HEALTH ECONOMICS OF NEW AND UNDER-USED VACCINES IN DEVELOPING COUNTRIES:

STATE-OF-THE-ART ANALYSES FOR HEPATITIS B AND ROTAVIRUS IN VIETNAM

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HEALTH ECONOMICS OF NEW AND UNDER-USED VACCINES IN DEVELOPING COUNTRIES:

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Hong Anh Thi Tu
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Promotors:

Prof. dr. M.J. Postma

Dr. H.J. Woerdenbag

Reading committee:

Prof. dr. B.W. Lensink

Prof. dr. J.R.B.J. Brouwers

Prof.dr. H.W. Frijlink

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CHAPTER 1

GENERAL INTRODUCTION

Demographics and Healthcare System in Vietnam

Vietnam is a country in South East Asia, with a surface area of 331,668 square kilometers. Geographically, it is bordered by China to the North, Cambodia and Laos to the East and the South China Sea to the West. The country consists of 64 provinces and four regions: the Northern, Central, Highlands and Southern parts. In 2010, the population was estimated at 87 million [1]. The gross national income (GNI) per capita was US$ 1,010 in 2009 [1]. The estimated health expenditure in 2008 was 7.3% of the gross domestic product (GDP), with government expenditure accounting for only 38.5% of total expenditure for health [2]. Vietnam was ranked 113 on the Human Development Index[1] with a life-expectancy of 75 years in 2010. The under-five mortality rate was 19 per 1,000 live births [3].

The Vietnamese health system is a mixed public-private provider system, in which the public sector plays a major role in healthcare provision, policy making, research and training. The private sector has grown steadily since the health sector reform in 1989, but is mainly active in outpatient care while inpatient care is still provided through the public sector. The healthcare network is organized under state administrative units: central, provincial, district, commune and village levels, with the Ministry of Health coordinating at the central level. In the public sector, there are 774 general hospitals, 136 specialized hospitals and 11,576 primary health centers [4]. As of 2008, the number of doctors, nurses and pharmacists per 1,000 inhabitants was 0.65, 0.78 and 0.12, respectively [4]. The uniqueness of the Vietnamese health system is characterized by the establishment of the grassroots healthcare network, which provides health services at the lowest levels, (i.e. commune and district). It is the foundation for healthcare achievements highlighted by the attainment of national healthcare goals for the entire population. A milestone was the delivery of healthcare services to the people in the most remote regions, that are highly inaccessible and where transport is difficult. Additionally, the contribution from the private sector to the Vietnamese health system has increased remarkably during the past two decades since the health care reform, highlighted by the presence of 83 private hospitals, accounting for ~8.2% of the total number of hospital nationwide thus far [4].This helps to reduce the overload of patients in public hospitals in Vietnam.

The goals of Vietnam's health system is to provide curative care of diseases, preventive care through immunization, training and education of the healthcare workforce and developing health policies. In this thesis, I focus on the immunization strategies in Vietnam and explicitly on the health economics of immunization strategies against selected diseases, applying new and underused vaccines.

Immunization is a very important part of the public health in Vietnam and the immunization system is organized from the lowest level of the health system (so-called the commune health center). In very remote areas where transport is cumbersome and not easily accessible, outreach posts and mobile services are additionally provided. Due to limited human resources for health especially in rural and remote regions, the majority of immunization in Vietnam is provided through fixed immunization days

[1] The Human Development Index (HDI) is a summary composite index that measures a country's average achievements in three basic aspects of human development: health, knowledge, and a decent standard of living.

(~2 days per month) at community health centers. However, in bigger cities, immunization services are provided daily. Universal vaccination against selected diseases is implemented through the Expanded Programme on Immunization (EPI), which is centrally run by the National Institute of Hygiene and Epidemiology (NIHE) [5]. Figure 1 describes the operational structure of the National Expanded Programme on Immunization.

Expanded Programme on Immunization

The EPI in Vietnam was established to promote and provide free universal childhood immunization. The program started in 1981 and is one of the most successful national priority health programs. In 1989 the goal of universal childhood immunization in Vietnam was achieved, with a national coverage of 87%. At present, there are 9 vaccines in the EPI's immunization schedule: bacillus-calmette-guerrin (BCG), diphtheria-tetanus-pertussis (DTP), hepatitis B, polio, measles, tetanus, cholera, Japanese encephalitis (JE) and typhoid. Some are generally administered on a national level and others are administered in high risk areas only (Table 1).

In addition, the government of Vietnam has set up several national EPI goals to be achieved by 2012, which include achieving universal immunization at a national coverage of 90% of children; maintaining the nation's polio-free status; eliminating maternal and neonatal tetanus, eliminating measles; achieving hepatitis B control by 2012, and introducing new vaccines such as rotavirus vaccines [5;6].

The scope of this thesis is to focus on health economic aspects of the implementation of hepatitis B vaccination, which has been universallyimplemented in Vietnam since 2002, and of rotavirus vaccination, which ispotentially included in the EPI in the near future. In particular, the rotavirus vaccine has recently been recommended by the World Health Organization (WHO) on universal implementation worldwide.

Hepatitis B immunization

Epidemiology

The hepatitis B virus (HBV) is one of the most prevalent blood borne viruses worldwide and is a major cause of chronic liver diseases and hepatocellular carcinoma (HCC) [7;8]. Vietnam is a high-endemic country of HBV infection. Several epidemiological studies carried out in Vietnam showed that the prevalence of chronic hepatitis B surface antigen (HBsAg) carriers is between 8.8% and 20.5% across different populations and regions in Vietnam [9;10]. Therefore, with the population estimated at 87 million in 2010 [1], a large number of Vietnamese people will be at risk of premature death due to HBV infection. In addition to the costly antiviral therapy to treat chronic hepatitis B infection, HBV immunization has become one of the best preventions against the disease. Therefore, in 1992, the WHO recommended that all countries should include universal HBV vaccination in their national immunization programs [11].

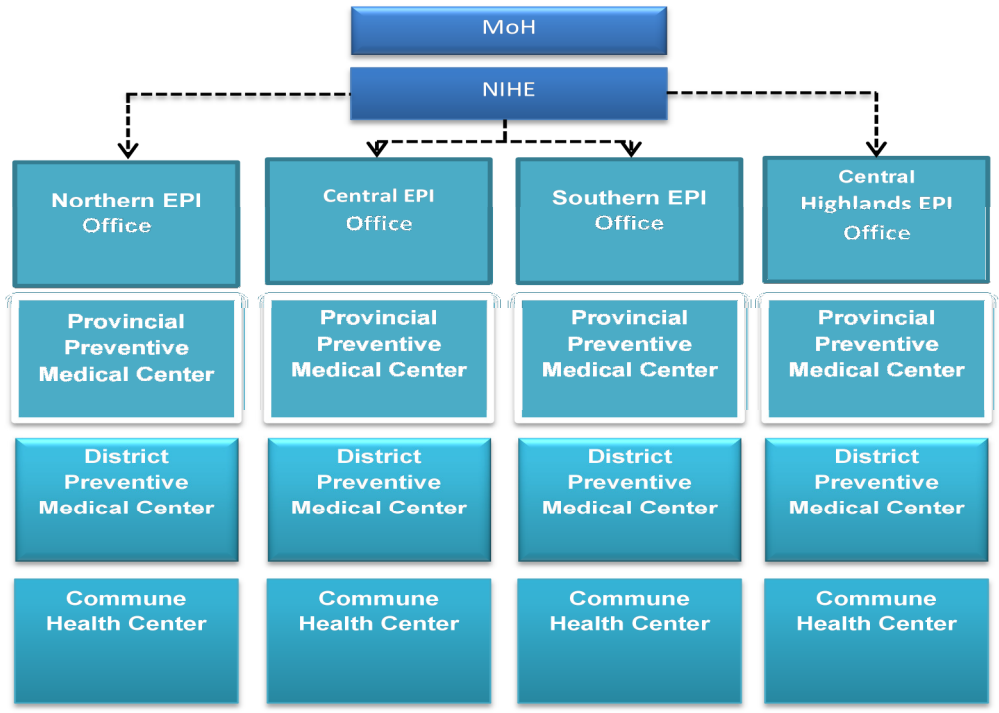

Figure 1 Operational structure of EPI system in Vietnam [5]

Vaccine	Targeted time of administration	Total no. of doses	Where applied
Bacillus-calmette-guerrin (BCG)	At birth	1	Nationwide
Diptheria-Pertussi-Tetanus (DPT)	2,3,4 months	3	Nationwide
Hepatitis B (HepB)	At birth, 2, 4 months	3	Nationwide
Oral Polio Vaccine (OPV)	2,3,4 months	3	Nationwide
Measles	9 months, 6 years	2	Nationwide
Tetanus	Pregnant women	2	Nationwide
Neonatal tetanus	Child-bearing age women (CBAW) 15-35	3	High risk areas
Cholera	2-5 years	2	High risk areas
Japanese Encephalitis (JE)	1-5 years	3	High risk areas
Typhoid	3-10 years	1	High risk areas

Table 1 National Immunization Schedule for Vietnam [5]

Immunization

Hepatitis B immunization is part of the EPI's activities in Vietnam since 1997. Initially a locally produced vaccine was used, but supply constraints limited its usage to a small number of districts. Financial support from the Global Alliance for Vaccines and Immunization (GAVI) enabled the introduction of hepatitis B vaccine (produced outside of Vietnam) on a national level, covering about half of the districts in 44 provinces in 2002, and the remaining districts in these provinces in 2003. Locally produced vaccine is still used in the other 17 provinces. However, universal HBV immunization was only completed by mid-2003 in Vietnam. In particular, the hepatitis B third dose coverage increased from less than 20% in 2000 to more than 90% in 2005 [12]. In the meanwhile, the policy on hepatitis B birth dose was gradually changed from administration within 3 days of birth to less than 24 hours after birth, according to the WHO recommendation [12]. Universal hepatitis B immunization will support the regional hepatitis B control goal to reduce HBsAg+ prevalence to 2% in under-5 year children by 2012 [13].

Rotavirus immunization

Epidemiology

Diarrhoea is a leading cause of child mortality and rotavirus has been identified as the most common cause of severe diarrhoea [14;15]. A large share of the mortality and morbidity caused by diarrhoea occurs in developing countries such as Vietnam [16]. Results from a sentinel surveillance network for rotavirus conducted in six major hospitals in four principal cities in Vietnam in 1998 showed that rotavirus was detected in 56% of all under five-year-old children, who were hospitalized for severe diarrhea [16;17]. The national data indicate that approximately 15.4% of all deaths among these children are due to diarrhoea. If rotavirus were associated with one quarter or one half of these diarrhoeal deaths, the yearly rotavirus-associated deaths among under five-year-old children would be between 4%-8% or, correspondingly, 1 in every 300 children would die of rotavirus-related diarrhoea [16;17]. With the 2010 birth cohort of more than 1,550,000 newborns, the risk for children to suffer from rotavirus-related morbidity and mortality would be very high.

Immunization

Currently, rotavirus vaccines have not yet been introduced in the EPI in Vietnam although two worldwide-approved rotavirus vaccines, RotaTeq® (Merck) and Rotarix™ (Glaxo Smith Kline), have been available since 2006 [18;19]. These vaccines have demonstrated good protection against rotavirus infection and against rotavirus-related severe diarrhoea [20-22]. Studies on rotavirus immunization using either these vaccines have proved their effectiveness in potentially protecting the lives of nearly 2 million children in the next decade alone [23] as well as its acceptable economic impacts to countries' healthcare systems. Therefore, the WHO has expanded its recommendations to include rotavirus vaccines into countries' immunization programs [24]. Importantly, the WHO and the GAVI have committed to provide financial support to developing countries such as Vietnam in expediting the introduction of such vaccines [24;25].

Aim and Outline of the Thesis

The general aim of this thesis is providing an overall picture of the cost-effectiveness of the current universal hepatitis B immunization and the recommended universal rotavirus immunization in the developing world with a specific focus on Vietnam as the example. The actual analyses are carried out to evaluate the cost-effectiveness results using Vietnam's epidemiological and costing data. In the absence of local data, data from other countries, where the epidemiology of hepatitis B and rotavirus are the most similar to Vietnam, have been used. All cost-effectiveness analyses are performed using Markov models. Based on the cost-effectiveness results on universal immunization against hepatitis B and rotavirus, recommendations are provided to Vietnamese health decision-making authorities in order to find appropriate ways for sustaining immunization, appropriate policies to support the success of the EPI program are proposed and evidence is provided supporting applications for external funding from the international health community.

The thesis is structured into two parts. In **Part I** the epidemiology and economics of hepatitis B immunization in developing countries are presented, with a focus on Vietnam. In particular, **chapter 2** is a comprehensive review of hepatitis B immunization programs in developing countries. Cost-effectiveness results of immunization strategies in the developing world are summarized to provide information on the success and challenges that developing countries have achieved and encountered during the implementation of universal hepatitis B immunization. The chapter sets the scene for the original studies presented in the subsequent chapters. **Chapter 3** presents a cost-of-illness study of chronic hepatitis B in Vietnam. The study summarizes the financial burden an average Vietnamese would bear when being chronically infected with hepatitis B, as well as the cost burden incurred to the health system of Vietnam regarding the disease in its various stages. In **chapter 4** a cost-effectiveness analysis was performed to assess results of the current universal hepatitis B immunization in Vietnam. In this study, additionally a cost-effectiveness affordability curve was derived to propose different budgetary thresholds at which hepatitis B immunization would become both cost-effective and affordable for the Vietnamese government. For comparison, a contrasting picture of the hepatitis B situation in a developed country, the Netherlands was provided as an annex to this chapter. In this annex, information on drug utilization for the treatment of chronic hepatitis B was presented using information on drug use from pharmacy-dispensing data from community pharmacies in northern Netherlands. The data were obtained from the University of Groningen's IADB.nl database (www.iadb.nl), which harbours information on drug utilization from 55 community pharmacies and covers more than 500,000 people since 1999. Additionally, the methodology for pharmacy data gathering was applied to Vietnam, enabling the aforementioned cost-of-illness study in chapter 3.

Part II of the thesis discusses the potentials and challenges of implementing rotavirus immunization in developing countries, again with a focuson Vietnam. **Chapter 5** provides an overview of cost-effectiveness results of universal rotavirus immunization in the developing world once the vaccine is officially included in countries' immunization programs. Cost-effectiveness results of immunization strategies in the developing world are summarized to provide information on the effectiveness and

challenges that developing countries would achieve and encounter if the vaccine were introduced based on the WHO's recommendations. The chapter also emphasizes the important role of the GAVI in assisting developing countries to introduce rotavirus vaccines. To resolve several challenges faced by developing countries in carrying out rigorous studies on cost-effectiveness of rotavirus vaccination, **chapter 6** provides an overview of several cost-effectiveness models on rotavirus vaccination, which would eventually benefit middle and low-income countries in designing cost-effectiveness analyses using new or adapting existing models. In a more elaborated and practical fashion, **chapter 7** presents a cost-effectiveness analysis of rotavirus vaccination in Vietnam using one of the economic models recommended in **chapter 6**. The study presents the results of rotavirus vaccination in Vietnam as well as challenges faced by the Vietnamese health sector if vaccination were introduced in the future. Finally, in **chapter 8** the main findings of the studies as presented in the previous chapters are summarized and discussed and an outlook and future perspectives are given. In more details, challenges and limitations faced by developing countries in estimating the cost-effectiveness of preventive interventions for infectious diseases are pointed out. More importantly, suggestions on how to improve the quality of cost-effectiveness studies are suggested. Recommendations are also provided to aid health decision-making in Vietnam and other developing countries for a sustainable and good immunization program against infectious diseases in children in the future.

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PART I

Economic evaluations of hepatitis B vaccination for developing countries

CHAPTER 2

Economic evaluation of hepatitis B vaccination for developing countries

Hong Anh T. Tu

Herman J. Woerdenbag

Sumit Kane

Arthorn Riewpaiboorn

Marinus van Hulst

Maarten J. Postma

Expert Review of Vaccines 2009; 8(7): 907-920

Summary

Economic evaluations, in particular cost-effectiveness, are important determinants for policy makers and stakeholders involved in decision-making for health interventions. Up until now, most evaluations of cost-effectiveness of hepatitis B vaccination have been performed in developed countries. Appropriate health-economic studies on this topic specifically targeted at the developing world are essential in order to justify adding another vaccine into the existing Expanded Program on Immunization in these countries. We present a systematic review of economic evaluations of vaccination against HBV for developing and less-developed countries. Vaccine price, the discount rate, incidence and prevalence of HBV infection were found to be major drivers of cost-effectiveness. Data accuracy and reliability were also major issues, with major potentials for improvement in studies of these countries. The choice between monovalent or combination vaccines (diphteria, tetanus and polio-hepatitis B) poses new challenges to cost-effectiveness analysis. It is concluded that for many developing countries implementation of universal immunization against HBV to reduce the level of endemicity of hepatitis B is an appropriate strategy, and probably cost effective in many settings. Given their limited financial resources, developing countries should properly plan how to achieve this. Further country-specific economic evaluations and related gathering of high-quality data must be conducted in developing countries in order to raise both public awareness of the effectiveness and economic attractiveness of universal immunization against HBV.

Introduction

HBV is one of the most prevalent blood borne viruses worldwide, responsible for liver diseases and hepatocellular carcinoma. It is an important public health problem in developing countries where the endemicity of the disease is generally high or intermediate and is less a problem in developed countries (Table 1). Despite the availability of effective vaccines for two decades, HBV still contributes substantially to global morbidity and mortality. It is estimated that over 350 million people in the world are currently chronically infected with HBV [101]. They are at high risk of death from liver cirrhosis and liver cancer diseases that kill over 1 million people each year. The epidemiology of HBV is one of the key factors in determining the cost-effectiveness of the vaccination program against the virus. Over time, thanks to universal HBV vaccination in developing countries, more and more children in these countries benefit from vaccination, which in turn reduces the level of endemicity in high and intermediate-risk countries.

In 1992, the WHO recommended that all countries should include universal HBV vaccination in their national immunization programs. In particular, three doses of the HBV vaccine should be supplied regardless of the prevalence of infection. The WHO set this target for all highly endemic countries by 1995 and two years later for all other countries [102]. However, owing to reasons such as different levels of endemicity and poor availability of funds for universal vaccination, strategies have not been fully implemented across the world. In December 2007, 171 countries had included the HBV vaccine into their national infant immunization programs compared to 31 countries at the start in 1992 [103]. In various developed countries, HBV vaccination has been limited to specific risk groups (ethnic minorities, healthcare workers, sexual partners of chronically infected persons, homosexual men and children of immigrants from high-endemic countries). In developing countries, universal HBV vaccination has mostly been given to newborns and infants, and not yet been extended to other groups such as adolescents owing to the financial limitations. However, hepatitis B continues to be an important public health problem in these areas because the infection is spread by maternal transmission at birth.

Children in the poorest countries do not receive HBV vaccines because their governments cannot afford it (high vaccine prices compared to limited budgets given to the health sector), the poor healthcare infrastructure (vaccine storage facilities, delivery systems) and there is a lack of effective public health policies. Recently, however, with the support of the Global Alliance of Vaccines and Immunization (GAVI), vaccines have been made available for many developing and less-developed countries [104].

Thus far, little is known about cost-effectiveness and cost-utility of vaccination against HBV in the developing world as compared to the developed world. Very few such studies have assessed hepatitis B immunization in developing countries. This review aims to give a systematic view on HBV vaccination, with a focus on developing countries and economic evaluation. The paper summarizes the results and methodologies of the formal CEA and other economic evaluations on different HBV vaccination strategies. Furthermore, we analyze the current implementation of HBV immunization strategies in developing countries and the constraints (fund availability, vaccine costs, and so on) faced by them in

attempts to introduce HBV vaccine into their routine immunization programs. Up front, we realize that divergent results on cost-effectiveness ratios of various immunization strategies might sometimes be related to methodological issues in economic evaluations, in addition to other aspects such as demography, cultural characteristics and prevalence of HBV. Intuitively, for developing countries, vaccine price is among the most critical factors and cost-effectiveness is key in deciding upon the introduction of the vaccine into the national Expanded Program on Immunization (EPI). This review concludes with an explanation of possible options to assist health policy-makers of developing countries to formulate appropriate health policies in making this vaccine available to their people in a cost-effective manner.

Level of endemicity	Prevalence (%)	Chronic carrier Rate[2] (%)	Regions	Recommended strategies
High	70-95	8-20	Tropical Africa, South America (Amazon Basin)South-East Asia, parts of China and the Pacific Basin	Universal infant vaccination (+/- HBIG administration)
Intermediate	20-55	2-7	Southern Europe, Eastern Europe, Russia, Middle East, Japan, North Africa, the Indian Sub-continent, parts of South and Central America	Universal immunization of infants and/or adolescents or immunization of high-risk groups (all ages)
Low	4-6	<2	North America, Western Europe and Australia	Universal immunization of infants, adolescents or both groups Immunization of high-risk groups Immunization of infants in subpopulations with high endemicity

HBIG: Hepatitis B immunoglobin
Data taken from [28-30]

Table 1 Distinction between regional immunization strategies against HBV, based on levels of HBV endemicity

Methodology

Search Strategies

Relevant economic evaluations of hepatitis B vaccination were searched using the PubMed and Embase databases. Keywords for retrieval were 'hepatits B' and 'cost(-)effectiveness' or 'cost' or 'costs' or 'economic evaluations' and 'vaccination' and 'developing countries'. In total, 202 potentially relevant articles published between 1993 and 31 January 2008 were retrieved. Figure 1 describes in detail the diagram of the literature search.

Eligibility criteria

Further eligibility criteria stipulated that:

- Studies should be strictly classifiable in one of the formal health-economic categories of cost-effectiveness, cost-utility, or cost-benefit analysis (CEA, CUA and CBA, respectively);
- Studies should be written in languages that could be mastered by the authors' team [1]

Abstracts retrieved from the electronic databases were independently screened by two members of the research team (Maarten J Postma and Hong-Anh T Tu). Disagreements were resolved through discussion. Studies that were deemed relevant at this first screening were retrieved in full-text format and screened by one reviewer for further eligibility. After excluding letters and editorials, 11 different original articles of research results were identified (Figure 1).

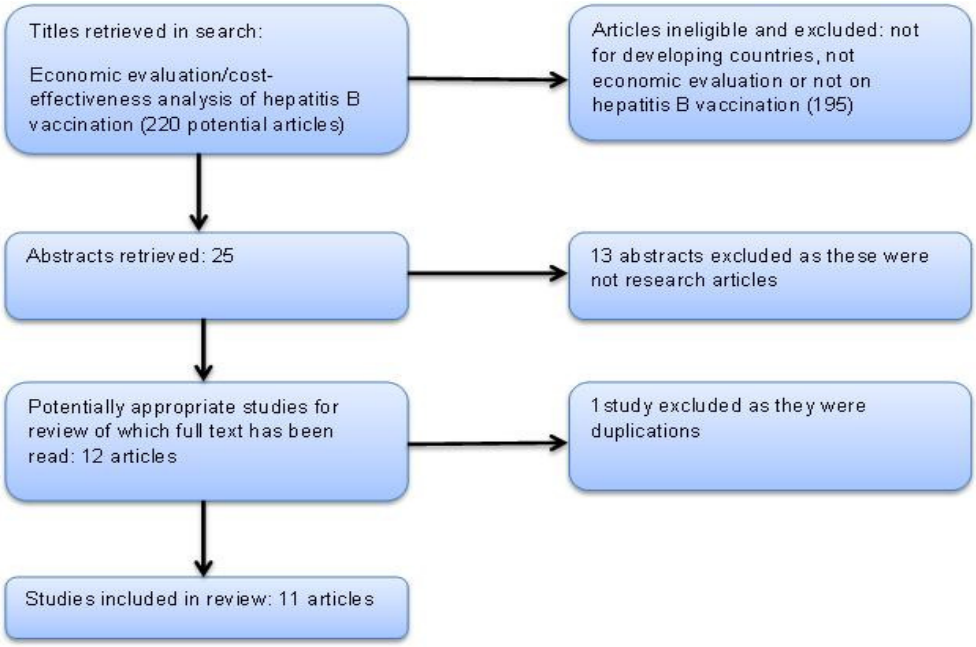

Figure 1. Economic evaluations/cost-effectiveness/cost-utility/cost-benefit analyses of hepatitis B vaccination/immunization

Data abstraction

Detailed information was abstracted using a pre-specified data extraction form. Items of the form included author(s), publication year, country, approach, validation/calibration of models, type of sensitivity analysis, perspective and outcome.

For our review, we specifically focus on economic modeling, the perspectives taken (societal vs. healthcare), discount rates, vaccine costs, epidemiology of HBV and specific immunization strategies (universal vs. selective). Generally, these aspects are well known to reflect important issues in the health-economics of vaccines

Results

General

We found 11 relevant studies in total, focusing on the economic evaluation of HBV vaccination in developing countries. Three of the studies [2-4] belong to the Western Pacific Region. Data shows that

the Western Pacific Region accounts for 50% of deaths from hepatitis B despite the fact this region only accounts for one third of the world's population [5]. All countries in this region have introduced HBV immunization into their national vaccination programmes. The region has set 2012 as the target date for reducing the current level of endemicity of 8%-10% to less than 2% among children under five years old and to less than 1% as the final goal [106]. Three studies come from India [1, 6, 7], a country of intermediate endemicity of HBV. Four out of 11 studies [8-11] are from Africa. All of African countries involved in these studies were eligible for GAVI fund support. In Africa, by 2000 only six countries had introduced the HBV vaccine into their national immunization programmes, however, 25 additional countries implemented vaccination in 2005. The African region has set a goal of integrating the hepatitis B vaccine into the national immunization programmes of all countries in the region by 2009 [12]. One study originated from Iran [13] in the Middle East".

The oldest paper that emerged from our search was from 1993 [11] dealing with an analysis of costs and benefits of HBV vaccination in China and the most recent one was from 2007 [8], addressing the economic evaluation of HBV vaccination in low-income countries, using cost-effectiveness analysis inclusive affordability curves. Most of the developing countries under study could be classified into intermediate or high endemicity (Table 1). The most relevant aspects of these studies are summarized in Table 2.

Study Characteristics

Depending on the level of endemicity of HBV across countries as well as on the fund availability for implementing hepatitis B immunization, the choice of the specific immunization strategy can be either universal or targeted (selective). Universal vaccination strategies were evaluated in 8 of the 11 studies. All focused on universal vaccination of newborns and infants. Targeted vaccination strategies were evaluated in 2 of the 11 studies (i.e. vaccination of high-risk groups). One study did not specifically focus on either strategy but rather performed an inventory of potential cost components.

Specific vaccination strategies differed on details among these studies. In particular, the differences related to the exact comparisons made in the analyses. These aspects are summarized in Table2.

Detailed Results on Economic Evaluations of Hepatitis B Immunization Strategies against HBV

Universal Vaccination

Prevention of HBV infection by universal vaccination has long been recognized as an effective means for reducing healthcare costs associated with the disease [14]. The effectiveness of universal HBV immunization programmes has been demonstrated in many countries; epidemiological data and economic evaluations have shown that universal HBV vaccination is potentially highly cost-effective. However, universal vaccination is still being postponed in many countries such as in the UK, the Scandinavian countries and the Netherlands [15], also due to uncertainties on the actual cost-effectiveness of the vaccine. From a healthcare point of view, one could argue that vaccinating the entire population to prevent the transmission of the virus, potentially leads to reducing the burden of various hepatitis B-related diseases. Below, we briefly summarize all studies included in our review.

Kim *et al.*analyzed the situation in the Gambia, being the first African country in which HBV immunization was introduced on a routine basis to newborns, in 1990 [8]. Striking in this study was the use of cost-effectiveness affordability curves, which gave probabilities of a vaccination programme to be both cost-effective and affordable by showing different acceptability thresholds. A multivariate uncertainty analysis was conducted to drive the affordability curve and showed the probability of an affordable programme under different budget options.

This is the only study in the review, which applied formal cost-effectiveness affordability curves. The cost-effectiveness affordability curves can also provide information to decision makers for choosing a proper vaccine programme while facing uncertainties about the health and economic outcomes of such a programme, as well as of the resources required to make the programme run. The authors concluded that it was cost-effective for universal infant vaccination to be implemented in the Gambia when cost-effectiveness thresholds exceeded US$ 97 per DALY averted and not cost-effective when the thresholds were less than US$ 25 per DALY averted (the Gambia's per-capita GDP equals approximately US$ 300). With an estimated US$47 per DALY averted, from a payer's perspective, the possibility of the programme being cost-effective would be 65%.

Vimolket *et al.* [2] conducted a cost-effectiveness analysis of maternal HBsAg screening and vaccinating at-risk babies in Thailand. Four vaccination strategies were suggested: screening all pregnant women for HBsAg, vaccination plus HBIG to those who have HBsAg positive (1); screening all pregnant women for HBsAg and HBeAg (if HBsAg+) and providing the vaccine and HBIG to those HBeAg+ (2); universal vaccination of all neonates (3); and no vaccination (4). Assessing these four strategies, the authors recommended that universal newborns vaccination to be continued, as the cost-effectiveness per case prevented was lowest (US$ 37.76) compared to the other alternatives. The authors emphasized that if the funds were available, the second strategy would be additionally worthwhile since it both promoted universal vaccination and protected at risk newborns to HBsAg+ mothers with both vaccination and provision of HBIG. This will certainly increase the efficacy of the overall HBV prevention programme. However, this in turn raises the issue of supplying HBIG and equipments for HBsAg pregnant mothers, which may reflect major constraints in many developing countries. Different from the study in Gambia, the study did not analyze any cost-effectiveness thresholds to further guide decisions on funding immunization strategies against HBV.

Griffiths *et al.* [22] performed the first cost-effectiveness study of a health intervention in Mozambique [9]. Mozambique receives support from the GAVI in the introduction of HBV vaccine. However, in the long run the country itself has to finance the vaccine procurement. The authors wanted to calculate the cost-effectiveness of introducing the HBV vaccine into the national immunization programme. A strong point of this study is the application of a model designed for WHO in estimating disease burden caused by HBV, which helps to calculate exact numbers of deaths averted by age and sex due to the introduction of HBV vaccine in the Mozambique. A further advantage of the model is the limited amount of data required for specific calculations. Cost per DALY averted and the number of deaths averted annually were used as the outcomes. The incremental costs of introducing the combination vaccine

(DPT-Hepatitis B) and monovalent hepatitis B vaccine were calculated. The authors convincingly showed that the monovalent vaccine against HBV was more cost-effective than the combined vaccine of DPT and HBV (US$15 and US$36 per discounted DALY averted, respectively or US$178 and US$436 per death averted, respectively). It was also estimated that nationwide 4,000 deaths were averted per annum by the introduction of the vaccine.

Aggarwal *et al.* elaborated on the cost-effectiveness of universal HBV immunization of newborns for low-income and intermediate endemic countries using a Markov model [1]. The study showed that universal vaccination against HBV in early childhood reduced the hepatitis B carrier rate from 4% to 1.15%. Estimated life expectancy and QALY gains were 0.173 years (61.072 vs. 60.899) and 0.213 QALYs (61.056 vs. 60.843 QALYs). The incremental ratios per LYG and QALY were US$16.27 and US$13.22, respectively. Compared to the GDP per capita in India, these figures show that universal immunization against HBV may be highly cost-effective. The authors also emphasized that the results from this study could be used for other low-income and intermediate-endemic countries that are comparable to India and thus help health administrators of those countries in decision making regarding universal HBV vaccination. However, the study also stressed some constraints in conducting this type of research. In particular, this concerned limited available data in low-income and intermediate-endemic countries on diseases progression, absence (of information on) treatment of hepatitis B complications and the cost components building a cost-effectiveness analysis of HBV vaccination. For example, this specific study had to use data from other regions such as disease progression data from high-endemic and low-income countries.

In another study focusing on India, Prakash addressed a different point of view [7]. Instead of conducting a cost-effectiveness analysis per se, Prakash analyzed crucial parameters potentially affecting cost-effectiveness of universal HBV immunization. India is classified as a country of intermediate to high hepatitis B endemicity with a prevalence rate of 2.5-10% [16]. Costs of the vaccine and vaccine efficacy were important factors influencing the analysis. Vaccine price per pediatric dose was around US$0.75 if purchased through EPI programme. If the costs of the vaccine could be reduced to US$0.60, the cost per DALY averted would be reduced another approximate 5%. At the time of this study, India had not integrated the HBV vaccine into the national EPI due to its large population and the relatively high vaccine price. Also, HBV prevalence was rather intermediate than high by that time [17]. These sheer numbers raised the question of how to make universal hepatitis B immunization in India implementable and cost-effective. Targeted immunization did not seem to be a feasible option for an overpopulated country as India since it would not relevantly affect transmission and only achieve limited prevention in an at-risk subpopulation (such as newborns to hepatitis B-infected mothers).

In contrast to the two above-mentioned Indian studies, Sahni *et al.* shifted the analysis towards cost-benefit of universal immunization against HBV [6]. They compared selective vaccination against HBV given to newborns of HBsAg-positive mothers and universal vaccination given to all newborns. The authors argued that in the particular context of India - where 65% of mothers delivered at home - universal HBV vaccination of newborns was not cost-beneficial because the discounted cost of saving

each QALY (Rs 259,610 or US$ 5,192; at 3% discount rate) was ten times higher than the per capita GNP (Rs 20,250 or US$ 405). It was concluded that universal immunization was not cost-beneficial if compared with selective immunization.

In another cost-benefit analysis from 1995, Liu *et al.* concluded that universal vaccination in China would be cost-saving with BCRs[2] between 42.41 and 48.01 [3]. The study analyzed mass vaccination of all newborns in Jinan City in 1990. The author analyzed three different strategies: (i) screening and vaccination of all newborns born to HBsAg+ mothers with 3x10µg vaccine; (ii) screening and vaccination of only those children born to HBsAg+ mothers with a relatively high dosage (3x30µg); and (iii) vaccination of all newborns with a normal dosage. The administration of vaccination to newborns was assumed at 0, 1 and 6 months, respectively. The second strategy appeared to be the most cost-beneficial strategy. Yet, the other two strategies also seemed very beneficial, and the study concluded that if there was enough supply of HBV vaccines, all newborns should be vaccinated.

The Gambia was one of the African countries that actively introduced the hepatitis B vaccine into its national immunization programme in 1986. Hall *et al.*calculated that adding the hepatitis B vaccine to the EPI in Gambia would increase the marginal cost to US$4.2 per child for three doses of vaccine [11]. Similar to other studies, vaccine price contributed the biggest part in the increase of the total cost of the EPI programme (80%). The study showed that through vaccination against HBV, the cost per averted death from liver cancer would be between US$150-200, which would be comparable with other EPI vaccines. It was obvious in the study that vaccine price per dose was the major factor which could be manipulated to improve cost-effectiveness. A combined vaccine against DPT and hepatitis B could reduce the vaccine price and improve the cost-effectiveness by hedging the cost of labeling and administration (for example, personnel costs, storage and supplies). At the time the Gambia's study was conducted, the GAVI fund did not yet exist and the study did not clearly show if hepatitis B vaccination was cost-effective. However, 13 years later, when Kim *at al.* conducted another study in the Gambia, routine immunization was estimated to be very cost-effective in that country [8]. These authors concluded that vaccinating infants against HBV reduces the burden of HBV-related diseases by more than 80%.

All universal HBV vaccination programmes discussed in this review were done on newborns and infants (8 studies) [1,2,5-9,11]. Universal vaccination of newborns was generally considered cost-effective and appropriate for the control of HBV infection in regions of medium and high endemicity, which is the case in most developing countries. A further common conclusion from all of the studies was that vaccine price was an important and critical factor influencing cost-effectiveness and the decision of health administrators of respective countries to introduce the vaccine in their national immunization programmes. Results also showed that EPI programmes could effectively facilitate the implementation of HBV immunization through discount procurement of the vaccine with the support from GAVI,

[2] BCR is the ratio of the benefits of a project relative to its costs. For the BCR, both benefits and costs are expressed in monetary terms.

extending vaccine coverage through administration together with DPT, and using existing facilities set up within the EPI framework. However, the combination vaccine DPT-hepatitis B cannot be used "at birth", because the pertussis component is contra-indicated until 6 weeks of age. Thus, if countries want to use the combined of DPT- hepatitis B vaccine, the birth dose would be monovalent hepatitis B vaccine, and from the second dose onwards the combined vaccine can be used. The other option would be to start the vaccination series from the six weeks onwards with the combined vaccine.

Targeted Vaccination

Two of the studies included in this review focused specifically on target groups: pre-marriage couples in Iran [12], and soldiers in the People's Liberation Army in China [3].

In the study from Iran, Adibi *et al.* were convinced that in the Iranian society, targeted vaccination of pre-marriage couples was an effective and feasible way to prevent virus transmission [12]. The study underpinned that targeted immunization did help to protect this at-risk population (at the time this study was conducted, Iranian children of 10 years or older had not received HBV vaccination). Two strategies to reduce HBV infections were tested: (i) HBsAg screening to find those would-be couples that are HBsAg positive and provide them with HBV vaccination, single dose HBIG and condoms; and (ii) HBsAg screening as in the first strategy in addition to HBcAb screening in HBsAg negative spouses of HBsAg + persons followed by the same protocol to HBcAb negatives. The first strategy was found a bit more expensive than the second (US$ 202 vs. US$ 197). However, the authors yet seemed to favor the first strategy because it consisted of fewer steps and would be easier to manage.

In the most recent Chinese study on HBV, Hu *et al.* did an assessment of the cost-effectiveness of vaccination against HBV targeted at soldiers serving in the People's Liberation Army (PLA) [3]. To identify the optimal vaccination strategy, the authors evaluated two different strategies: (i) immediate vaccination; and (ii) screening and vaccination. Both were compared with no vaccination. DALYs were used to assess the effectiveness of the respective strategies. A hypothetical cohort of 1,000 men and women was monitored for 5 years and separated into four groups according to age (15-20; 20-30; 30-40; >50). It was concluded that screening followed by vaccination was the most cost-effective scheme for this particular population with US$57 per DALY, compared to immediate vaccination with US$61.89 per DALY. It was suggested that the sooner vaccination was implemented the more beneficial it would be for the PLA. This was the only study in the review focusing particularly on adults.

It is clear that universal immunization against HBV in developing countries where HBV endemicity is high or intermediate is cost-effective and cost-beneficial on the long run. However, funding issues and resource mobilization are still big barriers for developing countries. Griffiths *et al.*came to the conclusion that the full benefits of a vaccination programme were only realized after some time (in the case of the study in Mozambique, it required 40-50 years) [9]. This concern should not distract from the importance and urgency of executing a universal or targeted vaccination programme in a given country. Griffiths *et al.* concluded that targeted vaccination against HBV should only be a temporary solution as long as financial resources are not available to initiate a universal programme [9].

One study by Edmunds *et al.* focused on the analysis of composition of cost components when introducing HBV vaccine into Ethiopia's EPI [10]. The authors introduced a method for estimating the additional costs incurred of introducing a new vaccine. It was concluded that the cost of the hepatitis B vaccine was the majority part of the cost of introducing HBV vaccine into the EPI. The cost-effectiveness of HBV vaccine would be most sensitive to the vaccine cost. This is the only study, which was not focused on either universal or targeted vaccination but on cost composition.

General model characteristics

Table 3 shows that the vaccine price per pediatric dose ranged from US$0.27 to US$1 for the monovalent hepatitis B vaccine provided that administration cost was not included in these vaccine costs. It was shown that through national EPI programme, the hepatitis B vaccine could be procured at reduced prices, which helped countries much in introducing the vaccine into their national immunization programmes. The adult dose, as shown in the Iran study, was much higher at US$4.8 per dose than for newborns. Net costs per health outcome indicator (QALY, DALY, LYG, or death averted) were very diverse across countries and studies. These diversities could be explained by the selection of different cost base years, epidemiological data, costing techniques, applied modeling techniques and varying discount rates. Indeed, given the potential large time span between HBV infection and hepatitis B disease, there was a big difference between discounted and non-discounted outcomes within and across studies. A Markov model was generally used for disease progression and the typical structure is drawn in Figure 2.

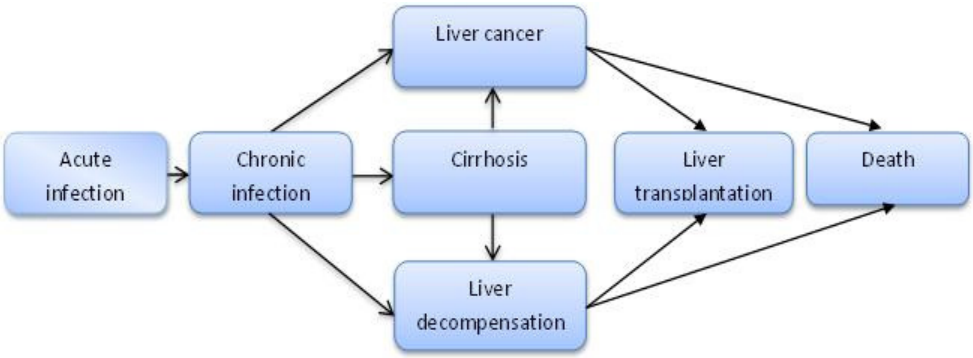

Figure 2: Markov Tree Model

Discounting

Discounting addresses the issue of translating values obtained from one time period to another. Discounting makes current costs and benefits worth more than those occurring in the future because of an opportunity cost to spending money now and there is desire to enjoy benefits now rather than in the future. Cost and benefits, certainly often in case of vaccination, often occur at different point in time.

For example, in the case of HBV vaccination benefits are not generated immediately, but obviously only after a period of time, in terms of a reduced incidence of cirrhosis and liver cancer [18].

As summarized in Table 3 three studies used the same discount rate of 3% per year for both cost and health effects [7-9], which is in line with the WHO guidelines on discounting [19]. Three studies discussed in this review only discounted costs and not health effects. They all applied the recommended rate of 3%. In a few studies in this review, health outcomes were both reported discounted and undiscounted in the base case. Two studies used 6% only for costs [10,11]. For example, in the Gambia's study by Hall *et al.*[23]the 6% discount rate was the difference between the interest rate of treasury bills and the national inflation rate in mid-1988 [11]. Three studies [2-4] did not state any discount rate. In the case of Thailand [2], the authors only calculated costs and effects for one year and discounting was thus not required. Insufficient information is available from the two Chinese studies [3,4].

Methodological Issues

Study types

The studies reviewed in this paper mainly concerned cost-effectiveness analyses (CEA) and cost-benefit analyses (CBA) (see Table 2). Of the 11 studies, eight were cost-effectiveness analyses (i.e. health gains expressed in one-dimensional natural units, infections prevented or life-years gained) [1,3,6-11], two were cost-benefit analyses (i.e. health gains converted into monetary terms, such as dollars) [2,5], and one analysis combined both techniques [12]. Some of the CEAs could be further classified as cost-utility analyses or CUAs (i.e. health gains expressed in integrated units adjusted for quality, such as quality adjusted life-years (QALYs) or DALYs) [3,5-8]. The explanation for the popularity of CEAs over CBAs may be that valuing health in monetary terms is quite difficult. Moreover, cost-minimization analysis (CMA) was only applied in of the study by Edmunds *et al.*, where CMA was applied next to CEA [10]. The authors mentioned CMA as an instrument to investigate reductions in vaccine price and to show potentials for improving cost-effectiveness of HBV vaccination in low-income countries.

Most of the studies performed CEAs from a societal perspective except for the study conducted by Kim *et al* [24], in which a CEA was carried out from both the societal and the healthcare perspectives [8]. The results of the CEAs in our review were quite divergent, depending on various factors such as the specific vaccination strategies compared, particular populations considered, outcome measurements used etc. Vimolket *et al.* [2] and Hu *et al.* [4] both conducted CEAs of various strategies giving different results based on the specific context of HBV in Thailand and China. Different from other studies such as in Hall *et al.* [11], Griffiths *et al.* [9] concluded that monovalent vaccines against HBV would be more cost-effective than the combined DPT-Hepatitis B vaccine. The results in this study perhaps could be explained by the context of Mozambique and the deviation between the procured price of the monovalent vaccine from the combined vaccine. Our findings in this respect are similar to the conclusions of Beutels in an earlier review [20]. Although different methodologies and different types of economic analyses could lead to divergent results even for the same country on the short run (e.g. universal vaccination against HBV was cost-effective in India in one study [6] but not if analyzed by Sahni *et al.* [6]), all authors of studies under review came to the same conclusion that hepatitis B vaccination was cost-effective in the long-run. Vaccine price was identified as the most influential factor

affecting the cost-effectiveness of immunization against HBV and whether this vaccine was integrated into the national immunization programmes in several studies [6,7,9-11].

Modeling approaches

Cost-effectiveness analyses in this review used different modeling approaches. Theoretically, basic typologies of models used in the CEAs concerns static versus dynamic and decision tree versus Markov model (Figure 2).

Some studies explicitly used a Markov model, for example, Prakash [7] and Aggarwal *et al.*[1]. Some problems with these Markov models did emerge. For example, in the study by Aggarwal *et al.* acute or fulminant stages of the disease were not included[1]. Moreover, there were few published data on the disease progression rate especially for the low- and intermediate-income countries to fill the Markov models that were applied. Thus, the authors had to apply rates from other regions. The point of unreliable data on costs of treatment was raised by Griffith *et al.* [9] in the study for Mozambique. Four studies from Thailand [2], Iran [12] and China [3,4] used straightforward decision trees for calculation. Yet, unable to grasp all the details of more complex Markov models or even dynamic models, decision trees may certainly provide insights in the crude relations between costs, savings and health gains within the cost-effectiveness framework.

All studies in the review applied static models (see Table 2). Dynamic transmission models were not applied in these studies. Typically, dynamic models take the spread of infections explicitly into account and generally use formal mathematics to define its structure. Oppositely, in a static model, the force of infection is constant over time (or changes as a function of age or other individual-based factors) [21]. In a dynamic model, the probability of an individual acquiring an infection is dependent on the contact patterns of that individual in the interactions with others, the infectiousness of the infection and the distribution of infections within the population over time [21].

Uncertainty analysis

Uncertainty analyses have been applied in various studies (Aggawal *et al.*[1], Prakash *et al.* [7], Kim *et al.*[8], Griffiths *et al.* [9], Hall*et al.*[11]). They were used to deal with different types of uncertainties popular in cost-effectiveness analyses (such as parameters uncertainty, model uncertainty, and modeling process uncertainty). For example, in the study by Kim *et al.*, a multivariate uncertainty analysis examined the affordability of a vaccination under different budget options [8]. In Aggawal *et al.,* one way sensitivity analysis and Monte Carlo simulation were utilized to examine the robustness of the study's results [1]. In Prakash *et al.*, parameters uncertainty was inherent, where the epidemiology was the most crucial factor affecting the cost-effectiveness of the vaccination programme [7]. In Griffiths *et al.,* probabilistic uncertainty analysis show how much cost-effectiveness ratios can deviate [9]. In this study, cost-effectiveness was found to be most sensitive to the epidemiology of HBV infection and the rate of clearance of HBsAg. In the study by Hall *at al.* [11], uncertainty analysis was applied to the change of vaccine price [11].

Discussion and Policy Recommendation

Most of the existing studies on HBV immunization in high- and intermediate-endemic developing countries provide clear evidence that universal HBV immunization of newborns and infants is cost-effective or even cost-saving in comparison with no vaccination. Only one study by Sahni *et al.* concluded that universal immunization against HBV was not economically attractive on the short term [6]. The conclusion by Sahni *et al.* emphasized that countries' traditions (for example, 65% of mothers in India deliver babies at home) might have important impacts on the outcomes of economic evaluations of vaccination programmes. In terms of epidemiology, in high- and intermediate-endemic countries, universal immunization appears to be the most cost-effective option to combat HBV infection related morbidity.

So far few studies on the economic evaluations of HBV vaccination were done in developing countries, thus, the results and conclusions summarized in this review might not be representative for the current situation in all these countries. Some studies in the review even date back to the early 90's, e.g. the study from China [3] in 1995 and the study from Gambia in 1993 [11]. In these studies, the data might be out-of-date and the current HBV epidemiology in these countries might have changed. In particular, the determinants for designing an appropriate HBV vaccination programme depend on many time-varying factors (e.g. epidemiology, funding, demography, cultural practices, etc).

The studies, albeit few in number, have shown that for developing and less-developed countries, it is very important to design an effective and appropriate HBV vaccine policy in order to make the vaccine available for universal immunization against HBV. To shape such a policy, many determinants should be considered, including both vaccine value and health systems characteristics. Both may be of equal importance in this. Vaccine value characteristics include the disease burden to be prevented, safety and performance, and cost effectiveness. For policy makers in countries with limited health budgets, disease burden has been the most important factor in setting priorities for current and new vaccines to be integrated into the national immunization programmes. In other words, the higher the endemicity, the more urgent and attractive it is to introduce a new vaccine into the routine vaccination programme of the country [22]. The second vaccine value characteristic relates to safety and performance. One of the concerns for health policy makers is the safety and low rates of side effects when making a decision to introduce a new vaccine. Hepatitis B vaccine has been proven to be effective with duration of immunity up to 15 years and with an efficacy up to 75-90% [23]. All of the studies in this review also assume a vaccine efficacy of up to 90%. Cost-effectiveness is the final vaccine characteristic to determine whether a vaccine should be introduced. Economic evaluations and cost-effectiveness analyses help determine if vaccination is economically attractive for the society in the long run and if vaccines' effectiveness outweighs the costs. Many studies in the review have concluded that vaccine price is a critical factor influencing the cost-effectiveness of the immunization programme.

The second set of crucial factors considered by policy makers relates to the health-system characteristics. An important question is whether the health care system can support the proposed intervention. For example, is reliable cold storage available and can the required number of doses be

administered at appropriate times? In the case of the HBV vaccine, an additional important question to be asked is whether indeed a birth dose can effectively be implemented within 48 hours for children from HBV-positive mothers. Thus, introduction of a new vaccine requires a well-functioning infrastructure, including well-trained staff.

HBV is moderately to highly endemic in developing and less-developed countries. However, lack of financial resources has prevented many countries in the region from launching universal immunization. Thus, all universal immunization strategies against HBV studied in this review were targeted at newborns and infants. Facing such constraints as financial viability, resource limitations, poor health infrastructure, universal vaccination against HBV for adolescents or a wider population, for example in catch-up settings, could not yet be achieved in these countries.

Certain limitations have been found in the studies throughout the review. In all studies reviewed in this paper, static models or straightforward calculations without formal models were used for evaluating the cost-effectiveness of different immunization strategies against hepatitis B. Dynamic models were not utilized in any of the studies conducted in this review, possibly because they required a lot of input data, which is indeed one of the major limitations faced by developing countries. Lack of data is a striking disadvantage of studies conducted in developing countries if compared to studies in developed countries. In particular, several dynamic models were applied and developed in research for developed countries, such as the study by Kretzschmar *et al.* [24]. Further limitations refer to different methodologies and a variety of uncertain parameters crucially influenced the results of economic evaluations of the vaccination programmes. One example is the application of the same or of different discount rates for costs and health effects, an issue yet to be resolved but imminently influencing outcomes of HBV economic analyses.

There are a lot of ongoing debates on whether health outcomes/effects and costs should be discounted at the same rate, which should theoretically be so if market perfection exists. Gravelle *et al.* argued that when health effects are valued in monetary terms as in a CBA, both cost and health effects should be discounted at the same rate [25]. However, when health effects are measured in quantities (QALYs) as in CEAs and the value of health effects increases over time, it was argued that health effects should be discounted at a lower rate than costs [25]. Literature shows that there are also other economists, who favor using a lower rate for health effects than for costs. Parsonage *et al*. recommended that health effects should be discounted at a lower rate than cost, which in turn was reflected by the UK Department of Health's recommendations for evaluation of health interventions during the nineties and early 21st century [26]. This review is not intended to advise which discount rates to be used for health and effects, it merely describes which rates have been applied. It is useful to present both discounted and non-discounted cost and health effects since there are a large difference between results. It assists policy-makers in the judgment of a future life against a present investment and consequently makes a suitable decision in choosing the appropriate health interventions in a particular country. None of the studies attempted to use a lower discount rate for health effects.

A further limitation concerns the data. Different studies have addressed the issue of unreliable data of treatment costs on complications of hepatitis B. Limited data on disease progression rate is available, carrier rate is under reported. For example, studies also show that due to data limitations, a lot of assumptions were made in analysis (e.g. in Sahni *et al.* findings in a small part of India was generalized to the whole country; epidemiological data in Aggarwal *et al.*was gotten from other regions, etc). Generally, Cooper *et al.* also came to the same conclusion about the different sources of data, the need to make various assumptions on disease progression, non-transparency of identifying input data to use in these models [27] and even the bias created by researchers in choosing model structures and parameter values as inputs in models. Another problem is that none of the studies took the impact of herd immunity into account when estimating the long-term effects of hepatitis B vaccination. It is yet difficult to predict whether its inclusion would indeed drastically further improve cost-effectiveness and with which size.

It is obvious that the vaccine price and the type of vaccine (monovalent or combined DTP-hepatitis B) chosen can be important determinants in implementing universal immunization in the developing world. Vaccine price has been shown as a constraint for deciding to introduce the vaccine into the national immunization programmes because it accounts for the larger part of the incremental cost generated due to the introduction. EPI programmes can effectively help to introduce the immunization against HBV and the vaccine procurement at a discount price. Few studies mentioned the importance of the GAVI fund [8,9] as a financial tool to help low-income countries to introduce the new and underused vaccines. Countries, which are considered to benefit from the fund, have the opportunities to vaccinate their newborns against HBV through their EPI programmes. Programmes costs, such as administration costs, costs related to keeping up the cold chain, etcetera, were mentioned in all cost-effectiveness evaluations. It was obvious that programme costs also contributed substantially to the total vaccination costs. However, EPI programmes also have advantages in this respect, for example in assisting the negotiations for procurement of hepatitis B vaccine at discount prices and in allowing use of existing facilities for the introduction of a new vaccine such as trained staff and existing cold chains.

Developing countries need to raise cost-effectiveness issues even more than developed countries, in order to decide between universal and targeted vaccination strategies. Developed countries are currently of low endemicity due to the success of universal vaccination and/or “at-risk” strategies for targeted vaccination and lower baseline prevalence levels prior to vaccination implementation. In the developing world, where hepatitis B morbidity and mortality is the highest, cost-effectiveness of HBV vaccination is very attractive [28-30]. Sooner or later, such developing countries should implement universal vaccination for broader populations (not only for newborns and infants but also for adolescents and health workers). Using a combined vaccine (Hepatitis B-DPT vaccine) instead of a monovalent vaccine to increase the coverage and to reduce the administration costs might be an option to further improve cost-effectiveness.

Some authors in the studies reviewed emphasized the contribution and benefits of the GAVI Alliance. GAVI Alliance is an organization, which mobilizes financial support from international donors and

organizations in supporting low-income countries by providing funding for new and underused vaccines including HBV vaccines. Thanks to the GAVI Alliance, children in many developing and less-developed countries in Africa and Asia have accessed to immunization against HBV, which makes the plan of integrating HBV vaccine into countries' immunization programme more feasible.

The results of the review show that immunization (either universal or targeted) against HBV is cost-effective from the health care point of view and cost-savings for the society in the long run in terms of avoiding future treatment cost. Obviously, in general, immunization is a good preventive care practice. However, to make economic evaluations more rigorous and more properly designed, studies on cost-effectiveness against HBV should be conducted in the developing world. Their outcome will assist policy-makers in designing appropriate health interventions and for planning the necessary resource allocation for executing HBV vaccination strategies. Universal vaccination in developing countries generally provides a relevant issue, in order to let policy makers know about financial needs and cost-effectiveness in implementation. In the end this all contributes to the battle against life- threatening diseases caused by the HBV.

Conclusion and Expert Commentary

On the basis of the available international literature on the economic evaluations of HBV immunization in the developing world, we conclude that it is cost-effective to implement universal immunization against HBV. Vaccine price is a dominant factor constraining developing countries from effectively implementing HBV vaccination universally. Possible options to overcome this problem include combined vaccines and support from the international community. Still, further high-quality economic evaluations are needed in the near future, for example, using dynamic models for simulating the spread of HBV in populations in developing countries.

Five-Year View

WHO has recommended that developing countries implement universal immunization against HBV. Each region has developed its own plan in order to achieve this goal. For example, the Western Pacific Region has set a goal to reduce chronic HBV infection rate to less than 2% by 2012 among children of five years old. Achieving this will however have high costs attached to it. On this issue and in general, decision makers in these countries must make choices about the best way to spend the limited resources available for the health of their populations. To be able to help policy makers to take evidence informed policy decisions on the issue, the research community must come up with convincing and locally relevant evidence. Therefore, high quality economic evaluations have to be done on the cost-effectiveness of HBV immunization in different settings in the next five years. The cost-effectiveness of combined vaccines also deserves to be explored in the near future. Such combined vaccines may present options for relevant efficiency gains and cost savings. Such evidence would also be critical to gather financial support from international donors (e.g. GAVI fund). Countries that have more established infant immunization programmes, higher capacity and greater resources should consider having universal immunization programmes at least for children under 5 years old. Also, in the next 5

years, developing countries should develop protocols or guidelines on different strategies for vaccination of older children (e.g. catch-up or patch-up) depending on the country context.

Key Issues

- We found evidence that developing countries with intermediate and high prevalence of HBV infection greatly benefit from HBV immunization. Universal immunization against HBV would have great impact in reducing endemicity and would be cost-effective in the long run.
- Evidence that the high price of the HBV vaccine was the key determinant restraining developing countries from implementing universal immunization against HBV. Combined vaccine (DPT-Hepatitis B) is a potentially a viable cost effective alternative.
- We found that dynamic modeling was not applied in any cost-effectiveness analysis study reviewed as the needed data is not available. Dynamic modeling has been applied in research on cost-effectiveness analysis studies from developed countries. It would be very valuable if in the future, when data is available, developing countries look into the possibilities of applying dynamic models in their economic evaluations on HBV too. This would help improve the quality and value of research on cost-effectiveness analysis of HBV in the developing world.

Author/ Publication year	Country	Study objective	Detailed analysis	Types of economic analysis	Approach
Kim *et al*, 2007 [8]	Gambia	To identify the level of affordability for hepatitis B vaccination from the payer's perspective by using affordability and cost-effectiveness affordability curves	Comparison of cost-effectiveness between vaccination and non-vaccination	CUA	Universal[1]
Vimolket *et al*, 2005 [2]	Thailand	To evaluate the cost-effectiveness by comparing four different infant vaccination strategies against HBV infection in Thailand	Comparison of vaccination strategies depending on test results: 1 screening for HBsAg, and vaccination; 2 screening for HBsAg, then HBeAg, and vaccination; 3 universal vaccination of all neonates; and 4 no vaccination	CEA	Universal
Griffiths *et al*, 2005 [9]	Mozambique	To perform a CEA on the introduction of the HBV vaccine into the routine infant immunization services in Mozambique by calculating the costs per death and DALY averted	Cost composition analysis of introducing the HBV vaccine into a country's national immunization program and cost comparison between the use of monovalent HBV vaccine and combination vaccine (DPT-Hepatitis B) for infants	CUA	Universal
Adibi *et al*, 2004 [12]	Iran	To assess the economic aspects of HBV transmission prevention for pre-marriage couples in Iran (intermediate HBV endemicity)	Evaluation of various strategies: 1 HBsAg screening for HBsAg+ person of the would-be couples followed by HBV vaccination, single dose HBIG and advice on condom protection; and 2 HBsAg screening followed by HBcAb screening in the HBsAg- spouses of the HBsAg+ persons and applying the above protocol only to HBcAb negative	CEA	
Aggarwal *et al*, 2003 [1]	India	To assess the cost-effectiveness of universal childhood immunization in India	For the analysis a specific Markov model was developed to grasp all the details of HBV in India	CUA	Universal
Prakash, 2003 [7]	India	To identify the cost-effectiveness of universal HBV immunization in India	Specific interest was directed at identifying crucial factors influencing cost-effectiveness	CUA	Universal
Hu *et al*, 2001 [4]	China	To select an optimal vaccination approach and provide basis for decision-making on the control of hepatitis B infection in the People's Liberation Army in China	Comparison of vaccination strategies with different administration strategies depending on test results: 1 screening for HBsAg prior to deciding on vaccination; 2 immediate vaccination; and 3 no vaccination	CUA	Targeted
dmunds, 2000 [10]	Ethiopia	To identify the cost-effectiveness of adding HBV vaccine into EPI of Ethiopia	Cost composition analysis of introducing hepatitis B vaccine into a country's national immunization program	CEA, CMA	N/A
Liu *et al*, 1995 [3]	China	To estimate the cost-benefit of vaccinating newborns against HBV	A decision-tree model was explicitly developed to analyze costs and benefits	CBA	Universal
Hall *et al*, 1993 [11]	Gambia	To estimate cost-effectiveness of introducing the HBV vaccine into the national immunization program in the Gambia	Cost composition analysis was applied using incidence of liver cancer and registered hepatitis B as indicators and specific comparison between the use of the monovalent HBV vaccine and combination vaccine (DPT-Hepatitis B) for infants	CEA	Universal

[1]Immunization give to the whole general population or to all within a certain age group of the population (newborns, adolescents, adults, and so on)
[2]Immunization programs selectively targeting individuals at risk of hepatitis B virus
CBA: Cost-benefit analysis; CEA: Cost-effectiveness analysis; CUA: Cost-utility analysis; DALY: Disability-adjusted life year; DPT: Diptheria/pertussis/tetanus; HBcAb: Hepatitis B core antibody; HBIG: Hepatitis B immunoglobin; HBsAg: Hepatitis B surface antigen; NA: Not available

Table 2 Economic evaluations on hepatitis B vaccination in developing and low-income countries as published in the international literature between 1993 and January 2008

Authors (country, year)Original price level	Methods and perspective	Disease-related treatment costs	Base case discount rates (%)		Target groups	Vaccination costs per vaccinated person (US$ 2000)	Vaccination strategies: results (US$ 2000)
			Costs	**Effects**			
Kim *et al.* [8] (Gambia, 2007) (2002 Dalasi)	Static model: single birth cohort Perspective : society and health care payer	NA	3	3	Infants	NA	$41.45/averted DALY (societal perspective) $24.69/averted DALY (payer's perspective Cost-saving from a societal perspective
Griffiths *et al.* [9](Mozambique, 2005) (2001 Metical)	Static model : single closed cohort followed to age 40-60 years (time span: 40 years) Perspective: Society	NA	3	0 or 5	Infants	$0.81 (monovalent vaccine) $3.6 (DTP-Hepatitis B)	$163.30/death averted ($687.16/discounted death averted) (monovalent vaccine) $13.76/averted DALY ($17.43/discounted averted DALY) (monovalent vaccine)
Sahni *et al.* [6] (India, 2004) (2001, Rupee)	Static model: single closed cohort monitored for 1 year. Time span: 45 years Perspective: Society	NA	3	0	Newborns	$4.2	$2,909.12/QALY ($8,893.71/discounted QALY)
Adibi *et al.* [12] (Iran, 2004) (2003, Rial)	Static model: Perspective: Society and healthcare	NA	3	0	Premarriage individuals	$14.4	$202 and $197 per chronic infection prevented respectively
Aggarwal *et al.* [1] (India, 2003) (2002, Rupee)	Static model : two hypothetical cohorts Perspective : Society	NA	3	0	Newborns	$3.0	$14.48/LYG and $11.76/QALY
Prakash, [7](India, 2003)	Static model: closed cohort. Time span: lifetime Perspective: Society	NA	3	0 or 3	Newborns	$2.25	$47.86/DALY
Hu et al. [4] (China, 2001)	Static model: closed cohort. Time span : 5 years Perspective : Society	NA	NS	NS	People's Liberation Army soldiers	NA	DALY of $57.18 (screening followed by vaccination) DALY of $61.89 (immediate vaccination)
Edmunds [25]10] (Ethiopia, 2000) (1996, Ethiopian Birr)	Perspective: healthcare	NA	6	NS	Infants	$1.5	NA
Liu et al. [3](China, 1995)	Perspective: society	NA	NS	NS	Newborns	NA	BCR from 42.41 to 48.01
Hall et al. [11](Gambia, 1993)	Perspective: society	NA	6	NS	Infants	$3	US$150-200 per death averted

BCR: Benefit-cost ratio; DALY: Disability-adjusted life year; DPT: Diptheria/pertussis/tetanus; HBsAg: Hepatits B surface antigen; LYG: Life year gain; NA: Not available; NS: Not specified

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CHAPTER 3

Cost-of-illness of chronic hepatitis B infection in Vietnam

Hong Anh T. Tu

Arthorn Riewpaiboon

Herman J. Woerdenbag

Hoa. H. Le

Diep M. Le

Maarten J. Postma

Shu Chuen Li

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Summary

Objectives: To estimate the total financial burden of chronic hepatitis B (CHB) infection for Vietnam by quantifying the direct medical, the direct non-medical and indirect costs among patients with various stages of CHB infection

Methods: Direct medical cost data were retrieved retrospectively from medical histories of inpatients and outpatients in 2008 from a large referral hospital in Hanoi, Vietnam. Direct non-medical and indirect costs data were obtained from face-to-face interviews of outpatients from the same hospital. The treatment cost per patient per CHB infection stage was multiplied by the total estimated patients in Vietnam to get the total cost-of-illness for the nation.

Results: Nationally, the total cost attributable to CHB infection and its complications in 2008 was estimated to be approximately US$ 4.4 billion with the direct medical cost accounting for about 70% of that estimate. The cost of antivirals was the major cost driver in treating chronic HBV infection. The per-patient total annual direct medical cost increased with the severity of the disease with the estimated costs for CHB infection and hepatocellular carcinoma as US$ 450.35 and US$ 1,883.05, respectively. When compared with the 2008 gross domestic product (GDP) per capita of around US$ 1,024, the financial burden of treating chronic HBV infection is very high in Vietnam.

Conclusion: This study confirmed that chronic HBV infection poses a significant financial burden for the average patient and that lacking treatment would become a social issueis a social issue in Vietnam. Although vaccination against HBV has been universally implemented, more healthcare investment and the greater availability of affordable medications are still needed to attain equity in proper treatment for patients with HBV infection.

Introduction

Hepatitis B virus (HBV) is one of the most prevalent blood-borne viruses worldwide with chronic HBV infection afflicting over 350 million people [1]. Major clinical consequences of HBV infection include liver failure, cirrhosis and hepatocellular carcinoma (HCC) [2,3]. These complications lead to more than one million deaths each year [3-5]. Thus, HBV infection is an important public health problem, especially for developing countries where the endemicity is often either intermediate or high.

Vietnam is one such high-endemic country for HBV infection [6]. Population surveys from the two biggest cities, Hanoi and Ho Chi Minh City, have shown a positive hepatitis B surface antigen (HBsAg+) rate of 9-14% [7,8]. High HBsAg+ prevalence in Vietnam is supported by another small survey of children in rural regions. In this survey, the HBsAg+ rate was 19.5% [9]. While there is very little data in Vietnam on the proportion of patients who were HBsAg+ and have chronic hepatitis B (CHB) infection, cirrhosis or HCC , the international literature has reported that 75-80% of patients with CHB, 34% of patients with cirrhosis, and 72% of patients with HCC were also HBsAg+ [10]. Hence, chronic HBV infection and the resulting liver diseases would pose a heavy burden for the Vietnamese healthcare system.

For the average Vietnamese patient, whose annual income is around US$ 1,024 [11], the cost of treatment for diseases stemming from HBV infection is significant. Moreover, antiviral drugs remain very expensive. Comprehensive analyses of the financial burden of HBV infection in Vietnam, however, are very limited. In view of this, we conducted a cost-of-illness (COI) study of HBV infection using data from one major referral hospital in Vietnam and we aimed to extrapolate the results to the entire country. Our analyses should provide the Vietnamese decision makers some guidance on resource allocation for health, particularly for HBV related conditions.

Material and Methods

The study contains two parts: 1) quantification of the direct medical cost and 2) quantification of the direct non-medical cost and the indirect cost of HBV infection. The financial burden to the Vietnamese society is represented by the total cost (direct medical, direct non-medical, and indirect costs) multiplied by the estimated number of infected subjects in Vietnam. The study protocol was approved by the Director of Bach Mai Hospital in Hanoi, where the study was carried out. Bach Mai Hospital is one of the largest hospitals in Vietnam and is a highly specialized multi-disciplinary medical facility with a focus on internal medicine. It contains 1400 beds and is the most active in treating hepatitis B patients in Hanoi.

In the cost analysis, the study followed the bottom up approach [12]. The direct medical costs were estimated from retrospective analysis whereas the direct non-medical costs and the indirect costs were obtained from patient interviews.

Part 1: Measurement of direct medical cost

Data were collected from medical and financial records of Bach Mai Hospital from 1 January to 31 December 2008. The records for all inpatients treated at the Department of Infectious Diseases and all outpatients treated at the Infectious Diseases Unit of the Outpatient Department were included.

Patients were classified into four groups: (i) chronic hepatitis B (CHB), (ii) compensated cirrhosis (CC), (iii) decompensated cirrhosis (DC) and (iv) hepatocellular carcinoma (HCC). Using the codes established by the International Classification of Diseases, 10th Revision (ICD-10), we identified and retrieved information on HBV patients classified under B18 (CHB patients), K74 (CC and DC patients) and C22 (HCC patients). Patients coded with K74 were subsequently differentiated as either CC or DC through clinical diagnosis from patient case notes.

Cost consideration

The total direct medical cost related to the treatment of chronic HBV and associated complications included clinic visit cost (outpatient visits and hospitalizations), investigation cost (laboratory tests and procedures), drug costs (antiviral drugs and other medicines) and other services (bed costs, meals, and so on).

The study assessed resource utilization based on hospital charges in 2008 and is expressed in US$ at the exchange rate of US$ 1 = VND 17,803 [13]. Because Bach Mai Hospital is a public non-profit healthcare institution with most service charges based on cost recovery, the use of charge for the estimation of costs would be the most appropriate approach [14].

Calculation of direct medical cost

The total annual direct medical cost per patient from each category of chronic HBV infection was calculated by summing the average annual cost for inpatient admission and outpatient admission as described by:

Annual cost/patient = Cost per visit x Visits per year + Cost per admission x Admissions per year

where visits per year are the aggregated visits of observed patient cases divided by aggregated observed patient cases and admissions per year are the aggregated admissions of observed patient cases divided by aggregated observed patient cases.

Part 2: Measurement of direct non-medical and indirect costs

Direct non-medical costs were defined as expenses that were due to illness but did not involve the direct purchase of medical services (e.g. travel expenses, accommodation, meals etc.). Indirect costs were earnings and productivity loss that resulted from work absence, directly attributable to the illness, by either the patient or the caregiver.

Estimations of direct non-medical and indirect costs were collected through interviews of patients treated in the Outpatient Department during the study period. Informed consents were obtained for all patients in the study. In the cases where no consenting subject for a particular category of clinical

diagnosis (described above) was available, physicians were interviewed as surrogates for their opinions on the likely costs to the patient.

In the interviews patients were asked several standardized questions including socio-demographic characteristics, patients' view on HBV infection as a financial burden, time spent for outpatient visits (including traveling time), extra expenses incurred for outpatient visits (including direct non-medical expenses), job loss as a result of HBV infections, and the need for informal care (caregivers quitting their jobs or employment of domestic help to provide care).

Calculation of direct non-medical and indirect costs

The direct non-medical and indirect costs for both working and non-working patients were calculated as described below.

Because a significant proportion (around 70%) of patients at Bach Mai Hospital resides outside Hanoi city, travel time to the hospital, expenses on travels, meals and lodging were important components of the direct non-medical cost. In this study, medical leave (i.e., number of day-offs) and time-off (i.e., number of hours taken off) were combined as one cost item in the indirect cost category while productivity loss was considered a separate cost item.

For the working group, medical leave and time-off were the components for the indirect cost. The annual cost of day-offs for medical leave was calculated by multiplying the days taken for medical leave by the average daily wage rate. The annual time-off cost for outpatient visits was calculated by multiplying the total time-off by the average hourly earnings. For daily and hourly wage calculation, a 5-day work week and an 8-hour work day were assumed.

For the non-working group, productivity loss was used as the indicator of indirect cost and was calculated using the assumption that minimum wage was the monthly wage [15].

Estimation of prevalence

To extrapolate from this hospital-based study to Vietnam's population, the values from the cost analysis were multiplied by the estimated prevalence of patients across various disease stages of chronic HBV infection. However, these prevalence data are not available in Vietnam. Consequently, data were extrapolated from results of studies on HBV infections and HBV-related cirrhosis in Vietnam in 2005, which were estimated at 10.05% and 481 per 100,000, respectively [16]. Assuming the same prevalence rate as in 2005 and extrapolating to the 2008 population in Vietnam of 86,084,547 [17], the estimated number of HBV carriers was 8,651,497 and the number with cirrhosis was 414,067. No official data on the ratio of CC to DC cases was available in Vietnam, but the ratio of CC to DC at Bach Mai Hospital was 8:1. Using this ratio as a guide, it would translate to approximately 368,059 CC and 46,007 DC cases.

The prevalence of HCC was estimated by multiplying the HCC incidence rate and average duration of HCC. Thus, with an incidence rate of 0.019% in 2005 [16] and the average survival of HCC patients of 1 year [18-20], the prevalence of HCC cases in Vietnam in 2008 was 16,356.

The total number of CHB cases was determined by subtracting the number of cirrhosis and HCC cases from total chronic HBV carriers, which was estimated to be 8,221,074.

Sensitivity analysis

We conducted both one-way and two-way sensitivity analyses for the cost estimates. For the direct medical cost, two one-way sensitivity analyses were performed. In the first sensitivity analysis, the lower and upper limits of the cost components (95% CI) from the direct medical cost calculation were tested and the number of patients was unchanged. In the second sensitivity analysis, the cost component remained constant and the number of patients in different chronic HBV disease stages was varied by:

- using the prevalence rate of HBV-infected patients of 8 to 16% [7-9;21]as the lower and upper limits, respectively, for estimating number of chronic HBV carriers
- using survival times from 5 months to 16 months [22-25] as the lower and upper limits, respectively, for estimating prevalence of HCC subjects
- applying the base-case ratio of liver cirrhosis cases to chronic HBV carriers of 4.79% [16] to the lower and upper limits of chronic HBV carriers to estimate the lower and upper limits for the number of liver cirrhosis cases.

For direct non-medical and indirect costs, two one-way sensitivity analyses were also performed. In the first analysis the 25th and 75th percentiles of the indirect cost were tested. In the second analysis the number of patients in each disease stage was varied as was done for the direct medical cost.

Two-way sensitivity analyses were conducted to test the combined effects of varying both the number of subjects and the treatment costs. However, only the best- and worst-case scenarios were examined.

A sensitivity analysis was performed to determine how the number of patients on antiviral treatments would change as a result of reducing the number of patients from all disease categories in the base-case by 20% while the number of patients on other medications and medical services remained constant. We then evaluated the difference in the total direct medical cost that resulted from this variation.

Results

Direct medical cost

A total of 904 patient cases (470 outpatient and 434 inpatient) were included for analysis, consisting of 226 CHB, 203 CC, 117 DC, and 358 HCC cases. The mean age of the inpatient cases was 46.4 years (range: 13-83 years) and 82.8% were males. The mean age of the outpatient cases was 39.4 years (range: 15-61 years) and 59% were males. Virtually all of the subjects (99% for inpatients and 100% for outpatients) were Kinh, the most dominant ethnic group in Vietnam.

Overall service utilization and direct medical cost analysis of chronic HBV infections by disease stages

Annual healthcare utilization for each disease stage and the estimated average annual treatment cost per patient for each disease stage are listed in Table 1 and Table 2, respectively, with the lowest cost in

CHB patients (US$ 450.35) and the highest in HCC patients (US$ 1,883.05). On average CHB patients made the fewest outpatient visits (3.84 trips/year) while DC patients made the most (5.7 trips/year). Patients with HCC had the most hospital admissions per year and patients with DC had the longest hospital stay (13.54 days).

Disease stages[1]	Chronic hepatitis B	Compensated cirrhosis	Decompensated cirrhosis	Hepatocellular carcinoma
Outpatient visits				
per person per year	3.84 (3.02-4.66)	4.31 (2.65-5.97)	5.7 (3.79-7.61)	5 (3.09-6.91)
No. hospitalizations				
per person per year	0.17 (0.12-0.22)	0.27 (0.21-0.48)	0.51 (0.37-0.65)	2.34 (2.11-4.45)
Length of stay				
per admission (days)	2.35 (2.11-2.59)	2.50 (2.02-2.98)	13.54 (9.87-17.20)	12.76 (10.87-14.65)

[1]Liver transplant program was not established at Bach Mai Hospital.

Table 1 Annual outpatient visits and hospitalizations for patients with chronic HBV infection by disease stages in Vietnam in 2008[1]

Cost composition of chronic HBV infection

Table 2 shows that the annual direct medical cost of the treatment increased with disease progression. Drug costs accounted for approximately 70% of the direct medical cost for CHB, CC and DC and 46.81% in HCC cases. Inpatient care constituted about 63% of the direct medical cost in HCC but only 2% for CHB and 5% for CC. Expenses on antiviral drugs were about 15% in CHB, 27% for CC and DC, and 2% for HCC. Expenses on laboratory tests and procedures were done extensively for HCC (~44%). Expenses on medications other than antivirals were extensively used in all disease stages accounting for more than 45% of the total direct medical cost.

Similar to the findings from the Singaporean study (26), lamivudine was the most frequently used antiviral agent in our study. This finding is likely due to the fact that lamivudine is currently the only agent reimbursed by the health insurance of Vietnam. Based on the estimated prevalence for the different chronic HBV disease stages, the base-case direct medical cost associated with the different chronic HBV stages is shown in Table 3A. The total direct medical cost in 2008 was estimated to be US$ 4 billion.

The one-way sensitivity analysis for estimating direct medical cost, where the cost components were varied and the number of patients was unchanged, revealed that the estimated direct medical cost in 2008 was between US$ 2.8 and 5.5 billion. The reverse one-way sensitivity analysis, where the cost component remained constant and the number of patients was varied, showed the estimated direct medical cost in 2008 ranging between US$ 3.2 and 6.4 billion. The two-way sensitivity analyses, however, resulted in a range of US$ 2.2 to 8.8 billion (Table 3B).

The sensitivity test, where the number of patients on antiviral treatment was reduced by 20% but the number of patients on other medical services was unchanged, resulted in a 3% reduction in the total direct medical cost (Table 4).

	Chronic hepatitis B	Compensated cirrhosis	Decompensated cirrhosis	Hepatocellular carcinoma
Total cost (US$)	450.35 (319.73-599.66)	690.43 (376.05-1,234.37)	1,114.50 (642.45-1,723.78)	1,883.05 (1,228.03-3,870.65)
Outpatient cost	439.85 (313.87-582.88)	658.18 (361.52-1,147.15)	795.60 (505.41-1,110.13)	697.90 (412.17-1,007.95)
Inpatient cost	10.49 (5.87-16.78)	32.25 (14.53-87.23)	318.90 (137.04-613.65)	1,185.15 (815.85-2,862.70)
Cost composition (%)				
Antiviral drugs[2]	14.85%	23.97%	27.06%	1.69%
Other medications[2]	54.28%	46.59%	40.73%	45.11%
Examination/laboratory tests, procedures[3], other services[4]	29.22%	28.03%	29.90%	43.97%
Consultations	1.65%	1.41%	2.32%	9.22%
Total	100.00%	100.00%	100.00%	100.00%

[2] Cost of medications = $\sum$ (Medication price$_i$ x amount$_i$)
[3] Cost of examinations and laboratory tests = $\sum$ (Unit cost$_i$ x Utilization frequency$_i$)
[4] Other services include bed cost and meals

Table 2 Average annual direct medical cost (in US$) per patient with chronic HBV infection by disease stages and cost compositions in Vietnam in 2008

A. Base-case estimates			
Disease category	**Number of patients**	**Mean direct medical cost per patient (US$)**	**Total direct medical cost per year (US$)**
CHB	8,221,074.00	450.35	3,702,344,156.83
CC	368,059.00	690.43	254,118,890.27
DC	46,007.00	1,114.50	51,274,910.42
HCC	16,356.00	1,883.05	30,799,174.35
Total	**8,651,497.00**	**4,138.33**	**4,038,537,131.88**

B. Sensitivity analysis				
Disease category	**Range of estimated number of patients**	**Range of estimated direct medical cost**	**1st one-way sensitivity analysis (US$)[5]**	**2nd one-way sensitivity analysis (US$)[6]**
CHB	6,533,015-13,058,282	319.73-599.66	2,628,542,811-4,929,838,419	2,942,130,126-5,880771,131
CC	308,322-616,644	376.05-1,234.37	138,409,271-454,322,691	212,874,616-425,749,232
DC	38,540-77,080	642.45-1,723.78	29,557,257-79,306,656	42,953,185-85,906,371
HCC	6,887-21,521	1,228.03-3,870.65	20,085,706-63,308,668	12,968,124-40,525,388
Total	**6,886,764-13,773,528**	**2,566.26-7,428.47**	**2,816,595,045-5,526,776,434**	**3,210,926,051-6,432,952,122**
Disease category	**Range of estimated number of patients**	**Range of estimated direct medical cost**	**2-way sensitivity analysis (best case scenario) (US$)**	**2-way sensitivity analysis (worst**

CHB	6,533,015-13,058,282	319.73-599.66	2,088,815,738	7,830,512,048
CC	308,322-616,644	376.05-1,234.37	115,944,939	761,168,906
DC	38,540-77,080	642.45-1,723.78	24,760,006	132,869,790
HCC	6,887-21,521	1,228.03-3,870.65	8,457,139	83,300,879
Total	**6,886,764-13,773,528**	**2,566.26-7,428.47**	**2,237,977,823**	**8,807,851,623**

CHB- Chronic hepatitis B, CC- Compensated cirrhosis, DC- Decompensated cirrhosis, HCC- Hepatocellular carcinoma
[5] Lower and upper limits of the cost components (95% CI) from the direct medical cost calculation were tested and the number of patients was unchanged
[6] Cost components remained constant and the number of patients per disease stage was varied

Table 3 (A) Base-case estimates and (B) sensitivity analyses of total direct medical cost of chronic HBV infection by disease stages in Vietnam in 2008

Direct non-medical and indirect costs

Financial burden of illness survey

A total of 51 chronic HBV patients participated in the study. The mean age of the patients was 36.12 years (range: 16-59 years) and 64.7% were males. All participants considered chronic HBV infection as a financial burden that heavily influenced the household's income.

Indirect cost components of caregivers and loss of job

None of the participants in the financial survey reported job loss, the need to employ caregivers, or family members giving up employment to provide care as consequences of chronic HBV infections. The study results showed these elements had minimal impact on indirect costs for chronic HBV carriers in Vietnam.

Direct non-medical cost and indirect cost

Because the cost distribution was skewed, the median rather than mean values were used to calculate indirect costs. Many patients were from the surrounding provinces to the hospital and their travel time often consisted of a whole working day. Thus, expenses on transportations, meals and lodging were higher than medical leave, time-off and productivity loss. The cost item representing medical leave and time-off was the second largest cost component of the direct non-medical and indirect costs (Table 4).

Disease category	Medical leave and time off	Productivity loss[7]	Transportation, meals, accommodation	Annual direct non-medical and indirect costs
CHB	1.04	15.32	22.62	38.98
CC	1.73	25.53	148.85	176.11
DC	17.63	71.49	154.11	243.23
HCC	76.19	80.27	153.12	309.58
Total	**96.59**	**192.61**	**478.70**	**767.90**

[7]Monthly cost of reduced productivity = Reported loss of productivity x monthly wage rate where:
Reported loss of productivity = number of sick days due to HBV/total number working days of a month.

Table 4 Annual direct non-medical and indirect costs (US$) of chronic HBV infection by disease stages per patient in Vietnam in 2008

From our study, the base-case estimation for total direct non-medical and indirect costs for all the different chronic HBV disease stages in Vietnam was roughly US$ 375 million (Table 5A). Results of one-way sensitivity analyses for estimating direct non-medical and indirect costs are summarized in Table 6B. Varying the cost components while keeping the number of patients in various stages unchanged resulted in a wider impact (US$ 153 million-929 million) than the reverse situation where the costs were unchanged and the number of patients was varied (US$ 299 million-600 million). In two-way sensitivity analyses where both the number of patients and the non-direct medical costs (direct non-medical and indirect costs) were varied, the total cost was between US$ 122 million and US$ 1.5 billion (Table 5B).

Cost-of-illness for chronic HBV infection estimation

When the total cost-of-illness for chronic HBV infection in Vietnam was compared for the various disease stages, chronic HBV infection was the most costly condition, estimated at US$ 4 billion. Furthermore, the ratio of direct to indirect cost increased with progression of disease severity (Table 6). Direct medical cost was the major component of the total treatment cost of HBV infection patients, accounting for approximately 70% of the expenses.

A. Base-case estimates				
Disease category	**Number of patients**	**Mean direct non-medical and indirect cost per patient (US$)**		**Total direct non-medical and indirect cost per year (US$)**
CHB	8,221,074.00	38.98		320,429,256
CC	368,059.00	176.11		44,846,050
DC	46,007.00	243.23		7,756,533
HCC	16,356.00	309.58		2,417,703
Total	**8,651,497.00**	**767.90**		**375,449,542**
B. Sensitivity analysis				
Disease category	**Range of estimated number of patients**	**Range of estimated direct non-medical & indirect cost**	**1st one-way sensitivity analysis (US$)**	**2nd one-way sensitivity analysis (US$)**
CHB	6,533,015-13,058,282	15.01 – 100.15	123,363,341-823,309,245	254,634,496-508,967,017
CC	308,322-616,644	62.30 – 244.91	22,931,607-90,141,550	37,567,371-75,134,743
DC	38,540-77,080	113.90 – 250.86	5,240,034-11,541,475	6,497,619-12,995,238
HCC	6,887-21,521	130.25 – 238.14	2,130,329-3,894,954	1,017,980-3,181,189
Total	**6,886,764 -13,773,528**	**321.45 - 834.05**	**153,665,312-928,887,224**	**299,717,467-600,278,186**
Disease category	**Range of estimated number of patients**	**Range of estimated direct non-medical & indirect cost**	**2-way sensitivity analysis (best case scenario) (US$)**	**2-way sensitivity analysis (worst case scenario) (US$)**
CHB	6,533,015-13,058,282	15.01 – 100.15	98,032,753	1,307,737,174
CC	308,322-616,644	62.30 – 244.91	19,209,723	151,022,492
DC	38,540-77,080	113.90 – 250.86	4,389,558	19,336,503

HCC	6,887-21,521	130.25 – 238.14	896,981	5,124,939
Total	6,886,764-13,773,528	321.45-834.05	122,529,015	1,483,221,108

CHB- Chronic hepatitis B, CC- Compensated cirrhosis, DC- Decompensated cirrhosis, HCC- Hepatocellular carcinoma

Table 5 (A) Base-case estimates and (B) sensitivity analyses of total direct non-medical and indirect costs of chronic HBV infection by disease stages in Vietnam in 2008

Disease category	Direct medical cost	Direct non-medical and indirect costs	Cost-of-illness	Ratio of direct medical cost to direct non-medical and indirect costs
CHB	3,702,344,157	320,429,256	4,022,773,413	11.6:1
CC	254,118,890	44,846,050	298,964,940	5.7:1
DC	51,274,910	7,756,533	59,031,443	6.6:1
HCC	30,799,174	2,417,703	33,216,878	12.7:1
Total	**4,038,537,132**	**375,449,542**	**4,413,986,674**	

CHB- Chronic hepatitis B, CC- Compensated cirrhosis, DC- Decompensated cirrhosis, HCC- Hepatocellular carcinoma

Table 6 Direct medical cost, direct non-medical and indirect costs, total cost-of-illness for different stages of chronic HBV infection in Vietnam in 2008 (US$)`

Discussion

To the best of our knowledge, this is the first cost-of-illness study for chronic HBV infections in Vietnam. Our results clearly showed that CHB infection and its complications impose a significant financial burden on the Vietnamese society and healthcare system. If all patients with CHB and its various disease stages were treated in hospitals, the total annual cost would amount to approximately US$ 4.4 billion, which is approximately 5% of the GDP of Vietnam in 2008.

In reality the Vietnamese government's expenditure on health accounted for only a quarter of the total national health expenditure with the remainder coming from patients' out-of-pocket payment (27-29). Even if the individual patient is responsible for only part of the treatment costs of chronic HBV infections, the current low Vietnamese GDP per capita of US$ 1,024 (11) would still make the partial cost a significant financial burden for the average Vietnamese patient. Furthermore, as 80% of the population works in the agricultural sector with low wages, the number of HBV patients who cannot bear these costs would be substantial and therefore many may be under-treated or untreated.

As a consequence of these costs, many patients turned to traditional medicines as an alternative. From interviews with physicians from Bach Mai Hospital, it appeared that only 1% of patients with CHB infection and other complications received hospital treatment. One suggested solution to alleviate the financial burden for individual patients seeking chronic HBV treatment is to continue and upgrade the operation of the existing Health Care Funds for the Poor (HCFP), which has been in place in Vietnam since 2000.

In our study, expenses on medications were the largest cost driver for the direct treatment cost for CHB, CC and DD. These costs accounted for more than 70% of the total direct medical cost. However, this finding differs from another published study in which laboratories tests were extensively conducted (26). The difference may be explained by the high drug prices in Vietnam.

While the prices of nucleosides are becoming less expensive, they are still very costly in Vietnam. As a result, antiviral therapy is affordable for only a small proportion of HBV infected patients. This problem is exacerbated by the higher drug prices in public pharmacies (30), where many patients with chronic HBV infections would purchase their medications. In fact, prices for drugs in general and branded drugs in particular are many times higher in the Vietnamese market than in many of the other countries in the region (31). For chronic diseases, one-month treatment cost might be equivalent to 22 days' minimum wages for generic drug and up to 50 days' wages for an innovator brand (30). Contributing factors to the high drug prices in Vietnam include an inefficient procurement process and a lack of sound regulations on mark-ups. Thus, if more generic drugs could either be manufactured domestically at a lower cost or be allowed to enter the Vietnamese market at a lower price, then affordability of chronic HBV treatment would increase as a result of the lowered drug prices. The one-way sensitivity analysis investigating the number of patients on antiviral treatment also showed that a decrease in the number of patients would result in a small reduction in the total direct medical cost. Resource utilization pattern for the direct medical costs in this study was consistent with other published studies; direct medical costs increase with disease progression (26, 32-34).

Direct non-medical and indirect cost accounted for approximately 6% of the total treatment cost for CC and DC and 12% for CHB and HCC. This study differs from other studies on the same subject in that the direct non-medical costs resulting from lodging, transportation and meals were considered. Because many chronic HBV patients reside outside of Hanoi, these costs could be quite high and even exceed the total indirect cost. This naturally would lead to the suggestion of establishing more healthcare institutions in rural areas. Improved health care access in rural areas where approximately 80% of the Vietnamese population resides would also ameliorate the common problem of patient overloading of hospitals in major Vietnamese cities.

While other studies on this topic used health insurance data [26-28], our study used medical records of Bach Mai Hospital. A study using data from the medical and financial records would not only provide a more detailed breakdown but also more accurately capture resource utilization compared to studies using health insurance data. Furthermore, hospital records allow for the identification of items not covered by health insurance and information on patients without health insurance, which represent a large proportion of the Vietnamese population.

Our study also has several limitations. One limitation is the issue of representativeness of the patient sample. Many inpatients after discharge do not return to outpatient clinics for follow-up. Ideally, they would have to go back for post-discharge assessment and therapy. However, in reality this does not happen in Vietnam for a number of reasons. Many chronic HBV patients live in provinces distant from Hanoi and are agricultural workers with very low income. Thus, it is not easy for them to travel to the

hospital for regular outpatient visits. Hence, our outpatient samples were from those who attended the outpatient clinic and may not be truly representative as evident that formal care was not required by any of the participants.

In addition, our study was confined to the northern area of Vietnam and we only collected data from one central hospital albeit the biggest in the North and not in other two regions of the country (Central and the South). However, as medications accounted for ~70% of the total cost in our study and there is little variation in drug prices across Vietnam, this would allow an extrapolation to the whole country. Likewise, minimum wage was applied in estimating medical leave and time-off for the indirect cost, and there would not be much deviation of direct non-medical and indirect cost when our results are extrapolated to different regions in Vietnam.

However, extrapolation of treatment cost collected from one hospital to the national level could be prone to overestimating the treatment cost of chronic HBV infection in Vietnam. Nonetheless, in lieu of any cost information in Vietnam, our results could be viewed as a potential scenario that provides an estimation of what the “might be” quantum of the cost to fill in an existing information gap.

Finally, we were unable to retrieve the expenditure data on traditional medicines in treatment of chronic HBV infections either; thus underestimating the total treatment costs. In Vietnam, there is a fairly large population seeking care from traditional medicines rather than western medicines despite a lack of published studies on their efficacy and safety. Besides cultural and traditional belief in traditional medicines, there is also the benefit of easier access and lower costs. Although patients may still need to travel far to access to traditional medicine, they will not need to do it regularly as traditional healers can prescribe medicines for several months if financial conditions of patients disallow frequent travels.

Even with these potential limitations, this study, as the first and only COI study on chronic HBV infection in Vietnam, still provides valuable information for health care decision makers in resource allocation and planning. The heavy financial burden presented here suggests that the continuation of universal immunization against HBV is the optimal long-term solution to minimize HBV-associated costs. Universal infant immunization against HBV in Vietnam started later than other countries in the Asia-Pacific region, however, the coverage has now reached more than 90% nationwide [29]. To reduce the prevalence of chronic HBV cases in Vietnam, catch-up HBV vaccination will also be required. Another suggestion is the implementation of universal health insurance that would at least partially subsidize the treatment cost of chronic HBV infection. However, universal health insurance would definitely require additional financial resources, which likely require support from international organizations.

Conclusion

We showed that chronic HBV infection potentially imposes a heavy financial burden on Vietnam, and patients with chronic HBV infection clearly face many difficulties in attaining the appropriate treatment. Our results showed that prices of antivirals were still very high making the chronic HBV treatment very expensive in Vietnam. If medical care for HBV infection and its complications is to be accessible to

those in need, at the least the costs of drugs must either be reduced or be subsidized for the poor. Beside the direct medical cost, direct non-medical cost was for the first time taken into consideration and appeared to be a substantial component of the indirect cost in Vietnam.

Given the high prevalence of HBV infection in Vietnam, it is imperative that steps be taken at various levels to address the problem. In addition to universal vaccination of newborns against HBV, a re-consideration of Vietnamese policies on drug pricing, treatment of chronic HBV infections, and other initiatives for the prevention of infection are required.

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CHAPTER 4

Cost-effectiveness analysis of hepatitis B immunization in Vietnam:

Application of cost-effectivenessaffordability curves in healthcare decision making

Hong Anh T. Tu,

Robin de Vries

Herman J. Woerdenbag,

Shu Chuen Li,

Hoa H. Le,

Marinus van Hurst

Maarten J. Postma

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Summary

Objectives: To perform a cost-effectiveness analysis and to identify the cost-effectiveness affordability levels for a newborn universal vaccination program against hepatitis B virus (HBV) in Vietnam

Methods: Using a Markov model, we simulated a birth cohort using 1,639,000 newborns in Vietnam in 2002 and estimated the incremental cost-effectiveness ratios (ICERs) for quality-adjusted-life-year (QALY) gained following universal newborn vaccination against HBV. Two types of analyses were performed, including and excluding expenditures on the treatment of chronic hepatitis B and its complications. In addition, we used Monte Carlo simulations to examine cost-effectiveness acceptability and affordability from the payer's perspective and constructed a cost-effectiveness affordability curve to assess the costs and health effects of the program.

Results: In the base-case analysis, newborn universal vaccination against HBV reduced the carrier rate by 58% at a cost of US$ 42 per carrier averted. From the payer's perspective, ICER per QALY gained was US$ 3.77 which is much lower than the 2002 Gross Domestic Product (GDP) per capita estimate of US$ 440. Vaccination could potentially be affordable starting at a budget of US$ 2.1 million. At the cost-effectiveness threshold of US$ 3.77 per QALY and an annual budget of US$ 5.9 million, the probability that vaccination will be both cost-effective and affordable was 21 percent.

Conclusions: Universal newborn vaccination against HBV is highly cost-effective in Vietnam. In low-income, high-endemic countries, where funds are limited and the economic results are uncertain, our findings on the cost-effectiveness affordability options may assist decision-makers in proper health investments.

Introduction

The hepatitis B virus (HBV) is one of the most prevalent blood borne viruses worldwide and is a major cause of chronic liver diseases and hepatocellular carcinoma (HCC) [1,2]. It is an important public health problem for developing countries where the endemicity is generally high. Currently, it is estimated that 350 million people in the world are chronic HBV carriers, as demonstrated by the presence of the surface antigen of HBV (HBsAg) for more than 6 months [3]. These individuals are at much higher risk of liver damage;15-40% of the infected patients eventually develop cirrhosis, liver failure or HCC, contributing to more than 1 million deaths annually [1,4,5]. Epidemiological studies have reported that the prevalence of chronic HBsAg carriers is between 8.8% and 20.5% across different populations and regions in Vietnam [6,7]. Therefore, with a population of 86 million in 2010, Vietnam would have more than 7.5 million people who are at risk of premature death as a result of HBV infection.

For high-endemic regions of chronic HBV infections, universal vaccination of newborns against HBV could be a feasible and effective solution for the prevention of HBV infection [8]. Studies have shown that vaccination against HBV is cost-effective in the developing world [9]. In Vietnam, a locally produced hepatitis B vaccine was first introduced into the Expanded Program of Immunization (EPI) in 1997, but its use was limited because of supply constraints [10]. Universal vaccination against HBV was not completed until mid-2003 with the support from the Global Alliance for Vaccines and Immunizations (GAVI) starting in 2002 [10]. To date, data is lacking regarding the impact of universal vaccination of newborns in Vietnam from a health-economic perspective. While cost-effectiveness analyses of universal vaccination against HBV have been extensively performed for many developed countries, such analyses are still scarce for the developing world [9]. However, economic studies, specific for developing countries, suggested that HBV vaccination is cost-effective and may even be cost-saving [9].

In order to aid decisions on the allocation of scarce healthcare resources, it is important to assess the cost-effectiveness of any large scale prevention programs, which require substantial resource inputs. Properly conducted economic analyses can also identify the programs that would provide the best value. In this paper we estimated the cost-effectiveness of the current HBV vaccination program for the Vietnamese situation. Additionally, cost-effectiveness affordability curves were constructed to estimate the impact of the budget on the vaccination program**.**

Methods

Modeling approach

We designed a decision analytic model to estimate the cost-effectiveness of universal vaccination against HBV compared with no vaccination. A Markov model simulating disease progression was linked to a decision tree (figure 1). The analyses were performed using the simulation software TreeAge Pro, version 2009 (Treeage Software Inc., Williamstown, MA, USA).

In the model we focused only on chronic hepatitis B infections because chronic infections comprise the largest burden of the disease and published clinical data on acute hepatitis B infections are currently

lacking for Vietnam. The Vietnamese birth cohort of 2002 was selected because universal vaccination against HBV was completed in mid-2003; thus, we can compare the impacts before and after universal HBV vaccination. Type 1 mortality was assumed (i.e., everyone lives to the life expectancy, which is 75 years in Vietnam). Each Markov cycle was defined as 1 year. The Markov health states used in the model were: (1) alive, (2) immunity, (3) chronic hepatitis B, (4) compensated cirrhosis, (5) decompensated cirrhosis, (6) HCC and (7) death.

Parameters

Probabilities

The transition probabilities used in the model represent the natural course of chronic hepatitis B infections and were obtained from international literature(through PuBMed), particularly from studies in high-endemic Asian countries where the epidemiology of hepatitis B infections is more similar to that of the Vietnamese situation (Table 1). In the cases where there were two or more studies reporting estimates for a particular transition probability, we combined the outcomes of the studies using a random effect model to account for possible heterogeneity [11].

In Vietnam the reported prevalence of HBsAg carriers was between 8.8% and 20.5% in 2002 (6;7). For the purpose of our study, we took the mean of the two values (14.7%) as the base-case prevalence of HBsAg carriers. Other parameters such as vaccine coverage, vaccine efficacy, vaccine wastage were also taken from published literature (Table 1). The vaccine coverage for newborns in Vietnam was reported to be 70% (range of 45%-94%) [12]. The efficacy of the monovalent vaccine against HBV from a 3-dose schedule (0, 2 and 4 months) was approximately 84% (range of 65%-95%) [13-15]. In Vietnam, the hepatitis B vaccine was provided in the form of two-dose vials. Thus, the vaccine wastage was estimated at 12.5% (range of 5-25%) [12,16]. Vaccine wastage was calculated by the following formula:

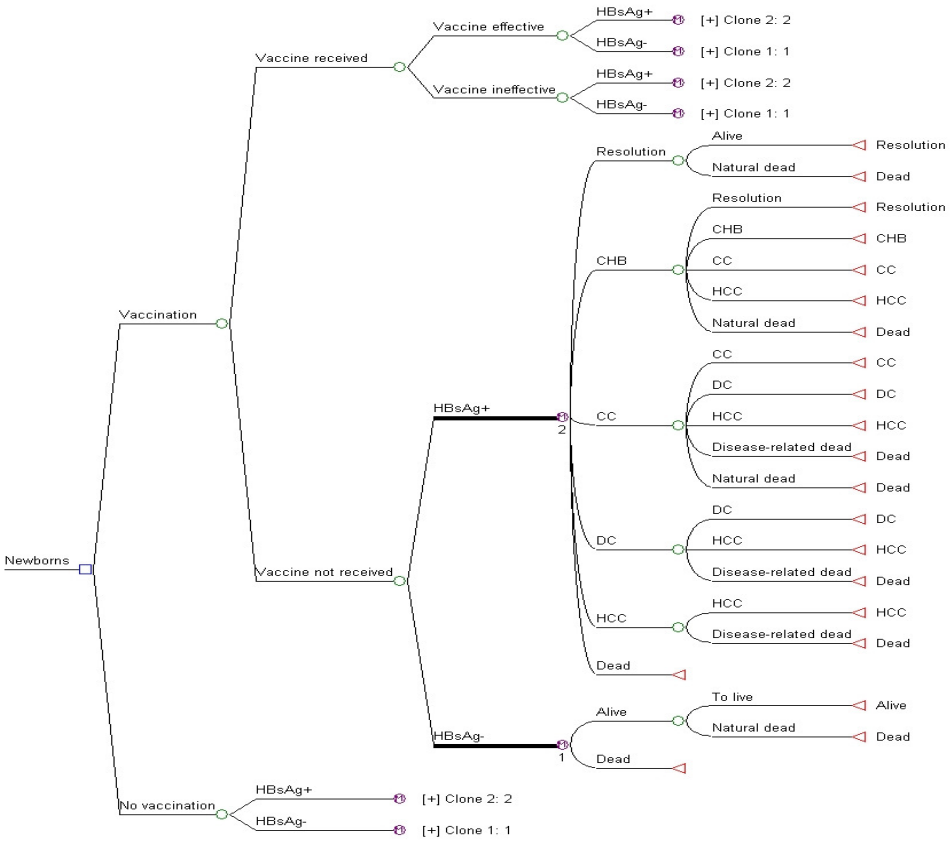
*Vaccine wastage = [(Amount of vaccines purchased-Amount of vaccines used)/Amount of vaccines purchased]*100*

Cost estimates

The cost-effectiveness analysis was performed from societal, healthcare, and payer's perspectives. The affordability analysis was conducted from the payer's perspective only. For the societal perspective, we included the direct medical costs (vaccination cost and the averted costs of treatment for chronic hepatitis B infections and hepatitis B-related cases), the direct non-medical costs (travel, meals and lodging), and the indirect costs (productivity loss). For the healthcare perspective, vaccination cost and direct medical costs were included. For the payer's perspective, where the Vietnamese government or international organizations are the main payers for vaccination programs,we included only the vaccination cost because we explicitly wanted to assess the affordability of implementing a vaccination program.

Treatment cost of chronic hepatitis B and its related progressions were taken from a previous cost-of-illness study we conducted for Vietnam (data is available upon request). However, the costs in that study were calculated for year 2008. To convert the costs back to year 2002 levels (matching the birth

cohort used in this study), we used the country's gross domestic product deflators. All costs were reported in US$ based on a conversion rate of 1 US$ = 17,803 Vietnamese Dong [18].



[1]CHB = Chronic hepatitis B; CC = Compensated cirrhosis; DC = Decompensated cirrhosis; HCC = Hepatocellular carcinoma; HBsAg = Hepatitis B surface antigen

Figure 1 Decision analytic model for estimating the cost-effectiveness of universal hepatitis B vaccination in Vietnam[1]

The hepatitis B vaccine used for newborns in Vietnam was Euvax-B and it was purchased through GAVI's financial support from 2002-2008. The cost of the vaccine alone was approximately US$ 1 [19,20]. Including the administration costs, the full cost per dose was estimated to be US$ 1.50 (range of US$ 0.5-3.5) [19,20]. In this study, we did not take into account indirect costs such as time and money spent by parents to bring the child for immunization. However, we included the direct non-medical costs and the indirect costs that resulted from complications of chronic hepatitis B infections (e.g., chronic hepatitis B, compensated cirrhosis, decompensated cirrhosis and hepatocellular carcinoma).

Quality of life (QOL)

Due to a lack of data on specific QOL estimates for Vietnam, we used QOL estimates based on various international sources (Table 1). The utility values range from 0 (death) to 1 (perfect health).

Other assumptions

In the model we made several assumptions: (i) all chronic hepatitis B infections occurred in the first year of life; (ii) the mortality and losses of QALY and LYGs that were due to acute hepatitis B infections were ignored; (iii) the simulation continued until 99.9% of the cohort had deceased; and (iv) the hepatitis B unrelated death rate was based on the age-specificity mortality of the Vietnamese population (19). In the absence of age-specific mortality rates for 2002, we used the rates from 2006 under the assumption that mortality rates remained constant between 2002 and 2006.

Sensitivity analysis

To evaluate the uncertainties associated with cost-effectiveness outcomes, we performed probabilistic sensitivity analyses for all three perspectives. The model input parameter values and the associated distributions are shown in Table 1 [21]. For each scenario we conducted 5000 Monte Carlo simulations. The results were subsequently presented in cost-effectiveness acceptability and cost-effectiveness affordability curves from the payer's perspective only. We then evaluated affordability based on the joint distribution of simulated incremental costs and health gains of HBV vaccination. Affordability analysis was done with the assumption that vaccination programs for infants were indivisible, which means it cannot be done for only a fraction of infants because in Vietnam universal hepatitis B vaccination is for every child. Using the theory and methodology described by Sendi and Briggs [22], we generated a cost-effectiveness affordability curve by capturing the points in the cost-effectiveness (C-E) plane under the horizontal lines representing different budget levels.

Several univariate analyses were performed to assess the effects of uncertainties surrounding input parameters on the outcomes. However, only the analyses from the payer's perspective are shown. The parameters included in the univariate analyses were vaccine coverage, vaccine wastage, vaccine price, vaccine efficacy, and HBV prevalence rate.

Outcome measurement

The two effectiveness outcomes investigated in the model were life-years-gained (LYG) and quality-adjusted-life-year (QALY). In addition, we calculated the ICER per LYG and per QALY for different scenarios (vaccination vs. no vaccination).

Parameter	Base-case estimates	Range	Distribution	References
HBV prevalence (%)	14.70	8.80-20.50	Triangular	[6,7]
Vaccine coverage (%)	70.00	45.00-94.00	Triangular	[12]
Vaccine efficacy (%)	84.00	65.00-95.00	Triangular	[13-15]
Vaccine wastage (%)	12.50	5.00-25.00	Triangular	[12;16]
Immunization cost/child (US$)	4.50	1.50-10.50	Triangular	[19;20]
Disease progression				
Outcome from chronic hepatitis B				
Resolution	0.006183		Gamma (26.56, 4295.75)	[24-26]
Chronic hepatitis B	#[1]			
Compensated cirrhosis	0.022989		Gamma (32.98, 11434.66)	[27-31]
Hepatocellular carcinoma	0.009100		Gamma (10.27, 1128.91)	[24,26-28,30,32-35]
Disease non-related deaths	Life-table		Beta	[23]
Outcome from compensated cirrhosis				
Compensated cirrhosis	#			
Decompensated cirrhosis	0.069139		Gamma (58.66, 848.48)	[37,38]
Hepatocellular carcinoma	0.016121		Gamma (5.72, 354.72)	[37]
Disease-related death	0.033146		Gamma (11.04, 333.05)	[3,29,39]
Disease non-related deaths	Life-table		Beta	[23]
Outcome from decompensated cirrhosis				
Decompensated cirrhosis	#			
Hepatocellular carcinoma	0.05		None	[40]
Disease-related deaths	0.245262		Gamma (39.29, 160.21)	[41]
Outcome from hepatocellular carcinoma				
Survival	0.088710		Gamma (232.75, 2623.75)	[42,43]
Disease-related death	#			
Cost estimates (US$)				
Treatment cost (Healthcare perspective)				
Chronic hepatitis B	270		Gamma (535.2326; 1.98155)	Data available upon request
Compensated cirrhosis	564		Gamma (348.5901; 0.61709)	
Decompensated cirrhosis	1559		Gamma (10515.865; 6.74428)	
Hepatocellular carcinoma	1901		Gamma (13148.086; 6.91638)	
Treatment cost (Societal perspective)				

Chronic hepatitis B	347		Gamma (885.83; 2.55)	
Compensated cirrhosis	746		Gamma (607.98; 0.81)	
Decompensated cirrhosis	1774		Gamma (13615.48; 7.67)	
Hepatocellular carcinoma	2111		Gamma (16222.215; 7.68)	
Discount rate (%)	0 or 3			
Quality of life (QoL)				
Chronic hepatitis B	0.92	0.90-0.98	Triangular	[44-46]
Compensated cirrhosis	0.82	0.75-0.95	Triangular	
Decompensated cirrhosis	0.55	0.25-0.75	Triangular	
Hepatocellular carcinoma	0.55	0.25-0.75	Triangular	

[1]The hash mark (#) is used in place of the probability expression for one branch, in order to have TreeAge Pro automatically calculate the complement during calculations.

Table 1 Base-case estimates and corresponding distributions for deterministic and probabilistic analyses

Results

Baseline results

The results of the base-caseanalyses comparing universal hepatitis B vaccination with no vaccination are presented in Table 2. Under the framework of the model, implementing universal vaccination of newborns reduced HBV prevalence by 8.66% (a change of 58%) from 14.70% to 6.04% and increased the expected LYG and the QALY gained per person by 0.80 years and 0.95 years, respectively. The cost incurred to prevent one HBV infection case was estimated to be US$ 41.79. From the payer's perspective the ICER per LYG and QALY gained were estimated at US$ 4.52 and US$ 3.77, respectively. From the societal and healthcare perspectives, universal vaccination of newborns against HBV dominated no-vaccination (i.e., more effective and cost-saving).

Parameter	Unvaccinated cohort	Vaccinated cohort	Change with vaccination
HBV carrier rate (%)	14.70%	6.04%	-8.66%
Discountedexpect life-years/person	27.21	28.01	0.80
Discounted QALY gained per person	26.94	27.90	0.95
No. of new infections for the cohort	240,114	98,927	-141,187
No. of primary liver cancer cases	2,185	900	-1,285
No. of premature deaths	2,366	975	- 1,391
Life-time cost incurred from societal perspective (US$) per person	1,151.52	478.03	- 673.49
Life-time cost incurred from healthcare perspective (US$) per person	910.00	378.00	-532.00

Cost incurred from payer's perspective (US$) per person		3.60
ICER per LYG (US$) from payer's perspective		4.52
ICER per QALY gained (US$) from payer's perspective		3.77
Cost of preventing a HBV carrier		41.79
Total vaccination cost of birth cohort (US$)		5,900,400

Table 2 Base-case results for vaccination vs. no vaccination strategies against HBV for newborns where HBV carrier rate is 14.7%, vaccine coverage is 70%, vaccine efficacy is 84%, vaccine wastage is 12.5% and discount rate is 3%

Results of one-way sensitivity analyses

The results of univariate sensitivity analyses from the payer's perspective are presented in a tornadogram, showing the ranges of ICERs for routine universal HBV vaccination compared to no vaccination (figure 2). The results revealed that ICER values were most sensitive to vaccine price and HBV prevalence rate, moderately sensitive to vaccine efficacy, and less sensitive to vaccine wastage. Because the applied model in the study was a static design, sensitive analysis on vaccine coverage did not affect the results of the ICER per LYG and per QALY (data not shown).

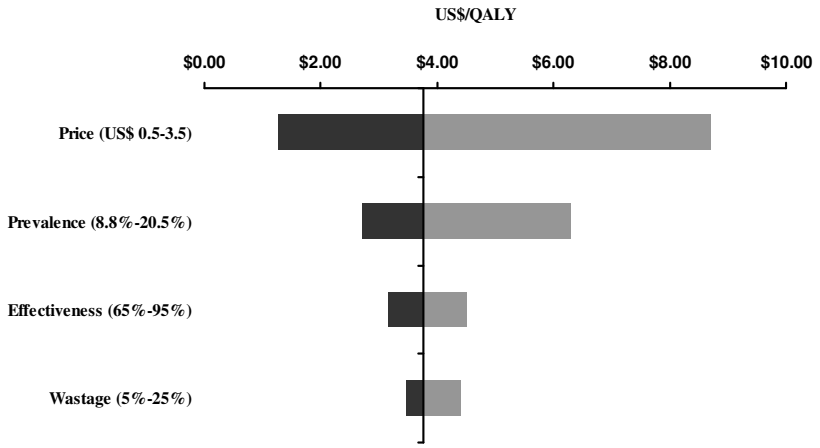


Figure 2 Results of univariate sensitivity analyses showing the ranges of ICERs for universal newborns HBV vaccination compared to no vaccination in Vietnam (payer's perspective)

Results of probabilistic sensitivity analysis

Cost-effectiveness (C-E) plane

The cost-effect pairs from 5000 Monte Carlo simulations, which accounted for the uncertainties surrounding all input parameters, are shown on C-E planes for the societal, healthcare, and payer's perspectives (figure 3). Under the societal and healthcare perspectives, all points lied in the southeast

quadrant (lower cost and greater effectiveness), confirming that from these perspectives universal vaccination dominates no-vaccination.

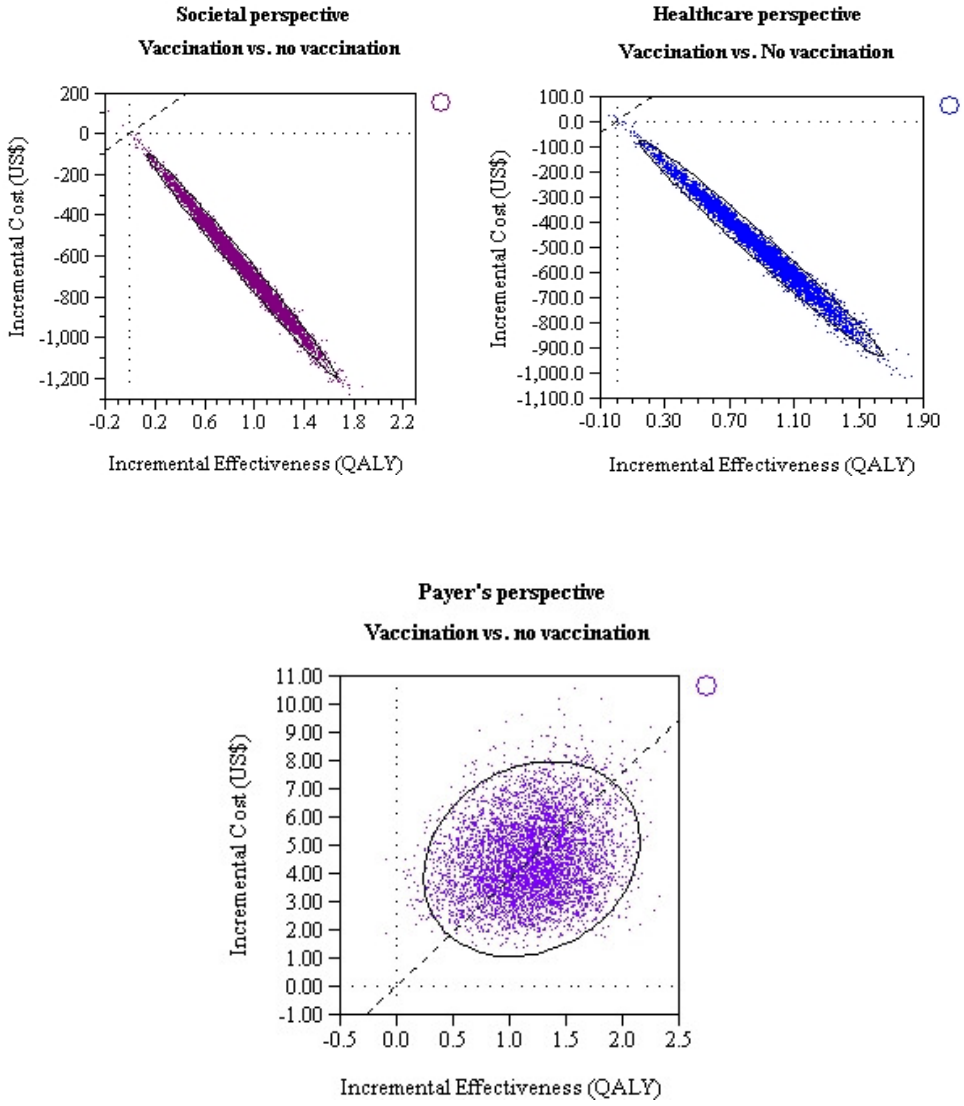
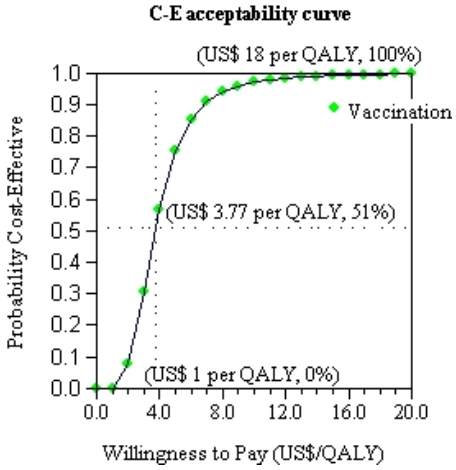


Figure 3 5000 Monte Carlo simulations of incremental cost-effectiveness ratios plotted on a C-E plane comparing vaccination vs. no-vaccination

Cost-effectiveness acceptability curve

We further presented the uncertainty of the C-E plane on a cost-effectiveness acceptability curve (CEAC) for the payer's perspective (figure 4). The CEAC reports the probability that infant universal vaccination against HBV would be cost-effective for a range of WTP thresholds. For the base-case threshold of US$ 3.77 per QALY, the probability of cost-effectiveness for the vaccination program was 51%. At the WTP threshold of US$ 18 per QALY, the probability of cost-effectiveness reached 100%, but decreased to 0% when the WTP threshold was less than US$1 per QALY.



F**igure 4** Cost-effectiveness (C-E) acceptability curve for universal newborn vaccination against HBV in Vietnam (payer's perspective

Affordability curve

To overcome the above limitation of the cost-effectiveness acceptability curves, affordability curves were generated to explain the impacts of financial resources on the vaccination program. Accounting for the uncertainties of all parameters, the curve visualizes the probabilities of affordability for a vaccination program given different budgetary levels.

The focus of this study was to assess the impact of the budget on vaccination alone. Thus, all affordability and subsequent cost-effectiveness affordability analyses were explicitly evaluated from the payer's perspective. The results indicated that the vaccination program would not be affordable when the budget is less than US$ 2 million. In contrast, vaccination would always be implementable when the budget exceeds US$ 13 million. Thus, the implementation of infant HBV vaccination in Vietnam would require between US$ 2 and 13 million. For the base-case scenario with a vaccination budget of US$ 5.9 million per year (Table 2), the probability that the program would be affordable was only 26% because of the uncertainties surrounding the program cost.

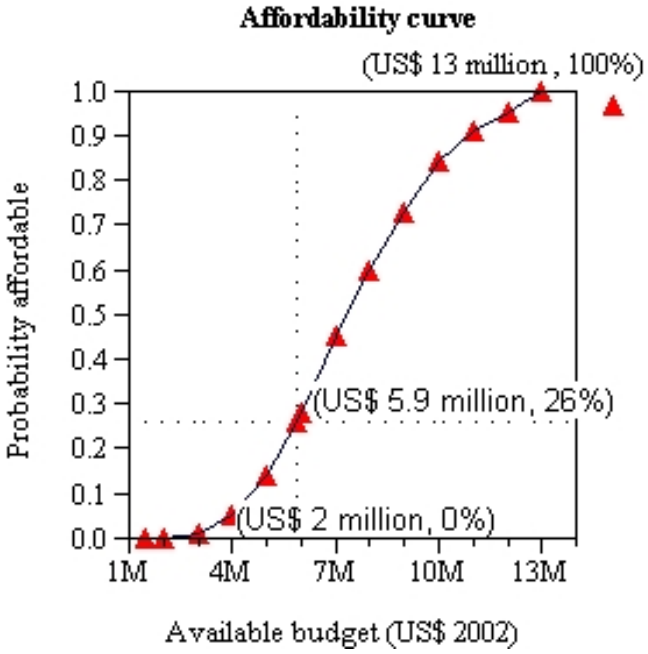


Figure 5 Affordability curve to explain the impacts of financial resources on the universal newborn HBV vaccination program in Vietnam (payer's perspective)

Cost-effectiveness affordability curve

The ideal situation is for the vaccination program to be both cost-effective and affordable. Combining the cost-effectiveness acceptability curve and the affordability curve, the cost-effectiveness affordability curve presented various scenarios for a vaccination program to be both cost-effective and affordable at different cost-effective threshold values and budgets (figure 6). The analyses showed that if the budget is less than US$ 2 million, the probability for the vaccination program to be cost-effective and affordable is 0%, regardless of the WTP threshold. In the base-case scenario with a cost-effective threshold of US$ 3.77 per QALY and a budget of US$ 5.9 million, the probability for the vaccination program to be both cost-effective and affordable was 21 percent. If the budget was increased to US$ 10 million, the program would have a 65% probability of being cost-effective and affordable at a WTP threshold of US$ 6.5 per QALY. Under the most ideal situation where the budget reaches US$ 13 million and the WTP threshold reaches US$ 18 per QALY, the vaccination program would be 100% cost-effective and affordable.

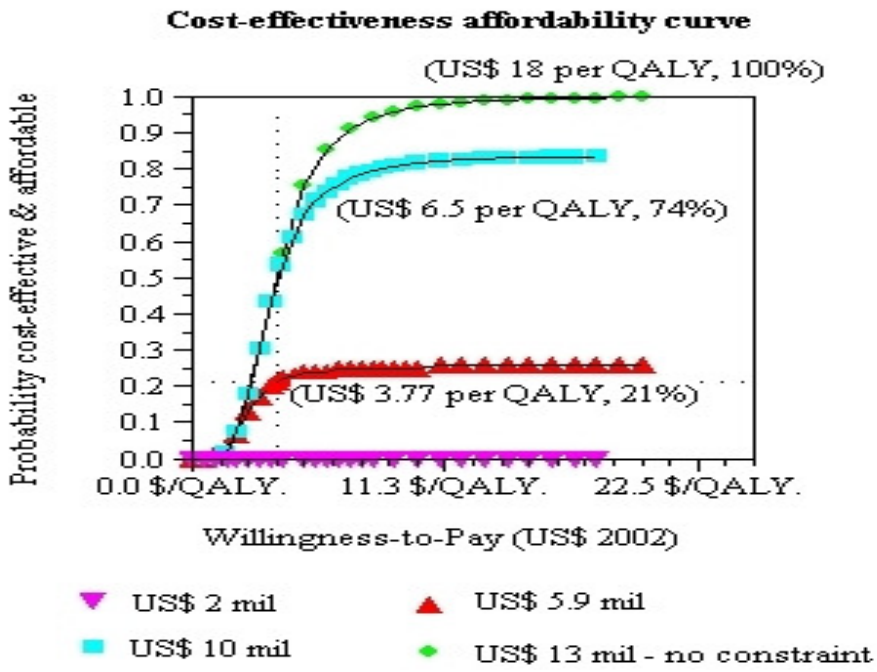


Figure 6 Cost-effectiveness (C-E) and affordability curve presenting various scenarios for universal newborn vaccination against HBV in Vietnam to be both cost-effective and affordable at different cost-effective threshold values and budgets (payer's perspective)

Discussion

The results from the baseline analyses showed that universal newborn vaccination against HBV could reduce the HBV carrier rate by approximately 60 percent. Using the World Health Organization's criteria for cost-effectiveness [47], our analyses suggest that vaccination against HBV in Vietnam is highly cost-effective from the payer's perspective. The incremental cost-effectiveness ratio was only US$ 3.77 per QALY, which is much lower than three times the GDP per-capita in Vietnam for 2002 [48]. One-way sensitivity analyses showed that vaccine efficacy and vaccine wastage had little impact on cost-effectiveness whereas changes to vaccine price and HBV prevalence rate markedly influenced the cost-effectiveness of the program.

From the societal perspective, when the treatment costs of complications were included, universal newborn vaccination not only dominated no-vaccination but also was a cost-saving strategy. Vaccinating Vietnamese newborns against HBV could potentially save US$ 1 billion by averting the treatment costs of chronic hepatitis B infections and associated complications such as compensated cirrhosis, decompensated cirrhosis and hepatocellular carcinoma.

Considering that the country's GDP per-capita was approximately US$ 440 in 2002 [48] and assuming that the cost for a fully-immunized child was US$ 4.5 as was done in this study, vaccination remained quite an acceptable and affordable option even for a Vietnamese household to pay out-of-pocket. However, with an annual birth cohort of 1,639,000 in 2002, universal vaccination against HBV for newborns could amount to a very large investment for the Vietnamese government. As investment in health is still limited in Vietnam and resource allocation among health interventions is quite competitive, the cost of universal vaccination poses a heavy financial burden when the GAVI's support for Vietnam in the EPI program is terminated. This financial implication should prompt the Vietnamese health decision makers to access the processes involved in setting priorities and allocating limited resources among different childhood vaccination programs. In this context, the importance of examining affordability and cost-effectiveness should be taken in consideration. Furthermore, our results may aid the Vietnamese government in the application for further financial support from the GAVI.

The results from probabilistic sensitivity analyses in our study partly addressed concerns regarding a number of uncertainties surrounding a universal vaccination program against HBV. By constructing the cost-effectiveness acceptability curve, this study reported the probabilities that a vaccination program is cost-effective over a range of willingness-to-pay thresholds. However, cost-effectiveness does not imply affordability. Application of the affordability curve showed that the newborn vaccination program against HBV in Vietnam could start as low as US$ 2,100,000 but becomes 100% cost-effective and affordable with an annual budget of at least US$ 13 million (figure 5). Even at this maximum level of investment, the program cost is extremely modest in comparison to the treatment costs of chronic HBV infections in Vietnam that could amount to more than US$ 1 billion. In addition, a vaccination program will gradually reduce HBV prevalence in Vietnam. Therefore, continuing the vaccination program appears to be a wise health investment.

Our study confirms that vaccination is absolutely cost-effective in Vietnam from the payer's perspective and is a cost-saving intervention from the societal and healthcare perspectives. These results are in agreement with other studies in high-endemic and intermediate-endemic countries. Because Vietnam is a high-endemic country regarding HBV infection, a universal newborn vaccination program is a "must-do" strategy.

However, this study has a few limitations. First, we applied a simple static Markov model of the disease instead of a dynamic model. Because of the lack of data and information, we opted to focus only on the chronic part of the hepatitis B infection and ignored the acute and fulminant stages of hepatitis B infection. However, morbidity from these clinical presentations was short-lasting and mortality constituted only a small proportion of hepatitis B related deaths. Therefore, the inclusion of these factors in our model would likely result in the vaccination strategy being even more cost-effective. Second, there is an absence of published epidemiological data on hepatitis B in Vietnam. As a result, we used published data from other countries in the region where extensive research on the disease had been conducted [25,31,34,35,40], and in the cases where no data were available at all, we used data from the western world. This is justified because disease progression rates appear to be stable across

populations. Third, we did not have age-specific disease progression rate and we assumed the same prevalence rate for all age groups. This might underestimate the number of infections that would occur in this birth cohort and that current prevalence is a rough estimate for infections that might occur to the population. Fourth, the study did not take into account the indirect herd-immunity effects; doing so would likely result in a more favorable cost-effectiveness for the vaccination strategy.

As the first cost-effectiveness study on universal newborn vaccination in Vietnam, the outcomes are very encouraging and informative. The results will assist policy makers in evaluating the continued support for universal vaccination against HBV infection. Our findings will also be informative for health-policy decisions in other highly endemic countries of HBV prevalence. In addition, our study demonstrated how the application of cost-effectiveness affordability curve could be used for resource planning of other health interventions, especially for new and underused vaccines. To fully evaluate impacts of HBV vaccination in Vietnam, future studies applyingdynamic models of HBV infection to account herd immunity and acute fulminant stages of the disease are recommended.

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ANNEX 1

Results of a Retrospective Database Analysis of Drug Utilization and Costs for Treatment of Chronic Hepatitis B Virus Infection in the Northern Netherlands between 2000 and 2006

Hong Anh T. Tu

Jens H.J. Bos

Herman J. Woerdenbag

Sipke T. Visser

Jan C. Wilschut

Sander van Assen

Lolkje T.W. de Jong-van den Berg

Maarten J. Postma

Clinical Therapeutics 2010; 32 (1): 133-144

Summary

Objectives: The main aims of this work were to describe patterns of medication use in the treatment of chronic hepatitis B virus (HBV) infection in patients in the northern part of the Netherlands and to compare these practices with established guidelines. In addition, the duration of use and the costs of these treatments were investigated.

Methods: We selected subjects from the University of Groningen's IADB.nl database; by 2006, the database provided information about drug utilization from 55 community pharmacies in the northern Netherlands and included a population of 528,911 individuals, of which 49% were male. Eligible subjects had received ≥1 prescription for drugs used to treat chronic HBV infection (ie, lamivudine, pegylated interferon-α2a, pegylated interferon-α2b, adefovir, tenofovir, and entecavir) between the years 2000 and 2006. The annual prevalence and cumulative incidence of HBV treatment per 1000 people covered in the database were calculated and stratified by sex. Kaplan-Meier survival analysis was used to analyze the duration of use. Drug costs in the treatment were calculated for all patients or per patient, and by drugs used per subperiod (2000–2003 and 2004–2006). Treatments for hepatitis C virus and HIV were excluded from the analyses.

Results: From the database, we identified 59 patients (46 male, 13 female), aged 25 to 60 years, who received ≥1 prescription for a medication to treat chronic HBV infection between 2000 and 2006. The overall prevalence of people using chronic treatments for HBV was between 0.03 and 0.06 per 1000 during the years of the study. The cumulative incidence of treatment was ~0.01 per 1000 per year (ranging from a high of 0.021 in 2000 to a low of 0.009 in 2006). When stratified by sex, there were more male than female subjects who received medications for HBV. Lamivudine was the most commonly prescribed drug, followed by adefovir and pegylated interferon-α2b. In 2000 and 2001, lamivudine was the only medication prescribed for the treatment of chronic HBV. From 2002 to 2006, the prescription rate for lamivudine dropped from 90% to 61%. In contrast, the prescription rate for adefovir increased from 4% in 2003 to 36% in 2006. Pegylated interferon-α2b remained stable at 8% to 11% between 2002 and 2006. Twenty-five percent of patients had stopped HBV treatment by the end of 1 year. Fifty-five percent had stopped by 3 years. Seventy-seven percent of patients received their first HBV prescription from a medical specialist. Per patient, the cost of drug therapy was highest with adefovir. From 2004 to 2006, the cost of adefovir therapy accounted for 49% of total expenditures for the treatment of chronic HBV (equivalent to €128,037; as of January 2010, €1.00 = US $1.43). The second and third most expensive drugs were tenofovir and pegylated interferon-α2b (€33,700 and €33,250, respectively). Costs incurred per patient increased over the years of the study period.

Conclusions: The overall prevalence and cumulative incidence of patients with treatments for chronic HBV were relatively low in the northern part of the Netherlands between 2000 and 2006. The prescribing and utilization patterns were in agreement with international and Dutch guidelines. Given the low numbers of prescriptions, the costs also remained relatively low.

Introduction

Hepatitis B virus (HBV) is one of the most prevalent blood-borne viruses worldwide, causing chronic liver diseases and hepatocellular carcinoma (HCC). It is an important public health problem for developing countries, where the endemicity is generally high or intermediate, as well as in developed countries. It is currently estimated that >350 million people in the world are chronically infected with HBV. They are at risk of death from liver cirrhosis and HCC, which cause the deaths of >1 million people worldwide each year [1].

In the Netherlands and in Scandinavian countries, the carrier rates for HBV are estimated to be <2% [2–4]. In the Netherlands, the estimated seroprevalence of hepatitis B surface antigen and hepatitis B core antigen antibodies are ~0.2% and ~2.1%, respectively [5]. Notified new cases of chronic hepatitis B were estimated at 1443 (0.01%) in 2005 [6].Despite relatively low endemicity, the Dutch health authorities have begun considering nationwide universal infant vaccination against HBV [7, 8]. Until now, only infants from ethnic minorities and specific risk groups (such as those whose biological parents are drug users or men who have sex with men) are provided with targeted vaccination against HBV. Cost-effectiveness is one of many issues that must be considered in the decision about whether to implement universal HBV vaccination. In addition, there may be regional differences in the occurrence of HBV infection within the Netherlands; for example, it is possible that the occurrence of HBV might be relatively low outside the major urban areas in the western Netherlands.

The availability of antiviral drug treatment of chronicHBV infection has largely improved treatment over the last decade, but such treatment has also becomes more complicated, creating the need for treatment guidelines for chronic HBV. Existing guidelines include the European Association for the Study of the Liver (EASL) [9], the Asian-Pacific consensus statement [10], and the guidelines of the American Association for the Study of Liver Diseases (AASLD) [11].

In the EASL guidelines of 2009, interferon-α (IFN-α), pegylated IFN-α (PEG-IFN-α), lamivudine, adefovir, tenofovir, entecavir, and telbivudine are now all suggested drugs for treatment of chronic HBV infection in Europe [9]. The Asian-Pacific consensus statement of 2008 provides recommendations on the treatment of chronic HBV infection using the following drugs approved in Asia: IFN-α, PEG-IFN-α2a, lamivudine, adefovir, entecavir, and telbivudine. In addition, clevudine has been approved in Korea and thymosin-α1 has been approved in several countries in Asia [8]. In the AASLD guidelines of 2007, IFN-α, PEG-IFN-α2a, lamivudine, adefovir, entecavir, and telbivudine are the recommended drugs for the treatment of chronic HBV infection [9]. The list of recommended drugs differs depending on the time when these guidelines were published. The Dutch guidelines published in July 2008 for the treatment of chronic HBV infection were based on these international guidelines [7–9]. **Table I** shows the drugs recommended for the treatment of chronic HBV infection according to the Dutch guidelines.

The main objectives of the current study of information from a claims database were to describe the actual prescribing and drug utilization patterns, duration of use, and costs of drug use in the treatment of

chronic HBV infection in patients in the northern Netherlands, and to compare our findings with national and international treatment guidelines [7–10].

Group	Name (substance)	Approval date in NL[1] (dd/mm/yyyy)	ATC-code
Interferons	Interferon alfa-2a	24-08-1999	L03AB04
	Interferon alfa-2b	09-03-2000	L03AB05
	Peginterferon alfa -2a	20-06-2002	L03AB11
Antiviral Drugs	Adefovir Dipivoxil	06-03-2003	J05AF08
	Entecavir	26-06-2006	J05AF10
	Lamivudine	29-07-1999	J05AF05

The approval date by College ter Beoordeling van Geneesmiddelen (CBG) or Medicines Evaluation Board (MEB); ATC-code: Anatomical Therapeutic Chemical classification code [30]

Table 1 List of drugs for the treatment of chronic hepatitis B included in the Dutch guidelines of 2008

Methods

Setting and Population

Information on drug use and related costs from pharmacy-dispensing data from community pharmacies in the northern Netherlands was obtained from the University of Groningen's IADB.nl database (formerly called the InterAction DataBase). Dutch patients typically register at a single community pharmacy; therefore, this pharmacy can provide an almost complete listing of the subject's prescribed drugs [15]. By 2006, the database provided information about drug utilization from 55 community pharmacies in the northern Netherlands and included a population of 528,911 individuals, of which 49% were male. The database's pharmacy information includes, among other data, the name of the drug dispensed, anatomic–therapeutic–chemical (ATC) classification, date of prescription, number of days covered by the prescription, and the number of defined daily doses based on the definition of the World Health Organization [14]. However, over-the-counter (OTC) drugs and in-hospital prescriptions are not included. Cumulatively, the database includes data for nearly 1 million people, dating back to 1999 (~6% of the total population of the Netherlands) [16, 17]. In this study, we retrospectively reviewed patients' data from 2000 to 2006.

Internal Review Board and Human Rights Issues

Because this was a retrospective analysis of information from a single database, internal review board approval was not necessary, and human-rights protocols were not required. The information in the database is anonymous, so subject identity was protected.

Selection Criteria

We selected, from the IADB.nl database, all patients who received ≥1 prescription between 2000 and 2006 for the treatment of chronic HBV infection. Such prescriptions were identified by the ATC codes listed in Table I, as well as those for tenofovir (ATC code J05AF07) and PEG-IFN-α2b (ATC code L03AB10), which are also used in daily practice and recommended by international guidelines for the treatment of chronic HBV infection [9–11]. Because some of the drugs used to treat patients with chronic HBV infection may also be used for other infections and diseases, such as HIV or hepatitis C virus (HCV), some patients were excluded to limit the sample to the patients who were most likely to have been treated for chronic HBV infection. We aimed to identify patients using drugs for HBV treatment alone, rather than combination treatment for other and/or concomitant viral infections. The strategy applied for selecting patients who were most likely to have chronic HBV infections is depicted in Figure 1.

The first step was to discriminate between groups of patients in the data obtained from the database. The drugs listed in box 1 of **Figure 1** were used as the first inputs to discriminate for HBV, but may also have been used for HIV and HCV infection treatment. The second step was to exclude HIV-infected patients, whom we defined as those who received ≥1 prescription per month of a combination of ≥2 drugs from the list of HIV drugs or to receive combined antiviral drug therapy (box 2). The third step was to exclude HCV-infected patients, identified as those who received drugs listed in box 3; for chronic HBV infection, PEG-IFN-α treatment should last >40 weeks and not be combined with ribavirin.18 Patients using IFN-α were also excluded because this drug is used in the treatment of other diseases, such as multiple sclerosis [19–22]. In the IADB.nl database, it was impossible to distinguish between patients who were using IFN-α to treat chronic HBV and those using the drug for other reasons; the information in the database is related to individual prescriptions and not to the complete medical history. Thus, to avoid the possibility of including patients who were not infected with chronic HBV, we excluded all patients, and instead considered only patients who used other drugs approved for the treatment of chronic HBV infection: lamivudine, PEG-IFN-α2a, PEG-IFN-α2b, adefovir, entecavir, and tenofovir. (Thus, IFN-α was not a criterion we considered for screening our patients and was not included in the filters shown in Figure 1.) Ultimately, the remaining patients were considered to have chronic HBV infections.

To validate the filters applied in this selection of subjects from the database, clinicians who specialize in the treatment of infectious diseases reviewed the lists of drugs used to treat HIV, HCV, and HBV. After we identified HBV-infected patients from the IADB.nl database, we randomly selected subsets of included and excluded subjects and the lists of drugs they had used. The clinicians identified the disease of these patients based on the list of prescribed drugs given to such patients. All patients in the subset were correctly identified as being infected with HBV or were correctly excluded. This validated our approach to selecting patients with chronic HBV infection.

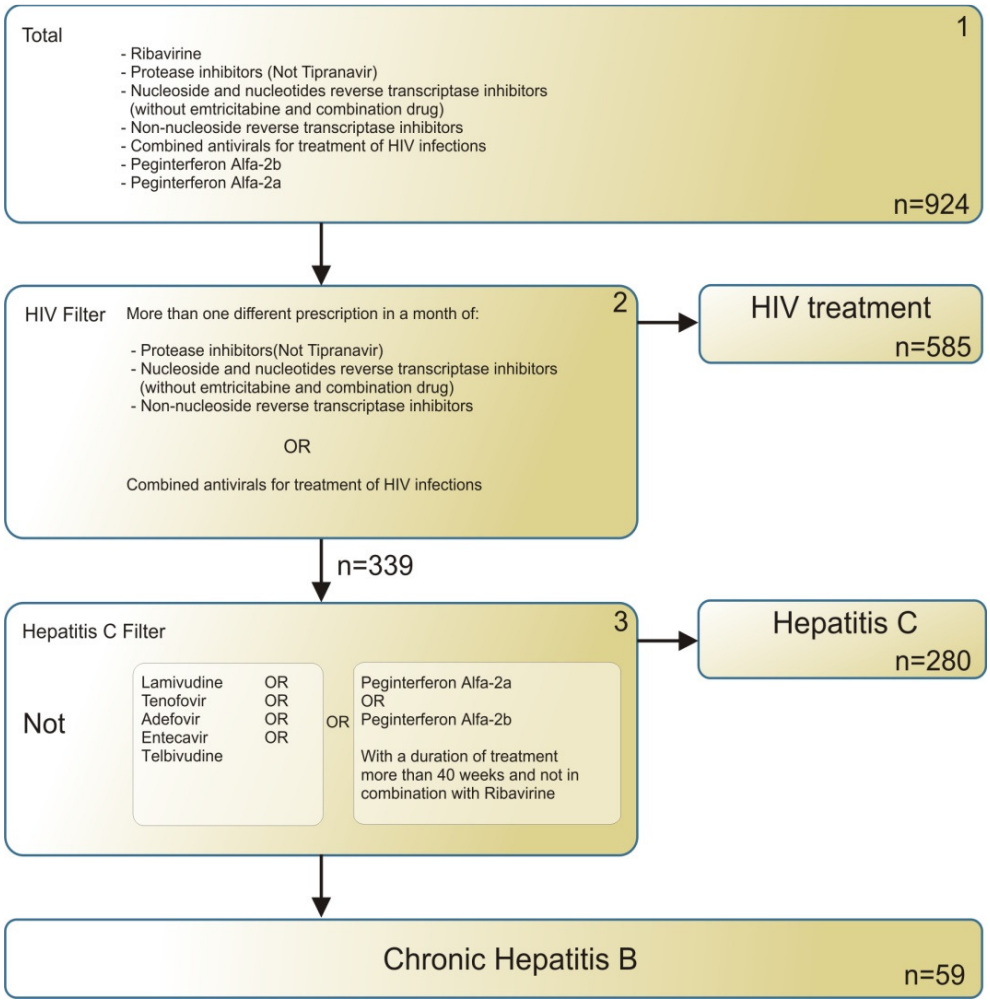

Figure 1 Flow scheme used to select chronic HBV-infected patients from the IADB.nl database

Data Analyses

The annual prevalence of chronic HBV infections per 1000 people was calculated by counting the number of patients receiving ≥1 prescription for a medication for chronic HBV infection in a given year, divided by the total population covered in the database in that year and then multiplied by 1000. We stratified prevalence by sex. Cumulative incidence was calculated by counting the number of patients who were identified as receiving new prescriptions for medications to treat chronic HBV infection, divided by the total population covered in the database in that year, multiplied by 1000. The continuity correction method, which is used for very small proportions, was used to calculate the 95% CI values [23].A Kaplan-Meier survival curve was constructed to examine the duration of drug use in the treatment of chronic HBV infection for treatment initiators using the standard methodology.

A treatment initiator was defined as someone who existed in the database for ≥180 days before the initial prescription of anti-HBV treatment. We defined 180 days as the lag time between a prescription and the subsequent prescription, as is typically done in this type of drug utilization analysis. If a subject stopped using the drug for >180 days, he or she would be counted as a treatment initiator when treatment was resumed. (The 180-day threshold for defining treatment cessation was used because it is a standard in pharmacoepidemiology research and because patients with chronic HBV infection are typically seen every 3–6 months.) The starting date was defined as the date on which a patient received his or her initial prescription of drugs for the treatment of chronic HBV. To identify the date when therapy ended, we calculated the number of days of duration for every prescription, based on the daily dosage and the prescribed number of units (eg, tablets, capsules) for each patient. The number of days between the starting date and the end date was subsequently calculated. Duration of drug use was considered to be censored if the last recorded prescription was within 180 days.

Additionally, data regarding the cost of drugs used in the treatment of chronic HBV infection were retrieved from the IADB.nl database. We calculated the total cost of the drugs for either all patients or per individual for the period from 2000 through 2006, based on the Dutch pharmacists' official price list [24].For this purpose, prescriptions of drugs for the treatment of chronic HBV infection were linked to the Z index,the official price index for all drugs and their specific formulations registered for the Dutch market. Total costs were calculated for 2 subperiods (2000–2003 and 2004–2006) to visualize the cost effects of differences in the patterns of drug prescriptions. In particular, 2003 was chosen as the cutoff because several new antiviral drugs for chronic HBV treatment were introduced to the Dutch market that year (eg, adefovir, tenofovir, entecavir) [14].We calculated the annual total drug cost per subject for chronic HBV treatment by dividing the total cost of drugs per year for all patients by the number of patients who received ≥1 prescription for the treatment of chronic HBV infection in a given year.

Results

Overall Utilization

From the IADB.nl database, we identified 59 subjects (46 men and 13 women), ranging in age from 25 to 60 years, who had received ≥1 prescription for the treatment of chronic HBV infection in the period from 2000 through 2006. The total number of prescriptions for chronic HBV medications during this period was 716 (a mean of 12.1 prescriptions per subject). The number of patients increased from 15 in 2000 to 33 in 2006 ($P < 0.001$).

Figure 2 shows the overall prevalence of patients who were treated for HBV infection, stratified by sex and year. The overall prevalence increased every year during the study period from 0.03 to 0.06 per 1000 people in the database. Prevalence among women was considerably lower than among men. Female prevalence remained stable from 2000 to 2002 at 0.01 per 1000 women in the database, slightly increased from 2002 to the end of 2003, but decreased from 2004 to 2006. The prevalence for men increased only slightly from 2000 to 2003, but it greatly increased between 2004 and 2006.

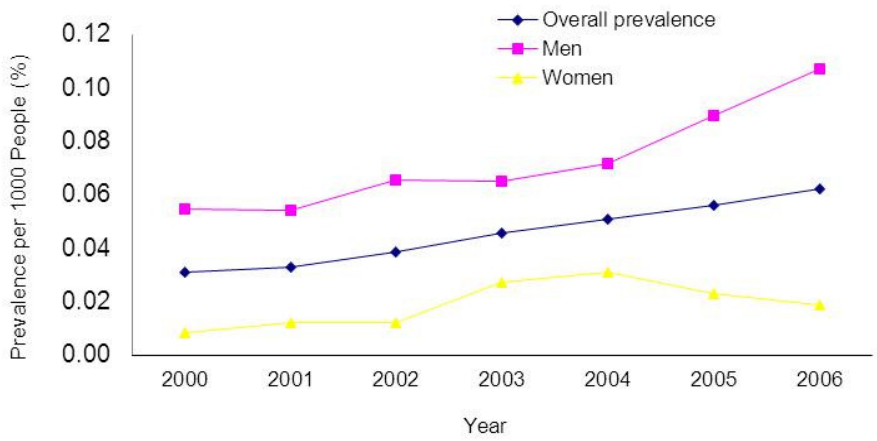

Figure 2. Prevalence of hepatitis B virus (HBV) infection per 1000 people in the IADB.nl database in a retrospective analysis of prescription claims for drugs to treat HBV infection, dispensed from 2000 to 2006, in the northern Netherland. Patients with suspected coinfection with hepatitis C virus or HIV were excluded.

The total number of patients in the population covered by the IADB.nl database is shown in **Table II**, along with annual cumulative incidence. The cumulative incidence was stable at ~0.01 per 1000 people between 2001 and 2006, ranging from an overall high of 0.021 in 2000 to an overall low of 0.009 in 2006.

Year	Population (n)	Initial patients	Cumulative incidence	95% Confidence interval[1]
2000	486,138	10	0.021	0.011-0.037
2001	489,871	5	0.010	0.004-0.024
2002	495,551	5	0.010	0.004-0.023
2003	502,146	6	0.012	0.005-0.026
2004	511,475	7	0.014	0.007-0.028
2005	518,219	5	0.010	0.004-0.022
2006	528,911	5	0.009	0.004-0.022

[1] 95% confidence interval (CI) were calculated using the 'Score with CC-method', which is applied for very small proportions [31]

Table 2 Population included in the IADB.nl database and cumulative incidence of chronic HBV infected patients per 1,000 persons per year, in a retrospective analysis of prescription claims for drugs to treat HBV infection in the northern Netherlands from 2000 through 2006.

Per-Year Utilization Patterns

Figure 3 shows changes in drug use over the study period (2000–2006). Lamivudine was the most prescribed anti-HBV drug overall. In 2000 and 2001, it was the only drug prescribed for the treatment of

patients with chronic HBV infections. In 2002, 90% of patients used lamivudine. From 2003 to 2006, the proportion of prescriptions for lamivudine among all anti-HBV drugs remained fairly stable (61%–70%). The proportionate use of PEG-IFN-α2b remained relatively constant from 2002 to 2006 (8%–11%). In the era of the new antiviral drugs (eg, adefovir, tenofovir, entecavir) being introduced to the Dutch market, adefovir became the second most prescribed drug for chronic HBV infection; the proportionate use of adefovir substantially increased from 4% to 36% between 2003 and 2006. The use of tenofovir remained stable following its introduction to the Dutch market in 2002. However, with the introduction of the other new antiviral drugs, there appeared to be a switch from monotherapy (2000, 2001, and 2003) to combined drug therapy (2002 and 2004–2006); switching patients to newer antiviral medications also appeared to be common. Based on the information from the IADB.nl database, it appeared that the only combination therapy used was lamivudine plus adefovir.

Prescribers' characteristics were analyzed for treatment initiators. In particular, 43 subjects initiated treatment during the study period. Of these patients, 10 (23%) received their first prescriptions from a general practitioner and 33 (77%) received their first prescriptions from a medical specialist. Individual drug choices were quite similar between general practitioners and specialists; for example, all initial prescriptions were for monotherapy.

We divided the study period into 2 subperiods (2000–2003 and 2004–2006) to further investigate differences in the patterns of initial prescriptions. It became obvious that the proportion of lamivudine use among treatment initiators dropped by 21% from the first to the second subperiod (from 80% to 59%). During the second subperiod (2004–2006), adefovir became the second most prescribed drug, after lamivudine, among treatment initiators (29%).

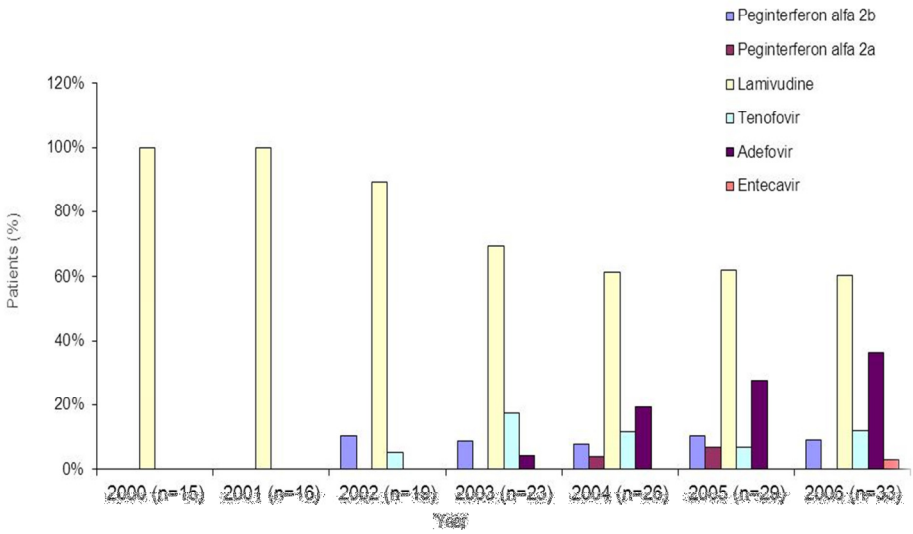

Figure 3. Distribution of prescription claims for drugs to treat chronic hepatitis B virus (HBV) infections among patients in the northern Netherlands between 2000 and 2006, based on retrospective analysis of the IADB.nl database. Patients with suspected

Duration of Use

After 3 years, 55% of users were still taking medication for chronic HBV infection (**Figure 4**). The respective proportions of patients who still used the drug after 1 and 2 years were estimated at 75% and 68%, respectively, suggesting relatively good persistence.

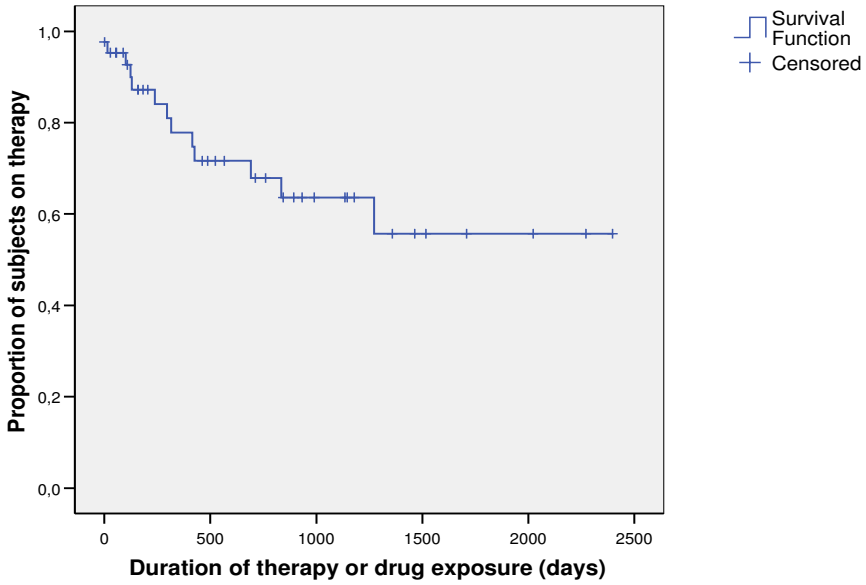

Figure 4. Kaplan-Meier survival curve showing duration of drug use in a retrospective analysis of prescription claims for drugs to treat hepatitis B virus infection, dispensed from 2000 to 2006, in the northern Netherlands, based on a retrospective analysis of the IADB.nl database. Patients with suspected coinfection with hepatitis B or HIV were excluded.

Cost Incurred by Drug Use

Figure 5 shows the cost of drugs to treat chronic HBV infection in relation to total expenses for chronic HBV treatment. No costs were incurred for entecavir and PEG-IFN-α2a in the period from 2000 to 2003 because they were not used for the treatment of chronic HBV infection until 2004, based on information in the IADB.nl database. Costs for adefovir therapy increased substantially from subperiod 1 (2000–2003) to subperiod 2 (2004–2006); in subperiod 2, they amounted to €128,037 (as of January 2010, €1.00 = US $1.43)25 and represented 49% of all expenditures for chronic HBV therapy. Although the purchase price for lamivudine was almost the same in the 2 subperiods, the proportion of overall anti-HBV treatment that was attributable to lamivudine therapy decreased from 62% in subperiod 1 to 19% in subperiod 2. Thus, expenditures for novel drugs increased over time. Expenditures for PEG-IFN-α2b remained constant between subperiod 1 and subperiod 2. The annual costs per patient for anti-HBV drugs increase from subperiod 1 (2000–2003) to subperiod 2 (2004–2006), from €950 to €2947 (Figure

6). In 2006, these per-patient costs were €171 per 1000 people in the general population, or €0.18 per capita.

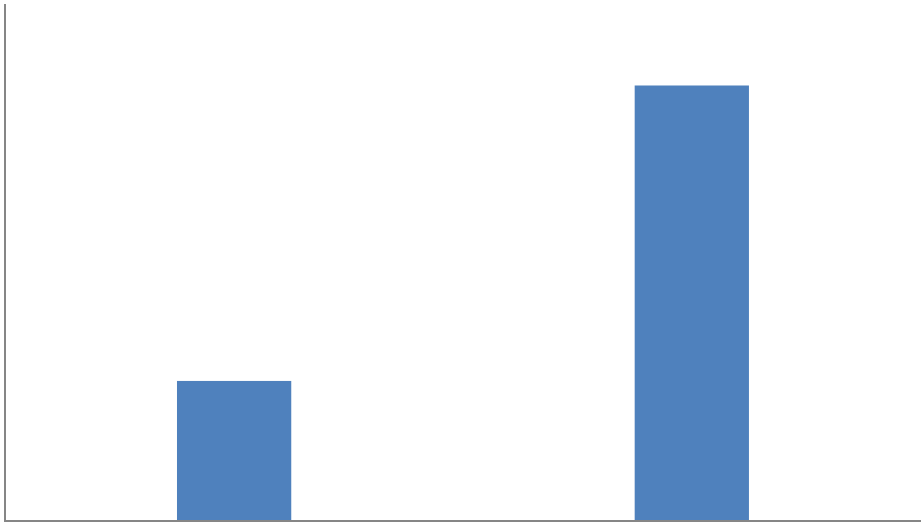

Figure 6. Annual per-patient costs (in 2 subperiods: 2000-2003 and 2004-2006) for drugs to treat chronic hepatitis B virus infection in the northern Netherlands, based on a retrospective analysis of prescription claims in the IADB.nl database. Patients with suspected coinfection with hepatitis C virus or HIV were excluded.

Discussion

Principal Findings

During the study period from 2000 to 2006, the annual prevalence of chronic HBV infection appeared to increase steadily, based on database information regarding prescriptions for anti-HBV medications. Lamivudine was the most frequently prescribed drug, followed by adefovir, as recommended by international and Dutch guidelines [9–12]. Lamivudine was the only drug prescribed from 2000 to 2001, as it was the first nucleoside analogue approved in the Netherlands for the treatment of chronic HBV infection. From 2000 to 2001, no other antiviral drugs were available on the Dutch market [14]. When more antiviral drugs were introduced to the Dutch market, the prescription rate for the older drugs (ie, lamivudine) decreased, and the prescription rate of newer drugs (e.g., tenofovir, adefovir) increased. Our results also indicated that combined therapy seemed to be more popular from 2004 to 2006; the combination of lamivudine and adefovir was the only one used. PEG-IFN-α was used for a very small and stable number of patients over the years. PEG-IFN-α2b and tenofovir were not recommended for the treatment of chronic HBV infection in the Dutch guidelines [12]. However, the utilization of these 2 drugs was stable among the population investigated in this retrospective database analysis. Prescription patterns for drugs to treat chronic HBV infections in the Netherlands were generally consistent with the recommendations of international guidelines [9–11].

In terms of duration of drug use, 25% of patients (n = 9) stopped using drugs for treatment of chronic HBV infection within 1 year after initiation; 68% (36 patients) were treated for >2 years. Fifty-five percent (34 patients) continued the therapy for >3 years. This illustrates the chronicity of the disease and related drug use; clinical guidelines call for patients to receive therapy for chronic HBV infection for an extended period, or even for the rest of their lives. In addition, most of the patients in the IADB.nl database used nucleoside or nucleotide analogues (e.g., lamivudine, adefovir, tenofovir, entecavir) rather than PEG-IFN. A disadvantage of using nucleoside or nucleotide analogues is that they typically require prolonged or indefinite therapy because the sustainability of their response after treatment discontinuation is limited [26].

In this retrospective analysis of Dutch prescription data, more men than women were treated for chronic HBV infection; the between-sex difference in infection prevalence increased over the course of the study period. This is unsurprising, given that men who have sex with men are considered to be at particularly high risk of HBV infection, which might have been increasingly detected with the risk-group–based approach to vaccination in the Netherlands in recent years [27]. Other populations at high risk for HBV infection include persons who have multiple sexual contacts, immigrants from areas of moderate or high endemic HBV prevalence, and intravenous drug users. Although the database used in the present study included information about sex, it did not include information about subjects' ethnicity. The patients identified in the IADB.nl database were in the age range of 25 to 60 years.

Adefovir, which was introduced to the Dutch market in early 2003, appeared to be the most costly drug for the treatment of chronic HBV infection. Lamivudine was the most prescribed drug; expenditures for this drug remained steady over the period investigated. Annual mean per-subject expenditures for anti-HBV drugs increased from 2000 to 2006. This may have been partly the result of higher prices for newer drugs.

Study Strengths and Weaknesses

As noted previously, this study was conducted with the IADB.nl database, which contains information about prescriptions dispensed in the Netherlands. The IADB.nl database has several strengths. It includes information about 528,911 people for a large period of time (from 1999 to the present), providing detailed dispensing records. Moreover, it also provides information about costs incurred for the purchase of drugs to treat chronic HBV infection over the course of a given year.

However, the database could not provide information about the actual use of dispensed medicines. Therefore, the present study describes patterns of drug dispensing, rather than drug use; it is possible that the 2 may differ. Furthermore, the database does not contain medical records; thus, diagnoses must be inferred from the drugs dispensed, rather than determined more directly. By trying to filter out patients who might have received antiviral medications for other diseases, we may have underestimated the number of patients with chronic HBV infection. For example, we excluded users of IFN-α because this medication may be used to treat other diseases, even though it was the first medication used to treat HBV infection. Also, no information about drugs obtained OTC or in hospitals was available; however, the role of such drugs in the treatment of chronic HBV may be minor. Despite these

limitations, the IADB.nl database makes it possible to retrospectively evaluate drug use in a relatively large and well-defined population. Further work should seek to link the IADB.nl prescription database with other databases comprising medical, diagnostic, and virologic information.

According to Dutch treatment guidelines [12], the recommended duration of therapy with PEG-IFN-α is 1 year for all patients, and the required duration of therapy with nucleoside or nucleotide analogues is longer. Our results suggest that prescriptions forchronic HBV infection in the Netherlands conform to this recommendation. The primary difference between actual practice and the Dutch guidelines was that tenofovir and PEG-IFN-α2b were prescribed for the treatment of chronic HBV infection in practice, even though the guidelines do not yet recommend such use in the Netherlands. However, the Dutch guidelines were published relatively recently, so patients who were treated for chronic HBV infection before their publication may have received therapy that did not conform to the current recommendations.

The results of the present analysis indicate relatively low prevalence and incidence of HBV infection in the Netherlands during the study period, which supports previously published findings.6 In fact, the prevalence we observed (0.03–0.06 per 1000) is low compared with the overall prevalence of chronic HBV infection in the Netherlands (0.2%) [12]. However, it should be noted that the present analysis included only patients who received pharmacotherapy, and excluded those who were likely to have been coinfected with HCV or HIV. The general prevalence of 0.2% includes patients who do not receive pharmacotherapy, as well as those with coinfections.

Our results also indicate that switching to newer antiviral drugs and prescribing combined therapy (particularly lamivudine plus adefovir) have become more common since 2004. A previously published study reported that combination therapy with lamivudine and adefovir was associated with higher rates of response and lower rates of resistant mutations than lamivudine monotherapy [28]. The combination of IFN-α or PEG-IFN-α with lamivudine is also associated with higher rates of treatment response than lamivudine monotherapy [11].

Despite the relatively low prevalence of HBV infection in the Netherlands, the Dutch health authorities are currently considering a nationwide universal infant vaccination against HBV [7,8].It should be noted that the occurrence of HBV infection might be greater in urban areas, and the epidemiology of HBV in the Netherlands may be influenced by populations originally from regions where HBV infection is more common [23,27,29,30]; more immigrants live in the large cities in the western Netherlands (e.g., Amsterdam, Rotterdam, the Hague). The IADB.nl database covers the population of the northern part of the Netherlands, where considerably fewer immigrants live. However, the low rate of treatment and modest expenditures for anti-HBV therapy in the northern Netherlands do not support the inception of a national HBV vaccination program.

Conclusions

The results of this retrospective analysis of information from the IADB.nl database indicate that the prevalence of chronic HBV infection in the northern Netherlands was modest between 2000 and 2006,

based on the numbers of prescriptions for and the expenditures for pharmacotherapy to treat the disease during the study period.

To our knowledge, this is the first study of drug utilization and costs for the treatment of chronic HBV infection in the Netherlands. Patients with chronic HBV infections may be coinfected with either HIV or HCV, but patients taking pharmacotherapy that suggested such coinfections were excluded from the present analysis. Further research is needed to explore drug utilization in HIV–HBV or HBV–HCV coinfected patients.

Acknowledgement

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PART II

Rotavirus vaccination in developing countries with focus on Vietnam

CHAPTER 5

Economic evaluations of rotavirus immunization for developing countries: a review of the literature

Hong Anh T. Tu

Herman J. Woerdenbag

Sumit Kane

Mark Rozenbaum

Shu Chuen Li

Maarten J Postma

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Summary

Diarrhoea is a leading cause of mortality for children under-five-years old, and rotavirus is identified as the main cause of severe diarrhoea worldwide. Since 2006, two rotavirus vaccines, Rotarix and Rotateq, have been available in the market. These vaccines have proved to have high efficacy in developed countries. Clinical trials are being undertaken in Asia and Africa, and early clinical results find that the vaccine significantly reduces severe diarrhoea episodes due to rotavirus (48.3% for Asia and 30.2% for Africa). The World Health Organization (WHO) recommended that rotavirus immunization be included into all national immunization programs. Based on WHO's recommendations, the Global Alliance for Vaccines and Immunization (GAVI) decided to provide financial support of rotavirus immunization in the developing world. In this review, we attempted to ascertain the cost-effectiveness of universal rotavirus immunization in developing countries. After an extensive literature search, we identified and evaluated 15 cost-effectiveness studies conducted in the developing world. The results from these studies showed that rotavirus immunization is a cost-effective strategy and the "best hope" for prevention of rotavirus-related diarrheal disease. However, rotavirus vaccines are expensive and the vaccine price appears as the most challenging and crucial factor to decision-makers regarding whether to introduce this vaccine into developing countries' immunization. All the studies concluded that rotavirus immunization is cost-effective but it might not be affordable for the developing world at present. Developing countries will definitely rely on the financial support from international organizations to introduce rotavirus vaccination. It is recommended that more cost-effective research with updated data be conducted and new rotavirus vaccine candidates be developed at cheaper price to speed up the introduction of rotavirus immunization in the developing world.

Introduction

Globally diarrhoea is a leading cause of child mortality. Annually, worldwide, around 1.8 million children under the age of five die from diarrhoeal diseases and rotavirus is identified as the most common cause of severe diarrhea [1-3]. Rotavirus infection has been reported to be responsible for more than 2 million hospitalizations and roughly 527,000 deaths [4]. The burden of disease of rotavirus infection is considered high in both developed and developing countries. However, the disease mortality caused by rotavirus is a more serious public health concern in the developing world as more than 85% of the rotavirus-related deaths occur in Africa and Asia [5]. Correspondingly, rotavirus infection and its consequences have become a heavy economic burden to both national healthcare systems and families in many low-income countries.

In addressing high rotavirus-related diarrhoeal hospitalizations and mortality rates among young children, immunization against this virus appears to be the most promising prevention strategy. This is particularly so for regions in Asia and Africa, where living conditions are poor and medical services are limited thus enhancing potentials for rotavirus infections to develop into more severe complications.

Since 2006, two approved rotavirus vaccines, Rotateq (Merck) and Rotarix (Glaxo SmithKline), are available worldwide. These vaccines have demonstrated good protection against rotavirus infection and as such a good preventive agent against rotavirus-related severe diarrhoea and hospitalizations [6-11]. Therefore, the World Health Organization (WHO) recommends the inclusion of rotavirus vaccination into countries' immunization programs [12]. However, the costs of current generations of rotavirus vaccines are high in comparison to the current budgets spending for vaccines for prevention of childhood illnesses in many developing countries [13,14].

The decision to incorporate rotavirus vaccination into national immunization programs must be based on evidence including evidence on cost-effectiveness of such a strategy. At the global level as rotavirus vaccines is introduced into national immunization programs of developing countries, often with financial support from global initiatives, monitoring the implementation of these strategies is very important to ensure that the public fund is not being used suboptimally. Part of the assessment should include conducting cost-effectiveness analyses of rotavirus immunization in developed and developing countries, both prior and after potential introduction.

In this review, we systematically summarize the international peer reviewed literature on economics and cost-effectiveness of rotavirus immunization with a focus on studies performed in the developing world. This focus is justifiable on the ground that it is in the developing world where the burden of rotavirus-related disease is the highest and the challenge of assuring vaccine performance the greatest when introducing rotavirus vaccination into countries' national immunization programs most urgent. This paper shows the results and methodologies of formal cost-effectiveness analyses, different vaccine pricing scenarios, under which rotavirus immunization might be affordable and acceptable, and challenges faced by governments of developing and low-income countries when considering to introduce rotavirus vaccines into their routine immunization schemes.

Methods

Criteria for cost-effectiveness evaluation of healthcare interventions

All cost-effectiveness studies included in this review used one of the following standards set by either the WHO or the World Bank to assess the cost-effectiveness of rotavirus immunization in countries where studies were carried out.

WHO Commission on Macroeconomics and Health

There is no formal threshold for cost-effectiveness evaluations of healthcare interventions in developing countries. The WHO's Commission on Macroeconomics and Health suggests that interventions are considered "very cost-effective", "cost-effective" and "not cost-effective" when their costs are less than the Gross Domestic Product (GDP) per capita per disability-adjusted life year (DALY), three times GDP per capita per DALY and higher than three times GDP per capita per DALY, respectively (102).

The World Bank

For developing countries (a country of low- or middle-level of GDP per capita is labeled a developing country [World Bank definition] [103]), an intervention is defined as highly cost-effective if an incremental cost effectiveness ratio (ICER) is ≤ US$ 227 per DALY averted [15]. For low-income countries (a low-income country is a country with 2008 gross national income per capita at US$975 or less [World Bank definition] [103]), an intervention is defined as highly cost-effective if an ICER is ≤ US$ 166 per DALY averted (15).

Search strategies

Economic evaluations of rotavirus vaccination were searched using PubMed and Embase databases. Keywords for retrieval were "rotavirus" or "rotavirus gastroenteritis" and "cost-effectiveness" or "cost-benefit" or "cost-utility" or "economic cost" or "cost" or "costs" or "economic evaluation" and "vaccination" or "immunization" and "developing countries" or "low-income countries". We decided to select studies between 2000 and August 2010 because rotavirus vaccines are very new vaccines, which have been available in the market only since 2006.

Eligible criteria

Further eligibility criteria stipulated that:

- Studies should be strictly classifiable in one of the formal health-economic categories of cost-effectiveness, cost-utility or cost-benefit analysis (CEA, CUA and CBA, respectively).
- Studies should be written in English and only peer-reviewed journals were considered.
- Studies were strictly conducted in developing or low-income countries.

All abstracts retrieved from the electronic databases were independently screened and reviewed by two team members (MJ Postma and HA Tu). Disagreements were resolved through discussions. Eligible abstracts were later retrieved in the full-text format and screened by another reviewer (HJ Woerdenbag) for confirming eligibility. Reference sections of the retrieved articles were manually searched for any potential missing studies.

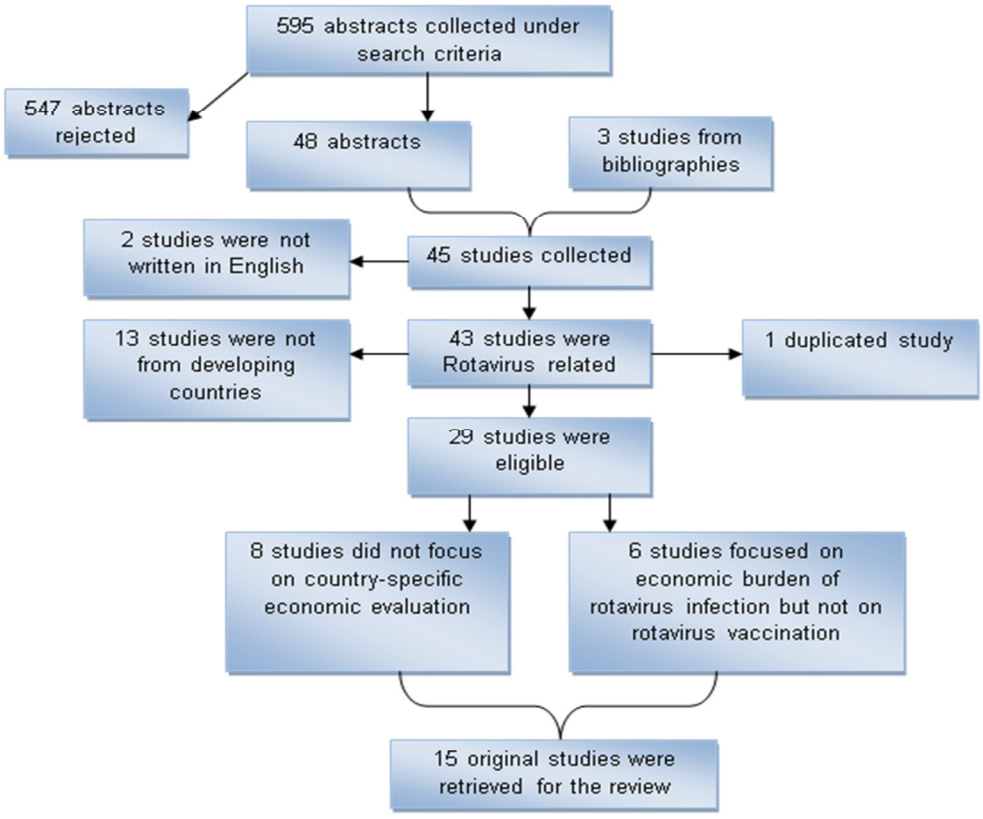

Figure 1. Search results and culling process of retrieving economic evaluations/cost-effectiveness/cost-utility/cost-benefit analyses of rotavirus vaccination/immunization

Data abstraction

Detailed information was abstracted using a pre-specified data extraction form. Items in the form included author(s), publication year, country, approach, validation/calibration of models, type of sensitivity analysis, perspectives taken and outcomes included.

In this review, we specifically focus on economic modeling, perspectives taken (societal, healthcare, payer), and discount rate as they are important factors for cost-effectiveness analyses. Generally, these aspects are well known to reflect important issues in the health economics of vaccines, especially for new and underused vaccines.

Results

General

In total, 138 potentially relevant articles published between 2000 and August 2010 were retrieved. Figure 1 describes the flow chart of the literature search. After culling according to the eligibility criteria, we found 15 studies conducted in 13 developing countries focusing on the economic evaluations of

rotavirus immunization between 2000 and August 2010. Of these, 8 studies took place in Asia [14,16-21]; 3 came from Africa [22,23] and 4 were done in Central and Latin America [24-27]. Eight studies were conducted in GAVI Alliance-eligible countries [13,14,17-20,23]. The search result and culling process are shown as per Figure 1.

The oldest study emerging from the search was from 2005 [16] and the most recent study was published in 2010 [13]. The most relevant aspects of these studies are summarized in Table 1.

Study characteristics

Most studies being review evaluated the cost-effectiveness of universal rotavirus immunization [13,14,16-21,23,24-28] except for the study by Ortega *et al. [22]*, being a cost-benefit analysis. In all studies, universal rotavirus immunization was evaluated and no study was found for targeted immunization. This is not surprising given the general notion that no clear risk factors for rotavirus infections can be identified. Thirteen studies modeled impacts of universal rotavirus immunization on children under 5 years of age [14,16-24,26-28], while two studies [13,25] modeled impacts of universal immunization of children up to only two years old. Details are provided in Table 1.

Perspectives taken in evaluation rotavirus immunization

All studies under review followed the WHO's generic protocol for monitoring the impact of rotavirus immunization [29]. All cost-effectiveness analyses were conducted from either the societal perspective (e.g., including direct medical cost, direct non-medical cost and indirect cost, n = 14) or/and the healthcare perspective (e.g., including direct medical cost and direct non-medical cost, n = 15). In other words, there is only one study, which was conducted solely from the healthcare perspective.

Detailed results on economic evaluations of rotavirus immunization

Cost-effectiveness analysis

Cost-effectiveness analyses (CEAs) were carried out in two countries in Africa [32;33]. In Malawi rotavirus infection is very common in children. The country is eligible for the highest support from the GAVI Alliance for co-financing new vaccines. Berry *et al.*conducted a CEA of universal rotavirus immunization in Malawi [13]. This study differs from others because impacts of rotavirus immunization were evaluated in children under two years old only, which can be considered as a conservative approach. Importantly, the study considered impacts of both the GAVI Alliance subsided vaccine price and the marketed vaccine price on the cost-effectiveness result. The study shows that at both the GAVI-subsided and the marketed vaccine price, universal rotavirus immunization in Malawi is cost-effective, with ICERs per DALY of US$ 5.07 and US$ 74.73, respectively. Sensitivity analyses revealed that under both vaccine pricing schemes, the cost-effectiveness was most sensitive to vaccine efficacy, vaccine price and rotavirus-related mortality of under-two-year-old children. The authors also noted that even at a relatively low preliminary estimate of vaccine efficacy of 49%, the vaccine still presents a very good value for money. Adding rotavirus vaccination to Malawi's immunization program was recommended as very advantageous to public health.

In a study conducted in Kenya it was shown that universal rotavirus immunization could prevent 55% of deaths, 65% of hospitalizations and 59% of clinic visits, all related to rotavirus infection [23]. The program would be cost-saving if the vaccine price was less than or equal to US$ 1.03 per dose (including administration). The study revealed that outpatient cost was a major part in the treatment costs (and potential savings) of rotavirus infection in Kenya. The authors concluded that when vaccine price was below US$ 7.35, 9.26, and 20.31 per dose based on thresholds of the WHO, World Bank and the Kenyan GDP per capita in 2006, which was US$ 580, respectively, rotavirus immunization would be cost-effective. However, these pricing thresholds are much higher than the GAVI-subsidized price of US$ 0.30 per dose that is offered to developing and low-income countries, thus making immunization cost-saving only if Kenya receives financial support from the GAVI Alliance. The authors also emphasized that the GAVI's additional financial support is only available for the first 5 years of vaccines implementation. After that, Kenya will have to finance rotavirus immunization by itself with the risk of becoming unaffordable to Kenyan government in the long run, although mentioned threshold prices do provide some room for still being cost-effective at higher pricing. It is notable that at the time the study was carried out, only early results of rotavirus vaccine trials were available in Africa. The authors considered it very important to continue surveillance on the impact of immunization on the disease burden in Kenya.

Several economic evaluations on rotavirus vaccination have been performed in Asia to assess the potential cost-effectiveness of the vaccine. The most recent CEA comes from Thailand. Similar to many studies in the developing world, the authors wanted to explore the feasibility if rotavirus immunization were introduced to Thailand [28]. The study highlighted that universal rotavirus immunization could be cost-effective in that country, saving 109,918 outpatient visits and preventing 419 deaths per year. The break-even price calculated from the healthcare perspective was quite high (US$ 6.2 per dose), which almost equals the current market price of available rotavirus vaccines in Thailand. Yet, for rotavirus immunization to be affordable in Thailand, the vaccine price should be lower than the current market price of US$ 7 per dose. In addition, Thailand is not a GAVI-Alliance eligible country; therefore, it will not receive concessional purchase price for rotavirus vaccines. This indicates that implementing rotavirus immunization in Thailand could be a financial challenge for the government.

Two CEAs were carried out in Vietnam. The first study, being the oldest one included in this review, explored the impact of universal rotavirus immunization from both the societal and healthcare perspectives [16]. Cost data were collected and compared for urban and rural areas. Direct medical costs were about 1.5 times higher in urban areas than in rural areas. In contrast, the total cost per outpatient visit was higher in rural than in urban areas. Hospitalizations accounted for 75% of the total direct medical cost. The authors concluded that introducing rotavirus immunization might potentially reduce 70% of related outpatient visits, 84% of hospitalizations and 83% of deaths and probably become a cost-effective strategy in Vietnam. The cost-effectiveness of the program would be most sensitive to rotavirus-related mortality rate and vaccine price. The medical break-even point occurred when the vaccine price was estimated at US$ 1.04 for a two-dose vaccination regime (Rotateq). It was clear from the study that vaccine price was the key driver for deciding whether to include rotavirus

vaccine into the Vietnamese routine immunization. At the time the study was conducted in 2005, the GAVI Alliance did not provide financial support for rotavirus vaccination yet.

The second Vietnamese study by Kim *et al.* was the first to conduct a cost-effectiveness analysis of universal rotavirus immunization in a developing and low-income country by applying a complex Markov model [19]. Many comparable studies only used a simple static model with the assumption that each child would be infected with rotavirus only once in his or her life-time. However, these authors embarked in exploring the impact of rotavirus immunization by developing a Markov model, which captured the key features of rotavirus infections such as allowing a child to get up to four infections during the child's lifetime. The model also took into account partial immunity by wild type infection that varies depending on the number of past infections. Another difference of this study compared to almost all studies in this review was the inclusion of vaccine wastage in the model and the use of a probabilistic sensitivity analysis to test the robustness of the results including parameters' uncertainty. The study revealed that cost-effectiveness was most sensitive to vaccine price, vaccine efficacy against severe diarrhoea and discount rate. In summary, the study showed that rotavirus immunization would reduce the incidence of severe cases of rotavirus gastroenteritis by 67%. Vaccination appeared to be a cost-effective strategy, as the ICER per DALY was US$ 540 and US$ 550 from societal and healthcare perspectives, respectively, values that were lower than GDP per capita in 2009 [15]. However, the authors argued that for a developing and low-income country like Vietnam, favorable cost-effectiveness of an immunization program does not necessarily implies affordability for the country's healthcare system when the resource is limited. Obviously, rotavirus vaccine is still quite expensive, thus posing a financial hurdle for its introduction into the national immunization. Nonetheless, both the studies by Fischer *et al. [16]* and Kim *et al.* confirmed the cost-effectiveness of rotavirus immunization in Vietnam [19].

In China, the Lanzhou lamb rotavirus vaccine has already been developed and licensed since 1998, but rotavirus immunization has not yet been integrated into the EPI. Wang *et al.* conducted a cost-effectiveness study to assess potential benefits of universal rotavirus immunization by using this vaccine [21]. The authors concluded that in China rotavirus immunization was cost-effective, especially in remote rural areas. In contrast to other studies, the analysis was performed from the patient's perspective where all out-of-pocket payments were considered. It was clear that in the absence of health insurance in rural areas in China, treatment cost are borne by the patient's family and thus, the patient's out-of-pocket expenditures would be the major hurdle for the introduction of rotavirus immunization. The strength of this study compared to other studies is that it did not rely heavily on many assumptions. Much data was derived empirically from a prospective, population-based diarrhoeal surveillance. The authors themselves also conducted a cost-of-illness study to collect the cost incurred due to rotavirus infection. Univariate and probabilistic sensitivity analyses showed that the cost-effectiveness of rotavirus immunization was most sensitive to vaccine price. The authors concluded that in China where 80% of people live in the rural areas, rotavirus immunization should be considered as a potential, cost-effective measure against rotavirus infection.

Wilopo *et al.* in a study in Indonesia confirmed that rotavirus immunization can effectively reduce the disease burden and rotavirus-associated healthcare cost [14]. The study evaluated the possibility to introduce rotavirus vaccine in the Indonesian national immunization program. It showed that immunizing children of less than 5 years old reduced deaths, hospitalizations, outpatient visits by 76.5%, 84%, and 70%, respectively. Immunization would become cost-saving with the vaccine price less than US$ 2.7 per dose from the healthcare perspective. Vaccine cost was the main driver influencing the program's cost-effectiveness. Similar to all other studies under review, rotavirus immunization in Indonesia was considered a cost-effective intervention. However, affordability of a rotavirus immunization program is uncertain to the government despite its obvious cost-effectiveness results. This is congruent with findings from the studies by Kim *et al*[19] and Tate *et al [23]*. Indeed, available rotavirus vaccines have been argued as costly vaccines and they face likely competition by other childhood vaccines for gaining the limited budget allocation. The authors emphasized the need for external financial support from international organizations and less-costly produced rotavirus vaccines in Indonesia in order to make universal rotavirus immunization affordable.

Two studies were carried out in the Central Asia. With a set-up comparable to other cost-effectiveness studies on rotavirus immunization, Flem *et al* performed their research in Kyrgyzstan [17], a GAVI Alliance-eligible country [105]. The authors analyzed the disease cost in terms of direct medical, direct non-medical and indirect costs due to rotavirus infection and estimated the future savings from immunization against the disease. A detailed cost composition showed that medical costs accounted for 52% of the total cost-per-episode of rotavirus admission, while the remaining 48% were generated from the direct non-medical and indirect cost. Out-of-pocket payment to take care of inpatients and outpatients contributed substantially to the total treatment cost. From a detailed sub-analysis, it appeared that families of children with diarrhea used almost 62% of their savings, which in turn reduced household expenses by 31% in order to shift funds to cover illness expenses. Through the cost-effectiveness analysis, it was calculated that rotavirus immunization for children under five years old would reduce 63% of direct medical costs or 66% of the total cost of treatment. Rotavirus immunization would be cost-effective at a vaccine price per child of less than US$ 9.41 per dose. The program would become cost-saving for the Kyrgyz government at the GAVI-subsided price of US$ 0.3 per dose and also in the range of US$ 0.5-1 per dose if the societal perspective is taken. Sensitivity analyses revealed that the program's cost-effectiveness was most sensitive to mortality rate, vaccine efficacy against mortality and vaccine price. The study was carried out at the time Kyrgyzstan received GAVI's financial support for rotavirus immunization. However, the future possibility for immunization being affordable is still questionable when the country would eventually rely on its own funding in sustaining immunization. The study's strength lies in applying the same methods for economic evaluation, which has been applied in similar studies in Eastern Europe region. This enables comparisons within the same region and income strata. However, it also encountered several similar limitations as other studies in terms of calculation of the disease costs, which are of often difficult to measure and estimated with broad ranges of uncertainty in developing countries.

The second study carried out in Central Asia came from Uzbekistan [18]. Like Kyrgyzstan, Uzbekistan is a GAVI Alliance-eligible country. In general, the country has high vaccine coverage and a well-established infrastructure for vaccines delivery. The authors conducted a cost-effectiveness analysis on universal rotavirus immunization in Uzbekistan using both the national and international data on mortality. Based on the national data, rotavirus immunization would be cost-effective at vaccine prices up to US$ 8 per dose. In contrast, using the international data, rotavirus immunization could be cost-effective at the vaccine price up to US$ 25 per dose. It was concluded that the cost-effectiveness results were most sensitive to mortality rate and vaccine price were most crucial in determining the cost-effectiveness results. Rotavirus immunization could prevent 91% of hospitalization cost, of which direct medical costs accounted for 89% (equivalent to US$ 328,154 for the healthcare system). The authors also estimated out-of-pocket expenses spent by families on hospitalizations, which was around 37% of families' incomes. This figure clearly supported that rotavirus infection is a heavy financial burden for Uzbek individuals due to the long hospitalization in the rotavirus treatment protocol in Uzbekistan. The authors suggested to shorten the hospitalization stay in order to save costs incurred by these individuals beyond healthcare insurance cover. The study also faced several limitations. The cost incurred by outpatient visits was neglected and the reported indirect cost was low as the data was collected only by interviewing women, who traditionally do not work in Uzbekistan. However, this was the first study in a former Soviet Union's country, which aimed to quantify the financial burden caused by rotavirus infection. It would definitely support health decision makers in such countries to develop a proper rotavirus immunization plan.

The most recent cost-effectiveness study on rotavirus immunization in Latin America comes from Columbia and was done by De la Hoz*et al [25]*. Different from all other studies, the authors measured the impact of using the two available vaccines (Rotarix vs. Rotateq) by comparing immunization against "no vaccination" for three hypothetical cohorts (immunization using Rotarix, immunization using Rotateq and no immunization). This approach could capture costs and effects from all possible immunization scenarios using available vaccines in the market. The results showed that rotavirus immunization could be highly cost-effective in Columbia, with the average cost-effectiveness ratio (ACER) of approximately US$ 1,063 per DALY if comparing vaccination with no vaccination. Compared to no immunization,it would bring a 27% and 25% reduction in hospitalization and death averted for Rotarix and a 30% and 28% reduction in hospitalization and death averted for Rotateq. Rotavirus immunization would become cost-saving at the vaccine price of US$ 3 per dose. Sensitivity analyses also revealed that vaccine price and vaccine efficacy are the critical variables to the cost-effectiveness results. The authors emphasized that although both vaccines have high potentials of being beneficial to the Expanded Program on Immunization (EPI) program in Columbia and could potentially reduce the mortality rate in the country, the final choice on vaccination still has to be made by the health decision makers. Using Rotateq resulted in a higher reduction rate of hospital admissions and deaths, but the three-dose course for children requires more logistics and investment. In contrast, Rotarix requires only two doses, and thus reducing a lot of direct non-medical and indirect cost of caregivers as well as the cost of the health system. The authors further suggested that selecting appropriate immunization strategies depends on

the choice of vaccines. To do that, surveillance and identification of the rotavirus strains related to the disease are needed.

Rose *et al* evaluated the cost-effectiveness of mass immunization in India using one specific rotavirus vaccine [20]. In contrast to comparable studies conducted in other developing countries where the complexity of the disease epidemiology was ignored, the authors of this Indian study took a different approach in their economic evaluation. In the model, the simulations of sequential events, from infection to symptoms development, use of health services, disease outcomes, recovery and re-infection for a heterogeneous birth cohort were explicitly taken into account. Similar to Kim *et al [19]*, the model in this study shared some key features of rotavirus infection such as incorporating partial immunity from previous infections and the possibility of being re-infected. However, the major strength of this model is that it simulates clinical events and health services while accounting the effects of each individual's age, infection and vaccination history. Vaccine efficacy was also adjusted to account for specific rotavirus strain distributions in India. Methodologically, the Markov model used in this study was the most sophisticated and most complex compared to other CEAs included in this review. The authors also concluded that universal rotavirus immunization was cost-effective in India and the results were reconfirmed by one and two-way sensitivity analyses. An interesting finding emerging from this study was the sensitivity of ICERs to the probability of using outpatient services. This in fact was the only parameter that could plausibly increase the ICERs to a value greater than one time GDP per capita while being varied.

In the most recent study from Brazil, de Soarez *et al* conducted a cost-effectiveness analysis of universal rotavirus vaccination in that country [26]. Brazil is one of the first countries, that has implemented universal rotavirus immunization using the Rotarix vaccine since 2006. The study was performed from both the societal and healthcare perspectives. In the healthcare approach, only costs incurred from public health facilities were calculated, although 30% of healthcare services in Brazil come from the private sector. The authors developed a decision tree model to simulate the disease progression in the case of rotavirus infection. The disadvantage of this model was that it only allowed each child to get one rotavirus infection during his or her lifetime. The study concluded that universal rotavirus immunization in Brazil was proven very cost-effective from both societal and healthcare perspectives. The authors argued that if the model were allowed to capture rotavirus re-infections, rotavirus immunization would become even more cost-effective. Results from sensitivity analyses showed that cost-effectiveness of immunization would be the most sensitive to rotavirus incidence, proportion of severe, moderate and mild diarrhea episodes, vaccine coverage and vaccine prices. Cost-effectiveness results were not sensitive to treatment cost or discount rate. The break-even point for immunization would be US$ 9.98 and US$ 4.24 per dose from the societal and healthcare perspective, respectively. The authors also emphasized that in a populous country like Brazil, where there is a huge regional and socio-economic difference, using only local data on costs to represent the national values might undermine the accuracy of the results. Like all other CEA studies, indirect effects of herd immunity were not considered as no data was yet available from the literature. Despite these shortcomings, results of this study appeared to be valid and robust and confirmed that introducing

rotavirus vaccination in Brazilian National Immunization Program in 2006 was justifiable from the economic point of view.

In an earlier study from Brazil, Constenla *et al* performed a cost-effectiveness analysis of rotavirus vaccination in the country [24]. The authors explored the benefits of mass rotavirus immunization by calculating the savings from the medical treatment of gastroenteritis, number of averted hospitalizations, outpatient visits, deaths and DALYs. The outcome measures of this study were different from the study by de Soarez *et al*, where the authors aimed to calculate the number of life-years saved and deaths averted [26]. It was shown that rotavirus vaccination possibly saved Brazil's healthcare system US$ 19.3 million of direct medical costs. Cost-effectiveness results were most sensitive to vaccine price, vaccine efficacy and rotavirus-associated mortality rate. The authors argued that at US$ 7-8 per dose, the program would be cost-effective according to the WHO's definition. However, it might not be affordable in Brazil if the government eventually had to fully finance the entire immunization program. As calculated, if the vaccine price was estimated at US$ 2.17 per dose, immunization would be considered cost-saving. In all cases, rotavirus immunization reduced outpatient visits, hospitalizations and deaths averted by 77%, 76% and 73%, respectively. The authors also recommended the herd immunity be considered to better estimate the full benefits of rotavirus immunization.

Valencia-Mendoza *et al* evaluated the cost-effectiveness of universal rotavirus immunization using the pentavalent vaccine, Rotateq, in Mexico [27]. The authors measured the cost-effectiveness outcomes in various dimensions: incremental cost per case prevented, death averted and life-year gained. By conducting sensitivity analyses, it was shown that the leading determinants of the cost-effectiveness results were case fatality, vaccine price, vaccine efficacy, serotype prevalence, and annual waning of efficacy. More specifically, the cost-effectiveness of vaccination was very sensitive to the number of case fatalities, which implies that the vaccine might contribute significantly more to public health in the poorer areas and where access to prompt medical care is limited, both enhancing case-fatality rates. When vaccine price was less than US$ 15 per dose, immunization would be very cost-effective. Interestingly, cost-effectiveness was insensitive to the medical cost of the disease, which is different from the findings by Rose *et al [20]*. However, the model was based on the healthcare perspective where only direct medical cost was considered. Direct non-medical cost on transportation, foods etc and indirect cost of productivity loss of caregivers were ignored but might contribute substantially if considered. Similar to the analysis in Kenya [23], affordability of immunization was again debated in spite of its potentially favorable cost-effectiveness.

Cost-benefit analysis

This review locates only one cost-benefit analysis (CBA), a study carried out in Egypt [22]. The authors aimed to calculate benefit-cost ratios (BCRs) based on various vaccine prices (worst-case, base-case, and best-case scenarios). In the base-case scenario, the BCR was 0.0726:1, which implied that introducing rotavirus immunization in Egypt would not be a cost-saving strategy explicitly from the Ministry of Health's perspective. However, rotavirus vaccination could reduce outpatient visits, hospitalizations and mortality by 91%, 90% and 88%, respectively. Rotavirus immunization also

contributed to 63% reduction in the morbidity. Sensitivity analyses showed that vaccine price was the most critical parameter followed by the rotavirus incidence, and the frequency of outpatient visits. This study looked at the financial burden of the disease only from the Ministry of Health's perspective, in which only the direct medical cost was considered. Despite its preliminary results, the study proved that immunization was clearly beneficial to the Egyptian society in terms of the health and economic gains related to reduced morbidity and mortality as well as the saved treatment cost incurred from rotavirus infection. The study's results revealed that vaccine price is a crucial factor influencing the cost-saving of the program. The authors suggested more in-depth similar research be carried out in that country.

Methodological Issues

General model characteristics

Almost all studies included in this review used simple decision tree models of rotavirus infections. Consequently, they encountered several limitations. The model applied in these studies only allows a child to be infected once with rotavirus during his/her life-time [14,17,18,21,23,24,26,27], and hence could not fully incorporate all key features of rotavirus infection (e.g., allowing more than one rotavirus infection during the life of a child). This creates some uncertainties in the ICERs as the potential impact of these key features that were not incorporated remained unexplored. To overcome these issues, Kim *el al* in the study in Vietnam developed a Markov model which allowed up to four re-infections per child [19]. In addition, their Markov model also considered partial immunity by wild type infections. In a similar analysis Rose *et al* in the study in India developed a Markov model, which additionally captured the shifts in the mix of inpatient and outpatient care that might result from decreased severity of symptoms among vaccinated children who became infected [20]. However, a common limitation that all reviewed studies encountered is the exclusion of the herd immunity in the analysis. This issue has been acknowledged and discussed in several papers[14,20,24,26,30]. Had herd immunity been considered in the analyses, the effects of universal immunization might be enormous. However, to do this, there should be data available on the magnitude of herd immunity. Partial immunization has also been reflected in the modeling across several studies [22,24,26]. For example, in the study by de Soarez *et al*, effects of immunization with one dose versus two doses of the Rotarix vaccine was considered [26]. Regarding the effect due to the type of vaccines, most of the studies modeled on the use of the monovalent two-dose vaccine (Rotarix) [14,17-20,23,24,26]. One study made a cost-effectiveness analysis by comparing the two available vaccines (Rotarix and Rotateq) [27] whereas another focused on the cost-effectiveness of Rotateq vaccine alone [34]. The study from China conducted a CEA using a Chinese-manufactured vaccine [21].

In terms of the methodology, all studies are quite similar in the way they carried out cost-effectiveness analyses. All CEAs were performed from either healthcare (only direct medical cost) or societal perspectives (including direct non-medical cost and indirect cost) or both. Only one study under review conducted a CBA [22]. The studies being review differ in the way cost items were collected and cost categories were defined. This happens because countries have different healthcare structures and the way costs collected would depend on the country-base context. Nevertheless, no study collected treatment cost of rotavirus infection throughout the entire country. Either the treatment cost was

collected in one region (urban vs. rural) or from hospitals (central vs. regional vs. district) and then extrapolated nationally. Hence, the treatment cost might not represent the true treatment cost in a country. However, these limitations were discussed in all studies.

Basic typologies of models used in the CEAs are static versus dynamic or decision tree versus Markov models. Fourteen studies in this review were CEAs with twelve studies of these CEAs used decision trees in modeling [13,14,16-21,25-28]. The similarity of these decision tree models was that they only captured one rotavirus infection per child during the first 5 years of their life. A few studies tried to develop a more complex decision tree model in an attempt to incorporate as many possible health outcomes from rotavirus infection [13,26,27]. In contrast to very simple decision tree models, Markov models would enable capturing more than one infection per child during his or her life. It is notable that two Markov models developed are quite comprehensive and sophisticated [19,20]. These models indeed could capture many additional features of rotavirus infections such as allowing multiple rotavirus infections, factoring in acquisition of partial immunity from previous infections, the changing effects of individual's age, the impacts of vaccine efficacy due to different strains, and the timing of clinical events (e.g., time interval corresponds to episodes of rotavirus infection). Nevertheless, none of the studies tried to apply dynamic modeling in conducting CEAs. This could be due to the lack of available data on rotavirus epidemiology. Herd immunity was also not taken into account in any of the studies due to the same reasons.

Discounting

Discounting refers to the translation of values obtained from one time period in future to the present value. Discounting makes current costs and benefits worth more than those occurring in the future owing to an opportunity cost to spend money now and a desire to enjoy the benefits now rather than in the future. As summarized in Table 1, in the study by de Soarez *et al* the cost and health effects were discounted at the highest discount rate of 6% [26]. The authors argued that it was considered as the most appropriate discount rate for developing countries. The remaining 14 studies in the review applied a 3% discount rate per year for both cost and health outcomes [13,14,16-25,27,28], which is in line with the WHO's guidelines on discounting [31].

Study types

Cost-effectiveness analyses (i.e., health gains expressed in integrated units adjusted for quality or infections prevented or life-years gained) were conducted in 14 studies [13,14,16-21,23-28]. Only one study [22] focused on a cost-benefit analysis (CBA). The effectiveness outcomes investigated in CEAs were life-year gained (LYG) and DALY, and quality-adjusted-life-year (QALY) was not utilized in any of the studies. Possible reasons are that it was difficult to measure quality of life of a child under 5 years old and published literature on QALYs for rotavirus-related diarrhoea is not available.

All studies being review followed the WHO's generic protocol for research on rotavirus immunization [32]. As described in Table 2, in addition to calculating ICERs in monetary value per DALY as the most common health outcome indicator, cost-effectiveness results of rotavirus immunization were also expressed in terms of reduction of hospitalizations, outpatient visits, number of deaths averted, number

of reduced severe cases, and the direct medical cost saved when comparing immunization vs. no-immunization.

Model parameters

It appeared from all analyses that the cost-effectiveness results were most sensitive to variation in vaccine price. Although cost-effectiveness results revealed that rotavirus immunization was either cost-effective or very cost-effective in developing countries, vaccine price appeared to be unaffordable to governments of developing countries where the rotavirus vaccines have to compete with other less expensive childhood vaccines (e.g. hepatitis B or polio) for the limited resources.Hence, vaccine price has become one of the most important factors in decision making of whether to include this vaccine into the country's routine immunization program. Mortality rate and vaccine efficacy are other two factors having substantial impacts on cost-effectiveness results. So far, clinical trials of vaccine efficacy are being conducted in several developing countries and results will soon be released. Therefore, many studies in this review have to use vaccine efficacy data from developed countries where clinical data is available. Rotavirus-related mortality rate is not available in any of the studies being review, thus all studies had to use diarrhoea-related mortality rate, which is naturally higher.

Uncertainty analyses

Due to the fact that results of rotavirus vaccination depends largely on many parameters like vaccine price, vaccine wastage, vaccine efficacy, diarrhea incidence, case-fatality rate, severity of, diarrhea, hospitalization costs, mortality, and morbidity, there is a huge uncertainty surrounding the cost-effectiveness results of rotavirus immunization. Therefore, in all studies, sensitivity analyses were conducted to test the robustness of the results. Several studies even conducted probability sensitivity analysesto test the effects of multiple parameters simultaneously [19,20].

Discussion

All reviewed studies on rotavirus immunization in developing and low-income countries provide clear evidence that universal rotavirus immunization of children under 5 years old is either cost-effective or very cost-effective, but the vaccine price is still expensive and not yet affordable by the healthcare system of these countries. However, sensitivity analyses have shown that even at a vaccine price as high as US$ 25/dose [35], rotavirus immunization would still be cost-effective. Since all studies included in this review explored the possibility of introducing universal rotavirus vaccination into countries' national EPI rather than evaluated an actual ongoing immunization, almost all studies have provided several scenarios under which immunization would be breaking-even, cost-effective, very cost-effective or cost-saving. By evaluating these scenarios, it helps vaccine manufacturers, the GAVI Alliance and various national governments to seriously consider the feasibility and affordability to introduce rotavirus vaccination into countries' routine immunization programs by either providing rotavirus vaccines at a much cheaper price or developing new generations of vaccines at lower costs.

All studies followed the WHO's generic protocol in evaluating diarrhea [33], and therefore, the cost-effectiveness analyses were conducted in similar manner. Even with two studies developed

sophisticated and complex Markov models rather than applying decision tree models to capture all manifestation of rotavirus infections (i.e., allowing re-infections in the disease transitional model or to consider partial immunization vs. fully immunization) [19,20], all studies came to the same conclusion that universal rotavirus immunization is cost-effective. This is in spite of the fact that cost data were collected in different way. The perspectives (i.e., either societal or health care), in which CEAs were carried out would be appropriate based on the objectives of the studies.

Studies' results showed that for developing countries, where access to medical services, especially when urgent care is limited, rotavirus immunization appears as the best prevention against severe diarrhea caused by rotavirus. Rotavirus immunization might reduce greatly the number of hospitalizations, outpatient visits, deaths as well as a significant amount of treatment cost incurred from rotavirus infection per year. It is notable that though rotavirus related diarrhoea is one of the most deadly diseases in children in the developing world, it is also the most preventable disease. Rotavirus immunization takes effect immediately. This is different from other infectious diseases such as hepatitis B for which the benefits of immunization only become apparent in 30-40 years. Hence, rotavirus vaccination is a worthwhile healthcare investment and the best prevention against rotavirus-related diarrhoea. However, rotavirus immunization is still a costly intervention for developing and low-income countries where the cost of the vaccine is a major challenge for its introduction. All studies in this review concluded that without the financial support from international health organizations, developing countries would not be able to implement universal rotavirus immunization at least at present or in the near future. Finally, concerns on inefficiencies in the delivery of a complete course and getting vaccinations on time to all children were raised, and these concerns should be considered and addressed.

The cost-effectiveness analyses included in this review were undertaken while many clinical trials were still ongoing in Asia and Africa. Therefore, one issue needing exploration was vaccine efficacy. While rotavirus vaccine efficacy was shown to be very high in industrialized countries, it seemed to have much variation in developing countries and heavily depending on country-wide situations. One of many features of the rotavirus is that it has various genotypes and these genotypes differ from country to country. Kim *et al* also mentioned that the genotype distributions differed widely across studies and even within Vietnam, leading to a wide range of adjusted vaccine efficacy ranging between 46% and 81% [19].

Furthermore, even though the incidence of rotavirus infection is similar between developed and developing countries [20,24], the severity of the disease manifestation differs greatly across countries. It has been shown that the local case fatality is one of the most influential parameters to cost-effectiveness results of the immunization program [26]. This is explainable because the quality, accessibility and availability of healthcare services differ across and within countries. It is worthwhile to recommend that, in addition to implement rotavirus immunization, developing healthcare infrastructure, nutrition improvements, education for oral rehydration therapy should be considered as a combined prevention and treatment strategy to enhance the control of diarrhoeal disease.

In all studies, vaccine price was the dominant parameter influencing the cost-effectiveness results and hence the decisions of health policy makers. Even confirmed to be cost-effective, this does not imply rotavirus immunization is affordable by developing countries. For low-income countries, this would require the heavy financial support from international organizations such as the GAVI Alliance's fund. Economic evaluations can provide useful information for the GAVI Alliance in making plans to help eligible countries in introducing rotavirus vaccination. The results of these studies also help governments and GAVI to negotiate with vaccine producers to obtain a cheaper vaccine price. Another suggestion is the possibility to develop less expensive rotavirus vaccines. Many reviewed studies showed that if the vaccine price were US$ 2-3/dose, immunization would become cost-saving and affordable by the countries' healthcare systems. This translates in a 50-60% reduction of the current vaccine price. At the moment, the GAVI Alliance is accepting applications from its eligible countries for rotavirus vaccines financing. The subsidized price given by GAVI is budgeted at US$ 0.30 per dose [13,34], which is much lower than the current market price of US$ 7 per dose [26]. If developing countries are to benefit from the GAVI subsidized vaccine price, rotavirus immunization might become affordable in the developing world.

The review points to several limitations faced by the various studies. First is the lack of epidemiological data. Many studies in this review had to use data instead from developed countries in the modeling [18,23,28,34]. Thus, the authors suggested more surveillance studies on rotavirus epidemiology in countries around the world. Second is the application of disease transitional models. Many studies used simple static decision tree models, allowing only one infection of rotavirus-related diarrhoea. However, in reality, nearly every child under 5 years of age gets more than one rotavirus infection in his or her life time[12]. Herd immunity was not considered in any reviewed study partly because no published data is available. In the same manner, dynamic models were not utilized in any study though a few studies had developed more complex disease progression models to capture different genotypes, more infections per child, results of partial immunization against rotavirus [13,19,20]. Another limitation is the lack of data on rotavirus vaccine efficacy in developing countries. Rotavirus vaccines have been available only since 2006, thus many clinical trials are still being conducted. This leads to the applying of data from a developed country to a developing country, which might over-estimate the results of cost-effectiveness analyses.

Despite various concerns faced by developing countries in introducing rotavirus vaccination in their national immunization program, it is obvious that rotavirus immunization is a "worth-to-do" intervention from the healthcare point-of-view. Eventually, developing countries have to implement rotavirus immunization as it saves many lives of young children, especially in the most marginalized and impoverished regions where living conditions and quality of healthcare are still under-developed. To prepare the developing world in introducing rotavirus vaccination into routine immunization, substantial financial assistance is definitely needed from international organizations.

Conclusion & Expert Commentary

Based on the available international peer reviewed literature on the economic evaluations of rotavirus immunization in the developing world, we conclude that it is cost-effective to implement universal rotavirus immunization. So far, vaccine price is the most crucial factor hindering developing countries from introducing rotavirus vaccination into their routine immunization programs. Despite the cost-effectiveness of rotavirus vaccination, the vaccine price appears to be too expensive and unaffordable to all developing countries. It is evident that without the support from international organizations like the GAVI Alliance or World Health Organization (WHO), implementation of universal rotavirus immunization will be very difficult. In addition, post-marketing surveillance and clinical trials on the efficacy of rotavirus vaccines should be strengthened to ensure maintenance of acceptable cost-effectiveness of the program.

Five-Year View

In 2006, the WHO has recommended that all countries in the world implement universal rotavirus immunization. This is the reason for the GAVI Alliance to decide on expansion of financial support for rotavirus immunization introduction in Asia and African and is now reviewing applications from eligible countries. If rotavirus vaccines were used in the most impoverished and poorest regions in the world, they would potentially prevent roughly 225,000 deaths per year and save 2.5 million lives in children between 2007 and 2025 [35]. It is obvious that with the GAVI's financial support, more countries in Asia and Africa will be able to implement rotavirus vaccination in the next 5 years. At present, rotavirus vaccines are still too expensive for developing countries to introduce into their national immunization program. However, several vaccine manufacturers in India, China and Brazil are working to develop promising new rotavirus vaccines candidates at a lower production cost, making rotavirus vaccines potentially affordable and available in the market in the near future. If this happens, it will expedite the implementation of universal rotavirus immunization in the developing world. Furthermore, more clinical trials on vaccine efficacy and high-quality cost-effectiveness studies on rotavirus immunization will be accomplished in developing countries in the next five years to confirm the cost-effective of such programs.

Key Issues

- Disease burden of rotavirus infection is highest in Asia and Africa where vaccines preventing rotavirus are not yet widely available and still very costly
- Rotavirus vaccination appears to be the "best hope" for prevention of rotavirus-related diarrhoeal disease, a major cause of mortality for children under five years age
- The price of rotavirus vaccines is the main factor restraining developing countries from implementing universal rotavirus immunization
- Cost-effectiveness studies in the developing world reveal that universal rotavirus immunization is cost-effective but not always affordable (continued on page 114)

Author (publication year)	Country	Study objective	Detailed analysis	Type of economic analysis	Discount rate	Immunization approach
Chotivitayatarakorn et al. (2010)	Thailand	To estimate rotavirus disease burden, impacts of vaccination and evaluate the cost-effectiveness of introducing rotavirus vaccination into the national immunization.	To use international disease burden data and local costing data to estimate the cost-effectiveness of rotavirus vaccination in Thailand	CEA	3	Universal
Berry et al. (2010)	Malawi	To examine cost-effectiveness of rotavirus vaccination using both GAVI-subsidized price and the market price	To use published data on disease burden, vaccine efficacy and healthcare costs to perform a cost-effectiveness analysis	CEA	3	Universal
De la Hoz et al (2010)	Columbia	To estimate the disease burden caused by rotavirus and to perform cost-effectiveness against rotavirus using Rotarix and Rotateq vaccines	Results of three vaccination strategies were compared among three hypothetical cohorts: no vaccination, vaccinated with two doses of Rotarix and vaccinated with three doses of Rotateq. Simulations were run in a Markov model for 24 months	CEA	3	Universal [1]
Kim *et al.* (2009)	Vietnam	To evaluate cost-effectiveness by reflecting additional uncertainties like re-infection, different degrees of partial immunity from natural infection	To develop a Markov model of rotavirus transmission to evaluate cost-effectiveness of vaccination against the disease and without vaccination	CEA	3	Universal
Rose et al. (2009)	India	To estimate cost-effectiveness of universal vaccination with live attenuated human rotavirus vaccine and the affordability of a program	To evaluate impacts of vaccination against rotavirus from both healthcare and societal perspectives in comparison without vaccination based on a Markov transitional model	CEA	3	Universal
Wang et al. (2009)	China	To assess the incidence and economic burden of rotavirus diarrhea and the potential cost-effectiveness of vaccination in a rural province in China	To apply a decision-analytic model in evaluating the cost-effectiveness of vaccination in rural China using real epidemiological and cost data from payer and societal perspectives	CEA	3	Universal
Wilopo et al. (2009)	Indonesia	To perform an economic evaluation of potentially integrating rotavirus vaccination into Indonesian national immunization program	To compare results of universal vaccination against rotavirus with no vaccination and identify the break-even point of the vaccination	CEA	3	Universal
Ortega *et al.* (2009)	Arab Republic of Egypt	To conduct cost-benefit and cost-effectiveness analyses of the national rotavirus vaccination from Ministry of Health and societal perspectives, respectively	To perform evaluation for three different strategies: no vaccination, partial and full vaccination and compare the results from these three vaccination strategies	CBA	3	Universal
Tate et al. (2009)	Kenya	To estimate disease burden among children <5 years, direct and indirect cost and potential impact of cost-effectiveness of vaccination against rotavirus in a Kenyan province	To perform a comparison of impacts between vaccination and no-vaccination against rotavirus and to conduct a cost-effectiveness analysis of the vaccination strategy	CEA	3	Universal
Flem et al. (2009)	Kyrgyzstan	To conduct a cost-effective analysis of introducing rotavirus vaccination	To estimate the cost burden due to rotavirus infection and based on this data a CEA of vaccination against rotavirus infection was performed	CEA	3	Universal
Constenla et al. (2008)	Brazil	To perform a cost-effectiveness analysis of the national rotavirus vaccination against rotavirus from the healthcare perspective	To compare between vaccination and no-vaccination strategies against rotavirus infection based on the reduction of hospitalizations, outpatient visits and averted death and to identify a reasonable price of vaccine in Brazil	CEA	3	Universal

de Soarez *et al.* (2008)	Brazil	To conduct a cost-effectiveness analysis of a universal rotavirus immunization for children < 5 years in Brazil	To use local data to evaluate cost-effectiveness of a rotavirus vaccination program	CEA	6	Universal
Valencia-Mendoza et al. (2008)	Mexico	To assess the cost-effectiveness of integrating pentavalent rotavirus vaccine into the national immunization program	To use a Markov model for modeling the vaccination of a birth cohort and to compare the cost and disease burden of rotavirus between vaccination and no-vaccination using Rotateq vaccine	CEA	3	Universal
Isakbaeva *et al.* (2006)	Uzbekistan	To perform cost-effectiveness of rotavirus vaccination from both healthcare and societal perspectives	To compare the cost and effects of vaccination and no-vaccination against rotavirus. To identify parameters influencing the cost-effectiveness results	CEA	3	Universal
Fisher *et al.* (2005)	Vietnam	To pilot test WHO generic protocol by assessing the country's rotavirus disease burden in terms of costing based on the actual data.	To assess the national rotavirus disease burden using the local data in a cost-effective analysis	CEA	3	Universal

[1] Immunization given to the children <= 5 years of age
CEA: Cost-effectiveness analysis; CBA: Cost-benefit analysis; DALY: Disability-adjusted life year; GAVI: Global Alliance for Vaccines and Immunization

Table 1 Economic evaluations on rotavirus vaccination in developing and low-income countries as published in the international literature between January 2000 and August 2010

Study, published year, country	**Vaccine**	**Vaccine price (US$)**	**Birth cohort (year)**	**Age group**	**Vaccine efficacy (%)**	**Incidence[1]**	**Averted outcome (%)**			**ICER/DALY (US$)**	**Break-even point (US$/course)**		
							Deaths	**IPD admission**	**OPD visits**			**Direct medical cost**	**Other costs**
Chotivitayatarakorn et al, 2010, Thailand	Rotarix	7	932,000 (2007)	0-5	85%	0.93-1.35 / person-year	419	46,542	109,918	370/DALY (h)	BE @US$ 6.2/dose	6,351,366	5,715,118
Berry et al, 2010, Malawi	Rotarix	5.5 or 0.15[2]	582,211 (2008)	0-2	49.5%		2,582	11,354	28,590	74.73/DALY		80,748	
De la Hoz et al, 2010, Columbia	Rotarix & Rotateq	7.5	929,630 (2003)	0-2	40-85 (Rotarix) & 40-60-95 (Rotateq)[3]	0.013/child/ year	300 (25%) for Rotarix or 350 (28%) for Rotateq	35,012 (27%) for Rotarix or 33,798 (30%) for Rotateq		663/DALY for Rotarix	CS if a dose < $3	8.1 million for Rotarix or 8.9 million for Rotateq	
Kim et al, 2009, Vietnam	Rotarix	5	1,644,000 (2004)	0-5	77%		1,090	22,600	105,300	540/DALY (s) or 550/DALY (h)			

Rose et al, 2009, India	Rotarix	7	25,000,000 (2007)	0-5	80.4%		41,000	203,000	1,794,500	134/DALY		$9/person	
Wang et al, 2009, China		5	5,000 (2004)	0-5	75%					0.08/case averted			
Wilopo et al, 2009, Indonesia	Rotarix	7	4,200,000 (2007)	0-5	70-80%	1,400/10,000 for boys & $1,300/10,000 for girls	8,148 (76.5%)	176,375 (84%)	488,547 (70%)	120.5/DALY	2.70 (h) or 3.79 (s)	11.67 million	1.779 mil
Ortega et al, 2009, Egypt	Rotarix	9.16	1,909,000 (2005)	0-5	64.5% for overall disease	0.19 episodes /child-year; mortality rate of 3/100,000	2,873 (88%)	47,508 (90%)	438,395 (91%)	363/DALY	CS if a course ≤ US$1.34	2,481,792	
Tate et al, 2009, Kenya	Rotarix	0.5-10	NA	0-5	78%		2,467 (55%)	5,724 (65%)	852,589 (59%)		CS if a course ≤ US$ 2.07		
Flem et al, 2009, Kyrgyzstan	Rotarix	0.3[1]	116,000 (2009)	0-5	63%-85%			2,921 (75%)	17,449 (56%)		BE @ US$ 0.65/dose or CS @ $1-$2/course	265,644 (63%)	105,076
Constenla et al, 2008, Brazil	Rotarix	7.0-8.0	3,471,000 (2003)	0-5	85%		1,317 (73%)	69,256 (76%)	423,652 (77%)	643/DALY (h)	CS if a course ≤ US$ 2.17 (h)	14.67 million	
de Soarez et al, 2008		7	3,300,000 (2004)	0-5	70%	5-year cumulative incidence of 1.2/child				cost/life-year saved = US$ 1,028(s) or US$ 1,713(h)	BE @ US$ 9.98 (s) or US$ 4.24 (h)/dose		
Valencia-Mendoza et al, 2008	Rotateq	10	2,000,000 (2006)	0-5	74%		612 (70%)	5,040 (66%)	71,464 (59%)	cost/life-year saved = US$ 4,283.75		7.6 million	
Isakbaeva et al, 2006, Uzebekistan	Rotarix	1-12.5	538,128 (2004)	0-5	93%	Mortality rate of 0.7/1000	350-1,150	4,801 (91%)		242/DALY @US$ 5/course		328,154	40,667
Fisher et al, 2005, Vietnam	Rotarix	0.5-10	1,639,000 (2004)	0-5		56% of diarrhoea-hospitalizations	5,001 (83%)	105,393 (84%)			BE @ US$ 1.04 (h) or US$ 2.08 (s) /course		

[1] rotavirus incidence for under-5 children
[2] GAVI Alliance-subsided price
[3] Rotarix: vaccine efficacy is 40% & 85% after first & second doses, respectively; Rotateq: 40%-60%-95% after first, second and third doses, respectively.
BE = Direct medical break-even; CS = cost-saving; CS: Cost-saving; DALY: Disability-adjusted life year; GAVI: Global Alliance for Vaccines and Immunization; h: Healthcare perspective; ICER: Incremental cost-effectiveness ratio; IP: Inpatient; NA: Not applicable; OP: Outpatient; s: Social perspective

Table 2 Results of economic evaluations of Rotavirus vaccination in developing countries

- Developing countries will have to depend on external financial support (e.g., GAVI, WHO) in order to expedite rotavirus immunization program

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CHAPTER 6

Comparative review of three cost-effectiveness models for rotavirus vaccines in national immunization programs: a generic approach applied to various regions in the world

M.J. Postma

M. Jit

M.H. Rozenbaum

B. Standaert

H.A.T. Tu

R. Hutubessy

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Summary

Background: This study aims to critically review available cost-effectiveness models for rotavirus vaccination, compare their designs using a standardized approach and compare similarities and differences in cost-effectiveness outcomes using a uniform set of input parameters.

Methods: We identified various models used to estimate the cost-effectiveness of rotavirus vaccination. From these, results using a standardized dataset for four regions in the world could be obtained for three specific applications.

Results: Despite differences in the approaches and individual constituting elements including costs, QALYs and deaths, cost-effectiveness results of the models were quite similar. Differences between the models on the individual components of cost-effectiveness could be related to some specific features of the respective models. Sensitivity analysis revealed that cost-effectiveness of rotavirus vaccination is highly sensitive to vaccine prices, rotavirus-associated mortality and discount rates, in particular that for QALYs.

Conclusions: The comparative approach followed here is helpful in understanding the various models selected and will thus benefit (low-income) countries in designing their own cost-effectiveness analyses using new or adapted existing models. Potential users of the models in low and middle income countries need to consider results from existing studies and reviews. There will be a need for contextualisation including the use of country specific data inputs. However, given that the underlying biological and epidemiological mechanisms do not change between countries, users are likely to be able to adapt existing model designs rather than developing completely new approaches. Also, the communication established between the individual researchers involved in the three models is helpful in the further development of these individual models. Therefore, we recommend that this kind of comparative study be extended to other areas of vaccination and even other infectious disease interventions.

Introduction

Various countries are currently in the process of evaluating whether or not to include rotavirus vaccination in their national immunization programs. Two rotavirus vaccines are currently available: Rotarix® and Rotateq™, marketed by GlaxoSmithKline (GSK) and Sanofi Pasteur MSD (SPMSD), respectively. Rotavirus vaccines have proven to be efficacious in preventing rotavirus-related disease, gastrointestinal disease and health-care use (GP-visits and hospitalizations) in infants and toddlers [1-3].

Health-economic properties of these new vaccines present one characteristic to be analysed with respect to their inclusion in National Immunization Programs (NIPs). Numerous health-economic analyses already exist regarding rotavirus vaccination, mostly in high-income country settings, some being single-country analyses but a few multi-country analyses [4-6]. Also, one critical review of these existing models has already been performed [7]. Recently, some studies have become available targeted at situations in low- and middle-income countries, involving all regions in the world (for example, Vietnam, China, Kenya and Colombia [8-11]). A review of these studies in Asia, Africa and South-America is in preparation [12]. Based on the favourable cost-effectiveness profile of many of the models applied in low- and middle-income countries, the World Health Organisation (WHO) advises inclusion of rotavirus vaccines in the NIPs [13]. However, in general, it is still not always clear which aspects these individual models differ on, what impact such differences have on the cost-effectiveness outcomes and which model might be preferred over the others in continental, regional or country-specific situations [14].

This study aims to critically review some of these available cost-effectiveness models for rotavirus vaccination, compare their designs using a standardized approach and compare similarities and differences in cost-effectiveness outcomes using a uniform set of input parameters. WHO has initiated this study to enable providing guidance to low- and middle-income countries if requested, on the strengths and weaknesses of existing health-economic models for rotavirus vaccination as a basis for decisions about whether or not to build their own models or to adapt existing models to local situations. In particular, our study intends to help WHO to guide individual countries on rotavirus modelling, specifically national decision makers who may have the interest, research capacity and resources to conduct their own cost-effectiveness analyses in generating evidence for decision making on whether or not to introduce rotavirus vaccination. Therefore, our analysis might be most suited for lower middle income countries that have some capacity to attract global partners for model adaptation, whereas most low income countries may not have sufficient technical capacity for building or adapting existing models. Notably, our goal is neither to advocate the use of specific models nor to recommend individual modelling groups over others.

Methods

Review of Models

Initially, we searched for existing health-economic models in the literature using PubMed, Embase and Web of Science. Although the search was not limited to the English language, the relevant papers that

emerged from the initial search and crude selection were all in English. A further selection was made for those models to be included in the detailed comparison based on various criteria, related to our goals of achieving diversity in terms of provenance (public versus private), methods (single-cohort models, multi-cohort models and so on) and specific vaccines to be incorporated by the model (that is, two individual vaccines exist that are slightly different). Modelling groups were selected and contacted, explicitly based on these criteria. However, availability, ease of access, complexity and time investment of the individual research groups appeared to be the strongest criteria in practice for inclusion in the final comparison. In particular for those models with a high degree of complexity, the time investment required appeared to prevent the groups from becoming involved in our comparison. Also, for these complex models resource requirements for this analysis presented a strong limitation, which could not easily be overcome given the limited funds available by WHO for the endeavour.

Comparative Framework

As described, various cost-effectiveness models were identified by the process described above. Their developers were contacted by a WHO officer (RH) to invite them to participate in the model comparison. Subsequently, the model inclusion was co-ordinated by 2 authors (RH & MP), while 1 author (MP) included his own group's model into the comparison. The process resulted in three models provided to us, including analyses using the standardized dataset specified below (Table 1). From all modelling groups at least one co-author was included in the author list of this paper. These models represented a balanced public-private mix involving one designed by the pharmaceutical industry (Roxanne Rotarix™ Analyses of Economics from GSK), one developed by public financing within a European-Union project (POLYMOD) and one privately financed (Sanofi Pasteur MSD) but developed by the University of Groningen within the context of an unrestricted grant (CoRoVa Consensus Rotavirus model Vaccination). Models included could be applied to modelling use of either vaccine (Rotarix or RotaTeq), hence ensuring that the unique features of the two vaccines were adequately represented in our analysis. In addition, both manufacturers were directly (Roxanne) or indirectly (CoRoVa) involved in the models. Only static models were compared; this posed both a disadvantage and an advantage. In particular, comparison with a dynamic model, which could explicitly analyze the effect of vaccination on the spread of rotavirus infection using mathematical modelling, would be extremely valuable. However, our selection of only static models for comparison enhances comparability of the individual models and facilitates understanding the differences that still remain between the models' outcomes.

	POLYMOD	**Roxanne**	**CoRoVa**
Developers	HPA	GSK	University of Groningen
Funding	EU	GSK	SPMSD
Software platform	Excel	Excel	Excel
Dynamic vs. Static	Static	Statistic	Static
Deterministic vs. stochastic	Deterministic	Deterministic	Deterministic
Open vs. closed	Open	Closed	Closed

Cohort vs. population-based	Multi-cohort	Cohort	Cohort
Special features	Stepwise waning	Breastfeeding effects modeled	In-between dose efficacies modeled

Table 1 Basic characteristics of the models investigated[a]
[a]Specific questions regarding the three models should be attended to Dr. Raymond Hutubessy (email address: hutubessyr@who.int)

The owners of the models provided access to their models through physical transfer of the software – accompanied with user guides and/or publications - and explained various concepts and characteristics of these models face-to-face, through e-mail contacts and telephone calls during 2009. Additionally, during a one-day consultation in 2009 at the WHO headquarters in Geneva, concepts and draft results were discussed with a large group of experts in epidemiology, immunology, vaccinology, political sciences and health economics. In the end, final calculations were performed by the modellers themselves using the most current model versions at the end of 2010 and extensively discussed during the winter of 2010/11. To summarize the way the three models were included in this analysis, we note that all the software for the models was physically available to the coordinating team (MP and RH), at least 2 face-to-face meetings between member(s) of the coordinating team and each research group were organized and final calculations were checked by the coordinating team and cross-checked for face validity by all the 3 individual research groups.

The standardized approach in comparing these models involved stepwise analysis of the structure, the input parameters required and specific assumptions underlying the models.

Details on Available Models

As mentioned, during the model selection process three models with corresponding results for the standardized input parameters became available to us. These were the POLYMOD-model [4,15,16], Roxanne [17-20], and CoRoVa [21-23].

The POLYMOD-model was developed in the context of an EU-funded project with the same acronym [4]. RVGE Rotavirus GastroEnteritis was modelled using an age-structured cohort model that followed cohorts of vaccinated and unvaccinated individuals (Table 1). For the first year of life, the cohort was stratified into monthly age groups, with one-year age bands applied beyond (one to five years old). The model was initially a single-cohort model; however, it was adapted to a multi-cohort model for the purpose of this exercise to allow a step-up in vaccination coverage. RVGE was stratified into mild disease with home treatment only, moderate disease with primary care visits (GP and/or hospital outpatient), severe disease with hospital ER-visits and/or admissions, nosocomial infections and death. QALY losses were incurred both by the index infants and their care givers. QALYs were taken from one specific study on the topic [23], which were quite comparable to those used in some other health-economic studies [5]. The model was designed by modellers based in England's Health Protection Agency (HPA) with input from modellers based in public health institutions in Belgium, Finland, France and the Netherlands and applied to model rotavirus epidemiology and cost-effectiveness of vaccination in the five countries of Belgium, England & Wales, Finland, France and the Netherlands. Unlike most static rotavirus models, waning vaccine immunity was explicitly incorporated into the model structure.

Further country-specific models – based on this multi-cohort, multi-country model – have been published, for example, for the Netherlands [16].

Roxanne was developed as a Markov cohort process tree [17]. It is programmed in Microsoft Excel 2007 using Visual Basic and contains both cost-effectiveness and budget impact modules. The model was initially parameterized with data from France [18], but allows data from any country to be used [19]. A precursor of the model has been used to estimate the cost-effectiveness of Rotarix® in the Netherlands [20]. Besides a comparison of vaccination versus no vaccination, the model was designed to additionally allow explicit comparison of two- and three-dose vaccination strategies. Obviously, outcomes in such analyses crucially depend on the exact characteristics and properties applied to the two- and three-dose vaccination schedules. Finally, Roxanne allows extensive probabilistic sensitivity analysis, using the At Risk add-in for Excel. A special feature of Roxanne involves the explicit inclusion of the modelling of maternal protection from (severe) infection through breastfeeding.

CoRoVa was initially developed for the specific Dutch situation and aimed at achieving consensus among various Dutch modelling groups that had previously worked on the cost-effectiveness of rotavirus vaccination [16, 20]. An age-structured cohort model was developed in Excel applying a time horizon of 5 years with time cycles of one month for children less than one year of age and annual thereafter [21-23]. Outcomes in the model were classified by severity and included home-treated community-acquired diarrhoea and rotavirus infection leading to GP consultations and/or hospital admissions (including emergency department visits), nosocomial infections and death. Specific characteristics of the model are the ability to take waning immunity, maternal protection against infection through breastfeeding, and herd protection into account. However, the model is not a transmission dynamic model because herd protection is incorporated by straightforward calculus only, using a static approximation based on a fixed fraction of the direct effects. In the base-case analysis for the Netherlands, QALY losses of caregivers were not included and the QALY decrement for children was based on a combination of two published studies performed in the Canada and the UK [24, 25]. Similar to the Roxanne-model CoRoVa also used the At Risk software for (probabilistic) sensitivity analyses.

Standardized Input Parameters

For this study, analyses of the models were provided regarding their structure and outcomes for 4 hypothetical countries, representative of different continents and income levels (low, middle or high), respectively classified into the WHO geographical regions and mortality strata [14]. In particular, sets of standardized input parameters were provided to the modellers and analysed for a hypothetical Afr E country representing the African region with high child and very high infant mortality; a hypothetical Sear D country representing the South-east Asian region with high child and adult mortality; a hypothetical Amr D country representing the South and Middle American regions with again high child and adult mortality; and a hypothetical Eur A country representing developed countries in the European setting. Tables 2, 3, 4 and 5 summarize the set of standardized input parameters. Rectangular age distributions were assumed, implying that life expectancy decreases with one year exactly for every one-year increase in the age of infants and toddlers considered. (For example, if life expectancy is 70 at birth, it

would be 69 at the age of 1, 68 at the age of 2 and so on). Simplifying assumptions were justified as our interest concerned the comparison between models rather than the exact representation of country-specific demographic, epidemiological and economic impacts.

Although the time horizon in the single- and multi-cohort models was lifetime, this effectively produced a time horizon of 5 years after the birth of the last cohort, since it is assumed that no rotavirus gastroenteritis occurs beyond the age of 5 years and vaccination is only investigated in infants in their first year of life. Various sources were utilised for parameter estimates as indicated in Tables 2, 3, 4 and 5 [1-5, 7, 14, 15, 20, 26-31]. However as the objective was comparative rather than to exactly mimic the situations of specific countries often plausible assumptions were made rather than exact replications of individual sources. Plausibility of assumptions was primarily based on the expert opinions of two of the authors (MP and MJ)

	Afr	Sear	Ams	Eur	Notes
Total # of life births	1,496,200	3,427,800	140,110	190,000	
Life expectancy at birth in years	54	66	73	80	average men & women
Population	34,255,722	141,822,276	5,486,685	16,500,000	
% of population < 5 years	16.75%	16.75%	16.75%	6.1%	
% urban	42%	23%	62%	100%	
Infant mortality (< 1 year of age)	64	45	21	4	per 1000 life births
Mortality < 5 years	104	57	26	0.5	per 1000 life births /yr
Population < 5 years	5,736,373	17,399,197	730,913	1,000,000	
Incidence mild rotavirus gastro-enteritis					
1st year after birth	1.4%	1.4%	1.4%	1.4%	in % per month
2nd year after birth	0.57%	0.57%	0.57%	0.57%	in % per month
3rd& 4th after birth	0.49%	0.49%	0.49%	0.49%	in % per month
Incidence of moderate	38.7%	38.7%	38.7%	33.1%	in % from mild
Incidence of severe	7.9%	7.9%	7.9%	12.1%	in % from moderate
Incidence of death	18.8%	12.5%	6.3%	0.05%	in % from severe
Incidence of nosocomial infections	33.3%	33.3%	33.3%	25%	% from severe (on top)

Table 2 Standardized dataset for the cost-effectiveness models in rotavirus vaccination: demography and incidence (Sources: [4,5,7,14,15,20,26,27])

	Afr	Sear	Ams	Eur	Notes
Efficacy, assuming a 2-dose schedule at 2 & 3 months (1 dose only between brackets)					
Mild	52% (52%)	52% (52%)	52% (52%)	87% (87%)	
Moderate	55% (54%)	55% (54%)	55% (54%)	92% (90%)	
Severe	60% (54%)	60% (54%)	60% (54%)	100% (90%)	
Waning of efficacy (annual)					
Mild & moderate	0.63	0.63	0.63	0.63	multiply each next
Severe	0.83	0.83	0.83	0.83	multiply each next
Coverage					
Dose 1	50%	50%	50%	50%	
Dose 2	40%	40%	40%	40%	
20 years after introduction	80%	80%	80%	96%	for both doses
Coverage improvement	linear	linear	linear	linear	
Per-dose vaccine costs (2 doses)					
2009-2014	7.5	7.5	7.5	45	
2015 & beyond	4	4	4	45	

Table 3: Standardized dataset for the cost-effectiveness models in rotavirus vaccination: vaccine characteristics (Sources: [1-5,7,15,20,28], expert opinions)

	Afr	Sear	Ams	Eur	Notes
Average length of hospital stay	4	4	4	4	days
Cost per hospital day	US$35	US$34	US$122	€550	
Cost per outpatient visit (health center/GP)	US$10.5	US$9	US$34.50	€40	Community acquired only
Out-of-pocket costs (comm.-acq. only)	US$0.50	US$2.5	US$5	€15	Diapers/travel/OTC
Total direct costs for nosocomial cases	US$15	US$15	US$50	€2,000	
Cost of productivity loss/day	US$1	US$5	US$10	€125	
Parents with work loss					
Non-hospitalized	20%	20%	20%	20%	
Hospitalized & nosocomial	75%	75%	75%	75%	
Days of work missed for parents					
Mild	1	1	1	1	
Moderate	1.5	1.5	1.5	1.5	

Severe	2	2	2	2	Also for nosocomial
Discount rates	3%	3%	3%	3%	Money&health
Administration costs per dose	US$0.53	US$0.46	US$0.46	€5	

(Note: all mild cases were treated at home, all moderate additionally in an outpatient setting, such as outpatient hospital, GP or health centre and all severe cases additionally in hospital; all cases have out-of-pocket costs), plausible assumptions based on literature [29-31] and expert opinions (MP & MJ))
GP: general practitioner; comm.-acq: community acquired; OTC: over the counter

Table 4 Standardized dataset for the cost-effectiveness models in rotavirus vaccination: health-care use and costs

	Afr	**Sear**	**Ams**	**Eur**	**Notes**
Disutility					
Mild	0.15	0.15	0.15	0.15	during 4 days
Moderate	0.25	0.25	0.25		during 4 days
Severe	0.7	0.7	0.7	0.7	during 4 days
Nosocomial	0.7	0.7	0.7	0.7	during 4 days
Death	1	1	1	1	per year
Age weighting (primarily considered for DALYs)	off	off	off	off	
Perspective	Societal& healthcare	Societal& healthcare	Societal& healthcare	Societal& healthcare	
Herd effect	off	off	off	off	

DALY: disability adjusted life year

Table 5: Utilities and some remaining issues [4,5,7,20,27]

Key parameters for all analyses were the incidence of rotavirus gastroenteritis (RVGE), the corresponding risks of rotavirus-related health-care use, as well as corresponding costs. All cases with RVGE were assumed to be treated at home. In particular, moderate cases were assumed to involve one additional outpatient visit (GP, health centre or hospital) and severe cases were assumed to involve: home treatment, an outpatient visit and a hospitalization. Some models had the additional option of severe cases not being hospitalized. Based on data from the clinical trials, vaccine efficacy could be specified for different outcomes and for high-income versus other countries.

Alternatively to what is expressed in Table 1, incidence could be expressed as average annual risks over the same 5 years considered in the data and modelling. In particular, the average annual risks at population level are 10,440, 4040 and 320 per 100,000 people in all developing regions for mild, moderate and severe, respectively. Correspondingly, figures for the Eur region are 10,440; 3460; and 419 per 100,000 people. Similarly, annual mortality risks are 60, 40, 20 and 0.21 per 100,000 population for the Afr, Sear, Amr and Eur regions, respectively.

Standardized Output

Model developers were requested to present a standardized set of output variables for one single cohort (for the multi-cohort model, the coordinating centre estimated the results for one cohort themselves). In particular, these were: total number of persons and (person-years if available) followed in the model; undiscounted number of mild cases of RVGE; undiscounted number of moderate cases of RVGE; undiscounted number of severe cases of RVGE; undiscounted number of outpatient visits (GP, outpatient or health centre; typically this would equal the number of moderate and severe cases); undiscounted number of hospitalizations (typically equal to the number of severe cases); undiscounted number of nosocomial cases (equal to 1/4 or 1/3 of the number of hospitalizations, in the Eur and other regions, respectively); undiscounted number of deaths; discounted direct outpatient costs; discounted direct inpatient costs; discounted vaccination costs; discounted and undiscounted QALYs due to deaths (difference between vaccination and no vaccination is equal to the number of life-years gained); discounted and undiscounted QALYs due to morbidity; cost/QALY from the health-care perspective; cost/QALY from the societal perspective; a sensitivity analysis was requested by varying parameters values through halving and doubling their base case values, except the discount rate which was investigated for alternative values of 0% and 4%.

In particular, cost-effectiveness was expressed in net costs per QALY gained by subtracting discounted savings from the reduced need for RVGE treatments from (discounted in the multi-cohort model) vaccination costs to provide the numerator and dividing by the QALYs gained (the denominator).

Results

Results of using the standardized dataset for the various regions in different models are shown in Tables 6 through 10 for all three models. In general, cost-effectiveness results are broadly similar and comparable.

	POLYMOD	Roxanne	CoRoVa
Health-care perspective			
Afr	$ 265*	$ 188-367**	$ 233-440**
Sear	$ 358*	$ 257-503**	$ 308-591**
Amr	$ 307*	$ 200-652**	$ 336-862**
Eur	€ 57,897	€ 50,999	€ 56,656
Societal perspective			
Afr	$ 260*	$ 185-364**	$ 231-438**
Sear	$ 328*	$ 241-487**	$ 293- 577**
Amr	$ 196*	$ 143-595**	$ 282- 809**
Eur	€ 49,427	€ 40,041	€ 44,263

*Note: based on future reduction of vaccine prices from $7.5 to $4; **Range given for previous upper and lower vaccine prices

Table 6 Comparative analysis on costs per QALY

	POLYMOD	Roxanne	CoRoVa
Undiscounted cases			
Mild	92,989	121,312	128,807
Moderate	49,051	70,126	54,559
Severe	5,092	9,589	5,277
Nosocomial	1,680	1,986	2,701
Death	955	1,789	1,524
Outpatient	54,143	70,126	54,559
Inpatient (comm. acq.)	5,092	9,589	5,277
Discounted savings			
Outpatient	$ 568,502	$ 716,305	$623,977
Inpatient	$ 973,247	$ 1,329,538	$753,884
Indirect	$ 108,916	$ 106,377	$ 81,486
Discounted net costs** (*1000)	$ 6759	$ 8,757-17,094	$ 9,250-17,467
Discounted QALYs			
Mortality	24,962	45,817	39,070
Morbidity	542	762	628

*Approximations for one cohort from the multi-cohort results; **Health-care perspective & range given for previous upper and lower vaccine prices if appropriate

Table 7 Afr- region, comparative analysis on components of the costs per QALY: cases prevented, costs averted and QALYs gained (approximated) for one birth cohort

	POLYMOD	Roxanne	CoRoVa
Undiscounted cases			
Mild	216,205	276,861	299,907
Moderate	114,255	159,129	127,020
Severe	11,887	22,086	12,325
Nosocomial	3,92	4,748	6,309
Death	1,486	2,752	2,366
Outpatient	126,142	159,129	127,020
Inpatient (comm. acq.)	11,887	22,086	12,325
Discounted savings			
Outpatient	$ 1,135,274	$ 1,135,274	$ 1,852,744

Inpatient	$ 2,208,959	$ 2,208,959	$1,712,40
Indirect	$ 1,267,227	$ 1,213,598	$ 948,564
Discounted net costs** (*1000)	$ 15,424	$ 19,969-39,083	$ 20,545-39,423
Discounted QALYs			
Mortality	41,822	75,969	65,244
Morbidity	1,261	1,731	1,462

*Approximations for one cohort from the multi-cohort results; **Health-care perspective & range given for previous upper and lower vaccine prices if appropriate

Table 8 Sear- region, comparative analysis on components of the costs per QALY: cases prevented, costs averted and QALYs gained (approximated) for one birth cohort

	POLYMOD	**Roxanne**	**CoRoVa**
Undiscounted cases			
Mild	8989	11,318	12,481
Moderate	4760	6,471	5,286
Severe	496	897	514
Nosocomial	164	193	263
Death	31	59	50
Outpatient	5256	6,471	5,286
Inpatient (comm. acq.)	496	897	514
Discounted savings			
Outpatient	$ 181,333	$ 216,626	$ 239,534
Inpatient	$ 330,083	$ 432,618	$ 255,186
Indirect	$ 105,467	$ 98,697	$ 78,947
Discounted net costs** (*1000)	$ 293	$ 346-1,127	$ 495-1271
Discounted QALYs			
Mortality	900	1,662	1,413
Morbidity	53	66	61

*Approximations for one cohort from the multi-cohort results; **Health-care perspective & range given for previous upper and lower vaccine prices if appropriate

Table 9 Amr- region, comparative analysis on components of the costs per QALY: cases prevented, costs averted and QALYs gained (approximated) for one birth cohort

	POLYMOD	Roxanne	CoRoVa
Undiscounted cases			
Mild	22,708	32,186	28,680
Moderate	10,360	14,580	10,430
Severe	1658	2,324	1,806
Nosocomial	415	528	452
Death	1	1	1
Outpatient	12,019	14,580	10,430
Inpatient (comm. acq.)	1658	2,324	1,860
Discounted savings			
Outpatient	€ 480,745	€ 556,984	€ 829,111
Inpatient	€ 4,643,286	€ 5,949,119	€ 4,714,920
Indirect	€ 1,322,021	€ 2,111,857	€ 2,088,993
Discounted net costs** (*1000)	€ 9,032,932	€ 9,842,807	€ 9,518,208
Discounted QALYs			
Mortality	25	27	26
Morbidity	131	166	142

*Approximations for one cohort from the multi-cohort results; **Health-care perspective

Table 10 Eur-region, comparative analysis on components of the costs per QALY: cases prevented, costs averted and QALys gained (approximated) for one birth cohort

However, there are differences in the building blocks of these cost-effectiveness ratios, for example, regarding estimations of QALY losses related to morbidity in the three models. The results for the CoRoVa-model were generally in between those for the other two. The Roxanne model generally predicts overall higher number of cases, most notably for hospitalized cases. This translates into relatively high inpatient savings that are however lowered by discounting and overall dominated by vaccination costs to render similar net discounted costs for all three models investigated. However, the POLYMOD model gave consistently lower results for these discounted net costs; this might be due to the approximation from results for the multiple cohorts to just one. Also, higher vaccination costs in later years in the multi-cohort model were offset by a higher number of cases averted in the single-cohort model, resulting in the comparable cost-effectiveness ratios between the two types of models. Results suggest that rotavirus vaccination could potentially be cost-effective in all regions, particularly in low and middle income countries. However, the standardized data set is highly generalised and not specific to any individual country, so conclusions to support policy making should not be drawn in the absence of country-specific analyses.

Figure 1 shows the sensitivity analysis performed on the model results, with the example of CoRoVa shown here (other models showed similar patterns). From previous work on cost-effectiveness of rotavirus vaccination [5, 7, 15, 19], it is well-known that generally these results are highly sensitive to the vaccine price, rotavirus-associated mortality and the discount rate. Our analysis shows the similar pattern for all regions investigated. However, there is an interesting shift observed in variables influencing the cost-effectiveness results between EU and non-EU countries. In the EU region the incidence of the disease is a driver followed by utility weights whereas in the non-EU region mortality is essentially driving the result.

Discussion

We identified various models used to estimate the cost-effectiveness of rotavirus vaccination. From these, results using the standardized dataset could be obtained for three specific applications (the POLYMOD, Roxanne and CoRoVa models). Despite differences in the approaches, cost-effectiveness results of the models were quite similar. Differences between the outcomes of the specific building blocks of the cost-effectiveness (i.e., vaccination costs, savings and QALYs gained) of the models currently investigated seem to relate to five aspects of the models: the multi-cohort nature of the POLYMOD model which assumed a step up in vaccination coverage (and hence in vaccination costs as well as cases prevented); the exact timing of the waning in the models and in particular the exact modulation of between-dose efficacies in the CoRoVa model; assumptions about the distribution of cases of different severity levels within the one-year age groups provided (for example, assuming a Weibull distribution in the Roxanne model); and the possibility in the models of experiencing subsequent episodes of rotavirus infections and/or experiencing episodes with multiple manifestations (for example, first moderate progressing to severe) and types of health-care use (for example, inpatient and outpatient, rather than just one of both).

Ergo, differences between the models on the individual components of cost-effectiveness could be related to some specific generic features of the models with regards to representing vaccine uptake and pricing, within age-group distributions, waning and between-dose efficacies and inclusion of additional groups and episodes in the general design of these models. Sensitivity analysis revealed that cost-effectiveness of rotavirus vaccination is highly sensitive to vaccine prices, rotavirus-associated mortality and discount rates, in particular that for effects. This is fully in line with other authors' findings [32].

Unfortunately, we were not able to include a model with a transmission dynamic approach in our model comparison, instead of the cohort approach followed in the three models analyzed. Emerging evidence that herd immunity effects might be relevant for rotavirus transmission and vaccination enhances the relevance of considering populations and transmissions between cohorts [33-35]. Inability to include these models was often related to the complexity of these models and the difficulties to adequately grasp these complexities in the standardized framework provided on inputs and outputs. However, for further work it is important to also analyse such dynamic models given their major advantage of incorporating infection dynamics including herd immunity effects and potential age shifts in epidemiology [36]. Also, differences in uptake between high-, middle- and low-income countries should be analyzed using dynamic models given the different impacts of coverage levels on herd immunity.

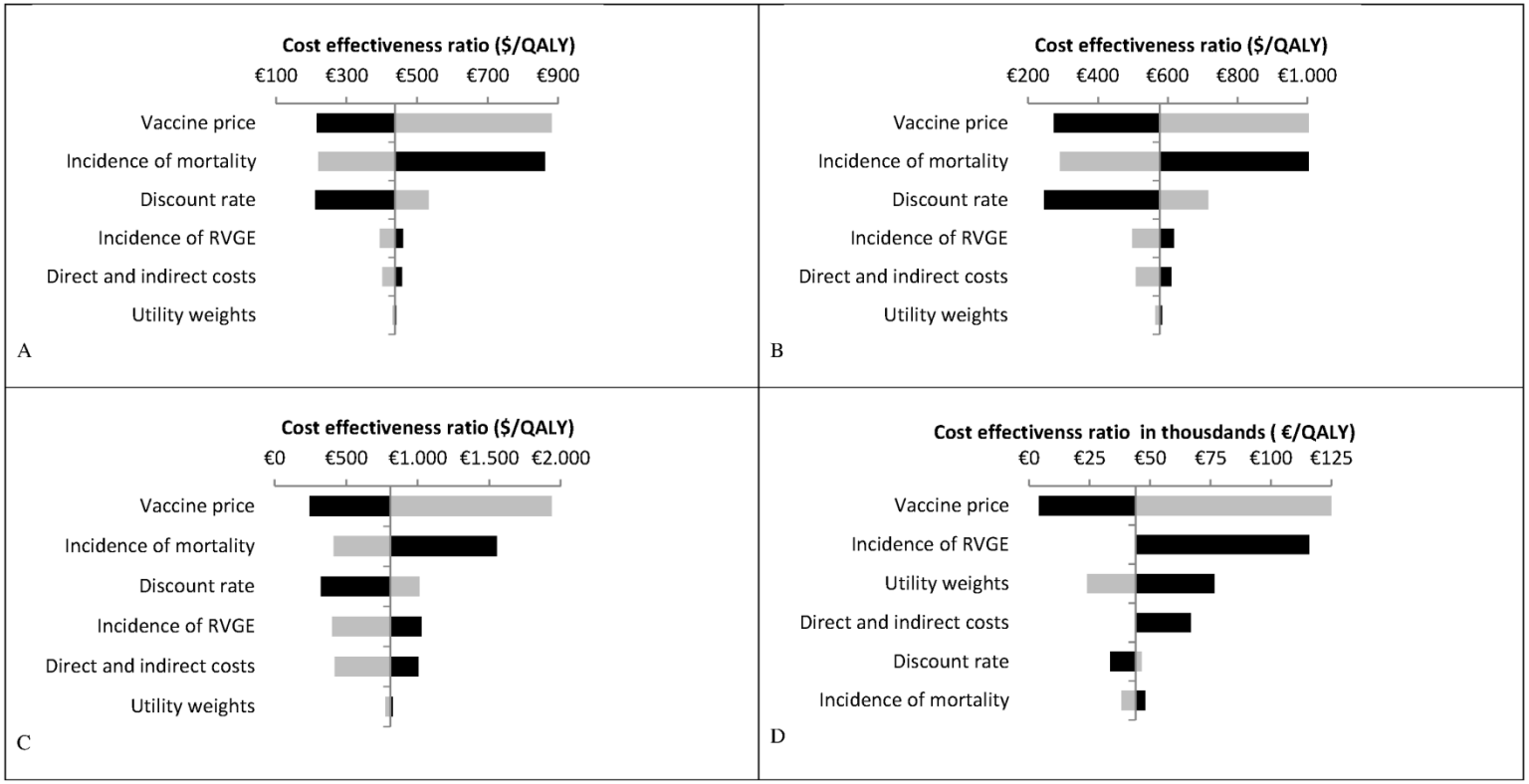

Figure 1. Sensitivity analyses on the base case cost effectiveness ratio using the CoRoVa model for Afr (a), Sear (b), Amr (c), and Eur (d) regions. Parameters were varied through halving and doubling, except for the discount rates which were 0% and 4% for both costs and health effects. Dark bars show the incremental cost effectiveness ratio after a 100% decrease in the parameter, whereas light bars show the incremental cost effectiveness ratio after a 100% increase (note that an increase in the incidence or the costs resulted in Graphs D for negative cost effectiveness ratios). Note that when the incidence of RVGE was increased or decreased, the total number of deaths was kept constant to identify the sole effect of incidence. QALY: quality adjusted life year, RVGE: rotavirus gastro enteritis.

The three models selected for our analysis were all basically developed for high-income countries. For reasons stated previously, other models – inclusive of models developed initially for low- and middle-income settings – could unfortunately not be considered in our comparison. As one consequence, all the publications arising from these models involved costs per QALY gained rather than costs per DALY averted. Although not undisputed, for low- and middle income settings DALYs rather than QALYs are the common metric used [27,37]. We do note that one specific study showed that results only slightly differ if DALYs are used instead of QALYs; in particular, it showed slightly more favourable cost-effectiveness for DALYs as the outcome [16]. However, it has been demonstrated that the decision about whether or not to include caregiver QALYs has a major impact on results [4,7]. The appropriateness of including QALYs beyond the index case of disease is being debated; it could be argued that caregivers' QALYs are particularly important for rotavirus as they can be measured directly, and hence may be more valid than QALYs in small children with RVGE, where proxy measurements have to be used [7,21,22].

Our findings for the regions Afr, Sear, Amr and Eur should not be considered as exact representative results and policy making should not directly be based on this. For example, it is very unlikely that the similarities assumed for the proportion of RVGE cases that are mild, moderate and severe are valid in real world. This simplifying assumption was made in order to test the models generically and consistently. Nevertheless, our results clearly indicate a general trend of increasingly more favourable cost-effectiveness when going from high- to middle and on to low-income countries, respectively. As the sensitivity analysis shows, this is obviously primarily related to vaccine pricing and the QALY-impact of averted mortality due to rotavirus infection. However for actual policy making, countries will need to either further consider the results from existing studies and reviews, or initiate country-specific cost-effectiveness analyses. For countries that have the capacity and resources to model the cost-effectiveness of rotavirus vaccine, our comparative analysis can help inform the design of new models or selecting existing models to support national-level decision making.

Hence, although our analysis is not meant to directly inform policy making, it offers considerable guidance for design and/or selection of a model for adaptation to individual (low-income) countries who want to conduct cost-effectiveness analyses. Scarce resources in these countries may direct the choice towards adapting an existing model rather than initiating the development of a new approach. Reassuringly, our analysis suggests that different models produce similar cost-effectiveness estimates, illustrating that the exact choice of which model to adapt may not be as crucial as the choice of assumptions and parameter values to incorporate in the model.

Conclusions

We conclude that our approach is helpful on two specific levels. Firstly, the comparative approach followed here is helpful in understanding the various models selected and will thus benefit (low-income) countries in designing their own cost-effectiveness analyses using new or adapted existing models. Secondly, we find that the communication between the individual researchers involved in the three models was helpful in the further development of these individual models and will be so in the future.

Therefore, we recommend that this kind of comparative study be extended to other areas of vaccination and even other infectious disease interventions, beyond the three areas that have been explored by WHO (pneumococcal vaccination, human papilloma virus vaccines and (here) rotavirus) [38-40].

Finally, the models reviewed in the exercise gave similar and comparable results which appear to have face validity. Hence it appears possible to recommend their use in policy settings, at least for high income countries. However, potential users of the models need to consider the specific building blocks of the cost-effectiveness models including the nature, scope, design and assumptions made and how they affect outcomes. Potential users of the models in low and middle income countries need to consider results from existing studies and reviews. There will be a need for contextualisation including the use of country specific data inputs. However, given that the underlying biological and epidemiological mechanisms do not change between countries, users are likely to be able to adapt existing model designs rather than developing completely new approaches. Also, transmission dynamic effects are likely to be important, particularly when considering the effect of vaccination (since vaccination can affect other cohorts besides those vaccinated). Hence, we would recommend that future cost-effectiveness tool comparison exercises include dynamic models.

Competing Interests

MP received a grant from SPMSD to perform research into the cost-effectiveness of rotavirus vaccination in the Netherlands, within the framework of MH his PhD-work. The grant was fully unrestricted and as such accepted by the Dutch Health Council to contribute to the advice on whether to integrate rotavirus vaccination in the Dutch National Immunization Program (discussion still ongoing; as of February 28th 2011). BS is an employee of GlaxoSmithKline Biologicals in Wavre (Belgium). All the other authors declare that they have no competing interests.

Authors' Contribution

MP & RH conceived the study. MP, MJ, BS, MR and HT integrated the results from different models and drafted the manuscript with input from the other authors. All authors provided advice on the methodology and the data analyses of tool comparison exercise. All authors read and approved the final manuscript.

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CHAPTER 7

Health economics of rotavirus immunization in Vietnam: potentials for favorable cost-effectiveness in developing countries

Hong-Anh T. Tu

Mark H. Rozenbaum

Peter C. Coyte

Shu Chuen Li

Herman J. Woerdenbag

Maarten J. Postma

Accepted by **Vaccine**

Summary

Introduction: Rotavirus is the most common cause of severe diarrhoea worldwide. Vietnam is situated in the region of high rotavirus infection incidence and eligible for financial support to introduce rotavirus vaccines into the Expanded Program of Immunization (EPI) from the GAVI. This study was designed to assess the cost-effectiveness of rotavirus immunization in Vietnam, explicitly the use of Rotateq® and to assess the affordability of implementing universal rotavirus immunization based on GAVI-subsidized vaccine price in the context of Vietnamese healthcare system for the next 5 years.

Methodology: An age-structured cohort model was developed for the 2009 birth cohort in Vietnam. Two strategies were compared: one being the current situation without vaccination, and the other being mass universal rotavirus vaccination. The time horizon of the model was 5 years with time cycles of 1 month for children less than 1 year of age and annual analysis thereafter. Outcomes included mild, moderate, severe cases and death. Multiple outcomes per rotavirus infection are possible in the model. Monte Carlo simulations were used to examine the acceptability and affordability of the rotavirus vaccination. All costs were expressed in 2009 US$.

Results: Rotavirus vaccination would not completely protect young children against rotavirus infection due to partial nature of vaccine immunity, however, would effectively reduce severe cases of rotavirus by roughly 55% during the first 5 years of life. Under GAVI-subsidized vaccine price (US$ 0.3/dose), the vaccine cost would amount to US$ 5.5 million per annum for 3-dose of the Rotateq® vaccine. In the base-case, the incremental cost per quality-adjusted-life-year (QALY) was US$ 665 from the health system perspective, much lower than per-capita GDP of ~ US$ 1,152 in 2009. Affordability results showed that at the GAVI-subsidized vaccine price, rotavirus vaccination could be affordable for Vietnamese health system.

Conclusion: Rotavirus vaccination in Vietnam would be a cost-effective health intervention. Vaccination only becomes affordable if the country receive GAVI's financial support due to the current high market vaccine price. Given the high mortality rate of under-five-year children, the results showed that rotavirus immunization is the "best hope" for prevention of rotavirus-related diarrhoeal disease in Vietnam. In the next five years, Vietnam is definitely in debt to financial support from international organizations in implementing rotavirus immunization. It is recommended that new rotavirus vaccine candidates be developed at cheaper price to speed up the introduction of rotavirus immunization in the developing world in general.

Introduction

Diarrhoea is a leading cause of child mortality. Globally, around 1.8 million children under the age of five die from diarrhoeal-related diseases per year and rotavirus has been identified as the most common cause of severe diarrhea [1,2]. Rotavirus infection has been reported to be responsible for more than 2 million hospitalizations worldwide and roughly 527,000 deaths annually [3]. A large share of the mortality and morbidity occurs in developing countries, such as Vietnam [4].

Vietnam was one of the two countries in Asia, besides Bangladesh, where the efficacy of the pentavalent rotavirus vaccine, RotaTeq®, was assessed in 2009 under a joint partnership between the PATH Rotavirus Vaccine Program and Merck [4]. A major outcome of this clinical trial was the establishment of vaccine efficacy against severe disease at 48.3% (95% CI 22.3%-66.1%) in Asia [4] or 63.9% (95% CI 7.6%-90.9%) in Vietnam. This supported the WHO's expanded immunization recommendations to promote the global use of rotavirus vaccines. Notably, Vietnam established sentinel hospital surveillance to assess the burden of rotavirus already back in 1998 [5]. This surveillance network later served as a model for 8 other countries in the Asian Rotavirus Surveillance Network [5,6].

Up to now, only two cost-effectiveness studies on rotavirus immunization have been conducted in Vietnam [7,8], confirming that implementing rotavirus vaccination in the Expanded Programme on Immunization (EPI) would be a cost-effective health-care intervention. However, these studies only evaluated the use of the monovalent Rotarix™ vaccine while ignoring the possible use of the pentavalent rotavirus vaccine in the EPI. Additionally, these previous studies did not account for between-dose vaccine efficacies and used vaccine efficacy data, which was done in other countries rather than Vietnam.

Considering the limitations of both studies, we performed a cost-effectiveness analysis on rotavirus immunization in Vietnam focusing explicitly on the use of RotaTeq® as one of the recommended vaccines to be introduced into countries' EPI. A major advantage of this approach is that it allows us to utilize the most updated and recently released results on RotaTeq® vaccine efficacy, which was conducted in Vietnam [4]. We applied a cost-effectiveness model developed by University of Groningen, but different from previous studies using this model [9,10], we additionally assessed the affordability of implementing universal rotavirus immunization based on the GAVI-subsidized price and market price in the context of the Vietnamese healthcare system for the next 5 years [11]. Finally, as a novel data source we included publications and reports written in the Vietnamese language, thus incorporating literature that is not internationally accessible and was not previously applied in the models.

Methods

Model

We applied the CoRoVa model (the Concensus Model on Rotavirus Vaccination) developed by University of Groningen for our analysis [10], see Figure 1. This model has been used previously to calculate the cost-effectiveness of rotavirus vaccination for both developing and developed countries [9,10]. We selected CoRoVa instead of other models for the Vietnamese context because of its ability to

capture more than 1 infection per child and to account for waning immunity, maternal protection against infection through breast feeding, and herd immunity [9]. In detail, we populated the Vietnamese 2009 birth cohort of 1,485,000 [12] in this age-structured cohort model and applied a 5-year time horizon with time cycle of 1 month for children less than 1 year of age and annually thereafter. Health outcomes from this model were classified by the four levels of severity of rotavirus-related diarrhoea: mild, moderate, severe and death. In particular, severe cases refer to rotavirus-related cases that require hospitalization. Mild and moderate cases are assumed to require home-treatment and outpatient visits to a health clinic, respectively. This classification is in accordance with an earlier published study [2]. The model is programmed in Microsoft Excel 2010. For probabilistic sensitivity analysis, the CoRoVa model uses the @RISK 4.5.4; Pallisade 2011, Newfield, NY.

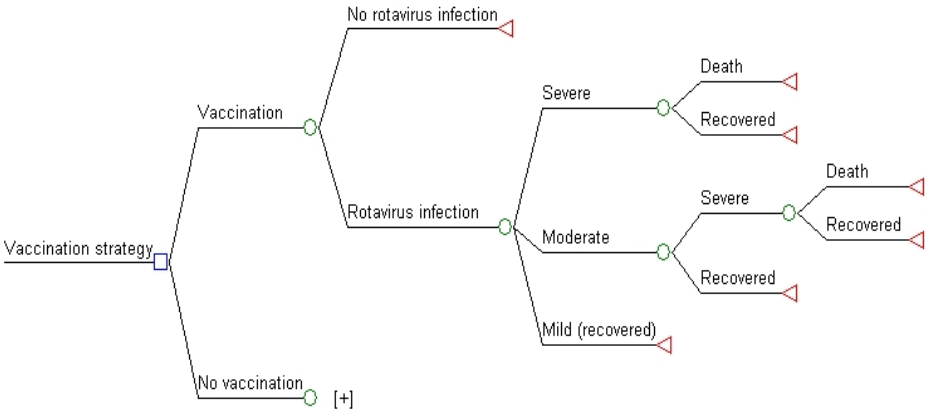

Figure 1 Decision analytic model for estimating the cost-effectiveness of universal rotavirus vaccination in Vietnam

Epidemiology

We obtained data on the cumulative age distribution of severe cases due to rotavirus gastroenteritis in Vietnam from the afore-mentioned sentinel surveillance study on disease burden of rotavirus carried out in the country [5,6]. Since similar data were not available for rotavirus cases rated as mild, moderate or rotavirus-related mortality, we assumed the same cumulative age distribution as for severe cases for the exact computation of the estimated number of mild, moderate, and deaths by age groups.

Computation of rotavirus-related deaths

The total number of rotavirus-associated deaths among children aged < 5 years in 2009 was estimated by applying the WHO's specific data on rotavirus-related mortality among <5-year children to the birth cohort in Vietnam [13], see Figure 2. The number of age-specific deaths was computed by applying the age distribution to the total rotavirus-associated deaths. Age-specific rotavirus-associated mortality was then calculated by dividing the age-specific deaths by the number of children in each different age group, see Table 1.

Calculation of severe cases

The age-specific number of rotavirus-associated severe cases was estimated by combining the number of deaths and the ratio between rotavirus-related deaths and hospitalizations of 1:31, according to the two previous Vietnamese studies [8,14],see Figure 2. The age-specific rate of severe cases was calculated by dividing the age-specific severe cases by the number of children in each age group, see Table 1.

Calculation of moderate cases

Numbers of moderate cases among under-5-year Vietnamese children were estimated by applying the ratio between rotavirus-related deaths and visits of 1:97 according to earlier studies [7,8], see Figure 2. The age-specific rate of moderate cases was calculated by dividing the age-specific moderate cases by the number of children in each age group, see Table 1.

Calculation of mild cases

No data were available on the number of Vietnamese cases among children under five-years with mild diarrhoea. Therefore, we estimated rotavirus-related mild episodes using data from an earlier study [2] together with information obtained from the Ministry of Health in Vietnam and expert opinions of local paediatricians [15]. The rate of age-specific mild cases was calculated similarly as for moderate cases, see Table 1.

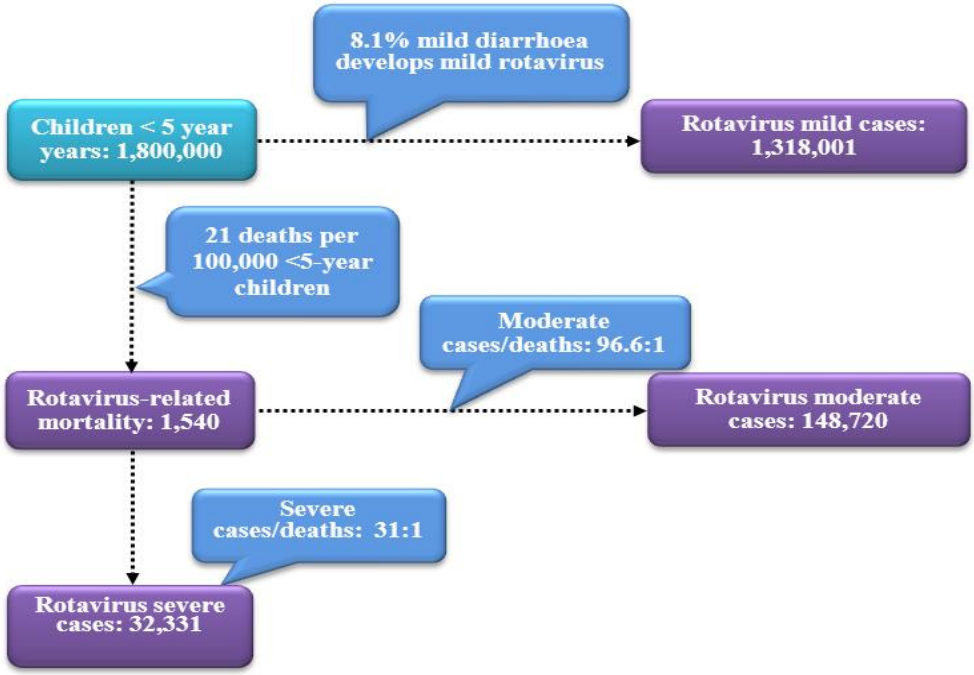

Figure 2 Scheme for estimation of rotavirus epidemiology in Vietnam

Age in years	Age in months	Mild	Moderate	Severe	Mortality rate
-	0	0.08830	0.00996	0.00217	0.000103
-	1	0.08838	0.00997	0.00217	0.000103
-	2	0.08847	0.00998	0.00217	0.000103
-	3	0.30643	0.03458	0.00752	0.000358
-	4	0.30673	0.03461	0.00752	0.000358
-	5	0.30703	0.03464	0.00753	0.000359
-	6	0.64997	0.07334	0.01594	0.000759
-	7	0.65061	0.07341	0.01596	0.000760
-	8	0.65125	0.07349	0.01598	0.000761
-	9	0.75868	0.08561	0.01861	0.000886
-	10	0.75942	0.08569	0.01863	0.000887
-	11	0.76017	0.08578	0.01865	0.000888
1	12	0.34014	0.03838	0.00834	0.000397
2	24	0.06863	0.00774	0.00168	0.000080
3	36	0.02718	0.00307	0.00067	0.000032
4	48	0.00889	0.00100	0.00022	0.000010
5	60	0.00889	0.00100	0.00022	0.000010

Table 1 Age-specific rotavirus-associated cumulative incidence rate

Vaccine efficacy, waning immunity and between-dose efficacy

Clinical trials on RotaTeq® vaccine efficacy carried out in Vietnam showed that vaccine efficacy against rotavirus-related severe cases was estimated to be 63.9% (95% CI 7.6-90.9) in Vietnam after two-year post vaccination [4]. The analysis showed that vaccine efficacy against severe cases was (72.3% (95% CI -45.2-97.2) during the first full season after vaccination and 64.6% (95% CI 47.7-93.9%) during the second full season [4]. Based on the difference in efficacy between first and second rotavirus seasons post-vaccination, we conservatively assumed that vaccine efficacy would exponentially decrease by 11% per year starting after the first year (waning).

No specific clinical data on RotaTeq® vaccine efficacy against mild or moderate rotavirus-related cases are available for the population living in Asian developing countries. For moderate cases, we used the RotaTeq® vaccine efficacy ratio between clinical visits and hospitalizations as published by Ruiz-Palacious et al (86% and 95.8%, respectively) [16]. Using this ratio and vaccine efficacy against severe cases (63.9%) in Vietnam, we subsequently calculated vaccine efficacy against moderate cases Vietnam (57.4%) as: (0.86/0.958)*0.639*100%. Vaccine efficacy against mild cases (52%) was taken from the literature [17-23], see Table 2. We conservatively assumed that vaccine efficacy against mild

and moderate cases would decrease at the same rate as for severe cases from the first to the second season.

To estimate between dose efficacy for a 3-dose RotaTeq® vaccine, we utilized data from a recent study on this subject, where the rates of combined hospitalizations and emergency visits (ED) between doses 1 and 2, and between doses 2 and 3 were reported at 82% (95% CI: 39-97%) and 84% (95% CI: 54-96%), respectively [24]. Based on this information, we estimated vaccine efficacy against severe disease between doses 1 and 2 at 52.4% (0.82*63.9%) and between doses 2 and 3 at 53.7% (0.84*63.9%). Again, we conservatively applied the same rate for estimating between-dose efficacies for mild and moderate cases.

For vaccine coverage, we assumed that RotaTeq® vaccine would be administered at the same time with Diptheria-Polio-Tetanus (DPT) vaccine in Vietnam (at 2,4 and 6 months). Therefore, the DPT vaccine coverage of 93% would also be applicable for the RotaTeq® vaccine [25], see Table 2.

QALY losses

As there are no data available on quality-of-life losses in Vietnam due to rotavirus infection, we applied the QALY losses in affected infants and children provided by a number of comparable studies [17,19,20,26] (Table 2). A under-5-years-old child normally requires at least one care giver (e.g., one parent) to take care when she/he is infected with rotavirus. In severe cases, even two care-givers (e.g., two parents) would be needed to take care for the sick child. In the base-case analysis, we did not include the QALY loss of caregivers. In sensitivity analysis, the QALY losses by caregivers were taken from earlier work [10].

Sensitivity and scenario analyses

We performed several sensitivity analyses in the study including univariate, multivariate, scenario-analytic, probabilistic approaches and affordability analysis.

Univariate sensitivity analyses were performed to explore impacts of different model input parameters on cost and health outcomes of rotavirus vaccination. We selected several parameters for examination by varying the value of one parameter by 25% while other parameters remained constant at their base-case value.

Several scenario analyses were analysed, including (i) base-case analysis where no QALY losses of care-giver is considered, (ii) inclusion of QALY losses of one care-giver and (iii) inclusion of QALY losses of two care-givers were performed.

Probabilistic sensitivity analyses (PSA) were performed by running 5000 Monte Carlo simulations using @RISK 4.5.4; Pallisade 2011, Newfield, NY. Distributions associated with input parameters are shown in Table 2 [27]. The PSA results are subsequently presented in cost-effectiveness acceptability curves (CEACs) from a societal perspective for all scenarios. We then evaluated affordability (only shown for the base-case analysis) based on the joint distribution of simulated incremental costs and health gains of rotavirus vaccination. The advantage of affordability curves is their ability to explain the impacts of

financial resources on vaccination. The curve visualizes affordable probabilities for a vaccination program given various budgetary levels while also taking into account the uncertainty of all parameters. Affordability analyses were performed under the assumption that childhood vaccination programs were indivisible, which implies that it could not be performed for a fraction of infants. This is realistic as in practice all vaccines implemented in the EPI in Vietnam are given to every child [28].

Costs

Direct treatment costs, and indirect costs incurred due to rotavirus-associated mild, moderate and severe cases were retrieved from a cost study previously conducted in Vietnam [7]. The analyses were carried out from both the healthcare (including only direct medical costs) and the societal (both direct medical costs, direct non-medical costs and indirect costs) perspectives. These cost items were collected in 2005, and we converted them to 2009 US$ (as reported in Table 2) to reflect current price levels, using the underlying growth rate in consumer prices.

Outcome measures

We calculated the incremental cost-effectiveness ratio (ICER) per QALY for the base-case and various scenarios and sensitivity analyses consistently comparing vaccination vs. no vaccination. Additionally, we examined the impacts of GAVI-subsidized and market RotaTeq® vaccine prices on ICER values. We used the WHO's definition on cost-effectiveness of health interventions to evaluate results of rotavirus vaccination in Vietnam [29].

Description	Base case value	Distribution	References
Vaccine coverage	93%	Triangular (90%; 93%; 98%)	[25]
Vaccine Efficacy			
Severe infections hospitalisation (2-year average, see Methods)	63.9%	Lognormal mean 0.639 (SE 0.2125)	[4]
Waning rate per year (exponential decrease)	11%	NA	[4]; calculated
Moderate infections requiring a clinic visit (assumption [b], see Methods)	57.4%	Lognormal mean 0.574 (SE 0.0819)	[4; 16]; calculated
Waning rate per year (exponential decrease)	11%	NA	Assumption
Mild infections treated at home (first year)	52%	Lognormal mean 0.52 (SE 0.0791)	[17-23]
Waning rate per year (exponential decrease)	11%	NA	Assumption
Rotavirus-related epidemiological parameters			
Mild	1,318,001	Normalised mean: 1,318,001 (90%CI; 1,317,366-1,318,636)[a]	[2; 15]
Moderate	148,720	Normalised mean: 148,720 (90%CI; 148,116-149,324)	[7; 8]
Severe	32,331	Normalised mean: 32,331 (90%CI; 32,038-32,624)[a]	[8; 14]
Deaths	1,540	Not varied	[13]
Age-dependent rotavirus-related proportion			
Mild, Moderate, Severe		Dirichlet	[27]
QALY losses			

Mild Moderate Severe	0.00164 0.00548 0.02110	Triangular (using 25% lower and upper)	[17; 19; 20; 26]
Total direct costs per case (healthcare perspective)			
Mild	4.64	Triangular (4.52; 4.64; 4.77)	[7]
Moderate	5.07	Triangular (4.86; 5.07; 5.27)	[7]
Severe	35.28	Triangular (28.80; 35.28; 41.76)	[7]
Total direct and indirect cost per case (societal perspective)			
Mild	8.65	Triangular (7.51; 8.65; 9.79)	[7]
Moderate	10.68	Triangular (10.29; 10.68; 11.08)	[7]
Severe	44.04	Triangular (40.65; 44.04; 47.43)	[7]
Total vaccination and administration cost per child			
3-dose, GAVI subsidized price	1.11	Alternative scenario	[11; 42]
3-dose, Market price	15.21	Alternative scenario	[43]
Discount rate	3%	Unvaried	[30]

NA: not applicable; SE: standard error
[a] Square root transformation was applied.
[b] (RotaTeq® EDV efficacy/RotaTeq® hospitalization efficacy (reference)) x RotaTeq® hospitalization efficacy for developing Asian countries) = (86%/95.8%)*63.9%= 57.4%

Table 2 Parameters used in the economic model

Results

Base-case results

Detailed results of the base-case scenario are presented in Table 3. Assuming 93% coverage, vaccination of a birth cohort of 1,485,000 would reduce rotavirus-related mild, moderate, severe cases and deaths by 44%, 49%, 54% and 54%, respectively. This reduction corresponds to a gain of 25,825 discounted QALYs and a saving of US$ 6.4 million in burden cost-of-illness due to rotavirus infection.

At the per-dose-GAVI-subsidized price of US$ 0.3 for the RotaTeq® vaccine, rotavirus immunization would become a cost-saving strategy. Vaccination would always be cost-saving when the RotaTeq® vaccine price <= US$ 0.9/dose and <=US$ 1.6/dose from the health system and societal perspectives, respectively. In contrast, at the per-dose market price of US$ 5, vaccination is not cost saving and results in an ICER per QALY of US$ 665 and US$ 556 from the health system and societal perspectives, respectively. These cost-effectiveness values are still less than the 2009 Vietnamese GDP-per-capita of US$ 1,159 [12], suggesting that rotavirus immunization is a cost-effective health intervention for the Vietnamese healthcare system according to WHO's definition for cost-effectiveness, see Table 3.

Univariate sensitivity & scenario analyses

The impacts of parameter changes on the results are presented in a Tornado diagram (Figure 3). Cost-effectiveness results of rotavirus vaccination were most sensitive to vaccine efficacy against severe

cases, rotavirus-related mortality. In contrast, total hospitalization cost and outpatient visit cost have minimal impact on the cost-effectiveness outcomes. Figure 4 shows that up to US$ 3.5 per dose, there were very small changes in the ICER value per QALY from the societal perspective.

	No vaccination	Vaccination [a]	Difference
Cases [b]	1,499,052	829,786	669,266
Mild	1,318,001	738,399	579,602
Moderate	148,720	76,528	72,193
Severe	32,331	14,859	17,471
Deaths	1,540	708	832
Total QALYs lost [c]	48,177	22,352	25,825
Total cost-of-illness [a, c]	$,14,139,897	$,7,699,471	$,6,440,426

Vaccine pricing scenarios	GAVI-subsidized price ($0.3/dose)	Market price ($5/dose)
ICER per QALY (healthcare perspective) [c]	cost-saving	$665
ICER per QALY (societal perspective) [c]	cost-saving	$556

[a] Costs are excluding vaccination costs
[b] Undiscounted
[c] Discounted

Table 3 Results from the base-case analysis

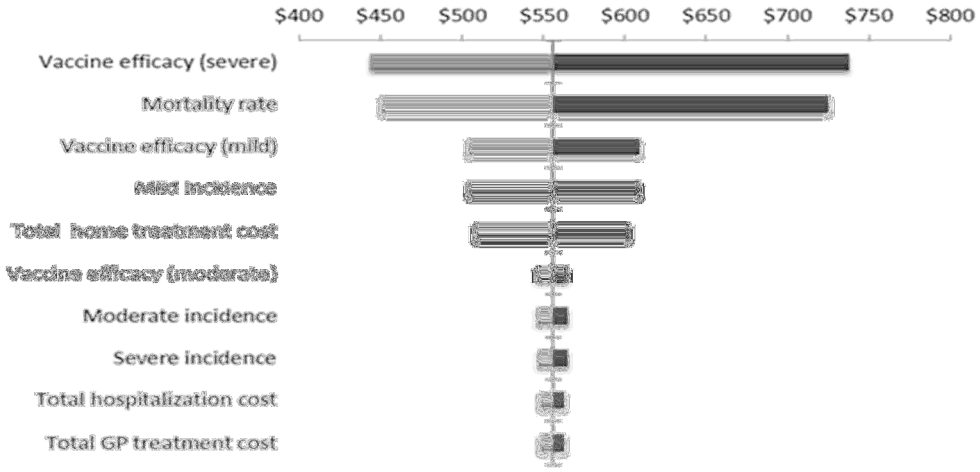

Figure 3 Results of univariate sensitivity analyses showing the ranges of ICERs for universal newborn vaccination against rotavirus compared to no vaccination in Vietnam (societal perspective)

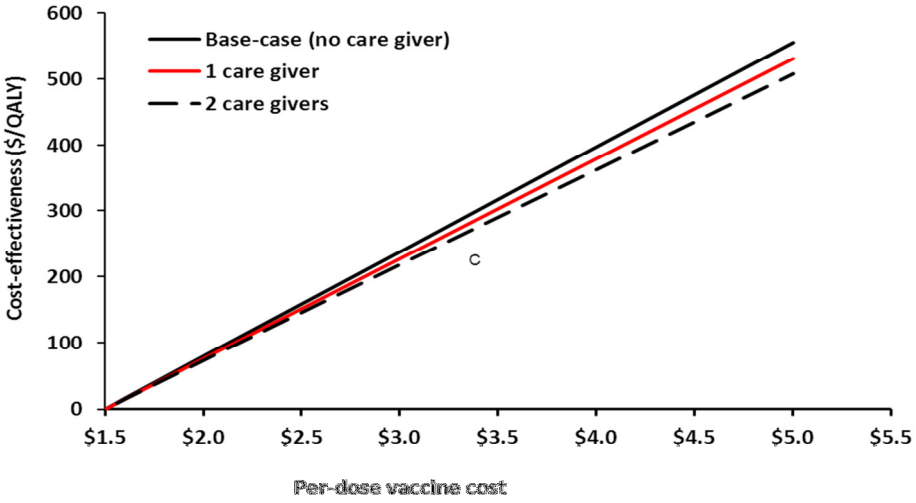

Figure 4 Diagram showing how vaccine pricing impacts on the ICER value under different assumptions for QALY-losses from the societal perspective

Probabilistic sensitivity analyses

Cost-effectiveness acceptability curves (CEACs)

Results of probabilistic sensitivity analyses from societal perspective are presented in Figure 5. The CEACs showed that at the threshold ICER per QALY of US$ 556 (the base-case value of ICER per QALY from the societal perspective), the probability for the vaccination program to be cost-effective would be 67.7%, 70.2% and 73.7% for scenarios with no care giver, one care giver and two care givers, respectively. If a US$ 1,000 threshold per QALY was applied (<1x per-capita-GDP), still >90% of simulations resulted in acceptable ICERs for all scenarios. If a threshold of US$ 3,000 per QALY was applied (<3x per-capita-GDP), >98% of simulations resulted in acceptable ICERs for all scenarios. Although the CEACs help to summarize the uncertainty surrounded the cost-effectiveness possibility of a rotavirus vaccination program, the curve is unable to inform the decision-makers regarding resources to fund vaccination programs, which remains a crucial factor for the Vietnamese healthcare sector and other developing countries.

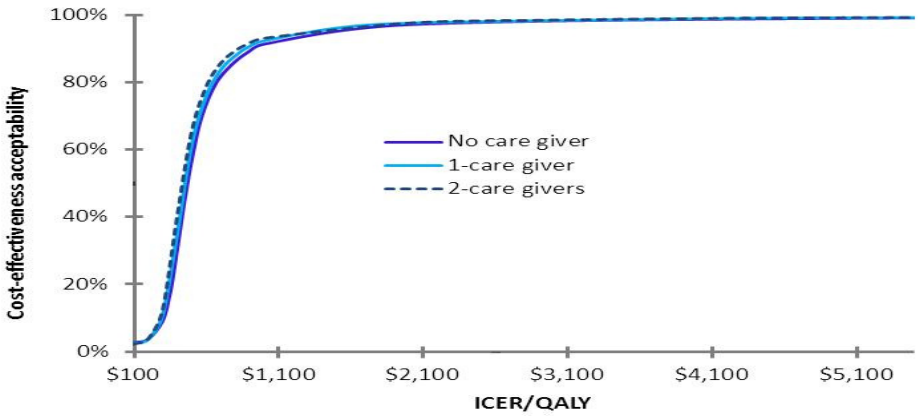

Figure 5 Cost-effectiveness (C-E) acceptability curve showing the probability that universal newborn rotavirus vaccination in Vietnam is cost-effective at different cost-effective threshold values (societal perspective)

Affordability curve

Figure 6 presents affordable scenarios where rotavirus vaccine is subsidized by the GAVI and when it is purchased at the market price of US$ 5 per dose. The results show that under GAVI-subsidy, rotavirus vaccination would always be fully implementable when the budget exceeds US$ 5.5 million. In contrast, vaccination would not be affordable with a budget ≤ US$ 1.5 million. Under the market scenario, vaccination would only be implementable at the minimum budget of US$ 10 million, which is almost 2 times higher than the needed budget for full vaccination under the GAVI-subsidy scenario. Rotavirus vaccination would always be implementable when the budget exceeds US$ 22 million.

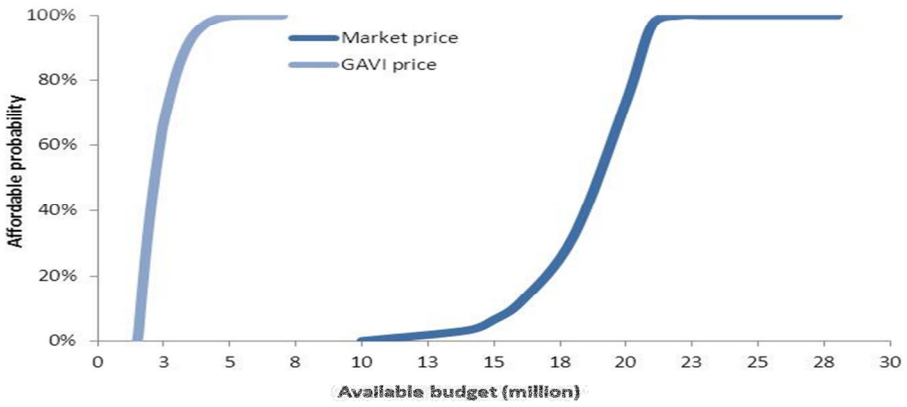

Figure 6 Affordability curves showing the probability that *rotavirus vaccination is affordable (for birth* cohort of 1,485,000) as a function of budget constraint (societal perspective and no care giver QALY-losses assumed)

Discussion

Our economic analysis indicates that inclusion of rotavirus vaccination in the EPI in Vietnam would be cost-effective or even cost-saving depending on the cost of the vaccine. At the base-case GAVI-subsidized price of US$ 0.3 per dose, rotavirus vaccination would be cost-saving from both analyzed perspectives (health care and societal). Rotavirus vaccination would reduce the number of rotavirus-related cases and deaths by approximately 50%.

From the societal perspective, at the current market price of US$ 5 per dose, rotavirus vaccination would be a cost-effective intervention according to the WHO's criteria for cost-effectiveness [29]. However, being cost-effective does not automatically mean that the intervention would be affordable for the Vietnamese healthcare. Indeed, when parameter uncertainties are taken into account, affordability analyses revealed that there was a big difference in required funds for rotavirus vaccination in Vietnam under the GAVI-subsidized and market situations. In particular, at the market vaccine price of US$ 5 per dose, a fully implemented vaccination program would cost US$ 22 million, while it would only cost US$ 5.5 million under the GAVI-subsidized price of US$ 0.3 per dose. Practically speaking, in 2009, total government spending in Vietnam on EPI activities was approximately US$ 8 million [30]. Compared to the total government health budget, the required investment by the government for universal rotavirus vaccination in case of no GAVI support would be more than triple. This implies that if the Vietnamese government has to fully finance vaccination by itself, implementation would be highly unrealistic. A possible solution would be to reduce rotavirus vaccine price either through the development of new generations of less expensive rotavirus vaccines or through subsidy by international organizations for developing countries like Vietnam. Next to possibilities of GAVI-subsidized programs, in fact, the Vietnamese Ministry of Health is testing a vaccine against rotavirus, which is domestically manufactured. Clinical trials are being carried out in Vietnam [31-36].

Our study confirms that rotavirus vaccination using the Rotateq® brand is cost-effective in Vietnam from both societal and health system perspectives. This is congruent with other studies in high-endemic and intermediate-endemic countries [8,37-41]. Our study also emphasizes the important role of donors such as the GAVI in financing vaccination programs. Indeed, Vietnam is still a developing country and relies heavily on external financial support. To assist a high-endemic country in implementing vaccination programs, financial support is indispensable. Our results may be useful to help Vietnamese government to apply for further financial support from the GAVI.

Compared to other studies conducted in Vietnam on the same subject [7,8], our results are similar by concluding that rotavirus vaccination is a cost-effective public health intervention. The results support the WHO's recommendations on universal rotavirus immunization worldwide. However, our study also differs from previous studies in Vietnam. Firstly, we used RotaTeq® vaccine instead of Rotarix™ vaccine in the analysis. The advantage of this was the utilization of the most updated local RotaTeq® vaccine efficacy data on severe cases, which was just completed in Vietnam. Using these data instead of the general efficacy data from other regions of the world probably gives more reliable estimates. Another difference was the application of an age-structured cohort model. The advantage of this model is its

ability to capture multiple infections per infected child, waning immunity as well as the impacts of breast feeding though the latter was not yet considered in our current analysis due to data availability. Additionally, the application of this model was supportive of another study initiated by the WHO, which offers guidance for design and/or selection of a model for adaptation to individual (low-income) countries who want to conduct cost-effectiveness analyses [9]. Finally, our study explored the impact of caregivers by considering scenarios where QALY losses of caregivers were included. This was not done in any earlier studies on the same subjects in Vietnam. The importance of including QALY losses of caregivers into our study was because a sick child normally is cared by a caregiver (e.g., parents, or family members). Other studies tend to ignore the impacts of caregivers. Carrying such type of analysis, we explored the important role of care-givers.

Our study, however, does encounter some limitations. The first limitation is the application of a static, step-wise model of the disease instead of applying a dynamic continuous model. In particular, the latter type of models allows the inclusion of herd immunity effects in the analysis. In the lack of data and information, herd immunity was not considered in the study. However, had herd immunity been included in the analysis, impacts of rotavirus vaccination would have been greater and favorable cost-effectiveness or even cost-saving would only have been further strengthened. The second limitation is the lack of data on vaccine efficacy for mild and moderate cases. We used data from various studies conducted in developed countries, thus the vaccine efficacy might be overestimated for a developing country. However, if the vaccine efficacy would be lower, rotavirus vaccination would prove to be even more cost effective. The third limitation is the lack of rotavirus epidemiology data in Vietnam. There was much estimation in different stages of rotavirus in the study. However, even at this high epidemiology, rotavirus vaccination was proved to be cost-effective. The fourth limitation is the utilization of treatment costs. The treatment cost of rotavirus-related diarrhoea was collected in 2005 and the cost must have changed in 2009. To overcome this, we have adjusted the cost by using the CPI to make it more updated. Indeed, rotavirus vaccination would be more cost-effective when the treatment cost of the disease was higher.

Our study shows that vaccine price was a crucial factor on the cost-effectiveness results and a heavy burden for any developing country's government in introducing a new vaccine. The current available market price (US$ 5 per dose) appears to be very expensive for the Vietnamese government suggesting that new generations of less costly rotavirus vaccines be developed or financial supports from the GAVI a decisive factor for the Vietnamese health system at least in the next 5 years.

The results of our cost-effectiveness analysis on the use of RotaTeq® vaccination in Vietnam should encourage health policy makers as well international donors, who are committed in supporting developing countries in combating infectious diseases in children as well as of supportive of the WHO's recommendation on universal rotavirus vaccination.

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CHAPTER 8

General Discussions and Conclusions

General Discussion, Conclusions and Future Perspectives

Discussion

The emphasis of this thesis is on economic evaluations of universal childhood immunization strategies against infectious diseases implemented within the Expanded Programme on Immunization EPI in developing countries with the focus on Vietnam. Two infectious diseases, hepatitis B and rotavirus were selected as examples. The former represents the current immunization strategy within the EPI and the latter represents the recommended vaccination strategy for the future. Adding new vaccines to routine infant immunization schedules is a financial challenge for Vietnam, requiring institutional and policy changes at the national level. In the context of the scarcity of resources, there is a need for prioritization of vaccines, planning to secure their sustainable supply, information on their affordability, assessment of their cost-effectiveness, and support from international organizations in providing funding for vaccination programs.

The research presented in this thesis explores the contribution of economic evaluations and provides tools to address some of the afore-mentioned issues. Analyses of this sort are still limited for developing countries and therefore considered valuable for the progress in the field. Hence, findings of this research may be useful for developing countries in formulating appropriate public health policies, mobilizing financial resources for vaccination programs and making plans for vaccines sustainability. The detailed findings are summarized and discussed below.

Cost-effectiveness analyses

In this thesis, the overall emphasis is on the different modeling techniques, which can be used to estimate the cost-effectiveness of (preventive) interventions against infectious diseases. In particular, the cost-effectiveness analyses against hepatitis B and rotavirus consist of both epidemiological and economic aspects and modeling of incidence numbers and costs are discussed in detail in Chapters 4 and 7, respectively. In Chapter 4, a Markov model for chronic hepatitis B infection was designed and in Chapter 7, an existing age-structured cohort model was adopted for the Vietnamese birth cohort. Though the applied models were static and did not yet account for the benefit of herd immunity of vaccination, such analyses are very useful in developing countries, in particular in view of their current scarcity. In fact, the cost-effectiveness analysis on universal childhood hepatitis B immunization presented in Chapter 4 was the first study ever carried out in Vietnam. It provides useful information for the Vietnamese health policy-makers on the performance of hepatitis B vaccination in the country. The modeling technique applied in that study could eventually be applied for economic evaluations of other vaccination programs within the EPI in Vietnam and in other (neighboring) countries. Chapter 7 presents a comparable assessment for the recommended rotavirus immunization in Vietnam. However, we did not design a disease Markov model ourselves for this study but applied an existing age-structured cohort model for the Vietnamese birth cohort that had been specially designed by our research group to be applied for developed countries. The overall aim was to explore the benefit for developing countries in utilizing existing disease models for their future research. This matter has been discussed in a comparative study on cost-effectiveness models designed for rotavirus vaccination in developed countries in Chapter 6. One of the strengths of the study in Chapter 7 is the utilization of the most

updated data on vaccine efficacy, which was actually carried out in Vietnam. This enabled us to provide more rigorous cost-effectiveness results on rotavirus vaccination than other similar studies on the same subject ever done in Vietnam (1, 2).

Budget impacts and affordability analyses

To assist health policy makers in budget preparation for various vaccination programs in Vietnam, besides conducting cost-effectiveness analyses of respective vaccination strategies, we performed budget impact and affordability analyses. The argument for doing this was that many healthcare interventions could be cost-effective but might not be affordable due to high expenses (e.g., high vaccine price). Indeed, for a developing country such as Vietnam, one of the most crucial factors for the government to decide whether to introduce a new vaccine or to extend vaccination to a larger population depends heavily on the budget availability. Hence, we presented a financial tool to assist health decision-making processes by running Monte Carlo simulations to account for uncertainty of all input factors of a vaccination program. The results of simulated iterations are presented in affordability curves and cost-effectiveness affordability curves based on the theory by Sendi & Briggs [3]. This methodology was applied in the studies described in Chapters 4 and 7. Budget impact and affordability analyses will definitely help inform decision makers on the level of required budgets for vaccination while facing the scarcity of resources. This methodology was, however, done under the assumption that a vaccination program was indivisible, meaning that vaccination cannot be administered to only a fraction of infants based on the arguments that this would be inequitable. This was reasonable in Vietnam as vaccination within the EPI is given free to every child. Results of our analyses will inform health managers of the minimum required budget for a vaccination program to be implementable and the maximum budget level at which vaccination would be fully implemented. The findings from the affordability analyses will be useful for governments in developing countries in making appropriate financial plans for different vaccination strategies and applying for additional funds from international organizations, such as the Global Alliance of Vaccines and Immunization (GAVI), that are committed to promote universal vaccination in the developing world.

Cost-of-illness

Treatment cost of a disease is, one of the two most important components for any cost-effectiveness analysis beside epidemiological data. However, data on this issue are still not yet available for almost all diseases in Vietnam and in most developing countries. To overcome this limitation, we carried out a cost-of-illness study to estimate the burden of chronic hepatitis B in Vietnam as an example, which is the subject of Chapter 3. The overall aim was to provide a methodology in estimating the burden of disease in the context of limited data available and to inform health policy-makers of the economic burden of the chronic hepatitis B to the Vietnamese society. Indeed, cost-of-illness research on hepatitis B has been done in various Asian countries and different methodologies were introduced [4-7]. However, these studies were conducted in countries, where an established recording system of patients and costs had been developed. In contrast, data recording is still an emerging and serious issue in Vietnam due to the poor facilities and infrastructure. By conducting the cost-of-illness of chronic hepatitis B infection, we tried to provide an approach to mitigate the data limitation for the treatment cost

estimation. We also tried to provide plausible explanations for the uncertainty surrounded cost estimations by conducting various sensitivity analyses (e.g., one way, two-way sensitivity analyses) to give a range within which the cost could be varied. This approach could potentially be applied for estimating the burden of many other diseases in countries where there is limited available data like Vietnam.

Regarding the treatment cost of rotavirus, we fortunately could make use of cost data derived from an existing study carried out in Vietnam [1]. However, to make the cost up-to-date, we adjusted the treatment cost of rotavirus infection by using the consumer price index.

The role of the GAVI and the international community

Throughout the research, the important role of the GAVI in providing financial support is indispensable. This is mentioned in Chapters 1 and 5 where hepatitis B and rotavirus immunization in developing countries were extensively reviewed. The crucial role of the GAVI is furthered explored in the consequential Chapters 3 and 7 where cost-effectiveness analyses of vaccination in Vietnam were carried out. In particular Chapter 7 went further to compare the required budget for rotavirus vaccination based on market vaccine and GAVI-subsidized prices. It was concluded that without the GAVI support the government of Vietnam might have to spend up to US$ 25 million for a full immunization program against rotavirus, while under the GAVI support, this necessary budget goes down to US$ 6 million. This is significant for Vietnam where healthcare programs are competing among limited resources. Indeed, statistical data from the Ministry of Health show that in 2009 the total expenditure for all EPI activities in Vietnam was approximately US$ 8 million [8]. Budget analyses revealed that the necessary funding for universal vaccination against hepatitis B and rotavirus in Vietnam would exceed the total budget given for all EPI activities. The results of our research would justify the support from the GAVI and provide positive health-economic evidences for international organizations, which are committed to help developing countries.

Strength of our research

Our research has embarked on different types of economic evaluations such as cohort-based, Markov-based cost-effectiveness analyses, affordability analyses, which as previously mentioned are still very limited in Vietnam. The application of advanced modeling techniques such as the application of Monte Carlo simulations, one-way or multivariate sensitivity analyses in our research helped clarify and understand the uncertainty in health economic evaluations and provide a reasonable explanation for the results obtained. The techniques applied may become useful tools for economic evaluations of other public health interventions in Vietnam and other developing countries, where the epidemiology of diseases is similar. They are discussed in details in Chapters 3, 4, 6 and 7.

Notably, health economics is still a new research area in Vietnam though it has been well recognized in developed countries. The embarkment of our research on this topic should provide insightful information for Vietnamese policy makers on assessing current and future public health programs and encouraging research institutions to promote health economic research. It eventually could become a strong and efficient evaluation tool for health care decision makers in evaluating the outcomes and making financial plans for health care programs.

Weaknesses of our research

While working on this research, one the most challenging and difficult issues we encountered was the poor quality and availability of both epidemiology and economic data, which might have affected the outcome of our research. However, this limitation cannot be circumvented, but should be coped with as good as possible. In reality, epidemiological data on hepatitis B infections has not yet been well recorded in Vietnamese hospitals due to the infrastructure. We could not retrieve data on disease progressions among different stages of chronic hepatitis B, thus, we had to use epidemiological data from other countries, where the hepatitis B epidemiology is more or less similar to Vietnam [9-13]. This is justified because disease progression rates appear to be stable across populations. The same situation was encountered for rotavirus disease. Though the rotavirus surveillance system was established in Vietnam in 1998 [14], there was no formal system to report rotavirus-related cases (e.g., mild, moderate, severe) nationally or regionally. These limitations suggest a better established surveillance system for diseases to be established in the country. This will not only benefit research but also provide the Ministry of Health with more updated disease burden information for the purpose of prevention and control. Additionally, better epidemiological surveillance would enable more rigorous estimation of the treatment cost of diseases.

The use of static models instead of dynamic models in the modeling studies (Chapters 4 and 7) resulted in the negligence of herd-immunity effects and consequently leads to the underestimation of cost-effectiveness of vaccination. However, this can be justified by the lack of epidemiological data in Vietnam in particular and in developing countries in general. It would be arguable that if dynamic models were applied for health economic evaluations and herd immunity were accounted in our studies, vaccination against hepatitis B and rotavirus would become even more cost-effective.

Conclusions

In this thesis, various types of economic evaluations were carried out to assess the impacts of vaccination strategies in Vietnam. Besides cost-effectiveness analyses to assess the cost and outcomes of universal vaccination against hepatitis B and rotavirus, affordable analyses to estimate the budget impacts on the implementation of vaccination and cost-of-illness to estimate the burden of disease were also implemented. These types of economic evaluations are very important in Vietnam as they are still rarely available especially in the health sector. Overall, our results show that universal childhood immunization in Vietnam is a cost-effective and a “must-do” public health intervention for countries, where the epidemiology of hepatitis B and rotavirus is similar and as high like in Vietnam (Chapter 4 and 7). The results of this thesis are in line with results that have been carried out in other developing countries. These have been discussed and summarized in Chapters 2 and 5. Results of our research also strongly support the WHO’s recommendation on universal vaccination against hepatitis B and rotavirus [r15]. Additionally, the data generated would assist Vietnamese health policy makers in making appropriate financial arrangement and making proper plans on healthcare prioritization. Our research also explored different tools and techniques (cost-effectiveness, affordability analyses, cost-of-illness, static modeling based on Markov- and cohort-based models) in economic evaluations in order to provide sound and efficient methodologies for evaluating other immunization programs in the

Vietnamese EPI (e.g., pertussis, polio, Hib, and so on). This would definitely assist health managers in making financial, management plans for healthcare activities. Moreover, the methodologies we introduced in this thesis may be useful for health researchers in Vietnamese academic institutions, who want to conduct health economic research for other healthcare interventions in Vietnam. These techniques have been discussed in detail in Chapters 3, 4, and 7. Specifically, in Chapter 6 a comparative study of several models for evaluating rotavirus vaccination would enables modelers not only in Vietnam but also in developing countries to apply existing models in their research. It would tremendously save energy, time and resources for researchers in the developing world in carrying out high-quality economic evaluations and to quickly learn from experience which has been done in developed countries.

Finally, the findings of the thesis emphasize the important role of international donors in continuously providing support to developing countries' governments in implementing childhood immunization. The important support from the international community, among which the GAVI is an active player would assist developing countries to achieve the Millennium Development Goals by bring down the under-five mortality rate and in combating against infectious diseases (16, 17).

Future perspectives

Results of our studies have illuminated new directions for future research. Dynamic modeling of vaccination against infectious diseases that provide more rigorous results of vaccination strategies is considered to be very important for developing countries. In addition to universal childhood vaccination, possible cost-effectiveness analyses of vaccination strategies, which are targeted not only at children but also at adolescents and at-risk population, will show to be very useful for Vietnam. Economic results on targeted vaccination may assist the Vietnamese government to consider extending vaccination to larger populations such as adolescents in the future. Finally, the use of the economic evaluation tools developed in our current research will add values in the evaluation of other vaccination programs in the Vietnamese EPI.

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SUMMARY

Vietnam is a country, where universal childhood immunization has been successfully accomplished through the Expanded Programme on Immunization (EPI). Currently, nine routine childhood vaccines have been included into the EPI and in the future new vaccines will be added to the program. Vietnam has received substantial technical support from the World Health Organization (WHO) and financial support from international organizations such as the Global Alliance on Vaccines and Immunization (GAVI) for the EPI activities. Thus far, very few cost-effectiveness analyses or economic evaluations on childhood vaccination have been conducted in Vietnam despite the importance of health economic evaluations in assessing health care interventions. Motivated by this, we decided to carry out cost-effectiveness analyses on hepatitis B and rotavirus vaccination, representing for under-used and new vaccines, respectively. The former is an existing vaccine in the EPI and the latter a newly recommended vaccine by the WHO. The goal is to provide concrete health economic evidence to the government and to international organizations who commit to provide support to immunization in the developing world. In-depth and advanced analyses were carried out on hepatitis B and rotavirus vaccination and are described in Part I and Part II of this thesis, respectively.

In Part I, a comprehensive picture of the cost-effectiveness of hepatitis B vaccination in developing countries is presented in a review (Chapter 2). Hepatitis B vaccination was found cost-effective and a crucial strategy to prevent hepatitis B infection in the developing world. Further economic evaluations on hepatitis B are described in the subsequent two chapters with the focus on Vietnam. Chapter 3 presents a cost-of-illness study aiming to estimate the disease burden of chronic hepatitis B infection to the Vietnamese society. The study presents a methodology for the cost estimation of a disease in countries where underlying data are not always readily available. It was shown that the treatment cost of chronic hepatitis B in Vietnam poses a very high financial burden for an average Vietnamese citizen and for the country as a whole, where healthcare programs strongly compete among the limited resources. Challenged by the economic burden of chronic hepatitis B infection, a cost-effectiveness analysis on the vaccination against hepatitis B in Vietnam was subsequently performed (Chapter 4). We applied a Markov model and advanced modeling techniques in order to estimate the health impact of vaccination. It became obvious that childhood vaccination against hepatitis B is always cost-effective for a high-endemic country of hepatitis B infection like Vietnam. Budget affordability revealed that hepatitis B vaccination is a necessary intervention in Vietnam to hedge expensive treatment costs of chronic hepatitis B and to reduce the morbidity and mortality of the disease.

In Part II, the possibility of introducing the rotavirus vaccine into the Vietnam's EPI was explored. Chapter 5 reviews the results of rotavirus immunization in the developing world. It was concluded that rotavirus immunization in developing countries is cost-effective and even potentially cost-saving, depending on the rotavirus vaccine price. All countries had expressed the need for external financial

support in implementing rotavirus vaccination. However, a major limitation (as presented in the review) was the application of simple decision tree models of rotavirus infection, which underestimate the real impact of vaccination. To assist developing countries with better but more complex and sophisticated models for economic evaluations, we carried out a comparative study on a number of existing disease models of rotavirus infection, which have been developed for use in the developed world (Chapter 6). The overall aim was to assist modelers in developing countries with adopting adequate existing models in order to obtain more rigorous and robust health economic results. For the purpose of illustration, in Chapter 7 we applied the CoRoVa model as specified in Chapter 6, by conducting a cost-effectiveness analysis on rotavirus immunization for children under five years of age in Vietnam. The results showed that rotavirus immunization could even become a cost-saving strategy in the country, depending on the vaccine price, and a rational prevention against diarrhoea-related diseases among children younger than five years. We explicitly compared the budget impacts on vaccination based on the market prices as well as on the GAVI-subsidized vaccine prices.

Overall, vaccination against hepatitis B and rotavirus in Vietnam is cost-effective and a crucial strategy to prevent hepatitis B and rotavirus infection. The analyses also emphasize the important role of the GAVI and other international organizations in expediting vaccination strategies in developing countries such as Vietnam where coping with the limited financial resources are a real challenge.

In conclusion, cost-of-illness, cost-effectiveness and affordability analyses are very useful health economic tools to guide decision makers in where to invest the scarce resources. For developing countries, where healthcare programs even more strongly compete for the limited resources, it is important to make choices based on evidence-based cost-effectiveness analyses. Ultimately, people living in the developing world will benefit from such rational decision making.

SAMENVATTING

Vietnam heeft middels het Expanded Programme on Immunization (EPI) een succesvol vaccinatieprogramma opgezet. Momenteel zijn negen vaccins in het EPI opgenomen en in de toekomst zullen nieuw ontwikkelde vaccins worden toegevoegd. Vietnam heeft hier technische ondersteuning voor gekregen van de Wereldgezondheidsorganisatie (WHO) en financiële ondersteuning van de Global Alliance on Vaccines and Immunization (GAVI). Tot nu toe zijn er nauwelijks economische evaluaties of kosteneffectiviteitsanalyses uitgevoerd naar vaccinaties bij kinderen in Vietnam, ondanks het belang hiervan. Dit motiveerde ons om kosteneffectiviteitsanalyses uit te voeren voor vaccinaties tegen hepatitis B en het rotavirus. Hepatitis B vaccins worden mogelijk te weinig gebruikt, terwijl het rotavirus vaccin een nieuw vaccin is. Hepatitis B vaccininatie is een reeds bestaand programma binnen het EPI, rotavirus is een voorbeeld van een door de WHO nieuw aanbevolen vaccin om in het EPI op te nemen. Ons doel is om concreet bewijs te leveren aan de overheid en aan internationale organisaties die zich commiteren aan het steunen van immunisatie in ontwikkelingslanden. Uitgebreide analyses zijn uitgevoerd voor hepatitis B en rotavirus vaccinatie en deze zijn beschreven in respectievelijk deel I en deel II van dit proefschrift.

In deel I wordt eerst een compleet beeld van de kosteneffectiviteit van het hepatitis B vaccin gegeven in de vorm van een systematisch review (hoofdstuk 2). Hepatitis B vaccinatie werd kosteneffectief bevonden en is een strategie gebleken om hepatitis B infecties te voorkomen in ontwikkelingslanden. Verdere economische evaluaties voor hepatitis B zijn beschreven in de volgende twee hoofdstukken, waarbij we ons richtten op Vietnam. In hoofdstuk 3 wordt een kosten van ziekten studie gepresenteerd om de ziektelast van chronische hepatitis B infectie te schatten voor de Vietnamese samenleving. We beschrijven een bruikbare methodologie voor de kostenraming van een ziekte in landen waar onderliggende data niet altijd direct beschikbaar zijn. De behandelkosten van chronische hepatitis B in Vietnam blijken een zeer hoge last te vormen voor de gemiddelde Vietnamees, maar ook voor Vietnam als land, waar de programma's in de gezondheidszorg sterk concurreren om de beperkt aanwezige middelen. Uitgedaagd door de economische last die chronische hepatitis B infectie met zich meedraagt, hebben we vervolgens een kosteneffectiviteitsanalyse van de vaccinatie tegen hepatitis B in Vietnam uitgevoerd. We hebben een Markov-model ontwikkeld en geavanceerde modelleringstechnieken toegepast om de impact van de vaccinatie in te kunnen schatten. De resultaten tonen aan dat vaccinatie van kinderen tegen hepatitis B altijd rendabel is voor een hoog-endemisch land met hepatitis B infectie, zoals Vietnam. De budget-impact analyse liet zien dat hepatitis B vaccinatie ook een haalbare interventie is in Vietnam, om hoge behandelkosten van chronische hepatitis B te voorkomen, en de morbiditeit en mortaliteit van de ziekte te beperken.

In deel II van het proefschrift is de mogelijkheid onderzocht om het rotavirus vaccin in Vietnam's EPI in te voeren. Hoofdstuk 5 geeft een overzicht van de resultaten van rotavirus immunisatie in

ontwikkelingslanden. De conclusie is dat rotavirus vaccinatie in ontwikkelingslanden kosteneffectief is en zelfs potentieel kosten besparend, afhankelijk van de vaccinprijs. Al deze landen hebben echter aangegeven financiële steun nodig te hebben voor de implementatie van rotavirusvaccinatie. Een van de beperkingen in de studies die tot dusver zijn uitgevoerd is de toepassing van een mogelijk te recht-toe-rechtaan beslisboommodel voor rotavirusinfectie, waardoor de impact van vaccinatie wordt onderschat. Om ontwikkelingslanden te helpen met betere, complexere en meer geavanceerde modellen voor economische evaluaties, is een vergelijkende studie naar verschillende bestaande ziektemodellen van rotavirus infectie uitgevoerd. Deze modellen zijn ontwikkeld voor gebruik in ontwikkelde landen. Het doel is om de gezondheidsautoriteiten in ontwikkelingslanden te helpen met het gebruiken van geschikte bestaande modellen om meer valide en robuuste gezondheidseconomische resultaten te verkrijgen. Om dit te illustreren hebben we in hoofdstuk 7 het CoRoVa model, zoals beschreven in hoofdstuk 6, toegepast door het uitvoeren van een kosteneffectiviteitsanalyse van rotavirusvaccinatie voor kinderen jonger dan vijf jaar in Vietnam. Uit de studieresultaten blijkt dat rotavirus immunisatie zelfs een kostenbesparende strategie in Vietnam zou zijn, afhankelijk van de vaccinprijs en de exacte ziektelast. We hebben expliciet de kosten voor de vaccinatie op basis van de marktprijzen vergeleken met die op basis van de door het GAVI-gesubsidieerde vaccinprijzen.

Vaccinaties tegen hepatitis B en rotavirus in Vietnam zijn mogelijk kosteneffectieve en haalbare strategieën om hepatitis B en rotavirusinfectie te voorkomen. De analyses benadrukken ook de belangrijke rol van de GAVI en andere internationale organisaties bij het versnellen van de ontwikkeling van vaccinatiestrategieën in ontwikkelingslanden zoals Vietnam, waar de beperkte financiële middelen de echte uitdaging vormen.

We concluderen dat analyses naar de kosten van ziekten, kosteneffectiviteitsanalyses en haalbaarheidsanalyses zeer nuttige gezondheidseconomische hulpmiddelen zijn voor het adviseren van beleidsmakers bij hun keuzes waar de schaarse middelen in te investeren. Voor ontwikkelingslanden, waar de gezondheidszorgprogramma's nog sterker concurreren voor de beperkte middelen, zijn keuzes op basis van dergelijke evidence-based economische analyses van cruciaal belang. Uiteindelijk zullen mensen in ontwikkelingslanden baat hebben bij een dergelijke rationele besluitvorming.

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CURRICULUM VITAE

Hong Anh Thi Tu was born in Hanoi, Vietnam. After finishing the high school in Hanoi, she was accepted to Boston College in the US for her bachelor education. Upon her graduation from Boston College, she worked for one year in Boston Financial Services. Hong Anh received her Master degree in Health Economics from the Heidelberg University in 2003 and her Master degree of Business Administration from the Vrije Universiteit Brussels (VUB) in 2007. She has worked for many health projects funded by international and non-governmental organizations in Vietnam like the World Bank, the Asian Development Bank, the World Health Organization, PATH, Pathfinder International and Ministry of Health in Vietnam and was a lecture in Department of Pharmaceutical Management and Organization in Hanoi University of Pharmacy. In 2007, she decided to pursue her doctoral degree in the Netherlands and wrote a research proposal, which was granted by the Dutch Higher Education (NUFFIC). In October 2007 Hong Anh started her PhD research in the Department of Pharmacoepidemiology and Pharmacoeconomics under the supervision of Prof. dr. M.J.Postma and Dr. H.J.Woerdenbag. Her PhD project was on health economics of new and under-used vaccines for developing countries with focus on hepatitis B and rotavirus. Hong Anh will obtain her PhD degree in January 2012. She has been accepted as a post-doctoral researcher on health policies and evaluation at the University of Toronto, Canada.

Hong Anh has ample experience in working in multi-national health implementation projects on communicable diseases control, HIV prevention and health financing in Vietnam, Laos and Cambodia. Her field of interest includes topics on health economics, health policies, budget impacts with the focus on the developing world. During her PhD study, Hong Anh had opportunities to attend in several international conferences on health-related topics, where she gave podium and poster presentations like International Health Economic Association (IHEA), and International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and Vaccine. In 2010, Hong Anh received the "PhD Top Publication Award" from SHARE research institute for her review on economics of rotavirus vaccination in developing countries published in Expert Review of Vaccines.