ECONOMIC EVALUATION OF ROTAVIRUS VACCINATION FOR MALAYSIA

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ABSTRACT

Rotavirus infection is an important cause of severe diarrhoea among children under-five years worldwide. Two rotavirus vaccines are available worldwide, that are safe, efficacious and recommended by the World Health Organization for inclusion into national immunisation programmes. Although widely regarded as cost-effective interventions, rotavirus vaccines are expensive. Vaccine introduction has been slow in middle-income countries like Malaysia, with low rotavirus mortality. Hence, an economic evaluation is necessary to inform evidence-based policy making surrounding the inclusion of rotavirus vaccines into the Malaysian national immunisation programme. In this thesis, a conceptual framework was developed for the economic evaluation of rotavirus vaccines in Malaysia. The burden of rotavirus was estimated, followed by the assessment cost-effectiveness, affordability and the benefits of rotavirus vaccines in providing financial risk protection and enhancing equity in Malaysia. The health and economic burden of rotavirus gastroenteritis in Malaysia was estimated using multiple local data sources. Cost-effectiveness of rotavirus vaccines was evaluated from the healthcare provider and societal perspectives, using an age-structured, multi-cohort model. A budget impact analysis was conducted to assess the affordability of a universal rotavirus vaccination programme to the Ministry of Health, Malaysia. As Malaysia has not determined a threshold for cost-effectiveness of interventions, this thesis explores vaccine price and affordability, at various cost-effectiveness thresholds suggested for Malaysia. A two-year prospective, hospital-based rotavirus study conducted at two public hospitals in Malaysia provided patient-level data for the exploration of illness-related healthcare expenditure and its impact on household income. On identifying income-related inequities in out-of-pocket healthcare payments for rotavirus gastroenteritis, an extended cost-effectiveness analysis was conducted to evaluate the distributional benefits of universal rotavirus vaccination in averting illness and providing financial risk

protection in Malaysia. This thesis found that rotavirus gastroenteritis results in a substantial health and economic burden in Malaysia, much of which was previously overlooked. Both rotavirus vaccines are likely to be cost-effective and affordable to the Ministry of Health, Malaysia, at prices negotiated in line with international tenders. Out-of-pocket healthcare expenditure for rotavirus especially impacts poor households. Universal vaccination would reduce rotavirus episodes and costs among all income groups, while the poor would particularly benefit in terms financial risk protection. The economic evaluation of rotavirus vaccines in this thesis is the first conducted in Malaysia. The evidence gathered here strongly suggests that rotavirus vaccines are a worthy investment for the government of Malaysia. The framework proposed in this thesis for economic evaluations of rotavirus vaccines in Malaysia, may be used for evaluations of other vaccination programmes in Malaysia, or other middle-income countries.

ABSTRAK

Jangkitan kuman rotavirus adalah punca utama cirit-birit di kalangan kanak-kanak dibawah umur lima tahun di seluruh dunia. Terdapat dua vaksin rotavirus yang selamat, berkesan dan telah disyorkan oleh *The World Health Organization* untuk dimasukkan dalam program imunisasi kebangsaan di seluruh dunia. Walaupun vaksin rotavirus dianggap secara meluas sebagai intervensi yang kos efektif, namun vaksin rotavirus adalah mahal. Didapati bahawa vaksin rotavirus lambat dimasukkan ke dalam program imunisasi kebangsaan, terutamanya di negara yang berpendapatan sederhana seperti Malaysia, dengan kadar kematian akibat cirit-birit rotavirus yang rendah. Oleh itu, penilaian ekonomi amatlah diperlukan bagi memaklumkan polisi tentang penyertaan vaksin rotavirus ke dalam program imunisasi kebangsaan di Malaysia. Dalam tesis ini, satu rangka kerja konsep telah dimajukan bagi penilaian ekonomi vaksin rotavirus di Malaysia. Beban cirit-birit disebabkan oleh jangkitan rotavirus dianggarkan bagi Malaysia, diikuti dengan penilaian keberkesanan kos vaksin rotavirus, kemampuan bajet, serta manfaat vaksin dari segi memberi perlindungan risiko kewangan dan mengurangkan ketidakadilan dalam perbelanjaan kesihatan di Malaysia. Beban dari segi bilangan kes dan kos cirit-birit rotavirus di Malaysia dianggarkan menggunakan pelbagai sumber data tempatan. Keberkesanan kos vaksin rotavirus telah dinilai dari perspektif pihak kesihatan dan juga dari perspektif masyarakat di Malaysia, dengan menggunakan model ekonomi kohort berstruktur umur. Analisa impak bajet dijalankan untuk menilai kemampuan kewangan Kementerian Kesihatan Malaysia bagi menaja program immunisasi rotavirus secara kebangsaan. Oleh disebabkan Malaysia belum lagi menetapkan ambang nilai bagi menentukan intervensi yang kos efektif, tesis ini menganggarkan harga vaksin dan kemampuan bajet, dengan menggunakan beberapa had kos efektif yang pernah dicadangkan untuk Malaysia. Data dari penyelidikan cirit-birit rotavirus yang telah dijalankan di dua hospital kerajaan di Malaysia telah dianalisa untuk mengetahui

perbelanjaan kesihatan bagi cirit-birit rotavirus dan kesan perbelanjaan ini terhadap pendapatan isi rumah. Seterusnya, analisa *extended cost-effectiveness analysis* telah dijalankan untuk mengkaji manfaat program vaksin rotavirus dalam mengurangkan beban penyakit dan memberi perlindungan risiko kewangan bagi semua pendudak di Malaysia, tanpa mengira pendapatan. Tesis ini telah mendapati bahawa beban rotavirus di Malaysia adalah lebih tinggi daripada yang dijangka sebelum ini. Kedua-dua vaksin rotavirus adalah kos efektif dan dalam kemampuan bajet Kementerian Kesihatan Malaysia, bila harga vaksin adalah selari dengan harga yang didapati oleh negara lain melalui tender antarabangsa. Didapati bahawa perbelanjaan kesihatan bagi cirit-birit rotavirus, lebih memberi kesan mudarat kepada orang miskin. Vaksin rotavirus dijangka memberi manfaat kepada semua rakyat dari segi pengurangan beban penyakit dan kos cirit-birit, namun golongan yang termiskin akan lebih bermanfaat dari segi perlindungan risiko kewangan. Penilaian ekonomi vaksin rotavirus dalam tesis ini adalah yang pertama dijalankan untuk Malaysia. Keputusan penilaian ini mengesyorkan bahawa vaksin rotavirus adalah pelaburan yang wajar bagi Kerajaan Malaysia. Rangka kerja yang dicadangkan dalam tesis ini untuk penilaian ekonomi vaksin rotavirus di Malaysia boleh digunakan untuk program kesihatan awam yang lain di Malaysia, dan juga di negara-negara yang lain yang setanding.

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BCG	:	Bacillus Calmette-Guérin
CHERG	:	Child Health Epidemiology Reference group
CI	:	Confidence Interval
DALYs	:	Disability-adjusted life years
DTaP	:	Diphtheria, tetanus and acellular pertussis
DTP	:	Diphtheria-Tetanus-Pertussis
EB	:	Enumeration Block
ECEA	:	Extended Cost-Effectiveness Analysis
EPI	:	Expanded Programme on Immunisation
EQ-5D	:	EuroQoL 5D
FDA	:	Food and Drug Agency
GDP	:	Gross Domestic Product
GNI	:	Gross National Income
HAS	:	Hospital Sultanah Bahiyah, Alor Setar
Hib	:	Haemophilus influenzae type b
HITAP	:	Health Intervention and Technology Assessment Program
HM	:	Hospital Melaka
HPV	:	Human Papilloma Virus
HRQoL	:	Health Related Quality of Life
HSB	:	Hospital Sungai Buloh
HSNZ	:	Hospital Sultanah Nur Zahirah
HT	:	Hospital Sultan Haji Ahmad Shah, Temerloh
HUI 2	:	Health Utility Index Mark 2
ICD-10	:	International Classification of Disease, 10th Revision
ICER	:	Incremental Cost-effectiveness Ratio
IMCI	:	Integrated Management of Childhood Illness
IPV	:	Inactivated poliomyelitis vaccine
JE	:	Japanese encephalitis
LQ	:	Living Quarter
MAR	:	Missing At Random
MCAR	:	Missing At Completely At Random
MMR	:	Measles-Mumps-Rubella
MOH	:	Ministry of Health

MR	:	Measles-Rubella
MSF	:	Médecins Sans Frontières
NHS	:	National Health Service
NHMS	:	National Health and Morbidity Survey
NICE	:	National Institute for Health and Care Excellence
NITAG	:	National Immunisation Technical Advisory Groups
OOP	:	Out-of-Pocket
OPV	:	Oral Polio Vaccine
OR	:	Odds Ratio
PAHO	:	Pan-American Health Association
PLI	:	Poverty line income
PPP	:	Purchasing power parity
QALYs	:	Quality-adjusted life years
RM	:	Ringgit Malaysia
SAGE	:	Strategic Advisory Group of Experts on Immunisations
SD	:	Standard deviation
SDGs	:	Sustainable Development Goals
TT	:	Tetanus Toxoid
UHC	:	Universal Health Coverage
UMMC	:	University of Malaya Medical Centre
UN	:	United Nations
UNDP	:	United Nations Development Programme
UNICEF	:	United Nations Children's Fund
US	:	United States
US$	:	United States Dollars
VSL	:	Value of Statistical Life
WASH	:	Water, Sanitation and Hygiene
WHO	:	World Health Organization
WHO-CHOICE	:	World Health Organization-CHOosing Interventions which are Cost-Effective
WHO-cMYP	:	WHO-comprehensive Multi-Year Plan for Immunization
WTP	:	Willingness-to-pay

CHAPTER 1: GENERAL INTRODUCTION

1.1 Introduction

Rotavirus diarrhoea is an important cause of diarrhoeal mortality and morbidity worldwide (Parashar et al., 2009). In Malaysia rotavirus mortality is low, with 15 deaths attributable to rotavirus estimated in 2008 (Tate et al., 2012). Rotavirus morbidity in Malaysia is substantial. In 2005, it was estimated that by the age of five years, one in 37 children will visit a clinic, one in 61 children will be hospitalised, and one in 15,000 children will die due to rotavirus gastroenteritis in Malaysia (Hsu et al., 2005).Two rotavirus vaccines are available, that are recommended by the World Health Organization (WHO) for universal vaccination in all countries worldwide (Strategic Advisory Group of Experts, 2009). Nevertheless, partly due to high vaccine prices and the likely underestimation of the true burden, rotavirus vaccines are not part of the national immunisation programme in Malaysia. Consequently, an economic evaluation is necessary to inform evidence-based decision-making on the public finance of rotavirus vaccines in Malaysia.

A fundamental concern in economics is the scarcity of healthcare resources relative to population needs. Health systems choose interventions with the aim of maximising population health within the constraints of limited budgets. Of importance however is not just the overall improvement of health, but ensuring that the distribution of benefits and costs are fair. The way costs and benefits are distributed reflect values of justice or fairness, important in society. Conventional economic evaluations focus on the narrow benefits of vaccination, namely in averting disease and healthcare costs, which undervalues the potential broader economic benefits of vaccines to individuals, households and society.

In this thesis, economic arguments are developed to inform policy on the inclusion of rotavirus vaccines into the Malaysian national immunisation programme. A framework is developed for the economic evaluation of rotavirus vaccines, in aid of evidence-informed decision-making on vaccine introduction in Malaysia. The health and economic burden of rotavirus gastroenteritis in Malaysia is comprehensively estimated, including deaths and episodes treated publicly, privately and at home. The cost-effectiveness, affordability and the broader economic benefits of rotavirus vaccination in providing financial risk protection across income groups are explored.

The chapter begins with Section 1.2, which explains the motivation behind this study and is followed by Section 1.3, which lists the study objectives. Next is Section 1.4, in which the public health significance of the study is discussed. The chapter concludes with Section 1.5, which presents the layout of this thesis.

1.2 Study motivation

Rotavirus infection is the most common cause of severe diarrhoea worldwide (Parashar et al., 2009). Rotavirus diarrhoea accounts for 453,000 deaths in children younger than five years of age, which is equivalent to 37 per cent of all diarrhoeal deaths, or five per cent of all deaths in children under the age of five years worldwide (Tate et al., 2012). The majority of rotavirus diarrhoeal deaths occur in low-income countries with inadequate access to healthcare. In high- and middle-income countries, mortality due to rotavirus diarrhoea is low, but the associated morbidity is high.

Rotavirus is highly infective and transmissible. As improvements in water, hygiene and sanitation does not reduce the incidence of rotavirus diarrhoea, rotavirus vaccines are the only effective preventive measure available. Since 2006, two oral rotavirus vaccines have been available internationally. Safety, efficacy and effectiveness of these vaccines have been proven in large clinical trials and post-licensure studies (Ruiz-Palacios et al., 2006; Vesikari et al., 2006). In 2009, the WHO recommended that all countries include rotavirus vaccines into national primary immunisation schedules (Strategic Advisory Group of Experts, 2009).

Although, rotavirus vaccines are widely known to be cost-effective interventions in low- and middle-income countries (Atherly, Lewis, Tate, Parashar, & Rheingans, 2012), rotavirus vaccines are more expensive compared to traditional vaccines included in the Expanded Programme for Immunisation (EPI). (Madsen, Ustrup, Fischer, Bygbjerg, & Konradsen, 2012). Thus, the decision for public finance of rotavirus vaccines is not immediately clear in middle-income countries with low rotavirus mortality, including Malaysia.

Rotavirus vaccination has a tremendous impact in the prevention of diarrhoeal deaths, especially in low-income countries. Low-income countries also have access to subsidised vaccine prices and innovative financing mechanisms, which promote the introduction of rotavirus vaccines. In high-income countries despite low rotavirus mortality, vaccination reduces the economic burden of rotavirus diarrhoea, in terms of caregiver wage loss and healthcare costs. Despite high vaccine prices in these countries, reduction in morbidity is an important consideration towards universal vaccination.

Malaysia, like most middle-income countries, is not eligible for external aid for vaccination programmes. Rotavirus mortality is low in Malaysia. The one previous estimate of rotavirus burden in Malaysia suggested substantial morbidity. However, this previous study focused mainly on rotavirus episodes treated at the public sector (Hsu et al., 2005), potentially underestimating the burden in Malaysia, where significant private sector provision of services occurs. In addition, this previous study did not consider rotavirus episodes not seeking formal treatment, underestimating caregiver productivity loss. Although, safe and effective vaccines are available, evidence of cost-effectiveness or 'value for money' is necessary to inform policy on vaccine introduction. Affordability of vaccination programmes are of practical concern to budget holders. The perception that rotavirus vaccines are expensive, is a barrier for its adoption in middle-income countries (E. A. S. Nelson, de Quadros, Santosham, Parashar, & Steele, 2013). For these reasons, economic evaluations are necessary to inform on the public finance of a rotavirus vaccines in middle-income countries, like Malaysia.

The basic economic problem faced by healthcare systems is the allocation of scarce resources[1] with the aim of maximising population health. Healthcare budgets are finite, and are largely dependent on the national economy. Especially during times of economic downturn, budgets are rationalised to provide the most health benefits. In the wake of the 1997 Asian Financial Crisis, the public health budget in Malaysia was cut by twelve per cent, leading the Ministry of Health (MOH), Malaysia to reprioritise services to maximise utilisation of resources and productivity (Suleiman, Lye, Yon, Teoh, & Alias, 1998).

Due to a variety of internal and external factors, the value of the Malaysian Ringgit (RM) plummeted by 26 per cent from January to October 2015 (Bank Negara Malaysia, 2015). The rapidly, decreasing value of the ringgit suggests imminent healthcare rationing. In the 2016 Malaysian National Budget, the operational budget for the MOH, Malaysia was decreased by one per cent from the previous year, or RM 21,431 billion as compared to RM 21, 714 billion in 2015 (Ministry of Finance Malaysia, 2015). Although the Prime Minister announced a recalibrated National Budget for 2016 on January 28th 2016[2], there was no official statement on the revision of the MOH annual budget[3] (Ministry of Finance Malaysia, 2016).

In the context of constrained budgets, policy-makers have to make choices between competing programmes or interventions. This is especially important as choosing a new programme may displace existing programmes or limit the implementation of other necessary programmes.

[1] While scarce resources usually refers to financial budgets, healthcare resources are specific to health systems and also include health personnel (labour), clinics or hospitals (capital), and other supplies like medications, needles and syringes.

[2] The 2016 National Budget was restructured due to reduced national revenue from a prolonged slump in oil prices and a need to reduce national fiscal deficits.

[3] The Health Minister made a statement expecting a ten percent budget cut in 2016, of about RM 250 to 300 million, in response to the Prime Minister's announcement of the unexpected amendment of the 2016 National Budget (Zahiid, 2016). This press statement was made on the 13th of January 2016, prior to the announcement of the revised 2016 National Budget on the 28th of January 2016 (Aziz, 2016).

Cost-effectiveness analysis informs on the efficient allocation of scarce resources towards improving population health. Traditionally, economic evaluations of vaccination programmes consider the narrow benefits of vaccination, namely health gains and averted costs to healthcare providers. This grossly undervalues the broader economic impact of vaccination, which includes concerns on health equity[4] and protecting the ill against the financial consequences of healthcare payments[5] (T. Bärnighausen et al., 2014; Bloom, Canning, & Weston, 2005; Jit et al., 2015; P. C. Smith, 2013).

Malaysia is widely credited as having achieved universal health coverage (UHC), through a public healthcare system that ensures access to needed care for all citizens, with minimal or no user fees (Savedoff & Smith, 2011). However, the existence of a parallel private healthcare system offering quality healthcare, exposes households to large out-of-pocket (OOP) healthcare expenditure (Jaafar, Noh, Muttalib, Othman, & Healy, 2013).

OOP payments for healthcare, or payments made directly at the point of receipt of care, may have detrimental impact on household welfare by displacing spending for essentials like food, education and shelter. OOP healthcare payments are a regressive form of health financing, impacting the poor more than the rich[6] (World Health Organization, 2000). Financial risk protection is a fundamental goal of health systems (World Health Organization, 2000, 2010), and can be defined as access to healthcare without incurring financial hardship as a result of paying for them[7] (Saksena, Hsu, & Evans, 2014).

Expenses paid OOP for rotavirus diarrhoea may not be large in magnitude, but may be large as a proportion of household income. A 2007 study at a public hospital in Malaysia

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[4] Equity concerns fairness in the distribution of health, healthcare or healthcare spending over individuals or groups of individuals in society.

[5] Broader economic values of health can be briefly divided into productivity related gains (including lost days of work for illness and lifetime improvement in productivity), community and health system externalities (including improvements in equity and financial risk protection) and impact to the broader economy (impact on public sector budget and macroeconomic impact) (T. Bärnighausen et al., 2014; Jit et al., 2015)

[6] There are inequities or unfairness in healthcare payments paid OOP. Even if the magnitude of healthcare payment is the same, the financial implications of these payments on rich and poor households are different. The poor have less savings and ability to cope with unexpected healthcare expenditure. OOP healthcare payments may deter the poor from accessing needed healthcare.

[7] Providing financial risk protection removes the financial barriers or hardship faced by the sick having to pay for healthcare. Financial risks of ill health include incurring healthcare payments that results in impoverishment or financial catastrophe.

found that on average OOP expenses for an episode of rotavirus diarrhoea was RM 766 (in 2013 RM), or 26 per cent of average monthly income of households surveyed (Chai & Lee, 2009). A universal rotavirus vaccination programme has the potential to reduce expenditure and provide financial risk protection against illness-related expenditure for all income groups. However, as the magnitude and distribution of these OOP healthcare expenses for diarrhoeal illness have not been described in Malaysia, and thus the potential benefits of rotavirus vaccines in alleviating this burden is not yet clear.

Currently, economic evidence is not a formal part of decision-making for the public finance of vaccines in Malaysia. In September 2009, the MOH announced the introduction Human Papillomavirus (HPV) vaccine to the Malaysian national immunisation programme[8], prior to publication of the results of cost-effectiveness analysis (Ezat & Aljunid, 2010). Presumably due to a lack of local evidence, a MOH technical review on the safety, efficacy and cost-effectiveness of HPV vaccines was based on published international evidence from 1990 to 2006 (Ministry of Health Malaysia, 2011a). However, in anticipation of the future need for economic evaluations and to encourage the generation of economic evidence, the MOH, Malaysia published a methodological guideline on economic evaluation of pharmaceuticals in 2012 (Ministry of Health Malaysia, 2012e).

Decision-making on public finance of vaccines should be transparent, evidence-based and consider multiple criteria. In order to prioritise healthcare interventions, first the public health importance of the disease should be established. The intervention must be proven to be safe, effective and of quality for adoption. Economic criteria of interest include cost-effectiveness, affordability and the ability of vaccination programmes to provide financial risk protection and improve equity. Decision-making should ideally be

[8] The HPV vaccine introduced universally to all school girls aged 13 years in Malaysia in 2010, was the most recent vaccine to be introduced into the Malaysian National Immunisation programme.

evidence-informed and consider multiple criteria, weighed against social value judgements.

1.3 Study objectives

In this thesis, economic arguments are gathered in aid of evidence-based policy making, with regards to the possible inclusion of the rotavirus vaccine into the Malaysian national immunisation programme. First, the contextual background motivating the economic evaluation of rotavirus vaccines in Malaysia is described, establishing the public health need and barriers for public finance. Next, the theoretical and conceptual basis for the allocation of scarce healthcare resources are reviewed and discussed. Following which a conceptual framework is developed for the economic assessment of rotavirus vaccines in Malaysia.

In view of establishing the importance of rotavirus gastroenteritis, and the subsequent evaluation of cost-effectiveness of vaccination, the health and economic burden of rotavirus gastroenteritis are comprehensively estimated in Malaysia. Rotavirus mortality and morbidity, are estimated in terms of episodes receiving outpatient and inpatient treatment, at public and private healthcare facilities, as well as those treated at home, and the economic costs of these episodes to the healthcare provider and society.

The cost-effectiveness and affordability of rotavirus vaccines are evaluated. A range of vaccine prices are suggested to aid policy-makers with vaccine price negotiations. In this thesis, patient-level data on OOP expenses for rotavirus gastroenteritis is examined to investigate the financial burden of healthcare payments on households and to explore the possible income-related inequities in distribution of healthcare payments. On identification of possible unfairness in distribution of healthcare payments, the benefits of publicly-financed rotavirus vaccines, in terms of providing financial risk protection and improving equity, are assessed. Finally, the economic evidence gathered are rationally discussed to inform policy and decision-making on the publicly-finance of rotavirus vaccination in Malaysia.

Therefore the specific objectives of this study are:

1. To develop a conceptual framework for the assessment of universal rotavirus vaccination in Malaysia.
2. To estimate the health and economic burden of rotavirus gastroenteritis to the healthcare provider and society in Malaysia.
3. To assess if public finance of universal rotavirus vaccination is cost effective and affordable to the Ministry of Health, Malaysia.
4. To explore the potential distributional effects of out-of-pocket expenditure for rotavirus gastroenteritis on households in Malaysia.
5. To explore the potential distributional benefits of universal rotavirus vaccination in providing financial risk protection to households in Malaysia.
6. To use the economic evidences derived from this study to rationally discuss the possible inclusion of rotavirus vaccines into the Malaysian national immunisation programme.

1.4 Significance of this study

This thesis seeks to establish the public health importance of rotavirus gastroenteritis and the need for public finance of rotavirus vaccines. The burden of rotavirus gastroenteritis is comprehensively estimated in Malaysia, considering all episodes of rotavirus including those seeking care at public and private healthcare sectors and those treated at home. This is particularly important as Malaysia has a mixed public and private healthcare system. In Malaysia, the public health system is financed mainly from general taxation, at minimal cost to the user. Private healthcare however is financed largely by OOP payments. Previous estimations of rotavirus burden in Malaysia concentrated on those seeking care at the public sector, and this under-estimates the wider societal costs of rotavirus diarrhoea. Comprehensive estimation of rotavirus burden allows for further evaluation of cost-effectiveness and affordability of vaccines.

Cost-effectiveness is a relative measure. At present, the MOH, Malaysia has not set a threshold for cost-effectiveness in Malaysia, making the determination of cost-effectiveness subjective. The WHO cost-effectiveness thresholds though widely used, were suggested for regional decision-making and have limited value in informing national resource allocation (Eichler, Kong, Gerth, Mavros, & Jönsson, 2004; Newall, Jit, & Hutubessy, 2014). Research groups worldwide have suggested several cost-effectiveness thresholds motivated by fundamental economic theories on resource allocation in the context of scarcity. These are the valuation of health on the basis of productivity or average income (human capital approach), the determination of health needs and its value by consumers of healthcare (consumer sovereignty) and the economic concept of valuing the benefits of the next best healthcare intervention foregone (opportunity costs). In this thesis, the cost-effectiveness and affordability of implementing a universal rotavirus immunisation programme are explored at various cost-effectiveness thresholds. Cost-effective prices are suggested to aid national negotiations for vaccine tenders.

In this thesis, prospective patient-level data was analysed to inform on possible income-related inequities of healthcare expenditure for rotavirus in Malaysia. This motivated the exploration of the benefits of universal rotavirus vaccination in providing financial risk protection across income groups in Malaysia.

This is the first complete economic evaluation of rotavirus vaccines in Malaysia. This thesis is contains a comprehensive estimation of the health and economic burden of rotavirus in Malaysia, and is the first to assess the cost-effectiveness and affordability of universal rotavirus vaccination in Malaysia. This is the first study to explore the distributional benefits of rotavirus vaccines in alleviating health events, while providing financial risk protection against illness-related expenditure in Malaysia. The framework developed during the course of this study may be useful for the economic evaluation of other public health interventions, both in Malaysia and other middle-income countries.

1.5 Layout of this thesis

This thesis is reported in eight chapters in order to answer the delineated objectives. Thesis chapters are summarised in Figure 1.1:

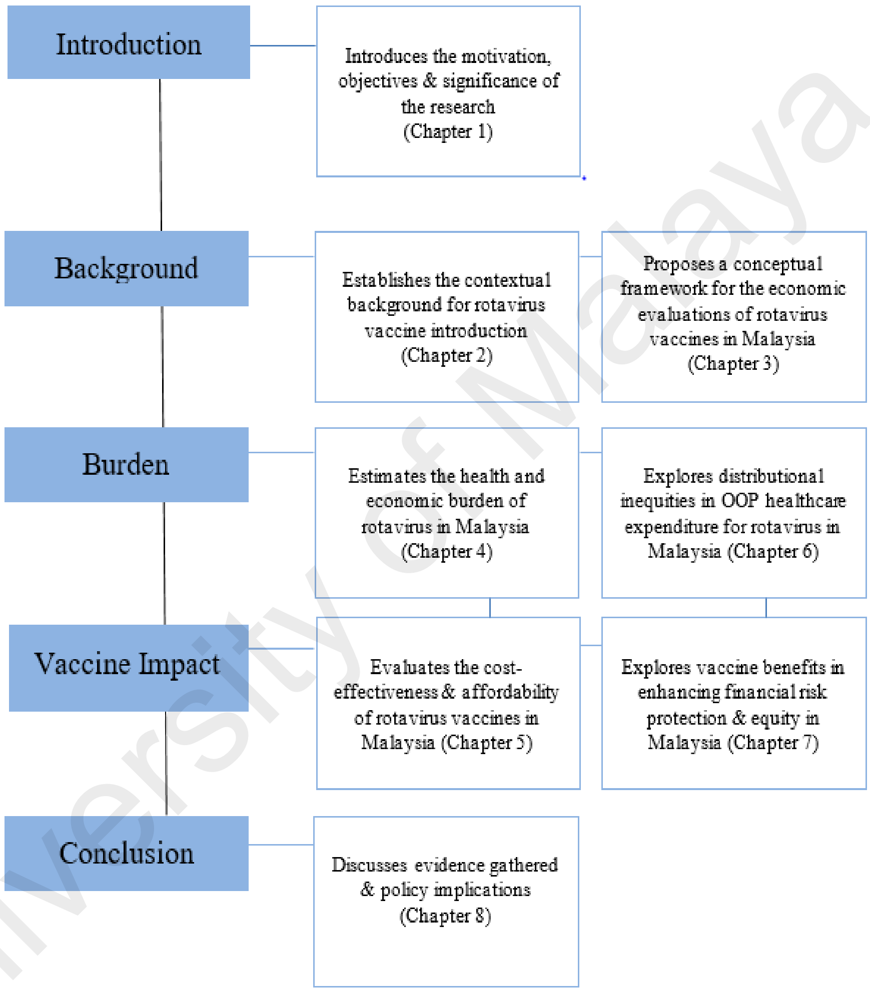

Figure 1.1: Outline of the thesis chapters

Chapter 1 This chapter introduces the research topic and objectives, while highlighting the study motivations and significance.

Chapter 2 This chapter describes the contextual background for the introduction of universal rotavirus vaccination in Malaysia, by establishing the public health need for rotavirus vaccines and the perceived barriers towards public finance of rotavirus vaccines.

Chapter 3 This chapter reviews the economic theories in the allocation of scarce resources, and proposes a conceptual framework for the economic evaluation of rotavirus vaccines in Malaysia.

Chapter 4 This chapter presents a comprehensive estimation of the health and economic burden of rotavirus gastroenteritis in Malaysia using multiple data sources.

Chapter 5 This chapter presents the evaluation of cost-effectiveness and affordability of rotavirus vaccines in Malaysia.

Chapter 6 This chapter explores the financial burden of healthcare expenditure on households for rotavirus gastroenteritis and investigates the possibility of income-related inequities in healthcare payments.

Chapter 7 In this chapter, the potential distributional benefits of universal rotavirus vaccination in alleviating rotavirus episodes, illness-related expenses and providing financial risk protection are explored.

Chapter 8 In this final chapter, the economic evidence gathered are rationally discussed, in order to make a recommendations towards rotavirus vaccine introduction in the Malaysian national immunisation programme.

CHAPTER 2: CONTEXTUAL BACKGROUND FOR THE ECONOMIC EVALUATION OF ROTAVIRUS VACCINATION

2.1 Introduction

Worldwide, diarrhoea is the second commonest cause of death in children under-five years of age, resulting in 0.8 million deaths or ten per cent of all deaths in 2010 (Liu et al., 2012). Rotavirus diarrhoea is a major cause of severe diarrhoea, responsible for more than a third of all diarrhoeal deaths, prior to the introduction of rotavirus vaccines (Tate et al., 2012). Two rotavirus vaccines are recommended for universal vaccination based on evidence of vaccine efficacy in all regions of the world (Strategic Advisory Group of Experts, 2009).

Malaysia is an upper middle-income country with a mixed public-private healthcare system. Public healthcare is financed by general taxation and is highly subsidised at point of contact, while the private sector is financed mainly by OOP payments that are not subsidised. Malaysia has a well-established national immunisation programme, with high coverage of childhood vaccines (Jaafar et al., 2013). Although rotavirus vaccines are recommended by the MOH, Malaysia, these ‘optional’ vaccines are not publicly-funded. Economic evaluation of rotavirus vaccines is necessary to inform universal vaccine introduction in Malaysia.

This chapter examines the global and national context that motivates the economic evaluation of rotavirus vaccines in Malaysia. The chapter begins with Section 2.2, which establishes the need for rotavirus vaccines by reviewing the existing evidence on pre-vaccination burden of rotavirus gastroenteritis, globally and in Malaysia. This is followed by a review of the epidemiology of rotavirus infection. Next Section 2.3, introduces the rotavirus vaccines and establishes the basis for the WHO recommendation for universal rotavirus vaccine introduction. Subsequently, this section identifies vaccine pricing mechanisms as a barrier towards the introduction of new vaccines to middle-income countries, necessitating economic evaluations of vaccination programmes. This is followed by Section 2.4, which provides a critical overview of Malaysia, the country and its healthcare system, with specific emphasis on its national immunisation programme. The chapter concludes with Section 2.5, which provides a chapter summary.

2.2 Epidemiology and burden of rotavirus

2.2.1 Global burden of rotavirus gastroenteritis

Rotavirus is an important cause of diarrhoeal mortality and morbidity worldwide. Rotavirus is the most common aetiological agent responsible for acute gastroenteritis in children globally. By the age of five years, almost every child worldwide will have had an episode of rotavirus gastroenteritis. By the age of five years, one in five children will visit a clinic, one in 65 children will be hospitalised, and approximately one in 293 children worldwide will die from rotavirus gastroenteritis (Parashar, Hummelman, Bresee, Miller, & Glass, 2003). A systematic review by J. Bilcke et al. (2009), conducted of prospective, community-based rotavirus studies, estimated a global incidence of 0.24 [95 per cent confidence interval (CI), 0.17 to 0.34] symptomatic rotavirus infections per person-year of observation for children below two years of age.

The WHO estimated that in 2008, rotavirus gastroenteritis resulted in 453,000 deaths among children under-five years worldwide. Rotavirus attributed 37 per cent of all diarrhoeal deaths and five per cent of all deaths in children under the age of five years. More than half of all rotavirus-related diarrhoeal deaths occurred in five countries worldwide; The Democratic Republic of Congo, Ethiopia, India, Nigeria and Pakistan (Tate et al., 2012).

Although the incidence of rotavirus gastroenteritis is similar worldwide, mortality rates vary considerably between countries. Almost 90 per cent of all rotavirus-related deaths occur in low-income countries. Diarrhoeal mortality is associated with poor access to health care and less than optimal management of severe diarrhoea. The underlying nutritional status of the child also influences survival (Parashar et al., 2009).

In high- and middle-income countries[9], even though rotavirus mortality is low, the incidence of rotavirus gastroenteritis remains high, despite good hygiene and sanitation. Rotavirus gastroenteritis causes considerable economic burden to healthcare systems and households, in terms of expenditure related to seeking healthcare and loss of wages (Meloni et al., 2011).

2.2.2 Burden of rotavirus gastroenteritis in Malaysia

Malaysia is an upper middle-income country, with an established healthcare system. As universal access to healthcare and appropriate management of diarrhoea is readily available in Malaysia, rotavirus mortality is low. However, diarrhoea attributable to rotavirus results in considerable morbidity in Malaysia (Hsu et al., 2005).

In a systematic review of the burden of rotavirus gastroenteritis and distribution of rotavirus strains in Asia, Kawai et al. (2012) estimated that the rotavirus mortality rate in Malaysia was less than 0.5 per 100,000 children under-five years. The WHO estimated that in 2008, there were 15 diarrhoeal deaths attributable to rotavirus among children younger than five years in Malaysia (Tate et al., 2012).

Hsu et al. (2005) published an estimate of the burden of rotavirus gastroenteritis in Malaysia, using national data from the MOH, Malaysia and the Department of Statistics, Malaysia. Data on hospitalisations, clinic visits and deaths for acute gastroenteritis among children under-five years from 1998 to 2000 were obtained. Rotavirus detection rates from a two-centre hospital-based surveillance and a community-based study (Yap et al., 1992), was used to estimate number of hospitalisations, clinic visits and deaths

[9] The World Bank categorised countries according to the Gross National Income (GNI) per capita, calculated using the World Bank's Atlas Method. In 2016, low-income countries were defined as those with GNI per capita of United States Dollars (US$) 1,045 or below; middle-income countries are defined as those with GNI per capita of between US$ 1,045 and US$12,736; and high-income economies are those with GNI per capita of US$ 12,736 and above. Middle-income countries are separated into lower and upper middle-income at a GNI per capita of US$ 4,125 (http://data.worldbank.org/about/country-and-lending-groups).

attributable to rotavirus. Hsu et al. (2005) estimated that by the age of five years, one in thirty seven children will visit a clinic, one in sixty one children will be hospitalised, and one in fifteen thousand children will die due to rotavirus gastroenteritis in Malaysia. While this is the only estimate of the health burden of rotavirus in Malaysia, the Hsu et al. (2005) estimate concentrated on admissions and clinic visits to public facilities, not considering home-treated episodes and inadequately considering privately treated episodes.

Lee, Poo, and Nagaraj (2007) estimated that on average, an episode of rotavirus gastroenteritis costs the healthcare provider RM 1,203 per hospitalised child (in 2013 RM). This study estimated annual costs of providing inpatient care for rotavirus gastroenteritis of RM 10.3 million to the healthcare provider in Malaysia, in 2013 RM. Chai and Lee (2009) estimated that on average direct medical costs paid OOP was RM 766 per child hospitalised for rotavirus gastroenteritis, and this expense constituted twenty-six per cent of average monthly income of households' surveyed.

Both these estimates of economic burden of rotavirus gastroenteritis were based on primary data collected at one tertiary-level, public hospital in the capital of city of Kuala Lumpur[10], Thus, the obtained costs may not be reflective of the healthcare costs in Malaysia (Chai & Lee, 2009; Lee et al., 2007). In addition, the Lee et al. (2007) estimate only considered the economic burden of inpatient episodes treated at public hospitals, omitting costs of outpatient-, privately- or home-treated episodes. Also the Lee et al. (2007) estimate was from the healthcare providers' perspective, and did not consider direct non-medical and indirect costs.

[10]Studies were conducted at University of Malaya Medical Centre (UMMC) a tertiary-level, teaching hospital located in the capital city of Kuala Lumpur. This public hospital is administered by the Ministry of Education and has a higher fee structure compared to public hospitals under the Ministry of Health, Malaysia.

As such, these previous studies may have underestimated the overall burden of rotavirus in Malaysia, which includes rotavirus episodes treated publicly, privately and at home, and the economic burden of these events to the healthcare provider and society.

2.2.3 Rotavirus epidemiology

2.2.3.1 Clinical picture

Rotavirus is the most common cause of severe, dehydrating diarrhoea in children (Parashar et al., 2003). The rotavirus virus destroys mature enterocytes located on the tips of the villi of the small intestine, limiting the absorptive capacity of the intestine and resulting in diarrhoea. The peak incidence for rotavirus infection is between six and 24 months of age[11]. (World Health Organization, 2013d).

After ingesting the virus, there is a two to four day symptom-free incubation period, during which the patient is infectious. Rotavirus infection has a wide clinical spectrum of illness, varying from an asymptomatic infection, to a mild gastroenteritis with transient, loose stools, or a moderate or severe gastroenteritis with fever, vomiting and dehydrating diarrhoea, that may result in death (World Health Organization, 2013d). Children under-two years of age are more likely to suffer from severe dehydrating diarrhoea, while adults and older children experience milder symptoms (Velázquez et al., 1996). Clinical symptoms usually last from four to eight days (Ward, Jiang, Farkas, & Bass, 2006).

Rotavirus gastroenteritis has no specific treatment. Diarrhoea and dehydration caused by rotavirus are treated symptomatically. Mild dehydration may be treated with oral rehydrating salts, while moderate and severe dehydration may require hospitalisation for intravenous rehydration (World Health Organization, 2013d).

[11] Children in low-income countries are subject to more severe infection at younger ages. In low-income countries, the first, severe infection occurs between the ages of six to nine months. In high-income countries, the age of the first infection may be delayed until two years of age.

2.2.3.2 Viral transmission

Rotavirus is highly infectious, with only a low infectious dose needed for transmission. An infected child can excrete up to a 100 billion viral particles per gram of stool, but as little as ten viral particles may result in rotavirus infection. Also, rotavirus viral particles may survive for weeks on surfaces (P. Dennehy, 2000).

Although the exact mode of transmission is yet unknown, rotavirus is directly transmissible through touch and the oral-faecal route, and indirectly transmissible through contact with contaminated fomites. Humans are the only reservoir for transmission of rotavirus infection (P. Dennehy, 2000; C. Singer et al., 2010).

Improvements in hygiene and sanitation does not reduce the incidence of rotavirus gastroenteritis. Hand washing and surface disinfection does not reduce viral transmission, neither does the availability of clean water and sanitation. Incidence of rotavirus gastroenteritis is similar in both high- and low-income countries. The universality of the rotavirus incidence in high- and low-income countries, irrespective of standards of sanitation and hygiene, is testament to the high transmissibility of the virus (Parashar et al., 2003; World Health Organization, 2013d).

2.2.3.3 Natural history of viral infection

The first rotavirus infection occurring between the ages of three months and two years, is the most severe. Each child is subject to multiple infections of rotavirus, with each subsequent infection milder than the previous. Each natural infection results in an antibody response that provides increasing immunity and protection against subsequent infections.

By the age of five years, every child worldwide would have had a rotavirus infection. Since, children are subject to multiple rotavirus infections and each infection provides increasing immunity against subsequent severe illness, rotavirus infections are rare after the age of five years (Bernstein, 2009).

Antibody response towards a natural infection is heterotypic, and provides protection against multiple serotypes. Asymptomatic infections appear to provide similar protection against severe illness as symptomatic infections. Rotavirus vaccines were developed to mimic the natural immunity provided by the first, severe rotavirus infections (Velázquez, 2009; Velázquez et al., 1996).

2.3 Rotavirus vaccines

2.3.1 Development of rotavirus vaccines

In line with the fourth Millennium Development Goal, there have been concerted global efforts to reduce under-five mortality by two-thirds between 1990 and 2015. The development of rotavirus vaccines, as well as the United Nations Children's Fund's (UNICEF) strategies to improve standards of water, sanitation and hygiene (WASH) and the WHO's Integrated Management of Childhood Illness (IMCI), are part of international efforts to reduce diarrheal deaths (United Nations Children's Fund, 2005; World Health Organization and UNICEF, 2013).

As improvements in water supply, hygiene and sanitation do not reduce rotavirus transmission, vaccination is the ideal preventive measure against rotavirus infection. Interest in the development of a rotavirus vaccine first started in the 1970s, soon after the virus was discovered (Bishop, Davidson, Holmes, & Ruck, 1973).

2.3.1.1 RotaShield®

The first rotavirus vaccine RotaShield® (Wyeth-Lederly, USA), a human rhesus reassortant, live-attenuated, orally administered vaccine, was licensed by the United States' Food and Drug Agency in 1998. Within a year of licensure, RotaShield® was withdrawn from the United States market due to an increased risk of intussusception. The risk of intussusception attributable to RotaShield® was one in ten thousand (Murphy, Smith, Gargiullo, & Schwartz, 2003).

Intussusception is a potentially fatal intestinal obstruction, caused by the 'telescoping' of the intestine. Its clinical features include vomiting, abdominal pain, bloody stool and a palpable abdominal mass (Murphy et al., 2003). Although the risk of intussusception attributable to RotaShield® was small, the harm caused was sufficient to warrant vaccine withdrawal, despite its potential benefits worldwide (Murphy et al., 2003).

2.3.1.2 Rotarix® and RotaTeq®

Since 2006, two second generation live-attenuated, orally administered rotavirus vaccines have been marketed internationally. These are the monovalent Rotarix® (GlaxoSmithKline, Rixensart, Belgium) and the pentavalent RotaTeq® (Merck & Co. Inc., USA) (World Health Organization, 2013d).

Rotarix® is a monovalent human rotavirus vaccine. Although the vaccine contains only the common circulating, wild-type G 1 P [8] serotype, it protects against other G-types. The Rotarix® vaccine is recommended to be given in two oral doses, in the first six months of life. The first dose is recommended to be administered from six weeks of life, with a minimum interval of six weeks between the first and second dose (C. Singer et al., 2010; World Health Organization, 2013d).

RotaTeq® contains five human-bovine reassortant viruses. It contains a bovine (WC 3 strain) and an attenuated human virus which encodes either the VP 4 protein (P 8) or the VP 7 protein (G 1, G 2, G 3, G 4). RotaTeq® is recommended to be given in three oral doses, within the first six months of life. A minimum interval of at least four weeks between doses is recommended. The first dose should be given between the six and twelve weeks of life. (Jiang, Jiang, Tate, Parashar, & Patel, 2010; C. Singer et al., 2010; World Health Organization, 2013d).

2.3.1.3 New rotavirus vaccines

Recently, China, Vietnam and India have developed, and locally-manufactured rotavirus vaccines. These vaccines are currently licensed for use only within these countries (Yen et al., 2014).

The Indian manufactured, orally administered Rotavac® vaccine (Bharat Biotech International Limited) has successfully completed phase III safety and efficacy trials (Bhandari et al., 2014), and is licensed for use in India from 2014. Bharat Biotech International Limited is currently seeking WHO prequalification for Rotavac®, so it may be available globally in the near future (Medecins Sans Frontieres, 2015).

The Lanzhou Lamb Rotavirus Vaccine (Lanzhou Institute of Biological Products) has been available in the private market in China since the year 2000. Rotavin-M® is manufactured by Polyvac, Vietnam and has been licensed for use in Vietnam since 2007 (World Health Organization, 2013d; Yen et al., 2014).

These new rotavirus vaccines are potentially more affordable than current vaccines. Bharat Biotech International Limited has made the commitment to offer Rotavac® at the price of US$ 1 per-dose (Medecins Sans Frontieres, 2015). However, as none of these vaccines are currently available internationally, they are not the focus of this thesis.

2.3.2 Safety and efficacy of rotavirus vaccines

Randomised controlled trials evaluating the safety and efficacy[12] of Rotarix® and RotaTeq® have been conducted in all regions of the world. The initial important trials conducted in Europe and the Americas proved the vaccines to be safe and efficacious (Ruiz-Palacios et al., 2006; Vesikari et al., 2006). In 2006, the WHO recommended the use of rotavirus vaccines in these regions (World Health Organization, 2007). Subsequent to vaccine efficacy results from clinical trials conducted in countries in Africa and Asia

[12] Vaccine efficacy is the extent with which the vaccine reduces disease incidence in the vaccinated as compared to the unvaccinated, within the ideal conditions of a clinical trial. Vaccine safety is a measure of the ability of vaccines to perform without untoward adverse effects. (Houweling, Verweij, & Ruitenberg, 2010).

(Armah et al., 2010; Zaman et al., 2010), the WHO expanded their recommendation of rotavirus vaccines to all countries worldwide (World Health Organization, 2013d).

Oral rotavirus vaccines are found to be safe and have sustained efficacy against severe rotavirus gastroenteritis and all cause gastroenteritis[13]. A 2011 Cochrane review of 41 clinical trials with a collective sample size of 186,263, found that both rotavirus vaccines were effective at reducing rotavirus diarrhoea (severe cases and cases of any severity) and all-cause gastroenteritis. In the first two years of life, Rotarix® and RotaTeq® prevented about 80 per cent of severe cases of rotavirus diarrhoea in low-mortality countries[14], and at least 40 per cent in high-mortality countries[15]. Rotarix® reduced severe cases of diarrhoea from all-causes by 35 to 40 per cent in low-mortality countries, and 15 to 30 per cent in high-mortality countries. Vaccination with RotaTeq® reduced severe cases of all-cause diarrhoea by 73 per cent to 96 per cent in low-mortality countries, and 15 per cent in high-mortality countries (Soares-Weiser et al., 2012).

Pre-licensure clinical trials for both Rotarix® and RotaTeq®, have shown that the risk of intussusception does not differ between the vaccine and placebo arms. Although a small, increased risk of intussusception of one to two excess cases of intussusception per 100,000 vaccinated infants was detected in trials conducted in Mexico (Rotarix®) and Australia (RotaTeq® and Rotarix®), this risk is five to ten times lower than that attributed to RotaShield® and is therefore considered negligible. The benefits of rotavirus vaccination in preventing hospitalisation and death outweighs this small risk of intussusception (Soares-Weiser et al., 2011; Soares-Weiser et al., 2012; World Health Organization, 2013d).

[13] All-cause gastroenteritis includes any diarrhoea episode irrespective of causative agent or diagnosis. For example diarrhoea may be due to viral or bacterial infections, or exposure to toxins or allergens (Soares-Weiser et al., 2012) .

[14] In this Cochrane review, countries were defined according to WHO mortality strata. Countries are defined as low-mortality countries in WHO strata A and B (very low or low child mortality, and low adult mortality); and high-mortality countries in WHO strata D and E (high child mortality, and high or very high adult mortality) (Soares-Weiser et al., 2012).

[15] Oral vaccines like rotavirus vaccines have lower efficacy rates in low-income countries, which have higher rotavirus mortality. Postulated reasons for lower efficacy rates in these settings include co-infection with gut bacteria, malnutrition reducing absorption of oral vaccines and interference of immunogenicity due to maternal antibodies in breast-fed infants (World Health Organization, 2007).

2.3.3 WHO recommendation for rotavirus vaccines

The safety and efficacy of both rotavirus vaccines have been proven in large phase III trials worldwide, in all regions of the world (Jiang et al., 2010; Strategic Advisory Group of Experts, 2009). While it was found that oral rotavirus vaccines had lower efficacy rates in high mortality, low-income countries in Asia and Africa, the potential impact of vaccines in preventing deaths and severe episodes in these settings are higher than in low mortality countries (Strategic Advisory Group of Experts, 2009).

In 2009, WHO’s Strategic Advisory Group of Experts on Immunisations (SAGE) recommended the inclusion of rotavirus vaccines for infants into all national immunisation programmes, with a stronger recommendation for countries where diarrhoeal deaths account for more than ten per cent of mortality among children under-five years of age (Strategic Advisory Group of Experts, 2009).

The SAGE recommendation for universal rotavirus vaccination is part of a comprehensive strategy for the prevention and control of childhood diarrhoea. These measures include the provision of clean water, improvement of hygiene and sanitation, ensuring the appropriate management of dehydration with oral rehydration salts and intravenous rehydration, and zinc supplementation (Strategic Advisory Group of Experts, 2009; World Health Organization, 2013d)

The SAGE also concluded that since the estimates of vaccine efficacy correlate inversely with rotavirus disease incidence, the efficacy and effectiveness data from a rotavirus vaccine study can be used in populations within the same mortality stratum. The mortality strata as defined by SAGE, is categorised according to a country’s under-five mortality rate: high mortality (highest mortality quartile), intermediate mortality (next quartile) and low mortality (lowest two quartiles) (Strategic Advisory Group of Experts, 2009).

2.3.4 Rotavirus vaccine introduction worldwide

As of the first of January 2015, 80 countries worldwide have introduced the rotavirus vaccines into their countries national immunisation programmes, including 37 Gavi-eligible[16] introductions and 25 introductions to non Gavi-eligible, middle-income countries (Figure 2.1). Among Asian countries, only the Philippines and recently Thailand have introduced the vaccines on a limited basis or pilot basis (PATH, 2016).

[16] Gavi, the Vaccine Alliance (formerly known as the 'Global Alliance for Vaccines and Immunisations') is a public-private global health partnership launched in the year 2000 to fund vaccines for children in the world's poorest countries. Its mission is: "to save children's lives and protect people's health by increasing access to immunisation in the world's poorest countries." (Gavi, 2015)

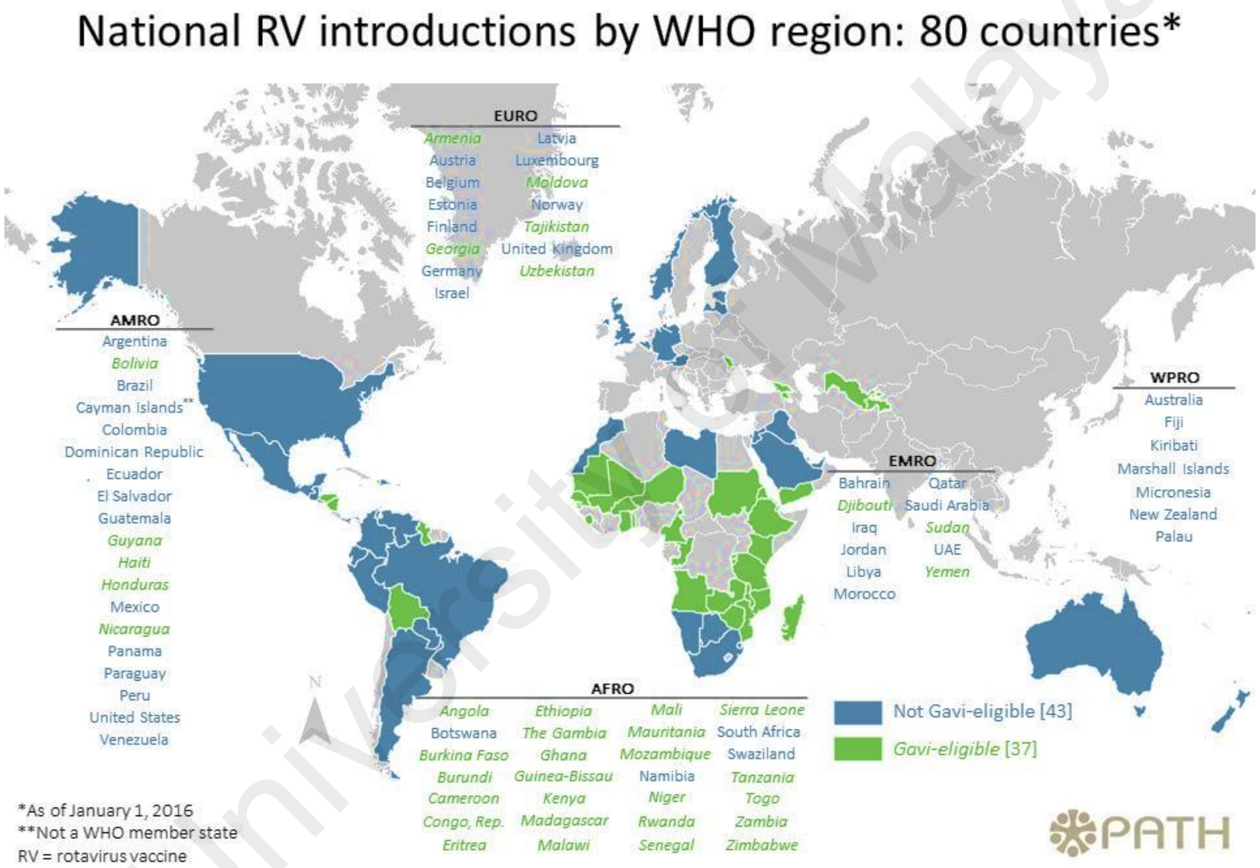

Figure 2.1: National rotavirus vaccine introductions by WHO regions

Source: (PATH, 2016)

2.3.5 Impact of rotavirus vaccines

Randomised controlled trials prove vaccine efficacy in the ideal settings of clinical trials. Post licensure surveillance studies inform on vaccine effectiveness, or the 'real world' impact of vaccines[17].

Post licensure surveillance from high- and middle-income countries have shown substantial reductions in rotavirus diarrhoeal admissions (49 to 89 per cent), all-cause diarrhoeal admissions (17 to 55 per cent) and reduction in all-cause diarrhoeal deaths in Brazil (22 per cent) and Mexico (35 per cent) (Lopman et al., 2012; Patel, Glass, Desai, Tate, & Parashar, 2012; Manish M Patel et al., 2011; Yen et al., 2014).

Herd immunity is indicated by rotavirus vaccine effectiveness greater than expected from the level of vaccine coverage (Tate et al., 2011). Herd immunity is the population-level effects of immunisation, where unvaccinated individuals are indirectly protected from infection by the presence of those immune to the disease. When a sufficiently large proportion of the population are vaccinated, infectious disease transmission is blocked as contact between the infectious and susceptibles are reduced (Fine, 1993).

Herd immunity confers protection against rotavirus infection among the unvaccinated, including those ineligible for vaccination, either due to age restrictions or contraindications (Patel et al., 2012; Yen et al., 2014). A systematic review of rotavirus vaccine impact studies found a median herd effect of 22 per cent (19 to 25 per cent) among rotavirus specific diarrhoeal outcomes and a median herd effect of 25 per cent (11 to 30 per cent) among all-cause diarrhoeal outcomes (Pollard et al., 2015).

2.3.6 Cost of new vaccines

The rotavirus vaccines are more expensive than the traditional vaccines in the Expanded Programme for Immunisation (EPI). The high prices of the new rotavirus

[17] Impact of vaccination programme are also influenced by the countries' immunisation system: the cold chain system, vaccine delivery, immunisation schedule, vaccine coverage and others.

vaccines are a barrier to their introduction into a publicly-funded, national immunisation programme, especially in low and middle-income countries (Madsen et al., 2012).

Following the market withdrawal of the first rotavirus vaccine, RotaShield® for a small but important risk of intussusception, the new vaccines underwent the largest safety trials in history. Rotarix® and RotaTeq® both underwent large pre-licensure trials, with samples size of 60,000 to 70,000 infants each, powered to detect the risk of intussusception. The conduct of these large clinical trials made rotavirus vaccines particularly expensive.

At the time of licensing in 2006, Rotarix® and RotaTeq® had cost about 132 times and 90 times more than traditional EPI vaccines (Madsen et al., 2012). Using the lowest available vaccine prices, the Médecins Sans Frontières (MSF) estimated the minimum cost to vaccinate a single child against twelve diseases in 2014[18] ranged from US$ 32 to US$ 46 (RM 101 to RM 145), or 68 times the cost of vaccinating a child against six diseases in 2001[19] (Medecins Sans Frontieres, 2015).

2.3.7 Dilemma of middle-income countries

The uptake of rotavirus vaccines in middle-income countries are particularly slow compared to low- and high-income countries. Middle-income countries, like Malaysia, are not eligible for subsidised vaccine pricing from the Gavi, The Vaccine Alliance[20] or UNICEF (Kaddar, Schmitt, Makinen, & Milstien, 2013). In Asia, despite WHO recommendation for rotavirus vaccine introduction, only the Philippines and of recent Thailand have introduced the vaccine on a limited or regional basis (PATH, 2016).

Tiered-pricing mechanisms are endorsed by vaccine manufacturers and bodies like Gavi, the Vaccine Alliance, in order to allow profits from the sale of vaccines to high-

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[18] Vaccines recommended by the WHO in 2014, protect against twelve diseases (tuberculosis, measles, rubella, diphtheria, tetanus, pertussis, hepatitis B, *haemophilus influenzae* type b, polio, pneumococcal diseases, rotavirus and human papillomavirus) (World Health Organization, 2015b).

[19] The EPI vaccines recommended by the WHO in 2001 protect against six diseases (tuberculosis, measles, diphtheria, pertussis, and poliomyelitis) (World Health Organization, 2013c).

[20] Gavi, the Vaccine Alliance supports the world's poorest countries. National incomes determine eligibility for new vaccine support. Countries with gross national income (GNI) per capita below than US$ 1,580, are eligible for Gavi support (Gavi, 2015).

and middle-income countries to make vaccination affordable for low-income countries (Medecins Sans Frontieres, 2015). High- and middle-income countries are offered higher vaccine prices in order to subsidise vaccine prices for low-income countries (GlaxoSmithKline, 2014). Eligible low-income countries receive Gavi, the Vaccine Alliance support for vaccines purchased at substantially lower prices (PATH, 2015).

While high-income countries may not have difficulty funding expensive vaccines, high vaccine prices are likely to be a barrier for new vaccine introduction in middle-income countries. Pricing opacity or the lack of transparency in pricing of vaccines offered to different countries, hinders governments from effectively negotiating for more affordable prices (Medecins Sans Frontieres, 2015; E. A. S. Nelson et al., 2013; Rappuoli, 2015).

2.4 The Malaysian context

2.4.1 Country background

Malaysia is a country in South East Asia with a total land mass of 330,803 square kilometres (Department of Statistics Malaysia, 2010a). Peninsular Malaysia in the west, is separated from East Malaysia, located in the island of Borneo, by the South China Sea. Peninsular Malaysia is bordered by Thailand to the north and Singapore to the south. East Malaysia shares land borders with Brunei and Indonesia in the island of Borneo. Malaysia is a federation of thirteen states and three federal territories.

Malaysia has a relatively young population of 29.7 million in 2013, with about 26 per cent below 15 years of age and nine per cent aged five years and below (United Nations, 2013). The birth cohort in Malaysia in 2012 was 508,774 live births (Department of Statistics Malaysia, 2012b). Malaysia has experienced rapid urbanisation, with 71 per cent of the population living in urban areas in 2013. The multi-ethnic population of Malaysia comprises of three main races, namely the Malays (67 per cent), Chinese (25 per cent) and the Indians (7 per cent) (Department of Statistics Malaysia, 2010b).

Malaysia is an upper middle-income country with a gross national income (GNI) per capita of current US$ 10,400 (RM 33,000) in 2013 (World Bank, 2014b). Malaysia is ranked sixty-second on the United Nations Development Programme's Human Development Index[21] with a life expectancy at birth of 74.7 years in 2014 (United Nations Development Programme, 2015). The under-five mortality rate in Malaysia was estimated at 8.5 deaths per 1,000 live births in 2013 (World Health Organization, 2013a).

2.4.2 The healthcare system in Malaysia

Malaysia has a dual public and private healthcare provider system. The main provider of public sector healthcare is the MOH (83 per cent), with contributions by federal agencies (eight per cent), the Ministry of Higher Education (six per cent), and others like the Ministry of Defence and local government. The public sector is funded mainly by general taxation, with minimal user fees. While, the private sector is funded largely by out-of-pocket payments (79 per cent), with limited contributions from private insurance (14 per cent) and employment benefit schemes (Ministry of Health Malaysia, 2012c).

In 2012, the total health expenditure for Malaysia was estimated at RM 42,256 million or 4.5 per cent of the gross domestic product (GDP), of which the public sector contribution was 53 per cent. In 2012, the MOH, Malaysia had the highest contribution of health expenditure amounting to RM 18,593 million or 44 per cent share of total health expenditure. This was followed by private out-of-pocket payments and private insurance which amounted to 37 per cent and seven per cent of the total health expenditure, respectively. In 2012, the per-capita spending on health was RM 1,432 (Ministry of Health Malaysia, 2012c).

In 2013, the MOH had 141 hospitals providing 39,728 beds nationwide, as well as 1,039 health clinics and 1,821 community clinics. The eight non-MOH, public sector

[21] The Human Development Index is a composite index measuring the average achievement of a country in three basic dimensions of human development: long, healthy life, knowledge and a decent standard of living (http://hdr.undp.org/en)

hospitals provided 3,709 beds. Also, there were 214 registered private hospitals with 14,033 official beds, and 6,801 licensed private clinics. The public sector provides 76 per cent of hospital beds and 36 per cent of outpatient clinics, while the private sector provides 24 per cent of hospital beds and 70 per cent of outpatient clinics. In 2013, there were 46,916 medical doctors, 89,167 nurses and 12,517 assistant medical officers nationwide, with a health provider to patient ratio of one in 633, one in 333 and one in 2,374 respectively (Ministry of Health Malaysia, 2014b).

As the major public sector healthcare provider, the MOH, Malaysia plays a social role by providing affordable, quality healthcare for all citizens at minimal user fees. The main thrust of the service is to provide universal health coverage (UHC), in terms of access to affordable and quality health services for all citizens, especially the rural, poor and marginalised. The MOH provides preventive, curative and rehabilitative services, while also being responsible for policy-making, regulation, research and development. The mission of the MOH is one of partnership and patient empowerment, leading to an individual's appreciation of the value of health and personal responsibility towards attaining and sustaining their full health potential. (Ministry of Health Malaysia, 2008).

The MOH, Malaysia is centrally funded and administered, while service provision is administered at the district and state levels. The MOH, Malaysia ensures access to care, through an extensive national network of clinics and hospitals. The primary healthcare infrastructure has a rural focus, with a referral system that connects primary care clinics, as a gatekeeper to primary-, secondary- and tertiary-level hospital care, at district, state, regional and general hospitals (Jaafar et al., 2013).

Primary health care facilities are provided mainly by static facilities, like health and community clinics, and also by mobile clinics and other outreach services. The current two-tier health system ensures that a health clinic covers a population of 15,000 to 20,000 people, while a community clinic covers 2,000 to 4,000 people[22]. A comprehensive range of services are offered at the primary health care facilities, including maternal and child health services, outpatient or curative care, dental services, laboratory services, communicable disease control, health promotion and others (Jaafar et al., 2013).

With economic growth and growth in personal affluence, the private sector expansion has accelerated in Malaysia. As the private sector is financed mainly by fee-for-service, it is driven by market forces. Healthcare services provided by the private sector are mainly curative and diagnostic, and are located mainly in urban areas. Private healthcare in Malaysia can be broadly divided into outpatient clinics, run by single or groups of general practitioners, and hospitals, of varying size and sophistication (Chee & Barraclough, 2007; Jaafar et al., 2013).

2.4.3 The Malaysian national immunisation programme

The EPI programme was launched by the WHO in 1977, following the successful eradication of small pox through a global immunisation campaign. The aims of the EPI to reduce the morbidity and mortality of preventable infectious diseases by providing universal access to immunisation for children worldwide, were thought to be essential to achieving the ‘Global Strategy for Health for All by the year 2000’ (World Health Organization, 1981). The first six diseases targeted by the EPI were polio, diphtheria, tetanus, tuberculosis, pertussis and measles (World Health Organization, 2013c). Currently, the WHO recommends twelve vaccines for routine immunisation of children. These include the Bacille Calmette-Guérin (BCG), hepatitis B, polio, diphtheria-tetanus-pertussis (DTP), *Haemophilus influenzae* type b (Hib), pneumococcal conjugate, rotavirus, measles, rubella, and HPV vaccines (World Health Organization, 2015b).

[22] The two-tier primary healthcare system was established in the 1970’s and consists of health and community clinics. Health clinics serve a population of up to 20,000 people, and are staffed by medical officers, dentists, pharmacists, assistant medical officers, and public health nurses. Services provided at health clinics include outpatient care, maternal and child health services, and dental care. Community clinics are smaller and serve a population of up to 2,000 people. Community clinics are staffed by community nurses and midwives, and mainly provide maternal and child health services (Jaafar et al., 2013).

In Malaysia, the national immunisation programme was first established in 1958 with the introduction of the DTP vaccine. Subsequently, the BCG vaccine was introduced in 1961, oral poliovirus vaccine (OPV) in 1972, tetanus toxoid (TT) in 1974, measles vaccine in 1984, rubella vaccine in 1988, Hepatitis B vaccine in 1989, and Hib and the measles-mumps-rubella (MMR) vaccines in 2002 (Ministry of Health Malaysia, 2004; Roesel & Banerjee, 2008).

The current Malaysian immunisation schedule includes a pentavalent combination vaccine containing diphteria, tetanus, acellular pertussis, inactivated polio virus and *Haemophilus influenzae* type b (DTaP/IPV/Hib), BCG, Hepatitis B, MMR, measles, tetanus, Japanese encephalitis and HPV vaccines. Measles and Japanese encephalitis vaccines are administered to high risk areas, on a regional basis (Imam, Phak, & Thomas, 2013; Ministry of Health Malaysia, 2016) (Table 2.1).

Vaccination is provided free of charge at birth at public hospitals, and during infancy at community and health clinics, throughout the country. A school-based health programme administered by the MOH, provides free vaccinations to pupils at public schools. (Roesel & Banerjee, 2008)

The Malaysian national immunisation programme is well established and successful. In 2013, national vaccine coverage was 99 per cent for BCG, 97 per cent for the third dose of DTaP/IPV/Hib, 95 per cent for MMR and 96 per cent for Hepatitis B. The most recent vaccine introduced was the HPV vaccine in 2010, and this is administered to schoolgirls aged 13 years. Even though HPV vaccination is not mandatory, in 2013 the third dose of HPV vaccine had a 94 per cent coverage in Malaysia (Ministry of Health Malaysia, 2014b).

In Malaysia, vaccines in the national immunisation programme are publicly-funded and compulsory. Although vaccination is available for free at government health clinics, parents may choose to vaccinate their children at private clinics. ‘Optional’ vaccines like the rotavirus, pneumococcal and varicella vaccines are recommended by the MOH, but are not publicly-funded. These 'optional' vaccines are available for purchase from private clinics or hospitals.

Rotavirus vaccines are costly at private practice, with the 2014 recommended retail price for Rotarix® and RotaTeq® being RM 122 per-dose and RM 74 per-dose, respectively (Ministry of Health Malaysia, 2014a). Since rotavirus vaccines are expensive, vaccine acceptance at private practice was found to be strongly influenced by the parents' ability to receive insurance reimbursement for vaccine payments (Kannan Kutty, Pathmanathan, & Salleh, 2010).

Table 2.1: National immunisation schedule, Ministry of Health, Malaysia

Immunisation	Age (Months)										Age (years)		
	0	1	2	3	5	6	9	10	12	18	7	13	15
BCG	1										if no scar		
Hep B	1	2				3							
DTaP/DT*			1	2	3					DT B*			B*
IPV*			1	2	3					B*	IPV		
Hib*			1	2	3					B*			
Measles						Sabah							
MMR									1		2		
JE (Sarawak)							1	2		B†			
HPV												2 doses	

B*, Booster doses; B†, Booster dose given at age 4 years; *pentavalent vaccine contains DTaP, IPV and Hib; BCG, Bacille Calmette-Guerin; DTaP, Diphteria, Tetanus, acellular pertussis; DT, Diphteria; T, Tetanus; IPV, Inactivated Polio Vaccine; Hib, Hemophilus influenzae type B; MMR, Measles, Mumps, Rubella; JE, Japanese Encephalitis; HPV, Human Papilloma Virus.

Source: (Imam et al., 2013; Ministry of Health Malaysia, 2016)

2.5 Summary

Rotavirus is an important cause of diarrhoea morbidity and mortality worldwide. By age five, nearly every child worldwide will have had at least one episode of rotavirus gastroenteritis (Parashar et al., 2003). Rotavirus diarrhoeal incidence does not reduce with improvements in hygiene and sanitation, as evident by the similar disease incidence in both low- and high-income countries (Tate et al., 2012; Ward et al., 2006). Rotavirus mortality varies considerably between countries, with almost ninety per cent of all rotavirus-related deaths occurring in low-income countries (Parashar et al., 2009).

Since 2007, two live attenuated, oral rotavirus vaccines are available internationally. The safety and efficacy of these vaccines were proven in large clinical trials and post-licensure studies. In 2009, the WHO's SAGE recommended that all countries include rotavirus vaccines into national primary immunisation schedules, as a part of comprehensive diarrhoeal control strategies (Strategic Advisory Group of Experts, 2009; World Health Organization, 2013d).

However, partially due to high vaccine prices, rotavirus vaccines adoption has been particularly slow in middle-income countries, like Malaysia, with low rotavirus mortality and without access to subsidised pricing (Madsen et al., 2012; E. A. S. Nelson et al., 2013).

Malaysia is an upper middle-income country, with a mixed public-private healthcare system. Mainly through a tax-financed public health system, the nation has achieved good health status as demonstrated by a life expectancy at birth of 75 years (United Nations Development Programme, 2015), and a low under-five mortality rate of nine deaths per 1,000 live births in 2013 (World Health Organization, 2013a). Private healthcare in Malaysia is funded mainly by out-of-pocket payments, and with services concentrated in urban areas. Although rotavirus vaccination are recommended by the MOH, Malaysia, these vaccines are 'optional' and are not publicly financed. Rotavirus vaccines are available for purchase at private health facilities at retail prices.

Currently, a formal, evidence-informed decision-making platform for vaccine introduction is lacking in Malaysia. In the next chapter, the economic theories behind the allocation of scarce resources, specifically those relevant to the public finance of vaccination programmes, are reviewed and discussed. Subsequently, a framework is developed for the economic evaluation of rotavirus vaccines in Malaysia.

CHAPTER 3: ECONOMIC EVALUATION OF VACCINES: THEORY AND CONCEPTS

3.1 Introduction

Among all public health programmes, it is beyond doubt that vaccines are a cheap and effective intervention for the prevention of infectious diseases (World Bank, 1993). Nonetheless, new vaccines are expensive, increasing the need for economic evaluations to inform policy on the public finance of vaccines. In Malaysia, an evidence-informed, decision-making framework for vaccine introduction into the national immunisation programme is at present lacking.

Traditional economic evaluation of vaccines emphasise principles of utilitarianism, or maximising the health benefits received from a fixed expense (Persad, Wertheimer, & Emanuel, 2009), failing to consider the equitable distribution of benefits and burdens in society (Culyer & Newhouse, 2000). Of practical concern to budget holders is the financial consequences of introducing a new programme, or its budget impact; which is also not traditionally included in economic evaluations (Garattini & van de Vooren, 2011).

A multi-criteria approach for decision analysis is recommended for systematic and transparent priority setting (Baltussen & Niessen, 2006). While the factors influencing healthcare decision-making are multiple and complex, decisions are often made in an ad-hoc manner without optimal use of evidence. For the accountable use of resources, healthcare decision-making should be based on pre-specified and evidence-informed criteria (Hutubessy, Henao, Namgyal, Moorthy, & Hombach, 2011).

In this chapter, a framework is proposed for the economic evaluation of rotavirus vaccines in aid of decision-making around the vaccine introduction into the Malaysian national immunisation programme.

The chapter begins with Section 3.2, which examines the economic theories informing the allocation of scarce resources, specific to vaccination programmes. This is followed by Section 3.3, which reviews different approaches used for decision-making on vaccine introduction. Next is Section 3.4, which discusses the criteria relevant for the evaluation of vaccination programmes. This is followed by Section 3.5, in which a framework is proposed for the economic evaluation of rotavirus vaccines in Malaysia. The chapter concludes with Section 3.6, which summarises the chapter.

3.2 Economic theories informing resource allocation for vaccination programmes

3.2.1 Argument for the public finance of vaccination programmes

Adam Smith theorised in the 1776 'An Inquiry into the Nature and Causes of the Wealth of Nations' utility (as cited in Slothuus, 2000, p. 2 to 4), that individuals act in rational self-interest towards self-benefit, however the 'invisible hand' of the free market allocates resources efficiently to maximise utility.

Adam Smith's 'invisible hand' can be seen as a metaphor for the unintended social benefits of individual actions. The idea of free market trade, channelling individual self-interest and market competition into social benefits, is the central justification behind the laissez-faire fundamentals of neo-classical economics[23].

According to neo-classical economic theory, free markets are the most efficient allocator of goods and services. Neo-classical economic thought was founded on the notion of 'consumer sovereignty', in which an individual acts in self-interest, making rational decisions to maximise individual utility. This idea has its origins in the market economy, where individuals choose between tradeable goods and services (Slothuus, 2000).

[23]Free market economies are markets which are free to function with minimum government intervention or regulation (protectionism, government provision of services or subsidy).

However, health[24] is not a market commodity that can be traded. Health is not exchangeable, as trade-offs in health outcomes between the sick and healthy are impossible (McGuire, Henderson, & Mooney, 1988). Unlike health, healthcare is a tradeable market commodity. However, the uncertainties in healthcare make it unique compared to other goods and services.

As described by Arrow (1963), the uncertainties involved in healthcare, among others, make the market for healthcare imperfect. Market failure in healthcare are due to several unique characteristics of health and healthcare: (1) uncertainties about future health and healthcare needs, (2) information asymmetry, (3) demand for healthcare is a derived demand for health, (4) externalities, and (5) monopoly.

Uncertainty in healthcare is the unpredictability of illness, the availability and effectiveness of treatment, and its outcomes; making individual decisions on the consumption of healthcare difficult. This difficulty is compounded by the fact that consumers of healthcare will never have as much knowledge or understanding of illness as healthcare practitioners. This information asymmetry limits the 'agency' of patients in the consumption of healthcare, leaving healthcare practitioners with the unwarranted responsibility of making healthcare decisions (Arrow, 1963).

Grossman (1972) in his seminal treatise 'On the Concept of Health Capital and the Demand for Health', theorised that the demand for healthcare, unlike that of other goods and services, is a derived demand for health. Individuals do not desire healthcare for its own sake[25], but for the utility or benefit received in improving health. The Grossman model of healthcare demand is exemplified in the demand for therapeutic drugs, as these interventions are consumed purposefully for the treatment or cure of disease.

[24] The Constitution of the WHO defines health in a broad and positive manner: 'Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity' (World Health Organization, 1946). This broad definition of health goes beyond the biomedical spectrum of wellness and illness.

[25] Healthcare on its own may be painful or unpleasant, and not desired for its own sake.

However, vaccines are different from therapeutic drugs in several ways. Vaccines are unique as the population-wide benefits of vaccination, makes them a public good (Beutels, Scuffham, & MacIntyre, 2008). When a critical proportion of the population are vaccinated, the entire population are protected from infection, including the unvaccinated (Fine, 1993). Herd immunity is a positive externality, not of interest to individuals, but which governments strive to achieve (Milstien, Batson, & Wertheimer, 2005).

In addition, vaccines are preventive interventions, administered to the healthy to prevent future illness[26]. Unlike therapeutic drugs, the benefits of vaccination are not immediately experienced by individuals. Vaccines though given to the healthy, may result in adverse events, although this risk is usually minor. Individual perception on the benefits and harms of vaccination, influences and likely reduces private demand for vaccines. (Beutels et al., 2008). Therefore, unlike the market for therapeutic drugs, which depends on an individual's willingness-to-pay, the market for vaccines depends on the governments' willingness-to-pay (Milstien et al., 2005).

Vaccines are innovative healthcare products that require considerable time and money invested towards research and development. Few multinational companies dominate the market and these monopolies limit available products. The resulting lack of competition, as well as procurement strategies and purchasing conditions unique to vaccines (see Chapter 2, Subsection 2.3.7, page 26), keep vaccine prices high (Beutels et al., 2008; Medecins Sans Frontieres, 2015; Milstien et al., 2005).

The imperfect market for healthcare and the population-wide, preventive benefits of vaccines in particular, are a few arguments for the public finance and provision of vaccines.

[26] Vaccines provide primary prevention, which is prevention of disease before its occurrence. This is in contrast to therapeutic drugs, which provide either (1) secondary prevention, by treating early disease and preventing disease progression or (2) tertiary prevention, by treating established disease to prevent onset of complications.

There are two concepts fundamental to economics: scarcity and choice. In any given economy, there will never be enough resources to meet all the needs and demands of people. Particularly in healthcare, resources are limited. Given that there are many competing programmes for investment, choices have to be made. Two broad goals of resource allocation are to ensure efficiency (to maximise health benefits from limited resources) and equity (to ensure fairness in distribution of the benefits and burdens of healthcare) (McGuire et al., 1988; Murray & Frenk, 2000; Musgrove, 1999).

3.2.2 Efficiency

Vaccines offer a direct protective effect against infection when given to individuals, but more importantly, when administered universally, vaccines have an additional social benefit of providing herd immunity (Beutels et al., 2008). Due to the population-wide benefits of vaccination, public policy for vaccination are often rooted in utilitarian philosophy.

Utilitarianism is a normative ethical philosophy based on the moral imperative that the best possible action is the action that maximises utility[27]. Utilitarianism emerged as a concept in the 18th century, with the views of Jeremy Benthem and John Stuart Mill (Driver, 2014). Utilitarianism judges policy by its consequences, which in the context of healthcare is health maximisation: 'the greatest good for the greatest number' (Persad et al., 2009).

A broad definition of efficiency is the allocation of scarce resources in such a way that maximises returns of its aims (Knapp, 1984). Efficiency is a measure determining the 'value for money' of healthcare interventions. Three concepts commonly discussed with efficiency are technical, productive and allocative efficiency. Technical efficiency is determined by physical production, and is achieved when production is organised to minimise the inputs required to produce a given output. Productive efficiency, or also

[27] Utility is an economic term referring to the satisfaction or welfare experienced by an individual as a consequence of consuming a good or service (http://www.investopedia.com/terms/u/utility.asp).

called cost-effectiveness efficiency, allows for direct comparison between alternative interventions. Productive efficiency is determined by both physical production and input prices, and is achieved when production is organised to minimise the cost of producing a given output. While both technical and productive efficiency is concerned with supply-side efficiency, allocative efficiency incorporates the demand-side. Allocative efficiency is concerned with the way resources are produced and distributed within a society[28]. (Culyer & Newhouse, 2000; Palmer & Torgerson, 1999).

In health economics, the optimum allocation of resources originates within the framework of welfare economics[29], which is rooted in the principles of utilitarianism. Welfare economics considers the well-being of all individuals in society as a whole. A main tenet of welfare economics is utility maximisation, in which rational individuals make choices to maximise their utilities. The resultant overall welfare of society is the sum total of individual utilities (Raftery, 1998). Within this framework, decisions made on public programmes have consequences for society as a whole.

Welfare economics make use of Pareto value judgements in resource allocation. Pareto optimum is a position in which it is impossible to allocate resources to improve an individual's welfare without impairing the welfare of at least one other person. Pareto efficiency is the ideal position in which a programme benefits at least one person without causing anyone to be worse off. Welfare economics references free market allocation of resources as Pareto optimal, meaning achieving allocative efficiency (Culyer & Newhouse, 2000, pp. 60-62).

Healthcare is unique among commodities in its reliance on non-market allocation. Evaluation of healthcare interventions, policies and programmes in terms of efficiency is necessary to inform on resource allocation decisions. Two different evaluation methods

[28] Within the framework of welfare economics, allocative efficiency is consistent with achieving Pareto optimal state, in which it is not possible to make at least one person better-off without making anyone worse-off (Culyer & Newhouse, 2000)

[29] Four tenets of neo-classical welfare economics are utility maximisation, consumer sovereignty, consequentialism and welfarism (Culyer & Newhouse, 2000).

are derived from two main normative economic frameworks: neo-classical welfare economics and extra-welfarism (Culyer & Newhouse, 2000).

The extra-welfarist approach is an adaptation of neo-classical welfare economics, and is more commonly used among health economists. While welfare economics aims to maximise utility, the extra-welfarism aims to maximise health, which is the outcome central to health policy. Welfare economic theory provides the foundation for cost-benefit analysis, while the extra-welfarist approach is the basis for cost-effectiveness or cost-utility analysis[30]. (Culyer & Newhouse, 2000, p. 96; Raftery, 1998).

The concept of opportunity costs is essential to health economics. As healthcare resources are scarce as compared to needs, the investment in one programme implies disinvestment in another. The opportunity costs or the 'shadow price' of investing in a particular programme is best measured by the health benefits foregone from the next best alternative programme displaced (Culyer & Newhouse, 2000, p. 97 to 98; Palmer & Raftery, 1999).

Welfare economics, places importance in 'consumer sovereignty' or the individual's valuation of their own utility. This is the theoretical basis for the money-metric measurement of benefits, or the consumer's 'willingness-to-pay' for improvement in health status and 'willingness-to-accept' for loss of health. Some of the limitations of this approach are the aforementioned uncertainties and imperfect information in health and healthcare, curbing individual agency in healthcare (Culyer & Newhouse, 2000, p. 60 to 62).

The human capital approach is a rival approach for the valuation of human life within the welfare economic framework. According to the human capital approach, the economic value of additional years of life is the value of economic production associated with those

[30] Cost-benefit analysis compares both costs and benefits in monetary terms. Due to the controversies in valuing human life in monetary terms, the extra-welfarist approach values outcomes in non-monetary terms. In cost-effectiveness analysis and cost-utility analysis, costs are measured in monetary units but outcomes are measured in non-monetary, health-related terms, like natural units of outcome for cost-effectiveness analysis and in quality-adjusted life years (QALYs) for cost-utility analysis (Culyer & Newhouse, 2000, p. 96; Raftery, 1998).

years. This economic value can be translated to additional earnings or income for extra life gained. The main controversy surrounding the valuation of health gain based on economic production, is the bias towards those working in the market sector (wage earners), as compared to those in the non-market sector (non-wage earners) or those not part of the work force (elderly or children) (Culyer & Newhouse, 2000, p. 98 to 99).

Utilitarian principles of health policy aim to maximise average population health. A critique of utilitarianism in public policy, is that it sacrifices the needs of the individual for the betterment of the collective. John Rawls criticised of the aggregation of utility pursued by utilitarianism as ignoring the interests of individuals: "Utilitarianism does not take seriously the distinction between persons" (Rawls, 1971, p. 21). Amartya Sen in his 1973 treatise 'On Economic Inequality' (as cited in Pereira, 1993, p. 17), famously criticised utilitarian principles for not considering the interpersonal distribution of sum benefits: "... maximising the sum of individual utilities is supremely unconcerned with the interpersonal distribution of that sum".

Aggregate measures of societal benefits, such as quality-adjusted life years (QALYs), are concerned with net improvements, masking variations in the distribution of benefits. Thus, using results of a cost-effectiveness analysis alone to decide resource allocation ignores other ethical concerns, namely of distributive justice or 'justice as fairness' (Dawson, 2011; Field & Caplan, 2012).

3.2.3 Equity

Equity is synonymous with fairness, which is grounded in the ethical principle of distributive justice. According to Whitehead (1992), equity has moral and ethical dimensions. Inequities in health are differences which are not only unnecessary and avoidable, but also deemed unfair and unjust. Equity in health implies that everyone should have a fair opportunity to achieve their full potential in health, and no one should be unfairly disadvantaged.

Braveman and Gruskin (2003) defined equity in health as the absence of systematic disparities in health, or its social determinants[31], between more or less advantaged social groups. The implication being that differences in health status, if due to disparities in wealth or social conditions, is unfair and unjust.

Although equitable distribution of health and healthcare resources are acknowledged as a moral imperative, there is little consensus on the theories and principles for just distribution (Culyer, 2001). Veatch in his 1981 publication 'A Theory of Medical Ethics' (as cited in McGuire et al., 1988, p. 46), identified four theories of distributive justice: (1) the entitlement theory (individuals are entitled to what they acquired justly)[32], (2) utilitarianism (maximising total benefits), (3) maximin (favouring the worst-off)[33] and egality (treating people equally). These theories of distributive justice are normative, and the choice of theory to inform health policy is based on societal norms and value judgements.

Most ideas for the fair allocation of available resources are based on egalitarian principles (Culyer & Newhouse, 2000). Egalitarian views of distributive justice calls for equality, either in individual net benefits; or the distribution of resources. While equality in health seems like a faultless ideal, this is an unrealistic goal for health systems. As described by Grossman (1972), healthcare is only one of many determinants in the production of health[34]. Unequal health status may be due to unavoidable physical or other differences, and is consequently not unfair (Whitehead, 1992).

[31] As explained by Sir Michael Marmot, social determinants of health are the conditions in which an individual is born, grows, lives, works and ages and the wider social, political and economic systems that shape these conditions (Marmot, Friel, Bell, Houweling, & Taylor, 2008).

[32] Robert Nozick in his 1974 treatise 'Anarchy, State and Utopia' (as cited in Pereira, 1993, p. 13 to 14),theorised that an individual is entitled to possess private property that is justly acquired, either through inheritance or earnings. Within this libertarian view of justice, subsidisation or redistribution based on needs would be an injustice. Free market determination of the price of healthcare, would mean that access to care is dependent on ability to pay, adversely impacting the poor.

[33] According to the John Rawls's Maximin principle, when distributing social goods, a just society seeks to maximise the welfare of the least well-off person in that society. Rawls hypothesised that behind the 'veil of ignorance', individuals opt for a much fairer society, with extensive freedom and fair opportunity, without extremes of unfairness in terms of wealth or social positioning (Pereira, 1993, p. 18 to 19).

[34] According to Grossman (1972), we inherit an initial stock of health, which depreciates with age, and can be increased through investment. Investment in health is made not just with the consumption of healthcare, but also through consumption of leisure activities and other goods and services.

The philosopher Ronald Dworkin (1981) argued that egalitarian principles, calls for equality in distribution of resources irrespective of needs, and not towards the end point of equality in welfare (as cited in Pereira, 1993, p. 10 to 11). In the case of healthcare, egalitarian views of distributive justice implies equal distribution of healthcare resources and not equal health status.

Equity in healthcare can be approached from two aspects, fairness in the distribution of benefits (health or healthcare) and fairness in financing of healthcare (distribution of the costs of healthcare). Of relevance in this thesis is the fairness in financing, or distribution of healthcare costs.

There are distinct differences in the concepts of equity and equality, in relation to fairness. While equity is synonymous with fairness, equality implies equal distribution of benefits or costs, which is not necessarily fair. In terms of healthcare financing, equal healthcare payments across all income groups may be unfair. Out-of-pocket payments, or payments for healthcare made at the point of access of care, have different welfare implications for the rich and the poor. The rich have better ability to cope with unexpected expenses, as they are more likely to access coping mechanisms like savings and loans (Alam & Mahal, 2014; Kruk, Goldmann, & Galea, 2009). Healthcare payments may deter the poor from seeking needed care, worsening inequities in the access of care.

Distributive justice, according to Aristotle is in giving ‘each his due’. Within this Aristotelian understanding, equity can be distinguished into two groups; that of horizontal and vertical equity. In the context of financial contribution to healthcare, horizontal equity relates to ‘equal contributions from households having an equal ability to pay’, while vertical equity means ‘higher contributions from households with a higher ability to pay’ (Culyer, 2001). Fairness in financing of healthcare is concerned with vertical equity. The emphasis on households of different income levels making payments according to ability to pay, is part of the concept of 'progressivity' in healthcare financing[35] (Culyer & Newhouse, 2000).

3.3 Evidence based framework for vaccine introduction

Economic evaluations are routinely used in many countries, to inform decision-making on vaccine introduction. Commonly, cost-effectiveness is the sole criteria used for decision-making (ISPOR, 2015). In a consensus statement from the European Vaccine Economics Community, experts attested to the usefulness of economic evaluations with a broader focus, including assessment of affordability and equity. The experts examined three approaches for decision-making on vaccine introduction. These were the pure threshold approach (in which cost-effectiveness is the deciding criteria), the multi-criteria decision analysis (which incorporates cost-effectiveness with multiple weighted criteria) and the use of informal judgement (multiple criteria including cost-effectiveness considered through the lens of value judgements) (Ultsch et al., 2015).

A cost-effectiveness is a relative measure, usually with thresholds set as a reference measure to inform allocation decisions (Eichler et al., 2004). Several countries like the United Kingdom, Australia, Thailand and Canada have defined cost-effectiveness thresholds. Other countries, like Malaysia, have not fixed a formal cost-effectiveness threshold for decision-making (ISPOR, 2015). Cost-effectiveness thresholds make decision rules straightforward and transparent[36]. However, the use of threshold measures does not consider other relevant criteria like disease severity, burden, affordability or equity.

Priority setting in healthcare, particularly for vaccines requires multiple criteria. Erickson, De Wals, and Farand (2005) proposed a multi-criteria analytical framework for

[35] Progressivity in healthcare financing implies that the richer person contributes a greater proportion of income towards healthcare payments. Where else in a regressive health financing system, the poor pay proportionately more for healthcare than the rich. A proportional system implies that healthcare payments account for the same proportion of income for everyone, irrespective of income.

[36] Efficiency is expressed by the incremental cost-effectiveness ratio (ICER), which compares the differences in costs with health gains between alternative interventions. An intervention may be considered cost-effective if the ICER falls below a defined cost-effectiveness threshold.

systematic evaluation of new vaccination programmes in Canada. The comprehensive list of criteria proposed included disease characteristics and burden, vaccine characteristics, immunisation strategies, social and economic costs and benefits, feasibility, acceptability, and the legal, political and ethical considerations.

The use of multiple criteria for decision-making is complex and requires weightage of each criterion[37] (Ultsch et al., 2015). Kimman et al. (2006) suggested a checklist-based approach for assessing all necessary evidence for vaccine introduction. The National Immunisation Programme Review Committee of the Health Council of the Netherlands proposed a hierarchal decision-making framework around introduction of a publicly-funded vaccine. This proposed framework is hierarchical because an affirmative answer is assumed for each criteria before moving to the next criteria (Houweling et al., 2010). Piso and Wild (2009) proposed a step-wise approach, allowing a sequential assessment of relevant criteria towards vaccine introduction.

Despite formalising decision-making on vaccine introduction into rational frameworks, most agree that prioritisation should be rooted in social value judgements. Social values and norms however are not quantifiable, and require informal judgement. However, considering social values judgements, encourages public acceptance of vaccination programmes, while ensuring that the best possible protection is given to the whole population (Field & Caplan, 2012; Houweling et al., 2010; Kimman et al., 2006).

3.4 Criteria for the evaluation of vaccination programmes

In this section, some of the criteria relevant for decision-making on rotavirus vaccine introduction into national immunisation programmes are considered.

[37] For example, providing equitable services may not be efficient. Ensuring that services target the poor, rural communities, may prove to be expensive and not an efficient use of resources.

3.4.1 Health and economic burden

The first step in priority setting towards vaccine introduction, is to establish the importance of the infectious disease and the need for intervention. In the past, vaccines have targeted diseases that have resulted in high mortality or severe disability, for example small-pox, polio and diphtheria. New vaccines target childhood illness like chicken pox or rotavirus gastroenteritis, that are less deadly but are nevertheless significant, in terms of healthcare utilisation and loss of caregiver productivity (Houweling et al., 2010).

It is important to have accurate estimates on the national health and economic burden of rotavirus, for disease prioritisation. The seriousness of the health burden can be quantified in terms of deaths and illness incidence according to healthcare utilisation. The economic burden includes direct and indirect costs from the healthcare provider and societal perspective. Since public health measures like improvement in water, hygiene and sanitation does not reduce rotavirus transmission, an effective rotavirus vaccine is an important preventive measure. Estimation of the pre-vaccination burden will indicate the potential burden averted by implementing the universal vaccination programme.

3.4.2 Safety, efficacy and quality

Vaccine safety is a measure of the ability of vaccines to perform without untoward adverse effects. The concept of safety in vaccination has long been upheld with stringent standards. The ethical principle considered in vaccination is the Latin caveat - ‘primum noncere’ or ‘first, do no harm’. This fundamental principle of non-maleficence, is taught to all healthcare professionals and is part of the Hippocratic Oath. In accordance to the principle of non-maleficence, the ethical principle of beneficence is a positive requirement to contribute towards the welfare of others, while avoiding causing harm (Field & Caplan, 2012).

Vaccines are biological agents given to healthy individuals, most of whom are children, to provoke a protective immune response against illness. Standards of vaccine safety are therefore rigorous and much higher than those that need to be met by manufacturers of therapeutic medicines. Any potential adverse events associated with vaccination should be weighed against and found not to diminish the public health benefits of vaccination (Dawson, 2011; Field & Caplan, 2012; Houweling et al., 2010).

As discussed in Chapter 2 (Subsection 2.3.2, page 20), the safety, efficacy and quality of rotavirus vaccines were proven in large pre-licensure clinical trials and post-licensure surveillance studies.

3.4.3 Cost-effectiveness

Safety, efficacy and quality are the three traditional hurdles pharmaceutical companies have to overcome before the licensing of drugs or vaccines. Cost-effectiveness can now be considered the fourth hurdle (Erickson et al., 2005; Houweling et al., 2010).

Decision-makers increasingly rely on cost-effectiveness analysis to inform on the efficient allocation of scarce healthcare resources. A cost-effectiveness analysis in an economic evaluation is designed to assess value for money. Efficiency is expressed by the incremental cost-effectiveness ratio (ICER), which compares the differences in costs with health gains between alternative interventions.

The WHO recommends that cost-effectiveness be considered as a criteria in the evaluation of new vaccine introduction into national immunisation programmes (Hutubessy et al., 2011; World Health Organization, 2005b, 2014a). However, cost-effectiveness should not be the sole criteria in medical decision-making. Cost-effectiveness informs on productive efficiency, which is choosing the option that produces the most benefit for the least cost. A cost-effectiveness analysis does not inform on affordability or equity. The rotavirus vaccine may be found to be cost effective, but the high costs entailed may make public finance of vaccination programmes unaffordable.

The primary goal of health systems is health maximisation, or reducing the morbidity and mortality from disease. Decisions made purely on the basis of a cost-effectiveness, run the risk of choosing vaccines on the basis of costs and not prioritising public health interventions that effectively reduce human suffering, death, or disability (Black, 2013).

3.4.4 Affordability

New vaccines, particularly rotavirus vaccines, are expensive compared to traditional vaccines in the EPI (Madsen et al., 2012).

Policy makers need to relate the financial costs with the national health budget, to better anticipate and plan for future expenses. A budget impact analysis is complementary to cost-effectiveness analysis, in providing additional information on the allocation of limited healthcare resources. The budget impact analysis is conducted to inform the budget holder on the affordability of investment in vaccination programmes and the ability to remain within the annual budget.

Costs in a budget impact analysis are financial costs to the budget holder, while a cost-effectiveness analysis considers economic costs from a societal perspective. While reduction in productivity loss are of interest to society, they are of little consequence to budget holders, as productivity savings from vaccination are not passed on to the health service (Garattini & van de Vooren, 2011; Trueman, Drummond, & Hutton, 2001).

3.4.5 Equity and financial risk protection

Vaccines have long been regarded as cheap and effective interventions towards improving health (World Bank, 1993). However traditional evaluations of vaccines focus on health gains and savings to the health system, underestimating the broader benefits of vaccination, which includes improving equity and providing financial risk protection (T. Bärnighausen et al., 2014; Bloom et al., 2005; Deogaonkar, Hutubessy, van der Putten, Evers, & Jit, 2012).

In this thesis, it is proposed that economic evaluations of vaccines move away from the narrow perspective of health systems and explicitly consider the perspective of households, with equity and financial risk protection as additional criteria towards vaccine introduction

Towards achieving universal health coverage (UHC), health systems are obliged to provide access to healthcare services, while ensuring equitable distribution of benefits and burdens in society, and financial risk protection against the impoverishing impact of healthcare payments (World Health Organization, 2005a).

Reliance on out-of-pocket (OOP) healthcare payments, or direct payments for healthcare at the point of receipt of care, results in financial hardship among millions of people worldwide (Kruk et al., 2009; Ke Xu et al., 2007). Unanticipated illness-related expenditure above a certain threshold of household income may have an adverse impact on household living standards, and may be considered catastrophic (O'Donnell & Wagstaff, 2008; Ke Xu et al., 2010). Illness-related payments may force households into poverty or deepen the extent of poverty (Van Doorslaer et al., 2006).

Financial risk protection, an essential component in achieving UHC, can be defined as access to quality healthcare as needed without incurring financial hardship (Saksena et al., 2014). Governments are responsible to provide financial risk protection so that people are not deterred from utilising healthcare services, nor are they at risk of financial catastrophe or medical impoverishment (World Health Organization, 2010). Universal vaccination as an effective preventive measure against infectious disease may play a role in enhancing UHC, by averting illness and illness-related costs, thus providing financial risk protection to all.

3.4.6 Other considerations

Traditional economic evaluations fail to fully consider practical aspects of programme implementation, including the political, legal, institutional and social context in which decision-making takes place (Hauck, Smith, & Goddard, 2004).

Other considerations for implementation of vaccination programmes include the urgent priority of the disease and the demand for vaccines, either from the public or clinicians. This is particularly relevant during times of infectious disease outbreak, when vaccination may be the only reliable measure for disease prevention.

Public acceptance of vaccines and the opinion of politicians, media and special interest groups, influence decision-making and programme implementation. Social value judgements and ethics are important when introducing vaccination programmes, particularly to safeguard public interests and to ensure policy acceptance.

Although, these non-economic aspects may be considered by policy makers in view of vaccine introduction, assessing these factors is beyond the scope of this thesis.

3.5 The conceptual framework for economic evaluation of rotavirus vaccination in Malaysia

In this thesis, a conceptual framework is proposed for the economic evaluation of rotavirus vaccines in Malaysia. This framework considers the economic theories behind the allocation of scarce resources, and the economic criteria relevant to inform policy on public finance of rotavirus vaccines. While the conceptual framework proposed in this thesis was developed specifically to discuss the public finance of rotavirus vaccines in Malaysia, it may be used to inform decision-making on other vaccines and in different settings.

In the case of rotavirus vaccines, there are two available vaccines that have been proven safe, efficacious and of quality. Large phase III clinical trials conducted in all regions of the world have proven the safety and efficacy of rotavirus vaccines (Ruiz-

Palacios et al., 2006; Vesikari et al., 2006). These trials informed the WHO SAGE recommendations for inclusion of rotavirus vaccines into all national immunisation programmes (Strategic Advisory Group of Experts, 2009; World Health Organization, 2013d). However, in view of the high cost of rotavirus vaccines, economic evidences are needed to inform decision-making around vaccine introduction into national immunisation programmes.

In this thesis, the health and economic burden of rotavirus gastroenteritis are estimated, followed by the assessment of cost-effectiveness, affordability and the distributional benefits of rotavirus vaccines in providing financial risk protection to households in Malaysia. Rather than relying on a single criteria alone, information on disease burden, cost-effectiveness and affordability of the vaccine, distributional benefits of vaccines in providing financial risk protection and other criteria are gathered to collectively inform decision-making. The economic arguments are then discussed with consideration to the underlying societal values and norms in Malaysia. (Figure 3.1)

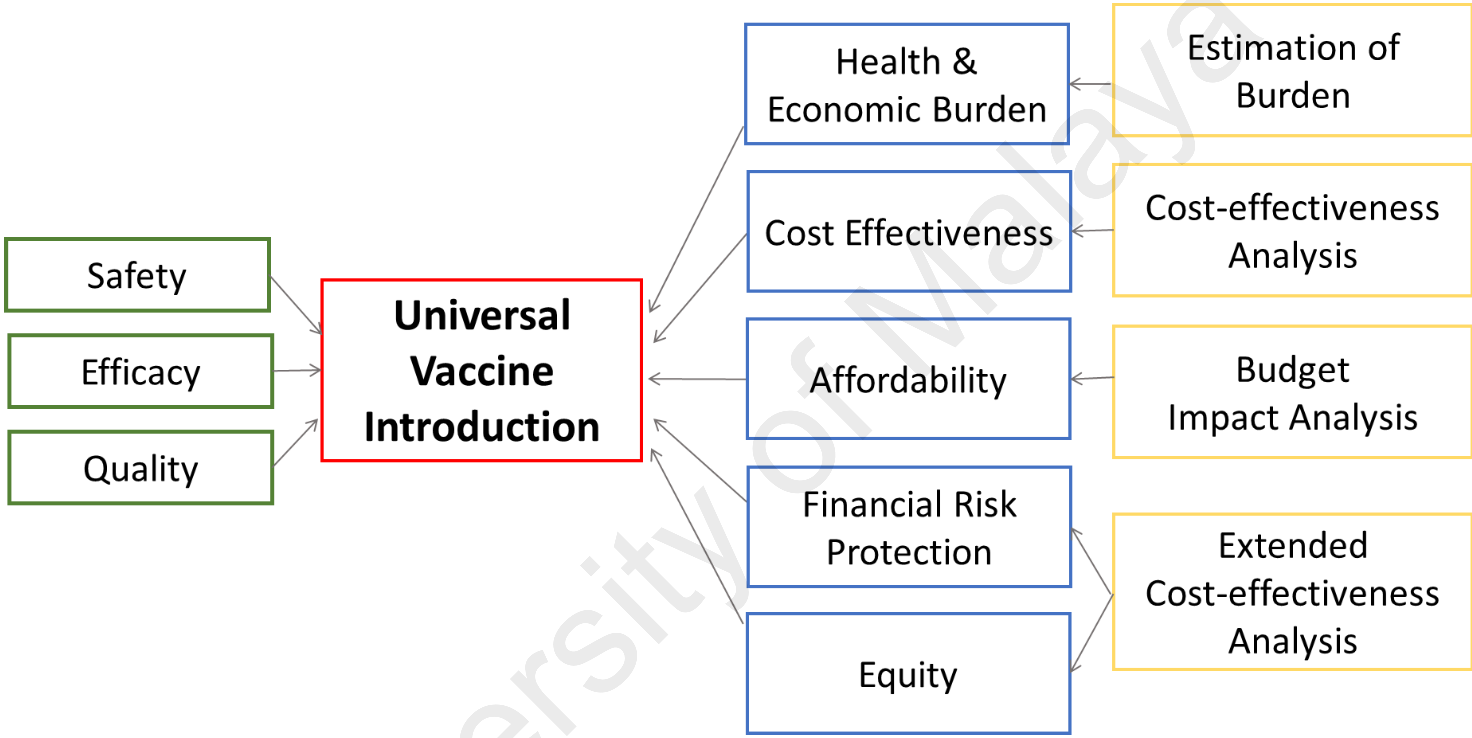

Figure 3.1: Conceptual framework for the economic evaluation of rotavirus vaccines in Malaysia

3.6 Summary

Vaccines are biological agents given to the healthy to provide protective immunity against infection. The nature of vaccines as a public good and the resultant market failure for vaccines, necessitate government intervention in the public finance and provision of vaccines.

Health systems aim to maximise of population health within the constraints of scarce resources. The efficient allocation of resources in vaccination is often evaluated using cost-effectiveness analysis. Although cost-effectiveness is often the sole economic criteria used, there are multiple criteria relevant to prioritisation in universal vaccine introduction, including equity, affordability and financial risk protection. Fairness in the financing of healthcare has moral and ethical dimensions important to society. While the affordability of a programme is of practical concern to budget holders, governments are responsible to ensure that all people have access to quality health services as needed, without the financial consequences of having to pay for healthcare (World Health Organization, 2010).

In this chapter, a conceptual framework was developed for the economic evaluation of rotavirus vaccines in Malaysia. Using this framework, the burden of rotavirus is estimated, together with the evaluation of cost-effectiveness, affordability and the non-health benefits of rotavirus vaccines in providing financial risk protection and enhancing equity in Malaysia. This framework is proposed for use for evidence-informed decision-making on the introduction of universal rotavirus vaccines in Malaysia.

In the next chapter, the health and economic burden of rotavirus is comprehensively estimated, with due consideration given to the complexity of the mixed public-private healthcare system in Malaysia.

CHAPTER 4: THE HIDDEN HEALTH AND ECONOMIC BURDEN OF ROTAVIRUS GASTROENTERITIS IN MALAYSIA: AN ESTIMATION USING MULTIPLE DATA SOURCES

4.1 Introduction

Worldwide, rotavirus gastroenteritis causes substantial mortality and morbidity. The WHO recommends two rotavirus vaccines for universal vaccination in all countries (World Health Organization, 2007). However, rotavirus vaccines are expensive, particularly for middle-income countries like Malaysia, which are not eligible for multi-national pooled purchasing schemes, such as those initiated by Gavi, the Vaccine Alliance (E. A. S. Nelson et al., 2013). Consequently, rotavirus vaccine introductions in middle-income countries have lagged behind those of high- and low-income countries (Dykstra, Glassman, Kenny, & Sandefur, 2015; PATH, 2016).

The problem is exacerbated by a poor understanding of the true burden of rotavirus gastroenteritis in middle-income countries. In these settings, diarrhoeal mortality is low but the burden of cases presenting to healthcare is potentially high. However, the healthcare burden is difficult to estimate in countries like Malaysia, as much of healthcare is supplied by the private sector[38] (Jaafar et al., 2013). Previous estimations of rotavirus burden in Malaysia have focused on diarrhoea treated at public facilities; inadequately considering privately-treated episodes and not considering home-treated episodes (Chai & Lee, 2009; Hsu et al., 2005; Lee et al., 2007). This substantially underestimates the overall burden of rotavirus in the country. Hence, a comprehensive estimate of disease burden is essential for decision-making around the introduction of a new vaccine, both in Malaysia and in other countries.

[38] Malaysia has a mixed public-private healthcare system, with the private sector providing 24 per cent of hospital beds and 70 per cent of outpatient clinics in the country (Ministry of Health Malaysia, 2014b).

This chapter aims to estimate the health and economic burden of rotavirus gastroenteritis in Malaysia. This includes the estimation of rotavirus deaths, hospitalisations and outpatient visits to public and private facilities, home-treated episodes and the economic burden of these events to the healthcare provider and society.

The chapter begins with Section 4.2, which describes the data sources, analytical methods and assumptions used in the estimation of the health and economic burden of rotavirus in Malaysia. Next, Section 4.3 presents the results of this estimation. This is followed by Section 4.4, which discusses study findings, limitations and its policy relevance. The chapter ends with Section 4.5, which provides the chapter conclusions.

4.2 Materials and methods

4.2.1 Study overview

In Malaysia, the diagnosis of rotavirus is not required for the management of diarrhoeal illness or the certification of diarrhoeal death. As such the burden of rotavirus gastroenteritis is not immediately clear, and must be estimated from the incidence of acute gastroenteritis in Malaysia.

To estimate rotavirus incidence, the incidence of acute gastroenteritis is multiplied with the proportion of gastroenteritis episodes attributable to rotavirus. This method for estimating the incidence of rotavirus gastroenteritis was described by Parashar et al. (2003) in the 2003 estimation of global rotavirus burden, and is widely used internationally (World Health Organization, 2002a). (Figure 4.1)

In this chapter, incidence of rotavirus deaths, episodes seeking formal care, which includes hospitalisations and outpatient visits to both public and private facilities, and episodes not seeking formal care or home-treated episodes, were estimated for Malaysia. Subsection 4.2.2 details the data sources and methods used for estimating rotavirus health burden in Malaysia.

The economic burden of rotavirus gastroenteritis was estimated from the healthcare provider and societal perspectives. From the healthcare provider's perspective, direct medical costs were estimated for hospitalisations and outpatient clinic visits. Costs from the societal perspective included direct medical, direct non-medical and indirect costs, for rotavirus deaths, episodes seeking formal care, as well as episodes treated at home. Subsection 4.2.3 details the data sources and analysis used for estimating the economic burden of rotavirus gastroenteritis in Malaysia.

The base year for analysis was 2013. All costs were inflated to 2013 Ringgit Malaysia (RM) using GDP deflators (Department of Statistics Malaysia, 2012a, 2013a, 2013b). The World Bank exchange rate for 2013 of US$ 1 to RM 3.15 was used in this analysis (World Bank, 2014a).

Figure 4.1 shows the conceptual framework for the estimation of the health and economic burden of rotavirus gastroenteritis in Malaysia.

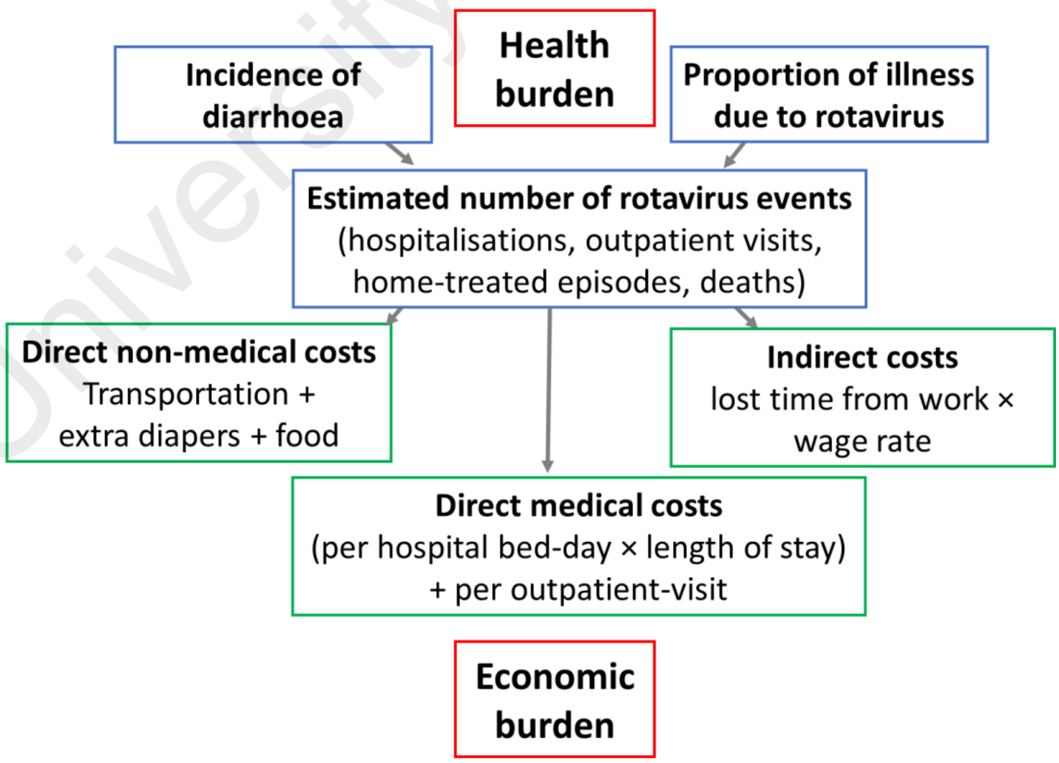

Figure 4.1: Conceptual framework for estimating the health and economic burden of rotavirus gastroenteritis in Malaysia

4.2.2 Estimating the health burden of rotavirus gastroenteritis

4.2.2.1 Hospitalisations

(a) ***Data source***

Since 1999, electronic records on hospital discharges from public hospitals and more recently from private hospitals are captured on an annual basis in a national database, by the Centre for Health Informatics, at the MOH, Malaysia. Public hospital discharges are collected from MOH hospitals only. Other public hospitals, like academic teaching hospitals and army hospitals, do not report hospital discharges to the national database.

Although private hospitals are required to provide annual hospital discharges to the MOH, Malaysia as a condition for licensing, reporting is not enforced. Thus, at present only about half of licensed private hospitals provide annual returns to MOH. However, data reporting by private hospitals has improved substantially within the last five years, due to sustained efforts by the MOH. (Table 4.1)

(b) ***Data analysis***

Data on children under-five years discharged from public and private hospitals in Malaysia, with the International Classification of Disease, tenth revision (ICD-10) aetiological codes for diarrhoea, were extracted from the national database for the years 2008 to 2013[39]. The ICD-10 codes for diarrhoeal illness are: undetermined aetiology [diarrhoea of presumed infectious aetiology (A09) and diarrhoea of presumed non-infectious aetiology (K52.9)]; bacterial (A00 and A02 - A05.9, but excluding A02.2); parasitic (A06.0 - A07.9, but excluding A06.4 - A06.7); viral (A08.0 – A08.5).

The data collection mechanism for public hospital discharges migrated from individual submissions to a web-based submission system in 2012, resulting in the post-2012 data being incomplete. Hence, 2011 was chosen as the reference year for public hospital

[39] Data for these years were the most recent available.

discharges. For private hospital discharges, the most recent available data from 2013 was used for this study[40].

To estimate discharges from all facilities in Malaysia, including those that were not reported to the national database, reported hospital discharges were multiplied with the number of beds from existing public and private healthcare facilities nationwide, and divided by the number beds of facilities reporting hospital discharges. By adjusting for non-response from hospitals using hospital beds, both the number and size of all hospitals in Malaysia were considered. The number of public and private hospitals, and operational beds in Malaysia was obtained from the Centre for Health Informatics at MOH, Malaysia.

Table 4.1 details diarrhoeal discharges for children under-five years reported to the MOH, Malaysia from public and private hospitals in Malaysia, over a for a six year period from 2008 to 2013.

Table 4.2 details the estimation of total diarrhoeal hospitalisations for children under-five years to public and private hospitals in Malaysia.

[40] The data collection mechanism for private hospitals remain unchanged, as a hard-copy or paper-based submissions.

Table 4.1: Annual diarrhoeal discharges for children under-five years in Malaysia, reported from 2008 to 2013

	Year					
	2008	**2009**	**2010**	**2011**	**2012**	**2013**
Public hospitals						
All discharges [a]	326,621	340,640	351,316	365,931	312,743	300,827
Diarrhoeal discharges [b] (%)	21,851 (6.7%)	24,545 (7.2%)	23,828 (6.8%)	23,450 (6.4%)	17,887 (5.7%)	19,259 (6.4%)
Private hospitals						
All discharges [a]	1,360	1,620	130,769	138,783	151,754	153,717
Diarrhoeal discharges [b] (%)	137 (10.1%)	16 (1.0%)	14,546 (11.1%)	17,278 (12.4%)	20,232 (13.3%)	15,886 (10.3%)

Note:

[a] Total hospital discharges for children under-five years reported annually to a national database at the Centre of Health Informatics, Ministry of Health, Malaysia.

[b] Diarrhoeal discharges for children under-five years was extracted from the database using ICD-10 diagnostic codes. [Subsection 4.2.2.1(b), page 59]

Table 4.2: Estimation of total diarrhoeal hospitalisations for children under-five years in Malaysia

Row	Item	Source	Public hospitals	Private hospitals
(1)	Diarrheal discharges reported	MOH [a]	23,450	15,886
(2)	No. of reporting hospitals	MOH [b]	96	107
(3)	No. of hospital beds in reporting hospitals	MOH [b]	18,694	12,572
(4)	Total hospitals in Malaysia	MOH [c]	142	209
(5)	Total hospital beds in Malaysia	MOH [c]	41,639	14,033
(6)	Total diarrhoeal hospitalisations in Malaysia	(1) x (5)/ (3) [d]	52,233	17,732

Note: MOH, Ministry of Health, Malaysia.

[a] Discharges reported to the national database at the Centre of Health Informatics, Ministry of Health, Malaysia. Diarrhoeal discharges at public hospitals for 2011, and at private hospitals for 2013, were used for the estimation. [Subsection 4.2.2.1(b), page 59];

[b] Number hospitals reporting discharges to the Centre of Health Informatics, Ministry of Health, Malaysia and their operational beds;

[c] Total number of hospitals and operational beds in Malaysia, was obtained from the Centre of Health Informatics, Ministry of Health, Malaysia;

[d] Reported diarrhoeal discharges were adjusted to account for all hospitals including those not reporting discharges to MOH, Malaysia. Reported hospital discharges were multiplied with the number of beds from all existing hospitals nationwide, and divided by the number beds of hospitals reporting discharges [Subsection 4.2.2.1(b), page 59].

4.2.2.2 Outpatient visits

(a) ***Data source***

i Data on outpatient visits from the Ministry of Health, Malaysia

Aggregated data on outpatient visits to MOH facilities is compiled annually by the Centre of Health Informatics at MOH, Malaysia. This information is routinely collected and tallied at each MOH facility and then reported monthly in an aggregated form to district and state health departments. Monthly returns on outpatient visits are entered into PER-PL206 return formats and reported electronically in an aggregated form, while the original patient-level data remains at each local facility (Ministry of Health Malaysia, 2012d). As such, the individual patient data were not available for analysis in this thesis.

The data on outpatient visits was aggregated by age group, facility type, and diagnostic groups. Data was stratified by age groups: under-ten years, ten to 19 years, 20 to 59 years, and more than 60 years. Outpatient visits were available for MOH public hospitals (emergency departments, general outpatient departments, and specialist clinics) and public health clinics[41]. Outpatient visits for acute diarrhoea were classified using ICD-10 diagnostic codes for Intestinal Infectious Disease (A00-09).

ii National Health and Morbidity Survey

The National Health and Morbidity Surveys (NHMS) are a series of nationwide household health surveys conducted by the Institute for Public Health, MOH, Malaysia. These surveys were carried out at regular intervals to assess community health status and disease patterns, health needs, household health expenditure and health-seeking behaviour of the Malaysian population. These nationwide surveys were conducted to

[41] Primary care services are general outpatient services provided without an appointment, on a walk-in basis. These services are available at MOH public health clinics and hospitals. At public health clinics, primary care services may be provided by medical assistants at smaller clinics, or also by medical officers and family medicine specialists at larger health centres. At public hospitals, general outpatient services are provided at the outpatient and emergency departments, and at satellite and specialist clinics. At smaller towns, outpatient departments provide general walk-in outpatient care services. However, at bigger cities like Kuala Lumpur, satellite clinics were established at various locations in the city to provide additional outpatient services, while aiming to decongest services at the busy hospital. The emergency department at hospitals, while primarily providing acute care, also provide general outpatient service to non-acute walk-in patients. Similarly, some specialist clinics inevitably provide general outpatient service (Noor Ghani & Yadav, 2008).

provide supplementary information to better enable the MOH, Malaysia to review health priorities, programme strategies and activities, to plan and allocate resources.

Initially the NHMS were conducted at ten year intervals (1986, 1996 and 2006). Subsequently, more frequent surveys were conducted at five year intervals (2011 and 2015).

The first NHMS conducted in 1986 (NHMS 1986), surveyed the population in Peninsular Malaysia only, and had a response rate ranging from 92 to 100 per cent. The second NHMS conducted ten years later in 1996 (NHMS 1996), surveyed Peninsular Malaysia, as well as Sabah and Sarawak, to provide information on health and disease morbidity for the entire nation. The NHMS 1996 had a response rate of 87 per cent.

The third NHMS conducted in 2006 (NHMS 2006), was a nation-wide, nationally representative, cross-sectional, household health survey, which aimed to provide community-based information to the MOH on load of illness, health utilisation patterns, household consumption costs for health care, specific health related behaviours and morbidity. NHMS 2006 included a module designed to determine the incidence, severity, impact on productivity and health-seeking behaviour of the community in relation to acute diarrhoeal illness. This nationwide survey was selected for use in this thesis, as it was the most recent survey to specifically evaluate acute diarrhoeal illness in Malaysia. Subsequent surveys had dropped the module evaluating acute diarrhoeal illness in Malaysia.

The NHMS 2006 was designed to provide data at both national and state levels, on the population living in private households in Malaysia. The sampling frame for the 2006 survey was informed by the Department of Statistics, Malaysia. In this survey, a two-stage, stratified random sampling was conducted, using sampling proportionate to the population size, to select Enumeration Blocks (EBs) and Living Quarters (LQs). EBs were contiguous geographical areas with identified boundaries, each of which had an average of 100 LQs. The EBs formed the sampling frame for the survey. At the first stage of sampling, the primary sampling unit was the EBs, while at the second stage, the secondary sampling unit was LQs. Each LQ had approximately 4.4 individuals, all of whom were included in the survey. Sample size was determined by the previous prevalence rate for health problems in Malaysia, response rate for the NHMS 1996, a margin of error of 1.2 and a design effect of two.

This nationwide health survey sampled households with a total of 59,938 individuals. All eligible household members in the LQs[42] were selected as respondents and were interviewed using structured questionnaires. Parents were interviewed as proxy for children 12 years and younger. The structured, pretested and piloted survey questionnaire was administered via a face-to-face interview by trained interviewers comprising of public health nurses from the MOH and part-time recruits.

There were a total of 56,710 eligible respondents for the module on acute diarrhoeal illness, representing 21,095,810 people on weighted counts, with a response rate of 98.3 per cent. Children under-five years comprised of 5,912 individuals, or 10.6 per cent of those interviewed.

The survey defined acute diarrheal illness as having three or more episodes of loose stools within a two week period prior to the interview. The overall incidence of self-reported acute diarrhoeal illness within a two week recall period was 5.0 per cent (95 per cent CI: 4.8 to 5.2), with incidence of 4.5 per cent (95 per cent CI: 3.9 to 5.1) in children under-five years of age (Ministry of Health Malaysia, 2006).

Age-stratified health utilisation patterns for children with self-reported acute diarrhoea, obtained from the NHMS 2006, was used in this thesis for the estimation of diarrhoeal outpatient visits in children under-five years in Malaysia (Ministry of Health Malaysia, 2006).

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[42] An eligible respondent was defined as a permanent resident, who was present at the LQ at the first visit for data collection, and had been residing at that particular LQ for at least four weeks. Written consent was obtained from eligible respondents.

(b) ***Data analysis***

For this current study, annual diarrhoeal outpatient visits for children under-ten years to MOH public facilities for 2012 was obtained from the Centre of Health Informatics, MOH, Malaysia. The data on annual diarrhoeal outpatient visits was aggregated by age groups. While, outpatient visits for children under-five years is relevant for this thesis, this data was unavailable from the MOH, Malaysia. The aggregated nature of the data did not allow extraction of outpatient treated diarrhoeal episodes among children under-five years.

As such, age specific health service utilisation patterns from NHMS 2006 was used to estimate diarrhoeal outpatient visits to public facilities for children under-five years in Malaysia.

Diarrhoeal outpatient visits for children under-five years was estimated by multiplying the reported number of diarrhoeal outpatient visits for children under-ten years to MOH outpatient facilities for 2012 (Ministry of Health Malaysia, 2012d), with the age specific ratio of diarrhoeal outpatient visits from the NHMS 2006 (the number of children under-five years with acute diarrhoeal illness seeking care at public facilities, divided by the number of children under-ten years with acute diarrhoeal illness seeking care at public facilities) (Ministry of Health Malaysia, 2006, p. 68).[43]

This estimation of diarrhoeal outpatient visits to public facilities for children under-five years in Malaysia is shown in Table 4.3.

[43] The NHMS 2006 found that among children under-five years with self-reported diarrhoeal illness, only 1.4 per cent sought outpatient care at army hospitals and none sought outpatient care at university hospitals (Ministry of Health Malaysia, 2006, p. 68). As such, diarrhoeal outpatient visits to non-MOH public clinics were assumed to be negligible in this thesis.

Table 4.3: Estimation of diarrhoeal outpatient visits to public facilities for children under-five years in Malaysia

Row	Item	Source	Public hospitals	Public clinics
(1)	0-9 years	MOH [a]	56,999	72,425
(2)	Age specific ratio of diarrhoeal outpatient visits	NHMS 2006 [b]	71%	58%
(3)	0-4 years	(1) x (2) [c]	40,410	42,158

Note:

0-9 years, children under the age of 10 years; 0-4 years, children under the age of five years.

MOH, Ministry of Health, Malaysia; NHMS 2006, National Health and Morbidity Survey 2006

[a] Annual diarrhoeal outpatient visits for children under-ten years at MOH facilities (public hospitals and clinics) as reported to the Ministry of Health, Malaysia (Ministry of Health Malaysia, 2012d)

[b] The ratio of the number of children under-five years with acute diarrhoeal illness seeking care at public facilities, divided by the number of children under-ten years with acute diarrhoeal illness seeking care at public facilities (public hospitals and public clinics) in Malaysia. This ratio was obtained from the NHMS 2006 (Ministry of Health Malaysia, 2006, p. 68)

[c] Annual diarrhoeal outpatient visits for children under-five years in Malaysia was estimated by multiplying the age specific ratio of diarrhoeal outpatient visits to public facilities with the reported annual under-ten diarrhoeal outpatient visits to public facilities.

As the Centre of Health Informatics at MOH, Malaysia does not collect data on outpatient visits to private facilities, health utilisation patterns from NHMS 2006 were used to estimate the number of diarrhoeal outpatient visits to private clinics in Malaysia.

The NHMS 2006 presents information on the place which care was first sought for acute diarrhoeal illness for children under-five years[44]. These can be broadly categorised into public hospitals (20 per cent), public clinics (26 per cent), private hospitals (three per cent), private clinics (49 per cent), and others (one per cent) (Ministry of Health Malaysia, 2006, p. 68).

Up to this point, this thesis estimates 152,523 diarrhoeal episodes in Malaysia, for under-five diarrhoeal hospitalisations (to public and private hospitals) and outpatient visits to public facilities (public hospitals and clinics). To estimate the number of diarrhoeal outpatient visits to private clinics in Malaysia, the estimate of 152,523 diarrhoeal episodes was multiplied with the proportion of diarrhoeal episodes among children under-five years receiving outpatient treatment at private clinics from NHMS 2006 (49 per cent), and then divided by the proportion of diarrhoeal episodes among children under-five years receiving inpatient treatment (at public and private hospitals) and outpatient treatment at public facilities in Malaysia, obtained from NHMS 2006 (49 per cent)[45] (Ministry of Health Malaysia, 2006, p. 68).

This estimation diarrhoeal outpatient visits to private clinics for children under-five years in Malaysia, is shown in Table 4.4.

[44] Places that care was first sought for acute diarrhoeal illness, as listed in NHMS 2006 included: government general hospital, government district hospital, government health clinic, government mobile clinic, university hospital, army hospital, private hospital, private clinic, estate hospital, estate clinic, traditional practitioner, pharmacy or Chinese medicine shop, non-governmental organisation clinics, religious leaders or spiritual healers, drug sellers, direct selling, village midwife, village headmen, friend, relative and others (Ministry of Health Malaysia, 2006, p. 68).

[45] The denominator from NHMS 2006 of 49 per cent, consisted of the proportion of diarrhoeal episodes among children under-five years receiving inpatient treatment at public hospitals (20 per cent) and private hospitals (three per cent), and outpatient treatment at public clinics (26 per cent). This figure corresponds to the estimate in this thesis up to this point (inpatient visits to public and private facilities, and outpatient visits to public facilities).

Table 4.4: Estimation of diarrhoeal outpatient visits to private clinics for children under-five years in Malaysia

Row	Item	Source	Episodes
(1)	Public hospital inpatient episodes	Estimation [a]	52,233
(2)	Private hospital inpatient episodes	Estimation [a]	17,732
(3)	Public hospital outpatient episodes	Estimation [b]	40,410
(4)	Public clinic outpatient episodes	Estimation [b]	42,158
(5)	Sum of estimated diarrhoeal episodes	(1) + (2) + (3) + (4)	152,532
(6)	Ratio for the estimation of diarrhoeal episodes receiving outpatient care at private clinics	NHMS 2006 [c]	99%
(7)	Private clinic outpatient episodes	(5) x (6)	151,239

[a] total diarrhoeal hospitalisations among children under-five years to public and private hospitals in Malaysia (See Table 4.2, page 62)

[b] total diarrhoeal outpatients visits among children under-five years to public clinics and hospitals in Malaysia (See Table 4.3, page 67)

[c] Ratio of the proportion of diarrheal episodes receiving outpatient treatment at private clinics (49 per cent) divided by the proportion of diarrheal episodes receiving inpatient treatment (at public and private hospitals) and outpatient treatment at public facilities, (49 per cent) from the NHMS 2006. (49 per cent ÷ 49 per cent = 99 per cent). (Ministry of Health Malaysia, 2006, p. 68)

4.2.2.3 Home-treated episodes

Home-treated diarrhoeal episodes were defined in this thesis, as diarrhoea for which formal treatment was either not sought or sought at facilities other than clinics and hospitals, like traditional healers, traditional Chinese medicine shops or pharmacists.

(a) ***Data source***

The study by Yap et al., conducted over a 12 month period in 1989, is the only community-based rotavirus surveillance conducted in Malaysia (Yap et al., 1992). This study was conducted with appropriate and rigorous methodology with the aim of detecting the proportion of diarrhoea attributable to rotavirus at a community setting (World Health Organization, 2002a). While the WHO generic protocol describes the methodology for the conduct of community-based rotavirus surveillance, this kind of community-based rotavirus study has not been conducted in many countries. This is presumably because community-based studies are resource intensive, involving frequent home visits, detailed history taking and stool sampling. In this thesis, this community-based rotavirus study provided the proportion of children with acute diarrhoea not seeking medical treatment for diarrhoea, and the rotavirus detection proportion for diarrhoeal episodes treated at outpatient and home settings [further details in Subsection 4.2.2.5(a), page 74].

The study by Yap et al. prospectively followed 156 children under-five years from 116 households, from the urban and suburban areas around Kuala Lumpur and Selangor, for one year. Stool was inspected on a daily basis by parents to examine for loose consistency. Parents were instructed to identify loose stool and obtain samples for analysis. Health workers conducted three home visits weekly, while medical doctors visited households monthly. Home visits were conducted to inquire on the occurrence of illness and to obtain stool samples. Stool was tested for rotavirus using an enzyme-linked immune absorbent test (ELISA) method and also a polyacrymide gel electrophoresis (PAGE) method with silver staining, both of which had similar sensitivity and specificity to the WHO ELISA tests at the time of the study (Yap et al., 1992).

During the 12 month study period, there were 60 episodes of diarrhoea reported from 34 of the 156 children. Stool samples were collected from 25 of the 34 children with diarrhoea. Of the 25 stool samples tested, three were positive for rotavirus (12 per cent). Six (18 per cent) of the 34 children with diarrhoea sought outpatient treatment, while one rotavirus positive child was hospitalised. Twenty-seven (79 per cent) children with acute diarrhoea did not seek medical treatment (Yap et al., 1992).

(b) ***Data analysis***

The only community-based rotavirus surveillance study in Malaysia found that 79 per cent of all children under-five years of age, with diarrhoeal symptoms did not seek treatment for diarrhoea (Yap et al., 1992). The ratio of acute diarrhoeal illness not seeking care (79 per cent) divided by those seeking care (21 per cent) from this community-based rotavirus study, was multiplied with the estimated number of acute gastroenteritis episodes seeking care (diarrhoeal hospitalisations and outpatient visits), to estimate the incidence of home-treated acute gastroenteritis in Malaysia.

4.2.2.4 Deaths

(a) ***Data source***

Diarrhoea specific mortality data for children under-five years was acquired from the Department of Statistics, Malaysia, for the years 2000 to 2008. These were the most recent available years for which mortality data was available. Prior to the year 2000, all mortality data was coded using ICD-9 codes.

In Malaysia, not all deaths are verified by medical professionals for the issuance of a death certificates[46]. Thus, diarrhoeal deaths were defined here as deaths that were medically certified with ICD-10 diagnostic codes for diarrhoeal deaths [as described in Subsection 4.2.2.1(b), page 59] and those that were certified by lay personnel as having died of diarrhoea.

(b) ***Data analysis***

In view of estimating the diarrhoeal deaths for children under-five years in 2013, a Runs test was used to test for randomness of the annual under-five years diarrhoeal mortality rate from 2000 to 2008[47] (Bradley, 1968). The null hypothesis of the Run's test is that the data sequence is produced in a random manner. As the resulting test statistic of -1.04 was less than the critical value of 1.96 (p-value of 0.15 was greater than 0.05), the null hypothesis was not rejected. This demonstrates that the mortality data varied at random around a constant mean at a 0.05 significance level, with a constant variance and no trend component.

As such, the mean acute diarrhoeal mortality rate for children under-five years from 2000 to 2008 of 11.96 diarrhoeal deaths per 100,000 live births (95 per cent CI: 9.18 to 14.74), was used to estimate 61 diarrhoeal deaths in children under-five years for 2013[48].

Table 4.5 shows the estimation of diarrhoeal mortality in 2013 among children under-five years in Malaysia.

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[46]All deaths in Malaysia must be registered with the National Registration Department through the Police Department before burial permits are issued. However, not all registered deaths are medically certified. Most non-medically certified deaths occur at home. Certification of death by lay persons without medical training (like police officers, village headmen, or other informants) uses descriptive codes based on illness symptoms prior to death (Faudzi et al., 2011). Adnan et al.(2012), found that from 1995 to 2010, medically certified deaths in Malaysia ranged from between 45 per cent to 57 per cent .The MOH, Malaysia has in place a under-five mortality reporting system to report all under-five deaths including those from the private sector and deaths outside hospitals. All under-five deaths are required to be investigated for substandard care or preventable cause of death. Verbal autopsies are recommended for non-hospital deaths, to identify probable cause of death, thus enabling ICD10 coding (Ministry of Health Malaysia, 2013).

[47]To obtain annual under-five diarrhoeal mortality rates for the years 2000 to 2008, annual diarrhoea deaths in children under-five years were divided by annual live births.

[48]Sixty one diarrhoeal deaths for 2013, was estimated by multiplying the average under-five mortality rate from 2000 to 2008 (11.96 per 100,000 live births) with the birth cohort for 2012 of 508,774 live births (Department of Statistics Malaysia, 2012b, p. 9) and divided by 100,000.

Table 4.5: Estimation of diarrhoeal mortality in children under-five years in Malaysia, 2013

Item	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2013 [a]**
Uncertified diarrhoeal deaths [b]	24	26	34	27	28	19	16	11	13	
Certified diarrhoeal deaths [b]	12	27	33	34	54	59	32	26	47	
Total diarrhoeal deaths [b]	36	53	67	61	82	78	48	37	60	61
Total under-five deaths [b]	4,872	4,424	4,252	4,158	4,044	4,010	3,652	3,741	3,887	
Percentage of under-five deaths due to diarrhoea	0.7%	1.2%	1.6%	1.5%	2.0%	1.9%	1.3%	1.0%	1.5%	
Annual live births [c]	549,543	515,985	484,037	480,083	477,768	469,204	465,112	472,048	487,346	508,774
Under-five mortality rate (per-1000 live births)	8.9	8.6	8.8	8.7	8.5	8.5	7.9	7.9	8.0	
Under-five mortality rate for acute gastroenteritis (per-100,000 live births)	6.6	10.3	13.8	12.7	17.2	16.6	10.3	7.8	12.3	11.96

Note:

[a] Total diarrhoeal deaths for children under-five years in 2013 (61 deaths), was estimated by multiplying the average under-five mortality rate for acute gastroenteritis from 2000 to 2008 (11.96 per 100,000 live births), with the annual birth cohort for 2012 (508,774 live births) (Department of Statistics Malaysia, 2012b, p. 9)

[b] Deaths for children under-five years from 2000 to 2008, were obtained from the Department of Statistics, Malaysia.

[c] Annual live births in Malaysia from 2000 to 2008, were obtained from the Department of Statistics, Malaysia.

4.2.2.5 Proportion of acute gastroenteritis attributable to rotavirus

(a) ***Overview***

To estimate incidence of rotavirus gastroenteritis, the proportion of diarrhoea attributable to rotavirus is multiplied with the incidence of acute gastroenteritis (Figure 4.1). The rotavirus detection proportions are different according to different health settings; with higher rates detected in diarrhoeal hospitalisations, followed by outpatient treated and home-treated diarrhoea (Parashar et al., 2003). Hospital-based and community-based surveillance are recommended to obtain rotavirus detection proportions in a country (World Health Organization, 2002a).

In this thesis, a systematic review and meta-analysis was conducted with the aim of obtaining the proportion of diarrhoea attributable to rotavirus in children under-five years hospitalised in Malaysia. Prospective, hospital-based rotavirus surveillance studies were selected to fulfil criteria based on the WHO Generic Protocol for hospital-based rotavirus surveillance (World Health Organization, 2002a).

Rotavirus detection proportion for diarrhoeal deaths was assumed to be the same as that of rotavirus-related hospitalisations, as hospitalisations and deaths both result from severe illness (Parashar et al., 2009; Parashar et al., 2003; Tate et al., 2012).

The community-based rotavirus surveillance study by Yap et al. provided rotavirus detection proportions for diarrhoea treated at outpatient settings (18 per cent) and home-treated (12 per cent) (Yap et al., 1992).

(b) ***World Health Organization generic protocol for rotavirus surveillance***

The WHO generic protocol for rotavirus surveillance was developed by the WHO Department of Vaccines and Biologicals in 2002, in anticipation of the availability of rotavirus vaccines. This protocol provides standardised methodology to allow countries to estimate the burden of rotavirus in the population.

The WHO protocol recommends prospective hospital-based surveillance for the estimation of incidence of severe rotavirus gastroenteritis. Severe rotavirus diarrhoea resulting in hospitalisations and death, are the main targets of rotavirus vaccines. Also, rotavirus hospitalisations incur a sizable economic burden to healthcare providers.

The WHO protocol recommends a duration of at least two complete years of surveillance to account for both seasonal and annual variation in rotavirus incidence[49]. As rotavirus diarrhoea rarely occurs after the age of five years, the generic protocol recommends that rotavirus surveillance be conducted in children under the age of five years[50]. The WHO protocol recommends that stool is tested for rotavirus using an enzyme immunoassay test (World Health Organization, 2002a).

(c) ***Systematic review of prospective hospital-based rotavirus studies in Malaysia***

A systematic search was conducted to select studies conducted in Malaysia based on the WHO recommendations for hospital-based rotavirus surveillance. Criteria for eligibility were as follows: (1) a prospective, hospital-based study, (2) of at least two years duration, (3) study conducted in Malaysia, (4) on children under-five years and (5) stool tested for rotavirus with an enzyme immunoassay test.

The literature was searched systematically to locate published articles in three major databases (PubMed, Scopus and Web of Science). Search terms used were 'rotavirus' AND ('gastroenteritis' OR 'diarrhoea' OR 'diarrhea') AND Malaysia. The search was limited to English language publications but with no specific range of publication dates. Citation search of identified articles and expert consultation was conducted to locate further papers.

After removal of duplicates, the titles and abstracts were screened to identify prospective, hospital-based rotavirus studies. Subsequently, full text articles were read to

[49] Rotavirus diarrhoea is a seasonal infection. As such, surveillance of at least a year is necessary to ensure rotavirus detection rates are not affected by seasonal variations. While, a minimum of two complete years will account for possible annual differences in rotavirus incidence.

[50] Inclusion of older children would result in an underestimation of rotavirus incidence.

identify studies that met the eligibility criteria to be included in the meta-analysis. Information was extracted on study period, duration and location, population age group and laboratory methods. For each study setting, the number of acute gastroenteritis cases, specimens tested, positive samples and rotavirus detection proportion were recorded.

A DerSimonian and Laird random effects model was used to pool outcomes from each individual study site, to calculate the mean and 95 per cent confidence interval for the rotavirus detection proportion among acute gastroenteritis related hospitalisations in children under-five years (DerSimonian & Laird, 1986). The random effects model was used to account for the inherent variability in different study settings and timings. Meta-analysis was performed using Microsoft Excel 2013, with methods described by Neyeloff, Fuchs, and Moreira (2012).

4.2.3 Estimating the economic burden of rotavirus gastroenteritis

4.2.3.1 Direct medical costs

(a) ***Overview***

The estimation of the economic burden of rotavirus gastroenteritis in Malaysia requires unit costs for inpatient and outpatient care, at both public and private health facilities. Since unit costs are not readily available in Malaysia, top-down costing methods, similar to those used for the estimation of the economic burden of dengue in Malaysia, were used in this study (D. S. Shepard, Hodgkin, & Anthony, 2000; D. S. Shepard et al., 2012; Suaya et al., 2009).

Multiple data sources were combined for this current estimation of unit costs. The following subsections detail the data sources and analysis used for the estimation of direct medical costs for rotavirus gastroenteritis in Malaysia.

(b) Data Source

i WHO-CHOICE project

The WHO-CHOICE project was initiated in 1998 to assist countries in making rational choices on healthcare resource allocations, based on evidence generated by cost-effectiveness analyses (World Health Organization, 2014c).

The WHO-CHOICE project allows for the estimation of unit costs of inpatient and outpatient care by 191 member states, through data collected from 49 countries (Adam, Evans, & Murray, 2003; World Health Organization, 2011). Presumably due to the lack of suitable data, Malaysia had not been included in the list of countries contributing data. Using econometric modeling, the WHO-CHOICE project predicts unit costs for countries in which data was not available. In the case of Malaysia, especially since Malaysian data was not obtained for the WHO-CHOICE project, it is preferable to use local data for costing.

WHO-CHOICE provides estimates of unit costs by facility-type based on ownership (public or private) and location (urban or rural areas).The facility-types used in the WHO-CHOICE project refers to differences in service characteristics, including differences in case-mix, technical capacity and skills available in facilities (World Health Organization, 2011).

Definitions of facility-types used in WHO-CHOICE can be obtained from Barnum and Kutzin, 'Public hospitals in developing countries: resource use, cost, financing' 1993. Definition of facility-types are as follows:

(1) Health centres with outpatient services only (no beds)

(2) Health centres with beds

(3) Primary-level hospitals: Hospitals intended for treating simple cases (e.g. 'district hospitals')

(4) Secondary-level hospitals: Hospitals intended primarily for treating referral cases (e.g. ‘specialist hospital’)

(5) Tertiary-level hospitals: Hospitals intended primarily for treating referral cases, with a teaching component (e.g. ‘teaching hospital’)

(Barnum & Kutzin, 1993; World Health Organization, 2011, 2014c)

ii Unit costs at public clinics

An unpublished 1995 costing study by Lim K.J., on the provision of outpatient services at eleven MOH public clinics in Kedah, provided average costs per-visit of RM 11.8 in 2013 RM (K. J. Lim, 1995; D. S. Shepard et al., 2012). These eleven clinics were similar to ‘health facilities with no beds’, as described in WHO-CHOICE (Barnum & Kutzin, 1993; World Health Organization, 2014c). Information on costs was collected for personnel, supplies, utilities, maintenance and training, and was derived mainly from the operating budget of the clinics involved.

iii Unit costs at primary-level hospitals

A study by Sabrina A.R. examined the financial performance of six primary-level hospitals around Malaysia for the year 2001. This study provided estimates of average outpatient costs of RM 136 per-visit (ranging from RM 32 to RM 245 per-visit) for primary-level hospitals in 2013 RM. (Table 4.7)

All of the six selected hospitals in this study were 93 bedded facilities with basic medical and surgical services provided by doctors without specialist qualifications. These hospitals were considered as belonging to the category of ‘primary-level hospitals without specialists’ from WHO-CHOICE (Sabrina, 2006).

iv Unit costs at tertiary-level hospitals

In this thesis, top-down costing of five urban, tertiary-level public hospitals in Malaysia was conducted to estimate average unit costs for inpatient and outpatient care at tertiary-level hospitals. The hospitals selected for costing were University of Malaya Medical Centre (UMMC), Hospital Sungai Buloh (HSB), Hospital Sultanah Bahiyah, Alor Setar (HAS), Hospital Melaka (HM) and Hospital Sultan Haji Ahmad Shah, Temerloh (HT).

The UMMC is a tertiary-level, teaching hospital administered by the Ministry of Education. The operating expenditure and workload of UMMC was obtained from the 2012 hospital annual report and updated to include salaries of academic clinicians. Academic clinicians are employed by the university, and as such their salaries are not included in the hospital's operating expenditure. The assumption was made that academic clinicians spent 60 per cent of their time on clinical service, while the remaining time was spent on academic and research duties. The cost of an outpatient visit was assumed at a fifth of the cost of an inpatient day at tertiary-level hospitals. These assumptions were previously used in studies costing medical services at UMMC (D. S. Shepard et al., 2012; Suaya et al., 2009).

Hospital websites were searched to obtain annual reports of tertiary-level MOH hospitals (Ministry of Health Malaysia, 2015). Also, hand-search for annual reports was done at the MOH library at Putrajaya. The lack of standardisation of annual reports and the unavailability of information on admission rates, clinic attendances, bed occupancy rate, and hospital expenditure, limited the selection to four tertiary-level MOH hospitals.

Table 4.6 details the estimation of unit costs for per-bed day and per-visit for UMMC and four tertiary-level MOH hospital in Malaysia.

The average costs obtained from UMMC and four tertiary-level MOH hospitals was estimated at RM 1,073 per-bed day and RM 215 per-visit. Average costs at UMMC and four tertiary-level MOH hospitals were used as estimates for unit costs at tertiary-level hospitals in this study (Table 4.7).

Table 4.6: Estimation of unit costs at tertiary-level public hospitals in Malaysia

Row	Item	Source	UMMC, 2012	HSB, 2013	HAS, 2012	HM, 2013	HT, 2012
(1)	Admissions	Hospital Report [a]	53,825	45,372	72,703	74,468	39,849
(2)	Number of registered beds	Hospital Report [a]	979	620	870	1,091	500
(3)	Occupancy rate	Hospital Report [a]	78%	82%	95%	85%	91%
(4)	Occupied beds	(2) x (3)	759	507	826	923	457
(5)	Annual bed days	(4) x 365	276,935	185,000	301,609	336,970	166,659
(6)	Outpatient clinic visits	Hospital Report [a]	800,426	191,077	142,011	305,098	73,347
(7)	Emergency visits	Hospital Report [a]	110,246	150,865	275,009	137,852	69,081
(8)	Total outpatient visits	(6) + (7)	910,672	341,942	417,020	442,950	142,428
(9)	Relative cost: visit/inpatient day	Shepard et al.	0.2	0.2	0.2	0.2	0.2
(10)	Ambulatory bed-day equivalents	(8) x (9)	182,134	68,388	83,404	88,590	28,486
(11)	Total bed-day equivalents	(5) + (10)	459,069	253,389	385,013	425,560	195,145
(12)	Operating expenditure, RM	Hospital Report [a]	480,416,375	316,371,637	387,737,008	341,906,332	229,830,084
(13)	Estimated salaries of academic clinicians devoted to service	Estimated [b]	37,037,595	-	-	-	-

Table 4.6: Estimation of unit costs at tertiary-level public hospitals in Malaysia (continued)

Row	Item	Source	UMMC, 2012	HSB, 2013	HAS, 2012	HM, 2013	HT, 2012
(14)	Revised operating expenditures, RM	(12) + (13)	517,453,970	316,371,637	387,737,008	341,906,332	229,830,084
(15)	Cost per bed-day equivalent [c], RM	(14)/(11)	1,127	1,249	1,007	803	1,178
(16)	Cost per outpatient visit [c], RM	(15) x (9)	225	250	201	161	236

Note:

All costs are expressed in 2013 Ringgit Malaysia

UMMC, University of Malaya Medical Centre; HSB, Hospital Sungai Buloh; HAS, Hospital Sultanah Bahiyah, Alor Setar; HM, Hospital Melaka; HT, Hospital Sultan Haji Ahmad Shah, Temerloh;

[a] Data from the 2012 UMMC Annual Report, 2013 HSB Annual Report, 2012 HAS Annual Report, 2013 HM Annual Report and the 2012 HT Annual Report;

[b] Estimated from the distribution of academic clinicians by department and their salary grades at the Faculty of Medicine, University of Malaya. Information on salary schemes for academic staff was obtained from the Department of Human Resources, University of Malaya.

[c] The average costs obtained from UMMC and four tertiary-level MOH hospitals, were used as estimates for unit costs at tertiary-level hospitals in this study. Average costs at tertiary-level hospitals was estimated at RM 1073 per-bed day and RM 215 per-visit. (Table 4.7)

(c) ***Data analysis***

i Costing of hospital bed-days

In this current study, costing methods were informed by a 2012 study estimating the economic burden of dengue in Malaysia (D. S. Shepard et al., 2012). In 2010, a dengue workshop gathered experts from the public and private health sectors and academia to discuss issues arising due to insufficient data in the estimation of dengue disease burden in Malaysia (D. Shepard et al., 2011). Two main conclusions from this expert workshop were used in the present study.

Firstly, the workshop participants had agreed that the description of tertiary-level or teaching hospitals, as provided by WHO-CHOICE, could refer to the state hospitals, national referral centres or teaching hospitals in the public sector in Malaysia, including UMMC. The Malaysian district hospitals could be categorised as either primary-level or secondary-level hospitals, depending on services provided. In the case of smaller district hospitals without specialists or with few basic specialties, the participants agreed that they should be categorised as primary-level hospitals. These would include the six district hospitals in the 2001 costing study (Sabrina, 2006). The remaining district hospitals could be considered as secondary-level hospitals.

Secondly, inpatient care at each hospital-type was assumed to be proportional to the number of beds in these facilities. The expert panel in the dengue study, agreed that tertiary-level beds made up 50 per cent of all hospital beds in the country. The corresponding figures for secondary- and primary-level hospital beds were 30 per cent and 20 per cent respectively. (D. S. Shepard et al., 2012).

In this thesis, inpatient care for diarrhoea at each hospital type was assumed to be proportional to the number of beds in these facilities. Distribution of hospitals by number of beds was derived from the expert workshop in the dengue study[51] (D. S. Shepard et al., 2012).

In this thesis, cost estimates by facility-types from WHO-CHOICE (primary-level, secondary-level and teaching hospitals) was used to derive cost-ratios for the estimation of unit costs for inpatient bed-days at public hospitals. (Barnum & Kutzin, 1993; World Health Organization, 2011). Cost-ratios are the ratio of unit costs for primary- and secondary-level hospitals compared with costs at tertiary-level hospitals. For example, unit costs per bed-day for primary-level hospitals was 74 per cent of costs at teaching hospitals. (Table 4.7)

Cost-ratio of primary-level hospital compared with teaching hospitals from WHO-CHOICE (74 per cent) was multiplied with estimated costs at tertiary-level hospitals (RM 1,073), to obtain estimates of unit costs per bed-day at primary-level hospitals of RM 795. (Table 4.7)

Cost-ratio of secondary-level hospital compared with teaching hospitals from WHO-CHOICE (77 per cent) was multiplied with estimated costs at tertiary-level hospitals (RM 1,073), to obtain estimates of unit costs per bed-day at secondary-level hospitals of RM 830. (Table 4.7)

The estimated unit costs by facility type was multiplied with the proportion of distribution of facilities derived from the dengue study, and the sum product of this for all facilities was the weighted average costs per bed-day of RM 944. (Table 4.7)

[51] In the years 2010 and 2011, there were no new MOH hospitals opening. In 2012, there were three new MOH hospitals. These were the Hospital Orang Asli Gombak (91 beds), Hospital Queen Elizabeth II, Sabah (400 beds) and Hospital Wanita dan Kanak-kanak, Likas (504 beds).

Hospital Orang Asli, Gombak, is a primary level hospital catering to the needs of the aboriginal community and has been in operation since 1954. This hospital was taken over by the MOH, Malaysia from the Aboriginal Development Department (Jabatan Kemajuan Orang Asli) in 2012.

Hospital Queen Elizabeth II, Sabah was previously a private medical centre in Sabah (Sabah Medical Centre) and was purchased by the MOH, Malaysia in 2009. Though it was fully operational from November 2009, this hospital was officially opened in 2012.

Hospital Wanita dan Kanak-kanak, Likas is a tertiary level hospital in Sabah specialising in the treatment of women and children (Paediatric departments, Obstetrics and Gynaecology, and Emergency Department).

As the addition of these three hospitals did not substantially change the number or the distribution of facilities and services in Malaysia, it was assumed that the distribution of hospitals by number of beds in Malaysia for 2013 was similar to that in 2010.

The average costs per bed-day of RM 944 was assumed to be equivalent to unit costs of public facilities. The unit cost estimates for tertiary-level hospitals of RM 1,073 per bed-day was assumed to be equivalent to unit costs at private facilities. (Table 4.7)

Duration of admission for an episode of rotavirus gastroenteritis (3.3 days) was obtained from a 2010 prospective hospital-based study (Lee, Lim, Chai, Kirkwood, & Lee, 2012). The full description of this dataset and its analysis is detailed in Chapter 6. Duration of admission for an episode of rotavirus gastroenteritis was multiplied by unit cost per bed-day, to obtain costs per inpatient treated episode. (Table 4.10)

Table 4.7 shows the estimation of unit costs per bed-day and per outpatient visit at healthcare facilities in Malaysia.

Table 4.7: Estimation of unit cost in healthcare facilities in Malaysia, 2013

Type of facility [a]	Distribution of facility (%) [b, c]	Unit cost (2008 RM) WHO-CHOICE	Cost-ratio by facility type [d]	Unit cost (2013 RM)
Cost per bed-day				
Primary-level hospital	20%	289.23	0.74	795.30
Secondary-level hospital	30%	301.73	0.77	829.67
Teaching hospital	50%	390.15	1.00	1072.80 [e]
Average cost per bed-day				**944.36** [f]
Cost per outpatient visit				
Health facilities with no beds	56%	25.50	0.48	11.80 [g]
Primary-level hospital	20%	53.20	1.00	135.76 [h]
Secondary-level hospital	30%	75.00	1.41	191.39
Tertiary-level hospital	50%	-	-	214.56 [e]
Average cost per outpatient visit at a hospital				**191.85**[i]
Average cost per outpatient visit				**91.02** [j]

[a] Definitions of facility levels used in WHO-CHOICE can be obtained from Barnum and Kutzin. ‘Public hospitals in developing countries: resource use, cost, financing’, 1993 (Barnum & Kutzin, 1993).

[b] Distribution of facility type by hospital beds, for estimation of cost per bed-day and cost per outpatient visits at hospitals was based on expert opinion (D. S. Shepard et al., 2012)

[c] Distribution of ‘health facilities with no beds’ was based on data from the Ministry of Health, Malaysia (Ministry of Health Malaysia, 2012d).
Fifty six per cent of diarrhoeal outpatient visits reported to MOH, Malaysia in 2012 were to public health clinics, while the remaining were to hospitals.

[d] Cost-ratios by facility type are the ratio of unit costs from WHO-CHOICE by facility type, used to estimate unit costs

[e] Average cost per bed-day from five tertiary-level hospitals in Malaysia was used to represent costs of ‘teaching hospital’ from WHO-CHOICE. Note that there are no equivalent unit costs for outpatient visits at tertiary-level facilities in WHO-CHOICE.

[f] The estimated unit costs by facility type was multiplied with the proportion of distribution of facilities, and the sum product of this for all facilities was the weighted average costs per bed-day of RM 944.
$[(20\% \times \text{RM}795.30) + (30\% \times \text{RM}829.67) + (50\% \times \text{RM}1072.80)] = \text{RM}944.36$

[g] Unit cost per-visit equivalent to ‘health facilities with no beds’ from WHO-CHOICE, was obtained from the 1995 costing study on outpatient services at 11 MOH public clinics in Kedah (K. J. Lim, 1995).

[h] Unit cost equivalent to ‘primary-level hospitals’ from WHO-CHOICE, obtained from the 2001 costing study of six primary-level or district hospitals (Sabrina, 2006)

[i] The estimated unit costs by facility type was multiplied with the proportion of distribution of facilities, and the sum product of this for all hospitals was the weighted average costs per-visit at hospitals of RM 192.
$[(20\% \times \text{RM}135.76) + (30\% \times \text{RM}191.39) + (50\% \times \text{RM}214.56) = \text{RM}191.85]$

[j] The estimated unit costs by facility type was multiplied with the proportion of distribution of facilities, and the sum product of this was the weighted average costs per outpatient visit of RM 91.
$[(56\% \times \text{RM}11.80) + (44\% \times 20\% \times \text{RM}135.76) + (44\% \times 30\% \times \text{RM}191.39) + (44\% \times 50\% \times \text{RM}214.56) = \text{RM}91.02]$

ii Costing of outpatient visits

Distribution of care to outpatient facilities was based on data collected on diarrhoeal illness treated at MOH outpatient clinics from the Centre for Health Informatics, MOH, Malaysia [Subsection 4.2.2.2(a)i, page 63]. Fifty six per cent of diarrhoeal outpatient visits reported to MOH, Malaysia in 2012 were to public health clinics, while the remaining were to hospitals (Ministry of Health Malaysia, 2012d).

Outpatient care at each hospital-type was assumed to be proportional to the number of beds in these facilities, in accordance to the conclusion of the expert panel discussion in the dengue study. Thereafter, the remaining forty-four per cent of outpatient visits was distributed to tertiary-level (50 per cent), secondary-level (30 per cent) and primary-level (20 per cent) hospitals. (Table 4.7)

The dengue workshop participants had agreed that the average cost per-visit of RM 12 for MOH clinics from the Lim K.J. study was considered to be reflective of the actual costs of service provision in the MOH clinics. (Barnum & Kutzin, 1993; World Health Organization, 2014c).

In this thesis, costs per-visit from the Lim K.J. study of RM 12 was used for outpatient costs at 'health facilities with no beds', costs per-visit from the Sabrina A.R. study of RM 136 was used for outpatient costs at primary-level hospitals, and average costs per-visit from UMMC and four MOH hospitals of RM 215 was used for outpatient costs at tertiary-level hospitals. (Table 4.7)

Cost estimates by facility-types from WHO-CHOICE was used to derive cost-ratios for the estimation of unit costs for outpatient visits at secondary-level hospitals (Barnum & Kutzin, 1993; World Health Organization, 2011).

Unit costs per outpatient visit for secondary-level hospitals were 141 per cent of the costs at primary-level hospitals. Cost-ratio of secondary-level hospital compared with primary-level hospitals from WHO-CHOICE (141 per cent) was multiplied with estimated costs for primary-level hospitals (RM 136), to obtain estimates of cost at secondary-level hospitals of RM 191 per-visit. (Table 4.7)

The estimated unit costs by facility type was multiplied with the proportion of distribution of facilities, and the sum product of this for all hospitals was the weighted average costs per-visit at hospitals of RM 192. (Table 4.7)

In this thesis, unit costs of RM 12 was assumed for public clinic visits (estimates of unit costs per outpatient visit for 'Health facilities with no beds' from the Lim K.J. study), RM 192 for public hospital outpatient visits (estimates of the average unit cost per outpatient visit at a hospital), and RM 215 for private clinic visits (average unit costs per outpatient visit at tertiary-level hospital). (Table 4.7)

4.2.3.2 Direct non-medical costs

Direct non-medical costs were transportation costs and costs of additional diapers and food consumed during an episode of rotavirus gastroenteritis.

The National Health and Morbidity Survey 2011 (NHMS 2011) is the fourth in a series of nationally representative household health surveys. NHMS 2011 was conducted five years after the NHMS 2006, with a specific aim to determine healthcare demand of the community, as well as to determine risk factors for cardiovascular disease among the adult population and the prevalence of other health related problems among the community in Malaysia (Ministry of Health Malaysia, 2011b, p. 9). The NHMS 2011 determined healthcare consumption costs and provided average costs for one-way travel to health facilities in Malaysia (Ministry of Health Malaysia, 2011b).

In this thesis, for the estimation of transportation costs, one-way travel costs from NHMS 2011 were doubled for an outpatient visit and quadrupled for a hospital admission. These were conservative assumptions for transportation costs, based on minimum travel requirements to and from healthcare facilities. Transportation costs were determined for illness episodes requiring inpatient care at public hospitals (RM 49), private hospitals

(RM 52), and outpatient care at public hospitals (RM 24), public clinics (RM 8) and private clinics (RM 11).

Costs for extra food and diapers was obtained from the 2010 hospital-based study conducted at two centres in Malaysia, which examined out-of-pocket healthcare expenditure associated with an episode of rotavirus gastroenteritis requiring hospitalisation (Lee et al., 2012). The full description of this dataset is detailed in Chapter 6. An average cost of RM 10 for extra diapers was used for all rotavirus gastroenteritis episodes regardless of severity. The costs of extra food (RM 2.25) was only applied for rotavirus gastroenteritis episodes requiring hospital admission. (Table 4.11)

4.2.3.3 Indirect costs

Indirect costs were defined as productivity loss for one parent or caregiver for the duration of diarrhoeal illness. Productivity loss was calculated by multiplying average daily wage with the days of work missed to care for an ill child with rotavirus diarrhoea.

The average duration of diarrhoeal illness in children under-five years of 2.7 days, obtained from NHMS 2006, was assumed to represent days of work missed for all rotavirus gastroenteritis episodes regardless of severity (Ministry of Health Malaysia, 2006). This is a conservative assumption for productivity loss, as although days of work lost for hospitalised diarrhoeal episodes may be greater than for milder episodes, data on work-day loss for the care of children with diarrhoea of every severity is unavailable.

The average monthly wage for both sexes in Malaysia of RM 2,052 was obtained from the 2013 Wages and Salaries Survey Report (Department of Statistics Malaysia, 2013c). As wage-earners were assumed to work six days a week, hence daily wage of RM 79, was calculated by dividing the average monthly wage by 26. Hence, the estimated productivity loss of RM 213 was estimated for an episode of rotavirus gastroenteritis. (Table 4.12)

4.3 Results

4.3.1 Health burden

The following subsections provide detailed results of the incidence of acute gastroenteritis, the proportion of acute gastroenteritis attributable to rotavirus and the incidence of rotavirus gastroenteritis in Malaysia.

4.3.1.1 Incidence of acute gastroenteritis

(a) ***Hospitalisations***

In 2011, 96 of the 142 public hospitals in Malaysia contributed data on hospital discharges to the national database. Among children under-five years, 23,450 (6.4 per cent) of 365,931 public hospital discharges had ICD-10 codes for acute gastroenteritis. (Table 4.1)

In 2013, 107 of 209 private hospitals in Malaysia provided data on hospital discharges to the national database. Of the 153,717 private hospital discharges in children under-five years, 15,886 (10.3%) had ICD-10 codes for acute gastroenteritis. (Table 4.1)

When reported data was adjusted for hospitals not reporting discharges, a total of 70,000 acute gastroenteritis hospitalisations among children under-five years was estimated annually for Malaysia, with 52,000 (75 per cent) discharges to public hospitals and 18,000 (25 per cent) to private hospitals. (Table 4.2)

Annually, the incidence of acute gastroenteritis hospitalisations was estimated at 27.5 episodes per-1,000 children. (Table 4.8)

(b) ***Outpatient visits***

In 2012, there were 129,424 acute gastroenteritis related outpatient visits reported to MOH facilities among children under-ten years. (Table 4.3)

Annually, 40,000 (17 per cent) acute gastroenteritis related outpatient visits to public hospitals (emergency department, general outpatient department, satellite clinics and specialist clinics), 42,000 (18 per cent) visits to public clinics (Table 4.3) and 151,000

(65 per cent) visits to private clinics were estimated for children under-five years (Table 4.4).

The annual incidence of acute gastroenteritis related outpatient visits was 91.9 episodes per-1,000 children under-five years. (Table 4.8)

(c) ***Home-treated episodes***

Annually, an estimated 1.2 million acute gastroenteritis episodes, among children under-five years were treated at home. The annual incidence of home-treated acute gastroenteritis was estimated at 475.3 episodes per 1,000 children under-five years. (Table 4.8)

(d) ***Deaths***

In 2008, a total of 60 (1.5 per cent) of the 3,887 deaths in children under-five years were acute gastroenteritis related; of which 47 (78 per cent) were medically certified and 13 (22 per cent) were certified by lay persons. (Table 4.5)

In 2013, the under-five mortality rate for acute gastroenteritis was estimated at 11.96 per 100,000 live births (95 per cent CI: 9.18 to 14.74). This results in an estimated 61 diarrhoeal deaths in 2013. (Table 4.5)

The annual incidence of diarrhoeal deaths was estimated at 2.4 deaths per 100,000 children. (Table 4.8)

Table 4.8 displays the health burden of acute gastroenteritis and rotavirus gastroenteritis, by health service utilisation in Malaysia.

Table 4.8: Health burden of rotavirus gastroenteritis among children under-five years in Malaysia, 2013.

	Annual no. of episodes		**Episodes per-1,000 children per-year [a]**	
	Acute gastroenteritis related	**Rotavirus gastroenteritis related [b]**	**Acute gastroenteritis related**	**Rotavirus gastroenteritis related**
Deaths	61	27	0.02	0.01
Hospitalisations	70,000	31,000	27.5	12.2
Outpatient visits	234,000	41,000	91.9	16.2
Home treated episodes	1,209,000	145,000	475.3	57.0
Total	**1,513,000**	**217,000**	**594.7**	**85.5**

Note:

[a] Diarrhoeal episodes per-1,000 children per year, were estimated by dividing annual number of gastroenteritis episodes with the total population of children under-five years. Total population under-five years (both sexes combined) in 2012 is 2,550,000 (Department of Statistics Malaysia, 2012b).

[b] To estimate the incidence of rotavirus gastroenteritis, the incidence of acute gastroenteritis is multiplied with the proportion of gastroenteritis episodes attributable to rotavirus. (Figure 4.1, page 58).
The proportion of acute gastroenteritis attributable to rotavirus at hospital settings and for deaths (44.5 per cent) was obtained by meta-analysis (See Figure 4.3, page 98).
The proportion of acute gastroenteritis attributable to rotavirus at outpatient settings (18 per cent) and home-treated (12 per cent) was obtained from a community-based rotavirus study (Yap et al., 1992). [See Subsection 4.2.2.5(a), page 74].

To estimate annual rotavirus deaths of 27 deaths among children under five years in Malaysia, estimated annual incidence of acute gastroenteritis (61) was multiplied with the proportion of acute gastroenteritis attributable to rotavirus (44.5 per cent).

4.3.1.2 Proportion attributable to rotavirus among children hospitalised for acute gastroenteritis

The systematic search of three databases provided a total of 94 citations; 39 from Pubmed, 38 from Scopus and 17 from Web of Science. No further articles were identified from citation search or consultation with experts. After duplicates were excluded, 27 articles on rotavirus in Malaysia were screened by title and abstract. Of these, a further 15 were excluded for not being prospective, hospital-based rotavirus surveillance studies. Three papers were discarded for being duplicate publications based on results of the same primary studies[52]. Full text articles of the remaining nine papers were read, and the eligibility criteria was applied.

A PRISMA flow diagram of the review process is shown in Figure 4.2.

[52] Duplicate publications refers to multiple publications of the same primary study. The primary study was published more than once on different aspects.

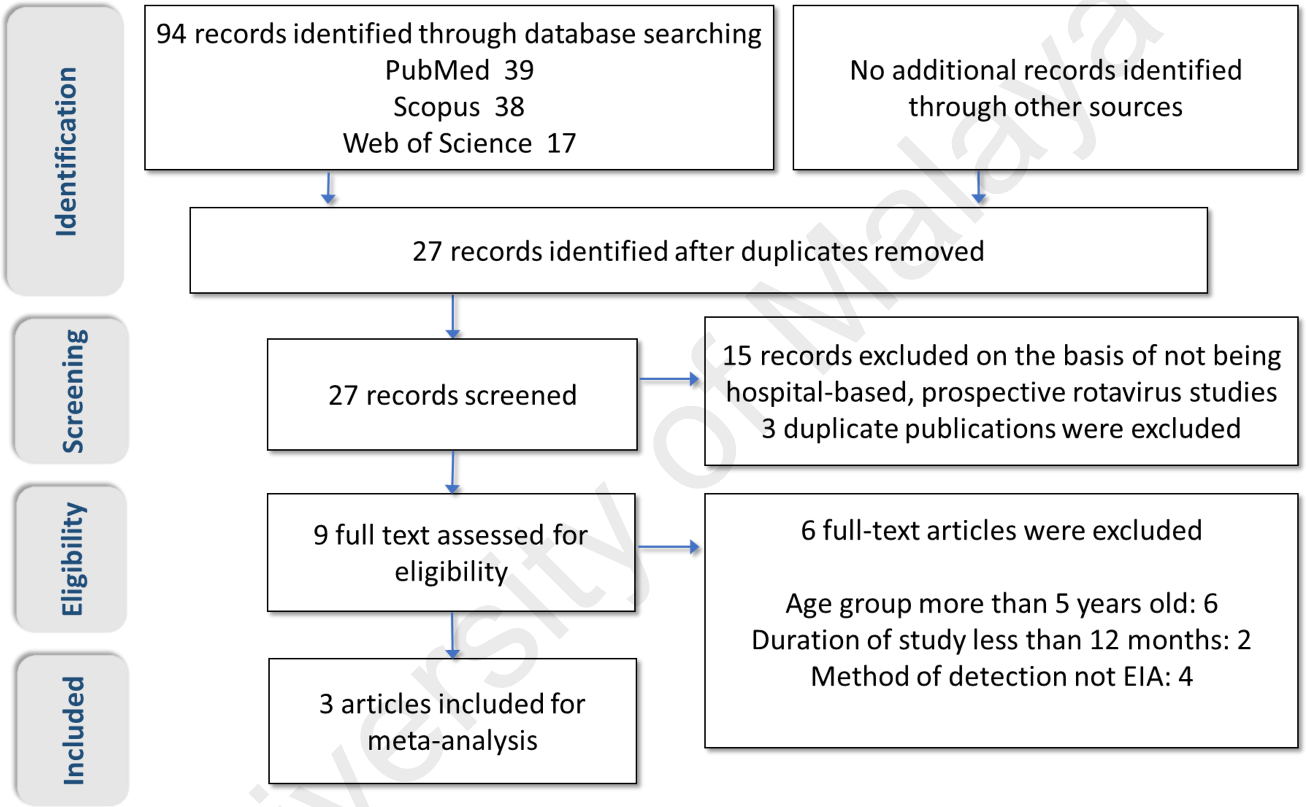


Figure 4.2: PRISMA flow diagram on the systematic review of hospital-based rotavirus studies in Malaysia

Note:

EIA- Enzyme immunoassay test; PRISMA- Preferred Reporting Items for Systematic Reviews and Meta-Analyses;

Duplicate publications refers to multiple publication of the same primary study material.

From 1982 to 2012, there were nine prospective hospital-based rotavirus surveillance studies conducted in Malaysia. These studies were conducted at Kuala Lumpur, and other locations including Kuching in Sarawak, Kota Kinabalu in Sabah, Johor Baru in Johor and Kuala Terengganu in Terengganu. Only three studies were conducted among children under-five years old. Five of the nine studies used EIA methods to test stool specimens for rotavirus. A total of 9,510 stool specimens were tested for rotavirus, with the rotavirus detection proportion of between 23 per cent and 50 per cent at each site.

Of these nine hospital-based rotavirus surveillance studies, a total of three studies met the predetermined eligibility criteria and were included in the meta-analysis (Hsu et al., 2005; Hung et al., 2006; Lee et al., 2012). These studies were conducted at different time points between the year 2000 and 2010, and at different geographic locations in Malaysia. A total of 5,586 stool samples were tested for rotavirus. The rotavirus detection proportion ranged from 32 per cent to 50 per cent at each individual study site (Table 4.9).

Each of these three studies were conducted at two study locations. The study by Lee et al was conducted in Kuala Lumpur and Kuala Terengganu (Lee et al., 2012). While the study by Hung et al. and the study by Hsu et al were both conducted in Kuala Lumpur and Kuching (Hsu et al., 2005; Hung et al., 2006). With exception of the Hsu et al. paper, which reported a summary figure for both sites, each of the published papers reported rotavirus detection proportions for each individual study site (Table 4.9).

Table 4.9 provides a summary of the three prospective hospital-based rotavirus surveillance studies selected for the meta-analysis.

Table 4.9: Summary of the hospital-based rotavirus studies selected for meta-analysis

Study Period	Study length	Age group (years)	RV-detection method	Location	No. of cases tested	No. of RV positives	RV-detection proportion	References
2001-2003	2 years	< 5	EIA	Kuala Lumpur & Kuching	2260	1130	50%	(Hsu et al., 2005)
2002–2003	2 years	< 5	EIA	Kuala Lumpur	1756	820	47%	(Hung et al., 2006)
				Kuching	912	445	49%	
2008–2010	2 years	< 5	EIA	Kuala Lumpur	385	161	42%	(Lee et al., 2012)
				Kuala Terengganu	273	87	32%	

Note:

RV- Rotavirus; EIA - Enzyme Immunoassay test; < 5, indicates children under-five years of age.

The rotavirus detection proportion from five individual study sites from these three papers were pooled for the meta-analysis. As there was considerable heterogeneity (I^2 = 81 per cent), a random effects model was applied for the meta-analysis. The pooled estimates of the rotavirus detection proportion in children under-five years hospitalised for acute gastroenteritis was 44.5 per cent (95 per cent CI: 39.6 to 49.4).

Figure 4.3 displays the forest plot and details the meta-analysis of rotavirus detection proportions from prospective hospital-based studies conducted in Malaysia.

Study	Location	No. of rotavirus positive	No. of cases tested	Rotavirus detection proportion	Standard Error	95% Confidence Interval
Hsu, 2005	Kuala Lumpur and Kuching	1130	2260	50.00	0.01	(47.08 - 52.92)
Hung, 2006	Kuala Lumpur	820	1756	46.70	0.02	(43.5 - 49.89)
Hung, 2006	Kuching	445	912	48.79	0.02	(44.26 - 53.33)
Lee, 2012	Kuala Lumpur	161	385	41.82	0.03	(35.36 - 48.28)
Lee, 2012	Kuala Terengganu	87	273	31.87	0.03	(25.17 - 38.56)
Effect Summary				**44.52**	**0.03**	**(39.61 - 49.43)**

Q = 26.7; I^2=81%;
Random effects model used for the pooled outcome estimate

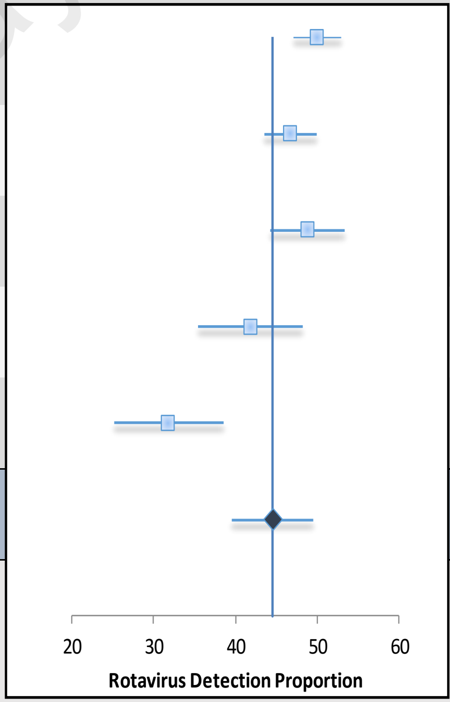


Figure 4.3: Meta-analysis of hospital-based rotavirus studies in Malaysia

Note:
This table shows data pooled from five study sites from three papers.
I^2 statistic describes the percentage of total variation across studies due to heterogeneity.

4.3.1.3 Incidence of rotavirus gastroenteritis

Approximately 27 rotavirus-related deaths were estimated to occur annually. Rotavirus gastroenteritis was estimated to result in 31,000 hospitalisations (75 per cent to the public sector and 25 per cent to the private sector), 41,000 outpatient visits (35 per cent to the public sector and 65 per cent to the private sector) and 145,000 episodes that are home treated (67 per cent of total episodes), annually. (Table 4.8)

The annual incidence of rotavirus among children under-five years was estimated at one death per-100,000 children; 12.2 hospitalisations per-1,000 children; 16.2 outpatient clinic visits per-1,000 children and 57.0 home-treated cases per-1,000 children. (Table 4.8)

4.3.2 Economic burden

Direct medical costs were estimated at RM 3,153 per-episode requiring hospitalisation and RM 174 per-episode receiving outpatient care (Table 4.10). Direct non-medical costs were estimated at RM 62, RM 23 and RM 10 respectively, for episodes requiring hospitalisation, outpatient and home-treatment (Table 4.11). Indirect costs were estimated at RM 213 per-episode of rotavirus gastroenteritis[53] (Table 4.12).

Annually, rotavirus gastroenteritis was estimated to incur direct medical costs of RM 105 million, for hospitalisations and outpatient visits. Of the direct medical costs, RM 72 million (68 per cent) were costs to the public sector, and RM 34 million (32 per cent) were costs to the private sector (Table 4.10).

Rotavirus was estimated to cost RM 156 million to society annually, of which a third was contributed by indirect costs (RM 46 million). Publicly, privately and home-treated episodes consist of 52 per cent, 27 per cent and 21 per cent of total societal costs. In Malaysia, rotavirus gastroenteritis was estimated to cost RM 61 per child under-five years

[53] Costs per-episode of rotavirus gastroenteritis was estimated by dividing total costs by the total number of rotavirus episodes.

annually[54]. This translates to societal costs of RM 3,153 per-episode requiring hospitalisation, RM 410 per-episode receiving outpatient care and RM 223 per home-treated episode (Table 4.13).

Table 4.10, Table 4.11 and Table 4.12 detail the estimation of direct medical, direct non-medical and indirect costs for rotavirus gastroenteritis in Malaysia according to health service utilisation.

Table 4.13 provides the economic burden of rotavirus gastroenteritis among children under-five years in Malaysia.

[54] Total societal costs of rotavirus diarrhoea (RM 156 million) was divided by the population of children under-five years (2.6 million) in Malaysia, to obtain annual societal costs of RM 61 per child under-five years in Malaysia.

Table 4.10: Estimation of direct medical costs for rotavirus gastroenteritis among children under-five years in Malaysia, 2013

	Rotavirus episodes ('000)	Unit costs per episode (RM)	Direct medical costs ('000 RM)
Hospitalisations [a, b]			
Public hospital	23	3,022	70,272
Private hospital	8	3,540	27,948
Outpatient visits [c]			
Public hospital	7	192	1,368
Public clinic	7	12	88
Private clinic	27	215	5,726
Home treated episodes	145	0	-
TOTAL	**217**		**105,402**

Note:

All costs are in 2013 RM;

[a] Unit costs of inpatient services of RM 944 per bed-day was estimated for public facilities, and RM 1,073 per bed-day was estimated for private facilities. Estimation of unit costs detailed in Subsection 4.2.3.1(c)i, page 82. See Table 4.7.

[b] To obtain cost per inpatient treated episode, the average duration of admission (3.3 days) was multiplied with cost per bed-day (Lee et al., 2012)

[c] Unit costs for outpatient visits of RM 192 was estimated for public hospital outpatients, RM 12 for public clinic outpatients and RM 215 for private clinic outpatients. Estimation of unit costs are detailed in Subsection 4.2.3.1(c)ii, page 87. See Table 4.7.

Table 4.11: Estimation of direct non-medical costs for rotavirus gastroenteritis among children under-five years in Malaysia, 2013

	Rotavirus episodes ('000)	Transportation costs per-episode [a] (RM)	Total transportation costs ('000 RM)	Diaper costs per-episode [b] (RM)	Total diaper costs ('000 RM)	Food costs per-episode [c] (RM)	Total food costs ('000 RM)	Direct non-medical costs ('000 RM)
Hospitalisations								
Public hospital	23	49	1,128	10	236	0.72	52	1,417
Private hospital	8	52	410	10	80	0.72	18	507
Outpatient visits								
Public hospital	7	24	173	10	72	0	0	246
Public clinic	7	8	63	10	76	0	0	139
Private clinic	27	11	302	10	271	0	0	573
Home treated episodes	145	0	0	10	1,474	0	0	1,474
TOTAL	**217**		**2,076**		**2,209**		**70**	**4,356**

Note:

All costs are in 2013 RM; RVGE, rotavirus gastroenteritis;

[a] One way transportation costs obtained from the National Health and Morbidity Survey 2011. Costs were doubled for outpatient episodes and quadrupled for inpatient episodes;

[b] Diaper costs per-episode obtained from the average costs for both hospitals were used in the 2010 hospital-based study (Lee et al., 2012);

[c] Additional food costs for an episode of diarrhoea hospitalised at University of Malaya Medical Centre was used for inpatient episodes .

Table 4.12: Estimation indirect costs for rotavirus gastroenteritis among children under-five years in Malaysia, 2013

	Rotavirus episodes ('000)	Duration of diarrhoea [a] (days)	Average daily wage [b] (RM)	Total indirect costs ('000 RM)
Hospitalisations				
Public hospital	8	2.7	79	4,955
Private hospital	23	2.7	79	1,682
Outpatient visits				
Public hospital	7	2.7	79	1,520
Public clinic	7	2.7	79	1,585
Private clinic	27	2.7	79	5,687
Home treated episodes	145	2.7	79	30,918
TOTAL	**217**			**46,348**

Note:

All costs are in 2013 RM;

[a] The average duration of diarrhoeal illness in children under-five years of 2.7 days, obtained from NHMS 2006, was assumed to represent days of work missed for all rotavirus gastroenteritis episodes regardless of severity (Ministry of Health Malaysia, 2006).

[b] The average monthly wage for both sexes in Malaysia of RM 2,052 was obtained from the 2013 Wages and Salaries Survey Report (Department of Statistics Malaysia, 2013c). Daily wage of RM 79, was calculated by dividing the average monthly wage by 26. Productivity loss was calculated by multiplying average daily wage with the days of work missed to care for an ill child with rotavirus diarrhoea. Indirect costs of RM 213 was estimated for per-episode of rotavirus gastroenteritis irrespective of severity.

Table 4.13: Economic burden of rotavirus gastroenteritis among children under-five years in Malaysia, 2013

	Rotavirus episodes ('000)	Direct medical costs [a] (RM '000)	Direct non-medical costs [b] (RM '000)	Indirect costs [c] (RM '000)	Total costs (RM '000)
Hospitalisations					
Public hospital	23	70,272	1,417	4,955	76,644
Private hospital	8	27,948	507	1,682	30,138
Outpatient visits					
Public hospital	7	1,368	245	1,520	3,133
Public clinic	7	88	139	1,585	1,812
Private clinic	27	5,726	573	5,687	11,987
Home treated episodes	145	-	1,474	30,919	32,393
TOTAL	**217**	**105,402**	**4,356**	**46,348**	**156,107**

Note:

All costs are in 2013 RM;

[a] Direct medical costs were estimated at RM 3,153 per-episode requiring hospitalisation and RM 171 per-episode receiving outpatient care. Direct medical costs were divided by number of rotavirus episodes to derive costs per-episode. See Table 4.10 for detailed estimation of direct medical costs;

[b] Direct non-medical costs were estimated at RM 62 per-episode requiring hospitalisation, RM 23 per-episode receiving outpatient care and RM 10 per home-treated episode. Direct non-medical costs were divided by number of rotavirus episodes to derive costs per-episode. See Table 4.11 for detailed estimation of direct non-medical costs;

[c] Indirect costs per-episode of rotavirus gastroenteritis was estimated at RM 213 per-episode. Indirect costs per-episode of rotavirus gastroenteritis is calculated by multiplying the average daily wage with the average duration of diarrhoeal illness. See Table 4.12 for detailed estimation of indirect costs.

4.4 Discussion

This study found that rotavirus has a substantial health and economic burden in Malaysia. It is estimated that rotavirus gastroenteritis results in 27 deaths, 31,000 hospitalisations, 41,000 outpatient visits and 145,000 episodes of home-treated diarrhoea, annually. Rotavirus incidence is estimated at one death per 100,000 children and 12 hospitalisations, 16 outpatient clinic visits, and 57 home-treated episodes per-1,000 children under-five years, annually (Table 4.8). Annually, rotavirus gastroenteritis was estimated to cost RM 105 million to the healthcare providers and RM 156 million to society. Productivity loss accounts for a third of the societal burden (RM 46 million). (Table 4.13)

This current work is the most recent and comprehensive estimation of national burden, and the only one to include data on annual discharges and outpatient visits from both public and private facilities. This study demonstrates the considerable health burden of rotavirus diarrhoea presenting to the private sector (25 per cent of inpatient treated and 65 per cent of outpatient treated episodes) and treated at home (67 per cent of total episodes) that were previously not adequately considered. These privately and home-treated episodes consist of 27 per cent and 21 per cent of total societal costs for rotavirus gastroenteritis in Malaysia.

Only one previous estimate of rotavirus burden in Malaysia has been published, and this inadequately considered privately treated episodes (Hsu et al., 2005). The study by Hsu et al. found that 3.3 per-1,000 children were hospitalised for rotavirus gastroenteritis in 1998, which may have been an underestimation. There are three main reasons for the differences in estimates rotavirus hospitalisations.

Firstly, Hsu et al. reported 27,873 acute gastroenteritis related discharges among children under-five years to MOH hospitals during the two-year study period (1999 to 2000). This translates to an average of 13,937 acute gastroenteritis related discharges reported annually to the MOH national database in that period. This figure is much less than the average of 21,000 acute gastroenteritis discharges reported annually from 2008 to 2013 (Table 4.1). A possible explanation for this is that the ICD-10 diagnostic coding of discharges has improved since the Hsu et al. study. The Hsu et al. study was conducted during the early years of establishment of the national database[55]. During this period, not all discharges were coded with ICD-10 diagnostic codes, resulting in considerable under-reporting of acute gastroenteritis.

Secondly, the Hsu et al. study did not directly collect private hospital discharges, as the national database only began compiling data from private hospitals after the year 2000. Hsu et al. adjusted for an additional 20 per cent of hospitalisations occurring at the private sector, estimating a total of 8,571 rotavirus-related hospitalisations annually in public and private hospitals in Malaysia. This estimate for rotavirus hospitalisations is very much lower than our current estimate. From 2010 to 2013, the national database captured an annual average of 17,000 acute gastroenteritis related discharges in children under-five years to private hospitals in Malaysia. (Table 4.1)

Thirdly, public hospitals not administered by MOH, including eight university and army hospitals, do not contribute hospital discharge data to the national database (Ministry of Health Malaysia, 2012b). In this current study, diarrhoeal discharges were adjusted using weightage of hospital beds, to account for all diarrhoeal discharges in Malaysia, including from facilities not reporting discharges to the national database. Hospitals not reporting discharges were not accounted for in the Hsu et al study. (Table 4.2)

The current study findings of 12.2 rotavirus hospitalisations per-1000 children per-year in Malaysia is within the range of results of a 2012 systematic review of the burden of rotavirus gastroenteritis in Asia. Kawai et al. (2012) found the incidence rotavirus-

[55] The national database started collecting public hospital discharges from MOH hospitals in 1999. The data collected by Hsu et al. was from 1999 to 2000.

related hospitalisation among children under-five years ranged from 2.1 to 20.0 episodes per-1000 children per-year in Asia.

The Hsu et al. (2005) study was likely to have underestimated the incidence of rotavirus outpatient visits, as this study failed to account for outpatient visits to private healthcare facilities in Malaysia. The previous study findings of 5.5 rotavirus-related outpatient visits per-1000 children under-five years did not include visits to private facilities.

It was important in this current study to include an estimate of outpatient visits to private facilities, as a substantial portion of the population utilises private healthcare in Malaysia. The NHMS 2006 found that 64 per cent of children seeking outpatient treatment for a recent illness sought private care (Ministry of Health Malaysia, 2006). The current estimate of 16.2 rotavirus-related outpatient visits per-1,000 children annually in Malaysia, is similar to findings from India (15.0 per-1,000 children), Philippines (12.1 per-1,000 children) and China (20.1 per-1,000 children) (Carlos et al., 2009; Lou, Xu, Wu, Tao, & Tong, 2011; Tate, Chitambar, et al., 2009). Also, the study findings are within the range of the Kawai et al. (2012) estimates for Asia of 5.6 to 45.3 rotavirus-related outpatient visits per-1000 children per-year.

This study found that 145,000 episodes of mild rotavirus gastroenteritis did not seek medical treatment, resulting in RM 32 million in indirect and direct non-medical costs, or 21 per cent of the total economic burden to society. This considerable hidden burden has not been previously explored in Malaysia. Although, mild diarrhoeal episodes do not present to the healthcare system, these are an important societal burden. Children with mild diarrhoea still require caregiver’s time, incurring productivity loss. However, estimating episodes treated at home has inherent uncertainty, as these episodes are not directly captured in inpatient or outpatient records and can only be derived by examining community healthcare utilisation patterns.

The estimates of home-treated episodes in this study, are based on health utilisation patterns from the only community-based study in Malaysia (Yap et al., 1992). While this study may be dated, it is the only community-based rotavirus study in Malaysia. In addition, on examining a series of National Health and Morbidity Surveys (1996, 2006, and 2011), it was found that health utilisation patterns for children under-five years seeking care for acute illness in Malaysia, did not change greatly in the fifteen year period examined (Ministry of Health Malaysia, 1996, 2006, 2011b).

The results of estimation of home-treated rotavirus gastroenteritis in this thesis is comparable with those of two international studies (J. Bilcke et al., 2009; Parashar et al., 2003).

Parashar et al. (2003) estimated that for every child requiring medical attention for rotavirus gastroenteritis, an additional three to five children develop illness that requires only home-treatment. The current study findings suggest that in Malaysia, the number of children with rotavirus diarrhoea that were home-treated (145,000) was about 3.5 times the number who sought outpatient care (41,000). This is within the range of estimates of home-treated episodes obtained when using the Parashar et al. expansion factor of four times of outpatient episodes (home-treated episodes range from 124,000 to 206,000 in Malaysia).

The J. Bilcke et al. (2009) meta-analysis estimated the global incidence of symptomatic rotavirus infections at 0.31 (0.19 to 0.50) per-person per-year in children under-two years. This would mean an annual average of 315,000 (193,000 to 509,000) symptomatic episodes in children under-two years in Malaysia. The current study estimate of 218,000 episodes of symptomatic rotavirus annually, among children under-five years in Malaysia, is well below this estimate.

Using national mortality data, this study estimated 61 acute gastroenteritis related deaths for 2013. There were 27 rotavirus deaths estimated in 2013, with an annual rotavirus mortality rate of 1.0 deaths per-100,000 children under-five years. These findings are consistent with those estimated for Malaysia, by the Child Health Epidemiology Reference group (CHERG) for WHO and UNICEF of 55 diarrhoeal deaths in 2010 (Liu et al., 2012) and slightly higher than the WHO estimate of 15 rotavirus deaths in 2008 (Tate et al., 2012). While rotavirus deaths are not high in Malaysia, these deaths are preventable with vaccination. Rotavirus vaccines have an important role in reducing child mortality.

The current estimation of the economic burden of rotavirus gastroenteritis on the health system in Malaysia is much higher than the estimation by Lee et al. (2007), of US$ 1.8 million (RM 6.8 million) in 2002. This 2002 estimation was based on average direct medical costs per-episode of rotavirus hospitalisation obtained from one university hospital and extrapolated for the whole country. The 2002 estimation was from the healthcare provider's perspective and did not consider costs to the private sector and episodes treated as outpatient or at home.

The current study findings estimated the healthcare costs for treatment of rotavirus requiring hospitalisation and outpatient treatment, as well as non-medical and indirect costs to society. The estimate of annual societal costs for rotavirus gastroenteritis of RM 61 (US$ 19) for a child under-five years in Malaysia, is similar to estimates for upper-middle income countries of US$ 15, when inflated to 2013 values (R. D. Rheingans et al., 2009). Comparing costs between countries are difficult because of inherently different economies, healthcare systems and different assumptions and methodologies used in the evaluations. However, the current estimation of direct medical costs per hospitalised episode of rotavirus of RM 3,153 (US$ 1,000) are comparable to costs in high-income countries in Asia like Japan (US$ 1,500-2,000) (Ito et al., 2011; Nakagomi et al., 2005; Sato, Nakagomi, & Nakagomi, 2011), Taiwan (US$ 330-760) (Chen et al., 2007; Lu et al., 2006; Mast et al., 2010), and Hong Kong (US$ 2,500) (E Anthony S Nelson et al., 2005) when costs are inflated to 2013 values.

This study has several limitations. Firstly, as there are no official unit costs for healthcare facilities in Malaysia, costs were estimated based on top-down costing methods (D. S. Shepard et al., 2000; D. S. Shepard et al., 2012; Suaya et al., 2009). Nevertheless, this current estimation is robust, as it used local data costing data from annual reports of five tertiary-level hospitals, costing studies of six primary-level hospitals and eleven health clinics, in addition to unit costs from WHO-CHOICE, to account for public and private healthcare facilities in Malaysia. Although these costing data are from different time frames, they are the best available to account for healthcare costs in diverse segments of the health sector in Malaysia.

Secondly, the estimation of outpatient attendances to public health facilities is conservative. Data from MOH captures outpatient attendances to MOH hospitals and primary healthcare clinics, but does not capture treatment for childhood diarrhoea given by nurses or midwives at maternal and child health clinics at MOH facilities[56]. These episodes can be assumed to be mild, as they are not referred to be treated by a medical officer. Also the reported data does not capture diarrhoeal outpatient visits to non-MOH public clinics (like university hospitals and army hospitals). However, the NHMS 2006 found that among children under-five years with self-reported diarrhoeal illness, only 1.4 per cent sought outpatient care at army hospitals and none sought outpatient care at university hospitals (Ministry of Health Malaysia, 2006, p. 68). As such, diarrhoeal outpatient visits to non-MOH public clinics were assumed to be negligible in this thesis.

[56] The MOH public health facilities, provide maternal child health (MCH) services in addition to general outpatient services, at various levels of care depending the facilities and the needs of the population. MCH clinics may be located in facilities together with outpatient services or in separate, smaller clinics close to villages and communities. MCH services are provided by nurses and midwifes at smaller clinics, but also by medical officers’ and Family Medicine Specialists’ at larger health centres.

Returns on outpatient diarrhoeal attendances are not recorded or collected at MCH clinics. MCH clinics provide child health services, and are mainly Well Baby Clinics, monitoring growth and development, nutrition and administering immunisations (Noor Ghani & Yadav, 2008). Mild diarrhoeal illness may be treated by nurses especially in smaller community clinics, but more severe episodes would be referred to the outpatient department for treatment by medical officers.

Since all except one study on rotavirus in Malaysia were hospital-based, the rotavirus detection proportion at outpatient clinics and for home-treated episodes was obtained from the only community-based rotavirus study conducted in 1988 (Yap et al., 1992). Nevertheless, the rotavirus detection proportion at outpatient clinics in Malaysia of 18 per cent is comparable to a 2012 pooled estimate of outpatient-based rotavirus studies in Asia of 23 per cent (Kawai et al., 2012). In addition, the rotavirus detection proportion for home-treated cases in Malaysia of 12 per cent is similar to the results of a community-based study conducted in Thailand (12.2 per cent) (Jiraphongsa et al., 2005).To better represent the proportion of acute gastroenteritis requiring hospitalisation, attributable to rotavirus for Malaysia, a meta-analysis was conducted of primary studies conducted at different time-points and regions in the country.

The estimation of transportation costs is conservative, as one-way transportation costs from NHMS 2011 was doubled for outpatient visits and quadrupled for hospitalisations. This resulted in an estimated transportation costs of RM 52 and RM 48 per-episode for private and public hospitals, based on data from NHMS 2011. This estimate is comparable to findings of a 2010 hospital-based rotavirus study at two public hospitals in Malaysia. In this 2010 study, average transportation costs for an episode of rotavirus gastroenteritis requiring hospitalisation in Kuala Lumpur was RM 60, while at Kuala Terengganu transportation costs was about RM 6 in 2013 RM. (Table 6.3, page 193).

The estimation for lost productivity is conservative, as days of work missed was assumed to be the same for all diarrhoea episodes, regardless of severity. In addition, the emotional impact of caring for a child with diarrhoea is not captured here. The stress and anxiety of caring for an ill child, or a qualitative loss of productivity beyond lost wages, could translate to higher economic costs, and is an avenue for future research. For the cost-effectiveness analysis, the health burden was expressed in terms of quality adjusted life years (QALYs). Health evaluation was conducted using Health Utility Index Mark 2

(HUI 2) questionnaires in children and EuroQoL 5D (EQ-5D) in adults, which measures quality of life over multiple dimensions including emotion and pain. Chapter 5 details the evaluation of cost-effectiveness of rotavirus vaccines in Malaysia.

Also, this study does not consider expenditure for informal care as this is not relevant in the Malaysian setting. The NHMS 2006 found that less than three per cent of children under-five years with acute diarrhoea sought care at non-medical facilities, like traditional healers or Chinese medicine shops (Ministry of Health Malaysia, 2006).

4.5 Conclusion

A comprehensive estimation of rotavirus gastroenteritis burden is necessary when considering the benefits of vaccines in preventing illness. This chapter demonstrates the considerable burden of rotavirus gastroenteritis in Malaysia, including episodes treated privately and at home, which were not well captured in previous studies. This provides vital information for the evaluation of cost-effectiveness and the broader economic impacts of vaccination, which are necessary for policy-making regarding universal vaccination.

In the next chapter, the cost-effectiveness and affordability of universal rotavirus vaccination are evaluated from the healthcare provider and societal perspectives in Malaysia.

CHAPTER 5: THE COST-EFFECTIVENESS AND AFFORDABILITY OF ROTAVIRUS VACCINATION IN MALAYSIA

5.1 Introduction

Rotavirus vaccines are widely regarded as cost-effective interventions in many countries (Atherly et al., 2012; R. D. Rheingans et al., 2009). However, high vaccine prices are a barrier for public finance of rotavirus vaccines in middle-income countries (Madsen et al., 2012; E. A. S. Nelson et al., 2013).

While cost-effectiveness analysis is designed to assess value for money, the affordability of vaccination programmes is of practical concern to budget holders. As Malaysia lacks a national threshold for the determination of cost-effectiveness of medical technologies, WHO-CHOICE thresholds have been used as an informal reference for cost-effectiveness. However, the WHO-CHOICE thresholds were meant for regional priority setting, and have acknowledged short-comings when used to inform national policy. The WHO-CHOICE thresholds are easily achieved and its use does not consider the affordability of interventions within the context of finite budgets. This reduces the value of cost-effectiveness analysis in informing resource allocation decisions (Marseille, Larson, Kazi, Kahn, & Rosen, 2015; Newall et al., 2014; Shillcutt, Walker, Goodman, & Mills, 2009).

In this chapter, the cost-effectiveness and affordability of incorporating rotavirus vaccines into the Malaysian national immunisation programme were evaluated. Cost-effectiveness was explored using various thresholds determined for Malaysia, with the aim of informing vaccine price negotiation. The chapter begins with Section 5.2, which presents study methods, data sources and assumptions used for the cost-effectiveness, threshold and budget impact analysis of rotavirus vaccines in Malaysia. Next Section 5.3, presents the results of this study. This is followed by Section 5.4, which discusses study findings, limitations and its policy relevance. The chapter ends with Section 5.5, which provides concluding statements.

5.2 Materials and methods

5.2.1 Study overview

In this chapter, cost-effectiveness of universal rotavirus vaccination in Malaysia is compared with the current scenario of 'no vaccination'. The cost-effectiveness of both Rotarix® and RotaTeq® were considered separately, from the healthcare provider's and societal perspective. The impact of rotavirus vaccines in reducing the health and economic burden of rotavirus gastroenteritis episodes was determined.

Cost-effectiveness was evaluated using the POLYMOD model, an age-stratified, static, multi-cohort model. Multiple cohorts of vaccinated and unvaccinated children, based on the 2012 Malaysian birth cohort of 508,774 live births (Department of Statistics Malaysia, 2012b), were followed from birth to age five years. Subsection 5.2.2 provides the rationale for the use of mathematical modeling in evaluating cost-effectiveness and explains the choice of models used in this current analysis.

The estimation of the health and economic burden of rotavirus gastroenteritis was detailed in Chapter 4. Results of that estimation provided inputs on rotavirus incidence and costs in Malaysia, for use in the cost-effectiveness analysis. Rotavirus gastroenteritis was divided into episodes requiring home-treatment, outpatient consultation, hospital admission, and those resulting in death.

The effectiveness outcome was expressed as the incremental cost-effectiveness ratio (ICER) or the ratio of net costs per unit of health benefits gained from vaccination. The ICER was reported in terms of net costs per-QALY gained. Net costs were defined as vaccination costs less the cost savings from reduced illness post vaccination. Health benefits were valued in QALYs.

In the base-case, the cost-effectiveness of Rotarix® was evaluated from the healthcare provider's perspective. In alternate scenarios, cost-effectiveness of RotaTeq® was evaluated and also from the societal perspective. In the base-case, QALY loss for the child and one caregiver was assumed. Health Related Quality of Life (HRQoL) weights for a home-treated episode of rotavirus gastroenteritis was assumed to be fifty per cent of episodes requiring medical care[57]. The Pan American Health Organization (PAHO) Revolving Fund prices[58] were used in the base-case, as the most likely tender price for rotavirus in Malaysia (Ministry of Health Malaysia, 2014a; PAHO, 2013). The Recommended Retail Price for Malaysia was used as the most likely market price.

A time horizon of five years was chosen for the cost-effectiveness analysis, as rotavirus gastroenteritis commonly occurs in children under-five years (World Health Organization, 2013d). All future costs and benefits were discounted at the rate of three per cent per annum, as recommended by the WHO (Walker, Hutubessy, & Beutels, 2010).

Parameters in the model are listed in Table 5.1. The assumptions in the base-case and alternative scenarios are presented in Table 5.2. Subsection 5.2.3 explains the economic assumptions and the parameters used in the model.

As Malaysia has not defined a threshold for cost-effectiveness, this chapter explores cost-effectiveness using three different thresholds for Malaysia. Threshold analysis was conducted to inform on cost-effective vaccine prices for vaccine price negotiations. Vaccine affordability was assessed with a budget impact analysis, comparing annual costs of vaccination programmes with the Malaysian public health budget.

Subsection 5.2.4 details the assumptions behind the scenarios tested during the sensitivity analysis. Subsection 5.2.5 explains the rationale behind the cost-effectiveness

[57] The HRQoL weights were obtained from a Canadian study conducted in an outpatient setting (Sénécal et al., 2008). Hence in this thesis, QALY loss for home-treated episodes was assumed to be fifty per cent of children treated at an outpatient setting. This assumption was previously used in the economic evaluation of rotavirus vaccines in the United Kingdom (Jit et al., 2009).The rationale behind these assumptions are explained in Subsection 5.2.3.3, page 136.

[58] The PAHO Revolving Fund for vaccine procurement in the Americas region, ensures the lowest negotiable vaccine prices worldwide through pooled purchasing mechanisms (E. A. S. Nelson et al., 2013).

thresholds and the methodology used for the threshold analysis. This is followed by Subsection 5.2.6, which presents the rationale and methods for the budget impact analysis.

The base year for analysis was 2013. All costs were inflated to 2013 RM using GDP deflators (Department of Statistics Malaysia, 2012a). The 2013 World Bank exchange rate of US$ 1 to RM 3.15 was used for conversions (World Bank, 2014a). Analysis was conducted using Microsoft Excel® Professional Plus 2013.

Table 5.1: Parameters used in the model

Parameter	Value	Source
<u>Demographics</u>		
Life expectancy at birth (years)	74	(World Health Organization, 2012a)
Infant mortality rate (per-1,000 live births)	7	(World Health Organization, 2012b)
Under-five mortality rate (per-1,000 live births)	9	(World Health Organization, 2012b)
Population under-five years	2,426,958	(United Nations, 2013)
Birth cohort	508,774	(Department of Statistics Malaysia, 2012b)
<u>Incidence of rotavirus gastroenteritis</u>		
Deaths (per-100,000 children per-year)	1	Chapter 4, page 99
Hospitalisation (per-1,000 children per-year)	12	Chapter 4, page 99
Outpatient visits(per-1,000 children per-year)	16	Chapter 4 page 99
Home-treatment(per 1,000 children per-year)	57	Chapter 4, page 99
<u>Utilities</u>		
QALYs for an episode		
Child	0.0022	(Brisson, Sénécal, Drolet, & Mansi, 2010)
Caregiver	0.0018	(Brisson et al., 2010)
<u>Cost of illness</u>		
Direct medical costs		
Hospitalisation	RM 3,153	Chapter 4, page 99
Outpatient visits	RM 174	Chapter 4, page 99
Direct non-medical costs		
Hospitalisation	RM 62	Chapter 4, page 99
Outpatient visits	RM 23	Chapter 4, page 99
Home-treatment	RM 10	Chapter 4, page 99
Indirect costs	RM 213	Chapter 4, page 99
<u>Vaccination Programme</u>		
Vaccine coverage	97%	(World Health Organization, 2013b)
Vaccine wastage	5%	(World Health Organization, 2014b)
Vaccine procurement costs per-dose		
PAHO revolving fund price		
Rotarix®	RM 20	(PAHO, 2013)
RotaTeq®	RM 16	(PAHO, 2013)
Market price		
Rotarix®	RM 139	(Ministry of Health Malaysia, 2014a)
RotaTeq®	RM 116	(Ministry of Health Malaysia, 2014a)
Additional administrative cost	RM 15	(De la Hoz-Restrepo, Castaneda-Orjuela, Paternina, & Alvis-Guzman, 2013)

Table 5.1: Parameters used in the model (Continued)

Parameter	Value	Source
<u>**Vaccine efficacy**</u>		
Rotarix®		
One-dose efficacy:		
Hospitalisation	96%	(Vesikari, Karvonen, et al., 2007)
Outpatient visits	88%	(Vesikari, Karvonen, et al., 2007)
Home-treatment	87%	(Vesikari, Karvonen, et al., 2007)
Two-dose efficacy:		
Hospitalisation	100%	(Vesikari, Karvonen, et al., 2007)
Outpatient visits	92%	(Vesikari, Karvonen, et al., 2007)
Home-treatment	87%	(Vesikari, Karvonen, et al., 2007)
Waning immunity (First to second season)		
Hospitalisation	92%	(Vesikari, Karvonen, et al., 2007)
Outpatient visits	83%	(Vesikari, Karvonen, et al., 2007)
Home-treatment	83%	(Vesikari, Karvonen, et al., 2007)
RotaTeq®		
One-dose efficacy:		
Hospitalisation	82%	(Iwata et al., 2013)
Outpatient visits	66%	(P. H. Dennehy et al., 2011; Iwata et al., 2013)
Home-treatment	62%	(P. H. Dennehy et al., 2011; Iwata et al., 2013)
Two-dose efficacy:		
Hospitalisation	84%	(Iwata et al., 2013)
Outpatient visits	68%	(P. H. Dennehy et al., 2011; Iwata et al., 2013)
Home-treatment	63%	(P. H. Dennehy et al., 2011; Iwata et al., 2013)
Complete dose efficacy:		
Hospitalisation	100%	(Iwata et al., 2013)
Outpatient visits	81%	(Iwata et al., 2013)
Home-treatment	75%	(Iwata et al., 2013)
Waning immunity (First to second season)		
Hospitalisation	90%	(Vesikari et al., 2006)
Outpatient visits	85%	(Vesikari et al., 2006)
Home-treatment	85%	(Vesikari et al., 2006)

Note:

All costs are in 2013 RM;

PAHO, Pan American Health Organization; QALY, Quality adjusted life years.

Table 5.2: Assumptions in the base-case and alternative scenarios

	Base-case	Alternative Scenarios
Vaccine	Rotarix®	RotaTeq®
Discount rate	Three per cent costs and benefits	Zero per cent costs and benefits; 4.5 per cent costs and 1.5 per cent benefits
Perspective	Health care provider	Societal
Caregivers affected	One	Zero, two
QALY adjustment for home-treated case	50 per cent of episodes seeking medical care	100 per cent of episodes seeking medical care
Price of vaccine	PAHO price	Market price

Note:

QALY, Quality-adjusted life-years; PAHO, Pan American Health Organization

5.2.2 Economic models used for cost-effectiveness analysis

5.2.2.1 Mathematical models

Mathematic models are used in various scientific disciplines to present the complexities of reality into more simple and comprehensible forms. In economic evaluations of vaccination programmes, models are used to bring together all relevant biological, clinical, epidemiological and economic factors from various sources (Kim & Goldie, 2008).

Models are used in situations where the conduct of experimental studies are impractical, infeasible or unethical. Although clinical trials provide the highest level of scientific evidence, trials rarely capture all relevant economic data for economic evaluations. Mathematical models are used to extrapolate beyond the immediate or intermediate end-points of trials to final end-points (Buxton et al., 1997; Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 2005; Jit & Brisson, 2011; Siebert, 2003; Szucs, 2005).

Models used in health economic evaluations or decision analytical models, are mathematical models that require complex, computer-based simulations. Decision analytical models can be divided into dynamic and static models (Beutels, Van Doorslaer, Van Damme, & Hall, 2003; Kim & Goldie, 2008).

Dynamic models are often used to model the complexities of infectious disease, such as transmission of infection from infectious to susceptible individuals. In dynamic models, the force of transmission, or the rate at which the susceptible individual becomes infected, changes with time, thus is dynamic. Dynamic models takes into account the indirect protection conferred by vaccination and the possibility of acquiring natural immunity. Results from a dynamic model usually indicates that the intervention is more cost effective than of the static model. This is because dynamic models are able to capture both direct and indirect benefits of vaccination (Beutels et al., 2003; Jit & Brisson, 2011).

In static models or models without interaction, the force of infection does not change with time. The force of infection is independent of the proportion of population that is infected (Jit & Brisson, 2011; Kim & Goldie, 2008).

5.2.2.2 Choice of economic model

Dynamic models are relatively complex; requiring more data and assumptions, as well as more skill to construct, understand and interpret the results (Bakir, Standaert, Turel, Bilge, & Postma, 2012; Jit & Brisson, 2011; Kim & Goldie, 2008). Advanced models are used to answer complex questions, like control measures for an epidemic. When advanced models are used to answer simple questions like cost-effectiveness, its results do not differ greatly from simple models (Bakir et al., 2012; Postma et al., 2011).

Static models are frequently used to evaluate the economic impact of rotavirus vaccines (Bakir et al., 2012; Beutels et al., 2003; Joke Bilcke & Beutels, 2009). Cost-effectiveness results for rotavirus vaccines when evaluated using different models, using the same input parameters have been similar and comparable (Bakir et al., 2012; Postma et al., 2011).

In this thesis, cost-effectiveness was evaluated using the POLYMOD model, a static, multi-cohort model (Jit et al., 2009; Jit & Edmunds, 2007; Jit, Yuzbashyan, Sahakyan, Avagyan, & Mosina, 2011; Tilson et al., 2011). The choice of model was informed by a WHO initiated review, designed to guide low- and middle-income countries on model design and choices for the economic evaluation of rotavirus vaccines. This review suggested that model choice may not be as crucial as the input parameters and assumptions used in economic evaluations. As the epidemiology of rotavirus infection does not vary much between countries, existing health economic models may be adapted to local contexts to evaluate cost-effectiveness of rotavirus vaccination (Postma et al., 2011).

Models examined in this review were the Roxanne (Rotarix® Analysis of Economics from GSK), the CoRoVa (Consensus Rotavirus model Vaccination) and the POLYMOD models. Standardised input parameters from four different regions were entered into the three different cost-effectiveness models. Results of the cost-effectiveness analysis were found to be broadly similar for all the models examined (Postma et al., 2011).

The POLYMOD model was chosen for use in this thesis based on its independence of funding. Unlike other models in the review, the POLYMOD was not designed or financed by the pharmaceutical industry. The POLYMOD model was independently developed as part of an European Union funded project, and was designed by modellers from several European countries (Postma et al., 2011).

In this thesis, cost-effectiveness was evaluated using the POLYMOD model, an excel-based, static model. The POLYMOD model is an age stratified multi-cohort model which accounts for different birth cohorts entering the model yearly, within a five year time frame. For the first year, the cohort is stratified into monthly age bands. Subsequently from one to five years old, yearly bandings are applied (Jit et al., 2009; Jit & Edmunds, 2007; Jit et al., 2011; Tilson et al., 2011).

5.2.3 Economic assumptions and parameters used in the model

5.2.3.1 Population demographics

Mortality rates and life expectancy for children under-five were obtained for Malaysia from the Global Health Observatory of the World Health Organization (World Health Organization, 2012a, 2012b). (Table 5.1)

5.2.3.2 Rotavirus incidence

Rotavirus incidence was classified into rotavirus episodes requiring home-treatment, outpatient treatment, hospital admission and those resulting in death. Estimation of rotavirus incidence for Malaysia was detailed in Chapter 4 (Subsection 4.2.2), and summaries of this estimation are provided here.

Annual rotavirus hospitalisations and outpatient visits of 12 and 16 per-1,000 children under-five years to both public and private healthcare in Malaysia, was estimated from acute gastroenteritis related discharges and outpatient visits reported to the MOH, Malaysia. The incidence of home-treated rotavirus of 57 episodes per 1,000 children under-five was estimated based on health utilisation patterns from a 1989 community-based rotavirus study (Yap et al., 1992). Rotavirus mortality of one per 100,000 children under-five years in 2013 was estimated from under-five diarrheal mortality rates obtained from the Department of Statistics, Malaysia. Proportion of diarrheal disease attributable to rotavirus for hospitalised episodes (44.5%) was estimated from a meta-analysis conducted of primary hospital-based rotavirus studies in Malaysia. The 1989 community-based study provided rotavirus detection proportions for acute gastroenteritis treated at outpatient (18%) and at home (12%) settings (Yap et al., 1992).

The age distribution of children with rotavirus gastroenteritis was obtained from a two-year hospital-based rotavirus study conducted in Kuala Lumpur and Kuala Terengganu, and applied to all episodes in the model. (23 per cent in children under 12 months, 37 per cent in children aged 12 to 23 months, 19 per cent in children aged 24 to 35 months, 11 per cent in children aged 36 to 47 months and nine per cent in children aged 48 to 59 months). Chapter 6 describes the findings of this hospital-based study. (Table 5.1)

5.2.3.3 Quality-adjusted life-years

Cost-utility analysis is a type of cost effectiveness analysis, in which health benefits are expressed using a utility-based measure[59], either QALYs or disability adjusted life years (DALYs). Utility-based measures express outcomes based on individual preferences for health states. QALYs are a composite measure of length and quality of life. QALYs account for both quantity and quality of life gained from a healthcare intervention. Health Related Quality of Life (HRQoL) values health states in a numeric

[59] Utility is an economic term for the wellbeing experienced by an individual in different health states.

scale, in which a year of life spent in perfect health is valued at one and death is valued at zero (Robinson, 1993).

DALYs averted and QALYs gained are very different health outcome measures (Robberstad, 2005). DALYs are recommended for use by WHO and World Bank, and are generally used by low-income countries (Edejer, 2003; World Bank, 1993). QALYs are preferred by economists in high- and middle-income countries (Brazier & Longworth, 2011; Henry, Hill, & Harris, 2005).

Malaysia is an upper middle-income country with no explicit threshold for cost-effectiveness. As such, health outcomes will be measured in QALYs in this study to allow for comparability between health interventions.

HRQoL measurement in young children have several difficulties. There is a lack of measurement tools specifically designed to evaluate health states in young children under-five years of age. Many of the health dimensions in health classification systems designed for adults are not relevant to a young children[60]. Also, young children lack the cognitive ability to complete a valuation[61], requiring adults to value the health states of a child. In addition, children are dependent on parents or caregivers. Thus, the impact of the health of a child on parental utility need separate consideration in economic evaluations (Griebsch et al., 2005). The challenges of health state valuation include the necessity of assessing a young child for a relatively mild and self-limiting illness, like rotavirus gastroenteritis (Beutels et al., 2008).

The United Kingdom's National Institute for Health and Care Excellence (NICE) in its reference case for health technology assessment, specified the use of preference-based measures designed specifically for use in children, like the Health Utility Index Mark 2 (HUI-2) for HRQoL assessment of children (Adlard, Kinghorn, & Frew, 2014).

[60] Young children are still developing, and a normal child under five years may require help to eat, dress, bathe or use the toilet. Thus, mobility and self-care, two dimensions of the EuroQoL 5D (EQ-5D) questionnaire, are not applicable in young children (Griebsch, Coast, & Brown, 2005).

[61] Health states are valued using either standard gamble, time trade off techniques or visual analogue scales.

HUI-2 is a generic multi-attribute, preference-based system for assessing HRQOL, designed specifically for children. HUI-2 measures quality of life over dimensions of sensation, mobility, emotion, cognition, self-care and pain. Each dimension is scored using between three to five levels, which range from "normal functioning for age" to "extreme disability". HUI-2 is suitable for self-completion by children above the age of eight years, while a proxy version is available for younger children[62]. This tool was developed by Torrance et al., based on interviews with parents of school age children in Canada (Feeny, Furlong, Boyle, & Torrance, 1995; Torrance et al., 1996).

Children are dependent on parents or caregivers, thus the impact of the health of a child on the parental utility should be considered in economic evaluations (Griebsch et al., 2005). Hence, QALY loss was considered for both the child and the primary caregiver in this thesis.

A prospective, community-based Canadian rotavirus study provided information on per-episode HRQoL weights for the child (0.0022) and caregiver (0.0018) used in this thesis (Table 5.1). QALY loss was calculated over three visits made over a two week period. QALY loss was measured for children under the age of three years presenting with diarrhoea at outpatient settings using HUI-2 questionnaires and Visual Analogue Scores (VAS), administered to caregivers. This same study also assessed the QALY loss for the primary caregiver of a child with diarrhoea, using the EuroQoL 5D (EQ-5D) questionnaire and VAS. (Brisson et al., 2010).

Data from this Canadian study was chosen for use in this thesis, as this study used caregivers as proxy to measure of a child's utility. This is preferable to another similar study conducted in the United Kingdom, in which clinicians were used as proxy (Martin, Cottrell, & Standaert, 2008).

[62] Adult caregivers may answer the HUI-2 as proxy for a young child.

The HRQoL weights from the Canadian study was obtained from an outpatient setting (Sénécal et al., 2008). Hence in this thesis, QALY loss for home-treated episodes was assumed to be fifty per cent of children treated at an outpatient setting. This assumption was previously used in the economic evaluation of rotavirus vaccines in the United Kingdom (Jit et al., 2009). This fraction of HRQoL detriments for home-treated episodes was varied between fifty per cent and hundred per cent in the sensitivity analysis. (Table 5.2)

5.2.3.4 Cost of illness

The estimation of the economic burden of rotavirus gastroenteritis was detailed in Chapter 4 (Subsection 4.2.3), and summaries of this estimation are provided here. In this current chapter, cost per-episode of rotavirus gastroenteritis by health service utilisation was used as model inputs for the cost-effectiveness analysis. From the healthcare provider's perspective, costs included were direct medical costs for hospitalisations and outpatient visits. While, from the societal perspective, costs included were direct medical, direct non-medical and indirect costs for all episodes of rotavirus gastroenteritis.

Direct medical costs per-episode of rotavirus gastroenteritis was estimated for inpatient and outpatient episodes. Multiple data sources were used for this estimation including local data from annual reports of five tertiary-level hospitals, costing studies of six primary-level hospitals and eleven health clinics, in addition to unit costs from WHO-CHOICE. Direct medical costs for an episode of rotavirus gastroenteritis receiving inpatient and outpatient care was estimated at RM 3,153 and RM 171. (Table 4.13)

Direct non-medical costs include transportation, additional diapers and food consumed during an episode of rotavirus gastroenteritis. Direct non-medical costs for rotavirus gastroenteritis episodes receiving inpatient, outpatient and home-treatment was estimated at RM 62, RM 23 and RM 10 per-episode respectively. (Table 4.13)

Indirect costs were defined as productivity loss for one caregiver for the duration of diarrhoeal illness. Productivity loss was calculated by multiplying average daily wage with the days of work missed to care for an ill child with rotavirus diarrhoea. Indirect costs of RM 213 was estimated for per-episode of rotavirus gastroenteritis irrespective of severity. (Table 4.13 and Table 5.1)

5.2.3.5 Vaccine coverage

Universal rotavirus vaccination if implemented is likely to be administered together with the routine DTP vaccines at two and three months for Rotarix® and at two, three and five months of age for RotaTeq® (World Health Organization, 2013d). Thus it was assumed that the rotavirus vaccine coverage would be the same as coverage of routine DTP vaccines in Malaysia. Rotavirus vaccine coverage was based on third dose DTP coverage of 97 per cent in Malaysia (World Health Organization, 2013b) (Table 5.1).

As the national immunisation programme in Malaysia is well established, no step-up in coverage was assumed for rotavirus vaccines (Jaafar et al., 2013).

5.2.3.6 Costs of the vaccination programme

Costs of the vaccination programme include vaccine procurement costs, additional administrative costs and vaccine wastage. Costs of the vaccination programme are detailed in the following subsections.

a) Vaccine procurement costs

The price at which vaccines are purchased for national immunisation programmes are not known in advance, and is likely to be substantially lower than current market prices. This is the result of competitive tendering process and price negotiations for bulk purchase of vaccines.

The Pan American Health Organization (PAHO) is a specialised public health agency that also serves as the Regional Office of the WHO, for the Americas region. The PAHO functions to enhance partnership to improve the health and quality of life in the 35 member countries in the Americas region (PAHO, 2015a).

The PAHO Revolving Fund is a regional cooperative mechanism for the bulk purchase of vaccines and related supplies for participating member states in the Americas region. Based on a central purchasing model, the fund handles vaccine procurement and pays for vaccines through a common fund, prior to being reimbursed by countries (DeRoeck et al., 2006). The PAHO Revolving Fund for vaccine procurement ensures the lowest negotiable vaccine prices through pooled procurement mechanisms, bulk purchasing and guaranteed supply [63] (E. A. S. Nelson et al., 2013).

The PAHO per-dose vaccine prices for 2013 of RM 20 for Rotarix® and RM 16 for RotaTeq®, were used as the most likely tender price for evaluation (PAHO, 2013). The 2013 Recommended Retail Price in Malaysia of RM 139 and RM 116 per-dose for Rotarix® and RotaTeq®, were used as most likely market price in the evaluation (Ministry of Health Malaysia, 2014a). (Table 5.1)

b) Additional administrative costs

Additional administrative costs are marginal programmatic costs, including costs for enhancing vaccine storage, cold chains, delivery, surveillance, training and advocacy (Edejer, 2003). In Malaysia, rotavirus vaccines are likely to be administered concurrently with other childhood vaccines. As such, costs for additional caregiver travel and productivity loss was assumed to be negligible.

To estimate additional administrative costs required for rotavirus vaccines in Malaysia, a recent review on cost-effectiveness studies that measured incremental non-vaccine costs was identified (De la Hoz-Restrepo et al., 2013). From this review, thirteen primary studies measuring additional administrative costs of rotavirus vaccination

[63] "Based on the principles of equity and solidarity, and thanks to economies of scale, all participating Member States have access to the same high-quality products, offered through the Revolving Fund at the lowest price, which is a single price independent of the country's size or economic situation."(PAHO, 2015b)

programmes, were identified. When the measured additional administrative costs were compared with the GNI per-capita of countries, additional administrative costs were found to be highly correlated with GNI per-capita (Pearson correlation coefficient of 0.79, p = 0.001). Additional administrative costs were found to have a linear relationship with GNI-per-capita. A high goodness of fit ($R^2 = 0.63$) validated the use of GNI per-capita for the prediction of additional administrative costs. Using a simple linear regression, the GNI per-capita of Malaysia was used to predict the additional administrative costs of RM 15.20 (US$ 4.83) for rotavirus vaccination. (Table 5.1)

Table 5.3 shows the thirteen cost-effectiveness studies identified that measured additional administrative costs for rotavirus vaccination programmes.

Table 5.3: Cost-effectiveness analysis studies with measured additional administrative costs

Country name	GNI per capita	Additional administrative costs per-dose	Reference
Kenya	$ 2,780	$ 1.75	(van Hoek et al., 2012)
Kenya	$ 2,780	$ 0.95	(Tate, Rheingans, et al., 2009)
United States of America	$ 53,750	$ 17.31	(Tucker et al., 1998)
United States of America	$ 53,750	$ 13.16	(Weycker, Sofrygin, Kemner, Pelton, & Oster, 2009)
Kyrgyzstan	$ 3,080	$ 0.73	(Flem et al., 2009)
Israel	$ 31,780	$ 4.08	(Chodick et al., 2009)
Gavi eligible countries	$ 1,580	$ 0.96	(Atherly et al., 2012)
Vietnam	$ 5,070	$ 1.58	(Kim, Goldie, & Salomon, 2009)
Australia	$ 42,450	$ 2.46	(Newall, Beutels, Macartney, Wood, & MacIntyre, 2007)
United Kingdom	$ 38,160	$ 14.07	(Jit & Edmunds, 2007)
United Kingdom	$ 38,160	$ 5.48	(Martin, Batty, Roberts, & Standaert, 2009)
Finland	$ 39,930	$ 4.49	(Takala, Koskenniemi, Joensuu, Mäkelä, & Vesikari, 1998)
Malawi	$ 750	$ 0.28	(Berry, Johns, Shih, Berry, & Walker, 2010)

Note:

GNI per capita is based on purchasing power parity (PPP), in current international dollars from the World Bank. GNI per-capita are in current international dollars based on the 2011 International Comparison Programme (ICP) Round;

Costs are inflated to 2013 US$ using GDP deflators from the World Bank.

Primary studies used in this analysis were sourced from a 2013 systematic review of incremental non-vaccine cost estimates included in cost-effectiveness analysis of rotavirus vaccines (De la Hoz-Restrepo et al., 2013)

GNI per-capita of Malaysia was used to predict the additional administrative costs of RM 15.20 (US$ 4.83) for rotavirus vaccination in Malaysia.

c) Vaccine wastage

Based on recommendations of the WHO-UNICEF comprehensive multi-year plan for immunization (cMYP), vaccine wastage of five per cent per-dose was included to the vaccine cost (World Health Organization, 2014b). (Table 5.1)

5.2.3.7 Vaccine efficacy

The WHO SAGE recommends that rotavirus vaccine efficacy could be extrapolated from countries within similar child mortality strata. The SAGE experts defined three mortality strata using countries' mortality rate for children under-five years divided into quartiles: high mortality (highest mortality quartile), intermediate mortality (next quartile) and low mortality (lowest two quartiles) (Strategic Advisory Group of Experts, 2009).

Malaysia had an under-five mortality rate of nine per 1,000 live births in 2013, and is categorised in the low mortality strata (World Health Organization, 2013a). In this thesis, vaccine efficacy was estimated for both Rotarix® and RotaTeq® in Malaysia, for both complete and incomplete regimes, for all episodes requiring inpatient and outpatient treatment, based on studies conducted in countries within the low mortality strata.

Based on the safety profile from pre-licensure trials (Phua et al., 2009; Ruiz-Palacios et al., 2006; Vesikari et al., 2009; Vesikari et al., 2006) and post-licensure studies (Buttery et al., 2011; Manish M. Patel et al., 2011; Shui et al., 2012), the risk of severe adverse events following immunisation was assumed to be minimal.

a) Rotarix®

A double-blinded, randomised, placebo-controlled trial conducted in six European countries assessed safety and efficacy of Rotarix® in preventing rotavirus gastroenteritis among infants in the first two years of life (Vesikari, Karvonen, et al., 2007). This study was chosen as it presented efficacy results for (1) complete and incomplete regimes of Rotarix® vaccine (two-dose and one-dose), (2) efficacy end-points against rotavirus episodes of any severity and severe rotavirus episodes, (3) and with a follow-up period of one year, all of which are relevant for this estimation of vaccine efficacy in Malaysia.

Although a rotavirus vaccine efficacy trial was conducted in high-income Asian countries, Singapore, Taiwan and Hong Kong, this study was not chosen for use in this thesis because efficacy results were only published for a two year follow-up period[64] (results for one year follow-up were not available) (Phua et al., 2009).

In the multi-centre European trial, follow-up for gastroenteritis episodes was from two weeks after the second vaccine dose through to two consecutive rotavirus seasons. Vaccine efficacy for two-doses of Rotarix® at the end of the first rotavirus season of 87.1 per cent (95 per cent CI: 79.6 to 92.1 per cent) against episodes of any severity, 91.8 per cent (95 per cent CI: 84.0 to 96.3 per cent) against episodes seeking medical attention, and 100.0 per cent (95 per cent CI: 81.8 to 100.0 per cent) against episodes requiring hospital admission (Vesikari, Karvonen, et al., 2007). These results were used for two-dose efficacy of Rotarix® (complete regime) against home-treated (87.1 per cent), outpatient (91.8 per cent) and inpatient treated (100.0 per cent) episodes in Malaysia, respectively. (Table 5.4)

This European trial found efficacy for one-dose of Rotarix® (partial regime) at the end of the first rotavirus season of 87.3 per cent (95 per cent CI: 80.3 to 92.0 per cent) against any rotavirus gastroenteritis episode and 96.0 per cent (95 per cent CI: 90.2 to 98.8 per cent) against severe episodes (Vesikari, Karvonen, et al., 2007). These results were used for one-dose efficacy of home-treated (87.3 per cent) and inpatient treated episodes (96.0 per cent) in Malaysia. (Table 5.4)

One-dose efficacy against rotavirus outpatient treated episodes of 88.1 per cent was estimated by multiplying the ratio of two-dose efficacy between rotavirus gastroenteritis

[64] For this economic evaluation of rotavirus vaccines in Malaysia, vaccine efficacy was estimated for complete and partial regimes of Rotarix® and RotaTeq®. Efficacy was estimated for one-dose (partial regime) and two-doses (complete regime) of Rotarix® at the end of the first rotavirus season (one year of follow-up), and also for one-dose and two-dose (partial regime), and three-dose (complete regime of RotaTeq®. Please see Table 5.4 for vaccine efficacy estimates. Efficacy results after the one-year follow-up period indicates waning efficacy, and was considered separately in the model.

episodes seeking medical attention and admissions (0.92), with the one-dose efficacy against rotavirus gastroenteritis admissions (96.0 per cent) (Vesikari, Karvonen, et al., 2007). (Table 5.1 and Table 5.4)

Table 5.4 shows the vaccine efficacy estimates for complete and partial regimes of Rotarix® and RotaTeq® vaccines, used in the base-case and worst case analysis.

Table 5.4: Estimates of vaccine efficacy used in the base-case and the worst-case scenario analysis

Base-case analysis	Vaccine efficacy					
	RotaTeq® [a]			Rotarix® [b]		
Doses	Home-treated	Outpatient	Inpatient	Home-treated	Outpatient	Inpatient
1	61.8%	66.4%	82.0%	87.3%	88.1%	96.0%
2	63.3%	68.0%	84.0%	87·1%	91·8%	100.0%
3	75.3%	81.0%	100.0%	-	-	-
Worst case analysis	**Vaccine efficacy**					
	RotaTeq®			**Rotarix®**		
Doses	**Home-treated**	**Outpatient**	**Inpatient**	**Home-treated**	**Outpatient**	**Inpatient**
1	61.5%	66.4%	82.0%	80.3%	82.8%	90.2%
2	40.5%	43.7%	54.0%	79·6%	84.0%0	81·8%
3	42.2%	49.6%	55.2%	-	-	-

[a] Source for estimation of efficacy for complete and partial regimes of RotaTeq® was a multicentre trial conducted in Japan and the REST trial (P. H. Dennehy et al., 2011; Iwata et al., 2013).

[b] Source for estimation of efficacy for complete and partial regimes of Rotarix® was a large, European multicentre trial (Vesikari, Karvonen, et al., 2007).

b) RotaTeq®

A recent multi-centre trial conducted in over 32 sites across Japan, assessed the safety and efficacy of RotaTeq® vaccines (Iwata et al., 2013). This study found RotaTeq® efficacy against rotavirus gastroenteritis due to any rotavirus regardless of serotype was 75.3 per cent (95 per cent CI: 42.2 per cent to 90.9 per cent) for episodes of any severity, and 81.0 per cent (95 per cent CI: 49.6 per cent to 94.3 per cent) for moderate-to-severe episodes, and 100.0 per cent (95 per cent CI: 55.2 per cent to 100.0 per cent) for severe rotavirus gastroenteritis, respectively (Iwata et al., 2013). These efficacy results were used as the three-dose (complete regime) RotaTeq® efficacy against home-treated (75.3 per cent), outpatient treated (81.0 per cent) and hospitalised (100.0 per cent) rotavirus gastroenteritis in Malaysia. (Table 5.4)

The Rotavirus Efficacy and Safety Trial (REST) was a large, multi-centre trial conducted to evaluate the safety and efficacy of RotaTeq® in 11 countries in Europe, Latin America and the Caribbean regions (Vesikari, Itzler, et al., 2007). A post-hoc analysis of the REST trial determined the between dose efficacy of RotaTeq® (vaccine efficacy before the completion of the three-dose regime), and provided the one-dose (82.0 per cent) and two-dose efficacy (84.0 per cent) for rotavirus gastroenteritis hospitalisations in Malaysia (P. H. Dennehy et al., 2011). (Table 5.4)

The multi-centre study from Japan provided distribution weights to estimate partial regime (one-dose and two-dose) efficacy against outpatient treated and home-treated rotavirus gastroenteritis (Iwata et al., 2013).

The ratio of three-dose efficacy between moderate-to-severe rotavirus gastroenteritis and severe rotavirus gastroenteritis of (0.81) (Iwata et al., 2013), was multiplied with two-dose efficacy against rotavirus hospitalisations (84.0 per cent) (P. H. Dennehy et al., 2011), to obtain two-dose efficacy against outpatient treated rotavirus episodes (68 per cent). The ratio of three-dose efficacy between moderate-to-severe rotavirus gastroenteritis and severe rotavirus gastroenteritis of (0.81) (Iwata et al., 2013) was multiplied with one-dose efficacy against rotavirus hospitalisations (82.0 per cent) (P. H. Dennehy et al., 2011), to obtain one-dose efficacy against outpatient treated rotavirus gastroenteritis (66.4 per cent). (Table 5.4)

The ratio of three-dose efficacy between rotavirus gastroenteritis of any severity and severe rotavirus gastroenteritis (0.75) (Iwata et al., 2013) was multiplied with two-dose efficacy against rotavirus hospitalisations (84.0 per cent) (P. H. Dennehy et al., 2011), to obtain two-dose vaccine efficacy against home-treated rotavirus gastroenteritis episodes (63.3 per cent). This ratio of three-dose efficacy between rotavirus gastroenteritis of any severity and severe rotavirus gastroenteritis (0.75) (Iwata et al., 2013) was multiplied with one-dose efficacy against rotavirus hospitalisations (82.0 per cent) (P. H. Dennehy et al., 2011), to obtain one-dose vaccine efficacy against home-treated rotavirus gastroenteritis episodes (61.8 per cent). (Table 5.1 and Table 5.4)

c) Waning efficacy

The rate of waning vaccine protection was determined from the difference in efficacy between the first and second rotavirus seasons post-vaccination. Evidence of waning efficacy is available for rotavirus gastroenteritis of any severity and those requiring admission and medical treatment for Rotarix® (Vesikari, Karvonen, et al., 2007) and for severe episodes and episodes of any severity for RotaTeq® (Vesikari et al., 2006). (Table 5.1)

5.2.4 Sensitivity analysis

Sensitivity analysis was performed to assess the robustness of the economic evaluation to the variation of key parameters. Input parameters were varied individually while others were fixed at base-case settings. As vaccination was found to be cost-saving[65] at base-case analysis, various pessimistic scenarios that would make the vaccination program less cost-effective were explored. The various worst-case scenarios explored are detailed here. (Table 5.2)

5.2.4.1 Incidence

Conservative estimates of rotavirus incidence was obtained using the same sources as the Chapter 4 estimation of rotavirus burden in Malaysia.

To obtain a conservative estimate of rotavirus hospitalisations in Malaysia, complete reporting of hospital discharges from all public and private facilities to the MOH, Malaysia was assumed. The unexpanded acute gastroenteritis discharges gave rise to annual estimates of 6.9 rotavirus hospitalisations per-1,000 children under-five years (See Table 4.2, page 62).[66]

Conservative estimates of rotavirus outpatient visits (6.8 per 1,000 children under-five years) were obtained by multiplying the proportion of children that sought care for diarrhoeal illness in the 1998 community-based rotavirus study (Yap et al., 1992), with the total population of children under-five years in Malaysia (3.8 per cent of all children under-five years in Malaysia sought care for acute diarrhoeal illness).

5.2.4.2 Costs

The conservative estimate of RM 1,162 and RM 72 per-episode for rotavirus gastroenteritis requiring hospitalisation and outpatient treatment was used in the worst

[65] These results of the cost-effectiveness analysis are presented in the results Subsection 5.3.1, page 164.

[66] Reported episodes of acute gastroenteritis hospitalisation (39,336 episodes) were multiplied with the rotavirus detection proportion of 44.5 per cent to obtain conservative estimate of 17,512 episodes of rotavirus gastroenteritis hospitalisations in Malaysia.

case scenario. These costs were estimated using the weighted average of unit costs by facility types from WHO-CHOICE. (See Table 4.7, page 85)

Unit costs by facility-type from WHO-CHOICE was multiplied with the proportion of distribution of facilities, and the sum product of this for all facilities was the conservative estimate of hospitalisation costs[67]. This figure was then inflated to 2013 RM and multiplied with duration of diarrhoeal illness (3.3 days) to obtain conservative costs per bed-day of RM 1,162.

Unit costs by facility-type from WHO-CHOICE and unit costs for tertiary hospitals in Malaysia was multiplied with the proportion of distribution of facilities, and the sum product of this for all facilities was the conservative estimate of outpatient costs[68]. This figure was then inflated to 2013 RM to obtain conservative costs per visit of RM 72.

5.2.4.3 Vaccine efficacy

The lower limit values of vaccine efficacy for Rotarix® and RotaTeq® from the sources used in the base-case efficacy estimation, were used to estimate efficacy in the worst-case scenario. Table 5.4 shows the efficacy for complete and partial regimes of Rotarix® and RotaTeq® vaccines, used in the worst case analysis.

Lower limit vaccine efficacy from the multicentre European trial was used for the conservative estimation Rotarix® vaccine efficacy (Vesikari, Karvonen, et al., 2007). Efficacy for two-doses of Rotarix® at the end of the first rotavirus season of 87.1 per cent (95 per cent CI: 79.6 to 92.1 per cent) against episodes of any severity, 91.8 per cent (95 per cent CI: 84.0 to 96.3 per cent) against episodes seeking medical attention, and 100.0 per cent (95 per cent CI: 81.8 to 100.0 per cent) against admissions. The lower limit of these efficacy results were used for conservative estimates of two-dose efficacy of

[67] Costs per bed day: $[(20\% \times \$86.6) + (30\% \times \$90.34) + (50\% \times \$116.81)] = \$102.83$

[68] Costs per outpatient visit:
$[(56\% \times \$7.63) + (44\% \times 20\% \times \$15.93) + (44\% \times 30\% \times \$22.46) + (44\% \times 50\% \times \$68.11) = \$23.62]$

Rotarix® (complete regime) against home-treated (79.6 per cent), outpatient (84.0 per cent) and inpatient treated (81.8 per cent) episodes in Malaysia, respectively.

The multi-centre trial conducted in Japan, provided conservative estimates of RotaTeq® vaccine efficacy (Iwata et al., 2013). This study found RotaTeq® efficacy against rotavirus gastroenteritis due to any rotavirus regardless of serotype was 75.3 per cent (95 per cent CI: 42.2 per cent to 90.9 per cent) for episodes of any severity and 81.0 per cent (95 per cent CI: 49.6 per cent to 94.3 per cent) for moderate-to-severe episodes and 100.0 per cent (95 per cent CI: 55.2 per cent to 100.0 per cent) for severe rotavirus gastroenteritis, respectively. The lower limits of these efficacy results were used as the three-dose (complete regime) RotaTeq® efficacy against home-treated (42.2 per cent), outpatient treated (49.6 per cent) and hospitalised (55.2 per cent) rotavirus gastroenteritis for the worst case scenario.

The same methods used in the base-case to estimate between-dose efficacy was used in this analysis. (See Subsection 5.2.3.7, page 131).

See Table 5.4 for vaccine efficacy estimates used in the worst case analysis.

5.2.4.4 Quality-adjusted life-years

In the base-case, QALY loss was assumed for one caregiver. In the sensitivity analysis, scenarios with no QALY loss and QALY loss for two caregivers was explored. In the base-case, home-treated episodes were assumed to have 50 per cent of the HRQoL detriments of those seeking medical care. This fraction of HRQoL detriments for home-treatment was varied between 50 per cent and 100 per cent during sensitivity analysis. (Table 5.2)

5.2.4.5 Discount rate

Sensitivity analysis was conducted at discount rates of zero per cent for costs and benefits (Hutubessy et al., 2011; World Health Organization, 2008), and the use of different discount rates for costs (4.5 per cent) and benefits (1.5 per cent), as used by the Netherlands was explored (College voor zorgverzekeringen, 2006). (Table 5.2)

5.2.5 Threshold analysis

Efficiency in a cost-effectiveness analysis is expressed by the ICER. The ICER is reported in terms of costs per unit of health gained, usually as QALYs gained. An intervention may be considered cost-effective if the ICER falls below a defined cost-effectiveness threshold.

A cost-effectiveness threshold is a reference measure that may be used explicitly or implicitly to inform resource allocation decisions (Eichler et al., 2004). Countries like the United Kingdom, Thailand, Australia and Canada have defined cost-effective thresholds for decision-making (ISPOR, 2015). Other countries like Malaysia, which have yet to formalise economic evaluations as part of resource allocation decisions for health technologies, do not have defined cost-effectiveness thresholds (Ministry of Health Malaysia, 2012e). WHO-CHOICE thresholds have been widely used as a measure of cost-effectiveness in low- and middle-income countries with no locally derived cost-effectiveness thresholds. As the use of WHO-CHOICE thresholds as a decision rule has many acknowledged shortfalls (Eichler et al., 2004; Newall et al., 2014), cost-effectiveness was explored in this thesis using different thresholds for Malaysia.

In this chapter, threshold analysis was conducted at cost-effectiveness thresholds derived using three different approaches: (1) the WHO-CHOICE thresholds (human capital); (2) the societal willingness to pay thresholds (consumer sovereignty) and (3) the marginal productivity thresholds (opportunity costs). The rationale behind these thresholds are described in the following subsections.

Threshold analysis was conducted to inform prices at which vaccination programmes are 'cost-effective' in Malaysia. Threshold prices are vaccine procurement prices below which vaccination programmes are cost-effective. At threshold prices, the net vaccination costs per-QALY gained (the ICER) are equal to the cost-effectiveness threshold.

5.2.5.1 WHO-CHOICE threshold

WHO-CHOICE thresholds were motivated by the human capital theory. Theodore Schultz first conceptualised the term 'human capital' in the 1960's. According to Schultz (1961), human capital could be invested to increase productivity. Investment in a person's stock of knowledge, skills and experience, with job training and education, would result in increased productivity in both the market sector of economy by increasing monetary earnings, and in the non-market sector by increasing utility (Becker, 1962). Michael Grossman (1972) modelled 'health capital' as a stock in human capital. The human capital approach values life according to a persons' contribution to society, commonly measured by GDP or GNI per capita[69].

The Commission for Macroeconomics and Health was the first to use a nation's GDP per capita[70] as a benchmark for cost-effectiveness. The Commission recognised health as a cornerstone of human capital development, the basis for individual productivity and a crucial element towards economic development. The value of human life was recognised as more than just average income and includes extra market value, such as utility produced during leisure time. Hence the value of an extra year of life was estimated at up to three times of annual earnings (World Health Organization, 2001, 2002b).

The WHO-CHOICE project advocated the use of GDP per capita as an indicator for cost-effectiveness. The WHO-CHOICE project broadly categorised interventions into three categories: those costing less than the GDP per capita are classified as 'very cost-effective', those between one and three times GDP per capita are 'cost-effective', and

[69] This implies the value of human life is equated to average income or productivity.
[70] GDP is the value of goods and services produced in a country in one year. GDP per capita is a measure of a countries economic output, calculated by dividing the GDP by the number of people in the country (the mid-year population). (World Bank, 2015a)

those above three time GDP per capita are ‘not cost effective’ (Edejer, 2003; World Health Organization, 2015c).

As Malaysia has no explicit threshold for cost-effectiveness (Ministry of Health Malaysia, 2012e), convention dictates the use of WHO-CHOICE thresholds as a reference for cost-effectiveness (Edejer, 2003; Walker et al., 2010). WHO-CHOICE thresholds have been widely used as a measure of cost-effectiveness in low- and middle-income countries with no locally derived cost-effectiveness thresholds. However, thresholds based on multiples of GDP per capita have major short-comings as a marker for policy making (Marseille et al., 2015; Newall et al., 2014).

WHO-CHOICE thresholds for cost-effectiveness analysis were formulated to aid regional priority setting and were not suggested for formulaic use for decision-making on national resource allocation (Edejer, 2003). Thresholds based on GDP per capita assume that governments are willing to pay up to the GDP of the country on health benefits, without any concrete evidence of societal willingness-to-pay (WTP)[71] (Marseille et al., 2015). The use of GDP based thresholds does not consider the affordability of the intervention within the context of finite budgets, and may lead to unsustainable healthcare costs (Marseille et al., 2015; Newall et al., 2014; Shillcutt et al., 2009; M. E. Singer, 2009).

The value of life as determined by the Commission of Macroeconomics and Health, of up to three times of average income was arbitrarily determined. These values were not based on empirical evidence, but rather on general assessment of economic literature (Newall et al., 2014).

In addition, the WHO-CHOICE thresholds sets a low bar for cost-effectiveness and are easily achieved. Many interventions with some effectiveness, are found to cost less than the annual GDP per capita, reducing the value of cost-effectiveness analysis in

[71] Hypothetically, if every person in the country receives an intervention that produces a QALY per person, and the net cost of the programme per person is the GDP per capita of the country, the nation will spend its entire GDP on the health gain.

informing on resource allocation decisions (Marseille et al., 2015). Hence, results of ‘cost-effective’ or even ‘very cost-effective’ in economic evaluations does not guarantee vaccine adoption by middle-income countries. A recent review of cost-effectiveness analysis results and subsequent implementation of universal vaccination programmes suggests that budget constraints, rather than cost-effectiveness based on arbitrarily defined thresholds, were more likely to influence decision-making (Newall et al., 2014).

In this thesis, the WHO-CHOICE thresholds were explored to obtain ‘cost-effective’ and ‘very cost-effective’ vaccine prices. The WHO-CHOICE thresholds provided prices for comparison with the ‘cost-effective’ prices obtained from the Societal WTP and Marginal productivity thresholds. Vaccine prices were ‘cost-effective’ when net costs per-QALY gained were between one and three times the 2013 GDP per capita of Malaysia of RM 33,204 (US$ 10,538) and ‘very cost-effective’ when below the 2013 GDP per capita. (World Bank, 2014a)

5.2.5.2 Societal willingness to pay threshold

Societal WTP thresholds are based on the principles of consumer sovereignty. Consumer sovereignty is an economic argument asserting that ultimately consumers’ preferences determine the allocation of scarce resources and the production of goods and services. This is the basis of the expected utility theory, which emphasises the ability and freedom of consumers to choose from a range of goods and services (McGuire et al., 1988, pp. 30-33).

Societal WTP thresholds are based on preferences of individuals within a society for specific health outcomes. Preference elicitations methods, either revealed or stated, are used to assign a monetary value to a QALY gained (Ryen & Svensson, 2014). Revealed preference measures examines real world healthcare allocation decisions for societal value of health gain. Stated preference measures assess individual WTP, either by contingent valuation methods or discrete choice experiments, according to hypothetical choices people make in relation to incremental risk of death or disease.

In contingent valuation methods, respondents are given hypothetical scenarios and are asked to state the price they are WTP to obtain a specific health benefit (Diener, O'Brien, & Gafni, 1998; Ryan et al., 2001). In discrete choice experiments, respondents are asked to choose between alternative hypothetical scenarios that differ in terms of price and health benefits (Ryen & Svensson, 2014).

Societal WTP thresholds are based on preferences of individuals within a society for specific health outcomes. However, the assumption that individual WTP reflects on societal preferences may not hold true. The individual is likely to evaluate personally experienced health benefits, like life extension, more highly compared to social benefits or externalities derived from public goods, like vaccination (Shiroiwa et al., 2010; R. D. Smith & Richardson, 2005). Individual preferences vary according to the characteristics of those studied, for example age, wealth, education, employment, and current health status. To reduce bias, the population surveyed should be sufficiently large, randomly sampled and representative of the national population (Cookson, 2003; R. D. Smith & Richardson, 2005).

Large variation in results of WTP may also be due to differing methods (discrete choice experiments or contingent valuation methods) and methodology used in evaluating QALYs, including study locations, perspective taken (social or individual), and sample population (general population or patient groups) (Mason, Baker, & Donaldson, 2008; Ryen & Svensson, 2014).

QALYs are a composite measure that includes both the length and quality of life. WTP per-QALY estimates obtained from HRQoL improvements may not be appropriate when evaluating policy affecting length of life and vice versa. A 2014 study found that the WTP for a QALY was significantly higher when the QALY gain came from life extension, rather than quality of life improvements. It was also found that the WTP for a QALY was dependent on the size of the QALY gain valued (Ryen & Svensson, 2014)

In this thesis, empirical findings from a local cross-sectional study, which employed contingent valuation methods, was used to derive a societal WTP threshold for Malaysia (Shafie, Lim, Chua, & Hassali, 2014). This cross-sectional study was conducted in Penang, Malaysia in 2010. Study participants were selected from geographical grids in Penang, by a random walking technique. Data was collected using predesigned questionnaires in face-to-face interviews of 347 respondents. Data on qualities of life, was collected using the EuroQol Visual Analog Scale (EQ-VAS), and the WTP for an additional QALY was elicited using a double-bound dichotomous choice via a bidding game approach.

This cross-sectional study determined an average societal WTP of RM 30,918 per-QALY gained in the state of Penang, Malaysia (Shafie et al., 2014). This WTP threshold was 0.81 times of the 2013 per-capita GDP of the state of Penang (RM 38,356) (Department of Statistics Malaysia, 2013b). By multiplying this fraction with the 2013 GDP per-capita for Malaysia of RM 33,284 (World Bank, 2014a), a societal WTP threshold of RM 26,766 (US $8,495) per-QALY gained was estimated in Malaysia, for threshold analysis in this thesis.[72]

5.2.5.3 Marginal productivity threshold

The concept of opportunity costs are fundamental to health economics. The opportunity cost of investing in a healthcare intervention is best measured by the health benefits that would have been achieved had the money been spent on the next best alternative (Palmer & Raftery, 1999; L. B. Russell, 1992). In economic evaluation of healthcare interventions, cost-effectiveness thresholds should ideally reflect opportunity costs of foregone benefits of next best alternative not implemented, in other words the

[72] This was done to adjust for individual variation of average wealth at the national level.

marginal productivity of health systems in generating health (Revill et al., 2014; Woods, Revill, Sculpher, & Claxton, 2015).

Local empirical data on marginal productivity would give insight into resource allocation decisions that maximise population health, however this data is lacking (Revill et al., 2014; Woods et al., 2015). The exception being a study by Claxton et al. which used data from the National Health Services (NHS) in the United Kingdom, to study the relationship between health expenditure for a range health programmes with changes in mortality[73]. This study of the marginal productivity of healthcare investments estimated a threshold of £12,936 (US$ 20,212) per-QALY for the NICE in the United Kingdom (Claxton et al., 2015).

In the absence of local empirical data, researchers at the University of York estimated cost-effectiveness thresholds for various countries by using estimates of benefits foregone from the NHS in the United Kingdom, the GDP per capita of the United Kingdom and other respective countries and the income elasticities of the Value of Statistical Life[74] (VSL).

The York study estimated marginal productivity thresholds for Malaysia ranging from RM 10,968 to RM 19,510 (Woods et al., 2015). These estimates were used in this thesis for threshold analysis

5.2.6 Budget impact analysis

While cost-effectiveness analysis examines the value for money of a vaccination programme, a budget impact analysis examines its affordability. The budget impact analysis is conducted to inform the budget holder on the ability to remain within the

[73] Using programme-level expenditure data from the NHS to study the relationship between expenditure for healthcare programmes and mortality.

[74] The Value of a Statistical Life (VSL) is an economic term, denoting the amount of money an individual (or society) is willing to pay to save a life (trade-off between mortality risks and money) (Viscusi & Aldy, 2003). Mortality risk reductions are important to quantify benefits of environmental and other policies. Estimates of VSL are transferred across countries with different income levels, by using income elasticity of the VSL (Hammitt & Robinson, 2011).

annual budget. Budget impact analysis is complementary to cost-effectiveness analysis, as it provides additional information for the allocation of scarce healthcare resources.

The costs in a budget impact analysis are financial costs to the budget holder. In a budget impact analysis, costs of interest are the costs incurred by the budget holder, or direct medical costs from the healthcare providers' perspective. In contrast, a cost-effectiveness analysis may consider all relevant economic costs from the societal perspective, including both direct and indirect costs. Reduction in productivity loss are of interest to society, but are of little consequence to healthcare budget holders, as productivity loss to caregivers and employers are not directly passed on to the healthcare service.

In a budget impact analysis, the time horizon considered is much shorter than that of a cost-effectiveness analysis. In a cost-effectiveness analysis the time horizon considered is usually long term, to take into account all possible costs and benefits. However, the time horizon in a financial budget is seldom longer than one to three years. This is because healthcare services cannot operate by overspending in the short term in anticipation of future benefits. In absence of additional funding to pay for new healthcare investments, existing programmes may need to be disinvested or reprioritised (Garattini & van de Vooren, 2011; Trueman et al., 2001).

In this thesis, a budget impact analysis was conducted to estimate the financial consequences of adoption of the rotavirus vaccine by the Ministry of Health, Malaysia. The inputs used in the budget impact analysis are the same used in the cost-effectiveness analysis. However, the budget impact analysis was conducted from the healthcare provider's perspective and within a time frame of one year.

There is no explicit threshold or margin to inform on affordability of a healthcare programme in Malaysia. As such, affordability is a consensus arrived at by comparing programmatic costs with the public health budget of Malaysia[75]. The Malaysian public health expenditure for the year 2012 was obtained from the Annual Report of the MOH, Malaysia. In 2012, a total of RM 15.2 billion was allocated to the operational budget of the MOH, Malaysia. The total operating expenditure of the MOH, Malaysia in 2012 was RM 16.8 billion (a 10.9 per cent increase from the allocated budget), out of which RM 3.4 billion was public health expenditure (Ministry of Health Malaysia, 2012a).

[75] The budget for a new vaccination programme would initially come from public health budget of the MOH, Malaysia.

5.3 Results

5.3.1 Base-case analysis

In a cohort of children followed from birth to five years of age, rotavirus gastroenteritis was estimated to result in 205,500 nonfatal episodes, 29,400 hospitalisations and 26 deaths or 1,293 QALY lost in Malaysia. Rotavirus gastroenteritis was estimated to cost RM 35.9 million to the healthcare provider and RM 46 million to society, annually. (Table 5.5)

At base-case assumptions, Rotarix® would prevent 138,700 nonfatal episodes (68 per cent), 24,600 hospitalisations (84 per cent), 21 deaths (84 per cent), and avert 1,003 of QALYs lost (78 per cent) from rotavirus gastroenteritis, annually. Rotarix® would avert RM 82.4 million (83 per cent) and RM 115.0 million (78 per cent) in costs to the healthcare provider and society, respectively. (Table 5.5)

At base-case assumptions, RotaTeq® would prevent 125,600 nonfatal episodes (61 per cent), 23,700 hospitalisations (81 per cent), 21 deaths (81 per cent), and avert 949 of QALYs lost (73 per cent) from rotavirus gastroenteritis, annually. RotaTeq® would avert RM 79.3 million (79 per cent) and RM 108.9 million (74 per cent) of costs to the healthcare provider and society, respectively. (Table 5.5)

At the PAHO prices of RM 20 per-dose of Rotarix®, the vaccination programme would cost RM 36.0 million and result in net savings of RM 46.4 million in direct medical costs. The ICER is cost saving from the healthcare provider's perspective, at RM – 46,288 per-QALY gained. From the societal perspective, the ICER is cost saving at RM -78,788 per-QALY gained (Table 5.5).

At PAHO prices of RM 16 per-dose of RotaTeq®, the vaccination programme would cost RM 15 million and result in net savings of RM 32.0 million in direct medical costs. The ICER is cost saving from the healthcare provider's perspective, at RM -33,731 per-

QALY gained. From the societal perspective, the ICER is cost-saving at RM -64,927 per-QALY gained (Table 5.5).

At market prices of RM 122 per-dose of Rotarix®, the ICER was RM 75,192 per-QALY gained from the healthcare provider's perspective, and RM 42,692 per-QALY gained from the societal perspective. (Table 5.6)

At market prices of RM 74 per-dose of RotaTeq®, the ICER was RM 127,343 per-QALY gained from the healthcare provider's perspective, and RM 96,146 per-QALY gained from the societal perspective. (Table 5.6)

At PAHO prices, both rotavirus vaccines were cost saving, from the healthcare provider's and societal perspectives, using all cost-effectiveness definitions[76]. (Table 5.6)

At market prices using the WHO-CHOICE cost-effectiveness thresholds, Rotarix® programmes were cost-effective, but RotaTeq® programmes were not cost-effective from the healthcare provider's perspective. Both vaccination programmes were cost-effective from the societal perspective. (Table 5.6)

Using the Societal WTP and Marginal productivity thresholds, both vaccines were not cost-effective at market prices, from the healthcare provider's and societal perspectives. (Table 5.6)

Table 5.5 shows the outcomes of vaccination with Rotarix® and RotaTeq® under base-case assumptions, from the healthcare provider's and societal perspectives.

Table 5.6 shows the discounted ICERs of Rotarix® and RotaTeq® vaccination programmes at PAHO and market prices.

[76]At WHO-CHOICE thresholds, vaccines are 'cost-effective' when the ICER is between one and three times the 2013 GDP per capita of Malaysia of US$ 10,538, and 'very cost-effective' when below the 2013 GDP per capita.
The societal WTP threshold for Malaysia is estimated at US $8,495 per-QALY gained.
The Marginal Productivity threshold is estimated from between US$ 3,481 to US$ 6,192 per-QALY gained.

Table 5.5: Outcomes of rotavirus vaccination compared with no vaccination under base-case assumptions

	No Vaccine	Rotarix®		RotaTeq®	
Rotavirus episodes					
Inpatient episodes	29,429	4,798	(24,631)	5,652	(23,777)
Non-fatal episodes	205,497	66,722	(138,775)	79,864	(125,633)
Deaths	26	4	(21)	5	(21)
QALYs lost					
Nonfatal QALYs	553	170	(383)	203	(350)
Life years lost from death	740	120	(620)	141	(599)
Total QALYs lost	1,293	290	(1003)	344	(949)
Healthcare provider costs					
Vaccine costs	0	35,984,615	(-35,984,615)	47,282,93	(-47,282,93)
Inpatient episodes	92,993,467	15,161,423	(77,832,043)	17,858,879	(75,134,588)
Outpatient episodes	6,777,322	2,183,045	(4,594,277)	2,629,349	(4,147,973)
Total healthcare costs	99,770,788	17,344,468	(82,426,320)	20,488,227	(79,282,561)
Total costs	99,770,788	53,329,083	(46,441,705)	67,771,162	(31,999,627)
Costs per QALY gained			- 46,288		-33,731

Table 5.5: Outcomes of rotavirus vaccination compared with no vaccination under base-case assumptions (continued)

	No Vaccine	Rotarix®		RotaTeq®	
Societal costs					
Inpatient episodes	101,085,173	16,480,675	(84,604,498)	19,412,846	(81,672,327)
Outpatient episodes	15,991,489	5,151,022	(10,840,467)	6,204,103	(9,787,386)
Home treated episodes	30,613,253	11,024,518	(19,588,735)	13,195,294	(17,417,959)
Total societal costs	147,689,914	32,656,215	(115,033,699)	38,812,242	(108,877,672)
Total costs	147,689,914	68,640,830	(79,049,084)	86,095,177	(61,594,738)
Costs per QALY gained			-78,788		-64,927

Note:

All costs are in 2013 RM;

Difference in outcomes between ‘vaccine’ and ‘no vaccine’ groups are given in the parenthesis (episodes, QALYs and costs prevented by vaccination);

An annual discount rate of three per cent is used for costs and benefits;

Pan American Health Organization (PAHO) Revolving Fund vaccine price for 2013 of RM 20 per-dose for Rotarix® and RM 16 per-dose for RotaTeq® were used (PAHO, 2013); The World Bank exchange rate for 2013 of US$ 1 to RM 3.15 was used in this analysis (World Bank, 2014a).

Costs and incremental cost effectiveness ratios (ICERs) are presented from the healthcare provider and societal perspectives; ICERs are expressed as costs per QALY gained.

Table 5.6: Incremental cost-effectiveness ratios of Rotarix® and RotaTeq® vaccination programmes at PAHO and market price

	PAHO price [a]	Market price [b]
	Cost per-QALY gained	**Cost per-QALY gained**
Healthcare provider's perspective		
Rotarix®	-46,288	75,192
RotaTeq®	-33,731	127,343
Societal perspective		
Rotarix®	-78,788	42,692
RotaTeq®	-64,927	96,146

Note:

Costs are in 2013 RM; QALY, Quality-adjusted life-years; Annual discount rate of three per cent for costs and benefits;

[a] PAHO prices are the Pan American Health Organization (PAHO) Revolving Fund per-dose price for 2013 (PAHO, 2013);

[b] Market price are based on the Recommended Retail Price per-dose of rotavirus vaccines for Malaysia in 2012 (Ministry of Health Malaysia, 2014a);

At WHO-CHOICE thresholds, vaccines are 'cost-effective' when the ICER is between one and three times the 2013 GDP per capita of Malaysia of RM 33,200, and 'very cost-effective' when below the 2013 GDP per capita;

The societal WTP threshold for Malaysia is estimated at RM 26,766 per-QALY gained;

The Marginal Productivity threshold is estimated from between RM 10,968 to RM 19,510 per-QALY gained.

5.3.2 Sensitivity analysis

During the sensitivity analysis, parameters were varied individually to observe changes in the cost per-QALY gained from vaccination, while other parameters were kept constant at base-case assumptions. Parameters that resulted in the most change in the cost per-QALY gained from vaccination were direct medical costs, incidence of rotavirus gastroenteritis requiring hospitalisation and vaccine efficacy. (Figure 5.1)

However, Table 5.6 shows that cost per-QALY gain was highly sensitive to vaccine price. This was apparent as both vaccines were cost-saving at PAHO prices at all cost-effectiveness thresholds, while both vaccines were not cost-effective at market prices, using the Societal WTP and Marginal productivity thresholds. (Table 5.6)

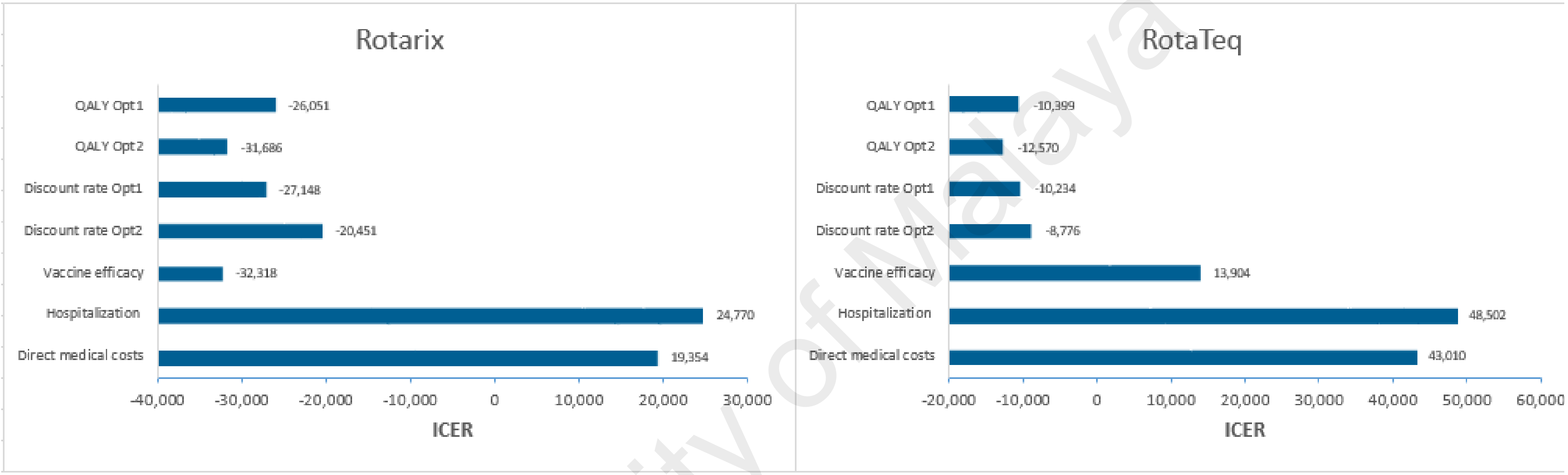


Figure 5.1: Tornado graph showing sensitivity analysis and effects on incremental cost-effectiveness ratio

Note:

QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio. ICERs are in RM per QALY gained.

The tornado graph shows the parameters that result in the most changes in the costs per QALY gained by vaccination from (a) Rotarix® and (b) RotaTeq, when they are varied individually and all other parameters are kept constant. Parameters resulting in small changes in cost per-QALY gained (less than ten per cent change) are not shown;

QALY Opt1: QALYs considered for one caregiver. Home-treated episodes are 100 per cent HRQoL weights of those seeking medical treatment;
QALY Opt2: QALYs considered for two caregivers. Home-treated episodes are 50 per cent HRQoL weights of those seeking medical treatment;
Discount rate Opt1: Costs are discounted at 4 per cent and benefits at 1.5 per cent;
Discount rate Opt2: Costs and benefits are discounted at zero per cent;

Please see Subsection 5.2.4, page 137, for description of the scenarios in the sensitivity analysis.

5.3.3 Threshold analysis

Using the WHO-CHOICE threshold, Rotarix® would be ‘cost-effective’ below RM 163 per-dose and ‘very cost-effective’ below RM 98 per-dose. At the Societal WTP threshold, Rotarix® would be ‘cost-effective’ below RM 92 per-dose. At the Marginal Productivity threshold, Rotarix® would be cost-effective between RM 76 and RM 85 per-dose. (Table 5.7)

Using the WHO-CHOICE threshold, RotaTeq® would be ‘cost-effective’ below RM 98 per-dose and ‘very cost-effective’ below RM 57 per-dose. At the Societal WTP threshold, RotaTeq® would be ‘cost-effective’ below RM 53 per-dose. Using the Marginal Productivity threshold, RotaTeq® would be cost-effective when priced between RM 44 and RM 49 per-dose. (Table 5.7)

‘Cost-effective’ programmes as defined using the WHO-CHOICE threshold are between three and five per cent of the 2012 public health budget and between 0.6 and one per cent of the operational budget of the MOH, Malaysia. Rotarix® vaccination programmes costing between RM 116 to RM 182 million, and RotaTeq® programmes costing between RM 111 to RM 174 million, annually. (Table 5.7)

While, at ‘cost-effective’ prices as defined by the Societal WTP and Marginal Productivity threshold, both vaccination programmes would cost about three per cent of the 2012 public health budget, and less than 0.65 per cent of the 2012 operating budget of the MOH, Malaysia. (Table 5.7)

A Rotarix® vaccination programme would cost about RM 183 million at ‘cost-effective’ prices as defined by the Societal WTP Threshold, and between RM 153 to 169 million at ‘cost-effective’ prices defined by the Marginal Productivity threshold. (Table 5.7)

A RotaTeq® vaccination programme would cost about RM 160 million at 'cost-effective' prices as defined by the Societal WTP Threshold, and between RM 131 to 147 million, at prices defined by the Marginal Productivity threshold. (Table 5.7)

5.3.4 Budget impact analysis

At PAHO prices of RM 20 per-dose, a Rotarix® vaccination programme would cost RM 36 million or about 1.1 per cent of the 2012 public health budget of the MOH, Malaysia, and about 0.2 per cent of the 2012 operating budget of the MOH, Malaysia. While at PAHO prices of RM 16 per-dose, a RotaTeq® vaccination programme would cost RM 47.3 million, or about 1.4 per cent of the 2012 public health budget and 0.3 per cent of the operating budget of the MOH, Malaysia. (Table 5.7)

At market prices of RM 139 and RM 116 per-dose, vaccination programmes with Rotarix® and RotaTeq® would cost RM 158 million and RM 200 million annually, or from between five to six per cent of the 2012 public health budget and approximately one per cent of the 2012 operating budget of the MOH, Malaysia. (Table 5.7)

Table 5.7 shows the results of the threshold analysis and budget impact analysis of both Rotarix® and RotaTeq® in Malaysia.

Table 5.7: Threshold analysis and budget impact analysis of rotavirus vaccines in Malaysia

	Price per dose (RM)	Price per course [a] (RM)	Total vaccine cost [b] (RM million)	% Public health budget [c]	% MOH budget [d]
Rotarix					
Base-case price	20	41	36	1.1%	0.2%
Market price	139	278	157	4.6%	0.9%
Threshold price:					
WHO-CHOICE [e]	98 to 163	196 to 326	116 to 182	3.4 to 5.3%	0.7 to 1.1%
Societal WTP [f]	92	183	109	3.2%	0.7%
Marginal Productivity [g]	76 to 85	153 to 169	93 to 102	2.7 to 2.9%	0.6 to 0.6%
RotaTeq					
Base-case price	16	49	47	1.4%	0.3%
Market price	116	347	200	5.9%	1.2%
Threshold price:					
WHO-CHOICE [e]	57 to 98	173 to 295	111 to 174	3.2 to 5.1%	0.7 to 1.0%
Societal WTP [f]	53	160	105	3.1%	0.6%
Marginal Productivity [g]	44 to 49	131 to 147	90 to 98	2.6 to 2.9%	0.5 to 0.6%

Note: All costs are in 2013 RM;

[a] Vaccine price per course was calculated for Rotarix® (two-dose course)and RotaTeq® (three-dose course);

[b] Vaccine costs were not discounted. Vaccine costs include cost of vaccine purchase, wastage and additional administrative costs.
(Total vaccine cost = cohort size × vaccine coverage × vaccine cost per dose)

[c, d] Public Health, and the MOH operational budget was sourced from the MOH, Malaysia operational expenditure for 2012 (Ministry of Health Malaysia, 2012a);

[e] At WHO-CHOICE thresholds, vaccines are 'cost-effective' when the incremental cost-effectiveness ratio (ICER) is between one and three times the 2013 GDP per capita of Malaysia of RM 33,200 and 'very cost-effective' when below the 2013 GDP per capita;

[f] The societal WTP threshold for Malaysia was estimated at RM 26,766 per-QALY gained;

[g] The Marginal Productivity threshold was estimated from between RM 10,968 to RM 19,510 per-QALY gained.

5.4 Discussion

In a cohort followed from birth to the age of five years in Malaysia, rotavirus gastroenteritis is estimated to result in 205,500 non-fatal episodes, 29,400 hospitalisations, and 26 deaths, with costs of RM 99.7 million to the healthcare provider and RM 147.7 million to society. Rotavirus vaccination would avert up to 67 per cent of non-fatal episodes and 84 per cent rotavirus hospitalisations. Although rotavirus mortality is comparatively low in Malaysia, preventable child deaths are unacceptable. This study demonstrates that rotavirus vaccines would effectively prevent approximately twenty deaths a year, among children under-five years in Malaysia. Rotavirus vaccination would result in annual savings of up to RM 82 million to the healthcare provider and RM 115 million to society. (Table 5.5)

At PAHO prices, both vaccines are cost-saving. However, interpretation of cost-effectiveness at market prices differ with thresholds used. When using the WHO-CHOICE thresholds, at market prices Rotarix® programmes are cost-effective and RotaTeq® programmes are not cost-effective from the healthcare provider's perspective; while both vaccines are cost-effective from the societal perspective. Using other cost-effectiveness thresholds (Societal WTP and Marginal productivity thresholds), both vaccines are not cost-effective at market prices, from both the healthcare provider and societal perspectives.

While the WHO-CHOICE thresholds are widely used in economic evaluations, these thresholds are easily achieved, negating its usefulness as a decision rule for national resource allocation. WHO-CHOICE thresholds were suggested for regional resource allocation and not for national decision-making. Achieving cost-effectiveness with WHO-CHOICE thresholds does not ensure affordability, which is crucial for adoption of a vaccination programme decisions (Marseille et al., 2015; Newall et al., 2014; Shillcutt et al., 2009). As such, threshold analysis was conducted in this thesis at various cost-effectiveness thresholds suggested for Malaysia.

The Societal WTP threshold for Malaysia used for this thesis, was based on an empirically measured individual WTP in a Malaysian population. The Societal WTP estimated was 0.81 times of the 2013 per-capita GDP of Malaysia (Shafie et al., 2014). These findings were within the range of that estimated by another recent cross-sectional, contingent valuation study conducted in the states of Penang, Kedah, Selangor, and Kuala Lumpur, using a stratified multistage cluster random sampling technique. This study determined an average WTP per-QALY gained of 0.59 to 0.84 times of GDP per-capita in Malaysia (Y. W. Lim, Shafie, Chua, & Hassali, 2014)[77]. Thailand, a neighbouring middle-income country uses a locally established threshold of 160,000 Baht or 0.9 times the annual GDP per-capita of Thailand (Teerawattananon, Tritasavit, Suchonwanich, & Kingkaew, 2014).

This cross-sectional study conducted in the state of Penang, is the first to empirically measure individual WTP for an additional QALY in Malaysia. However, this study had several limitations. In the absence of a population-based sampling frame, convenient sampling was performed in this study. Also, this study was conducted in the island state of Penang, with a wealthier population and a different ethnic distribution compared to the rest of Malaysia, thus may not be representative of the population distribution of the country (Shafie et al., 2014).

In this thesis, individual WTP from the Penang study was used to estimate societal WTP for Malaysia, by adjusting for differences in average wealth by using GDP per-capita. This preference based threshold is much lower than that of the WHO-CHOICE threshold and may be useful to inform policy. However, to make a meaningful contribution, there is need for a nation-wide, representative survey with appropriate

[77] This 2014 study was not used in this thesis, as it was still unpublished at the time of this writing. The study results were presented in a poster. http://www.ispor.org/ScientificPresentationsDatabase/Presentation/51577

methodology (random sampling and adequate sample size), to properly evaluate societal WTP in Malaysia. This is an area for future research.

However, individual valuation of health relates to personal income and not the healthcare budget. Thresholds based on consumer sovereignty approach (Societal WTP threshold), have limited usefulness in conditions of budgetary constraints, as interventions deemed cost-effective using these thresholds may prove to be unaffordable (Revill et al., 2014).

Health systems aim to allocate scarce healthcare resources in order to best maximise health gains for the population[78]. Cost-effectiveness analysis compare the costs and benefits of alternative healthcare interventions in aid of decision making. For results of cost-effectiveness analysis to align with aims of population health maximisation, cost-effectiveness thresholds should reflect the opportunity costs of health benefits foregone (Revill et al., 2014).

Researchers at the University of York estimated cost-effectiveness thresholds for various countries based on estimates marginal productivity from the NHS, combined with GDP per capita of the United Kingdom and other countries, with income elasticities of the value of statistical life. These thresholds were a first attempt to inform policy on resource allocation with the aim of population health maximisation (Woods et al., 2015).

The thresholds suggested by the University of York rely on the assumptions that the differences in the consumption value of health (individual and societal WTP) and marginal productivity of a health system in generating health, are constant across countries. Also, the NHS, in the United Kingdom was assumed to be typical of all health systems, in terms of efficiency of health production. These assumptions may lead to over- or under-estimation of thresholds, and these biases can only be over-come by examining country-level empirical estimates of marginal productivity.

[78] Utilitarian principles of efficiency. See Subsection 3.2.2, page 44.

The cost-effectiveness thresholds resulting from the York analysis are substantially lower than thresholds previously applied in many countries, especially the WHO-CHOICE thresholds of one to three times of GDP per capita. The upper bounds of these thresholds indicate values of 51 per cent of GDP per-capita for low-income countries and 71 per cent GDP per-capita for middle-income countries (Woods et al., 2015). The upper bounds of marginal productivity thresholds for Malaysia are 60 per cent of the GDP per capita of Malaysia. This is even lower than the Societal WTP threshold estimates (80 per cent of the GDP per capita of Malaysia).

Cost-effectiveness thresholds based on the human capital approach have little relevance to either societal WTP for interventions or healthcare budgets. While thresholds based consumer sovereignty are often aspirational, informing decisions based on what individuals in a society feel is appropriate to pay for health, (Woods et al., 2015) without consideration of budgetary constraints. When healthcare budgets are limited, policy-makers aim to maximise population health while remaining within budgets. Without the reference to affordability, cost-effectiveness analysis have little relevance in informing resource allocation.

The Marginal Productivity threshold is recommended for use in this thesis as a reference for cost-effectiveness. These thresholds suggested by researchers at York University were estimated based on empirical estimates of foregone benefits, from the English NHS and using international income elasticities of the value of health. These thresholds were determined in accordance to the health systems goal of population health maximisation within budgetary constraint, and reflects opportunity costs. While these figures are far from definitive, they are useful in this thesis to inform 'cost-effective' prices for rotavirus vaccines. These thresholds are a starting point for research on cost-effectiveness thresholds for Malaysia that reflect opportunity costs.

The thresholds suggested for Malaysia are 60 per cent of GDP per capita for Malaysia, and much lower than the WHO-CHOICE thresholds. Cost-effective vaccine prices are between RM 76 to RM 85 per-dose for Rotarix® (RM 153 to RM 169 per-course) and between RM 44 to RM 49 per-dose for RotaTeq® (RM 131 to RM 147 per-course). Vaccination programmes would cost between RM 93 and RM 102 million for Rotarix®, and between RM 90 and RM 98 million for RotaTeq®. Vaccination programmes cost approximately three per cent of the MOH public health budget and 0.6 per cent of the MOH operating budget for 2012.

Although tender prices are not known in advance, prices for vaccines in national immunisation programmes are often substantially lower than market prices. Policy-makers often require cost-effectiveness analysis to be conducted at market prices, at which rotavirus vaccination programmes are seldom cost-effective or affordable. High vaccine prices are a perceived financial barrier for inclusion of rotavirus vaccines in middle-income countries (E. A. S. Nelson et al., 2013).

While rotavirus vaccine prices are in the public domain for the PAHO Revolving Fund (RM 41 to 49 per course) and Gavi, the Vaccine Alliance (RM 15 per course), prices negotiated by individual governments are not available internationally. Tiered pricing mechanisms and price opacity of vaccines hinders the efforts of individual governments and aid organisations to effectively negotiate vaccine prices. Pricing opacity or the lack of transparency in vaccine pricing, allows pharmaceutical companies to implement unregulated differential pricing between countries[79] (Medecins Sans Frontieres, 2015; E. A. S. Nelson et al., 2013; Rappuoli, 2015). For these reasons, cost-effective prices determined in this thesis are of practical value to aid future price negotiations for rotavirus vaccines by the MOH, Malaysia.

[79] An example of this is the higher rotavirus vaccine pricing at Morocco and Tunisia, both non-Gavi eligible middle-income countries, compared to rotavirus vaccine prices in France, a high-income country (Rappuoli, 2015).

In low- and middle-income countries worldwide, rotavirus vaccines have been found to be cost-effective at low vaccine prices. A cost-effectiveness analysis of rotavirus vaccination in 72 GAVI-eligible countries found the cost per DALY averted was RM 42 for all GAVI-eligible countries combined. Rotavirus vaccination would be considered 'very cost-effective' according to the WHO-CHOICE threshold, for all GAVI countries as a group and in each country individually, as ICERs were less than the GDP per capita (Atherly et al., 2012).

A 2010 systematic review of economic evaluations of rotavirus vaccines in developing countries, concluded that although rotavirus vaccines were cost-effective interventions in developing countries, vaccine prices was the dominant parameter influencing cost-effectiveness. Lack of affordability was the main barrier for rotavirus vaccine introduction (Tu et al., 2011).

An estimation of cost-effectiveness of rotavirus vaccines in developing countries at different vaccine prices ranges, found that rotavirus vaccines were cost-effective in middle-income countries when prices are low. (R. D. Rheingans et al., 2009)

As there is no threshold in Malaysia to determine affordability of a vaccination programme, programme affordability can only be definitively determined by the budget holder. In this thesis, the results of a budget impact analysis (comparing programme costs with budgets) provide additional information to decision makers to gauge programme affordability.

In 2012, the total operating budget of the MOH, Malaysia was RM 16.8 billion, with RM 3.4 billion spent on public health (Ministry of Health Malaysia, 2012a). At PAHO prices, rotavirus vaccination programmes are about one per cent of the 2012 public health expenditure of the MOH, Malaysia. While at cost-effective prices, as defined by the Marginal Productivity thresholds, vaccination programmes are approximately three per cent of the public health budget. Hence, it is likely that a publicly financed, universal rotavirus vaccination programme in Malaysia, at negotiated vaccine prices in line with international tenders, would be cost-effective and affordable in Malaysia.

This study has several limitations. In this evaluation, additional administrative costs of vaccination programmes was derived by regression analysis of empirically measured costs conducted at different countries. Ideally, costing and financial planning for universal vaccination should be empirically measured, using guidance from the WHO-UNICEF cMYP immunisation (World Health Organization, 2014b). Unfortunately, empirical measurements of programmatic costs was beyond the scope of this study, as the information needed for this costing is not available outside the MOH.

As there are no local or regional evaluation on the impact of rotavirus gastroenteritis on young children, HRQol weights derived from a Canadian study was used in this evaluation (Brisson et al., 2010). The Canadian study used here is methodologically superior to a similar study conducted in the United Kingdom, as parents and not healthcare professionals were used to evaluate HRQoL loss in children (Martin et al., 2008). The methodological difficulties of estimating QALYs in children, including the lack of validated measurement tools specifically designed to assess children under the age of five years, hamper the conduct of these assessments in Malaysia. This is an avenue for future research.

Efficiency of vaccination programmes cannot be measured empirically prior to inclusion into a countries' national immunisation programme. As such, models are used in economic evaluations of vaccination programmes. Models synthesize all available parameter inputs, to make projections on health and economic impact. Assumptions are made and input parameters are often based on estimation. Thus, modelling is subject to uncertainty (Joke Bilcke & Beutels, 2009; Jain, Grabner, & Onukwugha, 2011).

In model based economic evaluations, uncertainty can be classified into methodological, model and parameter uncertainty (Joke Bilcke & Beutels, 2009; Briggs, 2000; Jain et al., 2011). Methodological uncertainty relates to lack of standardisation in analytical methods used. This for example, may be differences in time horizons, perspectives and cost-effectiveness thresholds. In this study, the main methodological assumptions used are based on international guidelines for economic evaluation (Drummond et al., 2005; Edejer, 2003). Model uncertainty relates to the choice of model structure, dynamic or static, used for evaluation. The choice of model is not crucial in evaluation of rotavirus vaccines, as cost-effectiveness results by different models using the same parameters, have been similar (Bakir et al., 2012; Postma et al., 2011). Simple static models are frequently used to evaluate economic impact of rotavirus vaccine, as the disease epidemiology and natural history is relatively uncomplicated (Bakir et al., 2012; Beutels et al., 2003; Joke Bilcke & Beutels, 2009).

Parameter uncertainty refers to the uncertainty on the true values of input parameters. Often multiple data sources of differing quality are synthesized for input into models, leading to parameter uncertainty (Joke Bilcke & Beutels, 2009). Sensitivity analysis is generally conducted to test the robustness of the study findings by varying parameters used in the model. In this study, univariate and scenario based sensitivity analysis revealed that that cost-effectiveness was sensitive to the variation in direct medical costs, incidence of rotavirus gastroenteritis hospitalisations and vaccine efficacy. However, rotavirus vaccines were found to be highly cost saving at base-case price and not cost-effective at market price. This demonstrates that cost-effectiveness is greatly influenced by vaccine price. As Malaysia has no explicit cost-effectiveness threshold, it was thus informative to conduct a threshold analysis at different thresholds to inform price negotiations.

5.5 Conclusion

Universal rotavirus vaccination is likely to reduce the health and economic burden associated with rotavirus, and depending on negotiated prices, is potentially cost saving and affordable in Malaysia. This first economic evaluation of rotavirus vaccines for Malaysia, suggests that rotavirus vaccines represent good value for money and are potentially affordable depending on negotiated vaccine prices. A range of cost-effective prices are suggested here to aid in vaccine price negotiations.

In the next chapter, data from a two year, hospital-based prospective rotavirus gastroenteritis surveillance study was examined to explore the household impact and income-related inequities of healthcare payments for rotavirus gastroenteritis requiring hospitalisation in Malaysia.

CHAPTER 6: HOUSEHOLD CATASTROPHIC HEALTHCARE EXPENDITURE AND IMPOVERISHMENT DUE TO ROTAVIRUS GASTROENTERITIS REQUIRING HOSPITALISATION IN MALAYSIA

6.1 Introduction

Rotavirus gastroenteritis results in substantial burden to the healthcare provider and society in Malaysia. The average costs incurred by households for an episode of rotavirus gastroenteritis requiring hospitalisation was estimated at RM 766 (range RM 186 to RM 2,914) in 2013 RM, which constituted 26 per cent of the average monthly household income in 2007 (Chai & Lee, 2009). Although the impact of healthcare payments on households due to rotavirus gastroenteritis is potentially high, this impact has not been fully explored in Malaysia.

Whilst out-of-pocket (OOP) healthcare expenditure incurred due to an acute diarrhoeal illness may not be large in magnitude, it may be financially catastrophic to some households. Direct medical costs paid OOP exceeding ten per cent of household income are widely considered to be catastrophic, as it can potentially disrupt household living standards (O'Donnell & Wagstaff, 2008). Unexpected healthcare payments, incurred OOP may push families into poverty.

The financial implications of OOP healthcare payments are different among the rich and the poor. The poor are likely to spend more of household income on basic necessities, like food, shelter and other essentials, thus are more vulnerable to unanticipated expenses. The rich have more resources and better ability to smooth consumption (Flores, Krishnakumar, O'Donnell, & Van Doorslaer, 2008; Kruk et al., 2009; S. Russell, 1996). Large OOP payments may deter the poor from seeking care, underestimating the financial consequences of ill-health (Ke Xu et al., 2006). Other than the costs of actual treatment, the cost of seeking care, including transportation and food, and the loss of income, may adversely impact household welfare (Alam & Mahal, 2014).

Hence a universal rotavirus vaccination programme has the potential to provide financial risk protection by alleviating the economic burden due to childhood diarrhoea, particularly for the poorest households. However, the magnitude and distribution of this household burden has not been previously described in Malaysia, so the potential benefit of rotavirus vaccination in this respect is still not clear.

In this chapter, economic costs incurred by households for an episode of rotavirus gastroenteritis requiring hospitalisation were assessed. The levels and distribution of catastrophic healthcare expenditure incurred, the poverty impact and income-related inequities of OOP healthcare expenditure were explored. This study was based on analysis of patient-level data from a two-year prospective, hospital-based rotavirus surveillance study conducted at two public hospitals in Malaysia.

The chapter begins with Section 6.2, which presents a study overview, a description of the study setting and data collection, as well as descriptions of the terms and methods used in the analysis. Next Section 6.3 presents the study findings. This is followed by Section 6.4, which discusses the study findings, limitations and policy relevance. The chapter ends with Section 6.5, which provides concluding statements.

6.2 Materials and methods

6.2.1 Study overview

In this chapter, primary patient-level data from a two-year, two-hospital rotavirus gastroenteritis surveillance study was analysed, to explore the magnitude and distributional effects of illness-related expenditure on households in Malaysia.

Data collection for this study was conducted from 2008 to 2010, and was led by two paediatricians Professor Dr. Lee Way Seah, from University Malaya Medical Centre

(UMMC), Kuala Lumpur and Dato' Dr. Jimmy Lee Kok Foo, from Hospital Sultanah Nur Zahirah (HSNZ), Kuala Terengganu[80].

This two-year, two-hospital, rotavirus surveillance study was conducted primarily to obtain the rotavirus genotype distribution in Malaysia, and these results were published in 2012 (Lee et al., 2012). Also collected was information on the clinical features, health service utilisation and management of acute gastroenteritis, and costs incurred by households for acute gastroenteritis episodes resulting in hospital admission. This collected information was not previously analysed or described, and is useful for the economic evaluation of rotavirus conducted in this thesis. This dataset was chosen for analysis in this thesis, because it was the most recent hospital-based rotavirus study conducted in Malaysia. Also, this dataset was chosen because it contained information on household expenditure for rotavirus gastroenteritis resulting in hospitalisation relevant to the objectives of this thesis.

Analysis of this dataset has also provided information for the estimation of national burden of rotavirus (Chapter 4) and cost-effectiveness of rotavirus vaccines (Chapter 5) in this thesis. Results of the analysis in this current chapter (Chapter 6), motivates and provides inputs for the extended costs effectiveness analysis (ECEA) to be described in Chapter 7.

A description of the hospital-based rotavirus study including the study settings and data collection are provided in Subsection 6.2.2 and 6.2.3. This is followed by Subsection 6.2.4, in which the study terms and measures used in the analysis are described.

[80] The author of this thesis was not involved in the study design or data collection for this hospital-based rotavirus study. The author performed the data entry, cleaning and analysis of the data set. The author of this thesis designed and conducted the data analysis for this chapter, the findings of which have been published (Loganathan, Lee, Lee, Jit, & Ng, 2015).

6.2.2 Study settings

The two-year, prospective, hospital-based study of rotavirus gastroenteritis was conducted from 1st April 2008 to 31st March 2010 at the paediatric departments of UMMC, Kuala Lumpur and HSNZ, Kuala Terengganu.

UMMC is a 1600-bedded, publicly-funded, teaching hospital under the Ministry of Higher Education, located in Kuala Lumpur, the federal capital of Malaysia. It serves the mainly urban populations of Kuala Lumpur and the neighbouring city of Petaling Jaya.

HSNZ is an 800-bedded, publicly-funded, general hospital under the MOH, Malaysia. It serves as the referral hospital for state of Terengganu, on the east coast of Malaysia and caters to a predominantly rural population.

Both UMMC and HSNZ are tertiary medical hospitals, serving very different catchment populations. UMMC serves the population of Kuala Lumpur and Selangor. Kuala Lumpur is 100 per cent urban, while more than 90 per cent of the population of Selangor live in urban areas. In contrast, HSNZ serves as a referral centre for the relatively rural state of Terengganu where about half of the population of the state live in rural areas (Department of Statistics Malaysia, 2010b).

6.2.3 Data collection

All children aged between one month and five years admitted for acute gastroenteritis at both hospitals were considered eligible for the study. Acute gastroenteritis was defined as an acute diarrhoeal illness with more than three episodes of loose stool within a 24 hour period, lasting less than ten days prior to admission. Children in immunocompromised states, with surgical conditions or systemic infections predisposing to diarrhoea were excluded from this study.

Written informed consent was obtained prior to inclusion into the study. After informed consent was obtained, trained study personnel interviewed parents or guardians using a standard, structured questionnaire. Faecal samples were obtained for rotavirus detection. Interviews were conducted at set time intervals; on admission and discharge of patients, and every 48 hours after discharge until the cessation of diarrhoea. Face-to-face interviews were conducted upon admission and discharge, while telephone interviews were conducted after discharge.

The questionnaire used in this study was derived from the WHO Generic Protocol for hospital-based rotavirus surveillance, and was designed to estimate the burden of rotavirus gastroenteritis (World Health Organization, 2002a). Information collected included health seeking behaviour, preadmission and inpatient management of diarrhoeal illness, and all expenses incurred before, during and after hospitalisation, as well as productivity loss of parents.

Stool samples were tested for rotavirus using a commercial kit, Premier® Rotaclone® (Meridian Biosciences, Cincinnati, Ohio). This enzyme immunoassay test has a sensitivity and specificity of 99 per cent and is recommended for rotavirus surveillance by the WHO (World Health Organization, 2002a). Stool samples that tested positive for rotavirus were deep frozen at −80°C, and sent to the Murdoch Childrens' Research Institute in Australia for genotyping. Details of the study protocol and results of viral genotyping have been published previously (Lee et al., 2012).

6.2.4 Description of terms

The dataset provided information of all costs (direct and indirect) incurred during the entire episode of diarrhoeal illness. In this section, the definitions used in this chapter and the underlying rationale for the analysis is explained.

6.2.4.1 Direct medical costs

Direct medical costs were all OOP healthcare expenditure incurred, including consultation fees and medication costs incurred prior to admission, as well as hospital bills paid for the current and any other hospitalisations within the same illness episode.

Full information on hospital bills paid by patients was collected at UMMC, however this information was not collected at HSNZ. Although the Finance Department at HSNZ was contacted, confirmation on hospital bills paid was not forthcoming. While, it was possible to estimate hospital bills from the daily ward charges and laboratory test charges, this would not accurately represent the OOP payments at MOH facilities.

In Malaysia, publicly provided healthcare services are highly subsidised. Also, a large segment of patients are exempt from fees including school children, pregnant mothers, public sector employees and their dependents, people with disabilities and the socioeconomically disadvantaged (Kananatu, 2002). Despite the subsidies, many do not settle hospital bills at MOH hospitals especially at rural settings. The NHMS 1996 which specifically looked at health seeking behaviour and OOP healthcare payments in Malaysia found that 92.5 per cent of respondents utilised government clinics and 66.4 per cent utilised government hospitals for free. Furthermore, this survey demonstrated that the average hospital charges paid in the state of Terengganu was a third that of payments made at Kuala Lumpur (Ministry of Health Malaysia, 1996).

For these reasons, the assumption was made that hospital bills paid at HSNZ were zero[81].

6.2.4.2 Direct non-medical costs

Direct non-medical costs included transportation costs, cost of extra diapers and special food. Transportation costs were defined as the additional expenditure related to travel while seeking care, including petrol and toll charges, parking fees and bus or taxi fares. The cost of extra diapers and special food was defined as expenditure above normal consumption due to illness.

[81] Although this could not be confirmed by the Finance Department at HSNZ, Kuala Terengganu, it was assumed that children were not charged for hospitals admissions for acute diarrhoeal illness at HSNZ.

6.2.4.3 Indirect costs

Indirect costs were defined as the loss of productivity of parents for the duration of illness. In this study, self-declared parental income and work-days missed due to illness was collected for both parents (mother and father). This allowed calculation of productivity loss for both parents.

For working parents with self-reported monthly income and work-days missed, productivity loss was calculated by multiplying daily wage with days of work missed. As it was assumed that wage-earners worked a six-day week, the daily wage was calculated by dividing the self-reported monthly income by 26.

Productivity loss for non-working parents or unpaid caregivers was not included. This is a conservative assumption, as caring for an ill child, would likely displace caregivers' time that would otherwise be spent on productive or leisure activities.

6.2.4.4 Catastrophic healthcare expenditure

(a) ***Background***

OOP healthcare expenditure are often unexpected and involuntary, and can be thought of as a 'health shock' (Adam Wagstaff, 2008). When a large fraction of household resources is spent on illness-related expenditure, less resources remain for the consumption of other basic needs, like food, education and shelter, and this may force households to sell assets or incur debt, leading to impoverishment (McIntyre, Thiede, Dahlgren, & Whitehead, 2006; S. Russell, 2004). OOP healthcare expenditure are payments for healthcare made directly at the point of care, and these may deter the poor from seeking needed care.

Unanticipated OOP healthcare payments above a certain threshold of household income may have an adverse impact on household living standards and can be considered to be financially catastrophic (Berki, 1986; O'Donnell & Wagstaff, 2008; Ke Xu et al., 2010).

Ideally, longitudinal data is needed to study household response to health shocks, in terms of changes in consumption of non-medical goods and services. The use of longitudinal data would better determine the impact of illness-related payments on household living standards (Gertler & Gruber, 2002). Since cross-sectional data is most often available, an approximation of the fraction of expense in relation to resources which disrupts household welfare is required[82] (Berki, 1986; O'Donnell & Wagstaff, 2008; S. Russell, 2004; Adam Wagstaff & Van Doorslaer, 2003; Ke Xu et al., 2003).

Medical spending is defined as catastrophic, when it exceeds a specified threshold or fraction of total household resources, over a given time period, usually a year (O'Donnell & Wagstaff, 2008). The idea being, spending a large fraction of household resources on healthcare must be at the expense of the consumption of other goods and services. However, there is no consensus on the threshold value at which healthcare spending depletes household resources and disrupts living standards. The threshold value set depends on whether the denominator used is total household resources[83] or non-discretionary expenditure (Adam Wagstaff & Van Doorslaer, 2003). As the threshold value selected is often arbitrary, sensitivity analysis is recommended to be performed around the threshold (Adam Wagstaff, 2008).

Healthcare expenditure exceeding ten per cent of total household resources are widely regarded as catastrophic by many, including researchers from the World Bank (McIntyre et al., 2006; Pradhan & Prescott, 2002; Ranson, 2002; Adam Wagstaff & Van Doorslaer, 2003). The rationale being, healthcare expenditure exceeding ten per cent of total household resources is likely to be at the expense of essential goods and services, forcing

[82] When using cross-sectional data, a threshold value is determined, above which healthcare expenditure is considered catastrophic.

[83] Total household resources are either measured as total household income or expenditure. The catastrophic impact of healthcare expenditure on households without savings are potentially higher than that of households with savings, and this may be reflected in changes in consumption patterns. The use of household income as a denominator for catastrophic expenditure, may not be reflective of reduction in current consumption or the use of other coping mechanisms like access to savings and loans. In contrast, the use of household expenditure as a denominator for catastrophic expenditure may reflect changes in household consumption (O'Donnell & Wagstaff, 2008).

households to reduce consumption of basic needs, sell assets or incur debt, and leading to impoverishment (S. Russell, 2004).

Researchers at the World Health Organization use the threshold of 40 per cent of ‘capacity to pay’, to define catastrophic payments (Ke Xu et al., 2003). The denominator of non-discretionary expenditure, or also called ‘capacity to pay’ is used as an indicator of living standards (Ke Xu et al., 2003). Non-discretionary expenditure or total household expenditure net of spending for basic necessities, is commonly indicated by non-food spending (Adam Wagstaff & Van Doorslaer, 2003). The idea being, subtracting expenses for basic necessities gives a better indication of a household’s ability to pay (Adam Wagstaff, 2008).

The definition of catastrophic healthcare expenditure using the numerator of OOP direct medical expenditure[84] is conservative. This narrow definition does not include all costs that impact household welfare, like direct non-medical expenditure and indirect costs, which are usually not collected in household income and expenditure surveys, commonly used in health systems research (Ke Xu et al., 2003).

When considered, indirect costs often exceed direct costs in detrimental household impact (McIntyre et al., 2006). In Indonesia, Gertler and Gruber (2002) found that loss of earnings resulted in greater health shocks to households compared to direct illness-related expenditure. Also, while some may forego seeking formal treatment to avoid OOP payments, households still suffer loss of earnings due to foregone work days by the sick person or caregivers (Alam & Mahal, 2014).

Another limitation associated with these threshold-based definitions of catastrophic healthcare expenditure, is that they fail to consider how expenses are financed, ignoring the households’ capacity to cope by drawing on current spending, savings, assets or loans to pay for healthcare. By not considering the source of funds, this limits the ability to

[84] OOP direct medical expenditure consists of the cost of medical care and treatment of illness paid OOP on the receipt of care.

identify households for whom healthcare is truly affordable[85] (Flores et al., 2008; Kruk et al., 2009). Also, these threshold-based definitions fail to consider those who do not seek healthcare due to high OOP healthcare payments (Adam Wagstaff, 2008).

The idea of catastrophic expenditure as a 'health shock' is that it is unexpected and unanticipated. Such unplanned healthcare expenditure displaces essential household consumption, disrupting household welfare. Spending a large fraction of household resources on healthcare could threaten living standards in the long term and lead to poverty, by triggering coping mechanisms like the sale of assets and debt accumulation (Alam & Mahal, 2014; McIntyre et al., 2006; Van Doorslaer et al., 2007).

(b) ***Measures used in this analysis***

Catastrophic healthcare expenditure was defined in this thesis as OOP direct medical costs exceeding ten per cent of monthly household income (O'Donnell & Wagstaff, 2008).

It is usual to define healthcare expenditure as catastrophic when it exceeds a fraction of household income over a given period of a year (O'Donnell & Wagstaff, 2008).In this chapter, OOP costs incurred were compared with monthly income. This is because illness associated with rotavirus is in the short term, with a duration of illness of no longer than a week. Also the first rotavirus infection is the most severe; the subsequent infections are milder or asymptomatic. As such, rotavirus episodes requiring hospitalisation are unlikely to be repeated (Bernstein, 2009). Considering that expenses incurred for rotavirus are over a short duration and are unlikely to be repeated, costs and income were not annualised in this analysis.

The measures used in this study give an indication on the short-term household impact of illness-related expenditure for an episode of rotavirus gastroenteritis requiring hospital admission. The limitation of the use of cross-sectional data, is that households in the short

[85] For example, wealthy households may spend large portions of income on non-essential healthcare like cosmetic surgery, which even though is expensive may be affordable to them. While, the poor may resort to selling assets or incurring debt, to pay for relatively small healthcare expenses, masking the impact of excessive expenses on income (S. Russell, 1996).

term may have better ability to cope with unexpected payments, which will not be detected here.

In this chapter, the threshold of ten per cent of total household income was used to indicate catastrophic expenditure. While the appropriate threshold for use as a marker of catastrophic expenditure is debatable, the threshold of ten per cent is used by researchers at the World Bank (O'Donnell & Wagstaff, 2008). The threshold of ten per cent is widely regarded as catastrophic when the denominator of total household income is used (O'Donnell & Wagstaff, 2008). Expenditure exceeding the threshold of ten per cent of total income is regarded to be at the expense of consumption of essential goods and services, adversely impacting household living standards (S. Russell, 2004). In this chapter, catastrophic expenditure was explored at different thresholds from five per cent to 20 per cent, as a sensitivity analysis. These results are shown in Figure 6.2.

In this chapter, catastrophic headcount or incidence of catastrophic healthcare expenditure was generated. The impact of all illness-related expenses, both direct and indirect costs on household income, were also considered. This was particularly important from the household perspective, as the economic burden on households, in addition to OOP direct medical costs, also include direct non-medical costs and productivity loss. The distributional impact of healthcare payments on households was explored over income quintiles.

6.2.4.5 Poverty impact

(a) ***Background***

Impoverishment has been described as the "processes of household asset depletion and income loss that cause consumption levels to fall below minimum needs" (S. Russell, 2004, p. 147). Illness can contribute to impoverishment through two main pathways. Firstly, illness may result in income loss, either through death or the loss of productive time. Secondly, illness-related expenses may lead to depletion of household assets and debt accumulation.

Illness can be considered impoverishing when a household's income was above the poverty line before making healthcare payments, but subsequent to payments fall below the poverty line. The poverty line being the income threshold below which even the minimum standard of living is not ensured (Ravallion, 2010).

Poverty is a complex and multi-dimensional phenomenon. Due to its multidimensional nature, poverty is often difficult to define. A common definition of poverty is whether households or individuals have enough resources to meet their basic needs (Coudouel, Hentschel, & Wodon, 2002; Narayan-Parker & Patel, 2000). Poverty has been defined as the lack of basic requirements for material well-being, especially food, but also monetary and physical assets, leading to physical deprivation. Poverty also has been described as a deprivation of individual capabilities, like a lack of education or health, which prevents the attainment of well-being (Narayan-Parker & Patel, 2000). Also, poverty has psychological, cultural and social dimensions, which encompass an individual's lack of power and independence that lead to the breakdown of social norms and social exclusion[86]. Under the multidimensional approach, poverty is also associated with the lack of infrastructure including roads, electricity, access to clean water and sanitation, education and healthcare (Narayan-Parker & Patel, 2000; Saksena et al., 2014).

While poverty is multidimensional, standard measures of poverty compare a monetary measure of household economic welfare, namely household income, with a poverty line. Households with income levels below the Poverty Line Income (PLI) are deemed poor. PLI being the minimum income sufficient to obtain the basic necessities in life, including food and non-food items (Zin, 2007).

[86] Social exclusion is the alienation and disenfranchisement experienced by the poor, which is manifested by the inability to participate in social activities (Narayan-Parker & Patel, 2000).

The threshold for absolute poverty is internationally determined, as the absolute minimum income for survival, for any person worldwide (Ravallion, 2010). International poverty lines allow for standardised monitoring between countries of global trends in poverty. International poverty lines[87] as determined by the World Bank, were used in the first Millennium Development Goal, as a measure of progress towards eradication of absolute poverty[88]. High- and middle-income countries have higher standards of living than low-income countries. Hence, international poverty lines are a modest measure, too low to meaningfully capture poverty in these settings (United Nations Development Programme, 2007).

Relative poverty interprets poverty in relation to the prevailing standards of living of society, thus is different between countries and over time. The poverty line under this approach may be calculated for a country, in terms of average income[89]. The concept of relative poverty, is that the income line is the minimum standard below which no household should fall below, and these standards should rise as the country becomes richer, with the rising standard of living (Ravallion, 2010).

The concept of PLI assumes the same minimum standard of living for all members of society. However, since individuals in a society have different basic needs[90] and also as prices differ according to geographic locations[91], the same poverty line can hardly be used for all in society. In keeping with this rationale, the Malaysian Government revised the methodology used to calculate the PLI for Malaysia, in the Ninth Malaysian Plan (Zin, 2007).

[87] International poverty line income, with the lower threshold of US$ 1 per day was calculated as the median of ten lowest poverty lines from the world's poorest countries. This threshold represents a minimum standard of living, also referred to as extreme poverty (Ravallion, Datt, & Walle, 1991). The international poverty line was updated to US$ 1.90 per-day, as of October 2015 by the World Bank.(World Bank, 2015b)

[88] The first Millennium Development Goal of reducing by half between 1990 and 2015, the number of people living on less than US$ 1 per day (United Nations Development Programme, 2007).

[89] Relative poverty compares the 'worse-off' in society with the average or 'norm' in society.

[90] Food and non-food needs differ for individuals depending on age and gender. For instance a child would have less caloric requirements than an adult.

[91] Difference in standard of living in different geographical regions or between urban and rural areas, explain price differences.

(b) ***Poverty Line Income for Malaysia***

The Household Income and Basic Amenities Survey is an income survey carried out twice in five years since 1973, by the Department of Statistics, Malaysia. The main objectives of this survey are to measure the economic well-being of the population, to collect information on the income distribution of households, and to identify poverty and accessibility to basic amenities. The 2009 Household Income and Basic Amenities Survey provided data for the calculation of the 2009 Malaysian PLI.

The calculation of the poverty line was based on methodology first introduced in 2004, which takes into consideration food and non-food PLI for households visited. PLI was determined separately for each household surveyed, considering household size and demographic composition, its location in Peninsular Malaysia or East Malaysia, and urban and rural area[92].

The food PLI was based on local expert recommendation on the minimum daily caloric requirement for an average family of five persons (8,725 kilo calories). The kilo calorie estimation was converted to a monetary value using retail prices. The non-food PLI was determined by examining spending patterns of low-income households in the survey. These non-food basic necessities include clothing, rental, electricity, transportation, communication and others (Department of Statistics Malaysia, 2009; Zin, 2007).

(c) ***Measures used in analysis***

In this thesis, the 2009 PLI, specific for urban and rural regions in Peninsula Malaysia in 2009, was used to determine medical impoverishment (Department of Statistics Malaysia, 2009). The 2009 PLI for Malaysia was appropriate for use in this current analysis, as the data collection for the hospital-based study was conducted from the years 2008 to 2010.

[92] This estimation takes into account individual consumption needs for a basic standard of living, which varies according to age and gender, and cost of living in different regional locations, and urban and rural areas.

Illness can be considered impoverishing when a household's income was above the poverty line before making healthcare payments, but subsequent to payments fall below the poverty line. A household was considered poor if its total monthly income falls below the poverty line.

The measures of medical impoverishment used in this thesis, compare illness-related expenditure against monthly income giving an indication of the short-term poverty impact due to illness-related expenditure. The long term consequences of illness-related payments is not explored in this thesis, because the transient nature of the illness.

The poverty headcount is the number of households with a total monthly household income below the poverty line, and is a measure of incidence of poverty (O'Donnell & Wagstaff, 2008). Poverty headcounts were explored before and after healthcare payments. The poverty impact of illness is the proportion of households that fall into poverty, after deducting OOP direct medical payments from household income. The poverty impact of direct and indirect costs on household income were also considered in this chapter.

6.2.4.6 Income-related inequity in healthcare payments

(a) ***Background***

The poor are particularly vulnerable to the burden of ill health. In a review of literature on the economic impacts of health shocks on households in low- and middle-income countries, Alam and Mahal (2014) found that OOP healthcare payments were particularly detrimental to poor households. Poor households were more likely to spend a larger portion of household income on healthcare payments. As a consequence, the catastrophic and impoverishing impact of healthcare payments were likely to be concentrated among the poor.

Poor households are more vulnerable and are less able to cope with unbudgeted OOP payments compared to the rich. The poor have less physical and financial assets and access to loans, thus less ability to buffer expenditure. Hence, the poor are more likely to cut back on consumption of basic necessities due to health shocks, compromising household welfare (Alam & Mahal, 2014).

As the poor have less resources, OOP payments may deter the poor from seeking care (O'Donnell & Wagstaff, 2008). Excessive reliance on OOP payments may ration services away from the poor to those with ability to pay, exacerbating inequities in healthcare access (Alam & Mahal, 2014; Ke Xu et al., 2003).

(b) ***Measures used in analysis***

In this study, concentration curves and indices were generated to explore income-related inequities in healthcare payments at both hospitals.

The concentration curve is a visual representation of health inequalities. The concentration curve examines inequalities in the distribution of a health variable of interest against a measure of living standard[93].

In this analysis, a concentration curve displays the share of OOP healthcare payments accounted for by the cumulative proportion of population groups, ranked from poorest to richest. The line of equality is the diagonal (45-degree) line, representing no inequality in OOP payments by household income. If the concentration curve falls on the line of equality, every individual irrespective of household income, pays the same OOP for an episode of rotavirus gastroenteritis requiring hospitalisation. The concentration curve that lies above the line of equality indicates OOP payments concentrated among poorer groups. In contrast, the concentration curve lies below the line of equality when OOP payments are concentrated among the richer groups (O'Donnell & Wagstaff, 2008).

Concentration curves may be used to identify the existence of income-related health inequalities. However, concentration curves does not measure the magnitude of

[93] The concentration curve could examine any health sector variable, including the distribution of health outcomes (mortality or morbidity), health behaviours (smoking, exercise, alcohol), healthcare programmes (uptake or success of programmes), or of interest in this study, OOP healthcare payments. A living standards measure is a socio-demographic variable (income, geography, social class, ethnicity) against which the distribution of the health variable of interest is assessed (O'Donnell & Wagstaff, 2008).

inequities, nor does it allow for comparison between regions. While the concentration curve is a visual representation of income-related health inequalities, the concentration index is used to quantify the degree of inequalities (Kakwani, Wagstaff, & Van Doorslaer, 1997; O'Donnell & Wagstaff, 2008; A. Wagstaff, Paci, & van Doorslaer, 1991).

The concentration index is defined as twice the area between the concentration curve and the line of equality. When the concentration index is zero, there is no income-related inequality in OOP healthcare payments. When the concentration index takes a negative value and the concentration curve lies above the line of equality, this indicates a disproportionate concentration of OOP payments among the poor. A positive concentration index and a concentration curve that lies below the line of equality, indicates that OOP payments are concentrated among the rich. The concentration index is valued between −1 and +1 (O'Donnell & Wagstaff, 2008).

6.2.5 Statistical Analysis

The original patient information sheets from both hospitals were obtained for this current study. The analysis for this study began with data entry and cleaning. Patient information sheets were scrutinised to confirm that each case fulfilled eligibility criteria. Of the 483 patients recruited at UMMC during the study period, 16 cases (three per cent) were discarded as they did not fulfil eligibility criteria. Likewise at HSNZ, 337 patients were recruited and 4 cases (one per cent) were excluded for not fulfilling eligibility criteria. The main reason for non-fulfilment was age; however one case was discarded because the patient did not have symptoms of diarrhoea.

Patients were divided into groups according to rotavirus status: all cases of acute gastroenteritis, rotavirus gastroenteritis and non-rotavirus gastroenteritis. Analysis was done separately to compare gastroenteritis groups at each hospital and subsequently the datasets were merged, to compare findings between both hospitals.

All costs, where appropriate, were presented as mean (± standard deviation, SD). Kolmogorov–Smirnov test was applied to test for normality of distribution. Independent sample t-test was used to test differences in means. Mann-Whitney U test was applied to test differences between groups when the assumption of normality was not met. A p-value of 0.05 was considered as statistically significant. The catastrophic impact of healthcare payments on households distributed by income quintiles was explored. Concentration curves and indices were generated, to explore the magnitude of income-related inequalities in OOP direct medical payments for acute gastroenteritis episodes at both centres.

Costs were inflated to 2013 price values using GDP deflators (Department of Statistics Malaysia, 2012a). All costs were reported as 2013 Ringgit Malaysia (RM). The World Bank exchange rate for 2013 of US$ 1 to RM 3.15 was used for currency conversion (World Bank, 2014a).

The Malaysian Poverty Line Income (PLI) for 2009, stratified for urban and rural areas in Peninsular Malaysia was used. PLI in 2009 for urban regions was used for Kuala Lumpur (RM 771), and for rural regions was used for Kuala Terengganu (RM 743) (Department of Statistics Malaysia, 2009).

Statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, Illinois, USA).

6.2.5.1 Handling of missing values of household income

The study datasets had missing values of household income. The original questionnaire used for data collection did not collect information on monthly household income. These variables were included after the start of data collection, to allow for estimation of indirect costs and the impact of OOP payments on household income. As such, the first 31 cases (seven per cent) from UMMC, Kuala Lumpur and 80 cases (24 per cent) from HSNZ, Kuala Terengganu did not contain information on household income. Over the course of the study, a further nine cases (two per cent) from UMMC and 47 cases (14 per cent) from HSNZ contained missing values for household income.

Table 6.1 shows missing values for total household income at UMMC and HSNZ.

Table 6.1: Missing values for total household income at UMMC, Kuala Lumpur and HSNZ, Kuala Terengganu

	UMMC		HSNZ	
Total sample	467	(100%)	333	(100%)
Household income not collected	31	(7%)	80	(24%)
Missing values	9	(2%)	47	(14%)
Total missing values (Household income)	40	(9%)	127	(38%)

UMMC, Universiti Malaya Medical Centre; HSNZ, Hospital Sultanah Nur Zahirah

The pattern of missing values for total monthly income at both centres was examined to inform appropriate measures to deal with missing values.

At UMMC, there was no difference in total direct costs between cases with missing total monthly income and those with no missing values (RM 614 vs. RM 596; $p = 0.79$). The Little's (1988) MCAR test was non-significant ($p = 0.79$) indicating that data was missing completely at random (MCAR) (Allison, 2001; Little, 1988).

At HSNZ, total direct costs were lower in those with missing values compared with cases with no missing values of total monthly income (RM 19 vs. RM 32; $p < 0.0001$). Significant results of the Little's MCAR test ($p < 0.0001$), suggests that data was either missing at random (MAR) or not missing at random (NMAR) (Schlomer, Bauman, & Card, 2010).

In rural areas, some may rely on a traditional subsistence economy and may not receive a fixed wage (e.g. farmers, fisherman). This may explain non-disclosure of monthly income at Kuala Terengganu. While the possibility of NMAR if ignored may bias results, there is no consensus on the appropriate methods to be used to reduce bias (Buhi, Goodson, & Neilands, 2008).

In this chapter, multiple imputations method was used for the HSNZ dataset with specifications to best deal with the missing values. In this hospital-based study, information was collected on clinical features and management of childhood diarrhoea, health-seeking behaviour and costs. Socio-demographic variables like parental education level, or housing status, which is usually appropriate for use in predicting income, was not collected.

As total household income was significantly correlated to direct costs, direct costs were used to predict household income. At HSNZ, the Pearson correlation coefficient was 0.2 ($p = 0.001$). However, direct costs do not sufficiently explain the variation in total household income ($F^2 = 0.05$).

Multiple imputations were performed using SPSS version 20.0 (SPSS Inc., Chicago, Illinois, USA). Total direct costs were used as the independent (predictor) variable and total household income as the dependent (outcome) variable. Linear regression was used for the imputation model and a monotone imputation method was used. Five imputed datasets were generated and a pooled result was used for analysis.

As the imputed and non-imputed datasets were found to give largely similar results, the imputed dataset was used for the estimation of costs. This allowed utilisation of the full sample for estimation of cost (Table 6.3). As direct costs did not fully explain total household income, case-wise deletion was used for missing values of total household income in the rest of the analysis. Analysis for the catastrophic and poverty impact of OOP payments, and the generation of concentration curve and indices was conducted using the non-imputed datasets (Figure 6.1, Figure 6.2, Figure 6.3 and Table 6.4).

6.3 Results

6.3.1 General findings

From the period of April 2008 to March 2010, a total of 800 children under-five years with acute gastroenteritis were admitted to the two study sites and 658 stool samples (82 per cent) were tested for rotavirus. Overall, 248 (37.7 per cent) samples tested positive for rotavirus. Of the 467 children admitted for acute gastroenteritis at UMMC, 385 (82 per cent) had stool tested and of these 161 (41.8 per cent) tested positive for rotavirus. At HSNZ, of the 333 children admitted for acute gastroenteritis, 273 (82 per cent) had stool samples tested, and 87 (31.9 per cent) tested positive for rotavirus. (Table 6.2)

At both hospitals, a hundred and fifty children (61 per cent) with rotavirus gastroenteritis were aged two years or younger. While the median duration of diarrhoea for an episode of rotavirus gastroenteritis was longer at UMMC compared to HSNZ (six days vs. five days; $p = 0.001$), there was no difference in the median duration of admission at both hospitals (3 days; $p = 0.264$). (Table 6.2)

Patients with rotavirus gastroenteritis had increased frequency of fever and vomiting, compared with non-rotavirus gastroenteritis. Majority of children admitted with acute gastroenteritis at UMMC had moderate dehydration (92 per cent), while 55 per cent of children admitted at HSNZ had mild dehydration. Work days missed by both mothers and fathers of patients with rotavirus gastroenteritis were both significantly more at UMMC than at HSNZ. (Table 6.2)

Table 6.2 compares the characteristics of children hospitalised for acute gastroenteritis and tested for rotavirus at UMMC, Kuala Lumpur and HSNZ, Kuala Terengganu.

Table 6.2: Characteristics of children hospitalised for acute gastroenteritis and tested for rotavirus at UMMC, Kuala Lumpur and HSNZ, Kuala Terengganu

Patient Characteristics	UMMC							HSNZ						
	All [a] (n = 467)		RVGE (n = 161)		non-RVGE (n = 224)		p-value[b]	All [a] (n = 333)		RVGE (n = 87)		non-RVGE (n = 186)		p-value[b]
Male (%)	59%		57%		58%		0.86	61%		62%		63%		0.83
Age, months (Median, IQR)	17	(21)	19	(22)	15	(18)	0.00	17	(20)	18	(2)	13	(15)	0.00
Degree of dehydration (%)														
None or mild	32	(7%)	9	(6%)	14	(6%)		182	(55%)	37	(43%)	112	(61%)	
Moderate	428	(92%)	148	(93%)	209	(93%)		144	(43%)	49	(56%)	71	(38%)	
Severe	5	(1%)	3	(2%)	1	(0%)	0.39	5	(2%)	1	(1%)	2	(1%)	0.02
Clinical Features														
Vomiting (%)	429	(92%)	156	(97%)	197	(88%)	0.00	272	(82%)	81	(93%)	142	76%	0.00
Fever (%)	412	(88%)	154	(96%)	186	(83%)	0.00	273	(82%)	70	(81%)	123	(66%)	0.02
Duration of diarrhoea, days (median, IQR)	5	(3)	6	(2)	5	(3)	0.04	5	(3)	5	(2)	5	(4)	0.91
Duration of hospitalisation, days (median, IQR)	3	(2)	3	(1)	3	(2)	0.49	3	(2)	3	(1)	3	(2)	0.00
Work days missed [c], days (mean ± SD)														
Mother	3.0	±1.5	3.1	±1.4	2.9	±1.7	0.42	0.9	±1.6	1.1	±1.5	0.7	±1.4	0.08
Father	1.7	±1.2	1.7	±1.1	1.7	±1.2	0.71	0.3	±0.9	0.6	±1.3	0.3	±0.8	0.07

Note: IQR, interquartile range; mean (± standard deviation, SD);

All, acute gastroenteritis; RVGE, rotavirus gastroenteritis; non-RVGE, non-rotavirus gastroenteritis;

UMMC, University of Malaya Medical Centre; HSNZ, Hospital Sultanah Nur Zahirah;

[a] All AGE indicates the entire sample of children admitted for acute gastroenteritis at both study sites. Of these 82 per cent were tested for rotavirus.

[b] The p-value is a result of statistical comparison between rotavirus and non-rotavirus groups at each hospital. A p-value of less than 0.05 was considered as statistically significant.

[c] Work days missed were presented for both parents, father and mother.

6.3.2 Direct and indirect costs

There was no difference in direct and indirect costs between rotavirus gastroenteritis and non-rotavirus gastroenteritis groups at UMMC. At HSNZ, patients with rotavirus gastroenteritis had higher consultation costs for preadmission care compared to non-rotavirus gastroenteritis groups (RM 16 vs. RM 10; $p = 0.03$), however other costs did not differ significantly between groups.

At UMMC, the average total direct costs for an episode of rotavirus gastroenteritis requiring hospital care was RM 367 (SD ± RM 190), of which 78 per cent was due to direct medical costs. Seventy-eight per cent of direct medical costs were contributed by direct hospitalisation payment, RM 223 (SD ± RM 172). The average direct and indirect costs were RM 700 (SD ± RM 391), of which productivity losses (48 per cent) was a major component. The average productivity loss experienced by both parents was RM 336 (SD ± RM 299).

All costs incurred by households at HSNZ were significantly lower than at UMMC. The mean direct costs for an episode of rotavirus gastroenteritis requiring admission was RM 26 (SD ± RM 29) at HSNZ. As direct hospitalisation charges at HSNZ were assumed to be zero, the main contributor for direct medical costs was preadmission consultations, RM 12 (SD ± RM 23). The average direct and indirect costs was RM 143 (SD ± RM 167), of which productivity losses for both parents accounted for 73 per cent of spending.

The mean direct and indirect costs incurred for rotavirus gastroenteritis were significantly higher in UMMC compared with HSNZ (RM 700 vs. RM 143; $p < 0.001$). The mean direct and indirect costs consisted 20 per cent of monthly household income in UMMC, as compared with only five per cent household income at HSNZ.

On average, households of patients at UMMC had higher income than those at HSNZ (RM 3986 vs. RM 2929; $p < 0.001$).

Table 6.3 compares costs incurred by households for children hospitalised for acute gastroenteritis and tested for rotavirus at UMMC, Kuala Lumpur and HSNZ, Kuala Terengganu

Table 6.3: Costs incurred by households for children hospitalised for acute gastroenteritis and tested for rotavirus at UMMC, Kuala Lumpur and HSNZ, Kuala Terengganu

Costs	UMMC				HSNZ			
	All [a] (n = 467) Mean ± SD	RVGE (n = 161) Mean ± SD	non-RVGE (n = 224) Mean ± SD	p-value[b]	All [a] (n = 333) Mean ± SD	RVGE (n = 87) Mean ± SD	non-RVGE (n = 186) Mean ± SD	p-value[b]
Preadmission consultation	82 ± 231	62 ± 35	101 ± 331	0.14	13 ± 22	18 ± 24	12 ± 23	0.05
Direct hospitalisation payment	225 ± 180	223 ± 172	222 ± 172	0.97	0	0	0	
Total direct medical costs	**307 ± 293**	**285 ± 176**	**323 ± 376**	**0.19**	**13 ± 22**	**18 ± 24**	**12 ± 23**	**0.05**
Transport	64 ± 52	64 ± 32	66 ± 66	0.67	8 ± 10	9 ± 15	7 ± 7	0.24
Food expenses	3 ± 11	2 ± 7	3 ± 14	0.30	0 ± 4	0 ± 0	1 ± 5	0.03
Diapers	14 ± 10	15 ± 11	14 ± 11	0.11	6 ± 8	5 ± 6	7 ± 9	0.08
Total direct non-medical costs	**81 ± 58**	**82 ± 39**	**83 ± 74**	**0.77**	**14 ± 14**	**14 ± 18**	**14 ± 13**	**0.82**
Total direct costs	**388 ± 309**	**367 ± 190**	**407 ± 395**	**0.24**	**27 ± 28**	**32 ± 32**	**26 ± 29**	**0.16**
Productivity loss mother	159 ± 241	163 ± 253	150 ± 232	0.62	58 ± 133	76 ± 125	47 ± 140	0.19
Productivity loss father	156 ± 146	163 ± 166	152 ± 134	0.47	23 ± 75	28 ± 95	23 ± 72	0.66
Total indirect costs	**320 ± 291**	**336 ± 299**	**306 ± 286**	**0.35**	**80 ± 149**	**104 ± 147**	**70 ± 154**	**0.16**
Total direct and indirect costs	**706 ± 486**	**700 ± 391**	**712 ± 562**	**0.82**	**111 ± 160**	**143 ± 167**	**101 ± 160**	**0.11**
Total monthly household income	3986	3947	3911	0.94	2929	3205	2795	0.22

Note:

All costs are reported in 2013 RM; mean (± standard deviation, SD);

All, acute gastroenteritis; RVGE, rotavirus gastroenteritis and non-RVGE, non-rotavirus gastroenteritis;

UMMC, University of Malaya Medical Centre; HSNZ, Hospital Sultanah Nur Zahirah;

[a] All AGE indicates the entire sample of children admitted for acute gastroenteritis at both study sites. Of these 82 per cent were tested for rotavirus;

[b] The p-value is a result of independent t-test between means of rotavirus and non-rotavirus groups at each hospital, alpha less than 0.05 is significant.

6.3.3 Catastrophic healthcare expenditure

As there was no difference in costs between rotavirus and acute gastroenteritis groups at both hospitals, the entire dataset (of all patients admitted with acute gastroenteritis) was analysed for the catastrophic and impoverishing impact of healthcare payments.

On average, direct medical costs paid OOP for hospitalisation of acute gastroenteritis at UMMC represented 11 per cent of the total monthly household income. Catastrophic healthcare expenditure was experienced by a third of households at UMMC. Households in the highest income quintile had the highest average OOP direct medical costs (RM 377; SD ± RM 563), followed by households in the lowest income quintile (RM 319; SD ± RM 208). OOP direct medical costs as a proportion of monthly household income was significantly lower (5.7 per cent) in the highest income quintile as compared to the lowest income quintile (23.2 per cent) ($p < 0.001$) (Figure 6.1). Eight per cent of households in the highest income quintile experienced catastrophic healthcare payments, as compared to 86 per cent in the lowest income quintile (Figure 6.2). When all direct and indirect costs were considered, 376 households at UMMC (88 per cent) experienced illness-related payments of more than ten per cent of monthly household income.

In contrast at HSNZ, direct medical costs were less than one per cent of the total monthly household income and only one household experienced catastrophic healthcare expenditure (Figure 6.2). Households in the highest income quintile had higher average OOP direct medical costs (RM 24; SD ± RM 35), compared to households in the lowest income quintile (RM 6; SD ± RM 14). This difference was statistically significant ($p < 0.001$) (Figure 6.1). When all direct and indirect costs were considered, 19 households (nine per cent) experienced illness-related expenditure of more than ten per cent of monthly household income.

Figure 6.1 displays mean out-of-pocket costs for acute gastroenteritis requiring hospitalisation by income quintiles.

Figure 6.2 shows households with catastrophic healthcare payments due to acute gastroenteritis requiring hospitalisation by income quintiles.

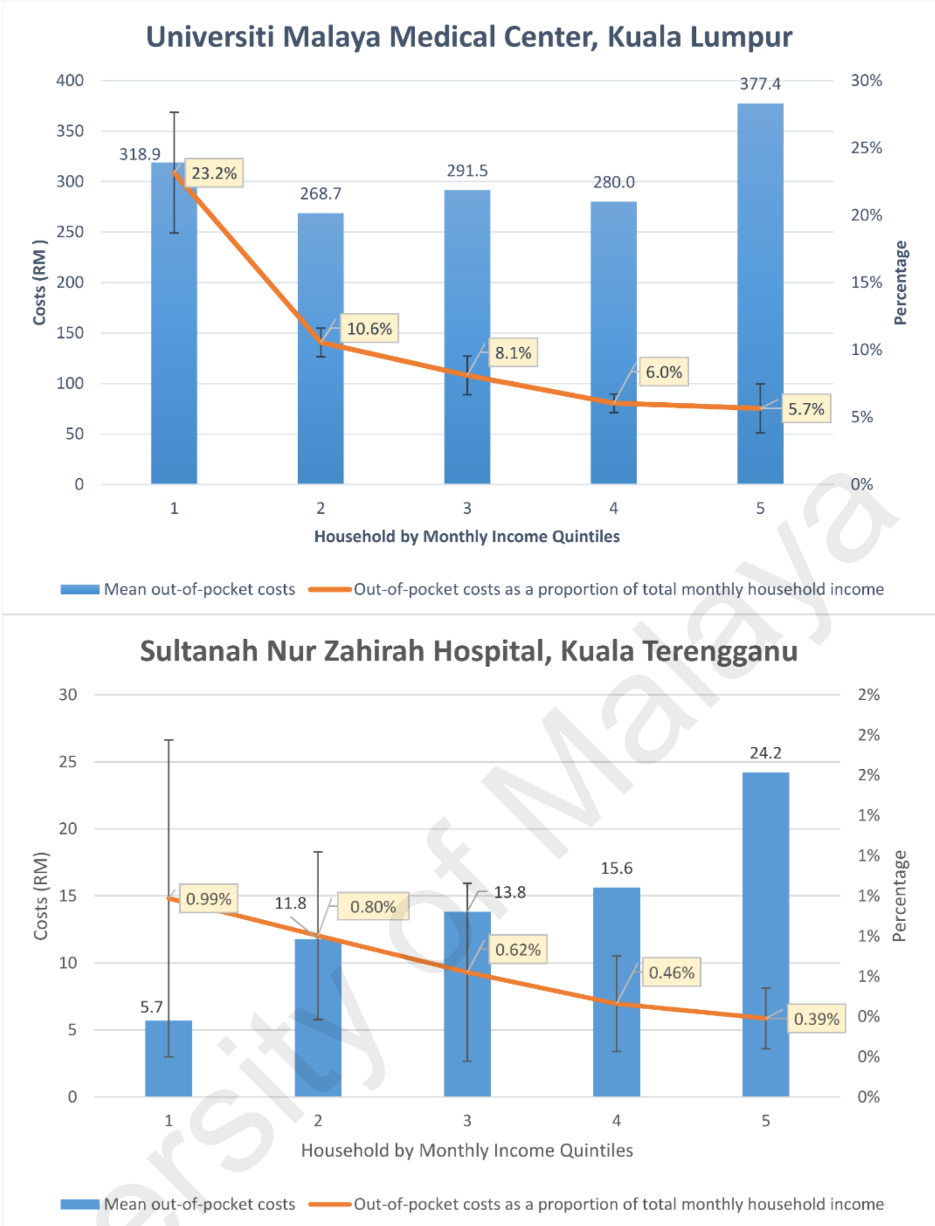


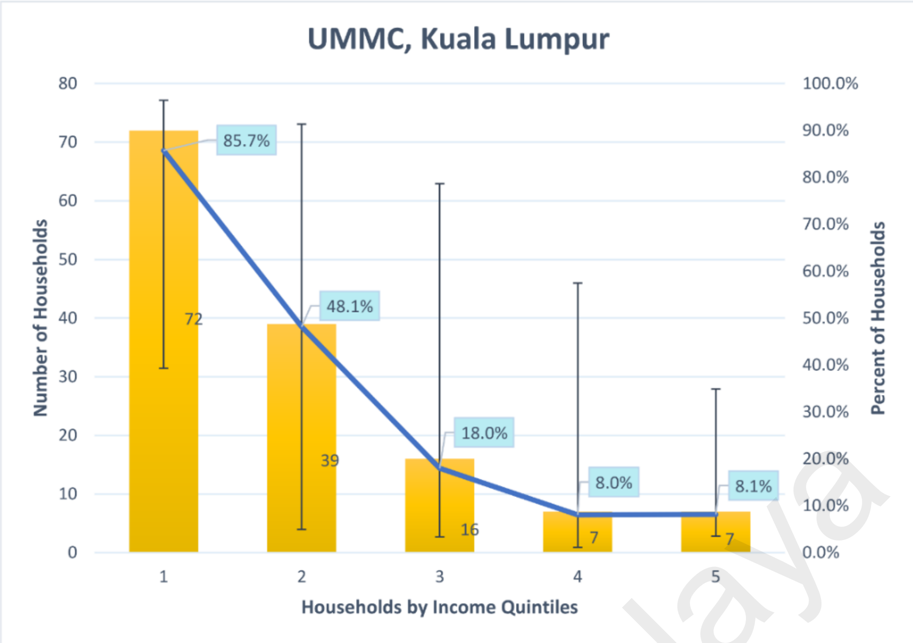
Figure 6.1: Mean out-of-pocket costs for acute gastroenteritis requiring hospitalisation by income quintiles at UMMC, Kuala Lumpur and HSNZ, Kuala Terengganu

Note**:**

Costs are in 2013 Ringgit Malaysia (RM);

UMMC, University of Malaya Medical Centre; HSNZ, Hospital Sultanah Nur Zahirah.

The blue bars denote average out-of-pocket direct medical costs to households by income quintiles (poorest to richest income quintiles), resulting from rotavirus diarrhoea episodes requiring hospitalisation. The red line denotes average out-of-pocket direct medical costs as a proportion of household income for each income quintile. Blue bars relate to the left-hand y-axis. Red lines relate to the right-hand y-axis. Error bars represent 95 per cent confidence interval of out-of-pocket costs as a proportion of household income



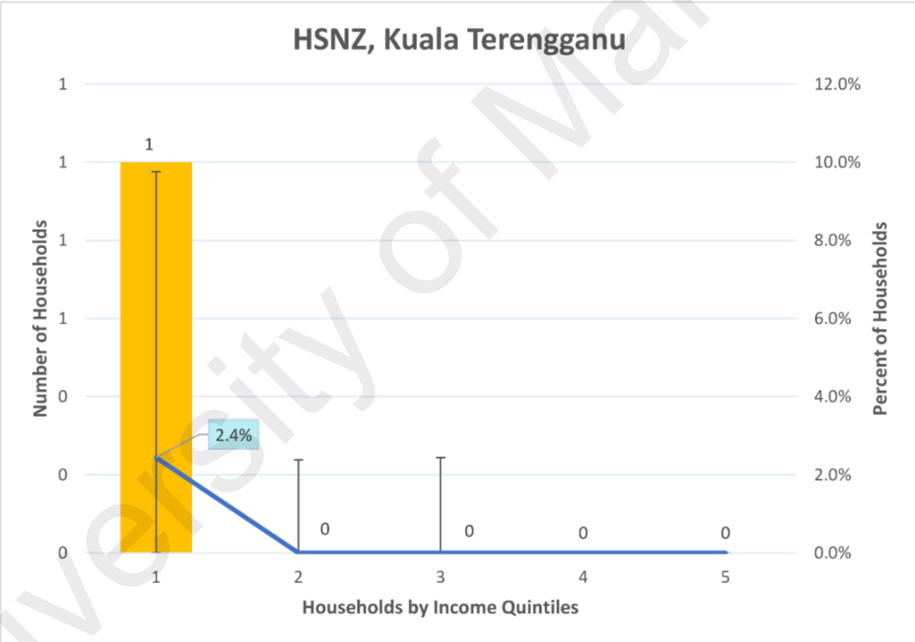


Figure 6.2: Households with catastrophic healthcare payments due to acute gastroenteritis requiring hospitalisation by income quintiles at UMMC, Kuala Lumpur and HSNZ, Kuala Terengganu

Note:

UMMC, University of Malaya Medical Centre; HSNZ, Hospital Sultanah Nur Zahirah;

The yellow bars denote the number of households that incur catastrophic healthcare payments due to acute gastroenteritis requiring hospitalisation by income quintiles (poorest to richest income quintiles). The blue line denotes the proportion of households per quintile that incur catastrophic healthcare payments. Yellow bars relate to the left-hand y-axis. Blue lines relate to the right-hand y-axis. Catastrophic healthcare expenditure is defined here as out-of-pocket direct medical costs above ten per cent of total monthly household income.
Error bars represent range of results using catastrophic payment thresholds ranging from five per cent to 20 per cent.

6.3.4 Poverty impact of illness-related payments

At UMMC, two households were below the poverty line prior to healthcare payments. Direct medical costs paid OOP displaced 11 households (three per cent) below the poverty line. When both direct and indirect costs were deducted from monthly incomes, 25 households (six per cent) were pushed below the poverty lines.

At HSNZ, the pre-payment poverty headcount was 30. However, no households were impoverished after direct healthcare payments and only one household incurred poverty after deducting direct and indirect costs from monthly income.

Table 6.4 shows the poverty impact of illness-related payments for acute gastroenteritis requiring hospitalisation at UMMC, Kuala Lumpur and HSNZ, Kuala Terengganu.

Table 6.4: Poverty impact of illness-related payments for acute gastroenteritis requiring hospitalisation at UMMC, Kuala Lumpur and HSNZ, Kuala Terengganu

	UMMC (n = 427)		HSNZ (n = 207)	
Poverty Headcounts (no, %)				
Pre-payment	2	(0%)	30	(14%)
Post-payment				
Post direct medical costs	13	(3%)	30	(14%)
Post direct costs	18	(4%)	30	(14%)
Post direct and indirect costs	27	(6%)	31	(15%)
Poverty Impact				
Post direct medical costs	11	(3%)	0	(0%)
Post direct costs	16	(4%)	0	(0%)
Post direct and indirect costs	25	(6%)	1	(0%)

Note: UMMC, University of Malaya Medical Centre; HSNZ, Hospital Sultanah Nur Zahirah;

Poverty Line Income in 2009 for urban regions was used for, Kuala Lumpur (RM 771) and rural regions, was used for Kuala Terengganu (RM 743) (Department of Statistics Malaysia, 2009).

6.3.5 Income-related inequity in healthcare payments

The concentration curves for both hospitals fell below the line of equality indicating payments made OOP were concentrated among the rich. The concentration index of UMMC was closer to zero compared to that of SZNH (0.03 vs. 0.24).

Figure 6.3 shows the concentration curves and indices of OOP healthcare expenditure requiring hospitalisation at UMMC, Kuala Lumpur and HSNZ, Kuala Terengganu.

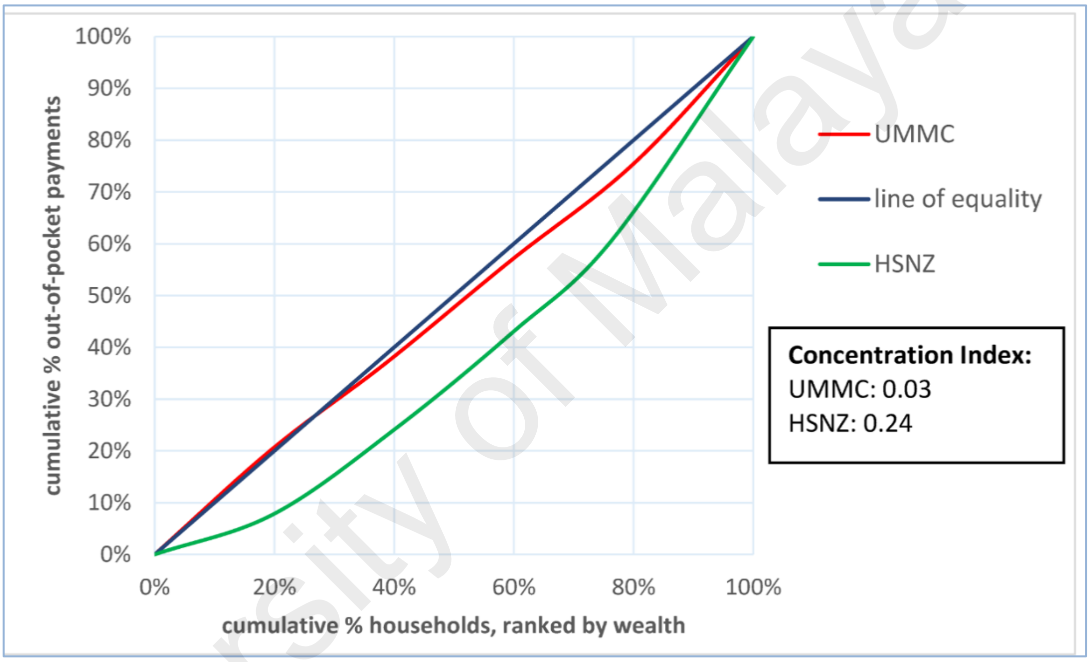


Figure 6.3: Concentration curves of out-of-pocket healthcare expenditure due to acute gastroenteritis requiring hospitalisation.

UMMC, University of Malaya Medical Centre; HSNZ, Hospital Sultanah Nur Zahirah;

The x-axis shows the cumulative proportion of households ranked by increasing household income;

The y-axis shows the cumulative proportion of out-of-pocket healthcare payments.

6.4 Discussion

This chapter shows that in Malaysia, the financial burden of diarrhoeal hospitalisations on households differs in urban and rural areas. Although households in Kuala Lumpur had higher income than those in Kuala Terengganu (RM 3986 vs. RM 2929, $p < 0.001$), all costs incurred in Kuala Lumpur were significantly higher than in Kuala Terengganu. On average, direct and indirect costs incurred by the households at UMMC, Kuala Lumpur for an episode of rotavirus gastroenteritis requiring hospitalisation was RM 706 (SD ± RM 486), which consisted 20 per cent of the total monthly household income. This is consistent with findings from a study conducted at UMMC in 2007. In that 2007 study, out-of-pocket direct medical costs for an episode of gastroenteritis requiring hospitalisation, consisted of 26 per cent of the average monthly household income (Chai & Lee, 2009). In contrast, direct and indirect costs due to an episode of rotavirus gastroenteritis requiring hospitalisation at HSNZ, Kuala Terengganu was a mere RM 143 (SD ± RM 167), or less than six per cent of the average monthly household income.

It is estimated that a third of households in the UMMC dataset experienced catastrophic healthcare payments. In addition, after the incurrence of direct and indirect costs, 25 households (six per cent) were pushed into poverty. This catastrophic impact of healthcare expenses on households is unexpected in Malaysia, which is widely credited to have achieved Universal Health Coverage (Savedoff & Smith, 2011). Malaysia has an extensive network of primary health clinics which provide free services for children, whilst admission to public hospitals are heavily subsidised (Chee & Barraclough, 2007). Analysis of nationally representative household survey data has shown a low incidence of catastrophic healthcare payments in Malaysia, with only two per cent of households spending more than ten per cent of total household budget on healthcare (Van Doorslaer et al., 2007). Also, the poverty headcount ratio for Malaysia in 2009 was estimated by the World Bank at 3.8 per cent of the population (World Bank, 2014b).

However, it is surprising that HSNZ which serves a predominantly rural population in Kuala Terengganu, only one household incurred catastrophic payments due to hospitalisation. While households at Kuala Terengganu are less wealthy, healthcare expenses incurred were also significantly lower at Kuala Terengganu (total direct medical costs for acute gastroenteritis at HSNZ compared UMMC; RM 13 vs. RM 307; $p < 0.001$). Low healthcare expenses incurred are a testimony to the success of the rural focus of public health services in Malaysia. Expenses at MOH health facilities are generally subsidised at all levels of care and in many forms (Kananatu, 2002). For example, even non-urgent patients in rural settings may be transported from primary health clinics to hospital for admission via free ambulance services. Lower cost of living at rural areas may explain lower direct non-medical costs like transport, food and diapers.

Interestingly, inequalities in OOP expenditure along the income quintiles were found. In Kuala Lumpur, households in the lowest income quintile paid more OOP for healthcare compared to all other households apart from those in the highest income quintile. Furthermore, households in the lowest income quintile were far more likely to experience catastrophic payments compared with those in the highest income quintile (86 per cent vs. eight per cent). This is important as it suggests that although the richest households paid more for healthcare, they were less likely to suffer change in living standards or incur debt due to healthcare expenses. In Kuala Terengganu, although healthcare expenditure was higher in the highest income quintile as compared to the lowest income quintile (RM 24 vs. RM 6; $p < 0.001$), these costs had minimal catastrophic impact. The concentration curves suggest that while OOP healthcare payments at both hospitals were concentrated among the rich, interventions to alleviate OOP payments were more likely to be pro-poor in rural compared to urban regions. These findings are supported by the concentration index which was closer to zero at UMMC compared to that at HSNZ (0.03

vs. 0.24). While the poor pay as much OOP as the rich in Kuala Lumpur, the poor were largely protected from OOP healthcare payments at Kuala Terengganu.

The National Health and Morbidity Survey 2006 showed that 47.6 per cent of children under-five years with acute diarrhoea first sought treatment at a private clinic (Ministry of Health Malaysia, 2006). In the present study, 79 per cent (353) of children at Kuala Lumpur, almost half of which belong to the two lowest income quintiles, had sought treatment at a private clinic prior to hospitalisation.

The higher fee structure at UMMC compared to HSNZ and different payment collection mechanisms may explain the higher direct hospitalisation payments at UMMC. UMMC is a teaching hospital under Ministry of Higher Education, and while fees are still subsidised, they are higher than other public hospitals under the MOH, Malaysia. As UMMC is the only public hospital in Petaling Jaya, a city with a population of more than a million, its fee structure impacts the poor. Our findings indicate an increased demand for affordable inpatient and outpatient healthcare services in Kuala Lumpur, which is unfulfilled by available public healthcare services.

Two rotavirus vaccines have been available internationally since 2006 (World Health Organization, 2013d) and although these vaccines are available commercially in the private market, Malaysia has yet to introduce the rotavirus vaccine universally. Findings in this chapter suggest that the economic burden of rotavirus gastroenteritis is particularly severe in poorer urban households, who are also least likely to purchase the vaccine privately (Kannan Kutty et al., 2010).

Traditionally, evidence on disease burden and the availability of a safe and effective vaccine that is cost-effective and affordable, was enough to inform decision-making around vaccine introduction. Increasingly, the broader economic impact of vaccination including improvements in financial risk protection and equity, are important considerations (Deogaonkar et al., 2012; R. Rheingans, Atherly, & Anderson, 2012;

Verguet et al., 2013). The World Health Report 2013 states that 'the goal of universal health coverage is to ensure that all people obtain necessary health services without risk of financial ruin or incurring poverty' (World Health Organization, 2013f, p. 5). This current study demonstrates that the introduction of a rotavirus vaccine into a national immunization programme may smooth the path towards universal health coverage by providing financial risk protection to households with the greatest need.

There are several limitations to this study. Both, income and costs obtained were self-reported, which may have led to under-reporting of wages or expenses being over-stated. To minimise bias, multiple interviews were conducted at different time points using a structured questionnaire. Imputation techniques were used to deal with missing values of household income.

The examination of the impact of healthcare expenditure on households should ideally be conducted using longitudinal data, to best estimate the extent of disruption of living standards due to health shocks. Here the catastrophic and poverty impact of acute gastroenteritis was examined using cross-sectional data from public hospitals in two different locations in Malaysia. Nevertheless, this current study was conducted to examine the burden of illness-related expenditure on households, which would potentially be averted by rotavirus vaccination, and not as an exploration of health financing in Malaysia.

While it is usual to define healthcare expenditure as catastrophic when it exceeds a fraction of household income over a year, OOP costs incurred are compared here with monthly income. Expenses incurred for acute diarrhoea is short term and are unlikely to be repeated, as such we do not annualise costs or income. This must be interpreted with caution as expenditure incurred over a single month may not have the same implications on household welfare as expenses over a year, as coping mechanisms like savings and loans are easier to obtain on the short term. Assuming that the effects of illness-related expenditure are felt all at once may overstate the catastrophic impact of payments in the short term, as these are likely to be smoothed over time by coping mechanisms (Adam Wagstaff & Van Doorslaer, 2003). However, large expenses in the short term, may adversely impact the welfare of poor households, with less ability to cope (Alam & Mahal, 2014).

As information on hospital charges actually paid by patients was unavailable at HSNZ, the assumption was made that these charges were zero. Although it was possible to estimate the hospital bill, this would not accurately represent the OOP payments made. While publicly provided healthcare services at MOH hospitals are highly subsidised, many patients do not settle hospital bills. Also, a large segment of patients are exempt from fees including school children, pregnant mothers, public sector employees and their dependents, people with disabilities and the socioeconomically disadvantaged (Kananatu, 2002). The National Health and Morbidity Survey 1996 found that 92.5 per cent of respondents utilised government clinics and 66.4 per cent used government hospitals for free. In addition, the average hospital charges paid in the state of Terengganu was a third that of payments made at Kuala Lumpur (Ministry of Health Malaysia, 1996). At Kuala Lumpur and urban areas, public hospitals are more likely to collect fees as the population served is wealthier. In 2012, the mean average household income for Kuala Lumpur was RM 8,586 per-month as compared to RM 3,967 per-month in Terengganu and the national average income of RM 5,000 (Economic and Planning Unit, 2012). In 2006, unpaid bills amounted to RM 26.1 million or around 0.3 per cent of the MOH budget (Jaafar et al., 2013).

Whilst HSNZ is representative of tertiary hospitals serving rural populations, UMMC may not be representative of all urban public hospitals in Malaysia. UMMC is unique in terms of its status as a teaching hospital and its location in Kuala Lumpur. As a teaching hospital under Ministry of Education, UMMC has a higher fee structure and payment collection mechanism than hospitals under the MOH. Also, UMMC serves the population in Kuala Lumpur, the federal capital of Malaysia, together with the neighbouring city of Petaling Jaya, in the state of Selangor, the most populous and population dense states in Malaysia. The Population and Housing Survey of 2010 reported that the population density in Kuala Lumpur (6,696 per square kilometre) and Selangor (668 per square kilometre) is much higher than the national average of 83 per square kilometre (Department of Statistics Malaysia, 2010b). The population UMMC serves is also considerably more affluent than in other areas.

The information on direct hospitalisation payments at UMMC was obtained through patient interviews. However, if a similar assumption of hospital charges being zero was made at UMMC, the differential impact of payments on households across income quintiles will not be seen.

This study has several strengths. This is the first study of its kind to explore the catastrophic and poverty impact of acute gastroenteritis in Malaysia. By examining costs incurred by households for rotavirus gastroenteritis in urban and rural settings by income quintiles, this allows for the exploration of the potential distributional consequences of universal rotavirus vaccination in Malaysia.

6.5 Conclusion

Although households in Kuala Lumpur have higher income than those in Kuala Terengganu, it is paradoxical that poor urban households may be more vulnerable to the financial impact of healthcare expenditure. The introduction of a universal rotavirus vaccination as an effective preventive measure against childhood diarrhoea, may substantially benefit all families; not only by reducing the disease burden, but also by providing financial risk protection to households with the greatest need.

In the next chapter, the distributional benefits of rotavirus vaccination in providing financial risk protection against the catastrophic and impoverishing impact of illness-related expenditure on households in Malaysia is explored.

CHAPTER 7: ENHANCING EQUITY AND FINANCIAL RISK PROTECTION WITH ROTAVIRUS VACCINATION IN MALAYSIA

7.1 Introduction

The United Nations General Assembly has unanimously endorsed the goal of achieving Universal Health Coverage (UHC) (United Nations, 2012). Towards achieving this goal, health systems are responsible for expanding the range of services that can be accessed, while ensuring equitable distribution of benefits, and financial risk protection against the catastrophic or impoverishing impact of healthcare payments (World Health Organization, 2010, 2013e).

The path to UHC is complex in middle-income countries with mixed public-private healthcare systems. Malaysia is widely credited as having achieved UHC through a public healthcare system that ensures access to subsidised healthcare for the whole population (Savedoff & Smith, 2011). However, perceptions of short-comings in public healthcare, including long waits to access care and inadequate staff numbers, lead patients to seek care in the private sector. This exposes many to the financial risks of OOP payments for private healthcare (Jaafar et al., 2013).

The previous chapter demonstrated that OOP expenses related to rotavirus gastroenteritis hospital admissions may result in financially catastrophic expenditure and even medical impoverishment, especially amongst the poorest. Such OOP healthcare expenditure is inconsistent with the stated aims of UHC, which is to deliver effective interventions as needed, while ensuring equitable distribution of benefits and financial risk protection for all.

Financial risk protection, an essential component in achieving UHC, can be defined as access to quality healthcare as needed without incurring financial hardship (Saksena et al., 2014). Preventive measures such as vaccination may be complementary to health financing strategies as a means to achieve UHC, since they remove the risk of having to pay for illness-related care.

In this chapter, extended cost-effectiveness analysis (ECEA) methods, which explicitly quantifies financial risk protection and distributional benefits of policy, are used to evaluate universal rotavirus vaccination in Malaysia. The chapter begins with Section 7.2, which provides a study overview and describes the rationale behind the use of the ECEA. This is followed by a description of data sources, parameters, and analytical methods used in the analysis. Next, Section 7.3 presents the study findings. This is followed by Section 7.4, which discusses the study findings and limitations. The chapter ends with Section 7.5, which provides the chapter conclusions.

7.2 Materials and methods

7.2.1 Study overview

In this chapter, rotavirus vaccines were evaluated from the perspective of households, using methods of an ECEA. An ECEA was used to evaluate the benefits of universal rotavirus vaccination distributed across national income quintiles in Malaysia, across three domains of (1) health gains - hospitalisations and clinic visits averted, (2) household healthcare expenditure crowded out – OOP direct medical costs averted, and (3) financial risk protection afforded - prevention of financially catastrophic and impoverishing payments.

Rotavirus incidence, health service utilisation, illness-related expenditure and other input parameters were obtained from multiple local data sources. Age-stratified cohorts were distributed into national income quintiles and followed from birth over the first five years of life in the POLYMOD model. The POLYMOD model is the static, multi-cohort model, used in Chapter 5 of this thesis to evaluate cost-effectiveness of rotavirus vaccines in Malaysia. (Jit et al., 2009; Jit & Edmunds, 2007).

The impact of monovalent Rotarix® (GlaxoSmithKline, Rixensart, Belgium) on rotavirus episodes and household expenditure was considered in the base-case. In alternate scenarios, the impact of RotaTeq® (Merck & Co. Inc., USA) and the additional effects of herd immunity were evaluated. Rotarix® was evaluated in the base-case, as this two-dose vaccine was found to be more cost-effective and affordable in Malaysia. Please refer to the results of cost-effectiveness and affordability in Chapter 5 (Subsection 5.3, page 149).

The base year for analysis was 2013. All costs are presented in 2013 Ringgit Malaysia (RM).A discount rate of three per cent per-year was used (Walker et al., 2010). Analysis was conducted using Microsoft Excel® Professional Plus 2013 and R version 3.2.0.

Parameters in the base-case are listed in Table 7.1. The rationale for use of the ECEA is described in Subsection 7.2.2. The data sources and parameters used in the model are described in Subsection 7.2.3 and 7.2.4. The analytical methods of the ECEA is described in Subsection 7.2.5. The scenario analysis is described in Subsection 7.2.6.

Table 7.1: Parameters included in the base-case

Parameter	Value	Source
Demographics		
Birth cohort	508,774	(Department of Statistics Malaysia, 2012b)
Vaccine efficacy [a]		Chapter 5, Subsection 5.2.3.7, page 131
<u>One-dose efficacy:</u>		
Against hospitalisation	96%	(Vesikari, Karvonen, et al., 2007)
Against outpatient visits	88%	(Vesikari, Karvonen, et al., 2007)
<u>Two-dose efficacy:</u>		
Against hospitalisation	100%	(Vesikari, Karvonen, et al., 2007)
Against outpatient visits	92%	(Vesikari, Karvonen, et al., 2007)
<u>Waning immunity</u> (First to second season)		
Against hospitalisation	92%	(Vesikari, Karvonen, et al., 2007)
Against outpatient visits	83%	(Vesikari, Karvonen, et al., 2007)
Vaccination programme		
Vaccine coverage	97%	(World Health Organization, 2013b)
Vaccine wastage	5%	(World Health Organization, 2014b)
Rotavirus incidence [b]		
<u>Hospitalisation</u>	12.2	Chapter 4, Subsection 4.2.2.1, page 59
Utilisation proportion of public care [c] (poorest to richest) (87%, 73%, 77%, 70%, 25%)		(Ministry of Health Malaysia, 2011b)
Utilisation proportion of private care [c] (poorest to richest) (13%, 27%, 23%, 30%, 75%)		(Ministry of Health Malaysia, 2011b)
<u>Outpatient visits</u>	16.2	Chapter 4, Subsection 4.2.2.2, page 63
Utilisation proportion of public care [c] (poorest to richest) (68%, 54%, 43%, 42%, 26%)		(Ministry of Health Malaysia, 2011b)
Utilisation proportion of private care [c] (poorest to richest) (32%, 46%, 57%, 58%, 74%)		(Ministry of Health Malaysia, 2011b)
Costs		
<u>Direct medical costs</u> (poorest to richest) (57, 93, 153, 241,824)		Chapter 6 (Ministry of Health Malaysia, 2011b)

Note:
Direct medical costs are presented in 2013 RM.

[a] The two-dose Rotarix® vaccine is used in the base-case analysis.
Estimation of vaccine efficacy for Malaysia was detailed in Chapter 5, Subsection 5.2.3.7, page 131;

[b] Incidence of rotavirus hospitalisations and outpatient visits were stated as episodes per 1,000 children per-year.

[c] Proportion of utilisation of public and private healthcare was obtained from NHMS 2011. These proportions were presented here for income quintiles, from the poorest to richest quintiles (Ministry of Health Malaysia, 2011b).

7.2.2 Rationale for the extended cost-effectiveness analysis

7.2.2.1 Financial risk protection

The World Health Report 2000 identified three fundamental goals of health systems: (1) health improvement, (2) increasing health system responsiveness, and (3) fairness in financing. Of relevance to this thesis, are the goals of health improvement and fairness in financing. Improving population health is not merely about raising the average level of health, but also involves reducing health inequities in a population. Fairness of financing means that every household pays a fair share of the total healthcare costs for the country[94]. This implies that households should not be impoverished or spend an excessive portion of income to obtain needed health care (Murray & Frenk, 2000; World Health Organization, 2000).

Towards achieving UHC, the World Health Report 2010 recommends that countries provide all people with needed health care of sufficient quality, while ensuring that no one suffers from financial hardship from receiving healthcare (World Health Organization, 2010).

World leaders have endorsed and pledged support to the Agenda for Sustainable Development by the year 2030. Seventeen Sustainable Development Goals (SDGs) with 169 targets were laid out as part of an integrated plan of action for sustainable development for fifteen years beginning from 1st January 2016. The eight target of the third SDG specifically targets UHC:

> "Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all." (United Nations, 2015).

[94] A 'fair' share implies progressivity in financing. In which the rich pay more as a proportion of household income on healthcare compared to the poor. To ensure that all people are protected from the financial consequences of healthcare, it may also mean that the poor may pay nothing at all.

The MOH, Malaysia has emphasised the need for a health system that is equitable, affordable and ensures UHC. This is clearly stated in the MOH Vision for Health:

> "Malaysia is to be a nation of healthy individuals, families and communities, through a health system that is equitable, affordable, efficient…" (Ministry of Health Malaysia, 2008, p. 4).

The Tenth Malaysia Health Plan (2011 to 2015) proposed a plan to restructure the current national healthcare system, to deal with challenges posed by increasing private healthcare spending. The proposal was for a restructured national health system that ensured UHC:

> "The restructured national health system is one that is responsive and provides choice of quality health care, ensuring universal coverage for health care needs of population based on solidarity and equity."(Ministry of Health Malaysia, 2010, p. 53).

Financial risk protection refers to how far people are protected from the financial consequences of ill health (Moreno-Serra, Millett, & Smith, 2011). Two main concepts are used to measure financial risk protection in health, and both these concepts relate to illness-related spending above a certain threshold of living standards (Moreno-Serra et al., 2011; Peter C Smith, 2005). The first measure defines illness-related expenditure as financially catastrophic if it exceeds a critical threshold of household income. The second measure defines illness-related expenditure as impoverishing if the household income is pushed below a pre-defined poverty line after payments (Saksena et al., 2014).

7.2.2.2 Extended cost-effectiveness analysis

Traditionally economic evaluation of vaccines have focused on the narrow benefits of the cost-effectiveness analysis, namely illness averted and costs savings to the healthcare system, underestimating the broader economic impacts of vaccination. The broader economic impacts of vaccination encompasses among others, the long term benefits of improved health to individuals and societies (including increased lifetime productivity which is linked with improved educational attainment, job performance and lifetime earnings), community and health system externalities (including improvements in equity and financial risk protection) and the impact to the broader economy (impact on public sector budget and macroeconomic impact) (Bärnighausen, Bloom, Cafiero-Fonseca, & O'Brien, 2014; Bloom et al., 2005; Deogaonkar et al., 2012; Jit et al., 2015).

The majority of economic evaluations of vaccination programmes focus on achieving efficiency, particularly on improving population health, ignoring broader considerations of equity and financial risk protection, which are fundamental health system goals. In this thesis, methods of an ECEA are used to evaluate the benefits of rotavirus vaccine in providing financial risk protection and reducing inequities in Malaysia.

The ECEA evaluates the consequences of health interventions in multiple domains of health gains, household healthcare expenditure averted, and financial risk protection afforded, across socio-economic strata. ECEA is a new methodology developed to inform policy on the universal public finance of programmes. Universal public finance is the government's financing of programmes for the benefit of all, irrespective of who is receiving it (Verguet et al., 2013).

ECEA has been used to inform on the benefits of public finance of universal rotavirus vaccination in India and Ethiopia (Verguet et al., 2013), measles vaccination in Ethiopia (Driessen, Olson, Jamison, & Verguet, 2015), HPV vaccination in China (Levin et al., 2015) and tuberculosis treatment in India (Verguet, Laxminarayan, & Jamison, 2015). Also, ECEA was conducted to inform health policy on selected interventions for public finance by the government of Ethiopia (Verguet, Olson, et al., 2015) and on tobacco taxation in China (Verguet, Gauvreau, et al., 2015).

The ECEA builds on the traditional cost-effectiveness analysis framework, while quantifying the broader value of universal vaccination starting with non-health benefits such as household healthcare expenditure averted, financial risk protection, and equity. These dimensions provide information in addition to the results of cost-effectiveness analysis, to better enable decision-makers to evaluate policy on the public finance of health programmes (Verguet, Laxminarayan, et al., 2015).

Firstly, the ECEA examines the direct financial implications of policy on households, as a result of crowding out private expenditure. Interventions like universal rotavirus vaccination by preventing of illness, also averts expenditure related to illness.

Secondly, the ECEA explicitly measures financial risk protection, an essential dimension considered by the WHO towards achieving UHC (World Health Organization, 2010). The ECEA methods exhibits a vector of poverty reduction, critical for stake holders like the Ministers of Finance, development agencies and other funders, when considering investments in health (Verguet, Laxminarayan, et al., 2015). The global importance of poverty eradication is exemplified with the SDGs, in which the first goal is a commitment to eradicate poverty in all its forms everywhere[95] (United Nations, 2015).

Finally, the ECEA evaluates the distributional consequences of policy across socio-economic strata of a population. Inequities may be evaluated by disaggregating key variables by wealth or income strata, residence (urban or rural), ethnicity, age, gender and others (Boerma, AbouZahr, Evans, & Evans, 2014). The ECEA allows measurement of both the levels and distribution of benefits of policy, which is vital towards monitoring progress towards UHC.

[95] The first SDG commits to eradicate poverty in all its forms. SDG Goal 1.1 states “By 2030, eradicate extreme poverty for all people everywhere, currently measured as people living on less than US$1.25 a day”. SDG Goal 1.2 states “By 2030, reduce at least by half the proportion of men, women and children of all ages living in poverty in all its dimensions according to national definitions” (United Nations, 2015).

Specifically, ECEA was used in this thesis to evaluate universal rotavirus vaccination in Malaysia, in three domains of (1) health gains - hospitalisations and clinic visits averted, (2) household healthcare expenditure crowded out – OOP direct medical costs averted, and (3) financial risk protection afforded - prevention of financially catastrophic and impoverishing payments, distributed across the income strata of the country.

7.2.3 Data sources

7.2.3.1 The National Health and Morbidity Survey 2011

The National Health and Morbidity Surveys (NHMS) are a series of nationwide household health surveys conducted by the MOH, Malaysia. These surveys are carried out at regular intervals to assess health status, disease patterns and health-seeking behaviour of the Malaysian population.

The NHMS 2011 is the fourth household health survey in this series and was conducted in 2011. The general aim of the NHMS 2011 was to provide community based health data to support the MOH, Malaysia in reviewing health priorities, strategies, activities and the planning of resource allocation. One of the specific aims of NHMS 2011 was to ascertain health care demand of the community in Malaysia. This included determining the load of illness, the health seeking behaviour, health utilisation patterns and healthcare consumption costs of the community in Malaysia.

The sampling frame for the NHMS 2011 was provided by the Department of Statistics, Malaysia, and was updated in 2010 prior to the National Population and Housing Census 2010. Based on this sampling frame, the country was divided into Enumeration Blocks (EBs), which were geographically contiguous areas with identifiable demarcations. In 2010, there were approximately 75,000 EBs in Malaysia, each containing between 80 to 120 Living Quarters (LQs). Each LQ had an average of 500 to 600 people. Sample size was determined by examining the prevalence rate for diseases and health problems in

Malaysia from the NHMS 2006, with a margin of error of between 0.01 and 0.05, and a confidence interval of 95 per cent.

The NHMS 2011 ensured national representativeness by using a two-stage, stratified sampling design, targeting both urban and rural areas[96], in all states in Malaysia. The two strata were the primary stratum, which consisted of all the states and Federal Territories in Malaysia, and the secondary stratum, which was made up of all the urban and rural areas within the primary stratum. Sampling was conducted in two stages, with the EBs as the primary sampling unit and the LQs within each sampled EBs, as the secondary sampling unit. A total of 794 EBs were selected from all the EBs in Malaysia. From each selected EBs, twelve LQs were selected randomly and all households within these selected LQs were included in the study.

A total of 9,528 LQs were sampled for this survey with 8,529 LQs eligible, and a response rate of 88.2 per cent at LQs. Each LQ had an average of 4.1 individuals. A total of 30,806 individuals were eligible and 28,650 were interviewed, with a response rate of 93.0 per cent of individuals (Ministry of Health Malaysia, 2011b).

For this current chapter, the NHMS 2011 provided information on the average OOP healthcare expenditure and utilisation patterns for both inpatient and outpatient care, at public and private health facilities by national income quintiles in Malaysia (Ministry of Health Malaysia, 2011b). The NHMS 2011 was chosen for use in this chapter, as it was the most recent national household health survey. Also the NHMS 2011 was conducted close to the study period of the 2010 hospital-based rotavirus study, which also provided data for this chapter (Lee et al., 2012).

[96] The classification of urban or rural areas for this survey was done by the Department of Statistics based on the population size of gazetted areas at the time of the 2010 census. An urban area was defined as a gazetted area with a combined population of 10,000 or more. While a rural area was defined as a gazetted area with a population of less than 10,000.

7.2.3.2 Hospital-based rotavirus study

The two-year prospective rotavirus study conducted at two public hospitals in Malaysia from 2008 to 2010, collected information on illness-related expenditure for all children younger than five years admitted for acute diarrhoea. This hospital-based rotavirus study was the source for OOP direct medical costs for public hospitals, used in this current analysis. This dataset was described and analysed in Chapter 6.

The national income quintiles used for this chapter was obtained from the NHMS 2011 (Ministry of Health Malaysia, 2011b). As income quintiles from the hospital-based rotavirus study (Lee et al., 2012) corresponds with the national income quintiles obtained from NHMS 2011, direct medical costs for rotavirus episodes treated at public hospitals by income quintiles was obtained from this hospital-based study.

Table 7.2 shows a comparison of income between the NHMS 2011 dataset and the hospital-based rotavirus study.

Table 7.2: Comparison of income quintiles between the National Health and Morbidity Survey 2011 and the hospital-based rotavirus study datasets

Income Quintile	NHMS 2011			Hospital-based rotavirus study		
	Mean	Minimum	Maximum	Mean	Minimum	Maximum
1 (poorest)	819	0	1,442	962	332	1,438
2	1,984	1,451	2,525	2,005	1,494	2,434
3	3,234	2,529	3,930	3,322	2,545	3,873
4	4,898	3,932	6,086	4,957	3,983	6,086
5 (richest)	10,556	6,096	62,685	8,228	6,196	16,598

Costs are in 2013 RM;

NHMS 2011 is the National Health and Morbidity Survey 2011. The hospital-based rotavirus study was conducted at University of Malaya Medical Centre, Kuala Lumpur and Hospital Sultanah Nur Zahirah, KualaTerengganu;

The mean, minimum and maximum values of income for income quintiles are reported for both datasets.

7.2.4 Parameters in the model

7.2.4.1 Vaccine characteristics

The rotavirus vaccines were assumed to follow the routine schedule for DTP vaccines in Malaysia. Thus, Rotarix® vaccines was assumed to be administered at the age two and three months. Rotavirus vaccine coverage was based on the third dose DTP coverage of 97 per cent in Malaysia (World Health Organization, 2013b). Subsection 5.2.3.7 (page 131) details the estimation of rotavirus vaccine efficacy, for both complete and partial regimes of Rotarix® in Malaysia (Table 7.1).

7.2.4.2 Rotavirus incidence

Rotavirus episodes considered here are episodes of rotavirus diarrhoea presenting to the healthcare system, requiring either inpatient or outpatient care, at public or private facilities. Episodes of rotavirus diarrhoea presenting to the healthcare system are relevant for consideration by budget holders and policy makers. The estimation of rotavirus incidence is detailed in Chapter 4, and a summary is presented here of parameters used in the ECEA.

The annual incidence of rotavirus hospitalisations of 12.2 per 1,000 children under-five years was estimated from diarrhoeal discharges to public and private hospitals in Malaysia, reported to the MOH, Malaysia (Subsection 4.2.2.1, page 59). The annual incidence of rotavirus outpatient visits of 16.2 per 1,000 children under-five years was estimated based on diarrhoeal outpatient visits reported to MOH, Malaysia. Outpatient visits were reported from MOH public health clinics and hospitals, and was estimated for private health clinics (Subsection 4.2.2.2, page 63).

The proportion of diarrhoeal disease attributable to rotavirus for hospitalised episodes (44.5 per cent) was obtained from a meta-analysis conducted of primary hospital-based studies in Malaysia [Subsection 4.2.2.5(c), page 75]. A one year, community-based rotavirus surveillance study provided rotavirus detection proportions for acute gastroenteritis treated at outpatient settings (18 per cent) [Subsection 4.2.2.5(a), page 74].

The age distribution of children presenting with rotavirus diarrhoea from the hospital-based study was applied to all episodes in the model (Lee et al., 2012). (23 per cent in children under 12 months, 37 per cent in children aged 12 to 23 months, 19 per cent in children aged 24 to 35 months, 11 per cent in children aged 36 to 47 months and nine per cent in children aged 48 to 59 months).

As rotavirus diarrhoea occurs in all children irrespective of socio-economic status (Parashar et al., 2003; World Health Organization), episodes of rotavirus gastroenteritis were distributed evenly across income quintiles. Malaysia has a tax-based, public healthcare system that guarantees access to healthcare for all people regardless of income. As such, the number of rotavirus gastroenteritis episodes receiving inpatient and outpatient treatment were not varied by income quintile. However, utilisation of public and private healthcare varies according to household income. Proportions of health service utilisation by income quintile were obtained from the NHMS 2011. This allowed for the distribution of health episodes to public or private care in each income quintile (Ministry of Health Malaysia, 2011b). See Table 7.1 for the incidence of rotavirus diarrhoea and proportions of utilisation of private and public care by income quintile in Malaysia.

Table 7.3 presents results of the distribution of rotavirus gastroenteritis episodes in Malaysia by income quintile.

Table 7.3: Distribution of annual rotavirus episodes by income quintile in Malaysia

Income quintile	Inpatient care					Outpatient care				
	Public	(%) [a]	Private	(%) [b]	Total	Public	(%) [a]	Private	(%) [b]	Total
1 (poorest)	5,403	(87%)	827	(13%)	6,230	5,593	(68%)	2,659	(32%)	8,252
2	4,576	(73%)	1,654	(27%)	6,230	4,438	(54%)	3,813	(46%)	8,252
3	4,805	(77%)	1,424	(23%)	6,230	3,567	(43%)	4,685	(57%)	8,252
4	4,392	(70%)	1,838	(30%)	6,230	3,467	(42%)	4,785	(58%)	8,252
5 (richest)	1,558	(25%)	4,672	(75%)	6,230	2,184	(26%)	6,068	(74%)	8,252
Total	20,733	(67%)	10,415	(33%)	31,148	19,250	(47%)	22,010	(53%)	41,260

Note:
Annually, rotavirus gastroenteritis was estimated to result in 31,000 hospitalisations and 41,000 outpatient visits (Table 4.8). Estimation of rotavirus burden for Malaysia is detailed in Chapter 4 (Subsection 4.2.2, page 59);

Rotavirus episodes were first distributed evenly across income quintiles, into episodes requiring inpatient and outpatient care. Subsequently, episodes were distributed by treatment sought at public or private healthcare using proportions of healthcare utilisation of public and private from NHMS 2011 (Table 7.1);

[a] Health utilisation proportions of public care at inpatient and outpatient settings, for each income quintile from the poorest to the richest, was obtained from NHMS 2011.(Ministry of Health Malaysia, 2011b);

[b] Health utilisation proportions of private care at inpatient and outpatient settings, for each income quintile from the poorest to the richest, was obtained from NHMS 2011. (Ministry of Health Malaysia, 2011b).

7.2.4.3 Direct medical costs

In this chapter, OOP direct medical costs were considered for rotavirus episodes seeking care (hospitalisations and outpatient clinic visits). Direct medical costs were healthcare expenditure paid OOP by patients, including costs for consultation, medication and hospital charges for an illness episode.

OOP direct medical costs for public inpatient care by income quintile was obtained from the 2010 hospital-based rotavirus study analysed in Chapter 6 (Lee et al., 2012). Mean OOP direct medical costs by income quintiles was obtained from the combined dataset of UMMC and HSNZ. These were RM 57, RM 93, RM 153, RM 241 and RM 824, for each income quintile from poorest to richest. (Table 7.1)

A ratio of OOP direct medical costs of private to public hospital care by income quintile, was obtained from the NHMS 2011. These ratios were 2.3, 1.9, 4.5, 6.5 and 18.4, for each income quintile from poorest to richest (Ministry of Health Malaysia, 2011b). These ratios of OOP direct medical costs of private to public hospital care (from NHMS 2011) was multiplied with the OOP direct medical costs for hospitalisations[97] (from the 2010 hospital-based study), to calculate OOP direct medical costs for private hospital inpatient care by income quintile in Malaysia. (Table 7.4)

OOP direct medical costs for public and private outpatient visits by income quintile were obtained directly from NHMS 2011 (Ministry of Health Malaysia, 2011b).

Table 7.4 shows average OOP direct medical costs for inpatient and outpatient care at public and private healthcare, per-episode of rotavirus gastroenteritis by income quintile in Malaysia.

[97] OOP direct medical costs from the 2010 study consisted of pre-hospitalisation consultation costs and hospitalisation costs. OOP direct medical costs for private inpatient care was calculated by multiplying hospitalisations costs from the hospital-based study, with the ratio of private to public OOP healthcare costs from NHMS 2011. The ratio of private to public OOP healthcare costs were 2.3, 1.9, 4.5, 6.5 and 18.4, for each income quintile from poorest to richest.

Table 7.4: Out-of-pocket direct medical costs per-episode of rotavirus gastroenteritis by income quintile in Malaysia

Income quintile	Direct medical costs			
	Inpatient care		Outpatient care	
	Public [a]	Private [b]	Public [c]	Private [c]
1 (poorest)	115.87	204.30	0.63	9.23
2	191.52	254.47	1.08	13.38
3	221.65	755.64	1.83	13.38
4	245.87	1,240.11	1.82	26.99
5 (richest)	288.68	2,400.72	0.20	44.63

Note:

Costs are in 2013 RM;

[a] OOP direct medical costs for public inpatient care was obtained from the combined dataset of UMMC and HSNZ, from the 2010 hospital-based rotavirus study (Lee et al., 2012). OOP direct medical costs from the 2010 study consisted of pre-hospitalisation consultation costs and hospitalisation costs;

[b] OOP direct medical costs for private inpatient care was calculated by multiplying hospitalisations costs from the hospital-based study, with the ratio of private to public OOP healthcare costs from NHMS 2011. The ratio of private to public OOP costs were 2.3, 1.9, 4.5, 6.5 and 18.4, for each income quintile from poorest to richest;

[c] OOP direct medical costs for outpatient visits to public and private healthcare was obtained directly from NHMS 2011 (Ministry of Health Malaysia, 2011b).

7.2.4.4 Catastrophic expenditure

Illness-related expenditure is regarded as financially catastrophic when it exceeds a certain fraction of household income, as it is likely to disrupt household living standards. While there is some debate on the appropriate threshold for use as a marker for catastrophic expenditure, the threshold of ten per cent of monthly household income was used in this thesis. The threshold of ten per cent has previously been used by researchers at the World Bank, to indicate catastrophic healthcare payments (O'Donnell & Wagstaff, 2008; Adam Wagstaff & Van Doorslaer, 2003).

The choice of threshold for catastrophic expenditure is normative. The rationale being expenditures above the threshold ten per cent of household income are considered to be at the expense of other goods and service, forcing households to reduce consumption of basic needs and disrupting household living standards (S. Russell, 2004).

The rationale for the estimation of catastrophic expenditure and the use of the catastrophic threshold of ten per cent of monthly household income in this thesis, was explained in Chapter 6 (Subsection 6.2.4.4, page 174).

7.2.4.5 Impoverishment

Healthcare payments are impoverishing, when households with incomes above the poverty line prior to payments, fall below the poverty line as a consequence of OOP healthcare payments. The poverty line income is the threshold below which even a minimum standard of living is not ensured (Ravallion, 2010).

In this chapter, a household is considered impoverished if total monthly income falls below the 2009 Poverty Line Income for Malaysia (RM 886 in 2013 RM), after payment of direct medical costs (Department of Statistics Malaysia, 2009, p. 99). Incidence of medical impoverishment is measured as the proportion of households impoverished due to rotavirus gastroenteritis related health spending. The rationale for the measure of impoverishment and the use of the Poverty Line Income for Malaysia was explained in Chapter 6 (Subsection 6.2.4.5, page 178).

7.2.5 Analytical methods

The national income quintiles used for this chapter was obtained from the NHMS 2011 (Ministry of Health Malaysia, 2011b). As income groups from the hospital-based rotavirus study (Lee et al., 2012) corresponds with the national income quintiles obtained from NHMS 2011, direct medical costs for rotavirus episodes treated at public hospitals by income quintiles was obtained from this hospital-based study.

A histogram plotted to visualise the distribution of household income, revealed a log-normal distribution of income by quintile. Also, a histogram plotted to visualise the distribution of OOP direct medical costs showed that direct medical costs divided into income quintiles had log-normal distributions.

Estimation of catastrophic and poverty impact of OOP direct medical costs was done using R version 3.2.0. The mean and standard deviation of each income quintile was used to generate log-normal income distributions of income. Direct medical costs was also distributed according to log-normal distributions, using mean and standard deviations of costs for each income quintile. Estimating the standard deviation of OOP direct medical costs by income quintile is shown in Subsection 7.2.5.1.

Subsequently, the proportions of those incurring catastrophic expenditure or impoverishment in each income quintile was estimated. The proportion of those incurring catastrophic expenditure were the proportion of those with OOP direct medical expenditure above the threshold of ten per cent of household income. The proportion of those with medical impoverishment, was the proportion of households with household income below the Malaysian Poverty Line Income after deducting OOP direct medical costs (RM 886 in 2013 RM) (Department of Statistics Malaysia, 2009, p. 99). This was excluding those with income below the poverty line prior to deduction of healthcare expenses.

To evaluate the impact of vaccination in reducing catastrophic and impoverishing payments, vaccine efficacy specific to inpatient and outpatient treated episodes was multiplied with the proportions of catastrophic payments and impoverishment for each of these categories.

7.2.5.1 Estimating the standard deviation for out-of-pocket direct medical costs by income quintile

Average OOP direct medical costs by income quintile was calculated by dividing the sum of inpatient and outpatient costs, with the incidence of rotavirus gastroenteritis for each income quintile.

Average OOP costs = (inpatient costs + outpatient costs)/Incidence

c_1	Hospitalisation costs	2010 hospital-based study
c_2	Pre-hospitalisations costs	2010 hospital-based study
u_1	Proportion of utilisation of public care	NHMS 2011
u_2	Proportion of utilisation of private care	NHMS 2011
m	ratio of private to public OOP direct medical costs	NHMS 2011
$c_1 + c_2$	Public inpatient costs	2010 hospital-based study
mc_1	private inpatient costs	Author's calculation

Inpatient costs = public inpatient costs + private inpatient costs

Inpatient costs

$$= \frac{[(\mathbf{c_1} + \mathbf{c_2})\,\mathbf{u_1} + (\mathbf{mc_1})\,\mathbf{u_2}]}{(\mathbf{u_1} + \mathbf{u_2})}$$

Since utilisation of public and private care was a proportion of total healthcare,

$$(\mathbf{u_1} + \mathbf{u_2}) = \mathbf{1}$$

Hence, Inpatient costs

$$= (\mathbf{c_1} + \mathbf{c_2})\,\mathbf{u_1} + (\mathbf{mc_1})\,\mathbf{u_2}$$

This formula was applied directly to the combined dataset of UMMC and HSNZ from the 2010 hospital-based rotavirus study, to obtain inpatient costs. Inpatients costs were then divided into income quintile, to obtain mean and standard deviations for each income quintile. These standard deviations by income quintile were used to distribute OOP direct medical costs according to log-normal distributions.

7.2.6 Scenario analysis

Alternate scenarios were considered to explore the uncertainty around vaccine impact estimates. These scenarios were (1) vaccination with RotaTeq® (Merck & Co. Inc., West Point, PA, USA), and (2) considering the benefits of herd immunity.

Scenario analysis was also conducted to evaluate the impact of vaccination on all illness-related costs relevant to households, including (1) direct costs – direct medical and non-medical costs, and (2) direct and indirect costs.

7.2.6.1 RotaTeq®

RotaTeq® is a pentavalent, live attenuated rotavirus vaccine recommended by the WHO for inclusion into the national immunisation programmes worldwide (World Health Organization, 2013d). The vaccination schedule for the three-dose RotaTeq® vaccine was assumed at two, three and five months of age, following the administration schedule of DTP vaccines in Malaysia. Chapter 5 details the estimation of RotaTeq® vaccine efficacy for complete and partial regimes (Subsection 5.2.3.7, page 135)

7.2.6.2 Herd immunity

Herd immunity is the protection conferred to unvaccinated individuals, when a sufficiently large proportion of the population is vaccinated. The indirect benefits of rotavirus vaccination have long been evidenced in numerous post-licensure studies in high- and middle-income countries worldwide (Lopman et al., 2012; Pollard et al., 2015; Seybolt & Bégué, 2012).

In this scenario the additional benefits of herd-immunity were included the evaluation. The POLYMOD model incorporates the benefits of herd immunity based on results of a transmission dynamic model of rotavirus vaccination in Belgium (Jit et al., 2009).

7.2.6.3 Direct non-medical costs

Direct non-medical costs are expenditure above normal consumption for transportation, diapers and food, during an illness episode.

Direct non-medical costs for public inpatient care by income quintile, was obtained from the 2010 hospital-based study (Lee et al., 2012). Direct non-medical costs for episodes requiring private inpatient care, and public and private outpatient care were obtained from the estimation of rotavirus burden shown in Chapter 4 (Subsection 4.2.3.2, page 88)[98]. These costs were distributed into income quintiles, by using weighted averages for transportation, diapers and food costs by income quintiles from the 2010 hospital-based study.

7.2.6.4 Indirect costs

Productivity loss was calculated by multiplying daily wage with days of work missed to care for an episode of rotavirus gastroenteritis.

The minimum monthly wage in Malaysia of RM 900 in 2013 was used as the benchmark for productivity loss in this chapter (Attorney General's Chambers Malaysia, 2012). This was a conservative assumption of productivity loss, as minimum wages is assumed for all income groups, including non-wage earning carers like housewives and those in the informal sector, without fixed wage rates. The average duration of diarrhoeal illness in children under five years of age of 2.7 days, was obtained from NHMS 2006, was assumed to represent days of work missed for rotavirus gastroenteritis episodes (Ministry of Health Malaysia, 2006). This is a conservative assumption, as work days lost were assumed to be the same for all diarrhoeal episodes regardless of severity.

As wage-earners were assumed to work six days a week, daily wage was calculated by dividing the monthly minimum wage by 26. The Malaysian monthly minimum wage was multiplied with the average duration of diarrhoea to estimate productivity loss of RM 93 per-episode.

[98] Estimation of direct non-medical costs for inpatient and outpatient care, at both public and private healthcare facilities are shown in Chapter 4 (Subsection 4.2.3.2, page 108).

7.3 Results

7.3.1 General findings

Rotavirus episodes were distributed evenly across income quintiles. However the utilisation of public and private services varied by income, with the rich utilising more private care, and the poor utilising more public care. Despite the availability of subsidised public care, the poorest still utilise private care, especially for outpatient treatment. (Table 7.3)

The richest spend the most on rotavirus-related direct medical costs compared to all other income groups especially the poorest (RM 824 vs. RM 57) (Figure 7.1). The richest are likely to incur higher healthcare expenditure due to the utilisation of more expensive private care (Table 7.4). The poor pay less than the rich in direct medical costs. However, the poorest are second only to the richest income quintile, in terms of OOP direct medical costs as a percentage of total household income (six per cent vs. ten per cent) (Figure 7.1).

OOP direct medical costs for rotavirus results in catastrophic expenditure among all income groups, and impoverishment among the poorest three income quintiles. Surprisingly, about forty per cent of the richest spent more than ten per cent of household income on direct medical costs for rotavirus, although none were impoverished. (Table 7.5)

Prior to deducting healthcare expenditure, forty per cent of those in the poorest quintile had income below the poverty line. Despite the high-frequency of catastrophic payments among the richest quintile, the poorest were vulnerable to health shocks with twelve per cent experiencing catastrophic payments and five per cent impoverished due to rotavirus-related expenditure. (Table 7.5)

Figure 7.1 shows average OOP direct medical costs for rotavirus gastroenteritis by income quintile in Malaysia.

7.3.2 Base-case analysis

Rotavirus vaccination resulted in substantial reduction of rotavirus episodes (76 per cent) and OOP direct medical expenditure (84 per cent), evenly across all income groups. Annually, rotavirus vaccination would result in savings of RM 16.7 million in OOP direct medical costs to households seeking care for rotavirus episodes. These benefits were evenly distributed across income quintiles.

Vaccination with Rotarix® averted catastrophic expenditure evenly among all income groups (83 per cent). While, poverty reduction benefits were concentrated among the poorest three quintiles (83 per cent).

Benefits of rotavirus vaccination are detailed in Table 7.5. Table 7.5 shows the outcomes of rotavirus vaccination compared with no vaccination by income quintile in Malaysia. The outcomes of rotavirus vaccination was expressed in terms of rotavirus gastroenteritis episodes, OOP direct medical costs, catastrophic and impoverishing healthcare payments.

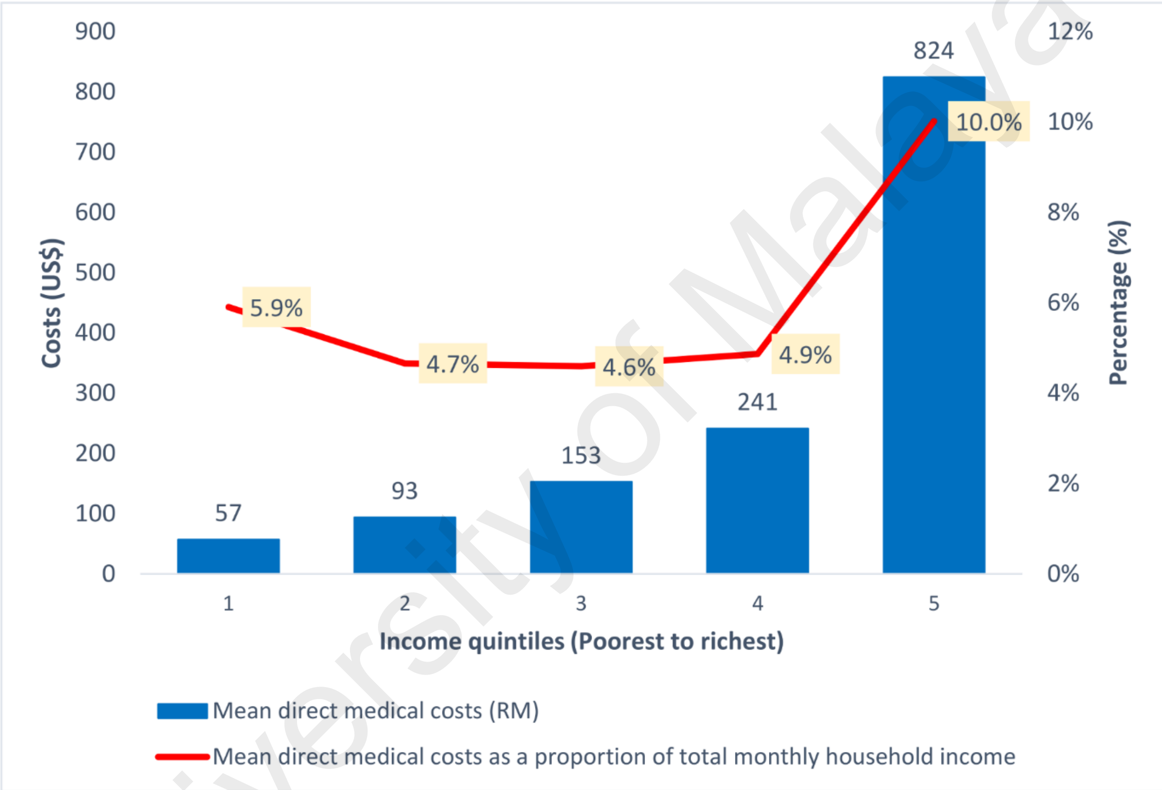


Figure 7.1: Average out-of-pocket direct medical costs for rotavirus gastroenteritis by income quintiles in Malaysia

Note:

All costs are in 2013 RM;

The blue bars denotes average out-of-pocket direct medical costs to households resulting from rotavirus diarrhoea episodes seeking care. The red line denotes average out-of-pocket direct medical costs as a proportion of household income for each income quintile. The blue bars relate to the left-hand y-axis. The red line relates to the right-hand y-axis.

Table 7.5: Outcomes of rotavirus vaccination compared with no vaccination by income quintile in Malaysia

Income quintiles	**(Poorest) 1**			**2**			**3**			**4**			**(Richest) 5**		
Vaccination	**No Vaccine**	**Vaccine**	**Δ**	**No Vaccine**	**Vaccine**	**Δ**	**No Vaccine**	**Vaccine**	**Δ**	**No Vaccine**	**Vaccine**	**Δ**	**No Vaccine**	**Vaccine**	**Δ**
Rotavirus episodes (×'000)	14.5	3.5	(76%)	14.5	3.5	(76%)	14.5	3.5	(76%)	14.5	3.5	(76%)	14.5	3.5	(76%)
OOP direct medical costs (×'000 RM)	823	131	(84%)	1,353	217	(84%)	2,210	351	(84%)	3,494	559	(84%)	11,937	1,880	(84%)
Catastrophic payments [a] (%)	11.54%	1.93%	(83%)	12.18%	2.02%	(83%)	12.89%	2.13%	(84%)	16.81%	2.78%	(84%)	42.33%	6.96%	(84%)
Impoverishment [b] (%)	5.01%	0.86%	(83%)	1.19%	0.20%	(83%)	0.52%	0.09%	(83%)	0.11%	0.02%	(79%)	0.05%	0.01%	(73%)

Note:

OOP, out-of-pocket costs; Costs are in 2013 RM;

Δ, the percentage difference between 'vaccine' and 'no vaccine' groups are shown in parenthesis. The vaccine group shows outcomes of Rotarix® vaccination;

[a] Proportions of catastrophic payments are the proportions of households with OOP direct medical costs for rotavirus gastroenteritis above ten per cent of total monthly household income;

[b] Proportions of medical impoverishment are the proportion of households with household income below the Malaysian Poverty Line Income, RM 886 in 2013 RM (Department of Statistics Malaysia, 2009, p. 99) after deducting OOP direct medical costs. This was after excluding households with income below the poverty line prior to deduction of healthcare expenses;

7.3.3 Scenario analysis

Both commercially available vaccines were found to have similar impact and distributional implications on rotavirus gastroenteritis incidence, expenditure, and financial risk protection.

Herd immunity provides substantial additional benefits in reducing rotavirus gastroenteritis episodes, direct medical costs, and alleviating the catastrophic and impoverishing impact of healthcare payments. Impact of RotaTeq® vaccines and the additional benefits of herd immunity are shown in Table 7.5.

When all household costs (direct and indirect costs) were considered, Rotarix® resulted in substantial reduction in household expenditure (81 per cent) and catastrophic expenditure (80 per cent) among all income groups. Rotarix® prevented impoverishment (80 per cent) among the poorest three quintiles. Vaccine impact on all household costs are shown in Table 7.7.

Table 7.6: Scenario analysis comparing the impact of both rotavirus vaccines and herd immunity on outcome measures

Income quintiles	(Poorest) 1			2			3			4			(Richest) 5		
Vaccination	**No Vaccine**	**Vaccine**	**Δ**	**No Vaccine**	**Vaccine**	**Δ**	**No Vaccine**	**Vaccine**	**Δ**	**No Vaccine**	**Vaccine**	**Δ**	**No Vaccine**	**Vaccine**	**Δ**
Episodes (×'000)															
RotaTeq®	14.5	4.2	(71%)	14.5	4.2	(71%)	14.5	4.2	(71%)	14.5	4.2	(71%)	14.5	4.2	(71%)
Rotarix®	14.5	3.5	(76%)	14.5	3.5	(76%)	14.5	3.5	(76%)	14.5	3.5	(76%)	14.5	3.5	(76%)
Herd Immunity	14.5	1.1	(93%)	14.5	1.1	(93%)	14.5	1.1	(93%)	14.5	1.1	(93%)	14.5	1.1	(93%)
Direct medical costs (×'000 RM)															
RotaTeq®	823	155	(81%)	1,353	256	(81%)	2,111	414	(81%)	3,494	659	(81%)	11,937	2,216	(81%)
Rotarix®	823	131	(84%)	1,353	217	(84%)	2,111	351	(84%)	3,494	559	(84%)	11,937	1,879	(84%)
Herd Immunity	823	34	(96%)	1,353	56	(96%)	2,111	90	(96%)	3,494	144	(96%)	11,937	480	(96%)
Catastrophic expenditure (%)															
RotaTeq®	11.54%	2.27%	(80%)	12.18%	2.39%	(80%)	12.89%	2.51%	(81%)	16.81%	3.28%	(80%)	42.33%	8.20%	(81%)
Rotarix®	11.54%	1.93%	(83%)	12.18%	2.02%	(83%)	12.89%	2.13%	(83%)	16.81%	2.78%	(83%)	42.33%	6.96%	(84%)
Herd Immunity	11.54%	0.49%	(96%)	12.18%	0.52%	(96%)	12.89%	0.54%	(96%)	16.81%	0.71%	(96%)	42.33%	1.76%	(96%)
Impoverishment (%)															
RotaTeq®	5.01%	1.01%	(80%)	1.19%	0.24%	(80%)	0.52%	0.10%	(80%)	0.11%	0.03%	(75%)	0.05%	0.02%	(68%)
Rotarix®	5.01%	0.86%	(83%)	1.19%	0.20%	(83%)	0.52%	0.09%	(83%)	0.11%	0.02%	(79%)	0.05%	0.01%	(73%)
Herd Immunity	5.01%	0.22%	(96%)	1.19%	0.05%	(96%)	0.52%	0.02%	(96%)	0.11%	0.01%	(94%)	0.05%	0.00%	(92%)

Note: Costs are in 2013 RM;

Δ, the percentage difference between 'vaccine' and 'no vaccine' groups are shown in parenthesis;

Scenarios compared here are vaccination with RotaTeq®, Rotarix®, and additional herd immunity. The scenario with Rotarix® is the base case scenario.

Table 7.7: Scenario analysis considering the impact of vaccination on household costs for rotavirus gastroenteritis

Income quintiles	(Poorest) 1			2			3			4			(Richest) 5		
Vaccination	**No Vaccine**	**Vaccine**	**Δ**	**No Vaccine**	**Vaccine**	**Δ**	**No Vaccine**	**Vaccine**	**Δ**	**No Vaccine**	**Vaccine**	**Δ**	**No Vaccine**	**Vaccine**	**Δ**
Costs (×’000 RM)															
Direct medical costs	823	131	(84%)	1,353	217	(84%)	2,211	351	(84%)	3,494	559	(84%)	11,937	1,880	(84%)
Direct costs	1,103	189	(83%)	1,879	323	(83%)	2,819	473	(83%)	4,175	695	(83%)	12,618	2,015	(84%)
Direct and indirect costs	2,456	513	(79%)	3,232	647	(80%)	4,172	798	(81%)	5,528	1,019	(82%)	13,972	2,340	(83%)
Catastrophic expenditure (%)															
Direct medical costs	11.54%	1.93%	(83%)	12.18%	2.02%	(83%)	12.89%	2.13%	(83%)	16.81%	2.78%	(83%)	42.33%	6.96%	(84%)
Direct costs	15.72%	2.77%	(82%)	17.87%	3.12%	(83%)	17.17%	2.93%	(83%)	20.92%	3.53%	(83%)	42.93%	7.10%	(83%)
Direct and indirect costs	36.64%	7.90%	(78%)	30.20%	6.44%	(79%)	23.10%	4.96%	(79%)	22.49%	5.06%	(78%)	52.89%	7.52%	(86%)
Impoverishment (%)															
Direct medical costs	5.01%	0.86%	(83%)	1.19%	0.20%	(83%)	0.52%	0.09%	(83%)	0.11%	0.02%	(79%)	0.05%	0.01%	(73%)
Direct costs	6.33%	1.24%	(80%)	1.60%	0.31%	(81%)	0.61%	0.12%	(80%)	0.11%	0.03%	(72%)	0.06%	0.02%	(73%)
Direct and indirect costs	15.28%	3.37%	(78%)	3.04%	0.64%	(79%)	1.07%	0.20%	(82%)	0.27%	0.06%	(79%)	0.04%	0.03%	(39%)

Note:

Costs are in 2013 RM;

Δ, the percentage difference between ‘vaccine’ and ‘no vaccine’ groups are shown in parenthesis.;

Scenarios compared here are the impact of Rotarix® vaccination on direct medical costs, direct costs, and direct and indirect costs. The scenario testing Rotarix® vaccination on direct medical costs is the base-case scenario.

7.4 Discussion

In this chapter, the study findings indicate that households in all income groups experience some degree of catastrophic payments due to healthcare expenditure for rotavirus gastroenteritis. However, only households in the three poorest quintiles were impoverished as a result of healthcare payments. Universal rotavirus vaccination helps alleviate catastrophic expenses among all income quintiles, and prevents impoverishment among the poorest quintiles.

Hence universal rotavirus vaccination, free at the point of use, can be considered as a pro-poor policy that reduces health and social inequalities. However, these benefits are not exclusive to the poor. The results in this chapter show that people in all income quintiles benefit in terms of financial risk protection. Preventive measures such as rotavirus vaccination are able to avert both the cost to households of actual treatment, which are highly subsidised in the Malaysian context, but also the cost of seeking care and productivity loss.

These findings suggest that universal, publicly-financed rotavirus vaccination, and potentially other childhood vaccines administered to all, may be best regarded as common goods to be made freely available to everyone, rather than a means-tested benefits programme targeted at the poor only. A publicly-financed, universal vaccination policy can be seen to protect all income groups, while protecting particularly the poorest from impoverishing medical payments. This has implications beyond Malaysia to other middle-income countries considering between alternative strategies towards UHC.

. Demonstrated in this analysis are the social values of fairness and distributive justice promoted by universal vaccination, by allowing access to health benefits and financial risk protection for all. Public-financing of programmes designed to promote equitable distribution of benefits, for example a basic package of essential care including childhood vaccines, enhance social solidarity.

Healthcare in many middle-income countries are often delivered by mixed public-private systems. In this environment, publicly-financed government healthcare delivery coexists with privately-financed market delivery, in which OOP payments dominate as a means of financing (Nishtar, 2010). Reliance on OOP payments may have detrimental consequences on household welfare, exacerbating poverty and inequities in terms of health outcomes and healthcare payments.

In Malaysia, the availability of a parallel private healthcare system exposes many to the financial risk of direct payments for healthcare (Chee & Barraclough, 2007). Household OOP expenditure in Malaysia is the largest source of financing in the private sector amounting to 79 per cent of spending in this sector, or 37 per cent of total health expenditure in 2012 (Ministry of Health Malaysia, 2012c). Our findings, that the rich opt-out of public care in Malaysia, has similarities with Thailand, where the better-off are at risk of catastrophic expenditure despite universal coverage (Somkotra & Lagrada, 2009). However, our findings demonstrate that the poor also rely on private healthcare, despite the heavy financial burden this often causes.

The financial consequences of illness on households are more than those directly related to the healthcare service, and include non-medical costs like transportation and productive time loss. Thus, financial risk protection is just one component of an even broader social protection mechanism, which may include paid sick leave on the short term and disability insurance in the long-term (Saksena et al., 2014). While this is not in the immediate purview of health systems, governments may be concerned in ensuring social protection against illness and its consequences.

Health financing strategies towards achieving UHC, either general taxation or insurance based, provide protection against OOP healthcare payments but not against non-medical spending associated with illness. In this thesis, universal vaccination is proposed as a social protection policy against medical and non-medical spending, associated with ill health.

This analysis has several limitations. There are no universally accepted definition of what is considered an “excessive” financial loss following illness, against which governments should protect their populations. Because of this, two widely accepted, threshold-based measures are used. The first defines healthcare expenditure as catastrophic, if it exceeds a defined threshold of household income over a specified duration of time. This acknowledges that households of any income can be badly hit by healthcare expenditure, even if they are not forced into poverty. The second defines healthcare expenditure as impoverishing when the post-expenditure household income falls below a fixed threshold. In both cases, the use of threshold-based metrics for measuring financial risk protection, has inherent methodological issues. These metrics may underestimate financial hardship, as the poor may be deterred from utilising healthcare as a result of high user fees. Also threshold-based metrics fail to consider coping mechanisms like savings, borrowing or selling of assets (Moreno-Serra et al., 2011; Saksena et al., 2014; Adam Wagstaff, 2008). Despite these acknowledged limitations, threshold-based metrics are well established and widely used by policymakers, thus chosen for this study.

Measures of financial risk protection are usually conducted for research on health systems financing. In health systems research, definitions of catastrophic expenditure usually compare all healthcare costs incurred by households against total household resources over a defined period, usually a year. This current analysis examines the effect of OOP healthcare payments for rotavirus gastroenteritis on household income, and the benefits of universal vaccination in alleviating this burden. The current analysis differs from health systems research in two ways. Firstly, the numerator used in this study are healthcare expenses specific for rotavirus diarrhoea and not all healthcare expenditure, generally used in health systems research.

Secondly, in this study healthcare expenditure is considered to be catastrophic when it exceeds a defined threshold of household income over a duration of one month. The duration of one month is used because rotavirus diarrhoea is an acute illness, with expenses incurred over a period of days and unlikely to be repeated (Bernstein, 2009). Hence in this thesis, costs incurred for rotavirus diarrhoea are compared with monthly income. Expenses over a short term have a different impact on household welfare compared to expenses over a longer period, as some households are better able to use current income, savings and established family or social networks to cope. Nevertheless, an unexpectedly large, one-time expense may adversely impact poor households with less resources to cope (Alam & Mahal, 2014).

The economic costs of diarrhoeal deaths are not considered here as Malaysia has low rotavirus mortality. In this thesis, 27 rotavirus gastroenteritis related deaths among children younger than five years, were estimated for 2013 (Table 4.8, p.92). While, rotavirus vaccination would substantially reduce rotavirus mortality in Malaysia[99], estimation of the productivity gain of mortality averted is likely to be more important in low-income countries, with higher rotavirus mortality.

Also, expenditure for informal care is not considered in this thesis as this is not relevant in this setting. The NHMS 2006 reported that less than three per cent of children under-five years with acute diarrhoea sought care at non-medical facilities, like traditional healers or Chinese medicine shops (Ministry of Health Malaysia, 2006).

[99] The analysis in Chapter 5 found that rotavirus vaccination would reduce 81 to 85 per cent of deaths due to rotavirus gastroenteritis in Malaysia, annually. (Table 5.5, page 169)

7.5 Conclusions

Universally administered rotavirus vaccines would benefit all in the population, but the poorest benefits the most in terms of financial risk protection. Towards achieving UHC, importance is placed on reducing societal disparities. In this thesis, it is proposed that well-designed universal vaccination programs complements health financing reforms in attaining and strengthening UHC.

Vaccines have long been regarded as cheap and effective interventions towards improving population health (World Bank, 1993). However traditional evaluations of vaccines focus on health gains and savings to the health system, underestimating the broader benefits of vaccination (T. Bärnighausen et al., 2014; Till Bärnighausen et al., 2014; Bishaia, Koenig, & Khan, 2003; Bloom et al., 2005; Deogaonkar et al., 2012).

In this thesis, it is proposed that economic evaluations of vaccines move away from the narrow perspective of the health systems and consider the perspective of households, with equity and financial risk protection as additional criteria towards vaccine introduction. The ECEA explicitly quantifies the broader value of universal vaccination starting with non-health benefits such as financial risk protection and equity. The tools employed here are easily adaptable to other settings with different immunisation programmes and health systems, to measure the essential role of vaccines towards UHC.

In the final chapter, the analytical findings of this thesis are discussed and policy recommendations are made.

CHAPTER 8: CONCLUSION AND RECOMMENDATIONS

8.1 Introduction

In this thesis, an economic evaluation was conducted to inform policy on public finance of rotavirus vaccines in Malaysia.

Rotavirus gastroenteritis is an important cause of severe childhood diarrhoea and deaths worldwide. Rotavirus is a resilient and highly contagious virus. Public health measures, such as improvement of hygiene and the provision of clean water and sanitation, do not reduce viral transmission. Consequently, rotavirus vaccines are the only effective preventive measure against rotavirus gastroenteritis. Although rotavirus vaccines are available that are recommended for universal vaccination by the WHO, these vaccines are not yet part of the Malaysian national immunisation programme. Therefore this study sought to gather economic evidence to inform policy on rotavirus vaccine introduction into the national immunisation programme in Malaysia.

Malaysia currently lacks an evidence-informed platform for decision making on vaccine introduction. As such, a framework was suggested in this thesis specifically for the economic evaluation of rotavirus vaccines in Malaysia. The health and economic burden of rotavirus gastroenteritis was comprehensively estimated, with the aim of establishing the public health importance of rotavirus in Malaysia. Subsequently, the cost-effectiveness and affordability of rotavirus vaccines were evaluated. In this thesis, the magnitude and distribution of the burden of illness-related payments for rotavirus diarrhoea on household were explored using data from two hospitals in Malaysia. On identifying income-related inequities in healthcare payments, the benefits of rotavirus vaccines in providing financial risk protection across income groups in Malaysia were explored.

In this final chapter, the economic evidence gathered in this thesis are rationally discussed to inform policy on the public finance of rotavirus vaccines in Malaysia. The chapter begins with Section 8.2, which discusses the policy implications of the study findings, in Malaysia and other countries. Next Section 8.3, identifies directions for future research. The thesis ends with Section 8.4, which presents the concluding statements.

8.2 Research significance

8.2.1 Policy lessons for Malaysia

Market failure in healthcare and the population-wide benefits of herd immunity, are strong motivators for the public finance of vaccines. However, economic evidence is not yet a formal part of the decision-making process on the public finance of vaccines in Malaysia. This is particularly important as new vaccines are more expensive and have less clear benefits than traditional EPI vaccines[100], making vaccine introduction decisions more complex. Therefore, a framework for the economic evaluation of vaccines is suggested in this thesis, to inform decisions on vaccine introduction. Although, this framework is suggested specifically for rotavirus vaccines in Malaysia, it may be used to evaluate other vaccines, and in other middle-income countries.

In this thesis, economic arguments are suggested for evidence-informed policy making on vaccine introduction. Cost-effectiveness is suggested here not as a 'gating-criteria' towards vaccine introduction, but as a vital component in the economic evaluations of vaccines. Cost-effectiveness together with a comprehensive estimate of health and economic burden, vaccine affordability, and benefits in enhancing equity and providing financial risk protection, are proposed as part of a range of economic evidence necessary to inform policy on vaccine introduction. This thesis proposes that economic evaluations of vaccines move beyond the narrow perspective of health systems and consider the perspective of households and society, with equity and financial risk protection as additional criteria towards vaccine introduction.

[100] Traditional EPI vaccines, like the polio, diphtheria and tetanus vaccines, have clear benefits in preventing mortality and disability. New vaccines like rotavirus vaccines, especially in low-mortality countries, have more benefits in preventing morbidity, in terms of reduction of illness and the associated economic burden.

Cost-effectiveness analysis are based on utilitarian principles, which aims to maximise population health within budgetary constraints. Using results of a cost-effectiveness analysis as the sole criteria for allocation decisions ignores vital considerations of equity, and the fair distribution of benefits and costs in society. While determination of cost-effectiveness is well-established in economic evaluations, assessment of the equity impact of interventions is relatively new. In this thesis, the novel methods of an ECEA were used to evaluate the benefits of rotavirus vaccines in providing financial risk protection across income groups (Verguet, Laxminarayan, et al., 2015). The ECEA explicitly quantifies the broader value of universal vaccination starting with non-health benefits such as financial risk protection and equity. The ECEA provides an important tool to understand the implications of vaccination for UHC beyond traditional considerations of efficiency.

The economic evaluation of rotavirus vaccines in this thesis is the first conducted in Malaysia. The evidence gathered here strongly suggest that rotavirus vaccines are a worthy investment for the government of Malaysia. This study has revealed the substantial health and economic burden of rotavirus in Malaysia, which vaccines are likely to alleviate. This study has also found that both rotavirus vaccines are cost-effective and likely to be affordable, depending on negotiated prices. Of importance to the health system goal of health maximisation, is the reduction in the health burden. Rotavirus vaccines substantially reduces episodes of rotavirus gastroenteritis and prevents up to 84 per cent of rotavirus deaths among children under-five years in Malaysia. Rotavirus vaccines reduces health events and household illness-related expenditure among the entire population, while protecting the poor in particular from impoverishment due to ill health. The public finance of rotavirus vaccines strengthens UHC, by providing health benefits and financial risk protection for the entire population.

In middle-income countries like Malaysia, with mixed public-private healthcare systems, the implications for public finance of vaccination programmes are unique. A strong private sector puts the population at risk of the catastrophic and impoverishing impact of healthcare payments (Jaafar et al., 2013). Vaccines as a part of basic package of publicly-provided health services, may function as a social protection mechanism against the financial consequences of ill health.

In Malaysia, rotavirus vaccines are currently only available for purchase at private healthcare facilities. Retail prices of rotavirus vaccines are prohibitively expensive and may preclude the poor from access to these essential vaccines. At current retail prices, each dose of rotavirus vaccine costs between six and seven per cent of the average monthly wage, or between thirteen and fifteen per cent of the minimum wage in Malaysia[101] (Attorney General's Chambers Malaysia, 2012; Department of Statistics Malaysia, 2013c; Ministry of Health Malaysia, 2014a). Thus universal rotavirus vaccination is particularly valuable in the Malaysian context, as it demonstrates the social values of fairness and distributional justice, by allowing access to health benefits and financial risk protection for all.

In this study, economic evaluation was conducted using the best available local epidemiological and costing data, taking into consideration the Malaysian health system and healthcare utilisation patterns. This study was conducted to answer a larger policy question of vaccine introduction in Malaysia, which has practical applications beyond the premise of academia. While the economic evidence resulting from this analysis are important, they are not the only relevant considerations towards vaccine introduction. The economic evidences gathered in this thesis fit within a larger, decision-making platform for vaccine introduction. This larger health technology assessment platform should

[101] Average wage in Malaysia US$ 651 per month (RM 2,502 per month) (Department of Statistics Malaysia, 2013c). Minimum wage in Malaysia is US$ 286 per month (RM 900 per month) (Attorney General's Chambers Malaysia, 2012). Recommended retail price for Rotarix and RotaTeq are US$ 44 (RM139) and US$ 37 (RM 136) per-dose (Ministry of Health Malaysia, 2014a).

ideally include evidence on vaccine safety and efficacy, cost-effectiveness and other economic criteria, as well as considerations of programmatic feasibility, ethics, values and social acceptability, and the legal and political context (Field & Caplan, 2012; Hauck et al., 2004; Ultsch et al., 2015).

The MOH, Malaysia through an extensive network of public health clinics, has a mature vaccine delivery system (Jaafar et al., 2013). Consequently, programmatic feasibility is not an issue in the Malaysian context. With investment in training and manpower, a rotavirus surveillance network, and additional cold-chain and laboratory capacity, among others (World Health Organization, 2005b), the public health system under the MOH, Malaysia would be well able to cope with an additional vaccine in the national immunisation programme.

The social context in Malaysia is unique. Malaysia has a multi-ethnic, multi-religious society, with Islam as the national religion. Although the government is secular, religious sensitivity influences policy. In 2008, the National Fatwa council issued a religious edict against the use of RotaTeq® vaccines (JAKIM, 2008). According to the official website, the fatwa was issued due to the alleged content of porcine derivatives in the vaccine manufacturing process and the perceived non-urgency of the burden of rotavirus in Malaysia (JAKIM, 2008). Such religious edicts have wide-spread repercussions affecting public sentiment and spurring the growth of anti-vaccination groups. The stance of the Malaysian Paediatric Association on this issue is positive, advocating for rotavirus vaccine introduction on the basis of its public health importance. The Malaysian Paediatric Association has countered the relevance of this edict with arguments based on Islamic jurisprudence (Musa, Ismail, & Chan, 2015; Nordin, 2014). The Malaysian Paediatric Association argued the relevance of this fatwa, by referencing a 2003 edict by the European Council of Fatwa and Research, on the permissibility of oral polio vaccines, which also contains trace elements of porcine trypsin (Nordin, 2014).

In this social context, health authorities have a role in engaging with the public and various special interest groups, to counter the spread of misinformation using scientific evidence (Musa et al., 2015). This thesis contributes to vaccine advocacy by providing health burden estimates which were previously not recorded, thus reinforcing the importance of vaccination for prevention of illness.

Vaccinology is an increasingly complex field. New vaccines like the rotavirus vaccines, unlike traditional vaccines in the EPI, are expensive. In low-mortality countries like Malaysia, rotavirus vaccines prevent illness and suffering, but result in few deaths. For these reasons, the WHO has recommended establishment of national technical advisory bodies to guide immunisation programmes. The establishment of National Immunisation Technical Advisory Groups (NITAGs) has been endorsed by all United Nations member states during the 2012 World Health Assembly, along with the endorsement of the Global Vaccine Action Plan (GVAP) 2011 to 2020 - a global framework to prevent millions of deaths worldwide by 2020, through equitable access to vaccination (World Health Organization, 2015a). NITAGs are independent bodies of multi-disciplinary experts, who generate and collate available evidence to empower policy-makers in making evidence-based decisions on immunisation programmes. Independence from the influence of lobbyists, special interest groups, industry, media and anti-vaccination groups, ensures the credibility of this process. (Adjagba et al., 2015; Duclos, 2010).

The Health Intervention and Technology Assessment Programme (HITAP) in Thailand is an example of a national agency that conducts economic appraisals of medical products and public health initiatives, to enable evidence-based policy making. The HITAP was established in 2007, as a semi-autonomous agency within the Ministry of Public Health in Thailand (Tantivess, Teerawattananon, & Mills, 2009). In Malaysia, a National Committee on Immunisation Practices was established in 2008 (NRC, 2015).

However, the role of this committee in evidence generation and the extent of its influence towards vaccine introduction is not clear.

Towards the use of economic evidence for national policy-making, benchmarks for national resource allocation decisions need to be set by the MOH, Malaysia. Although the MOH, Malaysia has produced methodological guidelines in an effort to standardise economic research, this work is still in a preliminary stage (Ministry of Health Malaysia, 2012e). Malaysia has yet to define a cost-effectiveness threshold to inform resource allocation decisions for public policy. In this thesis, cost-effectiveness thresholds for Malaysia are explored with the aim of aiding negotiations for vaccine prices. The findings of this thesis may stimulate further research, towards establishment of Malaysian cost-effectiveness thresholds.

In this thesis, it is proposed that economic evidence be a definitive part of health technology assessment for vaccine introduction in Malaysia. Evidences gathered in this thesis, will be disseminated to policy-makers, and the local and international scientific communities to aid policy on rotavirus introduction, advance research in novel approaches to economic evaluations, and for use in vaccine advocacy.

8.2.2 Policy lessons for other countries

Middle-income countries are diverse in terms of income levels[102], population size and structure, and burden of disease (Kaddar et al., 2013). Despite the fact that most of the world's poor live in middle-income countries, these countries do not have the same access to global aid and funding available to low-income countries for vaccine introduction (Glassman, Duran, & Sumner, 2011). As such, middle-income countries fall behind low- and high-income countries in introducing new and potentially lifesaving vaccines (Kaddar et al., 2013; PATH, 2015).

[102] The World Bank classifies middle-income countries as those with GNI per capita of between US$1,045 and US$12,736. Middle-income countries are further divided into lower- and upper- middle-income countries by a GNI per capita of US$4,125. (http://data.worldbank.org/about/country-and-lending-groups)

Malaysia is an upper middle-income, with a mixed public-private healthcare system. Therefore some of the challenges faced in Malaysia may be similar with other middle-income countries. Lessons learned from this thesis on the economic evaluation of rotavirus vaccines in Malaysia may be applicable to other middle-income countries.

The budgetary constraints faced by middle-income countries necessitate economic evaluations of vaccines. The framework suggested in this thesis, though specific for the evaluation of rotavirus vaccines in Malaysia, may be used as a guide for economic evaluation of vaccines in other countries. The uniqueness of this framework is in its consideration of multiple economic criteria beyond cost-effectiveness, including the health and economic burden of the disease, programmatic affordability, as well as benefits of the vaccine in enhancing equity and providing financial risk protection, all of which inform decision-making on vaccine introduction.

A salient lesson from this thesis, is the customisation of the economic evaluation to account for the complexity of health systems. Healthcare in most low- and middle-income countries are provided by mixed public-private health systems, in which provision of publicly-financed healthcare coexists with privately-financed healthcare (Nishtar, 2010). This thesis demonstrates an example of a country-specific economic evaluation that could easily be replicated in other countries.

In order to be relevant to national policy making, economic evaluations should utilise the best available local evidence and be cognizant to the permutations of the health system and population. Nevertheless, this may be challenging as most middle- and low-income countries lack expertise on the generation of economic evidence, in addition to the paucity of local data of quality (Kaddar et al., 2013). The research in this thesis would motivate other middle- and low-income countries to utilise available data in order to develop country-specific evaluations, while establishing mechanisms for better data collection.

The dominance of out-of-pocket payments in mixed health systems may be financially detrimental on households. This thesis is unique as it specifically considers the household perspective in an economic evaluation of universal rotavirus vaccination in Malaysia. From the households' perspective, poverty reduction, and financial risk protection, could be viewed as important aims of health systems that would strengthen the case for vaccine introduction. Middle-income countries like Indonesia, Sri Lanka, Viet Nam and others that have yet to introduce rotavirus vaccines could potentially benefit from the broader social and economic impact of rotavirus vaccination (PATH, 2016). The ECEA methodology explicitly quantifies the broader economic value of universal vaccination, in providing financial risk protection and enhancing equity. The tools employed in this thesis are easily adaptable to other settings, to measure the role of vaccines towards UHC.

Like Malaysia, many other countries have not defined a cost-effectiveness threshold for decision making on healthcare resource allocations. As the use of cost-effectiveness analysis increase, there will be a need for countries to define thresholds for transparent and consistent decision-making. The cost-effectiveness analysis conducted in this thesis considered WHO-CHOICE thresholds and different thresholds suggested for Malaysia, could inform the debate on appropriate cost-effectiveness thresholds in other countries.

8.3 Direction for future research

Economic evaluations of vaccines are considered a necessary part of resource allocation decisions in many countries. While the need for economic evidence is indisputable, this has yet to be formalised for use in vaccine-related health sector decisions in Malaysia. This thesis gathered economic arguments towards aiding decisions on public finance of rotavirus vaccines in Malaysia. While it is clear from the study findings, that rotavirus vaccines are a good investment in Malaysia, the scale of this debate warrants further exploration. To generate achievable policy strategies, there needs to be further research on the decision-making process in the country. Suggested here are studies that would fill identified research gaps for future economic evaluation of childhood vaccines.

Firstly, qualitative research should be conducted to identify the important dimensions and processes involved in decision-making on programme introduction in the MOH, Malaysia. This would be advantageous in making scientific and economic evidence more accessible and friendly to policy makers. This evidence may have a practical value in consolidating the role of NITAGs in Malaysia.

Secondly, qualitative studies should be conducted to explore the public's view on vaccination. This kind of exploration would provide insight to designing and delivering vaccination programmes with the aim of improving vaccine uptake and acceptance, in the light of individual and community needs.

Thirdly, the lack of a validated questionnaire to assess the health status of children under-five years, is an important area for research, both locally and internationally[103]. Evaluation of health status of children under-five years in the Malaysia setting would be facilitated by the construction of an appropriate questionnaire.

[103] Questionnaires available do not take into account the developmental aspects of a growing child.

The lack of unit costs of healthcare services is an important gap in conducting economic evaluations in Malaysia. Costing of services is particularly relevant for priority setting, planning and evaluation of public programmes in Malaysia. Given the complexity of the healthcare system, costing should be conducted at all levels of the health service, both in the public and private sector.

Also, clinical research on infectious disease or vaccine efficacy should include a costing component. Timely collection of necessary costing data would aid future economic evaluations of vaccines, and subsequent decision-making on vaccine introduction.

Finally, as cost-effectiveness thresholds have yet to be defined in Malaysia, this is an important avenue for future research. Studying the impact of changes in health sector investment decisions on population health outcomes, or in other words the opportunity costs of introducing new technologies, would help validate cost-effectiveness thresholds estimated for Malaysia by researchers at York University (Woods et al., 2015). A nationally representative, population-wide survey on the individual willingness-to-pay for health would also be useful to inform societal willingness-to-pay thresholds for Malaysia.

8.4 Conclusion

Findings of this thesis demonstrate a considerable health and economic burden of rotavirus in Malaysia to healthcare providers, society and households. Rotavirus vaccines, at prices negotiated in accordance to international norms, are likely to be a cost-effective and affordable intervention in Malaysia. In addition to reducing the burden of rotavirus and providing financial risk protection across all income groups, rotavirus vaccination protects the poorest households against the impoverishing impact of illness-related expenditure. The economic evidence gathered in this thesis suggests that universal rotavirus vaccination is a worthy investment for public finance by the MOH, Malaysia.

This thesis proposes that economic evaluation of vaccines move beyond the traditional considerations of cost-effectiveness and consider the broader economic benefits of vaccination in improving equity and providing financial risk protection. The framework developed here is important not only in the Malaysian setting, but also in other middle-income countries where economic evidence is not yet part of decision-making on vaccine introduction.

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Zin, R. M. (2007). Understanding the formulation of the revised poverty line in Malaysia. *Akademika, 70*, 21-39.

LIST OF PUBLICATIONS AND PRESENTATIONS

The following are papers published and manuscripts arising from this thesis:

1. Based on Chapter 6:

   Loganathan, T., Lee, W.-S., Lee, K.-F., Jit, M., & Ng, C.-W. (2015). Household Catastrophic Healthcare Expenditure and Impoverishment Due to Rotavirus Gastroenteritis Requiring Hospitalization in Malaysia. PLoS One, 10(5), e0125878. doi: 10.1371/journal.pone.0125878

2. Based on Chapter 4:

   Loganathan, T., Ng, C.-W., Lee, W.-S., & Jit, M. (2016). The Hidden Health and Economic Burden of Rotavirus Gastroenteritis in Malaysia: An Estimation Using Multiple Data Sources. The Pediatric Infectious Disease Journal, 35(6), 601-606.

3. Based on Chapter 7:

   Loganathan, T., Jit, M., Hutubessy, R., Ng, C.-W., Lee, W.-S., & Verguet, S. (2015). Rotavirus vaccines contribute towards universal health coverage in a mixed public-private healthcare system. Tropical Medicine and International Health (In acceptance).

4. Based on Chapter 5:

   Loganathan, T., Ng, C.-W., Lee, W.-S., Hutubessy, R & Verguet, S, Jit, M. (2015). Cost-effectiveness analysis of rotavirus vaccines in Malaysia: Informing thresholds for cost-effectiveness (In preparation).