TRANSPORT OF VACCINES AND SYRINGES

Question	Feedback
How are vaccines and syringes delivered to the facility?	
How many times per year are vaccines and syringes transported to the facility?	
Did the frequency of transport change with introduction of the pentavalent vaccine?	
Does the facility have any vehicles that are used for vaccine and syringe transport?	
If so, how many?	
List the model and make of vehicle and year of purchase.	
What was the purchase price of the vehicle/vehicles?	
How much did it cost to register each vehicle?	
How many years do you expect each vehicle to last?	
How many litres of fuel do you use for one trip to collect vaccines and syringes?	

How much does one litre of fuel cost?	
How much do you spend on driver salaries (per month)	
How much do you spend on vehicle maintenance costs (per year)?	
Notes	

COLD STORAGE OF VACCINES

Question	Feedback
What cold storage equipment do you have? Please list and include model and make numbers (examples include refrigerator, freezer, stand by generator, cold box, cold store).	
Please list the capacity of each cold storage equipment (cm3)	
How much do you spend on electricity per month?	
How much do you spend on ice packs per month?	
How much do you spend on kerosene per month?	
How much do you spend on spare parts per month?	
How much do you spend on maintenance per month?	
How much do you spend on gas per month?	
Do you have any other costs? If so, please list them.	

Notes	

SUPPLIES FOR VACCINE REGISTRY AND SOCIAL MOBILISATION

Question	Feedback
Did you make any changes to immunisation cards with introduction of the pentavalent vaccine?	
If so, how much did it cost?	
Did you spend any resources on social mobilisation for pentavalent vaccine introduction?	
If so, how much did you spend?	
Did you incur any other costs related to the vaccine introduction? If so, please list.	
Notes	

15 REFERENCES

1. Hajjeh RA, Privor-Dumm L, Edmond K, O'Loughlin R, Shetty S, Griffiths UK, Bear AP, Cohen AL, Chandran A, Schuchat A, Mulholland EK, and Santosham M, Supporting new vaccine introduction decisions: lessons learned from the Hib Initiative experience*. Vaccine*. **28**(43): p. 7123-9.
2. Evans AS, Causation and Disease: The Henle-Koch Postulates Revisited*. The Yale Jounal of Biology and Medicine*, 1976. **49**: p. 175-195.
3. Ward JI, Constance, M.V., *Haemophilus influenzae*, in Bacterial Infections of Humans, Epidemiology and Control, edited by Evans AS and Brachman PS, 1998, Plenum medical book company: New York and London.
4. Pittman M, The action of type-specific *Haemophilus influenzae* antiserum*. J. Exp. Med.*, 1933. **58**: p. 683-706.
5. Goldblatt D, Assari, T., Immunological basis for immunization. Module 9: *Haemophilus influenzae* type b vaccines*.* 2007: Geneva: WHO
6. Popovic T, Ajello, G., Facklam, R., Laboratory methods for the diagnosis of meningitis caused by Neisseria meningitidis, Streptococcus pneumoniae and *Haemophilus influenzae.* 1999. **WHO/CDS/CSR/EDC/99.7**: WHO
7. Wenger JD, Ward, J.I., *Haemophilus influenzae* vaccine, in Vaccines, edited by Plotkin WA and Offit PA., 2004. p. 229-268.
8. Barbour ML, Conjugate vaccines and the carriage of *Haemophilus influenzae* type b*. Emerg Infect Dis*, 1996. **2**(3): p. 176-82.
9. Stephens DS and Farley MM, Pathogenic events during infection of the human nasopharynx with Neisseria meningitidis and *Haemophilus influenzae, Rev Infect Dis*, 1991. **13**(1): p. 22-33.
10. Takala AK, Meurman O, Kleemola M, Kela E, Ronnberg PR, Eskola J, and Makela PH, Preceding respiratory infection predisposing for primary and secondary invasive *Haemophilus influenzae* type b disease*. Pediatr Infect Dis J*, 1993. **12**(3): p. 189-95.
11. Barbour ML, Booy R, Crook DW, Griffiths H, Chapel HM, Moxon ER, and Mayon-White D, *Haemophilus influenzae* type b carriage and immunity four years after receiving the Haemophilus influenzae oligosaccharide-CRM197 (HbOC) conjugate vaccine*. Pediatr Infect Dis J*, 1993. **12**(6): p. 478-84.
12. Barbour ML, Mayon-White RT, Coles C, Crook DW, and Moxon ER, The impact of conjugate vaccine on carriage of *Haemophilus influenzae* type b*. J Infect Dis*, 1995. **171**(1): p. 93-8.

13. Sekhar S, Chakraborti A, and Kumar R, *Haemophilus influenzae* colonization and its risk factors in children aged <2 years in northern India*. Epidemiol Infect*, 2009. **137**(2): p. 156-60.
14. Poyrazoglu S, Komec S, Gokcay G, and Ongen B, *Haemophilus influenzae* type b carriage among 3- to 24-month-old Turkish children*. Epidemiol Infect*, 2005. **133**(6): p. 1113-7.
15. Howard AJ, Dunkin KT, and Millar GW, Nasopharyngeal carriage and antibiotic resistance of *Haemophilus influenzae* in healthy children*. Epidemiol Infect*, 1988. **100**(2): p. 193-203.
16. Stephenson WP, Doern G, Gantz N, Lipworth L, and Chapin K, Pharyngeal carriage rates of *Haemophilus influenzae*, type b and non-b, and prevalence of ampicillin-resistant *Haemophilus influenzae* among healthy day-care children in central Massachusetts*. Am J Epidemiol*, 1985. **122**(5): p. 868-75.
17. Mohle-Boetani JC, Ajello G, Breneman E, Deaver KA, Harvey C, Plikaytis BD, Farley MM, Stephens DS, and Wenger JD, Carriage of *Haemophilus influenzae* type b in children after widespread vaccination with conjugate *Haemophilus influenzae* type b vaccines*. Pediatr Infect Dis J*, 1993. **12**(7): p. 589-93.
18. Takala AK, Santosham M, Almeido-Hill J, Wolff M, Newcomer W, Reid R, Kayhty H, Esko E, and Makela PH, Vaccination with *Haemophilus influenzae* type b meningococcal protein conjugate vaccine reduces oropharyngeal carriage of *Haemophilus influenzae* type b among American Indian children*. Pediatr Infect Dis J*, 1993. **12**(7): p. 593-9.
19. Midwinter KI, Hodgson D, and Yardley M, Paediatric epiglottitis: the influence of the *Haemophilus influenzae* b vaccine, a ten-year review in the Sheffield region*. Clin Otolaryngol Allied Sci*, 1999. **24**(5): p. 447-8.
20. Watt JP, Levine OS, and Santosham M, Global reduction of Hib disease: what are the next steps? Proceedings of the meeting Scottsdale, Arizona, September 22-25, 2002*. J Pediatr*, 2003. **143**(6 Suppl): p. S163-87.
21. Crawford SE, Daum, R.S., *Haemophilus Influenzae*, in Nelson textbook of Pediatrics, edited by Kliegman, Jenson and Stanton, 2004, Saunders Elsevier.
22. Bennett JV, Platonov AE, Slack MPE, Mala P, Burton AH, and Roberson SE, *Haemophilus influenzae* type b (Hib) meningitis in the pre-vaccine era: a global review of incidence, age distributions, and case-fatality rates*.* **WHO/V&B/02.18**, 2002: Geneva: WHO

23. Bedford H, de Louvois J, Halket S, Peckham C, Hurley R, and Harvey D, Meningitis in infancy in England and Wales: follow up at age 5 years. *Bmj*, 2001. **323**(7312): p. 533-6.
24. Karma P, Luotonen J, Pukander J, Sipila M, Herva E, and Gronroos P, *Haemophilus influenzae* in acute otitis media. *Acta Otolaryngol*, 1983. **95**(1-2): p. 105-10.
25. Lebedova V and Krizova P, The 2001 serological survey in the Czech Republic--Hib invasive disease *Haemophilus influenzae b. Cent Eur J Public Health*, 2003. **11 Suppl**: p. S25-30.
26. Likitnukul S, Systemic *Haemophilus influenzae* disease in Thai children. *Southeast Asian J Trop Med Public Health*, 1994. **25**(4): p. 672-7.
27. Tudor-Williams G, Frankland J, Isaacs D, Mayon-White RT, MacFarlane JA, Slack MP, Anderson E, Rees DG, and Moxon ER, *Haemophilus influenzae* type b disease in the Oxford region. *Arch Dis Child*, 1989. **64**(4): p. 517-9.
28. Adegbola RA, Mulholland EK, Falade AG, Secka O, Sarge-Njai R, Corrah T, Palmer A, Schneider G, and Greenwood BM, *Haemophilus influenzae* type b disease in the western region of The Gambia: background surveillance for a vaccine efficacy trial. *Ann Trop Paediatr*, 1996. **16**(2): p. 103-11.
29. Hanna J, The epidemiology and prevention of *Haemophilus influenzae* infections in Australian aboriginal children. *J Paediatr Child Health*, 1992. **28**(5): p. 354-61.
30. Chandran A, Watt, J.P., Santosham, M., *Haemophilus influenzae* vaccines, in Vaccines, edited by Plotkin WA and Offit PA, 2008. p. 157-175.
31. Watt JP, Wolfson LJ, O'Brien KL, Henkle E, Deloria-Knoll M, McCall N, Lee E, Levine OS, Hajjeh R, Mulholland K, and Cherian T, Burden of disease caused by *Haemophilus influenzae* type b in children younger than 5 years: global estimates. *Lancet*, 2009. **374**(9693): p. 903-11.
32. Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, Jha P, Campbell H, Walker CF, Cibulskis R, Eisele T, Liu L, and Mathers C, Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet*, 2010. **375**(9730): p. 1969-87.
33. Programme for the Control of Acute Respiratory Infections, Technical basis for the WHO recommendations on the management of pneumonia in children at first level health facilities. 1991, **WHO/ARI/91.20**, WHO
34. Tristram S, Jacobs MR, and Appelbaum PC, Antimicrobial resistance in *Haemophilus influenzae. Clin Microbiol Rev*, 2007. **20**(2): p. 368-89.

35. Levine OS, Schuchat A., Schwartz B, Wenger JD, Elliott J, Generic protocol for population-based surveillance of *Haemophilus influenzae* type b*.* 1995, WHO, Geneva
36. Munson RS, Jr., Kabeer MH, Lenoir AA, and Granoff DM, Epidemiology and prospects for prevention of disease due to *Haemophilus influenzae* in developing countries*. Rev Infect Dis*, 1989. **11 Suppl 3**: p. S588-97.
37. Russell FM, Biribo SS, Selvaraj G, Oppedisano F, Warren S, Seduadua A, Mulholland EK, and Carapetis JR, As a bacterial culture medium, citrated sheep blood agar is a practical alternative to citrated human blood agar in laboratories of developing countries*. J Clin Microbiol*, 2006. **44**(9): p. 3346-51.
38. Feikin DP, Mahoney F, *Haemophilus influenzae* type b (Hib) disease burden in Uzbekistan: WHO Hib rapid assessment tool. 10-16 November 2002.
39. Gellert GA, Wenger JD, and Brilla A, *Haemophilus influenzae* type b disease in Latvia*. Lancet*, 1994. **344**(8927): p. 959.
40. McIntyre PB, Leeder SR, and Irwig LM, Invasive *Haemophilus influenzae* type b disease in Sydney children 1985-1987: a population-based study*. Med J Aust*, 1991. **154**(12): p. 832-7.
41. Dagan R, Fraser D, Greif Z, Keller N, Kaufstein M, Shazberg G, and Schlesinger M, A nationwide prospective surveillance study in Israel to document pediatric invasive infections, with an emphasis on *Haemophilus influenzae* type b infections. Israeli Pediatric Bacteremia and Meningitis Group*. Pediatr Infect Dis J*, 1998. **17**(9 Suppl): p. S198-203.
42. Zielinski A, Tomaszunas-Blaszczyk J, and Kuklinska D, Epidemiology of childhood bacterial meningitis in Poland. Incidence of bacterial meningitis with special reference to *Haemophilus influenzae* type b among children 0-59 months old in the former Kielce and Bydgoszcz districts in Poland in 1998-1999*. Eur J Epidemiol*, 2001. **17**(8): p. 779-82.
43. Kojouharova M, Gatcheva N, Setchanova L, Robertson SE, and Wenger JD, Epidemiology of meningitis due to *Haemophilus influenzae* type b in children in Bulgaria: a prospective, population-based surveillance study*. Bull World Health Organ*, 2002. **80**(9): p. 690-5.
44. Minz S, Balraj V, Lalitha MK, Murali N, Cherian T, Manoharan G, Kadirvan S, Joseph A, and Steinhoff MC, Incidence of *Haemophilus influenzae* type b meningitis in India*. Indian J Med Res*, 2008. **128**(1): p. 57-64.
45. Rerks-Ngarm S, Treleaven SC, Chunsuttiwat S, Muangchana C, Jolley D, Brooks A, Dejsirilert S, Warintrawat S, Guiver M, Kunasol P, Maynard JE, Biggs BA, and

Steinhoff M, Prospective population-based incidence of *Haemophilus influenzae* type b meningitis in Thailand*. Vaccine*, 2004. **22**(8): p. 975-83.

46. Peltola H, Need for *Haemophilus influenzae* type b vaccination in Asia as evidenced by epidemiology of bacterial meningitis*. Pediatr Infect Dis J*, 1998. **17**(9 Suppl): p. S148-51.
47. Shetty S, Cohen AL, Edmond K, Ojo L, Loo J, O'Loughlin R, and Hajjeh R, A systematic review and critical evaluation of invasive *Haemophilus influenzae* type B disease burden studies in Asia from the last decade: lessons learned for invasive bacterial disease surveillance*. Pediatr Infect Dis J*, 2010. **29**(7): p. 653-61.
48. Cadoz M, Denis F, and Mar ID, [An epidemiological study of purulent meningitis cases admitted to hospital in Dakar, 1970-1979]*. Bull World Health Organ*, 1981. **59**(4): p. 575-84.
49. Bijlmer HA, van Alphen L, Greenwood BM, Brown J, Schneider G, Hughes A, Menon A, Zanen HC, and Valkenburg HA, The epidemiology of *Haemophilus influenzae* meningitis in children under five years of age in The Gambia, West Africa*. J Infect Dis*, 1990. **161**(6): p. 1210-5.
50. Campagne G, Schuchat A, Djibo S, Ousseini A, Cisse L, and Chippaux JP, Epidemiology of bacterial meningitis in Niamey, Niger, 1981-96*. Bull World Health Organ*, 1999. **77**(6): p. 499-508.
51. Wenger JD, Epidemiology of Haemophilus influenzae type b disease and impact of *Haemophilus influenzae* type b conjugate vaccines in the United States and Canada*. Pediatr Infect Dis J*, 1998. **17**(9 Suppl): p. S132-6.
52. Lau YL, Low LC, Yung R, Ng KW, Leung CW, Lee WH, Ho A, and Oppenheimer SJ, Invasive *Haemophilus influenzae* type b infections in children hospitalized in Hong Kong, 1986-1990. Hong Kong Hib Study Group*. Acta Paediatr*, 1995. **84**(2): p. 173-6.
53. Anh DD, Kilgore PE, Kennedy WA, Nyambat B, Long HT, Jodar L, Clemens JD, and Ward JI, *Haemophilus influenzae* type B meningitis among children in Hanoi, Vietnam: epidemiologic patterns and estimates of H. Influenzae type B disease burden*. Am J Trop Med Hyg*, 2006. **74**(3): p. 509-15.
54. Reinert P, Liwartowski A, Dabernat H, Guyot C, Boucher J, and Carrere C, Epidemiology of *Haemophilus influenzae* type b disease in France*. Vaccine*, 1993. **11 Suppl 1**: p. S38-42.
55. Tudor-Williams G, Frankland J, Isaacs D, Mayon-White RT, MacFarlane JA, Rees DG, and Moxon ER, *Haemophilus influenzae* type b conjugate vaccine trial in Oxford: implications for the United Kingdom*. Arch Dis Child*, 1989. **64**(4): p. 520-4.

56. Ward JI, Lum MK, Hall DB, Silimperi DR, and Bender TR, Invasive *Haemophilus influenzae* type b disease in Alaska: background epidemiology for a vaccine efficacy trial*. J Infect Dis*, 1986. **153**(1): p. 17-26.
57. O'Brien KL, Wolfson LJ, Watt JP, Henkle E, Deloria-Knoll M, McCall N, Lee E, Mulholland K, Levine OS, and Cherian T, Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates*. Lancet*, 2009. **374**(9693): p. 893-902.
58. Wolfson L, O'Brien, KL., Watt, JP., Henkle, E., Deloria-Knoll, MD., McCall, N., Lee, E., Mulholland, KE., Levine, OS., Cherian, T. for the Hib and Pneumococcal Global Burden of and Disease Study Team, Methods to estimate the global burden of disease due to *Haemophilus influenzae* type b and Streptococcus pneumoniae in children less than 5 years of age*. Lancet*, 2009. **Web annex**(374): p. 893-902.
59. Kelly DF, Moxon ER, and Pollard AJ, *Haemophilus influenzae* type b conjugate vaccines*. Immunology*, 2004. **113**(2): p. 163-74.
60. Eskola J, Kayhty H, Takala AK, Peltola H, Ronnberg PR, Kela E, Pekkanen E, McVerry PH, and Makela PH, A randomized, prospective field trial of a conjugate vaccine in the protection of infants and young children against invasive *Haemophilus influenzae* type b disease*. N Engl J Med*, 1990. **323**(20): p. 1381-7.
61. Ward J, Brenneman G, Letson GW, and Heyward WL, Limited efficacy of a *Haemophilus influenzae* type b conjugate vaccine in Alaska Native infants. The Alaska H. influenzae Vaccine Study Group*. N Engl J Med*, 1990. **323**(20): p. 1393-401.
62. WHO, Global and regional immunization profile*. http://www.who.int/immunization_monitoring/en/globalsummary/GS_GLOProfile.pdf*, WHO vaccine-preventable disease monitoring system.
63. Basu N, Cutts, F., Gasse, F., Ndumbe, P., Steinglass, R., LaForce, M., Sustainability of Achievements: Lessons learned from Universal Child Immunization. Report of a Steering Committee*.* 1996: New York
64. Saxenian H, Cornejo S, Thorien K, Hecht R, and Schwalbe N, An Analysis Of How The GAVI Alliance And Low- And Middle-Income Countries Can Share Costs Of New Vaccines*. Health Aff (Millwood)*. **30**(6): p. 1122-33.
65. GAVI, Who can apply? *http://www.gavialliance.org/support/who/index.php*.
66. Hajjeh RA, Privor-Dumm L, Edmond K, O'Loughlin R, Shetty S, Griffiths UK, Bear AP, Cohen AL, Chandran A, Schuchat A, Mulholland EK, and Santosham M, Supporting new vaccine introduction decisions: lessons learned from the Hib Initiative experience*. Vaccine*, 2010. **28**(43): p. 7123-9.

67. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL , Methods for the economic evaluation of health care programmes, 3rd edition. 2005, Oxford: Oxford University Press.
68. Palmer S and Torgerson DJ, Economic notes: definitions of efficiency. *Bmj*, 1999. **318**(7191): p. 1136.
69. Morris S, Devlin N., Parkin D, Economic analysis in health care. 2007: John Wiley and Sons, Ltd.
70. Viscusi WK, Aldy, J.E., The Value of a Statistical Life: A Critical Review of Market Estimates Throughout the World. *Journal of Risk and Uncertainty*, 2003. **27**(1): p. 5-76.
71. Buxton MJ, Drummond MF, Van Hout BA, Prince RL, Sheldon TA, Szucs T, and Vray M, Modelling in economic evaluation: an unavoidable fact of life. *Health Econ*, 1997. **6**(3): p. 217-27.
72. Medical dictionary. Decision analysis. 2011 [cited 2011 16 July]; Available from: http://medical-dictionary.thefreedictionary.com/decision+analysis.
73. Gold MR, Siegel, JE, Russell, LB, Milton, CW, Cost-effectiveness in health and medicine. 1996, New York: Oxford University Press.
74. Nord E, Discounting future health benefits: the poverty of consistency arguments. *Health Econ*, 2011. **20**(1): p. 16-26.
75. Sheldon TA, Discounting in health care decision-making: time for a change? *J Public Health Med*, 1992. **14**(3): p. 250-6.
76. Claxton K, Paulden M, Gravelle H, Brouwer W, and Culyer AJ, Discounting and decision making in the economic evaluation of health-care technologies. *Health Econ*, 2011. **20**(1): p. 2-15.
77. Eichler HG, Kong SX, Gerth WC, Mavros P, and Jonsson B, Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? *Value Health*, 2004. **7**(5): p. 518-28.
78. NICE, Guide to the methods of technology appraisal. 2008, http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf
79. World Health Organization, Cost-effectiveness thresholds. 2010. p. http://www.who.int/choice/costs/CER_thresholds/en/index.html.
80. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, Woolacoot N, and Glanville J, Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess*, 2004. **8**(36): p. iii-iv, ix-xi, 1-158.

81. Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C, and Luce BR, Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--Modeling Studies. *Value Health*, 2003. **6**(1): p. 9-17.
82. Brisson M and Edmunds WJ, Economic evaluation of vaccination programs: the impact of herd-immunity. *Med Decis Making*, 2003. **23**(1): p. 76-82.
83. Beutels P, Edmunds WJ, Antonanzas F, De Wit GA, Evans D, Feilden R, Fendrick AM, Ginsberg GM, Glick HA, Mast E, Pechevis M, Van Doorslaer EK, and van Hout BA, Economic evaluation of vaccination programmes: a consensus statement focusing on viral hepatitis. *Pharmacoeconomics*, 2002. **20**(1): p. 1-7.
84. Van Damme P and Beutels P, Economic evaluation of vaccination. *Pharmacoeconomics*, 1996. **9 Suppl 3**: p. 8-15; discussion 23-5.
85. Beutels P, Scuffham PA, and MacIntyre CR, Funding of drugs: do vaccines warrant a different approach? *Lancet Infect Dis*, 2008. **8**(11): p. 727-33.
86. De Jong MC and Bouma A, Herd immunity after vaccination: how to quantify it and how to use it to halt disease. *Vaccine*, 2001. **19**(17-19): p. 2722-8.
87. Jit M and Brisson M, Modelling the epidemiology of infectious diseases for decision analysis: a primer. *Pharmacoeconomics*, 2011. **29**(5): p. 371-86.
88. WHO, WHO guide for standardization of economic evaluations of immunization programmes, **WHO/IVB/08.14**, 2008, Immunization, Vaccines and Biologicals Department , Geneva.
89. Kim SY and Goldie SJ, Cost-effectiveness analyses of vaccination programmes : a focused review of modelling approaches. *Pharmacoeconomics*, 2008. **26**(3): p. 191-215.
90. Centre for Reviews and Dissemination, NHS EED (NHS Economic Evaluation Database), 2008, Centre for Reviews and Dissemination, University of York: York. www.crd.york.ac.uk/crdweb/
91. John Wiley & Sons Ltd, HEED: Health Economic Evaluations Database, 2008 Chichester, www3.interscience.wiley.com/cgi-bin/mrwhome/114130635/HOME
92. International Monetary Fund, Data and Statistics. 2009, http://www.imf.org/external/data.htm.
93. Centre for Reviews and Dissemination, Systematic Reviews: CRD's guidance for undertaking reviews in health care. January, 2009: University of York.
94. Guzmán AN RF, Consuelo DV, The cost-effectiveness of *Haemophilus influenzae* type b vaccine for children under 2 years of age in Colombia. *Rev Panam Salud Publica*, 2006. **20**(4): p. 248-55.

95. de Campora E and Pizzuti R, Use of the economic evaluation in the comparison of different vaccination programs against *Haemophilus influenzae* type b disease, *Ann Ig*, 1995. **7**(5): p. 329-38.
96. Martens LL, ten Velden GH, and Bol P, Costs and benefits of vaccination against *Haemophilus influenzae* type b*. Ned Tijdschr Geneeskd*, 1991. **135**(1): p. 16-20.
97. Zhou F, Santoli J, Messonnier ML, Yusuf HR, Shefer A, Chu SY, Rodewald L, and Harpaz R, Economic evaluation of the 7-vaccine routine childhood immunization schedule in the United States, 2001*. Arch Pediatr Adolesc Med*, 2005. **159**(12): p. 1136-44.
98. Fagnani F, Le Fur C, Durand I, and Gibergy M, Economic evaluation of a combined DTPa, hepatitis B, polio, Hib vaccine. Potential impact of the introduction of Infanrix-Hexa in the French childhood immunisation schedule*. Eur J Health Econ*, 2004. **5**(2): p. 143-9.
99. Fendrick AM, Lee JH, LaBarge C, and Glick HA, Clinical and economic impact of a combination *Haemophilus influenzae* and Hepatitis B vaccine: estimating cost-effectiveness using decision analysis*. Arch Pediatr Adolesc Med*, 1999. **153**(2): p. 126-36.
100. Clements DA, Cost of treatment and prevention of *Haemophilus influenzae* type b disease. An international perspective*. Pharmacoeconomics*, 1994. **6**(5): p. 442-52.
101. Levine OS, Ortiz E, Contreras R, Lagos R, Vial P, Misraji A, Ferreccio C, Espinoza C, Adlerstein L, Herrera P, and et al., Cost-benefit analysis for the use of *Haemophilus influenzae* type b conjugate vaccine in Santiago, Chile*. Am J Epidemiol*, 1993. **137**(11): p. 1221-8.
102. Midani S, Ayoub EM, and Rathore MH, Cost-effectiveness of *Haemophilus influenzae* type b conjugate vaccine program in Florida*. J Fla Med Assoc*, 1995. **82**(6): p. 401-2.
103. 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): p. 1563-6.
104. Hussain IHMI, Syed A, Sofiah A, Ong LC, Choo KE, Cost-benefit analysis of *Haemophilus influenzae* vaccination programme in Malaysia*. Buletin Kesihatan Masyarakat*, 1999. **5**(79).
105. 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): p. 75-83.

106. 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): p. 32-7.
107. Cochi SL, Broome CV, and Hightower AW, Immunization of US children with *Haemophilus influenzae* type b polysaccharide vaccine. A cost-effectiveness model of strategy assessment*. Jama*, 1985. **253**(4): p. 521-9.
108. Hay JW and Daum RS, Cost-benefit analysis of two strategies for prevention of *Haemophilus influenzae* type b infection*. Pediatrics*, 1987. **80**(3): p. 319-29.
109. Word Bank, Country Groups, Data and Statistics*. http://web.worldbank.org/WBSITE/EXTERNAL/DATASTATISTICS/0,,contentMDK:20421402~pagePK:64133150~piPK:64133175~theSitePK:239419,00.html*, Accessed 10 January 2012.
110. 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): p. 485-90.
111. 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): p. 653-61.
112. Hussey GD, Lasser ML, and Reekie WD, The costs and benefits of a vaccination programme for *Haemophilus influenzae* type B disease*. S Afr Med J*, 1995. **85**(1): p. 20-5.
113. Duke T, *Haemophilus influenzae* type b meningitis: how much better is prevention than cure? *P N G Med J*, 2002. **45**(3-4): p. 213-8.
114. 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): p. 391-400.
115. McIntyre P, Hall J, and Leeder S, An economic analysis of alternatives for childhood immunisation against *Haemophilus influenzae* type b disease*. Aust J Public Health*, 1994. **18**(4): p. 394-400.
116. Harris A, Hendrie D, Bower C, Payne J, de Klerk N, and Stanley F, The burden of *Haemophilus influenzae* type b disease in Australia and an economic appraisal of the vaccine PRP-OMP*. Med J Aust*, 1994. **160**(8): p. 483-8.
117. Trollfors B, Cost-benefit analysis of general vaccination against *Haemophilus influenzae* type b in Sweden*. Scand J Infect Dis*, 1994. **26**(5): p. 611-4.

118. 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): p. 5-10.
119. Livartowski A, Boucher J, Detournay B, and Reinert P, Cost-effectiveness evaluation of vaccination against *Haemophilus influenzae* invasive diseases in France*. Vaccine*, 1996. **14**(6): p. 495-500.
120. Pokorn M, Kopac S, Neubauer D, and Cizman M, Economic evaluation of *Haemophilus influenzae* type b vaccination in Slovenia*. Vaccine*, 2001. **19**(25-26): p. 3600-5.
121. 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): p. 176-84.
122. Platonov AE, Griffiths UK, Voeykova MV, Platonova OV, Shakhanina IL, Chistyakova GG, and Robertson SE, Economic evaluation of *Haemophilus influenzae* type b vaccination in Moscow, Russian Federation*. Vaccine*, 2006. **24**(13): p. 2367-76.
123. Broughton EI, Economic evaluation of *Haemophilus influenzae* type B vaccination in Indonesia: a cost-effectiveness analysis*. J Public Health (Oxf)*, 2007. **29**(4): p. 441-8.
124. Gessner BD, Sedyaningsih ER, Griffiths UK, Sutanto A, Linehan M, Mercer D, Mulholland EK, Walker DG, Steinhoff M, and Nadjib M, Vaccine-preventable *haemophilus influenza* type B disease burden and cost-effectiveness of infant vaccination in Indonesia*. Pediatr Infect Dis J*, 2008. **27**(5): p. 438-43.
125. Akumu AO, English M, Scott JA, and Griffiths UK, Economic evaluation of delivering *Haemophilus influenzae* type b vaccine in routine immunization services in Kenya*. Bull World Health Organ*, 2007. **85**(7): p. 511-8.
126. Murray CJL and Lopez AD, The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. 1996, Boston: Harvard School of Public Health.
127. DeRoeck D, Clemens JD, Nyamete A, and Mahoney RT, Policymakers' views regarding the introduction of new-generation vaccines against typhoid fever, shigellosis and cholera in Asia*. Vaccine*, 2005. **23**(21): p. 2762-74.
128. Shearer JC, Stack ML, Richmond MR, Bear AP, Hajjeh RA, and Bishai DM, Accelerating policy decisions to adopt *haemophilus influenzae* type B vaccine: a global, multivariable analysis*. PLoS Med*, 2010. **7**(3): p. e1000249.
129. Krishnan A, Determining the cost associated with vaccine preventable childhood diseases*.* 2001: New Delhi

130. Guzman NA, de la Hoz Restrepo F, Higuera AB, Pastor D, Di Fabio JL, Costos economicos de las neumonias et ninos menores de 2 anos de edad en Columbia. *Pan Americal Journal of Public Health*, 2005. **17**(3).
131. Hussain H, Waters H, Omer SB, Khan A, Baig IY, Mistry R, and Halsey N, The cost of treatment for child pneumonias and meningitis in the Northern Areas of Pakistan. *Int J Health Plann Manage*, 2006. **21**(3): p. 229-38.
132. Constenla D, Evaluating the costs of pneumococcal disease in selected Latin American countries. *Rev Panam Salud Publica*, 2007. **22**(4): p. 268-78.
133. Hussain H, Waters H, Khan AJ, Omer SB, and Halsey NA, Economic analysis of childhood pneumonia in Northern Pakistan. *Health Policy Plan*, 2008. **23**(6): p. 438-42.
134. Chola L and Robberstad B, Estimating average inpatient and outpatient costs and childhood pneumonia and diarrhoea treatment costs in an urban health centre in Zambia. *Cost Eff Resour Alloc*, 2009. **7**: p. 16.
135. Madsen HO, Hanehoj M, Das AR, Moses PD, Rose W, Puliyel M, Konradsen F, John KR, and Bose A, Costing of severe pneumonia in hospitalized infants and children aged 2-36 months, at a secondary and tertiary level hospital of a not-for-profit organization. *Trop Med Int Health*, 2009. **14**(10): p. 1315-22.
136. Anh DD, Riewpaiboon A, Tho le H, Kim SA, Nyambat B, and Kilgore P, Treatment costs of pneumonia, meningitis, sepsis, and other diseases among hospitalized children in Viet Nam. *J Health Popul Nutr*, 2010. **28**(5): p. 436-42.
137. Temple B, Griffiths UK, Mulholland EK, Ratu FT, Tikoduadua L, Russell FM. The cost of outpatient pneumonia in children <5 years of age in Fiji. Trop Med Int Health. 2011 Oct 18
138. Sinha A, Kim S, Ginsberg G, Franklin H, Kohberger R, Strutton D, Madhi SA, Griffiths UK, Klugman KP. Economic burden of acute lower respiratory tract infection in South African children. *Paediatr Int Child Health*. 2012;32(2):65-73.
139. Ayieko P, Akumu AO, Griffiths UK, and English M, The economic burden of inpatient paediatric care in Kenya: household and provider costs for treatment of pneumonia, malaria and meningitis. *Cost Eff Resour Alloc*, 2009. **7**: p. 3.
140. Burchett HE, Mounier-Jack S, Griffiths UK, Biellik R, Ongolo-Zogo P, Chavez E, Sarma H, Uddin J, Konate M, Kitaw Y, Molla M, Wakasiaka S, Gilson L, Mills A. New vaccine adoption: qualitative study of national decision-making processes in seven low- and middle-income countries. *Health Policy Plan*. 2012 May;27 Suppl 2:ii5-16.

141. Burchett HE, Mounier-Jack S, Griffiths UK, Mills AJ. National decision-making on adopting new vaccines: a systematic review. *Health Policy Plan*. 2012 May;27 Suppl 2:ii62-76.
142. Ians, Court questions government on vaccines, in India News. 2010, http://www.twocircles.net/2010sep15/court_questions_government_vaccines.html: New Delhi.
143. Anderson RM, May RM, Infectious Diseases of Humans: Dynamics and control. 1991, Oxford, UK: Oxford University Press.
144. Panagiotopoulos T, Antoniadou I, and Valassi-Adam E, Increase in congenital rubella occurrence after immunisation in Greece: retrospective survey and systematic review. *Bmj*, 1999. **319**(7223): p. 1462-7.
145. Auranen K, Ranta J, Takala AK, and Arjas E, A statistical model of transmission of Hib bacteria in a family. *Stat Med*, 1996. **15**(20): p. 2235-52.
146. Auranen K, Eichner M, Kayhty H, Takala AK, and Arjas E, A hierarchical Bayesian model to predict the duration of immunity to *Haemophilus influenzae* type b. *Biometrics*, 1999. **55**(4): p. 1306-13.
147. Auranen K, Back-calculating the age-specific incidence of recurrent subclinical *Haemophilus influenzae* type b infection. *Stat Med*, 2000. **19**(3): p. 281-96.
148. Leino T, Auranen K, Makela PH, Kayhty H, and Takala AK, Dynamics of natural immunity caused by subclinical infections, case study on *Haemophilus influenzae* type b (Hib). *Epidemiol Infect*, 2000. **125**(3): p. 583-91.
149. Leino T, Auranen K, Makela PH, Kayhty H, Ramsay M, Slack M, and Takala AK, Haemophilus influenzae type b and cross-reactive antigens in natural Hib infection dynamics; modelling in two populations. *Epidemiol Infect*, 2002. **129**(1): p. 73-83.
150. Makela PH, Kayhty H, Leino T, Auranen K, Peltola H, Ekstrom N, and Eskola J, Long-term persistence of immunity after immunisation with *Haemophilus influenzae* type b conjugate vaccine. *Vaccine*, 2003. **22**(2): p. 287-92.
151. Auranen K, Eichner M, Leino T, Takala AK, Makela PH, and Takala T, Modelling transmission, immunity and disease of *Haemophilus influenzae* type b in a structured population. *Epidemiol Infect*, 2004. **132**(5): p. 947-57.
152. Leino T, Takala T, Auranen K, Makela PH, and Takala AK, Indirect protection obtained by *Haemophilus influenzae* type b vaccination: analysis in a structured population model. *Epidemiol Infect*, 2004. **132**(5): p. 959-66.
153. Coen PG, Heath PT, Barbour ML, and Garnett GP, Mathematical models of *Haemophilus influenzae* type b. *Epidemiol Infect*, 1998. **120**(3): p. 281-95.

154. Coen PG, Heath PT, and Garnett GP, The Hib immunization programme in the Oxford region: an analysis of the impact of vaccine administration on the incidence of disease. *Epidemiol Infect*, 1999. **123**(3): p. 389-402.
155. McVernon J, Ramsay ME, and McLean AR, Understanding the impact of Hib conjugate vaccine on transmission, immunity and disease in the United Kingdom. *Epidemiol Infect*, 2008. **136**(6): p. 800-12.
156. Heath PT and Ramsay ME, *Haemophilus influenzae* type b vaccine--booster campaign. *Bmj*, 2003. **326**(7400): p. 1158-9.
157. Burton A, Monasch R, Lautenbach B, Gacic-Dobo M, Neill M, Karimov R, Wolfson L, Jones G, and Birmingham M, WHO and UNICEF estimates of national infant immunization coverage: methods and processes. *Bull World Health Organ*, 2009. **87**(7): p. 535-41.
158. Oladokun RE, Lawoyin TO, and Adedokun BO, Immunization status and its determinants among children of female traders in Ibadan, South-Western Nigeria. *Afr J Med Med Sci*, 2009. **38**(1): p. 9-15.
159. Clark A and Sanderson C, Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. *Lancet*, 2009. **373**(9674): p. 1543-9.
160. Knoll MD, O'Brien KL, Henkle E, Lee E, Watt JP, McCall N, Mangtani P, Global literature review of *Haemophilus influenzae* type b and *Streptococcus pneumoniae* invasive disease among children less than five years of age 1980–2005. 2009, **WHO/IVB/09.02**, Immunization, Vaccines and Biologicals
161. Last JM, A dictionary of epidemiology. 1983, Oxford University Press: New York.
162. Clemens J, Brenner R, Rao M, Tafari N, and Lowe C, Evaluating new vaccines for developing countries. Efficacy or effectiveness? *Jama*, 1996. **275**(5): p. 390-7.
163. Comstock GW, Evaluating vaccination effectiveness and vaccine efficacy by means of case-control studies. *Epidemiol Rev*, 1994. **16**(1): p. 77-89.
164. Dickersin K and Berlin JA, Meta-analysis: state-of-the-science. *Epidemiol Rev*, 1992. **14**: p. 154-76.
165. Deeks JJ, Altman DG, Bradburn MJ, Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis, in Systematic Reviews in Health Care. Meta-analysis in context, edited by Egger M, Smith GD, Altman DG, 2001, BMJ Books.
166. DerSimonian R and Laird N, Meta-analysis in clinical trials. *Control Clin Trials*, 1986. **7**(3): p. 177-88.

167. Higgins JP, Thompson SG, Deeks JJ, and Altman DG, Measuring inconsistency in meta-analyses. *Bmj*, 2003. **327**(7414): p. 557-60.
168. Cochrane Handbook for Systematic Reviews of Interventions, edited by Higgins and Green, March 2011, The Cochrane Collaboration.
169. Stieb DM, Frayha HH, Oxman AD, Shannon HS, Hutchison BG, and Crombie FS, Effectiveness of *Haemophilus influenzae* type b vaccines. *CMAJ*, 1990. **142**(7): p. 719-33.
170. Obonyo CO and Lau J, Efficacy of *Haemophilus influenzae* type b vaccination of children: a meta-analysis. *Eur J Clin Microbiol Infect Dis*, 2006. **25**(2): p. 90-7.
171. O'Loughlin RE, Edmond K, Mangtani P, Cohen AL, Shetty S, Hajjeh R, and Mulholland K, Methodology and measurement of the effectiveness of *Haemophilus influenzae* type b vaccine: systematic review. *Vaccine*, 2010. **28**(38): p. 6128-36.
172. Theodoratou E, Johnson S, Jhass A, Madhi SA, Clark A, Boschi-Pinto C, Bhopal S, Rudan I, and Campbell H, The effect of *Haemophilus influenzae* type b and pneumococcal conjugate vaccines on childhood pneumonia incidence, severe morbidity and mortality. *Int J Epidemiol*. **39 Suppl 1**: p. i172-85.
173. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, and Moher D, The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*, 2009. **6**(7): p. e1000100.
174. Lefebvre C, Clarke, M.J., Identifying randomised trials, in Systematic Reviews in Health Care. Meta-analysis in context, edited by Egger M, Smith GD, Altman DG, 2007, BMJ Books: London.
175. Mulholland K, Levine O, Nohynek H, and Greenwood BM, Evaluation of vaccines for the prevention of pneumonia in children in developing countries. *Epidemiol Rev*, 1999. **21**(1): p. 43-55.
176. Cherian T, Describing the epidemiology and aetiology of bacterial pneumonia in children: an unresolved problem. *J Health Popul Nutr*, 2005. **23**(1): p. 1-5.
177. Shann F, The management of pneumonia in children in developing countries. *Clin Infect Dis*, 1995. **21 Suppl 3**: p. S218-25.
178. Obaro SK and Madhi SA, Bacterial pneumonia vaccines and childhood pneumonia: are we winning, refining, or redefining? *Lancet Infect Dis*, 2006. **6**(3): p. 150-61.
179. Peltola H, Eskola J, Kayhty H, Takala AK, and Makela PH, Clinical comparison of the *Haemophilus influenzae* type B polysaccharide-diphtheria toxoid and the oligosaccharide-CRM197 protein vaccines in infancy. *Arch Pediatr Adolesc Med*, 1994. **148**(6): p. 620-5.

180. Santosham M, Wolff M, Reid R, Hohenboken M, Bateman M, Goepp J, Cortese M, Sack D, Hill J, and Newcomer W, The efficacy in Navajo infants of a conjugate vaccine consisting of *Haemophilus influenzae* type b polysaccharide and Neisseria meningitidis outer-membrane protein complex*. The New England journal of medicine*, 1991(25): p. 1767-72.

181. Gessner BD, Sutanto A, Linehan M, Djelantik IG, Fletcher T, Gerudug IK, Ingerani, Mercer D, Moniaga V, Moulton LH, Mulholland K, Nelson C, Soemohardjo S, Steinhoff M, Widjaya A, Stoeckel P, Maynard J, and Arjoso S, Incidences of vaccine-preventable *Haemophilus influenzae* type b pneumonia and meningitis in Indonesian children: hamlet-randomised vaccine-probe trial*. Lancet*, 2005. **365**(9453): p. 43-52.

182. Black SB, Shinefield HR, Fireman B, Hiatt R, Polen M, and Vittinghoff E, Efficacy in infancy of oligosaccharide conjugate *Haemophilus influenzae* type b (HbOC) vaccine in a United States population of 61,080 children. The Northern California Kaiser Permanente Vaccine Study Center Pediatrics Group*. Pediatr Infect Dis J*, 1991. **10**(2): p. 97-104.

183. Booy R, Hodgson S, Carpenter L, Mayon-White RT, Slack MP, Macfarlane JA, Haworth EA, Kiddle M, Shribman S, Roberts JS, and et al., Efficacy of Haemophilus influenzae type b conjugate vaccine PRP-T*. Lancet*, 1994. **344**(8919): p. 362-6.

184. Lagos R, Horwitz I, Toro J, San Martin O, Abrego P, Bustamante C, Wasserman SS, Levine OS, and Levine MM, Large scale, postlicensure, selective vaccination of Chilean infants with PRP-T conjugate vaccine: practicality and effectiveness in preventing invasive *Haemophilus influenzae* type b infections*. Pediatr Infect Dis J*, 1996. **15**(3): p. 216-22.

185. Levine OS, Lagos R, Munoz A, Villaroel J, Alvarez AM, Abrego P, and Levine MM, Defining the burden of pneumonia in children preventable by vaccination against *Haemophilus influenzae* type b*. Pediatr Infect Dis J*, 1999. **18**(12): p. 1060-4.

186. Mulholland K, Hilton S, Adegbola R, Usen S, Oparaugo A, Omosigho C, Weber M, Palmer A, Schneider G, Jobe K, Lahai G, Jaffar S, Secka O, Lin K, Ethevenaux C, and Greenwood B, Randomised trial of Haemophilus influenzae type-b tetanus protein conjugate vaccine [corrected] for prevention of pneumonia and meningitis in Gambian infants*. Lancet*, 1997. **349**(9060): p. 1191-7.

187. Vadheim CM, Greenberg DP, Partridge S, Jing J, and Ward JI, Effectiveness and safety of an *Haemophilus influenzae* type b conjugate vaccine (PRP-T) in young infants. Kaiser-UCLA Vaccine Study Group*. Pediatrics*, 1993. **92**(2): p. 272-9.

188. WHO, Standardization of interpretation of chest radiographs for the diagnosis of pneumonia in children. 2001. **WHO/V&B/01.35**: Geneva
189. Cherian T, Mulholland EK, Carlin JB, Ostensen H, Amin R, de Campo M, Greenberg D, Lagos R, Lucero M, Madhi SA, O'Brien KL, Obaro S, and Steinhoff MC, Standardized interpretation of paediatric chest radiographs for the diagnosis of pneumonia in epidemiological studies. *Bull World Health Organ*, 2005. **83**(5): p. 353-9.
190. WHO, Pocket book of hospital care for children. Guidelines for the management of common illnesses with limited resources, http://whqlibdoc.who.int/publications/2005/9241546700.pdf. 2005, Geneva.
191. Black SB, Shinefield HR, Fireman B, Hiatt R, Polen M, Vittinghoff E. Efficacy in infancy of oligosaccharide conjugate *Haemophilus influenzae* type b (HbOC) vaccine in a United States population of 61,080 children. The Northern California Kaiser Permanente Vaccine Study Center Pediatrics Group. *Pediatr Infect Dis J*, 1991 Feb;10(2):97-104.
192. Gessner BD, *Haemophilus influenzae* type b vaccine impact in resource-poor settings in Asia and Africa. *Expert review of vaccines*, 2009. **8**(1): p. 91-102.
193. Sterne JAC, Egger M, Smith GD, Investigating and dealing with publication and other biases, in Systematic Reviews in Health Care. Meta-analysis in context, edited by Egger M, Smith GD, Altman DG, 2001, BMJ Books: London.
194. Theodoratou E, Johnson S, Jhass A, Madhi SA, Clark A, Boschi-Pinto C, Bhopal S, Rudan I, and Campbell H, The effect of *Haemophilus influenzae* type b and pneumococcal conjugate vaccines on childhood pneumonia incidence, severe morbidity and mortality. *Int J Epidemiol*, 2010. **39 Suppl 1**: p. i172-85.
195. Baqui AH, El Arifeen S, Saha SK, Persson L, Zaman K, Gessner BD, Moulton LH, Black RE, and Santosham M, 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): p. 565-71.
196. Capeding MR, Nohynek H, Pascual LG, Kayhty H, Sombrero LT, Eskola J, and Ruutu P, The immunogenicity of three *Haemophilus influenzae* type B conjugate vaccines after a primary vaccination series in Philippine infants. *Am J Trop Med Hyg*, 1996. **55**(5): p. 516-20.
197. Singleton R, Hammitt L, Hennessy T, Bulkow L, DeByle C, Parkinson A, Cottle TE, Peters H, and Butler JC, The Alaska *Haemophilus influenzae* type b experience: lessons in controlling a vaccine-preventable disease. *Pediatrics*, 2006. **118**(2): p. e421-9.

198. Cowgill KD, Ndiritu M, Nyiro J, Slack MP, Chiphatsi S, Ismail A, Kamau T, Mwangi I, English M, Newton CR, Feikin DR, and Scott JA, Effectiveness of *Haemophilus influenzae* type b Conjugate vaccine introduction into routine childhood immunization in Kenya*. Jama*, 2006. **296**(6): p. 671-8.
199. Adegbola RA, Secka O, Lahai G, Lloyd-Evans N, Njie A, Usen S, Oluwalana C, Obaro S, Weber M, Corrah T, Mulholland K, McAdam K, Greenwood B, and Milligan PJ, Elimination of *Haemophilus influenzae* type b (Hib) disease from The Gambia after the introduction of routine immunisation with a Hib conjugate vaccine: a prospective study*. Lancet*, 2005. **366**(9480): p. 144-50.
200. Lagos R, Valenzuela MT, Levine OS, Losonsky GA, Erazo A, Wasserman SS, and Levine MM, Economisation of vaccination against *Haemophilus influenzae* type b: a randomised trial of immunogenicity of fractional-dose and two-dose regimens*. Lancet*, 1998. **351**(9114): p. 1472-6.
201. Bennett JV, Platonov AE, Slack MPE, Mala P, Burton AH, and Roberson SE, *Haemophilus influenzae* type b (Hib) meningitis in the pre-vaccine era: a global review of incidence, age distributions, and case-fatality rates*. WHO/V&B/02.18*, 2002: Geneva: WHO
202. von Gottberg A CC, Whitelaw A, Chhagan M, Flannery B, Cohen AL, de Gouveia L, Plessis MD, Madhi SA, Klugman KP, Invasive disease due to *Haemophilus influenzae* serotype b ten years after routine vaccination, South Africa, 2003-2009*. Vaccine*, 2011.
203. Mangtani P, Mulholland K, Madhi SA, Edmond K, O'Loughlin R, and Hajjeh R, *Haemophilus influenzae* type b disease in HIV-infected children: a review of the disease epidemiology and effectiveness of Hib conjugate vaccines*. Vaccine*, 2010. **28**(7): p. 1677-83.
204. Madhi SA, Petersen K, Khoosal M, Huebner RE, Mbelle N, Mothupi R, Saloojee H, Crewe-Brown H, and Klugman KP, Reduced effectiveness of *Haemophilus influenzae* type b conjugate vaccine in children with a high prevalence of human immunodeficiency virus type 1 infection*. Pediatr Infect Dis J*, 2002. **21**(4): p. 315-21.
205. Daza P, Banda R, Misoya K, Katsulukuta A, Gessner BD, Katsande R, Mhlanga BR, Mueller JE, Nelson CB, Phiri A, Molyneux EM, and Molyneux ME, The impact of routine infant immunization with *Haemophilus influenzae* type b conjugate vaccine in Malawi, a country with high human immunodeficiency virus prevalence*. Vaccine*, 2006. **24**(37-39): p. 6232-9.

206. Kind P, Lafata JE, Matuszewski K, and Raisch D, The use of QALYs in clinical and patient decision-making: issues and prospects. *Value Health*, 2009. **12 Suppl 1**: p. S27-30.
207. Gold MR, Stevenson D, and Fryback DG, HALYS and QALYS and DALYS, Oh My: similarities and differences in summary measures of population Health. *Annu Rev Public Health*, 2002. **23**: p. 115-34.
208. Torrance GW, Furlong W, and Feeny D, Health utility estimation. *Expert Rev Pharmacoecon Outcomes Res*, 2002. **2**(2): p. 99-108.
209. Griebsch I, Coast J, and Brown J, Quality-adjusted life-years lack quality in pediatric care: a critical review of published cost-utility studies in child health. *Pediatrics*, 2005. **115**(5): p. e600-14.
210. Petrou S, Methodological issues raised by preference-based approaches to measuring the health status of children. *Health Econ*, 2003. **12**(8): p. 697-702.
211. Burstrom K, Egmar AC, Lugner A, Eriksson M, and Svartengren M, A Swedish child-friendly pilot version of the EQ-5D instrument--the development process. *Eur J Public Health*, 2011. **21**(2): p. 171-7.
212. Wille N, Badia X, Bonsel G, Burstrom K, Cavrini G, Devlin N, Egmar AC, Greiner W, Gusi N, Herdman M, Jelsma J, Kind P, Scalone L, and Ravens-Sieberer U, Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. *Qual Life Res*, 2010. **19**(6): p. 875-86.
213. Ungar WJ, Challenges in Health State Valuation in Paediatric Economic Evaluation: Are QALYs Contraindicated? *Pharmacoeconomics*, 2011. **29**(8): p. 641-52.
214. Word Bank, World Development Report: Investing in Health. 1993: Oxford
215. Fox-Rushby J, Disability adjusted life years (DALYs) for decision-making?: an overview of the literature, ed. Office of Health Economics. 2002, London.
216. Mathers CD, Lopez AD., Murray CJL, The burden of disease and mortality by condition: data, methods and results for 2001, in Global burden of disease and risk factors, edited by Lopez AD, Ezzati M, Murray CJL, Jamison DT, 2006, Oxford University Press: New York. p. 45-240.
217. WHO, The global burden of disease: 2004 update. 2008, Geneva. http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en/index.html
218. Labeaud AD, Bashir F, and King CH, Measuring the burden of arboviral diseases: the spectrum of morbidity and mortality from four prevalent infections. *Popul Health Metr*. **9**(1): p. 1.

219. WHO, Global literature review of *Haemophilus influenzae* type b and Streptococcus pneumoniae invasive disease among children less than five years of age, 1980–2005. 2009, **WHO/IVB/09.02**

220. Torres A, Bueno, A., Suarez, L., Trejo, A., Infecciones invasivas por *Haemophilus influenzae* tipo b (Hib) en Tucumán-Argentina. *Arch Arg Pedi*, 1995. **93**.

221. Asturias EJ, Soto M, Menendez R, Ramirez PL, Recinos F, Gordillo R, Holt E, and Halsey NA, Meningitis and pneumonia in Guatemalan children: the importance of *Haemophilus influenzae* type b and Streptococcus pneumoniae. *Rev Panam Salud Publica*, 2003. **14**(6): p. 377-84.

222. Barton-Forbes MA, Samms-Vaughan M, and Irons B, Epidemiology of *Haemophilus influenzae* invasive disease in Jamaica, 1990-1993. *West Indian Med J*, 2000. **49**(3): p. 200-4.

223. Takala AK, Eskola J, Peltola H, and Makela PH, Epidemiology of invasive *Haemophilus influenzae* type b disease among children in Finland before vaccination with Haemophilus influenzae type b conjugate vaccine. *Pediatr Infect Dis J*, 1989. **8**(5): p. 297-302.

224. Peltola H and Virtanen M, Systemic *Haemophilus influenzae* infection in Finland. *Clin Pediatr (Phila)*, 1984. **23**(5): p. 275-80.

225. Booy R, Hodgson SA, Slack MP, Anderson EC, Mayon-White RT, and Moxon ER, Invasive *Haemophilus influenzae* type b disease in the Oxford region (1985-91). *Arch Dis Child*, 1993. **69**(2): p. 225-8.

226. Martin F, Campos Calleja, C., Bustillo Alonso, M., Infecciones invasivas por *Haemophilus influenzae* tipo B en la infancia (1981-1990). *An Es Pediatr*, 1993. **39**(2).

227. Muhlemann K, Alexander ER, Pepe M, Weiss NS, and Schopfer K, Invasive Haemophilus influenzae disease and epiglottitis among Swiss children from 1980 to 1993: evidence for herd immunity among older age groups. The Swiss *Haemophilus Influenzae* Study Group. *Scand J Infect Dis*, 1996. **28**(3): p. 265-8.

228. Dagan R, A two-year prospective, nationwide study to determine the epidemiology and impact of invasive childhood *Haemophilus influenzae* type b infection in Israel. The Israeli Pediatric Bacteremia and Meningitis Group. *Clin Infect Dis*, 1992. **15**(4): p. 720-5.

229. O'Dempsey TJ, McArdle TF, Lloyd-Evans N, Baldeh I, Laurence BE, Secka O, and Greenwood BM, Importance of enteric bacteria as a cause of pneumonia, meningitis and septicemia among children in a rural community in The Gambia, West Africa. *Pediatr Infect Dis J*, 1994. **13**(2): p. 122-8.

230. Ishiwada N, Cao LD, and Kohno Y, PCR-based capsular serotype determination of *Haemophilus influenzae* strains recovered from Japanese paediatric patients with invasive infection*. Clin Microbiol Infect*, 2004. **10**(10): p. 895-8.
231. Anglaret X, Buissonniere RF, Duval P, Morlat C, and Menager C, Invasive *Haemophilus influenzae* disease of Melanesian and Caucasian children in New Caledonia*. Pediatr Infect Dis J*, 1993. **12**(10): p. 888-9.
232. Gilbert GL, Johnson PD, and Clements DA, Clinical manifestations and outcome of *Haemophilus influenzae* type b disease*. J Paediatr Child Health*, 1995. **31**(2): p. 99-104.
233. Baraff LJ, Lee SI, and Schriger DL, Outcomes of bacterial meningitis in children: a meta-analysis*. Pediatr Infect Dis J*, 1993. **12**(5): p. 389-94.
234. de Jonge RC, van Furth AM, Wassenaar M, Gemke RJ, and Terwee CB, Predicting sequelae and death after bacterial meningitis in childhood: a systematic review of prognostic studies*. BMC Infect Dis*. **10**: p. 232.
235. Edmond K, Clark A, Korczak V, Sanderson C, Griffiths U, and Rudan I, Global and regional risks of disabling sequelae from bacterial meningitis*. Lancet Infectious Diseases*, 2010. **10**(5): p. 317-28.
236. Chang CJ, Chang HW, Chang WN, Huang LT, Huang SC, Chang YC, Hung PL, Chang CS, Chuang YC, Huang CR, Tsai NW, Tsui HW, Wang KW, and Lu CH, Seizures complicating infantile and childhood bacterial meningitis*. Pediatr Neurol*, 2004. **31**(3): p. 165-71.
237. Rasmussen N, Johnsen NJ, and Bohr VA, Otologic sequelae after pneumococcal meningitis: a survey of 164 consecutive cases with a follow-up of 94 survivors*. Laryngoscope*, 1991. **101**(8): p. 876-82.
238. Glinskaya IN GF, Chistenko GN, Fissenko EG, Levshina NN, Ushakevich IG, Nekrassova OV, Grinevich OV. Features of Hib infection epidemic process in Minsk City before immunization. in 2nd Russian Conference on Actual Problems of Meningococcal Infection and Purulent Meningitis, 2008. Moscow.
239. Gupta V, Hearing evaluation in children with bacterial meningitis*. Indian Pediatr*, 1993. **30**(10): p. 1175-9.
240. Chinchankar N, Mane M, Bhave S, Bapat S, Bavdekar A, Pandit A, Niphadkar KB, Dutta A, and Leboulleux D, Diagnosis and outcome of acute bacterial meningitis in early childhood*. Indian Pediatr*, 2002. **39**(10): p. 914-21.
241. George CN, Letha S, and Bai SS, A clinical study of chronic morbidity in children following pyogenic meningitis*. Indian Pediatr*, 2002. **39**(7): p. 663-7.

242. Cherukupally SR and Eavey R, Vaccine-preventable pediatric postmeningitic sensorineural hearing loss in southern India. *Otolaryngol Head Neck Surg*, 2004. **130**(3): p. 339-43.
243. Singhi P, Bansal A, Geeta P, and Singhi S, Predictors of long term neurological outcome in bacterial meningitis. *Indian J Pediatr*, 2007. **74**(4): p. 369-74.
244. Gupta M, Kumar R, Deb AK, Bhattacharya SK, Bose A, John J, Balraj V, Ganguly NK, Kant L, Kapoor AN, Watt J, Shearer J, and Santosham M, Multi-center surveillance for pneumonia & meningitis among children (<2 yr) for Hib vaccine probe trial preparation in India. *Indian J Med Res*. **131**: p. 649-58.
245. Bennett JV, Platonov AE, Slack MPE, Mala P, Burton AH, and Roberson SE, *Haemophilus influenzae* type b (Hib) meningitis in the pre-vaccine era:a global review of incidence, age distributions, and case-fatality rates. **WHO/V&B/02.18,** 2002: Geneva: WHO
246. Salomon JA, New disability weights for the global burden of disease. *Bull World Health Organ*, 2010. **88**(12): p. 879.
247. Peters DH, Yazbeck AS, Sharma RR, Ramana GNV, Pritchett LH, Wagstaff A, Better Health Systems for India's Poor. Findings, Aanalysis, and Options. Human Development Network. Health, Nutrition and Population Series, World Bank. 2002, Washington D.C.
248. Rechel B and McKee M, Health reform in central and eastern Europe and the former Soviet Union. *Lancet*, 2009. **374**(9696): p. 1186-95.
249. WHO, National Health Accounts. Global health expenditure database. *http://apps.who.int/nha/database/PreDataExplorer.aspx?d=2*, 2011.
250. Penchansky R and Thomas JW, The concept of access: definition and relationship to consumer satisfaction. *Med Care*, 1981. **19**(2): p. 127-40.
251. WHO CHOICE, Country specific unit costs. *http://www.who.int/choice/country/country_specific/en/index.html*, 2011. **Accessed 20 November 2011**.
252. National Sample Survey Organisation (NSSO), Socio-economic survey, sixtieth round 2007
253. Gupta M, Kumar R, Deb AK, Bhattacharya SK, Bose A, John J, Balraj V, Ganguly NK, Kant L, Kapoor AN, Watt J, Shearer J, and Santosham M, Multi-center surveillance for pneumonia & meningitis among children (<2 yr) for Hib vaccine probe trial preparation in India. *Indian J Med Res*, 2010. **131**: p. 649-58.
254. Anand K, Pandav, C.S., Kapoor, S.K., Cost of Services in a Sub-district level Hospital in Northern India. *Journal of the Academy of Hospital Administration*, 2005. **14**(2).

255. Anand K, Arora NK, Pandav CS, and Kapoor SK, Cost of curative pediatric services in a public sector setting. *Indian J Pediatr*, 2005. **72**(8): p. 657-60.
256. Balabanova D, McKee M, Pomerleau J, Rose R, and Haerpfer C, Health service utilization in the former soviet union: evidence from eight countries. *Health Serv Res*, 2004. **39**(6 Pt 2): p. 1927-50.
257. Richardson E, Boerma, W., Malakhova, I., Rusovich, V., Fomenko, A., Belarus: Health system review. Health Systems in Transition. 2008: European Observatory on Health Systems and Policies.
258. Cashin C, Access to Health Care in Rural Ferghana Oblast, Uzbekistan. 2001
259. Unicef and UNFPA, Multiple Indicator Cluster Survey. *http://www.childinfo.org/files/MICS3_Uzbekistan_FinalReport_2006_Eng.pdf*, 2006
260. Ministry of Health and Family Welfare, Report of the National Commission on Macroeconomics and Health. 2005: Government of India
261. Ministry of Health and Family Welfare GoI, International Institute for Population Sciences (IIPS) and Macro International Inc., , National Family Health Survey (NFHS-3). *http://www.measuredhs.com/what-we-do/survey/survey-display-264.cfm*, 2005-06: Deonar, Mumbai
262. European Observatory on Health Systems and Policies, Uzbekistan: Health System Review. Health Systems in Transition. Vol. 9. 2007.
263. Pritchard C, Sculpher, M., Productivity costs: Principles and practice in economic evaluation. 2000, London: Office of Health Economics.
264. Koopmanschap MA and van Ineveld BM, Towards a new approach for estimating indirect costs of disease. *Soc Sci Med*, 1992. **34**(9): p. 1005-10.
265. Sylla M, Les salaires au Sénégal: Etat des lieux, tendances et évolutions récentes. 2009: International Labour Organisation
266. Stack ML, Ozawa S, Bishai DM, Mirelman A, Tam Y, Niessen L, Walker DG, and Levine OS, Estimated economic benefits during the 'decade of vaccines' include treatment savings, gains in labor productivity. *Health Aff (Millwood)*, 2011. **30**(6): p. 1021-8.
267. Fleming JA, Dieye Y, Ba O, Mutombo wa Mutombo B, Diallo N, Faye PC, Ba M, Cisse MF, Diallo AG, Slack MP, and Weiss NS, Effectiveness of haemophilus influenzae type B conjugate vaccine for prevention of meningitis in Senegal. *Pediatr Infect Dis J*, 2010. **30**(5): p. 430-2.
268. Edmond K, Dieye Y, Griffiths UK, Fleming J, Ba O, Diallo N, and Mulholland K, Prospective cohort study of disabling sequelae and quality of life in children with bacterial meningitis in urban Senegal. *Pediatr Infect Dis J*, 2010. **29**(11): p. 1023-9.

269. Cisse MF, Breugelmans JG, Ba M, Diop MB, Faye PC, Mhlanga B, Mueller JE, Koffi D, and Gessner BD, The Elimination of *Haemophilus influenzae* type b meningitis following conjugate vaccine introduction in Senegal. *Pediatr Infect Dis J*, 2010. **29**(6): p. 499-503.
270. Ba O, Fleming JA, Dieye Y, wa Mutombo BM, Ba M, Cisse MF, Diallo AG, Sow I, Slack MP, Faye PC, Diallo N, and Weiss NS, Hospital surveillance of childhood bacterial meningitis in Senegal and the introduction of *Haemophilus influenzae* type b conjugate vaccine. *Am J Trop Med Hyg*, 2010. **83**(6): p. 1330-5.
271. Katz RT, Life expectancy for children with cerebral palsy and mental retardation: implications for life care planning. *NeuroRehabilitation*, 2003. **18**(3): p. 261-70.
272. Eyman RK, Grossman HJ, Chaney RH, and Call TL, The life expectancy of profoundly handicapped people with mental retardation. *N Engl J Med*, 1990. **323**(9): p. 584-9.
273. WHO, Life tables for WHO Member States, http://www.who.int/healthinfo/statistics/mortality_life_tables/en/; Accessed 10th May 2012.
274. Strauss DJ, Shavelle RM, and Anderson TW, Life expectancy of children with cerebral palsy. *Pediatr Neurol*, 1998. **18**(2): p. 143-9.
275. Hutton JL, Cooke T, and Pharoah PO, Life expectancy in children with cerebral palsy. *Bmj*, 1994. **309**(6952): p. 431-5.
276. Eyman RK, Grossman HJ, Chaney RH, and Call TL, Survival of profoundly disabled people with severe mental retardation. *Am J Dis Child*, 1993. **147**(3): p. 329-36.
277. Ministère de la Santé et de la Prévention Médicale Centre de Recherche pour le Développement Humain (CRDH), Senegal Demographic and Health Survey. 2005
278. Zuber PL, El-Ziq I, Kaddar M, Ottosen AE, Rosenbaum K, Shirey M, Kamara L, and Duclos P, Sustaining GAVI-supported vaccine introductions in resource-poor countries. *Vaccine*, 2011. **29**(17): p. 3149-54.
279. Kamara L, Milstien JB, Patyna M, Lydon P, Levin A, and Brenzel L, Strategies for financial sustainability of immunization programs: a review of the strategies from 50 national immunization program financial sustainability plans. *Vaccine*, 2008. **26**(51): p. 6717-26.
280. Wolfson LJ, Gasse F, Lee-Martin SP, Lydon P, Magan A, Tibouti A, Johns B, Hutubessy R, Salama P, and Okwo-Bele JM, Estimating the costs of achieving the WHO-UNICEF Global Immunization Vision and Strategy, 2006-2015. *Bull World Health Organ*, 2008. **86**(1): p. 27-39.
281. GAVI Alliance, Fifth GAVI Board Meeting, London, 21-22 June 2001, Summary report. 2001: Geneva

282. Lydon P. New Vaccines Introduction Grant. in GAVI Alliance Board Meeting presentation. 2007. Geneva: GAVI Alliance and WHO.
283. GAVI Alliance, GAVI Alliance & Fund Board Meeting, Geneva, Switzerland, 11 & 12 May 2007, FINAL Summary Report. 2007: Geneva
284. Wilson P, Giving developing countries the best shot: An overview of vaccine access and R&D. 2010: Oxam International and Médecins Sans Frontières
285. Maggon K, Industrial R&D paradigm shift to vaccines. *Biotechnology Journal*, 2009. **4**(4): p. 458-461.
286. Sheridan C, Vaccine Market Boosters. *Nature Biotechnology*, 2009. **27**(6): p. 499-501.
287. Milstien JB and Kaddar M, The role of emerging manufacturers in access to innovative vaccines of public health importance. *Vaccine*, 2010. **28**(9): p. 2115-21.
288. International AIDS Vaccine Initiative, Procurement and Pricing of New Vaccines for Developing Countries. *Policy Brief*, 2008
289. International AIDS Vaccine Initiative Policy Brief, Procurement and Pricing of New Vaccines for Developing Countries. 2008
290. Danovaro-Holliday MC, Garcia S, de Quadros C, Tambini G, and Andrus JK, Progress in vaccination against Haemophilus influenzae type b in the Americas. *PLoS Med*, 2008. **5**(4): p. e87.
291. WHO, Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies, Expert committee on biological standardization, 2010: Geneva http://www.who.int/immunization_standards/vaccine_quality/who_bs_2155_vaccine_prequalification_revised_procedure_ecbs_endorsed.pdf
292. International AIDS Vaccine Initiative, Procurement and pricing for new vaccines in developing countries. 2008
293. Milstien J, Munira SL, and McKinney SL, Issues in selection of DTwP-based combination vaccines. *Vaccine*, 2003. **21**(15): p. 1658-64.
294. WHO, Proper handling and reconstitution of vaccines avoids programme errors *Vaccines and Biologicals Update*, 2000. **34**(http://www.who.int/vaccines-documents/DoxNews/updates/updat34e.pdf).
295. WHO, WHO position paper on Haemophilus influenzae type b conjugate vaccines. (Replaces WHO position paper on Hib vaccines previously published in the Weekly Epidemiological Record). *Weekly Epidemiological Record*, 2006. **81**: p. 445-452.

296. National Technical Advisory Group on Immunization, NTAGI subcommittee recommendations on *Haemophilus influenzae* type B (Hib) vaccine introduction in India*. Indian Pediatr*, 2009. **46**(11): p. 945-54.
297. In the high court of Delhi at New Delhi (Civil original jurisdiction), A writ petition in public interest under article 226 of the constitution of India highlighting how irrational vaccines are being arbitrarily introduced and promoted by the government at the behest of vaccine manufactures and other vested interests, in Writ Petition (Civil) No. 13698 of 2009, P.i. litigation, 2009.
298. Indian Council of Medical Research, Minutes of the Expert group meetings on Hepatitis B and Hib vaccines. 2010.
299. Mudur G. Antivaccine lobby resists introduction of Hib vaccine in India. 2010 [cited 2012 5 April]; Available from: http://www.vaccineindia.org/index.php?option=com_content&view=article&id=446:antivaccine-lobby-resists-introduction-of-hib-vaccine-in-india&catid=30:current-news.
300. Kou U, Guidelines for estimating costs of introducing new vaccines into the national immunization system*.* 2002(WHO/V&B/02.11): Geneva: WHO
301. GAVI Alliance, Guidelines on country proposals. For Support for: New and Underused Vaccines Applicable for Proposal Round June 2011: Geneva
302. United Nations Population Secretariat, World Population Prospects: The 2010 Revision Population database 2010
303. WHO, Global and regional immunization profile, WHO vaccine-preventable disease monitoring system, 2011, *http://www.who.int/immunization_monitoring/data/data_subject/en/index.html*
304. Unicef, Vaccine price data*.* 2012: Copenhagen, http://www.unicef.org/supply/index_57476.html
305. Griffiths UK, Santos AC, Nundy N, Jacoby E, and Matthias D, Incremental costs of introducing jet injection technology for delivery of routine childhood vaccinations: comparative analysis from Brazil, India, and South Africa*. Vaccine*, 2011. **29**(5): p. 969-75.
306. The Government of Federal Democratic Republic of Ethiopia, Proposal for support submitted to the Global Alliance for Vaccines and Immunization (GAVI) and The Vaccine Fund*.* February 2005: Addis Ababa
307. Kanra G, Kara A, Demiralp O, Contorni M, Hilbert AK, Spyr C, and Viviani S, Safety and immunogenicity of a new fully liquid DTPw-HepB-Hib combination vaccine in infants*. Hum Vaccin*, 2006. **2**(4): p. 155-60.

308. National Bank of Ethiopia. http://www.nbe.gov.et/MEFR/MMEI%20Nov%2007.pdf. 2007 [cited 2007 May].
309. Ethiopian Federal Ministry of Health, Plan for the introduction of hepatitis B and *Haemophilus influenzae* type b vaccines into routine immunization in Ethiopia. 2005: Addis Ababa
310. WHO HQ WA, CDC Atlanta, LSHTM, Hib Initiative, WHO Ethiopia, Unicef Ethiopia, ESHE/USAID and Core Group/CDRA,, Final report on the post introduction evaluation of the pentavalent vaccine in Ethiopia. 2007
311. WHO, New Vaccine Post-Introduction Evaluation (PIE) Tool, 2010, **WHO/IVB/10.03**, Geneva
312. Ministry of Health, Federal Democratic Republic of Ethiopia, Improving EPI vaccine and cold chain management through rehabilitation plan. October 2004
313. WHO. Vaccine volume calculator. http://www.who.int/immunization_delivery/systems_policy/logistics/en/index4.html 2011 [cited 2011 November].
314. WHO Department of Vaccines and Biologicals, Product Information Sheets. 2008
315. Unicef, 2007 vaccine projections: Quantities and pricing. 2007: Copenhagen
316. Unicef, 2007 AD synge projections: Quantities and prices. 2007, http://www.unicef.org/supply/files/2007_AD_Syringe_Projections.pdf.
317. Stevenson S, Candries, B., Ethiopia. National Immunization Program. Costing and Financing Assessment. 2002
318. Mager IN FE, Germanovich FA, Volossar LA, Simanovich TN, Outcomes of Hib-meningitis incidence study and outlooks for immunoprophylaxis. *Epidemiology and Infectious Diseases» Magazine*, 2005. **3**.
319. WHO, Generic protocol for population-based surveillance of Haemophilus influenzae type b. Global Programme for Vaccines and Immunization, Vaccine Research and Development, 1995, **WHO/VRD/GEN/95.05**
320. Slack MPE, Report from visit to assess Bacterial Meningitis Sentinel Surveillance in Belarus. 2007
321. WHO, Estimating the local burden of *Haemophilus influenzae* type b (Hib) disease preventable by vaccination. A rapid assessment tool. 2001
322. Mendsaikhan J, Watt JP, Mansoor O, Suvdmaa N, Edmond K, Litt DJ, Nymadawa P, Baoping Y, Altantsetseg D, and Slack M, Childhood bacterial meningitis in Ulaanbaatar, Mongolia, 2002-2004. *Clin Infect Dis*, 2009. **48 Suppl 2**: p. S141-6.
323. Kasimova R, Comparative Study of PCR and Bacteriological Method in the Diagnostics of Meningitis *Journal Doctor*, 2007. **2**.

324. Thomas K, Lalitha, M.K.,Steinhoff, Are Haemophilus influenzae infections a significant problem in India? A prospective study and review. *Clin Infect Dis*, 2002. **34**(7): p. 949-957.
325. United Nations Population Secretariat, World Population Prospects: The 2008 Revision Population database, 2008
326. Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat, World Population Prospects: The 2006 Revision and World Urbanisation Prospects: The 2005 Revision. 2007
327. WHO, Technical bases for the WHO recommendations on the management of pneumonia in children at first-level health facilities. Programme for the Control of Acute Respiratory Infections. **WHO/ARI/91.20**. 1991, Geneva: WHO.
328. Reddaiah VP and Kapoor SK, Epidemiology of pneumonia in rural underfives. *Indian J Pediatr*, 1990. **57**(5): p. 701-4.
329. Tambe MP, Shivaram C, and Chandrashekhar Y, Acute respiratory infection in children: a survey in the rural community. *Indian J Med Sci*, 1999. **53**(6): p. 249-53.
330. Madhav SM, Dixit GC, Prakasam PS, Sundaram NS, Shrivastava KN, Datta KK, and Sharma RS, A study of two-weekly incidence of ARI in under-five children of rural area of Alwar (Rajasthan). *J Commun Dis*, 1990. **22**(4): p. 243-6.
331. Chhabra P, Garg S, Mittal SK, Satyanarayan L, Mehra M, and Sharma N, Magnitude of acute respiratory infections in under five. *Indian Pediatr*, 1993. **30**(11): p. 1315-9.
332. Singh MP and Nayar S, Magnitude of acute respiratory infections in under five children. *J Commun Dis*, 1996. **28**(4): p. 273-8.
333. Awasthi S and Pande VK, Seasonal pattern of morbidities in preschool slum children in Lucknow, north India. *Indian Pediatr*, 1997. **34**(11): p. 987-93.
334. Deb SK, Acute respiratory disease survey in Tripura in case of children below five years of age. *J Indian Med Assoc*, 1998. **96**(4): p. 111-6.
335. Sharma AK, Reddy DC, and Dwivedi RR, Descriptive epidemiology of acute respiratory infections among under five children in an urban slum area. *Indian J Public Health*, 1999. **43**(4): p. 156-9.
336. Acharya D, Prasanna KS, Nair S, and Rao RS, Acute respiratory infections in children: a community based longitudinal study in south India. *Indian J Public Health*, 2003. **47**(1): p. 7-13.
337. Bilcke J, Beutels P, Brisson M, and Jit M, Accounting for methodological, structural, and parameter uncertainty in decision-analytic models: a practical guide. *Med Decis Making*, 2011. **31**(4): p. 675-92.

338. Rudan I, Tomaskovic L, Boschi-Pinto C, and Campbell H, Global estimate of the incidence of clinical pneumonia among children under five years of age*. Bull World Health Organ*, 2004. **82**(12): p. 895-903.

339. Rudan I, El Arifeen S, Bhutta ZA, Black RE, Brooks A, Chan KY, Chopra M, Duke T, Marsh D, Pio A, Simoes EA, Tamburlini G, Theodoratou E, Weber MW, Whitney CG, Campbell H, and Qazi SA, Setting research priorities to reduce global mortality from childhood pneumonia by 2015*. PLoS Med*, 2011. **8**(9): p. e1001099.

340. Briggs A, Sculpher, M., Claxton, K., Decision modelling for health economic evaluation. 2006: Oxford University Press.

341. WHO CHOICE, Cost-effectiveness thresholds. 2010, http://www.who.int/choice/costs/CER_thresholds/en/index.html

342. Bassani DG, Kumar R, Awasthi S, Morris SK, Paul VK, Shet A, Ram U, Gaffey MF, Black RE, and Jha P, Causes of neonatal and child mortality in India: a nationally representative mortality survey*. Lancet*, 2010. **376**(9755): p. 1853-60.

343. Esposito DH, Tate JE, Kang G, and Parashar UD, Projected impact and cost-effectiveness of a rotavirus vaccination program in India, 2008*. Clin Infect Dis*, 2011. **52**(2): p. 171-7.

344. Isakbaeva ET, Musabaev E, Antil L, Rheingans R, Juraev R, Glass RI, and Bresee JS, Rotavirus disease in Uzbekistan: cost-effectiveness of a new vaccine*. Vaccine*, 2007. **25**(2): p. 373-80.

345. Rose J, Hawthorn RL, Watts B, and Singer ME, Public health impact and cost effectiveness of mass vaccination with live attenuated human rotavirus vaccine (RIX4414) in India: model based analysis*. Bmj*, 2009. **339**: p. b3653.

346. Scott JA, The global epidemiology of childhood pneumonia 20 years on*. Bull World Health Organ*, 2008. **86**(6): p. 494-6.

347. 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): p. 71-8.

348. Ross J, The use of economic evaluation in health care: Australian decision makers' perceptions*. Health Policy*, 1995. **31**(2): p. 103-10.

349. Schwarzer R and Siebert U, Methods, procedures, and contextual characteristics of health technology assessment and health policy decision making: comparison of health technology assessment agencies in Germany, United Kingdom, France, and Sweden*. Int J Technol Assess Health Care*, 2009. **25**(3): p. 305-14.

350. Drummond M and Sorenson C, Nasty or nice? A perspective on the use of health technology assessment in the United Kingdom. *Value Health*, 2009. **12 Suppl 2**: p. S8-13.
351. Drummond M and Banta D, Health technology assessment in the United Kingdom. *Int J Technol Assess Health Care*, 2009. **25 Suppl 1**: p. 178-81.
352. Al-Awaidy S, Griffiths UK, Nwar HM, Bawikar S, Al-Aisiri MS, Khandekar R, Mohammad AJ, and Robertson SE, Costs of congenital rubella syndrome (CRS) in Oman: evidence based on long-term follow-up of 43 children. *Vaccine*, 2006. **24**(40-41): p. 6437-45.
353. Griffiths UK, Bozzani, F., Mwenge, L., Muleya, L., Mumba, M., Costs of treatment of eye diseases and disorders: Prospective study from a missionary hospital in Zambia, *in preparation*, 2012.
354. Briggs A and Gray A, The distribution of health care costs and their statistical analysis for economic evaluation. *J Health Serv Res Policy*, 1998. **3**(4): p. 233-45.
355. Thompson SG and Barber JA, How should cost data in pragmatic randomised trials be analysed? *Bmj*, 2000. **320**(7243): p. 1197-200.
356. Griffiths UK, Rheingans, R., Walker, D., Guidelines for estimating the economic burden of dairrhoeal disease with a focus on assessing the costs of rotavirus diarrhoea. 2005, **WHO/IVB/05.10**: Geneva: WHO
357. Adam T, Evans DB, and Murray CJ, Econometric estimation of country-specific hospital costs. *Cost Eff Resour Alloc*, 2003. **1**(1): p. 3.
358. Rowland D and Telyukov AV, Soviet health care from two perspectives. *Health Aff (Millwood)*, 1991. **10**(3): p. 71-86.
359. McKee M, Figueras J, and Chenet L, Health sector reform in the former Soviet Republics of Central Asia. *Int J Health Plann Manage*, 1998. **13**(2): p. 131-47.
360. World Bank, Hospital Sector Reform in Uzbekistan - A Policy Note. 2008.
361. WHO Europe, http://data.euro.who.int/hfadb/. *European health for all database (HFA-DB)*, July 2011.
362. Ahmedov M, Rechel B, Alimova V, and Azimov R, Primary health care reform in Uzbekistan. *Int J Health Plann Manage*, 2007. **22**(4): p. 301-18.
363. Qadeer I, Health care systems in transition III. India, Part I. The Indian experience. *J Public Health Med*, 2000. **22**(1): p. 25-32.
364. Ma S, Sood NA Comparison of the Health Systems in China and India. 2008: Santa Monica, California: RAND Corporation
365. Balarajan Y, Selvaraj S, and Subramanian SV, Health care and equity in India. *Lancet*, 2011. **377**(9764): p. 505-15.

366. Rao M, Rao KD, Kumar AK, Chatterjee M, and Sundararaman T, Human resources for health in India. *Lancet*, 2011. **377**(9765): p. 587-98.

367. Sharma AK, National rural health mission: time to take stock. *Indian J Community Med*, 2009. **34**(3): p. 175-82.