ECONOMIC BURDEN OF DIARRHEAL DISEASES AND EFFECT OF VACCINATION – EXPERIENCE FROM A LOWER MIDDLE-INCOME COUNTRY

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A thesis submitted to the Department of Management Science of the University of Strathclyde for the degree Doctor of Philosophy, 2018

Declaration of Authenticity and Author's Rights

I declare that the work presented in this thesis is entirely my own work, where published sources have been used, full reference has been inserted. All Material showed in the text as published by the candidate as principal author has been used in the thesis. Details of the authors' contributions are provided in the Statement of Conjoint Work.

Any views and opinions expressed in this thesis are those of the author and do not necessarily represent the views of the University of Strathclyde.

This thesis has not been previously submitted for any other degree in this University or any other.

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Abstract

Diarrheal diseases remain one of the major global public health problems and a leading cause of morbidity and mortality in low- and middle-income countries like Bangladesh. Though the diseases are preventable and could be managed with low-cost interventions, the morbidity due to diarrheal diseases remains stable and has become the top causes of hospitalization of Bangladesh. Therefore, significant resources are consumed for treating patients with diarrhea. Among all of the diarrheal diseases, cholera and rotavirus are mainly responsible for severe diarrhea while endemic cholera is one of the largest burdens for Bangladesh. Vaccination is the most cost-effective investment for preventing the spread of vaccine-preventable diseases; Bangladesh is also committed to introduce cholera and rotavirus vaccination in the national Expanded Program on Immunization (EPI) schedule. This thesis investigates the health and economic burden of diarrheal diseases in Bangladesh and intends to generate evidence for policymakers about future nationwide cholera and rotavirus vaccination programs which have been inadequately studied. To achieve this aim, I have conducted a series of empirical studies for assessing the prevalence, economic burden of diarrheal diseases, economics of cholera vaccination, demand for cholera vaccines and the cost-effectiveness of future childhood rotavirus vaccination. The thesis is based on seven papers while five of them are primary survey-data driven and two of them are based on secondary data sources and modeling.

As cholera and rotavirus infections are life-threating conditions to high-risk people and children, the thesis sort out that such preventive programs could avert a substantial number of cases, deaths, and hospitalizations and appeared as a cost-effective investment. The thesis is also point out that there is a lack of good quality information on disease incidence, mortality, and the economic burden in the country. Therefore, further research is needed for proper understanding for priority setting in diarrhea control. The thesis also highlights the potential demand for cholera vaccines in the community; therefore, individuals may not wait for the public vaccination campaign if the vaccines are available in private market.

I believe that my thesis is provides a better understanding of the economics of diarrheal diseases and will contribute to the decision-making process regarding the prevention of diarrheal infections by strengthening the case for future oral cholera and rotavirus vaccination program in Bangladesh for the benefit of society.

Acknowledgement

I would like to express my deepest gratitude to my supervisor, Professor Alec Morton for his role as my main supervisor. Professor Alec Morton gave me the greatest support, guidance, understanding and help. It is my honour to have the opportunity to learn from Professor Alec Morton. This thesis would not have been possible without him. I am truly indebted.

A special thanks to my second supervisor Dr. Robert Van Der Meer for his excellent guidance. I am greatly indebted for his additional excellent supervision of my Ph.D. research program.

I would like to thank my elder brother Noor E-Islam for supporting me to chase my dream, for educating me and advice along the road.

I am very grateful to my beloved mother Mrs. Rashida Sarker and my father Abdur Rashid Sarker, who have been always supportive and encouraged me in every aspect of life and endless encouragement that kept me alive on the rocky road of the Ph.D. journey.

I owe my deepest gratitude to Dr. Marufa Sultana, I spent hours on the phone to discuss about various issues of the study. We have supported each other during our studies, and co-author on a couple of the papers in this dissertation, and she is always willing to give me good suggestions.

I would like to thank Dr Jahangir AM Khan, my previous supervisor for so many great suggestions during my Ph.D. project.

I would like to thank Dr. Firdausi Qadri, Dr. Ashraful Islam Khan and Dr. Ziaul Islam for their continued support during the implementation of various studies in my Ph.D. project. I would like to thank my colleagues (Rashidul Alam Mahumud, Nausad Ali, Nurnabi Sheikh and Raisul Akram) for their helpful comments and suggestions for this work.

I acknowledge with gratitude the commitment of University of Strathclyde Ph.D. Scholarship for financial support during my study. I would like to thank all the other participants, survey teams and other project personnel for their support during various studies in this Ph.D. project. Specially, I would like to thank the legendary Bangla pop singer Habib Wahid for his melodious songs that keep me alive in my Ph.D. journey at United Kingdom. Finally, I wish to express my love and gratitude to my beloved family for their understanding and endless love, throughout this venture.

Dedication

This thesis is dedicated to my parents Mrs. Rashida Sarker and Abdur Rashid Sarker

Statement of Conjoint Work

Chapters 4 through 10 are based on conjoint work with Professor Alec Morton (AM), Dr. Robert Van Der Meer (RVM) from University of Strathclyde, and my earlier colleagues Dr. Jahangir AM Khan (JAM), Dr. Ziaul Islam (ZI), Dr. Firdausi Qadri (FC), Dr. Marufa Sultana (MS), Dr. Amit Saha (AS), Dr. Fahima Chowdhury (FC), Dr. Ashraful Islam Khan (AIK), Dr. Alejandro Cravioto (AC), Dr. John David Clemens (JDC), Rashidul Alam Mahumud (RAM), Nausad Ali (NA), Dr. Tanvir M Huda (TMH), Nurnabi Sheikh (NS) and project personnel M. Salim Uzzaman (MSU) , Sabbir Haider (SH) and Hafizur Rahman (HR). I am principal author of all of the studies and contributed 90% of the work for all of the chapters. My earlier colleagues and project personnel are given valuable comments on the draft of all project papers. Dr. Robert Van Der Meer (RVM) and Professor Alec Morton (AM) commented on a previous version of chapter 4, chapter 5, Chapter 8, chapter 9 and chapter 10. My contributions to the conjoint work are summarized in the following table 0-1.

Table 0-1. Contributions to conjoint work.

Paper	Title of the paper	The PhD Author	The co-Author
1	Prevalence and health care seeking behavior for childhood diarrheal disease in Bangladesh	• Contributed to the conception and design • Contributed to acquisition, analysis, interpretation of data and drafted the manuscript • Accountable for all aspects of work ensuring integrity and accuracy • Drafted the paper and led the submission and revision process for journal publication	• Critically revised the manuscript: MS, NS, RAM • Supervised and contributed to developing the model: RVM, AM • Contributed to the draft paper: AM • Commented on the draft paper: RVM, AM
2	Economic cost of hospitalized diarrheal disease in Bangladesh: A societal perspective	• Conceived and designed the study • Accountable for all aspects of work ensuring integrity and accuracy • Performed the field experiments and analyzed the data • Drafted the paper and led the submission and revision process for journal publication	• Conceived and supervised the study: MS, JAM, RVM, AM • Field experiments and analyzed the data: RAM, MS, JAM, AM • Contributed to the draft paper: MS, RAM, NA, TMH, MSU, SH, HR, ZI, JAM, RVM, AM • Commented on the draft paper: JAM, RVM, AM
3	Cost of illness due to cholera disease in urban Bangladesh	• Contributed to the conception and design • Questionnaire development, field test and data collection	• Conceived and supervised the study: ZI, IAK, FQ, AS, FC, AIK and JAMK • Contributed to the draft paper: ZI, JAM

		• Analysis and interpretation of the data • Drafted the paper and led the submission and revision process for journal publication	• Commented on the draft paper: ZI, IAK, FQ, AS, FC, AIK and JAMK
4	Estimating the cost of cholera-vaccine delivery from the societal point of view	• Contributed to conceiving the study • Developed the conceptual framework and the model • Performed the tool development, field experiments and analyzed the data • Drafted the paper and led the submission and revision process for journal publication	• Contributed to conceiving the study: ZI, JAM • Supervised the study: ZI, JAM, FC, AS, AIK, FQ, AC, IAK • Contributed to developing the model and drafting paper: JAM • Commented on the draft paper: ZI, JAM, FQ, FC, AC, AIK, FC, AS, JDC, IAK
5	Willingness to pay for oral cholera vaccines in urban Bangladesh	• Conceived and designed the study and performed the field experiments • Contributed to developing the conceptual framework and the model • Analysis and interpretation of the data • Drafted the paper and led the submission process for journal publication	• Conceived and supervised the study: ZI, JAM, FQ, AIK, JDC, AM • Field experiments and analyzed the data: RAM, MS, NS, ZI, JAM, AM • Contributed to the draft paper: MS. RAM, NS, AIK, FQ, RVM, JAM, AM • Commented on the draft paper: JAM, AIK, FQ, RVM, AM
6	Economics of cholera vaccination in urban Bangladesh	• Contributed to conceiving the study • Developed the conceptual framework and the model • Performed the tool development, field experiments and analyzed the data • Drafted the paper and led the submission process for journal publication	• Conceived the study: JAM, FQ, AIK, JDC, AM • Supervised the study: JAM, RVM, AM • Contributed to drafting the paper: ZI, JDC, AIK, FQ, RVM, JAM, AM • Commented on the draft paper: JAM, AIK, FQ, RVM, AM
7	Cost-effectiveness analysis of introducing universal childhood rotavirus vaccination in Bangladesh	• Contributed to the conception and design • Developed the conceptual framework and the model • Performed the tool development and analyzed the data • Drafted the paper and led the submission and revision process for journal publication	• Conceived the study: AM • Supervised the study: RVM, AM • Contributed to drafting the paper: MS, RAM, AM • Commented on the draft paper: MS, RAM, RVM, AM

Signed: Date:

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List of abbreviations

ABM	Agent Based Model
ASEAN	Association of South East Asian Nations
BDT	Bangladeshi Taka
CBA	Cost Benefit Analysis
CBO	Community Based Organizations
CDD	Childhood Diarrheal Disease
CEA	Cost - Effectiveness Analysis
COI	Cost of Illness
CUA	Cost Utility Analysis
CV	Contingent Valuation
DALY	Disability- Adjusted Life Years
DES	Discrete Event Simulation
DGHS	Directorate General of Health Service
DHS	Demographic and Health Survey
DOMI	Diseases of the Most Impoverished
DSS	Demographic Surveillance System
EPI	Expanded Program on Immunization
GAVI	Global Alliance for Vaccines and Immunization
GBD	Global Burden of Study
HCA	Human Capital Approach
HRD	Hospital Records Departments
ICVB	Introduction of cholera vaccine in Bangladesh
Icddr,b	International Centre for Diarrhoel Disease Research, Bangladesh
IVI	International Vaccine Institute
IMCI	Integrated Management of Childhood Illness
IPD	Inpatient department
LMI	Lower- and Middle -Income
MIS	Management Information System
mL	Millilitre
MOHFW	Ministry of Health and Family Welfare
NGO	Not for profit organizations
NIP	National Immunization Program

NTTT	No Time To Think
OCV	Oral Cholera Vaccine
ORT	Oral Rehydration Therapy
ORS	Oral Rehydration Solution
OOP	Out -of -Pocket
OPD	Outpatients Department
QALY	Quality-Adjusted Life Years
TTT	Time To Think
UNICEF	United Nations International Children's Emergency Fund
WASH	Water, Sanitation And Hygiene
WHO	World Health Organization
WSS	Water and Sanitation System
WTP	Willingness To Pay

1 INTRODUCTION

1.1 A national public health emergency

Diarrhea is one of the highly prevalent communicable diseases in Bangladesh. The burden of diarrheal diseases is alarming as the disease is common in all age groups and children under five years of age suffer significantly (Bangladesh Bureau of Statistics 2013). Presently, the mortality due to diarrheal diseases was significantly reduced due to the introduction of Oral Rehydration Therapy (ORT) at the household level, promotion of breastfeeding, safe water supply, increased awareness through mass media, health education program, improvement of sanitation and other prevention strategies. However, the morbidity due to diarrheal diseases is stable during couple of decades and has become the uppermost causes of hospitalization according to the hospital records in Bangladesh. According to the Directorate General of Health Service (DGHS) of the Government Bangladesh, approximately 2.4 million diarrheal cases were registered (Figure 1) in 2016, and many diarrheal cases are managed in households without any involvement of healthcare providers and consequently, the real diarrheal burden remains unknown. The diseases are highly sensitive to climate, showing seasonal variations in many places of the country (Drasar et al. 1978). Relative humidity and temperature are the other important factors that influence the rate of replication of different infectious organisms (e.g., bacteria and protozoa) and the survival of enteroviruses in the environment which cause diarrheal diseases in Bangladesh (Black & Lanata 1995).

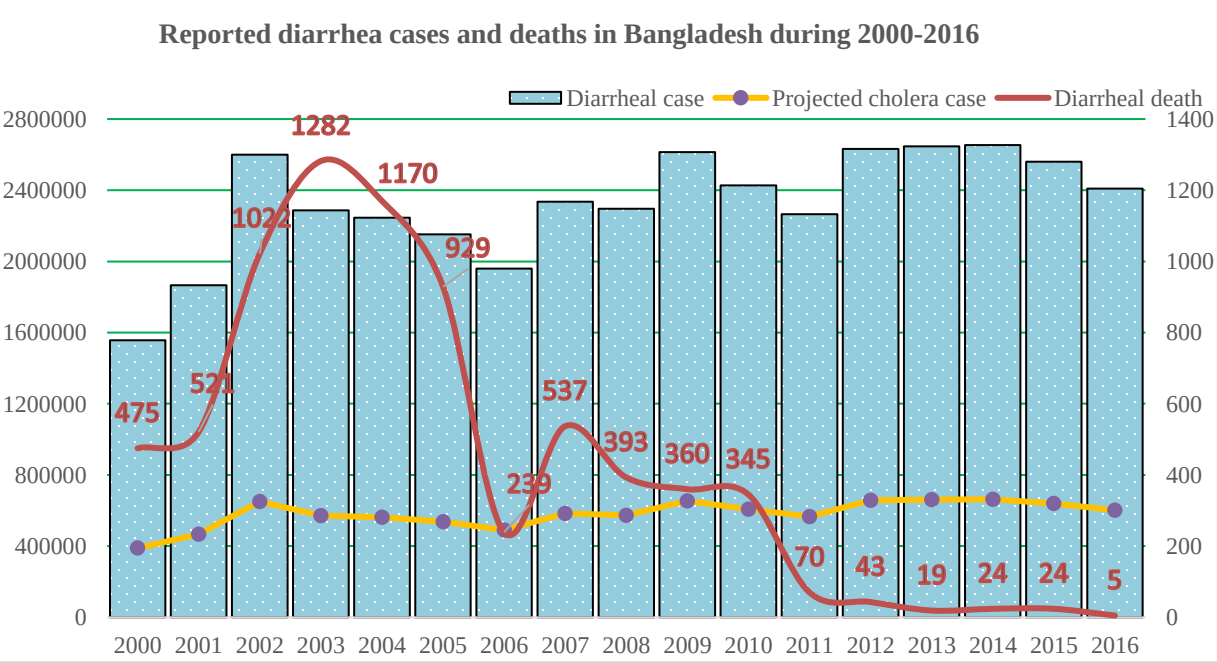

Figure 1-1 Diarrheal diseases in Bangladesh: Hospital-based surveillance, DHGS 2017

Hospitalization in public and private hospitals due to diarrhea requires substantial resources from a societal point of view and is a significant public health burden in Bangladesh. Resources might be in the form of cash or services as caregivers also are involved with managing patients particularly for under-five children (MOHFW 2017). If the patients seek care from private providers, then the cost is incured by the households. However, in public hospitals, the costs are often shared between the households and the providers, as the public healthcare facilities are highly subsidized in Bangladesh. In some some specialized diarrheal hospitals (icddr,b Dhaka Hospital, Mirpur Treatment Centre, Matlab Treatment Centre) and not for profit organizations (NGOs) in Bangladesh where the treatment costs are fully subsidized, and therefore a large number of patients frequently visit for care (Chowdhury et al. 2011; Colombara et al. 2014a; Hashizume et al. 2008; Paul et al. 2015). From the households' points of view, it is also important to know the economic cost for receiving care as the treatment cost could be averted if preventive control measures were initiated. Further, healthcare expenditure is continuously increasing in the public sector due to a large number of people accessing healthcare, and it is essential for the public health sector to use scarce resources efficiently by controlling excessive cost and improving the management of hospital operations (Riewpaiboon et al. 2007). Information on treatment cost analysis is essential for hospital administrators to make decisions for planning, budgeting, controlling and assessing the organization (Shepard et al. 1998). Therefore, it is vital to understand the total cost and its distribution so that both demand and supply side cost can be assessed separately. Finally, this estimation will lead to capture the actual cost-of-illness of diarrheal diseases as most of the previous studies (see chapter 2) solely depend either on an accounting based approach or one single perspective (e.g., provider, patients or households). The economic burden analysis is also crucial for allocating scarce resources for future diarrheal preventive strategies.

Vaccination against vaccine-preventable diseases through the Expanded Program on Immunization (EPI) is one of the most cost-effective health investments (WHO 2009d). In recent years, many newly developed vaccines are available for preventing various infectious diseases. However, most resource-poor countries do not have the opportunity regarding accessing, evaluating, and implementing these life savings vaccines (WHO 2005b). Therefore, a significant portion of the population, mainly children, who are most vulnerable, are deprived due to inaccessibility to the new vaccines (Moree & Ewart 2004). However, sometimes the new vaccines (such as rotavirus vaccine and cholera vaccine, e.g., *Duocoral*) seem to be more expensive as some of the targeted diseases (e.g. cholera) are relatively 'hidden' and, therefore, may lack demand from

public and political perspectives for the particular vaccines (WHO 2005c). After the invention and licensing of a new vaccine, policy-makers often require various information for supporting decision of introducing a new vaccine in national contexts. Most of the information requires health and the economic burden of vaccine-preventable disease, costs of vaccines, infrastructure such cold-chain facilities, transport, workforce and the effectiveness of vaccines (WHO 2007a; Parashar et al. 2006; WHO 2002). This information is quite crucial for a resource-poor country like Bangladesh. A decision-making study in Bangladesh observed that public health policy makers are only convinced to introduce a new vaccine after getting the insightful information of the burden of particular disease (Uddin et al. 2013). However, Richard et al. (1999) argued that along with the burden of disease studies, cost-effectiveness analysis is also necessary to improve the efficiency for the allocation of limited resources (Richard et al. 1999). Cost-effectiveness is particularly crucial as it is necessary to determine the extent of resources for improving the immunization program, to cover the cost of new vaccines and to allocate the available resources for an immunization program in the most optimal manner (Jamison et al. 2006). Policy analyses of any vaccination program often seek to answer the question: which immunization program achieves the best health outcomes per dollar spent? These analyses help decision-makers select programs that maximize health benefits for a given level of costs (Poulos et al. 2004). Economic evaluation of vaccination programs sometimes measures the benefits of those programs using costs of illness avoided (Miller 1998; Miller et al. 1998; Miller et al. 1999). For instance, evaluations of vaccine must adequately address whether the costs of purchasing and delivering a new vaccine are justified by its preventive benefits regarding public sector budgetary cost savings (Clemens et al. 1996). Financial sustainability is another critical issue in developing a successful vaccination program. It was observed that in a resource-poor setting, the decision to vaccinate sometimes solely depends on the society's willingness to pay for increased health benefits (Szucs 2005). Therefore, it is also crucial to understand the private value of the new vaccine for personal immunization and immunization of other household members so that cost-sharing mechanisms could be developed for sustainability of the immunization program.

In most cases, economic evaluation of introducing the vaccine are undertaken from the national and health system perspective because of data unavailability since local level analysis (household perspective or even social perspective) is often time-consuming and relatively costly and required detailed information. Drummond et al. highlighted that the results of the economic evaluation depend on the perspective assumed by the analyst, therefore sometimes the results are positive if we consider the broader societal perspective (Drummond et al. 2005) but negative if a narrower perspective is taken. Economic evaluation is one of the critical concerns in pharmaceuticals during

vaccine development process to assist in go/no-go decisions, future price settings, marketing strategies, and the planning of clinical trials and even for pricing and reimbursement decisions through contingent valuation methods (DiMasi et al. 2001; Jönsson 1997). Due to lack of economic assessment, the decision maker even delays or does not introduce the new health technology, for instance, a new vaccine in a country. Cost-effectiveness analysis mesure the efficiency of vaccination program costs to (1) the number of illnesses and death averted, (2) improve in quality-adjusted life years (QALYs) or reductions in disability-adjusted life years (DALYs), or (3) saving or averting in cost of illness (COI). Although cost-effectiveness analysis serves as a strategic decision-making criterion for public health interventions, it is also important to sort out who is more or less likely to benefit from the proposed intervention to ensure equity in health investment and financial protection of the worse off (Rheingans, Atherly, et al. 2012; Verguet, Olson, et al. 2015; Verguet et al. 2016; Levin et al. 2015; Verguet et al. 2013; Verguet, Laxminarayan, et al. 2015). At the same time, it is also crucial to compare the total cost and benefits of a vaccination program in light of whether the proposed vaccination program increases the general welfare of the society or not (Lucas et al. 2007). The willingness-to-pay (WTP) approach is widely used to value the health benefits of healthcare intervention (Drummond et al. 2005). Therefore, to measure the benefits of cholera vaccination in lower middle-income country context, community-based WTP study is crucial to comprehend the demand for future cholera vaccination cholera-endemic urban areas.

1.2 Aim of the thesis

The overarching aim of the thesis is to investigate the health and economic burden of diarreal diseases and to generate evidence for health policymakers for decision making nationwide cholera and rotavirus vaccination programs. For addressing the above issues, the project aims to estimate the economic burden of diarrheal diseases and to conduct the economic evaluation of cholera vaccination program against *vibrio cholera* in a high incidence urban area of Bangladesh. The study also investigates the economics of a future universal rotavirus vaccination program in the Bangladesh context. Cost-effectiveness and economic viability of the interventions was carried out to provide a complete picture considering the social perspective.

1.3 Research question and specific objectives

The following central research questions were investigated to accomplish the overall research aim of the study**:**

- What are the factors associated with childhood diarrheal disease (CDD)?

- What are the economic costs associated with the treatment of diarrhea?
- What are the societal costs of illness due to cholera?
- What are the costs of delivering cholera vaccine in a high-risk urban population?
- What is the maximum willingness to pay for oral cholera vaccine among households?
- Is the cholera vaccination program for a high-risk urban population cost-effective and economically viable?
- Will universal childhood rotavirus vaccination be cost-effective in Bangladesh?

To address the above queries, the specific objectives of the thesis are to:

- Explore the prevalence and health care seeking behavior associated with childhood diarrheal diseases (CDDs) and to identify the factors associated with CDDs at a population level in Bangladesh, (Paper I)
- Analyze the treatment costs, cost burden and coping strategies during diarrheal episode (paper II)
- Estimate the cost of illness for cholera treatment (paper III)
- Estimate the cost per fully-vaccinated individual and cost per vaccine-related activities, (paper IV)
- Capture the average willingness to pay for oral cholera vaccine (OCV) considering the individual and households' perspectives, (paper V)
- Evaluate health and economic implication of introducing cholera vaccination in urban Bangladesh, (study VI)
- Assess the cost-effectiveness of introducing universal childhood rotavirus vaccination in national Expanded Programme of Immunization in Bangladesh, (study VII)

Although the diarrheal related mortality is reducing substantially over the last decade, the morbidity remains as a global threat, therefore, the thesis may be contributing to improve understanding the economics of diarrheal diseases and would able to bring an added value to the research and analysis.

1.4 Thesis structure

This thesis is based on five published papers and two manuscripts (to be submitted) along with background, rationale, methods, discussion with future research and conclusions. Chapter 1 provides a summary of current scenario in relating to diarrheal diseases and the rationale for the project along with specific research questions. The next chapter focuses on the nature of diarrheal diseases, associated risk factors of cholera and childhood rotavirus infections. This chapter

highlights the existing preventive and control measures along with the rationale of vaccine introduction in resource-poor setting. This chapter also includes the available tools and techniques to evaluate the vaccination program along with existing related literature. Chapter 3 provides the setting of the study project and summary of methods and philosophical stance of this thesis. The empirical studies begin with chapter 4 (Study I) where the prevalence of childhood diarrheal disease and health care seeking patterns are documented, and the ends with the evaluation of rotavirus vaccination in Bangladesh (Chapter 10). Chapter 5 provides the economics of diarrheal diseases and the impact of treatment cost on household level. Chapter 6 to Chapter 9 focus on the economics of cholera infections along with future demand for cholera vaccine (Chapter 8). The cost-of-illness due to cholera and effects of oral cholera vaccination was documented in Chapter 6 and Chapter 8 while the estimation of vaccine delivery related cost measured in chapter 7. Discussion and conclusion are presented in Chapter 11. Authors' contribution has been reported at the end of each study. A statement of conjoint work has been attached to initial page of the thesis.

2 BACKGROUND

2.1 Global Burden of Diarrhea related illness

Diarrheal diseases are one of the major global public health problems and a leading cause of morbidity and mortality across the world. Global Burden of Disease Study reported that there were approximately 2.39 billion of diarrheal cases in 2015 globally (Vos et al. 2016; Liu et al. 2016). Childhood diarrheal diseases are responsible for 1.7 billion new cases and cause nearly half a million deaths of under-five children annually (WHO 2017c). Recent estimation by the United Nations International Children's Emergency Fund (UNICEF) reported that 9% of all deaths among the under-five children was caused by diarrhoea itself (UNICEF 2016). Despite all advancement in health technologies, improved management, and the increased use of oral rehydration therapy at a household level, diarrheal diseases still continue to be an overwhelming health concern (Kumar & Subita 2012). Although mortality associated with diarrheal illness has been reduced substantially, little decline in morbidity has been observed recent years (Mondal et al. 2009). The incidence of diarrhea remains at approximately two to three episodes per child per year among children under-five (WHO 2012d). While the burden of the diarrheal diseases is relatively lower in developed countries, it is a significant public health problem in low and middle-income countries, like Bangladesh, where the disease is particularly vulnerable for young children, as they are more susceptible to dehydration and nutritional deficiencies in cases of poor resource settings (Chowdhury et al. 2015). Management Information System (MIS) of the Directorate General of Health Service (DGHS) of the Government of Bangladesh published the statistical evidence of the health situation in Bangladesh on a regular basis and found that diarrheal disease was one of the primary reasons for hospitalisation in Bangladesh (Table 2-1).

Table 2-1 Top causes for hospital admission in district level hospitals in Bangladesh

Disease and health related conditions	Year wise Rank (%)						
	2008	2009	2010	2011	2012	2013	2014
Diarrheal infection	1 (12.40)	1 (13.0)	1 (9.30)	1 (11.15)	1 (12.24)	1 (12.65)	1 (10.67)
Assault	2 (9.40)	4 (4.10)	2 (7.21)	2 (7.48)	2 (7.91)	2 (7.12)	2 (4.92)
Pneumonia	3 (6.40)	3 (5.70)	3 (6.13)	3 (5.77)	3 (5.17)	3 (3.93)	3 (3.96)
Road traffic accident	-	5 (2.00)	5 (3.17)	6 (2.44)	4 (3.71)	4 (3.89)	4 (3.51)
Peptic ulcer	4 (3.30)	2 (7.6)	4 (3.76)	4 (3.45)	5 (3.22)	5 (3.4)	5 (3.18)

(Sources: DGHS-2016)

2.1.1 Definition and Aetiology

According to the World Health Organization, Diarrhea "is defined as the passage of three or more loose or liquid stools per day"(WHO 2017d). Diarrhea is often referred as an alteration of normal bowel movements, which is characterised by an increase in water content, volume, or frequency of stools which are sufficiently liquid to take the shape of a container (Ozguler 2015; Keusch et al. 2006). A diarrhoeal episode for both children and adults is considered as a passage of liquid or loose stools for at least three or more times within 24 hours prior to care (Deen et al. 2008). Diarrhea is caused by many infectious organisms, including bacteria (e.g., *Escherichia coli, Vibrio chollerae Shigella, Salmonella),* virus (e.g., *Rotavirus, Adenovirus, Norovirus)* and parasites (e.g. *Entamoeba Histolytia, Giardia Lamblia*). Walker and colleagues conducted a systematic review of the etiological agents of diarrhoeal disease among adults and identified that a diverse etiological agent were responsible for diarrhoea. This varied between the developing and developed world; they documented *V. cholerae O1/ O139* and *ETEC* as leading causes of hospitalization in the low and middle income countries, whereas *Campylobacter spp*. and *Shigella spp.* were common in high income countries (Fischer Walker et al. 2010). Further, rotavirus is the leading cause of severely-dehydrating diarrhoea in infants and young children, and responsible for approximately 60% and 40% of all diarrheal episodes in developing and developed countries respectively. However, this is not substantially common among the adults (Fischer Walker et al. 2010; Thapar & Sanderson 2004). Symptoms of diarrhoea can be 'acute waterway,' 'prolonged', 'persistent', and 'bloody diarrhoea.' Acute diarrhoea is the most common form of diarrhoeal disease, and is characterized by rapid dehydration and usually resolves within 14 days (Thapar & Sanderson 2004). In contrast, "prolonged" and "persistent" diarrhoea can last for "7 to 13 days" and "at least 14 days" respectively (Lamberti et al. 2012; Isanaka 1989). 'Bloody diarrhoea' or 'dysentery' is characterized by the visible or microscopic presence of blood in the stool, which is a sign of intestinal damage caused by infection (Keusch et al. 2006).

2.1.2 Burden of Cholera

Among all the diarrheal diseases, cholera is a substantial in the developing world and is endemic in Africa, Asia and has recently spread to America (Zuckerman et al. 2007). An estimated 1.4 billion of the total population globally are at risk for cholera and more than 90% among them are from cholera-endemic countries, with Bangladesh and India together constituting the largest share of this population (Ali et al. 2012; Ali et al. 2015). Cholera is a life-threatening, rapid dehydrating,

watery diarrheal disease that is transmitted through contaminated water or food, with presence of the causative agent *vibrio cholerae* O1 (or less frequently, O139). It is a highly infectious disease which is transmitted through the fecal-oral route, and affects all ages. Furthermore, if it is not addressed properly, it can lead to death within a short period of time (IVI 2013; Colombara et al. 2014b; Sarker et al. 2015; Ali et al. 2015). According to the latest estimation, up to 4 million new cases and 143,000 deaths occur worldwide due to cholera annually (Ali et al. 2015). Indeed, the number of reported cholera cases is increasing from all regions of the world. However, the World Health Organization (WHO) recognized that only 5%–10% of cholera cases were reported, indicating that there is an underestimation of the real burden of disease (WHO 2015a; Ali et al. 2012; WHO 2017a). Under reporting, usually related to fear of negative impact on the country's economy, such as travel, trade and tourists sectors that might be affected due to actual burden of cholera (WHO 2015a). However, the presence of other constraints, such as limited cholera surveillance system, inconsistency in case definition, and limited laboratory diagnostic capacities might lead the under-reporting of cholera cases. Cholera is highly prevalent in unsanitary conditions(WHO & Unicef 2013). Further, evidence suggests that cholera infection causes a potential economic burden for the families and the health sectors, due to mortality and morbidity triggered by this (Kirigia et al. 2009).

Endemic cholera has become one of the largest burdens for Bangladesh, with an estimated 109,052 new cases each year, leaving approximately 66 million people are at risk (Ali et al. 2015). There were over 3,000-5,000 deaths reported annually and with markedly higher caseloads after any natural disaster and frequent outbreaks in certain regions of the country (IVI 2013; Ali et al. 2015). The urban Dhaka, the capital of Bangladesh, has also faced several large cholera outbreaks during the major floods in 2004, 2007, and 2009. However, there are no reliable data available on the actual number of cholera cases. Based on the hospital-based surveillance system in urban Dhaka, it was estimated that in 2016, approximately 0.6 million new cases were exposed due to cholera (Figure1-1). Cholera had remained endemic in Bangladesh for approximately a century and hyperendemic in rural Bangladesh (Clemens et al. 2011; Glass et al. 1982).The endemicity of cholera in Bangladesh is demonstrated by the predictable yearly occurrence of the disease in the high-risk districts and the repetitive seasonal pattern of cholera outbreaks in either in spring or autumn, or both (Glass et al. 1982; Alam et al. 2006).

2.1.3 Burden of Rotavirus

Rotavirus is the most significant cause of severe diarrhoea among under-five children, with approximately 0.2 million among them dying each year globally due to this infection (WHO

2013c; Tate et al. 2016). The symptoms of rotavirus are diarrhoea associated with vomiting and fever, and the incubation period is at least 2 to 3 days (Velazquez et al. 1996). It is a leading cause of infantile gastroenteritis and accounts for 20% of diarrhoea-associated deaths (Lundgren & Svensson 2001). The mortality burden of rotavirus associated diarrhoea is highest in Asia and Africa (Bar-Zeev et al. 2015), and it is one of the most common causes of childhood diarrhoea-related hospital admissions throughout the world (Soares-Weiser et al. 2012a). The population-based incidence of hospitalization for rotavirus diarrhoea, varied from 10.8 to 19.6/1000 among under five children in Bangladesh (Zaman et al. 2009), while the case fatality rate is still unknown. A recent estimation suggested that rotavirus would cause nearly 6,000 deaths of under-five children in Bangladesh (Soares-Weiser et al. 2012a). Further, approximately 20% - 33% of hospitalisation was also caused by childhood rotavirus diseases, which demonstrates a considerable health and economic burden on the society (Unicomb et al. 1997; Zaman et al. 2009).

2.1.4 Risk factors and Treatment strategies

A number of risk factors are associated with diarrheal infections such as host factors, agent factors, domestic factors, behavioural factors, and environmental factors. The most important host factor is the immune system of individuals, which depends on nutrition, rest and even physical and mental stress (Keusch et al. 1992; Ochoa et al. 2004; Cohen et al. 2007). Agent factors are important for the occurrence of diarrheal diseases, including the virulence of the agents (Kotloff et al. 1999), whereas pathophysiology (Behrens 1991) and frequency of exposure is a function of both the agent factors and environment. Behavioural factors, such as the washing of hands before meals and after defecation, with soap and running water, and consuming seafood are significantly associated with a reduction of adult diarrheal cases (Ma et al. 2014). Further, mothers' hygiene and feeding practices; particularly during the weaning period and exclusive breastfeeding, could minimize the burden of childhood diarrheal diseases (De Zoysa & Feachem 1985; Alam et al. 1989).

In developing countries, diarrhea-related mortality and morbidity are directly linked with a limited access to potable water and proper sanitation system (Montgomery & Elimelech 2007). Poor sanitation system, lack of potable water and inadequate personal hygiene are significant risk factors for diarrheal diseases and accountable for up to 90% of all diarrheal cases in resource-poor settings (Gebru et al. 2014). Several studies also observed that epidemics of diarrheal diseases are associated with floods (Schwartz et al. 2006), socioeconomic status (Rahman et al. 2009), high population density, low education level, and the proximity of household clusters to contaminated surface water (Ali et al. 2002; D. K. Biswas et al. 2014; You et al. 2013), age related risk factors

(Lima & Guerrant 1992), absence of prenatal examination (Genser et al. 2006), urbanization (Colombara et al. 2014b), traditional beliefs and culture (Ellis et al. 2007), seasonal variations (S. K. Das et al. 2014) even the health care system itself (Mills et al. 2006).

There are various proven interventions, with a potential contribution for reducing diarrhea-related mortalities and morbidities; some of these interventions are specific, such as either for the prevention of diarrheal case or treating of patients, while others preventive program are general with the target to improve the surrounding environment or to improve the nutritional status of the children (J. K. Das et al. 2014). The vaccines and other life savings healthcare technology, such as oral rehydration solution (ORS), and zinc supplementation have a significant impact on diarrhea-related mortalities and morbidities. Das and colleagues summarised (figure 2-1) the nature of all interventions and its' delivery platforms in their review paper (J. K. Das et al. 2014). It is evident that the majority of diarrheal prevalence could be prevented by implementing water, sanitation and hygiene (WASH) strategies (Bhutta et al. 2013; Diouf et al. 2014). A couple of systematic reviews confirmed that hand washing (Ejemot-Nwadiaro et al. 2015) and point-of-use water treatment (Clasen et al. 2015) were effective interventions for reducing diarrhoeal diseases. Cairncross observed that risk of diarrhoea could be reduced by implementing hand washing with soap (48%), improved water quality (17%) and adequately excreta disposable (36%) in many developing countries (Cairncross et al. 2010). Since diarrhoea is manifested by dehydration in most of the cases, ORS has proven as effective treatment without any significant adverse effect (Ruxin 1994). Munos' study observed that up to 69% of diarrhoea-related mortality could be prevented by administrating ORS and recommended home fluids (Munos et al. 2010a). The promotion of exclusive breastfeeding (WHO Collaborative Study Team 2000) and complementary feeding practices (Jones et al. 2003) might strengthen the immune system of the children and thus could reduce the prevalence of childhood diarrhoea. Lamberti et al. found a significant relationship between breastfeeding and childhood diarrheal diseases. Furthermore, they observed higher risk of diarrhoea-related mortality among children who do not breastfeed compared to exclusively breastfed children (Lamberti et al. 2011).

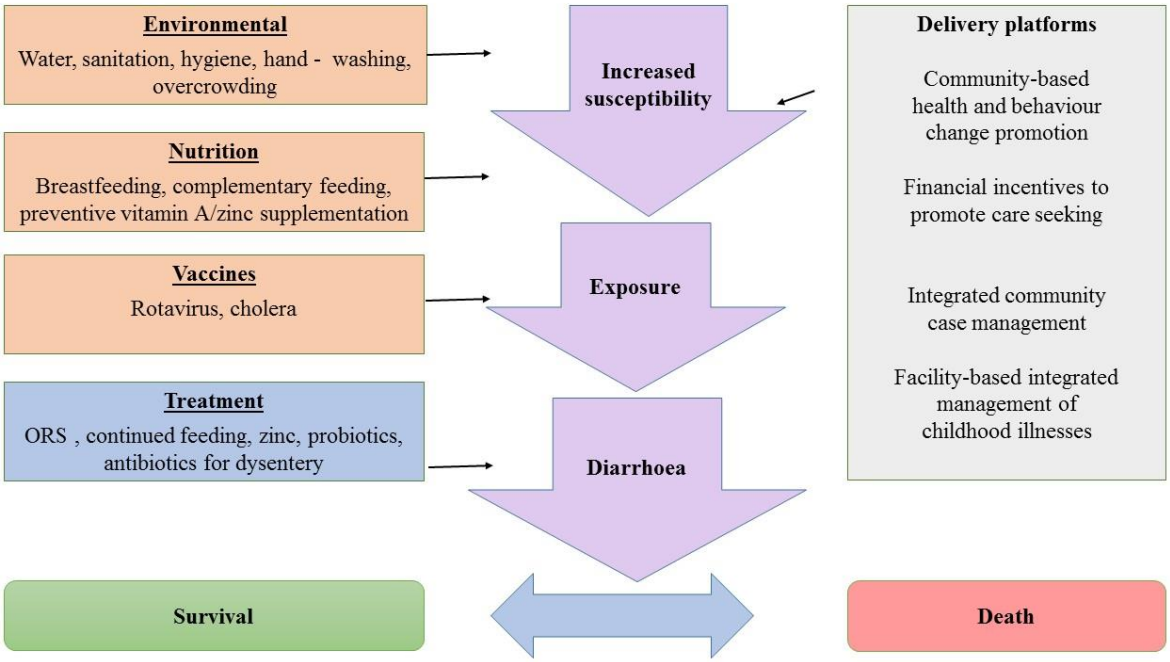

Figure 2-1 Interventions for prevention and treatment of diarrhoea; adapted from Das et al. Current Opinion in Infectious Diseases (2014) 37 (5) pp 451-458

Although WASH programs, such as improvements of water/sanitation infrastructure and personal hygiene contribute to decline the transmission of enteric pathogens, the vaccine can hasten the waning of diarrhoea-related mortalities and morbidities, particularly in epidemic and endemic settings (Levine et al. 2012). It was reported that nearly a third of episodes of severe diarrhea could be prevented by introducing vaccination against rotavirus and cholera infections globally (Fischer Walker et al. 2013). Newer *Shigella* and ETEC vaccines are also available, but such vaccines are not currently recommended by World Health Organization (J. K. Das et al. 2014). Antibiotics are also be used for treating diarrheal infections and WHO recommended antibiotics (such as ciprofloxacin, ceftriaxone or pivmecillinam) could reduce more than 99% of dysentery related mortalities (Traa et al. 2010). Recently, probiotic therapy is a potential treatment strategy for acute childhood diarrhea (Guarino et al. 2008). A literature review observed that probiotic therapy was effective for the treatment of diarrhoea and found a 14% reduction in the duration of diarrheal episodes (Applegate et al. 2013). Although the success of various interventions has already been proven, the prevalence of cholera and rotavirus diarrhoea is still disastrous in Bangladesh. As such, the Government of Bangladesh planned to introduce the vaccines (rotavirus and cholera) in a national EPI schedule (MOHFW 2010; Bdnews24 2017a). For assessing the effectiveness of cholera and rotavirus vaccines, the thesis estimated the cost and cost-effectiveness of vaccination in terms of cost per case, death and DALY averted.

2.2 Why Vaccines?

Vaccines are often considered as the "best buys" and one of the utmost achievements of the today's world for various perspectives. Vaccination programs bring health and economic benefits in several ways: reducing transmission of infections, incidence of diseases and case fatalities, improving health, saving out of pocket expenditure, avoiding productivity losses, avoiding the excessive pressure on the health system and reducing health inequities across the population (Flem et al. 2009; Saadatian-Elahi et al. 2016). Ozawa et al. (Ozawa et al. 2012) conducted a literature review in low-and-middle income countries to assess the economic benefit of vaccines and observed that most studies considered the narrower perspective of the economic benefits of vaccination, such as healthcare cost savings and/or care related productivity gains. The authors indicated that most studies ignored the societal benefits of vaccination, such as herd immunity. However, few studies reported vaccination might increase the Gross Domestic Product (GDP), billions of dollars in value of statistical lives could be saved and would reduce disease outbreaks (Meij et al. 2009; Ozawa et al. 2012; Flem et al. 2009; Troeger et al. 2014). Ozawa et al. also indicated the other broader economic benefits, such as the effects on vaccine in long-term morbidity status, productivity gains and future employment in the society were often ignored in these studies (Ozawa et al. 2012). Vaccinations reduce the future risk of diseases and contribute to welfare gains by avoiding anxiety and worry (Bärnighausen et al. 2014). Furthermore, vaccinations prevent disabilities and impairments, which might have negative impacts on individuals, their households and ultimately on societies , which is often considered as a 'broader benefit' of vaccination (Bärnighausen et al. 2014; Bärnighausen et al. 2011). Vaccination is positively related with the future school enrolment (Driessen et al. 2011) and the cognitive development of adolescents (Bloom et al. 2012). Recent studies observed that immunisation may reduce the households' catastrophic financial burden (Verguet, Olson, et al. 2015).

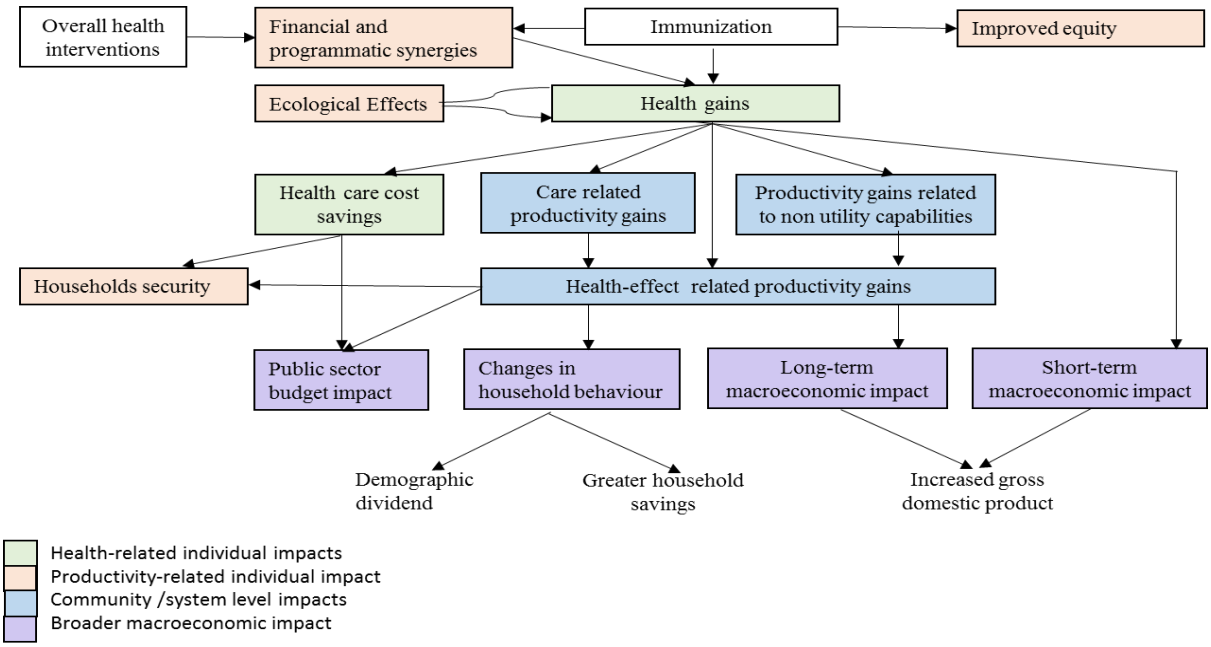

Figure 2-2 Broader economic impact of vaccine; adapted from Jit el al. BMC Medicine (2015) 13:2009

In light of the literature, Jit et al. built a conceptual framework mentioning the broader economic impact of vaccines and categorized four types of benefits (figure 2-2) from vaccination programs (Jit et al. 2015). On the individual level, benefits can be accrued in two ways: *firstly*, the vaccination improves health (by reducing morbidity and mortality) and reduces the out of pocket (OOP) expenses by avoiding treatment care. *Secondly*, productivity-related benefits, such as avoiding income /or productivity loss of patients and their caregivers, and other lifetime productivities, such as potential lifetime earnings, educational attainments, and cognitive improvements. Regarding community and system level impacts, vaccination has a potentiality for a positive level of externalities which has been catagorized as ecological effect (e.g., herd immunity, eradicate and reduced antibiotic usage), improved equity (e.g., equal distribution of health outcome), improve financial sustainability (through financial benefits and private demand estimates) and improved household security as a result of reducing risk of catastrophic expenditure. Broader economic indicators are classified as changes to household behaviour (e.g., economic improvement through female labour participation, household investment, productivity), public sector budget impact (i.e. changes individual's net transfer to the national budget over their lifetime), short-term macroeconomic impact (i.e. changes in GDP, changes in sectorial output) and long-term macroeconomic impact, i.e. changes in GDP (per capita) through labour supply and foreign direct investment.

2.2.1 Why Cholera vaccination in Bangladesh

Bangladesh is located within a broad delta formed by the Ganges and Brahmaputra rivers of South Asia; the country is exceedingly flat, with low-lying land, subject to annual floods, and a natural disaster-prone area. The Ganges River Delta and Bay of Bengal, including Bangladesh, are often considered the birthplace of the cholera disease (Siddique & Richard 2014). Bangladesh is now undergoing a rapid urbanisation process. However, about one-third of the urban population live in urban slums, which are often considered high risk areas for cholera diseases (Streatfield & Baumgartner 2013). According to the latest census, approximately 2.3 million people are still living in a total of 13,938 urban slums, whereas 47% of those slums are located in Dhaka, the capital of Bangladesh (BBS 2014). Cholera is a significant public health concern in those endemic hotspots , especially for children (37% of total population) as they are typically more vulnerable to cholera infection than the general population (Jeuland & Whittington 2009). Cholera occurs both as an endemic and epidemic way and cases are highest before and after the monsoons, as well as during and following the natural disasters (e.g., floods, cyclones).In urban Dhaka, flooding is a regular occurrence, especially in rainy season, and the cholera incidence and severity are both usually devastatingly high during the time of floods (Harris et al. 2008; Schwartz et al. 2006). However, a wide range of host and environmental factors, including malnutrition, access to healthcare services, pre-existing immunity, blood group, and other host genetic factors have been associated with the severity of cholera infection (Harris et al. 2005; Harris et al. 2009; Brown 2003). Researchers also found that over the last 10-15 years, cholera outbreaks have become more common and severe (Siddique et al. 2010; Schwartz et al. 2006; Harris et al. 2008). ORT is a proven treatment for dehydrating diarrhoea. However, such therapy does not have any impact on reduction of the incidence or to eliminate pathogens. The best long-term solution is to improve the water and sanitation system (WSS) throughout the country, which could then separate the faecal waste from the water and food supply. However, being a resource-limited country, it is highly ambitious for Bangladesh to develop and look to maintain fully functional WSS, as massive investment. Therefore, an interim low-cost approach may useful that can be reached to the people more quickly. Consequently, vaccination is now recognized as a major preventive intervention for controlling cholera infections (WHO 2010; Gaffga et al. 2007).

World Health Organisation recommended a multidisciplinary approach for tackling cholera, such as water sanitation intervention, health and hygiene-related awareness, and the development of disease surveillance. However, WHO prioritised the vaccination campaign with oral cholera vaccine (OCV), particularly for cholera endemic high-risk areas (WHO 2015b). Cholera endemic

high- risk areas mean the areas with limited access to health care facilities, poor sanitation and inadequate access to safe water, such as urban slums (WHO 2015a). Recently, many international donors have advocated the expansion of the cholera vaccination program in the developing world (Mahoney et al. 2007; Mahalanabis et al. 2008; Schaetti et al. 2012; Desai et al. 2016). Though the successful cholera control program depends on the improvement of water and public sanitation system, the OCV is a proven prevention strategy in various settings, particularly for the endemic cholera hotspots, disease outbreaks and for humanitarian crisis (Nogareda 2015; Desai et al. 2016). In this context, the World Health Assembly recommended OCV as a part of an integrated cholera prevention strategy, and is often considered as a short-term solution for controlling the outbreak (WHO 2011a; WHO 2010). Currently, there are two types of vaccines available globally: WC-rBS, killed whole cell monovalent with B subunit (e.g. Dukoral®) and WC, killed modified whole cell bivalent without the B subunit vaccine (e.g. Shanchol™, Euvichol® and mORCVAX™). There are currently 3 WHO pre-qualified oral cholera vaccines (Dukoral®, Shanchol™, and Euvichol®) available in the global market. Comparatively low-cost two doses of the Shanchol™ vaccine is recommended by WHO, as this vaccine provides a protection for at least five years (WHO 2015a; Bhattacharya et al. 2013). Shanchol™ is simple and safe to administer by swallowing 1.5 millilitre (mL) directly from the vaccine vial. The vaccine is available through a global stockpile for reducing cholera outbreaks, which is administrated by International Coordinating Group (WHO 2013b). Furthermore, herd protection is an important feature of OCV, and is directly linked with the vaccine coverage rate, if the coverage rate is high, the herd protection will cover a larger population (Ali et al. 2005).

2.2.2 Why rotavirus vaccination in Bangladesh

Rotavirus is the most common cause of gastroenteritis in young children globally, and a prime cause of hospitalization in low-income and middle-income countries (Keusch et al. 2006; Fischer Walker et al. 2013). To tackle this public health problem, many life-saving interventions, such as ORT and micro-nutrient supplementation, including encouragement of exclusive breastfeeding, have been implemented and have been proven as effective methods for preventing rotavirus infections (Munos et al. 2010b). Furthermore, improving water quality and sanitation, food quality, and maintenance of personal hygiene are also proven preventive measures that are often considered as long-term solutions and are linked with the socio-economic development of communities in broader aspects (Diop et al. 2015). However, these strategies have not had a great impact on reducing rotavirus infections globally (WHO 2013c). Furthermore, these interventions

often require a substantial amount of investment with a longer time of involvement for implementation. Implementing such interventions are often challenging for resource-poor settings like Bangladesh, where a huge number of the population live in various urban slums and are at high risk of childhood diarrheal diseases. Latest estimation show that 5,700 to 13,400 under-five children died due to rotavirus infections in Bangladesh (ICDDRB 2016). To reduce the childhood diarrheal disease, rotavirus vaccinations are highly recommended in National Immunization Programs (NIPs), particularly for those countries where diarrheal diseases contribute for more than 10% of total deaths (WHO 2009c). In this context, Bangladesh is highly committed to the introduction of rotavirus vaccine in the routine immunization program (Bdnews24 2017b).

2.2.3 Decision concerning new vaccines

Vaccines are often considered as the "best buy" in public health particularly for the poorest people of the world, as vaccination improve health outcomes at a lower cost than many preventive programs, and thus newer vaccines are often introduced rapidly in those settings (Shen et al. 2016; Stack et al. 2011). The Global Alliance for Vaccines and Immunization (GAVI) plays a significant role for funding of new vaccines (approximately 80 percent of financial support) in developing world. If not, it is difficult to reduce mortalities and morbidities caused by infectious diseases in many lower-and-middle income countries (Gavi 2015). However, the GAVI Alliance sets a benchmark for their funding strategies, which are based on a country's gross national income, and those that exceed US$ 1,580 (in 2015 price) are often considered as 'transition' countries. Therefore, such countries are required to invest their own finance for vaccination and need to make their immunization financing sustainable (Shen et al. 2016). However, UNICEF Vaccine Independence Initiatives support those countries that are transitioning from donor funding to self-funding for continuing their national vaccination program. These countries will ultimately take over the ownership of the immunization programs and will adopt the full cost of new vaccines. The new vaccines (e.g., rotavirus) are expensive to some extent and often appear as a largest cost driver of a vaccination program, even incurring at least fifty percent of the total immunization expenditure in many settings (Lydon et al. 2014; Shen, Fields, et al. 2014a).

However, the vaccine is not the single important issue; the success of a vaccination program depends on various factors, such as availability of infrastructure, logistics and cold chains, human resources, budget, and effective delivery strategies. Therefore, it is observed that in many developing countries the time lag is often 15-20 years after first licensure in developed countries (Ozawa et al. 2012). Shen et al. demonstrated that at least eight noticeable challenges are hindering for the introduction of a new vaccine to the routine immunization program (Shen, Fields, et al.

2014a). Among all of the challenges, they reported that "Policy, Standards and Guidelines" is the most crucial factor, as every country has its own immunization policy, policy making capacities and prioritises as per their own policy while the policy-making capacities also varies substantially. Since the World Health Organization has no direct policy-setting authority at the country level, therefore, the whole vaccination introduction process often delayed. Further, in resource-poor countries, the complexity is associated with the decision making process and often requires technical and political consideration (Hipgrave et al. 2014). Cold chain facilities and related logistics management are crucial for preserving vaccine at an optimum temperature and have become more complex due to nature of the vials (Techathawat et al. 2007; Matthias et al. 2007; Wirkas et al. 2007; Kartoglu & Milstien 2014). Further, effective and efficient vaccine delivery strategies are also necessary for ensuring the equity of service (Shen, Fields, et al. 2014b). In addition, active participation of communities have been shown to improve the vaccination coverage in many countries as community partnerships could build the trust among parties and an acceptance of the new vaccine (Wigle et al. 2013; LaFond et al. 2015; Oku et al. 2016).

Burchett et al. conducted a qualitative assessment of the decision-making process of introducing new vaccine in seven LMI countries. They found the funding availability, political prioritisation, and the evidence of burden of particular disease are the main drivers for introduction of a new vaccine (Burchett, Mounier-Jack, Griffiths, Biellik, et al. 2012). Many studies highlighted the political factors (Brooks et al. 1999; Bryson et al. 2010; Haas et al. 2009) and the evidence of burden of disease for introducing a new vaccine into the vaccination program (DeRoeck et al. 2005; Munira & Fritzen 2007). A systematic review study also indicated that the efficacy and effectiveness of the vaccine, disease burden, and financial issues are the common concerns of vaccine introduction (Burchett, Mounier-Jack, Griffiths & Mills 2012). However, Lin found that 'political rationality' is even more crucial for the decision-making process than 'technical rationality' (Lin 2003). A stakeholder analysis study concluded that burden of the disease, safety, and cost-effectiveness studies are substantial for decision makers, although ecological effects and the macroeconomic impact of vaccination are also often considered for vaccine introduction (Putten et al. 2015). Since substantial investment is involved for the implementation of the vaccination program, it is necessary to ensure the efficient use of those scarce resources. It was also observed that many decisions of new vaccine introduction into the EPI program come solely from the economic analysis (Hall & Sack 2015). The economic evaluation tools offer a variety of indications that assist policy makers in the process of prioritisation for the making of decisions against a new vaccine. However, the vaccination decision making process is too complex for policy makers, as it involves therapeutic uncertainties, patient's preferences, and values, as well as

the costs that are performed at different tiers and levels such as at national level, and local level, as well as households and individual level (Ulahannan 2002).

At the national level, the decisions are made based on its policies or programs for the entire population of the country. The national Ministry of Health officials, EPI managers, and their staff could play a central role in this process. Sometimes the functions of another ministry, such as the Ministry of Finance, also have a vital role (e.g., South Africa). However, in Bangladesh, the approval from such ministries are the formal official process as the Ministry of Health has the full control of national immunization plan and budget(Burchett, Mounier-Jack, Griffiths, Biellik, et al. 2012). Further, the nature of healthcare system and issues related to financing, affordability, and sustainability are the other vital elements for decision-making process for a vaccine's introduction (Hutubessy et al. 2011). Despite this, at the local level, the decision is even regionalized. For instance, after any natural disaster (like floods, cyclones) or man-made disaster (e.g., setting up of a refugee camp due to war), immediate action is often required, although budget restriction has a strong influence in the local decision-making process for a new vaccine. For household or individual level, the decision concerning a new vaccine depends on the economic conditions, consultation with physicians, the price of the vaccine itself, and the availability of vaccines in the local context. Furthermore, on a household level, detailed vaccination information and vaccination advice from health personnel might have a positive effects regarding new vaccines and a potential to increase the vaccination rates (Taylor et al. 2015). Several studies found that parent/recipient-provider trust could be a major factor for the acceptance of a new vaccine at the household level (Freed et al. 2010; Fredrickson et al. 2004; Freed et al. 2011).

. In the above discussions, we found various information usually required to introducing new vaccines in country context. The decision-making process concerning new vaccines depend on certain steps: firstly, the urgency of the vaccine in the country context; secondly, the effectiveness of the vaccine in real world applications; thirdly, the demand for this vaccine and; finally, the cost and benefit of implementing the new vaccination strategy for the welfare of the society. Therefore, a full economic evaluation is crucial for assessing the value of money (Helmchen & Lo Sasso 2010). To introduce a new vaccine quickly in a EPI system, Mahoney et al. identified that the determination of disease burden and cost-effectiveness analysis are the most important factors for a resource-poor country (Mahoney et al. 2007).

2.2.4 Economic evaluation of vaccines

Economic evaluation is a type of evidence-based decision-making tool for vaccine introduction (Jit et al. 2013). Resources like human, time, facilities, equipment and even knowledge are limited. Regarding healthcare, health needs often outstrip the available and often scarce resources, so priority settings are crucial for allocating resources efficiently. As such, economic evaluation is worthwhile for the justification of vaccine introduction and ensuring efficiencies (Hipgrave et al. 2014). The application of the economic evaluation in healthcare research has increased rapidly since the 1980s (Beutels et al. 2003). It allows an evaluation of all available alternatives, in terms of costs and consequences, and selecting the optimum one for ensuring the value for money. According to Drummond et al., economic evaluation is the 'comparative analysis of alternative courses of action regarding both their costs and their consequences' (Drummond et al. 2005). The basic task of the economic evaluation for vaccination program is to identify, measure, and value of the vaccines, and compare the costs and consequences of vaccines against new or existing alternatives. For any vaccination program, the immediate outcomes of the vaccination include a reduction of the risk of infection, reduction of cases and averted death. Subsequently, vaccination also affects the reduction of disease burden indirectly through herd immunity (Plotkin 2005). There are three types of full economic evaluation which are widely used to evaluate the introduction of new vaccines: cost-effectiveness, cost-utility, and cost-benefit analysis (Black 2013). Regarding the types of economic evaluation, the estimation of costs is same for all types of economic evaluation that are measured by its monetary value while the outcomes are varies. In cost-effectiveness analysis (CEA), outcomes are related to a natural unit, such as number of lives saved, person vaccinated. In the cost-utility analysis (CUA), utility is used for valuing the program effects (Drummond et al. 2005). The generic outcome usually expressed as cost per quality-adjusted-life-years (QALYs) and the disability adjusted life-years (DALYs) in vaccine evaluation studies. In cost-benefit analysis (CBA), both the costs and outcomes of the alternatives are measured in monetary units and a vaccination program is considered a good value for money when the value of the total benefits of the immunisation exceeds the costs of immunisation program (Cookson et al. 1997). Yet, the execution of full cost-benefit analysis is often a time consuming and intensive exercise (Morton & Lauer 2017).

Cost effectiveness analysis (CEA) has been used as a tool for addressing issues of efficiency in the allocation of scarce health resources (Hutubessy et al. 2003). The wider use of cost-effectiveness analysis is to evaluate the efficiency the new intervention compared with the existing and/or available practice. Basically, CEA helps to make a choice among various alternatives

regarding cost and effects (in terms of natural unit) of achieving specific objectives and are able to identify the programs that are potentially good buys (Tan-Torres Edejer et al. 2003). The health policy makers often use CEA for priority settings to ensure greatest health benefits with their available budget (Bertram et al. 2016). Cost-effectiveness methods are very well established, easy to understand and have a low cost implementation (Morton & Lauer 2017). For instance, if a health policy changes by additional resources (e.g., vaccines, staffs, and logistics), CEA are able to capture how effective the vaccination program might be and vice versa. Furthermore, because of practical simplicity and transparency, CEA is applied by non-health economist, public health manager, and donor and policy makers to assess in what way can the available resources utilize for better health outcome and provide the greatest returns. In last two decades, a wide range of vaccines have been developed, targeting various infectious diseases, and the CEA study is important for decisions of vaccine introduction into the EPI schedules, although reliable and high-quality country-specific data is crucial for such analysis (Lydon et al. 2014; Hutubessy et al. 2011; Bertram et al. 2016). Therefore, due to the lack of technical capacities and empirical data, many decision-makers in LMI countries often depend on the previous CEA studies in different settings (Jit et al. 2013).

For a better understanding of the health and financial benefits, a new form of CEA named 'extended cost-effectiveness analysis (ECEA)' has recently been developed (Verguet, Olson, et al. 2015; Verguet et al. 2016; Levin et al. 2015; Verguet et al. 2013; Verguet, Laxminarayan, et al. 2015), and has also been highlighted in the recent Disease Control Priorities (DCP 3) project. The latest ECEA was able to capture three important aspects, such as health maximization, financial risk protection and equity of priority setting in the health sector, which are also core indicators of universal health coverage (Lauer et al. 2017; WHO 2014c). Financial risk protection and equity are the main features of latest ECEA. However, it does not provide the decision rule. Instead, it provides information for decision makers and the methods adds often complexities and additional data is usually required for such analysis (Morton & Lauer 2017). This research project is conducted only in high risk urban area (i.e. slum) and practically, it is not possible to capture the variation of income (low-income community) and disease burden according to the socio-economic class and this vaccination study does not represents the country's overall scenario rather than the feasibility and effectiveness of introducing cholera vaccination in this context. Thus instead of ECEA, the project employed the cost-effectiveness analysis, as the method was very well established (Hutubessy et al. 2003; Tan-Torres Edejer et al. 2003; Bertram et al. 2016) .

Many studies argued that CEA alone cannot capture the broader impact of vaccination and therefore, cost benefit analysis should be also introduced (Bärnighausen et al. 2014; Bärnighausen et al. 2011; Deogaonkar et al. 2012; Ozawa et al. 2012). From a 'policy decision on new vaccine introduction study,' Jauregui et al. concluded that both CEA and CBA have significant roles for vaccine introduction in a country (Jauregui et al. 2011). It was observed that the benefits of any new vaccine were frequently measured using the avoided costs of illness (Miller 1998; Miller et al. 1998). However, a non-market valuation method such as contingent valuation method (CVM) was also used to derive the value of new vaccines where people can directly value the vaccines using stated preference techniques, which is widely known as the willingness to pay (NOAA 1993; Carson 2012; Kim et al. 2014; Bala et al. 1999; Olsen & Smith 2001; Klose 1999). Furthermore, the benefit estimation, using the WTP, is also consistent with the welfare economic approach, as the cost of pain, suffering and other non-health items are valued. WTP method is the most useful technique for capturing the value of preventive program concerning infectious diseases, when both patients and their caregivers are at risk of that infection (Brown et al. 2010; Beutels et al. 2003). For this purposes, a WTP survey was also conducted to assess the benefit of cholera vaccination in urban Bangladesh (Hammitt & Graham 1999; Carson 2012).

2.3 Existing studies

This sub-section describes the published literature about the health and economic burden of diarrheal diseases in the context of LMI countries. This review section consists of three subcomponents: the economics of diarrheal infections, economic evaluation of cholera vaccination and willingness to pay studies for cholera vaccination.

2.3.1 Economics of Diarrheal disease in Bangladesh

Globally, diarrhea is one of the leading cause of mortality and morbidity in South Asian countries (Black et al. 2010). Along with the health burden, diarrheal diseases have potential economic impact on diarrhoea affected households, on public health facilities, as well as the whole society. Public health facilities are highly subsidised in Bangladesh, so the treatment cost related to the vast number of diarrheal patients imposes financial burden for households as well as these public hospitals. In addition, households themselves shared a substantial economic burden for seeking care in the form of direct medical cost (e.g., medicine, drug) and non-medical cost (e.g., transportation, lodging). Therefore, a portion of households' resources are consumed by seeking care, which might have an impact on the other regular consumption or activities of households such as savings, productive investment, and other planned actions. Further, the situation becomes

worse when the poor households and/or income earner of family is exposed to diarrhea, as they cannot afford the excessive treatment cost that even lead them to a higher risk of mortality (Rheingans, Kukla, et al. 2012; Chowdhury et al. 2015). In addition, indirect costs, such as loss of income and/or productivity of patients and caregivers also have negative consequence for the households, especially for the daily wagers or informal workers. Therefore, in low-income settings, where the diarrheal diseases occur frequently, most of the households are continually balancing these economic costs with the health risks of diarrheal diseases (Rheingans, Kukla, et al. 2012).

There are several studies on the economic burden of diarrheal disease in LMI countries (Burke et al. 2013; Kosek et al. 2003; Bartsch & Lee 2014; MacIntyre & Villiers 2010; Bhuiyan et al. 2014; Pham-Duc et al. 2014), but the knowledge about treatment costs of a full diarrheal episode are still limited in the context of Bangladesh. Such studies are imperative for informing policies and allowing international comparisons (Konstantyner et al. 2016; Parashar et al. 2003). Ali and team conducted a costing study in a district hospital (Manikgonj) near the urban Dhaka (capital of Bangladesh) which captured the average treatment costs per patient from the hospital perspective in 1997 (Ali 2001). The study found that the provider costs per patient day for the management of IPD (inpatient department) and OPD (outpatients department) were US$ 4.04 and US$ 0.69 respectively. However, the study was conducted nearly two decades ago and failed to represent the country-specific scenario. Another hospital-based study was conducted in rural Bangladesh in 2010-2012 and was limited among under-five children. The study demonstrated that the average inflation-adjusted childhood diarrheal treatment cost per episode was US$ 6.99 in 2015 (Das et al. 2015). However, the laboratory cost of hospitals, income/productivity loss of the households were not considered in the study. Furthermore, the study was conducted in a diarrhoea surveillance hospital located in the rural area, and was thus unable to represent the overall scenario of the country (Das et al. 2015).

Rheingans and colleague conducted a multi-country analysis in Association of South East Asian Nations (ASEAN) region in 2001, focusing on childhood diarrhoea, and found the mean household costs were US$ 1.82, US$ 6.47 and US$ 3.33 for Bangladesh, Pakistan and India, respectively. The direct medical cost was the largest contributor for all of these three countries. The authors concluded that poor children and particularly female children were at high risks of mortality due to the limited access care because of affordability issues (Rheingans, Kukla, et al. 2012). However, the study did not consider the providers' points of view or the cost for adult patients (Rheingans, Kukla, et al. 2012). A community-based study conducted in an urban slum with high incidence of diarrhoea in Dhaka in 2007 and found that the cost of childhood diarrhoea per episode ranged

from US$ 1.81 to US$ 4.00, while the average episode was 3.76 days (Jahangir 2009). The study only focused on the population from the urban slum and did not consider the treatment cost of hospital perspective. Sultana et al (2013) initiated a diarrheal costing study in an urban slum of Southern Bangladesh in 2012 and observed that approximately US$ 5.56 was spent per day while the average duration of each episode of diarrhoea was 4 days. Therefore, approximately US$ 22.25 was spent per case. However, this study also did not represent the country level data (Sultana et al. 2013). Halim et al. conducted a costing study of similar settings in 2015 and found the average cost per diarrheal episode was US$ 14. However, they only considered direct-medical cost and income loss of patients (Halim & Haider 2017). None of the above studies represented the country scenario or consider the cost burden across socio-economic strata. Furthermore, none of the above studies reported the broader societal points of view and therefore might be underestimated the actual economic burden of diarrheal diseases. It is essential for the policymakers to understand the detailed information of the economic costs of diarrheal treatments, based on uniform methodologies with a national context. This is necessary for the prioritisation of diarrhoeal preventive program.

2.3.2 Economic Evaluation of Mass Cholera Vaccination program

Cholera is a neglected infectious disease that is transmitted via direct fecal-oral contamination or ingestion of contaminated water and food. The World Health Organization recommended that a multidisciplinary approach, including health and hygiene education, improvement of water and sanitation system, strengthening country-specific disease surveillance and an oral cholera vaccination campaign in targeted high-risk areas is essential for the tacking of cholera infections (WHO 2015b). However, in resource-poor settings and in densely populated areas (e.g., urban slum) the improvement of water and sanitation system is often challenging. These slums are often recognised as ‘high-risk’ area for cholera infection, as these areas are associated with unhygienic environment, fragile water and sanitation system, unhygienic housing and overcrowded population. The World Health Organization developed a global OCV stockpile for tacking cholera infections in high risk areas and humanitarian crisis. However, the demand for OCV often exceeds the supply of the vaccines (Desai et al. 2016). Therefore, a country cholera vaccination program is necessary for tackling any emergency situation. Under these circumstances, national policy-makers often require the complete information on cost and consequences for the adoption of any vaccination program. Although a good number of cholera vaccination studies are available, most of the studies are focused on feasibility and vaccine-effectiveness and only a limited number of

studies focus on costs and consequences of cholera vaccination (Teoh et al. 2018). Teoh and colleagues observed that various models (e.g., static, dynamic transmission models, mathematical model), threshold level (e.g., WHO, NICE), vaccine protection effect (e.g., direct effect, the indirect effect), perspective (e.g., health system, societal), sensitivity analysis (e.g., one-way sensitivity analysis, probabilistic sensitivity analysis) used in cost-effectiveness analysis of various vaccination program

For capturing the different scenario of economic evaluation for cholera vaccination program, an electronic literature search was conducted from inception to mid-September 2016. Literature were searched using Pubmed (MEDLINE), SCOPUS, Web of Science, EconLit, Research Paper in Economics (RePEc), CEA registry, Cochrane Library and World Bank e-Library and was limited to the English published literature. The search criteria were based on a broad combined search containing “cost-benefit analysis" OR ("cost-benefit" AND "analysis" OR "cost-benefit analysis" OR "cost-effective analysis" OR ("cost-effective" AND "analysis" OR "cost-effective analysis") OR ("economic" AND "evaluation" OR "economic evaluation") AND ("cholera" OR "cholera") AND ("vaccination" OR "vaccination"). From this search results, the titles and abstracts were examined on whether it met the criteria for the inclusion of this review. After the primary screening, relevant studies were reviewed. Articles were excluded if any of the three types of full economic evaluation (cost-effectiveness, cost-utility and cost-benefit analysis) of cholera OCV vaccination program were not reported. In the primary screening, a total of 430 articles were found in the search engines, based on the searching criteria. However, most of the papers did not meet the basic inclusion criteria. After removing the duplicate articles and carefully reviewing the abstracts, only 13 articles (Cookson et al. 1997; Murray et al. 1998; Naficy et al. 1998; Sack 2003; Cook et al. 2009; Jeuland, Lucas, et al. 2009; Jeuland & Whittington 2009; Jeuland, Cook, et al. 2009; Kim et al. 2011; Schaetti et al. 2012; Sardar et al. 2013; Troeger et al. 2014; Smalley et al. 2015) were found relevant, and which mentioned the full economic evaluation of OCV vaccination, as proposed by Drummond et al. (Drummond et al. 2005). Those studies are summarized below:

Table 2-2 General characteristics of OCV economic evaluation studies

Author, year	Country/ region	vaccine	Number of doses	Types of analysis	Vaccine protection period (years)	Perspective of analysis
(Cookson et al. 1997)	Argentina	CVD 103-HgR	1	CBA	3	Healthcare provider
(Murray, McFarland, and Waldman 1998)	Hypothetical stable refugee, High risk epidemic population	Dukoral (BS-WC)	2	CEA	1	Healthcare provider
(Naficy et al. 1998)	Hypothetical population of Sub-Saharan Africa	Dukoral (BS-WC)	2	CEA	2	National
(Sack 2003)	Hypothetical endemic population of rural Bangladesh	Dukoral (BS-WC)	2	CEA	3	National
(Cook et al. 2009)	Urban Slum, India	Dukoral (BS-WC)	2	CBA	3	Healthcare provider, societal
(Jeuland, Cook, et al. 2009)	Bangladesh, India, Indonesia, Mozambique	Dukoral (BS-WC)	2	CEA	3	Societal
(Jeuland, Lucas, et al. 2009).	Mozambique	Dukoral (BS-WC)	2	CBA	3	Societal
(Jeuland and Whittington 2009)	Not Specified (NS), Lower income country	Dukoral (BS-WC)	2	CBA	2 to 4	Societal
(S. Y. Kim et al. 2011)	Zimbabwe	Hypothetical reactive OCV	2	CEA	2	Health System
(Schaetti et al. 2012).	Zanzibar, Tanzania	Dukoral (BS-WC)	2	CEA	3	Healthcare provider, societal
(Sardar et al. 2013)	Zimbabwe	NS	NS	CEA	NS	NS
(Troeger, Sack, and Chao 2014)	Bangladesh	Shanchol™	2	CEA	3	Societal
(Smalley et al. 2015)	Bangladesh	Shanchol™	2	CEA	5	NS

CEA= Cost-effective analysis, CBA= Cost-benefit analysis, NS = Not specified

The above literature review indicated that, most of the studies are still limited, particularly with regard to the country context data representativeness and also types of costs and perspectives incorporated in the evaluation method. It is also found that most of the evaluation studies used the secondary source of data from existing databases or other country context dataset. This literature review observed that oral cholera vaccination was highly recommended by most of the studies,

specifically in cholera endemic regions. Further, it was observed that most of the studies used the static model and excluded the herd effect of OCV and also used the existing herd immunity related data from previous studies (Longini et al. 2007).

Table 2-3 Cost, outcome, data source and results of OCV studies

Author, year	Time horizon (year)	Direct medical cost	Direct non-medical cost	Indirect cost	Outcome measurement	Types of model	Indirect effect	Data source	Primary results	Influencing parameters
(Cookson et al. 1997)	3	Yes	No	No	Monetary	Static	No	Assumptions	Oral cholera vaccination appeared cost-beneficial	Cholera incidence rate, vaccine efficacy, vaccine coverage
(Murray, McFarland, and Waldman 1998)	1	Yes	No	No	Cost per DALY averted	Static	No	Secondary data sources & assumptions	OCV would be cost-effective option in a stable refugee population and in cholera epidemic settings	Incidence rate, price of vaccine, vaccine efficacy
(Naficy et al. 1998)	2	Yes	No	No	Cost per case prevented & cost per death prevented	Static	No	Secondary data sources from Malawi - & various assumptions	Cholera vaccination is a cost-effective option compared to the therapy alone	Price of vaccine, vaccine efficacy, time lag for vaccine effect, time lag for treatment effect
(Sack 2003)	3	Yes	Yes	Yes	Cost per death averted	Static	No	Assumptions including cost items and vaccine efficacy rate	The cost per death averted with treatment was $350	Cost of vaccine, vaccine efficacy rate
(Cook et al. 2009)	3	Yes	Yes	Yes	Monetary	Static	No	Secondary data source	A free vaccination program could be passed the societal cost-benefit test in high risk urban slums	Price of vaccine, cholera incidence
(Jeuland, Cook, et al. 2009)	3	Yes	Yes	Yes	Cost per DALY averted	Static	Yes	Secondary data source & assumptions	Without indirect effects of OCV, vaccination program would not cost-effective investment	Price of vaccine, incidence rate, case fatality rate, vaccine efficacy rate, indirect effect of vaccine
(Jeuland, Lucas, et al. 2009).	3	Yes	Yes	Yes	Monetary	Static	Yes	Secondary data source & assumptions	A lower user fee could make the mass vaccination program attractive and would able to pass the cost-benefit test.	Price of vaccine, User fee
(Jeuland and Whittington 2009)	NS	Yes	Yes	Yes	Monetary	Static	Yes	Published data source & assumptions	OCV program could be more economically attractive only if the cholera incidence is high	Production and delivery cost of the vaccine, cholera incidence rate, indirect protection

									and the cost per vaccination is low	
(S. Y. Kim et al. 2011)	NS	Yes	NS	NS	Cost per DALY averted	Static	Yes	Published data source & assumptions	OCV could be cost-effective investment particularly for high endemic regions	NS
(Schaetti et al. 2012).	3	Yes	Yes	Yes	Cost per DALY averted	Static	Yes	Published data source (including herd effect) & assumptions	OCV campaign is not cost-effective even after inclusion of herd immunity.	Price of vaccine, vaccination coverage, vaccine protective efficacies
(Sardar et al. 2013)	Life	NS	NS	NS	Cost per DALY averted	Dynamic	NS	Published data source	Hand hygiene with clean water supply intervention is the most cost-effective option than OCV	NS
(Troeger, Sack, and Chao 2014)	3	Yes	Yes	Yes	Cost per DALY averted	Dynamic	Yes	Published data source (including herd effect) & assumptions	The mass cholera vaccination could be a cost-effective investment if the cholera incidence rate is high otherwise not	Cholera incidence, case fatality ratio, vaccine cost, vaccine duration, and vaccine efficacy
(Smalley et al. 2015)	8	Yes	NS	NS	Cost per DALY averted	Math-matical	No	Published data source (including herd effect) & assumptions	OCV would be cost-effective if the case fatality rate is high and at least 1.5%;	NS

In this review, it was found that most of studies (8 of 13) had chosen the Dukoral (BS-WC) cholera vaccine. However, the efficacy related data and vaccine protection years was also varies (Murray et al. 1998; Cookson et al. 1997; Schaetti et al. 2012; Jeuland & Whittington 2009). The same pattern is also observed when the studies evaluated the vaccination program using the Shanchol™ vaccine (Troeger et al. 2014; Smalley et al. 2015). Most of the studies indicated that the economic evaluation results depend on the certain parameters, such as cholera incidence, price of vaccines, vaccine efficacy and coverage of vaccination and vaccine protection years. It is also observed that in most of the study settings, cost-effectiveness analysis used the narrower perspective (e.g. health system) instead of broader societal perspective and scarcity of primary cholera vaccination related data. Therefore, it is occasionally not authentic to measure the benefits of vaccination as the cost of vaccination was measured hypothetically instead of using the actual cost of vaccines. In addition, most of the studies engaged in health-related outcomes and used cost-effectiveness analysis rather than monetary related outcomes (i.e., cost-benefit analysis), in contrast to a welfare theory based approach (Kenkel 1997). Although this rapid review reflected the existing literature

of OCV vaccination and highlighted the importance of primary data generation, the review process has potential limitations as there might be unpublished studies or potential published studies in other languages, which were not captured in this review.

2.3.3 Willingness to Pay for OCV

Although vaccination is one of the most cost-effective and greatest public health achievements, the vaccine introduction and its sustainability is crucial in resource-poor settings as new vaccines are relatively expensive (Levine et al. 2011; Ozawa et al. 2012). Therefore, financing of new vaccines has become a major challenge, and the success of new vaccination program solely depends on global commitment and the technical and management capacity of the host countries (Shen et al. 2016; Bärnighausen et al. 2014). GAVI plays a critical role for funding in many LMI countries introducing new vaccines (approximately 80 percent of financial support) (Gavi 2015). However, GAVI sets a benchmark for its funding strategies, based on country's gross national income and categorized as 'transition' countries that need to arrange their own financing for the immunisation program (Shen et al. 2016). Bangladesh is going to enter the "transition arena", therefore, it is the time for substantial planning for finance of immunization program with own resources in order to make the immunisation program sustainable (Shen, Farrell, et al. 2014). One option could be private domestic contribution for vaccination financing in the form of user fees. In this aspect, it is essential to know the private demand for the particular vaccine and the willingness to pay (WTP), which is a well-recognized tool for such valuations (Kim et al. 2014).

Willingness to pay (WTP) is the maximum amount of money that individuals are prepared to give up for securing certain benefits (Johannesson & Jönsson 1991). The WTP tool is widely used for valuing various programs and considered as good value for money when the societal value of the total benefits of program exceeds the total costs of the program. In the healthcare sector, WTP tool used to capture the value of money according to individual's preference, for improving their health, as well improving the health of their family members. In vaccination studies, WTP applied to measure the monetary value of the vaccine, which also reflects the future demand for that vaccine. The demand for vaccines often varies among individuals and depend on various factors, such as severity of the disease, socio-economic factors and the ability to pay for vaccines (Bala et al. 1999). As per the approach, the societal benefits of any intervention are the sum of individuals' willingness to pay for that particular intervention that could provide policy advice for valuing the alternative program (Pauly 1995; Olsen & Smith 2001). Therefore, in health policy analysis, WTP

surveys are particularly important when the alternative option exists for addressing one particular public health problem. For instance, WTP could be applied for adopting a new vaccination strategy, as there are many other alternatives, such as improving water and sanitation system, strengthening the health system and treatment procedure, behaviour change communications, etc. are available for tackling the disease burden.

WTP is recognised as a theoretically correct approach as it is grounded on welfare economics; the valuation of benefits can be expressed as monetary units, like costs (Donaldson & Shackley 1997; Johannesson 1996; Pauly 1995; Drummond et al. 2005). In the private market, where goods are trading among producer and consumer, the willingness to pay for the particular goods can be observed from the consumer purchasing behaviour. However, health is a special type of good that is not fully traded in a private market. As such, indirect methods are also necessary to capture the WTP for particular health intervention (Folland et al. 2003; Bala et al. 1999). Two approaches are commonly used for eliciting WTP: revealed preference and stated preference. In revealed preference method, the consumer values the goods from their own choice and purchase accordingly (Drummond et al. 2005). In stated preference, the consumer values the goods that derived from their responses to questions about hypothetical choice rather from observed behaviour (Kim et al. 2014).

Contingent valuation (CV) is a stated preference technique for capturing the maximum WTP for specific goods that are not traded in the private market and originally developed in the area of valuing environmental benefits (NOAA 1993). In the healthcare sector, CV is recommended if the health gains are well defined and if respondents know what they are paying for (Johannesson & Jönsson 1991; Kobelt 2013). WTP is a powerful technique and has been widely used for capturing the demand for the new vaccines globally (Cook et al. 2007; Kim et al. 2008; Lucas et al. 2007; Islam et al. 2008; Whittington et al. 2009; Cook et al. 2009; Jeuland et al. 2010; Jeuland, Lucas, et al. 2009). A systematic review study observed that CV technique is widely used for capturing the demand for childhood immunization in many LMI countries (Yeung & Smith 2005). A structured questionnaire is usually required and questionnaire will be either open-ended or discrete (Johannesson & Jönsson 1991). In open-ended valuation, individuals are asked to state their willingness to pay using a bidding game technique (Randall et al. 1974) and then depending on the answer, the bid is lowered or raised until reaching the respondent's maximum willingness to pay. In discrete valuation questions, there are few options of answer and most of the questions are of the yes/no type and the respondents either accept or reject a bid (Johannesson & Jönsson 1991). Open-ended biding game techniques are frequently used in many vaccination studies and

recognized as an unbiased estimation (Drummond et al. 2005). However, the starting-point bias is associated with the bidding game techniques (Kartman et al. 1996), although some previous studies used this approach without observing any starting-point bias (O'Brien et al. 1998; O'Brien & Viramontes 1994).

Although willingness to pay for health interventions is popular recently, there is a limited number of studies found that focused particularly on vaccination. Ozawa et al. conducted a review of WTP studies among LMI countries and observed only 13 studies that were available which focused on new and future vaccines (Ozawa et al. 2012). However, several new vaccination trials are being conducted globally (Kairu-Wanyoike et al. 2014; Birhane et al. 2016; Slunge 2015). Kim et al. (2015) conducted a literature review among LMI countries to assess the magnitude of WTP values for vaccines and found that only 22 articles were available (Kim et al. 2014). It was also noticeable that the literature that focused on WTP for cholera vaccines are limited in number, although the OCV is a top priority for cholera endemic regions. The objective of this literature review is thus to identify the existing literature on WTP for cholera vaccines and sort out the maximum willingness to pay and the potential factors associated with their stated price.

A literature review was conducted using major electronic databases such as PubMed (MEDLINE), SCOPUS, Web of Science, Research paper in Economics (REPAC), Embase and Econlit to locate the peer-reviewed articles on the willingness to pay for cholera vaccine in the global context. The search was limited to English languages and from inception (i.e., January 1900) to the January 2017, according to the standard guidelines (Moher et al. 2009). The two-specific type of literature that was searched for either included the willingness to pay or the demand for cholera vaccine. The search string used in the above databases as Willingness AND pay AND ("cholera vaccines") OR ("cholera" AND "vaccines") OR "cholera vaccines" OR ("cholera" AND "vaccine") OR ("cholera vaccine") AND ("demand" AND ("cholera vaccines" OR ("cholera" AND "vaccines") OR "cholera vaccines" OR ("cholera" AND "vaccine") OR "cholera vaccine". A total of 95 articles were identified through the literature search. The initial review was based on the title of the articles. However, 60 articles were discarded after reviewing the abstract as those did not match with the inclusion criteria. Then another 19 articles were removed because of duplications. The full texts of the remaining 16 articles were reviewed in detail. However, among them, eight articles were excluded as they did not match with the objectives and contents of the study. Our search identified only 8 studies that particularly focused on the willingness to pay and demand of cholera vaccines, and all of the selected studies were conducted in low- and middle-income countries

(Cook et al. 2007; Kim et al. 2008; Lucas et al. 2007; Islam et al. 2008; Whittington et al. 2009; Cook et al. 2009; Jeuland et al. 2010; Jeuland, Lucas, et al. 2009).

Table 2-4 Summary of the characteristics of the WTP studies for OCV

Study and authors	Country	Study Aim	Name of vaccine	Target population	Elicitation method	Results
Reliability of stated preferences for cholera and typhoid vaccines with time to Think in Hue, Vietnam (Cook et al. 2007)	Hue, Vietnam	To assess the relationship of respondents' extra time to think on WTP	new-generation hypothetical cholera vaccines	Urban and semi urban household	Stated preference - CVM	Time to think (TTT) group had lower willingness to pay compared to Non Time to think (NTTT). Median WTP was US$ 5.92 for NTTT and US$ 2.65 for TTT groups (70% of vaccine efficacy).
Private demand for cholera vaccines in Beira, Mozambique (Lucas et al. 2007).	Beria, Mozambique	To assess the household's willingness to pay	Recombinant toxin B subunit killed whole-cell rBS-WC type cholera vaccine	Cholera endemic area	Stated preference - CVM	Average households WTP for vaccine (2 dose) was US$ 8.45. The per capita WTP was approximately US$ 1.4 for children and US$ 1.2 for adults.
Private demand for cholera vaccines in Hue, Vietnam (Kim et al. 2008)	Hue, Vietnam	To measure the private demand for OCV	Locally produced, first-generation Vietnamese vaccine without toxin B-subunit	Cholera endemic high-risk urban area	Stated preference - CVM	Median WTP was $5 and 17% of the sample would not pay for cholera vaccine. Respondents are not able to distinguish the comparative value of vaccine with different degrees of vaccine efficacy and protection years
Private demand for cholera vaccines in rural Matlab, Bangladesh (Islam et al. 2008)	Matlab, Bangladesh	To estimate household willingness to pay (WTP) for OCV	New-generation B subunit killed whole-cell (BS-WC) vaccine	Cholera endemic rural area	Stated preference - CVM	The average and median WTP per young children (age 1-5 years), school-age children (5-17 years) and per adults were US$ 2.40, US$ 1.20 and US$ 1.05; and about US$ 1.00, US$ 0.05 and US$ 0.00

						respectively. Many households had a little demand for OCV even at very lower prices
Rethinking cholera and typhoid vaccination policies for the poor: private demand in Kolkata, India (Whittington et al. 2009)	Kolkata, India	The number of cholera vaccine that would be purchased by the respondents for themselves and for their household members at a specified price	A combined vaccine against typhoid, paratyphoid A&B, and cholera (TABC)	A low-income slum (Tiljala) and a middle-class neighborhood of Kolkata	Stated preference - CVM	The median private economic benefit to a household with five members was US$ 15 for low income slum where US$27 in a middle-income neighbor-hood. The study observed that approximately 10% of all respondents were not willing to take the vaccine even if the price sets as zero.
Using private demand studies to calculate socially optimal vaccine subsidies in developing countries (Cook et al. 2009)	Based on earlier data Kolkata, India	To develop an economical framework for assessing the societal and economic effect of vaccination based on earlier study	Hypothetical cholera vaccine	Various sources of dataset, low income settings	Stated preference - CVM	The study indicated that if the vaccination subsidies is unknown, the vaccination could sell in market at full marginal cost.
A cost–benefit analysis of cholera vaccination programs in Beira, Mozambique (Jeuland, Lucas, et al. 2009).	Beria, Mozambique	To compare the net economic benefits of immunization strategies with and without user fees and herd immunity of cholera vaccination.	Recombinant toxin B subunit killed whole-cell rBS-WC type cholera vaccine	Hypothetical population of Mozambique	Stated preference - CVM and benefit-cost analysis	Based on earlier WTP survey data, the study showed that without incorporating user fee, oral cholera vaccination would not pass the cost-benefit test as the social costs of vaccination would outweigh the benefits.
Estimating the private benefits of vaccination against cholera in Beira, Mozambique: A Travel Cost Approach (Jeuland et al. 2010).	Beria, Mozambique.	To measure the impact of travel costs (transportation cost and waiting time cost) on demand for cholera vaccination	Recombinant toxin B subunit killed whole-cell rBS-WC type cholera vaccine	Endemic urban area of Beria who participated in vaccination trial	Revealed preference method (travel cost method)	The average individual and households WTP are approximately US$ 0.85 per capita and US$ 5.2 per household. The study concluded that revealed preference methods yield lower demand for

						vaccines than contingent valuation survey (stated preference).

*CVM= Contingent Valuation Method *OCV= Oral Cholera vaccine

In this literature review, a couple of observations have been noticed. Firstly, there are limited number of WTP studies that particularly focus on the demand for the cholera vaccine, although there are a number of cholera outbreaks occurring in different regions of the world (Page et al. 2015; Jain et al. 2016; Eibach et al. 2016; Lam et al. 2017; Clark 2017). All of the WTP studies were conducted a few decades ago, when the cost of vials was relatively high (e.g. Dukoral) and assumed various hypothetical vaccine efficacy and duration of protection years for developing CV scenario. Most of the survey is a part of Diseases of the Most Impoverished (DOMI) program, which was coordinated by the International Vaccine Institute to introduce the new generation of vaccines against cholera infections and report the potential demand for the cholera vaccine. The DOMI programs also conduct some secondary analysis with earlier survey data (Lucas et al. 2007; Jeuland et al. 2010; Jeuland, Lucas, et al. 2009).

Cook and colleagues (2006) conducted a survey driven study in Hue, Vietnam to assess the relationship of respondents' extra time to think and their WTP for cholera vaccine (Cook et al. 2007). A stated preference technique was adopted, and the sample was grouped into two groups: one was the time to think (TTT) group, and the other was the no time to think (NTTT) group. The first group (TTT) had an opportunity to think overnight regarding their choice of OCV, which was similar to the real-life choice situation, and then asked for their maximum willingness to pay for this vaccine. In contrast, the other group had no such opportunity to think overnight (NTTT). The study documented that TTT group had a lower average willingness to pay compared to NTTT group. This study concluded that using standard practices for stated preference survey (in a one-time interview or no time to think) might overstate the willingness to pay for the cholera vaccine. The similar findings were also observed in other settings (Lucas et al. 2007; Islam et al. 2008; Whittington et al. 2009). It was observed that many households had little demand for purchasing cholera vaccines, even at very lower prices (Islam et al. 2008; Kim et al. 2008), although the respondents often put the high values for vaccines for their younger children(Whittington et al. 2009; Islam et al. 2008). Earlier review study also documented that the WTP values were relatively lower for cholera and typhoid vaccines, due to short duration of diseases (Kim et al. 2014).

From the literature review, it was observed that a number of factors, such as price of the vaccine, income, education, sex, family size, perception about OCV, asset ownership, education, and risk

aversion pattern of the households were significant factors for the demand of future cholera vaccines (Lucas et al. 2007; Cook et al. 2007; Kim et al. 2008; Whittington et al. 2009). However, Lucas and colleagues observed that there was no significant relationship among incidence of diarrheal illness and prior experience with cholera infections and the demand of cholera vaccines. were found insignificant for this study (Lucas et al. 2007). However, risk averting behaviour on a household level appeared to be significant factor in other settings (Islam et al. 2008). Similarly, Kim and colleagues observed no significant association among WTP with vaccine efficacy and the duration of protective years (Kim et al. 2008). All the studies highlighted how the price of the vaccine was the main driver for the decision-making process of the respondents. Further, a high positive correlation was observed between WTP and income, thus lower and middle-income countries have comparatively lower WTP than high-income countries (Kim et al. 2014).

Jeuland and colleagues developed a travel cost model in early 2008 (Jeuland et al. 2010). The survey was conducted among the 1,300 households in various neighbourhoods of Beria, Mozambique. The study adopted revealed preference technique and found that the private demand for cholera vaccine was negatively associated with households' expenses regarding vaccination, such as transportation cost and time. Therefore, the long distance between the vaccination centres and other costly behaviours (e.g., unavailability of transport and higher transportation cost, long waiting time) could have detrimental effects on the future vaccination program. The study documented that one additional hour spent, due to receiving the vaccines, would cause approximately a 40% reduction of the quantity of vaccine demanded. Jeuland et al concluded that the revealed preference methods yielded a lower demand for vaccines than the traditionally stated preference survey, i.e., contingent valuation survey that was used in this thesis project.

3 MATERIALS AND METHODS

3.1 Study Design

The research work was designed based on the objectives of the thesis and driven by the key research issues. Each study was based on previously established economic theories and approaches (Drummond et al. 2005; Jit & Brisson 2011; Wagstaff & van Doorslaer 2003; Tan-Torres et al. 2003; O'Donnell et al. 2008). The studies employed this thesis project are used both community-based and hospital-based surveys, along with the hospital service statistics and disease surveillance dataset and secondary data sources. For primary data, a couple of structured questionnaires were developed (see annex) and piloted before the original survey.

This thesis is based on three main types of studies such as diarrheal prevalence related, cost related, and evaluation related. Study I is a descriptive study based on the latest DHS survey that explored diarrheal prevalence, associated factor and healthcare seeking pattern of childhood diarrheal infections in Bangladesh. Study II, III and IV highlighted the resources consumed due to treating diarrheal patients and specifically for ones with cholera infection. Study II focused on the economic burden of diarrheal diseases on a household and hospital level. The cost of cholera infection is discussed in study III, where a cost-of-illness study was carried out in the urban communities and then linked with hospital-based cholera treatment service statistics to capture the societal cost of illness (study VI). Study IV utilized the Demographic Surveillance System (DSS) dataset of the disease surveillance project titled 'Introduction of cholera vaccine in Bangladesh (ICVB)", where the total vaccination cost and distribution of vaccine delivery cost were measured. The study also highlighted the average cost per fully-vaccinated individual, while considering a broader societal perspective. The other studies of this thesis (V, VI and VII) were related to the economic evaluation studies where study V and VI belonged to Introduction of Cholera Vaccination in Bangladesh (ICVB); a mass oral cholera vaccination program in urban Bangladesh. Study V demonstrated the private demand for oral cholera vaccine using a household survey where the head of the household or the economic contributor of the families was the respondent, on behalf of the household. Study VI focuses on the economics of oral cholera vaccination, using the data from the study III and the DSS dataset of ICVB project. Study VII focused on universal rotavirus vaccination, using a published data source that was at the country level. As diarrheal infections still remain a devastating public health problem in Bangladesh, the above studies are expected to contribute in generating new knowledge, particularly in the area of 'economics of

diarrheal infections' and would bring added value to the research and analysis. The title, aims, and methods are summarized in table 3-1.

Table 3-1 Summary of aims, study population, methods and outcomes of the thesis

Study	Aim	Study population	Study methods	Sample size	Outcome
Study I: Prevalence and health care seeking behaviour for childhood diarrheal disease in Bangladesh	To capture the prevalence of health care–seeking behaviour associated with childhood diarrheal diseases (CDDs)	Under-five children	Publicly available BDHS data analysis	A total of 6,563 mothers who had children aged <5 years	Diarrheal prevalence, healthcare seeking pattern, determinants of CDDs
Study II: Economic cost of hospitalised diarrheal disease in Bangladesh: A societal perspective	To estimate the age and sex-specific economic costs of diarrheal disease considering a broad social perspective	Hospitalized patients	Hospital-based survey	A total of 801 diarrheal patients from public hospital	Inpatient vs. outpatient cost, cost burden and coping strategies
Study III: Cost of illness due to cholera disease in urban Bangladesh	Determine the average household cost of illness of cholera infection	Cholera confirmed patients	Community-based household survey	A total of 394 cholera patients/households	Average cost per episode, duration of episode, cost driver
Study IV: Estimating the cost of cholera-vaccine delivery from the societal point of view	To estimate the average cost per fully vaccinated individual and the vaccination cost distribution	All vaccinated population	Community Survey and Resource Analysis	N= 123,661	The cost per fully-vaccinated individual and cost driver
Study V: Willingness to Pay (WTP) for Oral Cholera Vaccines in urban Bangladesh	To analyse the average WTP and demand for cholera vaccine in urban population	High-risk urban population	Community-based contingent valuation household survey	N=1,051	Age-specific WTP, Demand curve of cholera vaccine
Study VI: Economics of cholera vaccination	Assessing the economic evaluation of oral cholera vaccines	Cholera Surveillance area (ICVB)	Surveillance database of ICVB	N= 94,675	Health and economic implication

in urban Bangladesh	in a high-risk area from the broader societal perspective.				of cholera vaccination
Study VII: Cost-effectiveness analysis of introducing universal childhood rotavirus vaccination in Bangladesh	Analysing future cost-effectiveness analysis of rotavirus vaccine: Societal and health system perspective	Under-five children	Secondary data sources	Static birth cohort (N= 15,175,000) according to latest report	Cost per life saved, Cost per death averted, Cost per DALY averted

3.2 Study setting

This thesis is based on the data generated in Bangladesh, a lower middle-income country, based on the World Bank definitions. Bangladesh is located in the north-eastern part of South Asia, and shares borders with India on three sides- the west, the north and the north-east, while the Bay-of-Bengal is on the southern part and Myanmar is located in the south-east part the country. The land area of the country is 147,570 square kilometres (56,977 square miles). According to the latest report published in 2014, the estimated population is 158.1 million, with a density of 1,077 per square kilometre (BBS 2015). Although the majority of people still live in rural areas, the urban population is rapidly growing. Bangladesh is primarily encompassed by floodplains, with hilly areas in the eastern and northern parts of the country. It is also the largest delta in the world, consisting of many large and medium rivers with an intricate web of canals. A tropical monsoon climate prevails in the country, with a warm, wet summer and a cool, dry winter. There are four distinct seasons - winter, spring, summer, and autumn. The monsoon season occupies the greater part of the summer. The geography and climate have made the country vulnerable to natural disasters and it is recognized as the sixth most natural disaster-prone country in the world (Reliefweb 2017). The frequent natural disasters include flood, cyclone, tidal surge, water logging, water and soil salinity, epidemics and various forms of pollutions. Despite these challenges, Bangladesh has reached a LMI country status in 2014, and has been targeted to improve its rank as a middle-income country by 2021 (The World Bank 2018).

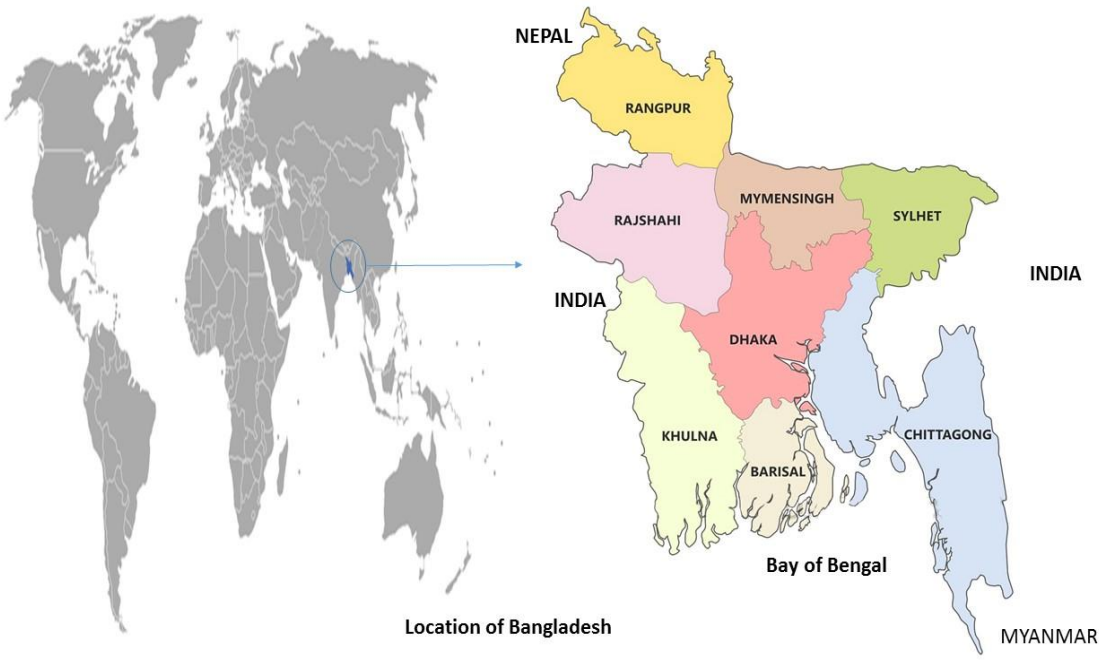

Figure 3-1 Map of Bangladesh (Source: Online web and modification by Sarker et al 2018)

3.3 Sample

The first study (study I) utilised the data generated from the latest Demographic and Health Survey (DHS) in Bangladesh. The DHS is a nationally representative cross-sectional household survey designed to obtain demographic and health indicators. Data collection was conducted from 28th June 2014 to 9th November 2014 and covered all the seven administrative divisions of Bangladesh. With a 98 percent response rate, a total 17,863 ever-married women aged 15-49 were interviewed for this survey. The detailed sampling procedure has been reported elsewhere (NIPORT 2016). In the DHS, information on the reproductive health, child health, and nutritional status were collected through the interview, from women aged 15-49 years. Mothers were requested to provide information about diarrhoea among under-five children, in the last two weeks preceding the survey. The data set was publicly available and accessible without restriction. However, before analysis, the approval was taken from the MEASURE DHS (Measure Demographic and Health Survey) program office for the use of this data set.

The second study (Study II) was conducted in six district hospitals from six divisions (larger administrative units) in Bangladesh (Figure 3-2), and these hospitals were randomly chosen. However, after random selection, the consent from the hospital authorities was required for the final recruitment. The names of the hospitals are Narshingdi district hospital (Dhaka), Cox's Bazar district hospital (Chittagong), Patuakhali district hospital (Barisal), Jhenaidah district hospital

(Khulna), Habigonj district hospital (Sylhet) and Joypurhat district hospital (Rajshahi). Public hospitals play a major role in providing access to treatments for a relatively large population, as the treatment cost in public hospitals is much less than private for-profit hospitals, and these hospitals are financed by non-governmental organizations (NGOs). Therefore, a large number of patients from all ranges of the socio-economic strata usually receive treatment from such hospitals. Although the government subsidised treatment in these public hospitals, substantial amount of private resources (e.g., transportation cost, medicine cost) are also consumed. A hospital-based survey was conducted to capture the household cost of illness in the selected study sites. A resource analysis study was also conducted in these public hospitals to measure the resources used in treating diarrheal patients and then valued. The provider's (i.e., public hospital) actual cost of illness was calculated as the provider's cost for treatment, and was devoid of any fees received from the patients for hospitalization, drug, diagnostic tests, etc. In this study, a total of 801 diarrheal patients were interviewed. The stratified random sampling technique was used where the sampling considered sex (male and female) and length of stay in the hospital (inpatients and outpatient) so that the possible variation of cost per patient could be measured (Salkind 2010). The central limit theorem suggested that at least 30 cases were required to calculate the mean with an assumption that the sample mean will be normally distributed (Levin & Rubin 1991). Therefore, at least 720 patients (30*2*2*6) were required from the six hospitals, whereas 60 inpatients and 60 out-patients of each hospital should be included for measuring the average cost of diarrheal infection per episode.

Selected District Public Hospital (DPH)

Narshingdi district hospital, Dhaka Division

Cox's Bazar district hospital, Chittagong Division

Potuakhali district hospital, Barisal Division

Jhenaidah district hospital, Khulna Division

Hobiganj district hospital, Sylhet Division

Joypurhat district hospital, Rajshahi Division

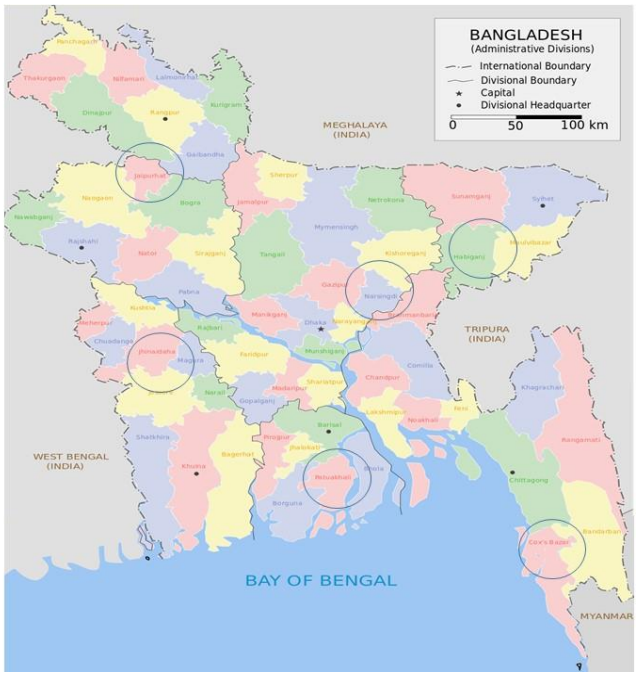

Figure 3-2 Study hospitals in Bangladesh (Source: Online web and modification by Sarker et al 2018)

Introduction of Cholera Vaccine in Bangladesh (ICVB) was conducted to prevent the risk of cholera infection in high risk urban area of Bangladesh. The program was launched in active participation with the Ministry of Health and Family Welfare (MOHFW) to measure the feasibility of delivering two doses of OCV (Shanchol) to all age groups (>1 year and above) in the high cholera risk urban setting of Dhaka, Bangladesh. The study was coordinated by International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b). In that campaign, ICVB provided a newly developed low-cost cholera vaccine using the mechanisms that is similar to what the government of Bangladesh used during its mass polio and measles vaccine campaigns. The project was located in Mirpur, Dhaka, Bangladesh (Figure 3-3) and targeted the high-risk urban population for diarrhoeal diseases. The high-risk population was defined using five criteria, such as overcrowding, poor sanitation, unhealthy and unhygienic living condition, unsafe water use, and low-income dwelling. Based on these criteria, Mirpur was selected as study area for this vaccination trial. It was observed earlier that *Vibrio cholerae* was the most common pathogen for diarrhoea, particularly for those who came from Mirpur area for seeking treatment (Chowdhury et al. 2011). The threes studies (Study III, IV and VI) were conducted in ICVB surveillance area.

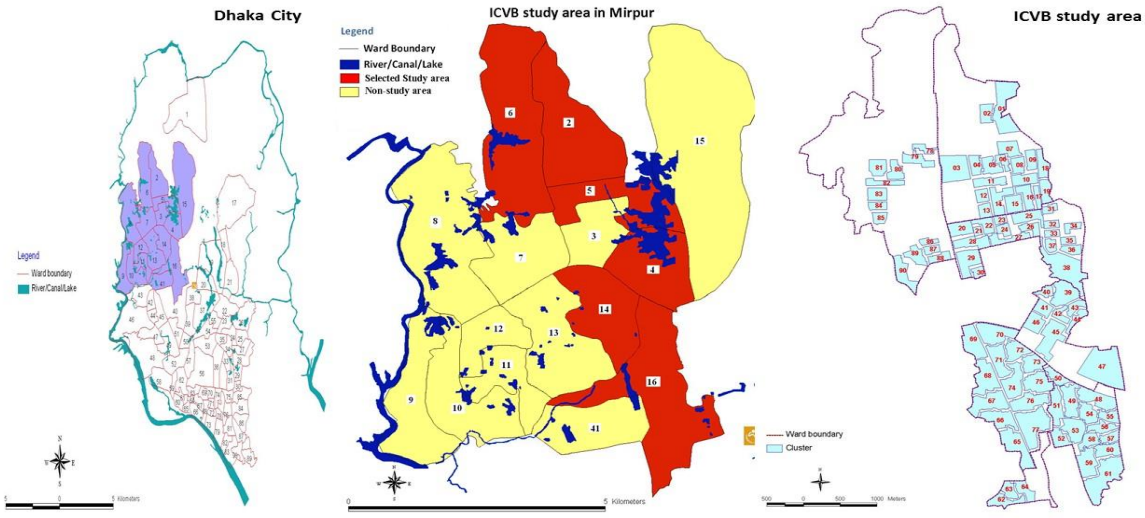

Figure 3-3 Surveillance area of ICVB

The ICVB project examined the feasibility and effectiveness of oral cholera vaccines in reducing the incidence of cholera in urban population. The project involves evaluation of a 2-dose regimen of killed whole cell oral cholera vaccine, Shanchol™ (manufactured by Shantha Biotechnics, in Hyderabad, India). The phase II clinical trials of the whole cell bivalent vaccine Shanchol™ that was conducted in Vietnam, India and Bangladesh have shown that this vaccine was safe and immunogenic for both adults and children (Anh et al. 2007; Mahalanabis et al. 2008; Saha et al. 2011). The latest WHO Fact sheet indicated that Shanchol™ provided at least 65% protection against cholera infections, for up to 5 years, from the vaccination in cholera-endemic settings (WHO 2016a). The ICVB project was conducted in six wards (lowest administrative units) in Mirpur (an urban area), Dhaka, Bangladesh. The Mirpur area is densely populated (approximately 2.5 million people) with a high proportion of 'high-risk populations' that are prone to cholera and other diarrhoeal infections. The wards in Mirpur were selected based on reports of a higher influx of diarrheal patients to Dhaka hospital of icddrb, over the last five years. The hospitalization rate, due to cholera, was at 2-6 per 1,000 people in the selected wards of urban Dhaka (Chowdhury et al. 2011).

Study III was on the household cost of illness of cholera infection. Those who lived in an ICVB surveillance area and sought care to the icddr,b hospitals and laboratory confirmed as cholera cases were enrolled as study sample. The household survey carried on within 14 days of receiving care. All confirmed cholera hospitalized cases, coming from one of the six wards in Mirpur during June–October 2011, were included in the study sample. A total of 394 confirmed cholera cases were identified and interviewed in the community through household survey. Study-V was

conducted in the same setting in 2011, after the oral cholera vaccination campaign was done. In this campaign, participants received two doses of the oral cholera vaccine, the first was on day 1 and the second was given at least 14 days after the first dose. A total of 141,844 people was vaccinated, while a total of 123,661 people received the complete two-dose schedule (fully vaccinated) and 18,178 people took only one dose (incomplete) of vaccine. Pregnant women and children under the age of one were excluded from the vaccination campaign.

Study V was conducted in Mohammadpur, Adabar, Hazaribagh and Kamrangirchar in urban Dhaka (Figure 3-4). A cross-sectional household survey was conducted to capture the maximum willingness to pay for future oral cholera vaccine to protect the households from cholera infections. According to an earlier study conducted in the same country context, it was found that 74% of respondents willing to pay for oral cholera vaccine for their family members (Islam et al. 2008). The following equation was applied for the sample size calculation for WTP study:

$$n = \frac{Z^2 P(1-P)}{d^2} = \frac{(1.96)^2(0.74)(1-0.74)}{(0.03)^2} = 821$$

Where, n=sample size to be calculated, p= proportion having the characteristic being measured (0.74), Z= value of normal distribution at 95% confidence level (1.96), d = tolerable standard error (0.03). Considering a 10% non-response rate, at least 903 households were required for this study. Consequently, a total of 1,051 households were randomly selected and interviewed for this study. The respondents were either the head of households or the economic contributor to the family.

The rotavirus vaccination evaluation study (Study VII) was based on country-specific secondary published and unpublished data sources. A decision model was developed and the model was applied to the all under-five children (N= 15,175,000) during the year of 2016 (Bangladesh Bureau of Statistics 2015).

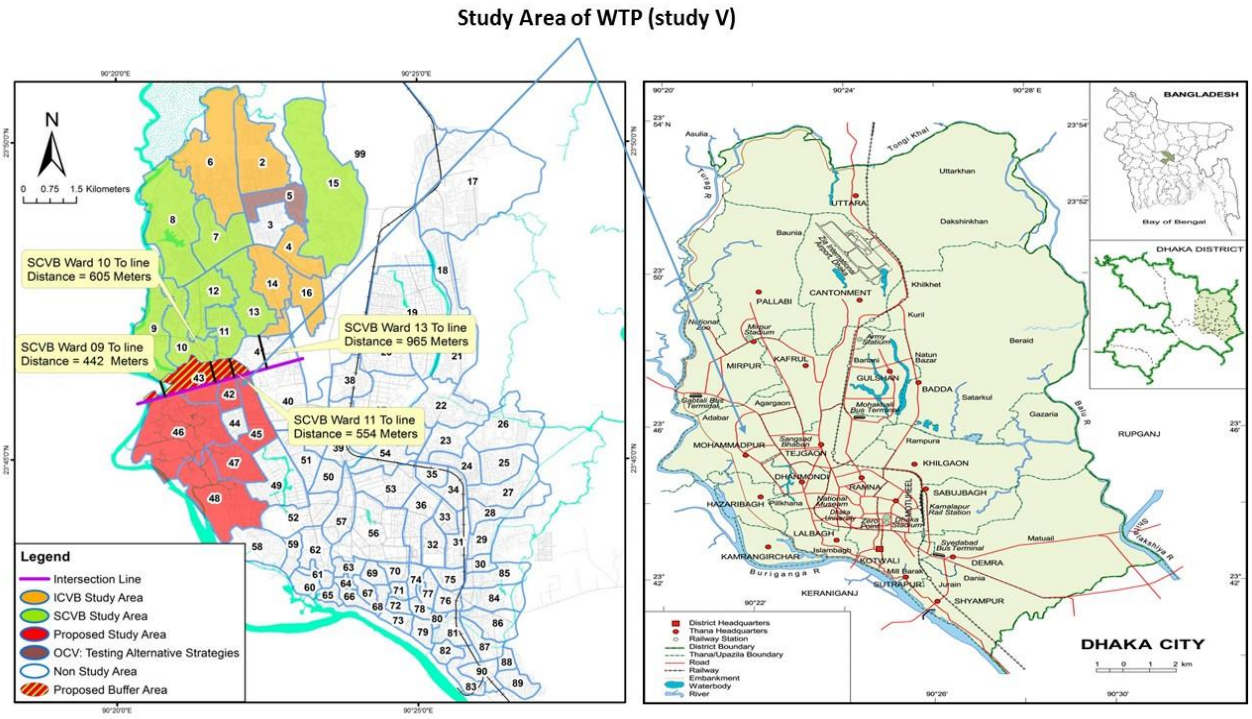

Figure 3-4 Study sites for WTP study (study V)

3.4 Perspectives:

The perspective means the viewpoint from which the analysis is being carried out (Sanders et al. 2016). The perspective of the analysis is crucial for economic evaluation as the costs and outcomes are dependent on which viewpoint is considered and who will be utilized the study results (Gray et al. 2011; Sartori et al. 2012). Gray and colleagues identified the key alternative perspectives as 'societal' and 'payers', which is often known as the health service perspective (Gray et al. 2011). However, the economic evaluation used various perspectives that were dependent on the decision makers, such as the patient's perspective, household's perspective, provider's perspective, health system perspective, public sector perspective, donor perspective, and the broader societal perspective. The chosen perspective basically determined which costs and outcome were to be included for the evaluation (Tolley & Rowland 1995). For instance, out-of-pocket costs and indirect costs, with consequences associated with the particular disease, are included in patients' perspective analysis, whereas the direct and indirect involvement of other members are included in the household's perspective analysis. In the health system perspective, only direct medical cost and consequences are considered (Group 2003), whereas in the public sector perspective, all costs and consequences associated with the government are included. All costs such as medical, non-medical and indirect cost (i.e. non-healthcare cost) and consequences are included in a societal

perspective, which is recommended by the Panel on Cost-Effectiveness in Health and Medicine (Gold et al. 1996). The National Institute for Health and Clinical Excellence (NICE) in England and Wales also ignored the productivity cost in their economic analysis, as NICE always tried to maximize the value for money from the National Health Service (NHS) budget (Gray et al. 2011; National Institute for Health and Clinical Excellence 2012). However, there is a strong theoretical argument for adopting societal perspective in economic evaluation which was based on welfare economics. Thus, without adopting societal perspectives, it is difficult to establish the equity impact of policy strategies as changing any policy will have effects on different individuals and groups within a society (Gray et al. 2011; Sculpher 2001).

As per the Panel on Cost-Effectiveness in Health and Medicine, the analysis was performed from the societal perspective, and aimed to include all costs and consequences of health interventions no matter who incurred them, including the time cost of patients and their caregivers (Study II, III, IV, VI and VII) (Gold et al. 1996). Furthermore, cost double counting was strictly avoided during the analysis, as per Drummond and colleagues (Drummond et al. 2005). However, practically, it was not possible to capture all types of costs and consequences of the health intervention properly. As Drummond et al. (Drummond et al. 2005) stated "We believe that economic evaluations in health care should, where feasible, consider the societal viewpoint, although on occasions analytical difficulties will preclude the full measurement and valuation of all costs and consequences in monetary terms." Study II, III and VI were performed from the societal points of view. The OCV delivery costs were captured from the societal viewpoints and four types of costs were captured: cost of the vaccine manufacture, cost of administering the vaccines and costs of travel to the vaccination sites and time cost to receive the vaccines (study IV). Individual and household perspectives were considered for capturing the demand for OCV in Bangladesh (study V). In the rotavirus vaccination study (study VII), both health system and societal points of view were considered. In the case of the health system perspective, the costs of rotavirus-related medical care and the costs of vaccination program were included. In societal perspective, direct medical cost (e.g., medicine, diagnostic), direct non-medical cost (e.g., transportation, lodging) indirect cost (e.g., income loss), and cost of vaccination program were included in the analysis (Gold et al. 1996).

3.5 Philosophical stance:

This section describes the philosophical stance of this research project, according to the ontological, epistemological and methodological points of view. Resource constraints are commonly recognized in healthcare sectors for LMI countries, like Bangladesh. This thesis attempted to capture the economic burden of diarrhea-related infections and to generate evidence for the decision to introduce a nationwide immunization program. The application of different methods of economic theories in a practical context (e.g. Bangladesh) could be useful for generating evidence-based knowledge for policy makers and the researchers who work for impact assessments. According to the core concept of positivism paradigm, the project was conducted independently whereas and data was collected in a structured manner, using survey and employed various experiments. Then several hypothesis were generated and used econometric models to observe the diarrheal disease burden (Tsoukas 1989; Guba & Lincoln 1994; Saunders et al. 2007). In positivism paradigm, it is often claimed that "scientific knowledge is utterly objective and that only scientific knowledge is valid, certain and accurate" (Crotty 1998). However, this statement often falls short in practicality as human behaviour often comprises of with differing views and opinions. In this regard, the post-positivism paradigm is developed, which is a less stringent form of the positivism paradigm. This research project was close to post-positivism and it involves quantitative techniques with survey designs.

3.5.1 Ontological issues:

Diarrhea, a highly infectious disease which is related to socio-economic status and associated with high morbidity and mortality, and economic loss of families and societies. The disease is caused by different types of microbes (e.g., bacteria, virus) and also caused by urbanisation, unhygienic environment, lack of potable water and hygiene. The OOP and indirect costs associated with the treatment procedure affect the daily livelihood of infected persons and their families, which then lead to the objectivism position rather than constructionism, as it assumes that "reality is caused by social process" (Neuman 2014). This project also documented the cost-effectiveness of cholera vaccination program in cholera endemic settings. The term 'positivism' is often used to describe the philosophy which underpins quantitative research. However, the ontological stance of positivism is a belief of realism, or some single knowable reality, which is based on the natural sciences (Denzin & Lincoln 1994). On an ontological point of view, positivists believe that reality is objectively specified, independent, and can be measurable by using scientific methods, which tends to lead to the conclusion that knowledge is quantifiable and is impartial. The post-positivists

also have similar believed. However, critical realism is the core philosophy of post-positivism, which indicates that error might be associated with observation in the nature of human limitations, and theories can be modified (Trochim 2006). In this paradigm, the reality can be discovered through realm of probability (Ponterotto 2005; Mertens 2008). Critical realism is nowadays considered to be the most common philosophical position of scientists particularly for quantitative scientific researchers. It provides some useful middle ground between the direct or naive realism of 'what you see is what you get' and the out-and-out scepticism of the anti-realists, for whom the entire social world is a series of social and psychological constructs. Therefore, this research project adopted the ontology of a critical realist, which indicated that reality does exist but due to the nature of human behaviour, it can only be known imperfectly.

3.5.2 Epistemological issues

Epistemology addresses the way to know the reality, which refers to "the nature of human knowledge and understanding that can possibly be acquired through different types of inquiry and alternative methods of investigation" (Hirschheim et al. 1995). Therefore, it is possible to explain, in a quantitative aspect, how the socio-demographic variables interact, influence and affect the proposed vaccination program. In this paradigm, the researcher often constructs models and tests these elucidations in experimental studies. In this project, different models were developed, hypotheses were tested, and possible explanations were provided. Multivariate analysis, as well as other statistical techniques, correlations, and comparisons of means were used. Thus, this project might able to generate reliable knowledge regarding a real scenario. The project tried to measure the reality of economics of diarrheal infections in a low-income community and the possible effectiveness of introducing new healthcare technology (e.g., vaccine). As per the post-positivists' epistemology, perfect objectivity was not achievable, but is approachable.

3.5.3 Methodological issues

Like positivism, post-positivists' paradigms support the quantitative methodology and survey design, as the project did. In this paradigm, a research methodology that includes setting objectives is required, needs a hypothesis, a measuring of the variables and sorting out the relationships between variables with a proper scientific explanation. According to the post-positivists' paradigm, the project was conducted based on data sources which were as valid and reliable as possible, which were collected through community survey and an inference was drawn with a proper explanation. In this project, a couple of structured questionnaires were developed, and were

surveyed in a quantitative nature with standard sample selection for avoiding the possible human biases.

3.6 Cost and outcome estimation:

All forms of economic evaluations are involved in the assessment of inputs - i.e., the use of resources and the level of outputs (e.g., health benefits). Costs were estimated by quantifying the various types of resources used in producing and f valued accordingly (Drummond et al. 2005; Sculpher 2001). The definition of costs used by this project were summarised in Table 3-2.

Table 3-2 Type of costs and definition

Perspective	Cost categories	Definition
Households	Direct costs of patient care	Out of pocket expenditure incurred by the patient in the course of treatment
	Direct medical cost	Direct medical costs included medicine costs, consultation fee, admission or registration fees, payments to paramedics during home visits for intravenous infusions, oral rehydrating solution, laboratory tests, diagnostic fees, and any other costs associated medical supplies.
	Direct non-medical cost	Additional costs in accessing treatment of the patients, such as transportation, lodging, food items, tips (informal payment), payment to caregiver for loss of regular work or payment for attending a patient, expenditure for materials such as utensils and other items such as mosquito coils and lighters for patients.
	Direct caregiver's cost	Out of pocket expenditure incurred by the caregivers in the patient's treatment
	Indirect cost	Income or productivity loss
	Indirect costs for patients	The earnings lost by patients while seeking treatment
	Indirect costs of caregivers	The earnings lost by the caregivers
	Intangible cost	Pain, anxiety, discomfort, and sufferings of patients and caregivers
	Total household cost	Total all direct and indirect costs borne by the households
	Cost burden	Percentage of households' income that was consumed by treating patients
Providers	Capital cost	Capital costs or assets are usually invested in a bulk amount and used over time
	Recurrent cost	The regular consumable cost in a year and regularly procured
	Fixed cost	Fixed costs are invested at one time to run the program for a specified period, no matter how many people were treated
	Variable cost	Costs varied with the number of patient's treated / vaccinated individuals
Societal	Total societal cost	Total household cost plus net cost of public provider

3.6.1 Costing methods

All cost components (inputs) were identified, measured and valued (Drummond et al. 2005). The study adopted a bottom-up micro-costing approach. In the bottom-up approach, all potential cost components were valued through the identification of resources used by patient, resulting in patient-specific unit costs (Brouwer et al. 2001; Wordsworth et al. 2005). Swindle et al. recommended the 'micro-costing' technique if there is a chance of wide cost variation among patients (Swindle et al. 1999). Wordsworth et al. found that a full bottom-up costing approach might be suitable for hospital services, as significant component of labour or overheads are involved in hospital services (Wordsworth et al. 2005). The combination of the bottom-up and micro-costing methodology is often believed a gold standard method for cost analysis in respect to hospital services. This method is reliable as it enables an identification of all the relevant cost components and sequentially measures and values them at most detailed level (Drummond et al. 2005). The bottom-up micro-costing approach is characterised by the identification of patient-specific resource use and hospital-specific unit costs.

3.6.2 Cost-Classification

The cost components depend on the viewpoint of analysis. For instance, travel expenses are one of the major cost drivers from the household perspective. However, this is excluded from public or private providers' perspective (Drummond et al. 2005). The cost classification (e.g., direct, indirect and intangible) and items (e.g., medicine, medical device) used in this project were summarised in Table 3-3. In the table 3-3, it was observed that, all type of costs (direct, indirect and intangible) incurred by households while only direct treatment costs are incurred by public provider. All types of treatment costs (direct, indirect and intangible) are excluded from private provider as private providers are profit maximiser.

Table 3-3 Cost classification for this project

Cost classification	Household	Provider	
		Private and/traditional	Public
Direct	Medicine	×	Capital
	Diagnostic		Furniture and transports etc.
	Consultation		Medical device/ instrument etc.
	Hospital expense		Building and others
	Transport		Recurrent
	Informal payment (tip)		Food cost
	Other cost (e.g., mobile bill, coil)		Program management cost and others
Indirect	Income / Earning loss	×	×

	Productivity loss		
Intangible	Cost of pain, discomfort, anger	×	×

'×' means 'excluded'

3.6.2.1 Household cost calculation

Household costs include all out-of-pocket costs related to the illness or illness-related disabilities that are incurred by the participants. The measurement of costs included the amount money paid to health care professionals in cases of home visits, to attend medical appointments outside their homes, diarrhoea-related medications, and expenses for any equipment/materials related to illness. To capture the households' cost of illness, both direct and indirect costs were captured. Direct costs consisted of two components: direct medical costs and direct non-medical costs. Direct medical costs included the amount of healthcare resources that were consumed during diarrheal episodes, such as medicine, diagnosis, registration fee, etc. The direct non-medical cost includes transportation, lodging, foods, informal payment, and payment for substitution, as well as the pay incurred for helping the patients.The indirect cost was considered the income loss as well as productivity loss because of travel to the health centre and costs due to absence from work because of illness related to the diarrheal Self-reported wage rates were used for estimating the income loss. The inclusion of care giving time was based on the assumption that time devoted to caregiving may represent forgone opportunities, such as labour, leisure or household work. This time included the length of time spent directly on patient care (by the patients themselves and by unpaid caregivers) and for attending any diarrhoea-related medical care. Time spent attending medical appointments outside the home were classified in one of two ways – firstly, the time away from paid employment, and secondly, the time away from leisure. The theory of human capital approach (HCA) was employed for estimating the productivity loss of the patients and their caregivers (Rice 1966). To capture the productivity losses for non-market activities, we used the age-specific and occupation-specific wage rates (Sarker et al. 2013; Poulos et al. 2012). We used age-specific wages for adults, teenagers and children aged 5 to 14 years. The minimum salary rate according to national level was given by the adult patients, one-half for the teenagers and three-quarters to capture productivity loss for children, while half of the average salary rate assigned to unpaid home workers considering their age group (Sarker et al. 2013; Poulos et al. 2012).

3.6.2.2 Household cost burden:

The household cost burden was measured as the percentage of the total household earnings that was consumed for the treatment course of the disease (Grietens et al. 2008). The excessive costs

can led to financial catastrophe for the household. However, the lack of financial protection schemes, like health insurance, would mean that relatively low treatment cost may still be financially catastrophic for the poor families. From the societal points of view, a particular disease might have catastrophic financial consequences if the disease is associated with higher productivity costs on patients and their families (Berki 1986).

3.6.2.3 Hospital cost:

Public hospitals are highly subsidised in Bangladesh. The patient-specific resource utilisation was captured from the hospital records to assess the provider cost of illness. All resources were categorised into fixed and variable items. Outpatient care referred to all the care provided that did not require hospital admission. In the case of outpatient visit, the data collectors conducted the interview with adult patient/caregiver and physicians and reviewed the patient records. All capital items were annuitized with their respective lifetimes. For capturing patients' specific cost, the following records were considered-

1) The length of stay in days at different levels of care (e.g. intensive care unit, paediatric unit and observation unit)
2) The type, frequency, amount, duration and route of administration of medicines (e.g. antibiotics and antipyretics), the amount of ORS and intravenous fluids. Data on medications recommended during discharge (if the hospital provides) directly related to the diarrhoea episode were also recorded, as well as their frequency, amount, duration and route of administration.
3) Laboratory tests (type and quantity).

Provider's actual cost of illness: In public hospitals or not-for-profit hospitals, the provider's actual cost of illness was calculated as the provider's costs for treatment, less any fees received from the patients for hospitalization, drug, diagnostic tests etc. However, in private hospitals or clinic, all costs were borne by the households.

Societal costs of illness: Societal costs of illness were the summation of total household costs of illness and provider's actual cost of illness (figure 3-5). This figure showed the various cost components and coping mechanisms of households along with treatment costs incurred by provider.

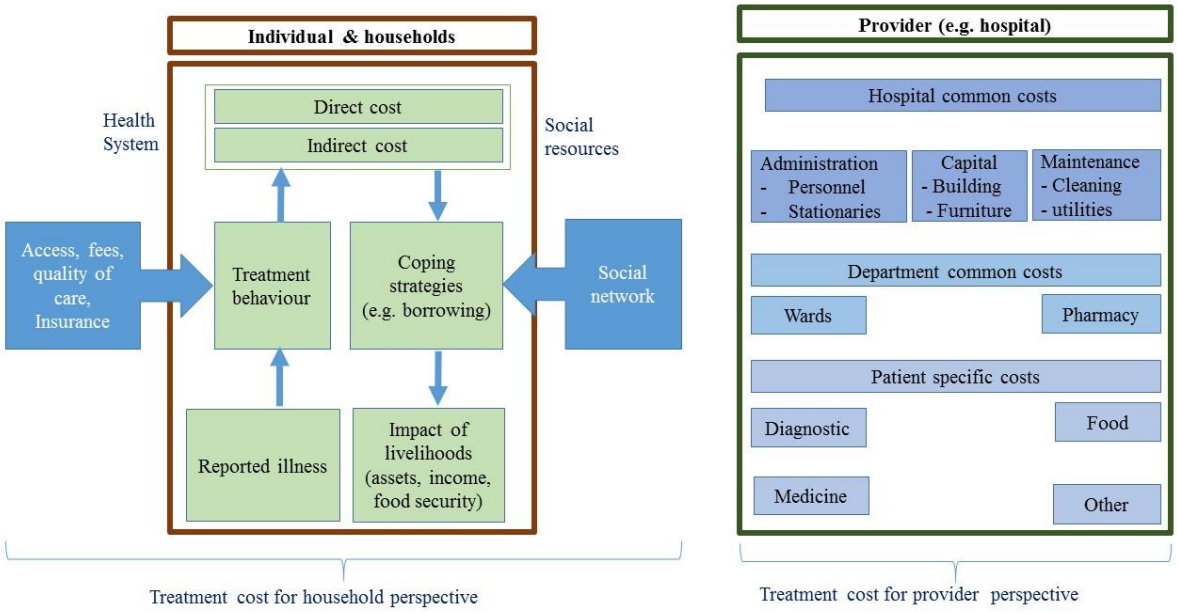

Figure 3-5 An analytical framework of cost-of-illness, adapted from Russells, S (2004) and modification

3.6.3 Outcome estimation

The economic evaluation relates the costs of the intervention against its benefits; it gives evidence for the value for money which is vital for decision makers for prioritising the health care programs (Poulos et al. 2004). Health outcomes are commonly measured in terms of cases averted, deaths avoided, gained life years or gained QALYs, or averted DALYs. DALY is widely used to estimate the global burden of disease and frequently used in international comparative studies by the WHO and World Bank (Kobelt 2013; Murray 1994).

QALYs and DALYs are frequently used as outcome measures in economic evaluation of public health intervention. QALYs are a measure of the individual's health status. The QALY weights generated from the utility of that health status (Gafni & Birch 1997). DALYs are a summary measure of population health that captures the impact of an intervention on both fatal and non-fatal health outcomes. The difference between the two tools is in how the DALY is based on a model of the population, whereas QALY is based on a model of the individuals (Airoldi & Morton 2009). In LMI country, DALY is frequently used for economic evaluation studies, whereas QALY is more common in high-income countries (Thiboonboon et al. 2016). A review study observed that DALY metrics is widely used in diarrheal vaccination program in resource-poor country

(Rheingans et al. 2014). There are various reasons for using DALY based analysis, such as lack of reliable data sources, country specific QALY weight, qualified manpower, and even the lack of appropriate guideline for economic evaluation. The advantage of DALY is that a single set of disability weight is used across countries, whereas QALY weighting depends on country specific and relatively costly process for generating the weights (Horton 2018). However, such QALY weights are still unavailable in the context of Bangladesh. Furthermore, WHO-CHOICE recommended DALYs to express the outcome of cost-effectiveness analysis for the purpose of comparability (Tan-Torres Edejer et al. 2003). It was observed that DALY based economic evaluation is mostly used in cholera vaccination program. (Jeuland, Cook, et al. 2009; Schaetti et al. 2012; Smalley et al. 2015; Troeger et al. 2014). This thesis project also adopted DALY based approaches for evaluating cholera vaccination programs. The cost and consequences of economic evaluation are summarized in Table 3-4.

Table 3-4 Measurement of costs and consequences in economic evaluation of vaccination program

Methods of analysis	Valuation of costs	Measurement of outcome	Cost-outcome comparison
Cost minimization analysis	Monetary units	None	None
Cost-effectiveness analysis	Monetary units	Natural unit (e.g. case or death saved)	Cost per outcome unit
Cost-utility analysis	Monetary units	Utility values (e.g., QALYs or DALYs)	Cost per QALY gained or cost per DALY averted
Cost-benefit analysis	Monetary units	Monetary units	Net costs, or benefit-cost ratio

Sources: Adapted from Drummond et al (2005).

For evaluation of cholera and rotavirus vaccination, a cost-effectiveness analysis was conducted according to the guidelines of the Disease Control Priorities Project (or DCP) and CHOosing Intervention that are Cost Effective (WHO-CHOICE) project (Tan-Torres et al. 2003; Jamison et al. 2006). The DALYs were captured based on the standard methodology proposed by Global Burden of Study (GBD) and compared with the cost-effectiveness threshold provided by the WHO-CHOICE guidelines (Tan-Torres Edejer et al. 2003). In addition, a WTP survey was carried out for capturing the benefits of the OCV (Hammitt & Graham 1999; Carson 2012).

3.6.4 Analytical model of vaccination

Economic evaluation of vaccination programs is often used various models, such as dynamic and static model. Many studies indicate that the economic evaluations, particularly the cost-effectiveness analysis are highly sensitive to the disease model selection (Lugner et al. 2010;

Jeuland, Cook, et al. 2009; Kim & Goldie 2008; Doorslaer et al. 2009). Kim and Goldie (2008) conducted a systematic review that focused on different models used in cost-effectiveness analysis of vaccination programs and were categorized into three primary theoretical models; static/dynamic, stochastic/deterministic; and aggregate/individual-based model. However, they observed that 90% of the studies adopted deterministic and aggregate level static models in vaccination studies (Kim & Goldie 2008).

The model may be 'open' or 'closed', depending on whether or not the model allows individuals to enter into the model. In open models, individuals often enter over time and also exit from the model overtime (Kim & Goldie 2008). The model may be also 'linear' and 'non-linear', model depending on mathematical equations (Kim & Goldie 2008). In a linear model, all of its functions will be represented by linear equation, otherwise the model is referred as non-linear model (Aris 1994). The conventional or static model is often like a decision tree model where the force of infection is constant over time. Age-structured SIER-type models (susceptible-exposed-infected-removed) are the main characteristics of 'dynamic' model which are supposed to simulate the transmission dynamics of infectious disease in time (Kim & Goldie 2008; Lugner et al. 2010; Longini et al. 2007; Fung 2014). The type of dynamic model will depend on disease while susceptible-infections- recovered (SIR) model is widely used in which host population is classified according to infection status(Wearing et al. 2005). The dynamic transmission model is crucial for capturing the herd immunity of vaccine which is typically specified with the set of differential equations (Dimitrov et al. 2014; Longini et al. 2007; Azman et al. 2015; Cai et al. 2017; Vos et al. 2016; Tuite et al. 2011; Kim et al. 2017; Kim et al. 2016; Garnett 2005; Edmunds et al. 1999; Brisson & Edmunds 2003). Further, the model might be an 'aggregate' or 'individual -based model'. In an aggregate model, individuals is often allocated to compartment based on their health status and then individuals of each compartment can move as per parameters value at aggregate level(Kim & Goldie 2008). Individual-based model often referred as 'microsimulation model' where the model can stimulate by incorporating the complex nature of disease transmission or human behavior (Weinstein 2006; Kim & Goldie 2008). Microsimulation model is further classified into individual-level Markov models, discrete-event simulation (DES) models, and agent-based models (ABM). The individual-level Markov model is computationally simple and can be implemented by Microsoft Excel, allowing the interaction among individuals while the DES model is particularly helpful for simulating a complex system involving the interaction among and between individuals and the surrounding environment (Brennana et al. 2006; Simpson et al. 2009; Kim & Goldie 2008). In the agent-based model, a system is modelled where the agents

(e.g. individuals) are allowed to act autonomously with their own behavioural rules and interactions between agents (Bonabeau 2002; Railsback & Grimm 2012). Due to the flexible modelling techniques , ABM is now familiar in the field of economic evaluation of the vaccines, along with other health interventions (Sander et al. 2009; Olsen & Jepsen 2010; Grüne-Yanoff 2011; Megiddo et al. 2016; DePasse et al. 2017; Megiddo et al. 2014).

To evaluate oral cholera vaccinations, the study employed the static empirical model, where all model inputs were obtained from the oral cholera vaccination trial in urban Bangladesh (Kim & Goldie 2008; Qadri et al. 2015). The advantage of the static model is that it requires minimum data, can be built and understood easily and developed at a low cost (Welte et al. 2005; Lugner et al. 2010). However, there are some limitations associated with the static model, as it assumes a constant force of infection and limited ability to capture random nature of event and also cannot capture the herd immunity (Kim & Goldie 2008). Thus, the static model is unable to examine the change in effect of vaccination among the unvaccinated population in the community, which could be captured through dynamic transmission model (Kim & Goldie 2008; Lugner et al. 2010). Since the dynamic transmission model is able to capture the indirect effect of reduced transmissions and the long-term effect of vaccination programs, it thus provides a higher cost-effectiveness ratio than the static model (Lugner et al. 2010). Therefore, the current study might have underestimated the actual benefit of the oral cholera vaccination. Earlier OCV study also concluded that incorporating herd immunity makes the vaccination program more attractive from economic perspective (Jeuland, Cook, et al. 2009). However, the dynamic model requires much more detailed data such as transmission probability, vaccine efficacy for susceptibility/infectiousness, proportion infections symptomaticm, and seasonal boost factors, which are limited in the study context. The dynamic transmission model is often problematic, as many uncertain parameters differ in transmissibility, and also time consuming and more difficult to understand (Welte et al. 2005; Kim & Goldie 2008). Furthermore, due to its flexibility, the application of agent-based models is increasing in the healthcare sector. However, this model requires enormous computational power, often time consuming while modeller's expertise is crucial for all types of models (Megiddo et al. 2014; Megiddo et al. 2016; Macal & North 2014; Chhatwal & He 2015; Tracy et al. 2018). Therefore, despite the limitations, it was observed that (from the literature review) most of the economic analysis of vaccination program used the static model, which led to the underestimating of the cost-effectiveness of the immunization program (Goldie et al. 2008; Wilder-Smith et al. 2017). However, many studies reported that the static model can be used if it ignored the indirect

effects as there are no particular evidence of harm and without herd immunity the vaccine appeared as cost-effective investment (Kim & Goldie 2008; Jit & Brisson 2011; Ultsch et al. 2016).
In this project, the cost-effectiveness cholera vaccination study was based on 2-year time horizon with ICVB surveillance data while the cost-effectiveness of rotavirus study is based on published data Thus, it was not possible to collect rigorous information that is essential for the dynamic model. Furthermore, it was not possible to capture the natural immunity among a population with endemic cholera (Longini et al. 2007). As such, many vaccination studies often excluded the concept of the 'indirect effect' of vaccine (Cook, Jeuland, Whittington, Poulos, Clemens, Sur, Anh, Agtinih, et al. 2008; Jit et al. 2011; Patel et al. 2013). To capture the total benefits (including herd protection) of OCV, a large geographic populations should be targeted which is beyond this study (Qadri et al. 2015).

3.6.5 Decision rules and Threshold levels

Resource scarcity is common in health care if the resources are used in delivering one particular health intervention (e.g., vaccination), then the resources are no more to deliver for other interventions (e.g., water and sanitation, treatment). This is called the opportunity cost of the resource. In cost-effectiveness analysis, this opportunity costs are often expressed using cost-effectiveness threshold levels and compared with the incremental cost-effectiveness ratio (ICER): the ratio of incremental costs to incremental health effect (Woods et al. 2016). Cost-effectiveness threshold is widely used to measure the poor, good and very good value for money for an investment (Hutubessy et al. 2003; Bertram et al. 2016). The intervention is considered as 'cost-effective' if the ICER is below a certain threshold value in correspondence to how much the society is willing to spend to gain a unit increase in effectiveness.

There is no single criteria for cost-effectiveness ratio below which a vaccination program or any other intervention should be adopted. Medical literature sometimes quote a threshold value based on cost per life-year saved and used the value of US$ 50, 000 per life-year saved in some high income countries (Szucs 2005). A vaccination program is cost-effective or not depend on the costs and outcome of the intervention. In a situation where the intervention implies an increase in costs, along with an increase in health effects, an incremental cost-effectiveness ratio (ICER) is then required to estimate and then compared with a threshold level (Drummond et al. 2005; Gray et al. 2011; Morton & Lauer 2017) NICE suggested the incremental cost-effectiveness ratio should be compared with a threshold range, from UK £20,000 to £30,000 per QALY gained, to establish whether this new technology justifies the efficient use of fixed budget (McCabe et al. 2008). Recently, the threshold level was being revisited by Claxton and colleagues and they

recommended the use of UK£ 12,936 (US $ 20,212) per QALY gained in the UK (Claxton et al. 2015). Furthermore, Woods et al. investigated the country level estimates of threshold level and estimated the cost-effectiveness threshold for Bangladesh could range from US$ 30 to US$ 427 per QALY in 2013 price level (Woods et al. 2015).

The most commonly used cost-effectiveness thresholds are based on per-capita gross domestic product (GDP) of the host country, as per report of the Commission on Macroeconomics and Health (WHO 2001). Due to the absence of locally established cost-effectiveness threshold level, the project adopted the WHO-CHOICE GDP threshold level for the cost-effectiveness analysis (Tan-Torres et al. 2003; Hutubessy, Chisholm, and Edejer 2003). Many oral cholera vaccination evaluation studies adopted the GDP threshold level (Jeuland, Cook, et al. 2009; Schaetti et al. 2012; Troeger et al. 2014; Smalley et al. 2015; Newall et al. 2014). According to the WHO-CHOICE threshold level, a vaccination program with an ICER less than annual GDP per capita of the reporting country (in this case, Bangladesh) is potentially 'very cost-effective', whereas ICER that is less than three times of the national annual per capita GDP is considered as a cost-effective intervention (Tan-Torres et al. 2003).

The WHO-CHOICE GDP thresholds has been criticized to some extent, as this threshold level does not consider the affordability, budget impact, sustainability of funding, feasibility of implementation or the value of other intervention (Morton 2010; Airoldi & Morton 2009; Woods et al. 2015; Bertram et al. 2016; Newall et al. 2014; Shillcutt et al. 2009). Newall and colleague observed that although vaccination studies in many countries appeared as cost-effective when considering the per capita GDP thresholds, those vaccination program were still not funded and the vaccination program was not implemented yet (Newall et al. 2014). There are various reasons for this, such as lack of expertise in interpreting the cost-effectiveness result, and various local context such as low political priority, budgetary constraints and, even in many LMI countries, implicitly or explicitly using different thresholds from the 'WHO-CHOICE threshold' during the decision making process of vaccine introduction (Burchett, Mounier-Jack, Griffiths, Biellik, et al. 2012; Newall et al. 2014). Nevertheless, the prime intention of WHO-CHOICE GDP based thresholds, was to guide the policy makers on value for money (Hutubessy et al. 2003). Therefore, other considerations relevant to country specific local context (e.g. affordability, fairness, feasibility, budget impact) should be used in the decision-making process (Bertram et al. 2016). Bertram and colleagues mentioned various factors that could influence the results of cost-effectiveness analysis, such as the reliability of data, the choice of comparator, whether subgroup analysis of target population is analysed, along with other relevant local contextual factors. This

would clearly indicate that a single fixed cost-effectiveness threshold should never be used as a stand-alone criterion for the decision making process (Bertram et al. 2016). Therefore, policy makers should consider the various context-specific factors, such as affordability, budget impact, feasibility, fairness and other relevant criteria for local context, along with the CEA results. However, relevant data is vital for such decision making process (Hutubessy et al. 2003; Newall et al. 2014; Bertram et al. 2016). This thesis project used the primary and secondary cost and outcome data for the cost-effectives analysis, where the outcome is measured as cost per case averted, cost per death averted, and cost per DALY averted against WHO provided GDP-threshold level and documented the affordability of oral cholera vaccination through a contingent valuation survey.

3.6.6 Reporting format of economic evaluation:

A standard reporting format of economic evaluation studies are important for clarification of findings. For ensuring transparencies and understanding of economic evaluation studies, Drummond and colleagues identified ten common queries which is also called the check list of economic evaluation studies (Drummond et al. 2005). In last decade, Hjlmgren et al. identified almost 25 guidelines that are available for reporting economic evaluation studies (Hjelmgren et al. 2001). The main concerns and disagreement are the choice of perspective, costs components, and the way of measuring benefits (Hjelmgren et al. 2001).. Recently, NICE developed an economic evaluation guideline after consultation with different stakeholders and is recommended for reporting as per guideline (National Institute for Health and Clinical Excellence 2012). Although, economic evaluation studies are continuously growing, many studies do not follow the economic evaluation guidelines properly and study findings are often poorly presented (Husereau et al. 2013). For tackling this aspect, International Society for Pharmacoeconomics and Outcomes Research (ISPOR) developed a Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement for economic evaluation findings, which was required for ten that the reviewers and readers could easily understand the methodological issues related to these studies. The CHEERS statements consist of a 24-item checklist, which is based on the previous health economic evaluation guidelines. In this project, studies VI and VII followed according to the CHEERS guideline. The checklist is attached at the end of the thesis (Annex).

4 CHILDHOOD DIARRHEAL DISEASE: PREVALENCE AND CARE–SEEKING BEHAVIOR

Study - **I**

Published: ***Global Pediatric Health***

Publisher: **SAGE Publication**

Volume: (2016) 3:1-12

DOI: 10.1177/2333794X16680901

Title of the paper: Prevalence and health care–seeking behavior for childhood diarrheal disease in Bangladesh (study I)

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Abstract

In Bangladesh, the burden of the diarrheal diseases is significant among children under five years old. The objective of the study is to capture the prevalence of and healthcare-seeking behavior for childhood diarrheal diseases (CDD) and to identify the factors associated with CDD at a population level in Bangladesh. We use a logistic regression approach to model careseeking based on individual characteristics. The overall diarrhea prevalence among under-five children was found to be 5.71%. Some factors found to significantly influence the healthcare seeking pattern were age and sex of the children, nutritional score, age and education of mothers, wealth index, and access to electronic media. The healthcare service could be improved through working in partnership with public facilities, private health care practitioners, and community-based organizations so that all strata of the population get equitable access in cases of childhood diarrhoea.

Keyword: Bangladesh, care seeking, childhood diarrhea, incidence, prevalence

4.1 INTRODUCTION:

Diarrheal disease is a major threat to human health and still a leading cause of mortality and morbidity worldwide (Murray & Lopez 1997). Globally, 1.5 million deaths and nearly 1.7 billion diarrheal cases occurs every year (WHO 2012a). It is also the second leading cause of death in children <5 years old and is responsible for the death of more than 760,000 children every year worldwide (WHO 2013a). In the latest UNICEF report, it was estimated that diarrheal diseases constituted 9% of all deaths among children <5 years old in 2015 (UNICEF 2016). Although the burden of the diarrheal diseases is much lower in developed countries, it is an important public health problem in low- and middle-income countries as the disease is particularly dangerous for young children, who are more susceptible to dehydration and nutritional losses in those settings (Chowdhury et al. 2015). In Bangladesh, the burden of the diarrheal diseases is significant among in children <5 years old (NIPORT 2016). Global estimates of the mortality resulting from diarrhea have shown a steady decline since the 1980s. However, despite all advances in health technology, improved management, and increased use of oral rehydration therapy, diarrheal diseases are also still a leading public health concern (Kumar & Subita 2012). Moreover, morbidity caused by diarrhoea has not declined as rapidly as mortality, and global estimates remain at between 2 and 3 episodes of diarrhea annually for children <5 years old (WHO 2012c). There are several studies assessing the prevalence of childhood diarrhoea from children under five years of age. However, in Bangladesh, information on the age-specific prevalence rate of childhood diarrhea is still limited, although such studies are vital for informing policies and allowing international comparisons (Konstantyner et al. 2016; Parashar et al. 2003).

Clinically speaking, diarrhea is an alteration in a normal bowel movement characterized by an increase in the water content, volume, or frequency of stools (Ozguler 2015). A decrease in consistency (i.e., soft or liquid) and an increase in the frequency of bowel movements to ≥3 stools per day have often been used as a definition for epidemiological investigations. Based on a community-based study perspective, diarrhea is defined as at least three or more loose stools within 24- hour period (A. H. Baqui et al. 1991). A diarrheal episode is considered as the passage of 3 or more loose or liquid stools in 24 hours prior to presentation for care, which is considered the most practicable in children and adults (Deen et al. 2008). However, “prolonged” and “persistent” diarrhea can last between 7 and 13 days and at least 14 days respectively (Lamberti et al. 2012; Isanaka 1989). The disease is highly sensitive to climate, showing seasonal variations in numerous sites (Drasar et al. 1978). The climate sensitivity of diarrheal disease is consistent with observations of the direct effects of climate variables on the causative agents. Temperature

and relative humidity have a directly influence on the rate of replication of bacterial and protozoan pathogens and on the survival of enteroviruses in the environment (Black & Lanata 1995).

Healthcare seeking is recognized to be a result of a complex behavioral process that is influenced by several factors, including socioeconomic and demographic and characteristics, perceived need, accessibility and service availability (Sikder et al. 2015; Koenig et al. 2016; Armitage et al. 2002). The patterns of care-seeking behavior also depend on the quality of healthcare providers, effectiveness, convenience, opportunity costs, and quality of services (Sarker et al. 2014; Rahman & Rahman 2013; Helman 1995; Chrisman 1977). In addition, symptoms of illness, duration, and an episode of illness as well as age of the sick person can be important predictors of whether and where people seek care during illness (Ahmed et al. 2000; Ahmed et al. 2005; Larson et al. 2006). Therefore, it is important to identify the potential factors related to care seeking behaviour during childhood diarrhea because without proper treatment, it can lead to death within a very short time (Sarker et al. 2015). Although there are few studies about healthcare-seeking behavior for diarrheal disease in different settings, such an analysis using a nation-wide sample has not been seen in this country context (Nasrin et al. 2013; Das et al. 2013; Chowdhury et al. 2015). The objective of this study is to capture the prevalence of and healthcare-seeking behavior associated with childhood diarrheal diseases (CDD) and to identify the factors associated with CDDs at a population level in Bangladesh with a view to informing policy development.

4.2 MATERIALS AND METHODS

4.2.1 Data

This study analyzed data from the latest Demographic and Health Survey (DHS) in Bangladesh. This DHS survey is a nationally representative cross-sectional household survey designed to obtain demographic and health indicators. Data collection was done from June 28, 2014 to November 9, 2014, covering all the 7 administrative divisions of Bangladesh. With 98% response rate, a total 17,863 ever-married women aged 15to49 years were interviewed for this survey. The detailed sampling procedure has been reported elsewhere (NIPORT 2016). In the DHS, information on reproductive health, child health, and nutritional status were collected through the interview with women aged 15 to49 years. Mothers were requested to give information about diarrhea episodes among <5 children in the past 2 weeks preceding the survey (Forsberg et al. 2007). The data set is publicly available online for all researchers. However, the approval was sought from and given by MEASURE DHS (Measure Demographic and Health Survey) program office to use this data set.

4.2.2 Variable description

In this study, 2 outcome variables were focused on : first, outcomes related to the diarrheal diseases among the <5 children in the past 2 weeks (‘1’ denoted for ‘occurrence of diarrhea’ for the indicated period and ‘0’ denoted for ‘no occurrence’), and second, health-care seeking behavior for diarrheal diseases, which were categorized as ‘No care’, ‘Public Care' (hospital/medical college hospital/specialized hospitals, district hospital, Mothers and Child Welfare Centre, Union Health Complex, Union Health & Family Welfare Centre, Satellite clinic/EPI outreach site),‘Private Care (private hospital/clinic, qualified doctors, NGO static clinic, NGO satellite clinic, NGO field worker), ‘care from the pharmacy’ and ‘Others’ (home remedy, traditional healer, village doctor herbals, etc.). For capturing the healthcare-seeking behavior for a young child, respondents were requested to give information about where they sought advice /care during the child’s illness. Nutritional index was measured by Child Growth Standards proposed by WHO, (z score of height for age [HAZ], weight for age [WAZ], and weight for height [WHZ]) and the standard indices of physical growth that describe the nutritional status of children as stunting – that is, if a child is more than 2 standard deviations (SDs) below the median of the WHO reference population (WHO 2006b). Mother occupation was categorized as homemaker or no formal occupation, poultry/farming/cultivation (land owner, farmer, agricultural worker, poultry raising, cattle raising, home-based handicraft), and professional. Access to electronic media was categorized as ‘Access’ and ‘No Access’ based on the household having radio/television. The source of drinking water was categorized as ‘Improved’ (piped into a dwelling, piped to yard/plot, public tap/standpipe, tube-well or borehole, protected well, rainwater, bottled water) and ‘Unimproved’ (unprotected well, unprotected spring, tanker truck/cart with the drum, surface water). In this study, types of toilet facilities were categorized as ‘Improved’ (flush/pour flush to piped sewer system, flush/pour flush to septic tank, flush/pour flush to pit latrine, ventilated improved pit (VIP) latrine, pit latrine with slab) and ‘Unimproved’ (facility flush/pour flush not to sewer/septic tank/pit latrine, hanging toilet/hanging latrine, pit latrine without slab/open pit, no facility/bush/field). Floor types were coded as ‘Earth/Sand and ‘Others’ (wood planks, palm, bamboo, ceramic tiles, cement, and carpet).

4.2.3 Data processing and analysis

After receiving the approval to use this data, data were entered, and all statistical analysis were executed by using statistical package STATA 13.0. Descriptive statistics were calculated for frequency, proportion and the 95% confidence interval. Bi-variate statistical analysis was performed to present the prevalence of diarrhea for different selected socio-demographic,

economic and community-level factors among children <5 years old. To determine the factors affecting childhood diarrhea and health care seeking, logistic regression analysis was used, and the results were presented regarding odds ratios (ORs) with 95% confidence intervals (CIs). Adjusted and unadjusted ORs were presented for addressing the effect of single and multifactors (covariates) in the model (Pourhoseingholi et al. 2012). Health care-seeking behavior was categorized as no-care, pharmacy, public/government care, private care, and other care sources to trace the pattern of health care-seeking behavior among different economic groups. Finally, multinomial multivariate logistic regression analysis was used to examine the impact of various socio-economic and demographic factors on care-seeking behavior. The results were presented as adjusted relative risk ratios (RRR) with 95% CIs.

4.2.4 Ethical approval

We analyzed a publicly available DHS dataset by contacting MEASURE DHS program office. DHSs follow standardized data collection procedures. According to DHS, written informed consent was obtained from mothers/caretakers on behalf of the children enrolled in the survey.

4.3 RESULTS

4.3.1 Background Characteristics

A total of 6,563 mothers who had children aged <5 years were included in the study. Among them, 375 mothers (5.71%) reported that at least one of their children had suffered from diarrhea in the 2 weeks preceding the survey. Socio-demographic characteristics of the respondents and study children are represented in Table 4-1. The mean age of the children was 30.04 ± 16.92 months (95% CI=29.62, 30.45), and age of children was almost equally distributed for each age category; 52%of the children were male. Considering nutritional status measurement, 36.40%,14.37%, and 32.8% of children were found to be stunted, wasted and underweight, respectively. Most of the children were from rural areas- 4,874 (74.26%) and lived in households with limited access (44% of the total) to electronic media. The average age of the mothers was 25.78 ± 5.91 years and most of them (74%) completed up to the secondary level of education. Most of the households had an improved source of drinking water (97.77%) and improved toilet (66.83%); however, approximately 70% households had an earth or sand floor.

Table 4-1 Distribution socio-demographic characteristics of mother and children <5 years old

Variable	n (%)	95 % CI
Child Age (in month)		
Mean age (mean ± sd)	30.04 ± 16.92	(29.62, 30.45)
< 12	1207 (18.39)	(17.47, 19.34)
12-23	1406 (21.43)	(20.45, 22.44)
24-35	1317 (20.06)	(19.11, 21.05)
36-47	1301 (19.82)	(18.87, 20.80)
48-59	1333 (20.30)	(19.35, 21.30)
Sex of Children		
Male	3414 (52.01)	(50.80, 53.22)
Female	3149 (47.99)	(46.78, 49.20)
Nutritional Index		
Height for Age (HAZ)		
Normal	4174 (63.60)	(62.43, 64.76)
Stunting	2389 (36.40)	(35.24, 37.57)
Weight for Height (WHZ)		
Normal	5620 (85.63)	(84.76, 86.46)
Wasting	943 (14.37)	(13.54, 15.24)
Weight for Age (WAZ)		
Normal	4411 (67.2)	(66.06, 68.33)
Underweight	2152 (32.8)	(31.67, 33.94)
Mothers age		
Mean age (mean ± sd)	25.78 ± 5.91	(25.63, 25.93)
Less than 20	886 (13.50)	(12.70, 14.35)
20-34	5140 (78.31)	(77.30, 79.29)
Above 34	537 (8.19)	(7.55, 8.88)
Mothers Education level		
No education	1126 (17.16)	(16.27, 18.09)
Primary	1840 (28.03)	(26.96, 29.13)
Secondary	3004 (45.78)	(44.57, 46.98)
Higher	593 (9.03)	(8.36, 9.78)
Mothers Occupation		
Home maker/no formal occupation	4651 (70.86)	(69.75, 71.95)
Poultry/farming/cultivation	1117 (17.02)	(16.13, 17.95)
Professional	795 (12.12)	(11.35, 12.93)
Number of Children		
Less than 3	4174 (63.60)	(62.43, 64.76)
3 and above	2389 (36.40)	(35.24, 37.57)
Number of under five children		
One	4213 (64.19)	(63.02, 65.34)
Two and above	2350 (35.81)	(34.66, 36.98)
Division		
Barisal	373 (5.68)	(5.15, 6.27)
Chittagong	1398 (21.30)	(20.33, 22.31)
Dhaka	2288 (34.87)	(33.72, 36.03)
Khulna	498 (7.60)	(6.98, 8.26)
Rajshahi	676 (10.29)	(9.58, 11.05)
Rangpur	667 (10.16)	(9.46, 10.92)
Sylhet	663 (10.10)	(9.39, 10.85)

Residence		
Urban	1689 (25.74)	(24.70, 26.81)
Rural	4874 (74.26)	(73.19, 75.30)
Wealth Index		
Poorest	1507 (22.96)	(21.96, 23.99)
Poorer	1224 (18.65)	(17.72, 19.61)
Middle	1277 (19.46)	(18.52, 20.44)
Richer	1305 (19.89)	(18.94, 20.87)
Richest	1250 (19.04)	(18.11, 20.01)
Access to electronic media		
Access	2901 (44.19)	(43.00, 45.40)
No access	3663 (55.81)	(54.60, 57.00)
Source of drinking water[1]		
Improved	6417 (97.77)	(97.39, 98.10)
Non-improved	146 (2.23)	(1.90, 2.61)
Type of toilet[2]		
Improved	4386 (66.83)	(65.68, 67.96)
Non-improved	2177 (33.17)	(32.04, 34.32)
Type of floor[3]		
Earth/sand	4541 (69.19)	(68.06, 70.29)
Other floors	2022 (30.81)	(29.71, 31.94)
Total (n=6,563)		

[1] [2] [3] categorized based on BDHS report, 2014

4.3.2 Prevalence of diarrheal disease

The prevalence and related factors are described in Table 4-2. The overall prevalence of diarrhea among children <5 years old was found to be 5.71%. The highest diarrheal prevalence (8.62%) was found among the children aged 12 to 23 months, followed by <1-year old children (6.25%). The lowest prevalence of diarrhea (3.71%) was found among the children aged between 36 and 47 months (Table 4-2). Diarrhea prevalence was higher among male (5.88%) than female children (5.53%). Stunted children were found to be more vulnerable to diarrheal diseases (7.31%) than the normal-weight children (4.80%). As regards diarrhea prevalence and age of the mothers, it was found that children of young mothers (those who were aged <20 years) suffered from diarrhea more (6.06%) than those of older mothers. In other words, as the age of the mothers increase, the prevalence of diarrheal diseases for their children falls. A similar pattern was observed with the educational status of mothers. The prevalence of diarrhea is highest (6.19%) among the children whose mothers had no formal education; however, their occupational status also significantly influenced the prevalence of diarrhea among children. Similarly, diarrhea prevalence was found to be higher in households having more than 3 children (6.02%) when compared with those having less than 3 children (5.54%) and also higher for households with more than 1 child <5 years old (6.13%). In terms of the divisions (larger administrative unit of Bangladesh), diarrhea prevalence

was found to be higher (7.10%) in Barisal followed by Dhaka division (6.98%). The lowest prevalence of diarrhea was found in Rangpur division (1.81%) because this division is comparatively not as densely populated as other divisions. Based on the socioeconomic status of the households, diarrheal prevalence was higher in the lower socioeconomic status households (Table 4-2). Such a disparity was not found for type of residence. A high prevalence was observed in households that had no access to electronic media (5.91 vs 5.47) and source of drinking water (6.73 vs 5.69) and had unimproved toilet facilities (6.78 vs 5.18).

Table 4-2 Prevalence and associated factors of childhood diarrhea

Variables	Prevalence of Diarrhea n (%)	Model-I	Model-II
		Unadjusted OR (95%CI)	Adjusted OR (95%CI)
Child Age (in month)			
< 12	75 (6.25)	1.73*** (1.19, 2.50)	1.88*** (1.27, 2.77)
12-23	121 (8.62)	2.45*** (1.74, 3.45)	2.44*** (1.72, 3.47)
24-35	68 (5.19)	1.42* (0.97, 2.07)	1.46*(1.00, 2.14)
36-47 (ref)	48 (3.71)	1.00	1.00
48-59	62 (4.62)	1.26 (0.86, 1.85)	1.31 (0.88, 1.93)
Sex of Children			
Male	201 (5.88)	1.07 (0.87, 1.31)	1.06 (0.85, 1.31)
Female (ref)	174 (5.53)	1.00	1.00
Nutritional Index			
HAZ			
Normal (ref)	200 (4.80)	1.00	1.00
Stunting	175 (7.31)	1.56*** (1.27, 1.93)	1.91*** (1.48, 2.47)
WHZ			
Normal (ref)	326 (5.80)	1.00	1.00
Wasting	49 (5.18)	0.89 (0.65, 1.21)	1.05 (0.74, 1.50)
WAZ			
Normal (ref)	255 (5.79)	1.00	1.00
Underweight	120 (5.56)	0.96 (0.77, 1.20)	0.71** (0.53, 0.95)
Mothers age			
Less than 20	54 (6.06)	1.64* (0.95, 2.68)	1.45 (0.81, 2.59)
20-34	300 (5.84)	1.54* (0.98, 2.42)	1.57* (0.97, 2.54)
Above 34 (ref)	21 (3.88)	1.00	1.00
Mothers Education level			
No education	70 (6.19)	1.34 (0.86, 2.11)	1.04 (0.62, 1.74)
Primary	108 (5.89)	1.27 (0.83, 1.95)	1.00 (0.62, 1.61)
Secondary	169 (5.63)	1.21 (0.80, 1.83)	1.06 (0.69, 1.64)
Higher (ref)	28 (4.68)	1.00	1.00
Mothers Occupation			
Home maker/no formal occupation	298 (6.40)	1.96*** (1.39, 2.77)	1.97*** (1.38, 2.83)
Poultry/farming/cultivation (ref)	38 (3.37)	1.00	1.00
Professional	40 (4.98)	1.50* (0.95, 2.37)	1.53* (0.95, 2.45)

Number of Children			
Less than 3 (ref)	231 (5.54)	1.00	1.00
3 and above	144 (6.02)	1.09 (0.88, 1.35)	3.00 (0.86, 1.45)
Number of under five children			
One (ref)	231 (5.48)	1.00	1.00
Two and above	144 (6.13)	1.13 (0.91, 1.40)	0.99 (0.78, 1.25)
Division			
Barisal	26 (7.01)	4.08*** (2.04, 8.16)	3.59*** (1.78, 7.24)
Chittagong	93 (6.68)	3.87*** (2.11, 7.10)	3.64*** (1.97, 6.75)
Dhaka	160 (6.98)	4.06*** (2.25, 7.33)	4.01*** (2.20, 7.30)
Khulna	17 (3.36)	1.88 (0.89, 3.98)	1.82 (0.86, 3.88)
Rajshahi	25 (3.65)	2.05** (1.02, 4.12)	2.11** (1.05, 4.25)
Rangpur (ref)	12 (1.81)	1.00	1.00
Sylhet	42 (6.37)	3.68*** (1.92, 7.04)	3.14*** (1.62, 6.09)
Residence			
Urban (ref)	97 (5.71)	1.00	1.00
Rural	278 (5.71)	1.00 (0.79, 1.27)	0.97 (0.73, 1.29)
Wealth Index			
Poorest	90 (5.96)	1.17 (0.84, 1.62)	1.17 (0.56, 2.44)
Poorer	79 (6.47)	1.27 (0.91, 1.79)	1.38 (0.69, 2.75)
Middle	73 (5.72)	1.12 (0.79, 1.58)	1.14 (0.62, 2.12)
Richer	68 (5.24)	1.02 (0.72, 1.44)	1.05 (0.68, 1.61)
Richest (ref)	64 (5.16)	1.00	1.00
Access to electronic media			
Access (ref)	159 (5.47)	1.00	1.00
No access	216 (5.91)	1.09 (0.88, 1.34)	0.94 (0.69, 1.29)
Source of drinking water			
Improved (ref)	365 (5.69)	1.00	1.00
Un-improved	10 (6.73)	1.20 (0.62, 2.31)	1.01 (0.51, 2.00)
Type of toilet			
Improved (ref)	227 (5.18)	1.00	1.00
Un-improved	148 (6.78)	1.33*** (1.07, 1.65)	1.23 (0.96, 1.58)
Type of floor			
Earth/sand	271 (5.98)	1.18 (0.93, 1.49)	1.09 (0.69, 1.72)
Other floors (ref)	103 (5.11)	1.00	1.00
Overall Prevalence	**5.71 (5.20, 6.23)**		

**p<0.10, **p<0.05, ***p<0.01*

4.3.3 Factors associated with childhood diarrhea

Table 4-2 shows the factors influencing diarrheal prevalence. For this purpose, 2 models were considered: using bivariate logistic regression analysis (model-I) and using multivariate logistic regression analysis (model-II) to control for any possible confounding effects. We used both unadjusted and adjusted odds ratio to address the effects of single factors. In model I, several factors such as the age of the children, age-specific height, age and occupations of mothers, as per divisions, and type of toilet facilities were found to be significantly associated with the

prevalence of diarrhea predicted directly by crude ORs. Finally, from model II, we also observed that child age, height for age, weight for age of the children, age and occupation of the mothers, and divisional distribution were identified as statistically significant factors for childhood diarrhea in Bangladesh. Diarrhea was significantly associated with the age of the children: 1- to 2-year-old children were at highest risk for exposure to childhood diarrhea followed by those <1 year old. From Table 2, it can be seen that children aged 12 to 23 months and those aged <12 months were 2.44 and 1.88 times more likely to have diarrhea than those in the age group of 36 to 47 months. Based on the age-specific height rate, we found that stunted children were 1.91 times more likely to experience diarrhea than nonstunted children (OR = 1.91; 95% CI = 1.48, 2.47). A dissimilar pattern was also observed for the weight of the child because the prevalence was lower for underweight children (OR = 0.71; 95% CI = 0.53, 0.95). Age and occupation of the mothers were also influencing factors for diarrheal disease. Children with relatively young mothers had a higher risk of diarrhea than those with older mothers. Geographic location was one of the vital influencing factors for diarrheal prevalence. From the distribution of diarrheal patients, it was found that the children who were most diarrhea prone were those who lived in Barisal region. From model II, it was found that the children who lived in Dhaka division were 4.01 times more likely to have diarrhea than those in Rangpur division (OR = 4.01; 95% CI = 2.20, 7.30). The Chittagong, Barisal, and Sylhet regions are mainly riverine areas, where there is a risk of seasonal floods and other natural hazards such as tidal surges, cyclones, and flash floods.

4.3.4 Healthcare Seeking Behaviour

Healthcare-seeking behavior is reported in figure 4-1. Among the total prevalence (375), a total of 289 mothers sought any type of care for their children. Most cases (75.16%) received service from any of the formal care services whereas approximately 23% of children did not seek any care; however, a small portion of patients (1.98%) received treatment from traditional healers and unqualified village doctors. Private providers were the largest source for providing care (38.62%) for diarrheal patients followed by the pharmacy (23.33%). In terms of socio-economic groups, children from poor groups (first 3 quintiles) often did not seek care. In contrast to those in rich groups (upper 2 quintiles). In particular, the highest proportion of not seeking care was found (39.31%) among the middle-income community. However, the choice of health care provider did depend on socio-economic groups because private treatment was popular among all socio-economic groups.

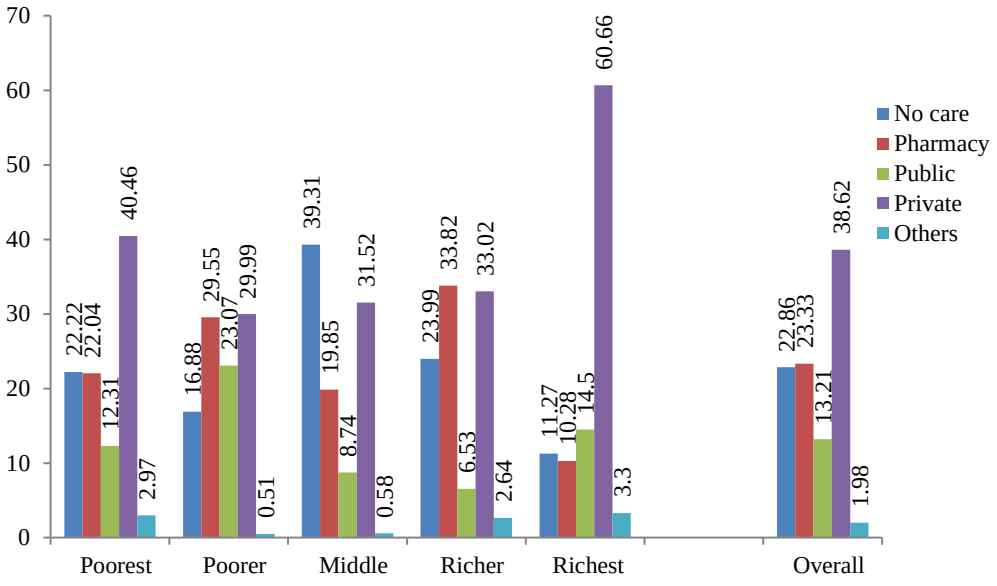

Figure 4-1 Proportion of treatment seeking behavior for childhood diarrhea

4.3.5 Determinants of care seeking behavior

Table 4.3 shows the factors that are closely related to the health care-seeking behavior for childhood diarrhea. From the binary logistic model, we found that age of children, height for age, weight for height, age and education of mothers, occupation of mothers, number of <5-year old children, wealth index, types of toilet facilities, and floor of the household were significant factors compared with no care. Our analysis found that stunted and wasted children saught care less frequently compared with others (OR = 2.33, 95% CI = 1.07, 5.08, and OR = 2.34, 95% CI = 1.91, 6.00). Mothers between 20 and 34 years old were more likely to seek care for their children than others (OR = 3.72; 95% CI = 1.12, 12.35). Households having only 1 child <5 years old were more likely to seek care compared with those having 2 or more children <5 years old (OR = 2.39; 95% CI = 1.25, 4.57) of the households. The results found that the richest households were 8.31 times more likely to seek care than the poorest ones. The same pattern was also observed for types of toilet facilities and the floor of the particular households. In the multivariate multinomial regression model, we restricted the health care source from the pharmacy, the public facility, and the private providers. After adjusting for all other covariates, we found that the age and sex of the children, nutritional score (height for age, weight for height of the children), age and education of mothers, occupation of mothers, number of <5-year-old children in particular households, wealth index, types of toilet facilities and floor of the household, and accessing electronic media were significant factors for care seeking behavior. With regard to the sex of the children, it was found that male children were 2.09 times more likely to receive care from private facilities than female

children. Considering the nutritional status of the children, those who were not stunted were found to be more likely to receive care from a pharmacy or any private sector (RRR = 2.50, 95% CI = 0.98, 6.38 and RRR = 2.41, 95% CI = 1.00, 5.58, respectively). A similar pattern was observed for children who were wasted when compared with those who were not, for care from the pharmacy (RRR = 4.09; 95% CI = 1.22, 13.78). Our results found that the children who lived in the wealthiest households compared with the poorest community were more likely to receive care from the private sector (RRR = 23.00; 95% CI = 2.50, 211.82). However, households with access to electronic media were more inclined to seek care from public providers (RRR = 6.43; 95% CI= 1.37, 30.17).

Table 4-3 Factors associated with health seeking behavior for diarrhea among under five children in Bangladesh

	Binary logistic regression[1]	**Multivariate Multinomial logistic model[1]**		
Variables	**Any care**	**Pharmacy**	**Public facility**	**Private facility**
	Adjusted OR (95% CI)	**RRR[2] (95% CI)**	**RRR[2] (95% CI)**	**RRR[2] (95% CI)**
Child Age (in month)				
< 12 (ref)	1.00	1.00	1.00	1.00
12-23	2.45* (0.93, 6.45)	1.97 (0.63, 6.16)	4.00** (1.01, 15.79)	2.55* (0.9, 7.28)
24-35	1.25 (0.45, 3.47)	1.02 (0.3, 3.48)	2.14 (0.47, 9.72)	1.20 (0.39, 3.68)
36-47	0.98 (0.35, 2.76)	1.44 (0.44, 4.77)	2.01 (0.47, 8.58)	0.51 (0.15, 1.71)
48-59	1.06 (0.36, 3.17)	1.06 (0.29, 3.84)	0.83 (0.14, 4.83)	1.21 (0.36, 4.07)
Sex of Children				
Male	1.70 (0.90, 3.20)	1.32 (0.63, 2.8)	1.41 (0.58, 3.45)	2.09** (1.03, 4.24)
Female (ref)	1.00	1.00	1.00	1.00
Nutritional Score				
Height for Age				
Normal	2.33** (1.07, 5.08)	2.50* (0.98, 6.38)	1.74 (0.57, 5.29)	2.41** (1.00, 5.8)
Stunting (ref)	1.00	1.00	1.00	1.00
Weight for Height				
Normal	2.34* (0.91, 6.00)	4.09** (1.22, 13.78)	1.43 (0.35, 5.84)	2.03 (0.72, 5.72)
Wasting (ref)	1.00	1.00	1.00	1.00
Weight for Age				
Normal	0.57 (0.23, 1.42)	0.48 (0.16, 1.42)	1.6 (0.41, 6.24)	0.46 (0.16, 1.29)
Underweight (ref)	1.00	1.00	1.00	1.00
Mothers age				
Less than 20	3.17 (0.66, 15.12)	1.25 (0.18, 8.51)	2.84 (0.33, 24.31)	5.43* (0.9, 32.84)
20-34	3.72** (1.12, 12.35)	2.85 (0.67, 12.03)	2.46 (0.48, 12.65)	5.17** (1.24, 21.57)
Above 34 (ref)	1.00	1.00	1.00	1.00
Mothers Education level				
No education (ref)	1.00	1.00	1.00	1.00
Primary	0.47 (0.18, 1.25)	0.47 (0.15, 1.45)	0.47 (0.11, 2.03)	0.53 (0.18, 1.60)
Secondary	0.37* (0.13, 1.04)	0.33* (0.10, 1.10)	0.63 (0.14, 2.81)	0.36* (0.11, 1.16)
Higher	2.84 (0.29, 28.06)	2.80 (0.24, 33.12)	5.07 (0.36, 70.89)	2.91 (0.27, 31.55)
Mothers Occupation				
Home maker/no formal occupation	0.57 (0.18, 1.84)	0.92 (0.22, 3.76)	0.85 (0.16, 4.56)	0.37 (0.1, 1.3)

Poultry/farming/cultivation (ref)	1.00	1.00	1.00	1.00
Professional	0.33* (0.08, 1.41)	0.58 (0.1, 3.3)	0.61 (0.08, 4.96)	0.18** (0.04, 0.89)
Number of Children				
Less than 3	1.90 (0.89, 4.04)	1.85 (0.76, 4.48)	1.46 (0.49, 4.38)	2.11* (0.90, 4.97)
3 and above (ref)	1.00	1.00	1.00	1.00
Number of under five children				
One	2.39** (1.25, 4.57)	2.21** (1.01, 4.84)	2.24 (0.85, 5.88)	2.68** (1.29, 5.56)
Two and above (ref)	1.00	1.00	1.00	1.00
Residence				
Urban (ref)	1.00	1.00	1.00	1.00
Rural	0.95 (0.40, 2.26)	1.13 (0.4, 3.13)	1.05 (0.32, 3.49)	0.83 (0.32, 2.16)
Wealth Index				
Poorest (ref)	1.00	1.00	1.00	1.00
Poorer	1.6 (0.64, 4)	2.21 (0.75, 6.46)	0.82 (0.22, 3.03)	1.52 (0.54, 4.22)
Middle	1.02 (0.36, 2.87)	1.42 (0.4, 5.08)	0.13** (0.02, 0.85)	1.32 (0.41, 4.24)
Richer	2.36 (0.53, 10.52)	4.07 (0.7, 23.61)	0.29 (0.03, 3.15)	2.67 (0.5, 14.18)
Richest	8.31** (1.15, 59.96)	3.29 (0.3, 36.49)	1.06 (0.05, 21.57)	23.00** (2.5, 211.82)
Access to electronic media				
Access	1.46 (0.59, 3.59)	1.22 (0.42, 3.58)	6.43** (1.37, 30.17)	1.17 (0.42, 3.27)
No access (ref)	1.00	1.00	1.00	1.00
Source of drinking water				
Improved (ref)	1.00	1.00	1.00	1.00
Un-improved	4.30 (0.45, 40.68)	2.81 (0.21, 38.15)	6.82 (0.43, 108.4)	5.15 (0.47, 55.76)
Type of toilet				
Improved (ref)	1.00	1.00	1.00	1.00
Un-improved	2.10** (1.00, 4.43)	2.52** (1.06, 5.97)	2.08 (0.72, 5.99)	1.82 (0.8, 4.16)
Type of floor				
Earth/sand	3.71** (1.05, 13.07)	2.35 (0.57, 9.75)	3.83 (0.52, 28.13)	5.33** (1.27, 22.3)
Other floors (ref)	1.00	1.00	1.00	1.00

**p<0.10, **p<0.05, ***p<0.001 and* [1] No-care reference group

4.4 DISCUSSION

The study attempted to measure the prevalence and healthcare-seeking behaviors regarding childhood diarrhea using a nationwide representative data. Though diarrhea can be managed with low-cost interventions, it remains the leading cause of morbidity for the patient who seeks care from a public hospital in Bangladesh (Sultana et al. 2015). According to the global burden of disease study 2010, diarrheal disease is responsible for 3.6 % of global DALYs (Murray et al. 2012). It has declined for children <5 years old from 41% of global DALYs in 1990 to 25% in 2010; however, children <5 are still vulnerable, and a significant proportion of deaths is occurr in the early stage of life- namely, the first 2 years of life (Mengistie et al. 2013; Murray et al. 2012). Our results showed that the prevalence of diarrhea is frequently observed in the first 2 years of life, which supports the previous findings from other countries such as Taiwan, Brazil and many other parts of the world that because of maturing immune systems, these children are more

vulnerable to gastrointestinal infections (Boschi-Pinto et al. 2013; Chen et al. 2010; Granzotto et al. 2010; WHO 2009a; Lins & Silva 2000). However, the prevalence of diseases is higher (8.62%) for the children aged 1 to 2 years than the children <1 year old. This might be because those infants are more dependent on the mother and require feeding appropriate for their age, which may lower the risk of diarrheal infections (Konstantyner et al. 2016). The study indicated that older mothers could be a protective factor against the diarrheal diseases, in keeping with the results of other studies in many low-and middle- income countries (Costa Fuchs & Gomes Victora 2002; Finlay et al. 2011; Diouf et al. 2014). However, the education and occupation of the mother are determining factors of the prevalence of childhood diarrhea.

Childhood diarrhea was also highly prevalent in some specific regions of the country. This could be because these regions, especially in Barisal, Dhaka and Chittagong divisions have rivers, water-reservoir, natural hazards, and densely populated areas than the other areas; however, most of the slums are located in Dhaka and Chittagong regions, which are already proven to be at high risk for diarrheal infections because of the poor sanitation system and lack of potable water. The results agree with the fact that etiological agents and risk factors for diarrhea are dependent on location, which indicates that such knowledge is a pre-requisite for the policy makers to develop prevention and control programs (Szwarcwald & Damacena 2008; WHO 2006a). Our study found that approximately 77% of mothers sought care for their children at different sources, including formal and informal providers (Sikder et al. 2015). Rapid and proper treatment for childhood diarrhea is important to avoid excessive costs associated with treatment care and adverse health outcomes (Shillcutt et al. 2016). The study found that approximately (23%) did not seek any treatment for childhood diarrhea. A maternal view that the illness was not severe enough could be the primary reason for not seeking care (Das et al. 2013). In developing countries such as Bangladesh, the diarrheal patients are often inadequately managed at home, resulting in poor outcomes; timely medical treatment is required to minimize the length of each episode and reduce mortality (Chowdhury et al. 2015).

The current study found that some factors significantly influence the health care-seeking pattern, such as age and sex of the children, nutritional score, age and education of mothers, wealth index, accessing electronic media and others (see Table 4-3). The sex and age of the child have been shown to be associated with mothers' care seeking behavior. A Kenyan study observed that that care-seeking is common for sick children in the youngest age group (0–11 months) and is slightly higher for boys than girls (Taffa & Chepngeno 2005). Our study results are consistentwith those of a similar study of Brazil, where it was found that male children were more likely to be hospitalized for diarrheal disease than female children (Konstantyner et al. 2016) which also

reflects the average cost of treatment in Bangladesh (Sarker et al. 2013). Age and education of mothers are significantly associated with treatment seeking patterns. An earlier study in Ethiopia found that the health care-seeking behavior of mothers is higher for younger mothers than for older mothers (Astale & Chenault 2015).

It was observed that in many countries such as Brazil and Bolivia, higher parental educational levels have great importance in the prevention and control of morbidity because knowledge about prevention and promotional activities reduce the risk of infectious diseases in children of educated parents (Maria et al. 2011; George et al. 2014). In Bangladesh it was found that higher educational levels are also associated with improved toilet facilities in both rural and urban settings, which means better access to sanitation and hygiene in the household (Colombara et al. 2014a). Again, evidence suggests that mothers younger than 35 years and also mothers who have completed secondary education exhibit more health care-seeking behavior for their sick children in many low-and middle-income countries (Taffa & Chepngeno 2005; Manna et al. 2013). Similarly, family size is one of the influencing factors because having a smaller family possibly allows parents to invest more time and money on their sick child (Astale & Chenault 2015). The study found that wealth status is a significant determining factor for seeking care, which is in line with earlier findings that poor socio-economic status is significantly associated with inadequate utilization of primary health care services (Navaneetham & Dharmalingam 2002; Taffa & Chepngeno 2005). The type of floor in the house also played a significant role, as in other earlier studies in Brazil (Vanderlei et al. 2003; Ichihara et al. 2015). Our study demonstrated that the household with access to electronic media, such as radio and television, are most likely to seek care from the public facilities for childhood diarrhea. Plausibly, this is because in these mass media, promotional activities including drama, advertisement, and behavior change messages were regularly provided. Further, it has been reported by another study that younger women are more likely to be exposed to mass media than older women, primarily because their level of education is higher (Ethiopia Central Statistical Agency and ICF International. 2012), which might have contributed to a better health care-seeking behaviour among younger mothers.

4.5 STRENGTH AND LIMITATIONS

The study results can be generalized at the country level because the study utilized data from a nationally representative latest household survey. However, there are several limitations to be aware of when interpreting these results. All of the information related to the childhood diarrhea was provided by the mothers, especially whether their children had diarrhea and/or were seeking

the treatment, which may have compromised precision of the data. Moreover, respondents were asked about their previous events. Therefore, the potential effect of recall bias on our results cannot be ignored.

4.6 CONCLUSIONS

Diarrhea is still an important public health issue in children younger than 2 years in Bangladesh. The prevalence of childhood diarrhea and care-seeking behaviour of mothers in Bangladesh is patterned by age, wealth, and other markers of deprivation, as one might expect from studies in other countries. Equitability of access is a concern, and interventions should target mothers in low-income households with less education and younger mothers. Since the households seeking care from various providers , therefore, the healthcare service could be improved through working in partnership with public facilities, private health care practitioners and community-based organizations (CBOs), so that all strata of the population get similar access during childhood diarrhoea.

Author contributions: ARS contributed to the conception and design; contributed to acquisition, analysis, and interpretation of data; drafted the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. MS contributed to the design, critically revised the manuscript, and gave final approval. RAM contributed to interpretation of data, critically revised the manuscript, and gave final approval. NS contributed to analysis of data, critically revised the manuscript, and gave final approval. RVM contributed to conception, critically revised the manuscript, and gave final approval. AM contributed to the conception and design, contributed to analysis and interpretation, critically revised the manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Acknowledgments: icddr,b is grateful to the Governments of Bangladesh, Canada, Sweden and the UK for providing core support. The authors would also like to the thank Health Economics and Financing Research Group for their comments on earlier version of the paper.

5 DIARRHEAL DISEASE: ECONOMIC COST AND CONSEQUENCES

Study - **II**

Published: ***Global Health Research and Policy***

Publisher: **BMC Publication**

Volume: (2018) 3:1

DOI 10.1186/s41256-017-0056-5

Title of the paper: **Economic costs of hospitalized diarrheal disease in Bangladesh: a societal perspective**

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Abstract

Background: Diarrheal diseases are a major threat to human health and still represent a leading cause of morbidity and mortality worldwide. Although the burden of the diarrheal diseases is much lower in developed countries, it is a significant public health problem in low and middle-income countries like Bangladesh. Though diarrhea is preventable and managed with low-cost interventions, it is still the leading cause of morbidity according to patients who sought care from public hospitals in Bangladesh indicates that significant resources are consumed in treating those patients. The aim of the study is to capture the inpatients and outpatient treatment cost of diarrheal disease and to measure the cost burden and coping mechanisms associated with diarrheal illness.

Methods: This study was conducted in six randomly selected district hospitals from six divisions (larger administrative units) in Bangladesh. The study was performed from the societal perspective which means all types of costs were identified, measured and valued no matter who incurred them. Cost analysis was estimated using the guideline proposed by the World Health Organization for estimating the economic burden of diarrheal diseases. The study adopted quantitative techniques to collect the household and hospital level data with structured and semi-structured questionnaires, observation checklists, analysis of hospital database, telephone interviews and compilation of service statistics.

Results: The average total societal cost of illness per episode was Bangladeshi Taka (BDT) 5,274.02 (US$ 67.18) whereas the average inpatient and outpatient costs were BDT 8,675.09 (US$ 110.51) and BDT 1,853.96 (US$ 23.62) respectively. The cost burden was significantly highest for poorest households, 21.45% of household income, compared to the richest quintile (4.21% of income).

Conclusions: Diarrheal diseases continue to be an overwhelming problem in Bangladesh. The economic impact of any public health interventions (either preventive or promotive) that can reduce the prevalence of diarrheal infections can be estimated from the economic data generated from this study.

Keywords: Bangladesh, Catastrophic expenditure, Cost-of-illness, Diarrhea, Out-of-pocket payment, Public hospitals.

5.1 BACKGROUND

Diarrheal diseases are a global public health problem and a leading cause of morbidity and mortality across the world. According to the latest Global Burden of Disease Study, about 2.39 billion diarrheal cases occurred globally and approximately 0.53 million of under five children died every year (Vos et al. 2016; Liu et al. 2016). Specifically, incidence and case-fatality ratios are much higher in lower and middle income (LMI) countries (Mashoto et al. 2014). In Bangladesh, diarrheal diseases are still very common among children under five years old (NIPORT 2016). In developing countries, diarrhea-related morbidity and mortality is directly linked with limited access to potable water and proper sanitation system (Montgomery & Elimelech 2007). Several studies observed that epidemics of diarrheal disease are associated with episodes of flooding (Schwartz et al. 2006), socioeconomic status (Rahman et al. 2009), urban status (Colombara et al. 2014b) high population density, low education level and the proximity of household clusters to contaminated surface water (Ali et al. 2002; D. K. Biswas et al. 2014; You et al. 2013). The diseases are highly sensitive to climate, showing seasonal variations in numerous sites (Drasar et al. 1978). Relative humidity and temperature influence the rate of replication of different types of pathogens such as bacteria and protozoa, and also are the survival of enteroviruses in the environment which is another cause of diarrheal diseases (Black & Lanata 1995). Diarrhea is an alteration in normal bowel movement characterized by an increase in water content, volume, or frequency of stools (Ozguler 2015). If the disease lasts “more than 7 days” and “at least 14 days” the terms “prolonged” and “persistent” diarrhea are used respectively (Rabbani et al. 2010; Lamberti et al. 2012).

Though diarrhea is preventable and managed with low-cost interventions, it is still the top cause of morbidity for patients who sought care from the public hospital system in Bangladesh (Sultana et al. 2015) and significant resources are expended in treating these patients. Diarrheal diseases affect people of all ages irrespective of their socio-economic status and are particularly prevalent among poor people. A significant cause for concern in Bangladesh is that approximately 26% of the people are below the poverty datum line. In some cases, the episode can be managed at home and does not require hospital treatment. However, considering the direct and indirect cost of households, it represents a substantial economic burden for the affected households (Shillcutt et al. 2016).

There are several studies about the economic burden of diarrheal disease in many countries (Burke et al. 2013; Kosek et al. 2003; Bartsch & Lee 2014; MacIntyre & Villiers 2010; Bhuiyan et al. 2014; Pham-Duc et al. 2014). However, knowledge about the treatment cost of a full diarrheal episode is still limited in Bangladesh; although such studies are vital for informing policies and

allowing international comparisons (Konstantyner et al. 2016; Parashar et al. 2003). There are several economic studies available focusing diarrheal diseases in Bangladesh (Ali 2001; Das et al. 2015; Rheingans, Kukla, et al. 2012; Jahangir 2009). Nevertheless, these studies did not consider the societal perspective to capture the average cost for diarrheal treatment. However, it is essential for policy makers to understand the precise information of the economic cost of diarrheal treatment based on uniform methodologies for setting priorities for health sector as well as for balanced allocation of scarce resources. The intent of this study is to estimate the age and sex specific economic costs of diarrheal disease considering a broad social perspective and to capture the healthcare seeking pattern during the diarrheal episode in Bangladesh.

5.2 METHODS

5.2.1 Study setting and sample

This study was conducted in public district hospitals in Bangladesh. Public hospitals play a major role in providing treatment for a relatively large population as the treatment cost in public hospitals is less than private for-profit hospitals and hospitals financed by non-governmental organisations (NGOs). A total of 801 diarrheal patients were randomly selected and interviewed from January to December 2015

5.2.2 Study perspective

A societal perspective was considered which means all types of costs were identified, measured and valued no matter who incurred them. The societal perspective is the summation of provider and household perspective which is recommended in the current standards for cost-effectiveness analysis methods (Siegel et al. 1996; Gold et al. 1996).

5.2.3 Costs estimates

Cost analysis was done by using the guideline proposed by the World Health Organization (WHO) for estimating the economic burden of diarrheal diseases (WHO 2005a). A bottom-up micro-costing approach was used to generate the cost of illness per episode per patient where all relevant cost components are identified and valued at the most detailed level (WHO 2005a; Drummond et al. 2005).

To capture the household economic cost of illness both direct and indirect costs were captured. *Direct costs* were defined as expenditure during treatment by households which consists of two parts: direct medical cost and direct non-medical cost. Direct medical expenses include those costs

consumed for healthcare resources during diarrheal episodes such as medicine, diagnosis, registration fees and others. The direct non-medical cost includes transportation, lodging, food items, informal payment, payment for helping the patients during treatment. There are other types of expenditure such as material costs for a mug, jar, plate, glass and other items such as a coil, lighter and other cost items of patients and their caregivers.

The *indirect cost* was considered the income loss and cost of productivity because of travel time to the health centre and costs due to absence from work because of illness related to the diarrheal disease. Self-reported wage rates were used for estimating the income loss. Productivity costs were estimated using a human capital approach which reflected the value of all unpaid time devoted to caregiving themselves, as well as family members and friends (Rice 1966). The inclusion of caregiving time are based on the assumption that time dedicated to caregiving may represent foregone non-market activities such as school, household chores, child care, and leisure or domestic work (van Roijen et al. 1996; Sarker et al. 2013). This time comprised time spent directly on patient care (by the patient and by unpaid attendants or caregivers), such as attending to diarrhea-related health care appointments. To capture the productivity losses for non-market activities, we used the age-specific and occupation-specific wage rates (Sarker et al. 2013; Poulos et al. 2012). We used age-specific wages for adults, teenagers and children aged 5 to 14 years. The minimum salary rate according to national level was given by the adult patients, one-half for the teenagers and three-quarters to capture productivity loss for children, while half of the average salary rate assigned to unpaid home workers considering their age group (Sarker et al. 2013; Poulos et al. 2012). Intangible or psychic costs such as costs related to suffering and grief were not measured in this study as those costs are not valued in the disease-specific cost of illness research (Chima et al. 2003; Sarker et al. 2013). Again, time cost of visitor and extra irregular expense borne by the patients, caregivers, and visitors on their way during the time of hospitalization were not included in the analysis. The household cost burden are measured by the percentage of total household earnings that was consumed by the treatment cost of diarrheal diseases (Grietens et al. 2008).

The average treatment costs for diarrheal diseases borne by the public hospitals were measured using the patient-specific treatment costs approach according to WHO guidelines (WHO 2005a). The average outpatients and inpatients visits costs were estimated. The costs included costs of diagnosis, laboratory cost, medicine costs, feeding costs, institutional cost and other associated costs borne by the hospitals for treating on a patient-specific basis. Shared costs were allocated according to the number of patient's days of hospitalization. Capital cost was annuitized with 3%

discount rate (Drummond et al. 2005). The provider actual cost of illness was calculated by the provider's cost for treatment devoid of any fees received from the patients for treatment purpose (e.g., hospitalization, drug, diagnostic tests). Finally, the societal cost of illness was estimated by adding provider's actual cost of illness per patients with the cost incurred per household.

5.2.4 Method of data collection

The study adopted quantitative techniques to collect the household and hospital level data including the structured questionnaire, observation checklist, hospital database, telephone interviews and compilation of service statistics. For capturing household level cost, respondents were the adult patients or the accompanying person who were the most familiar about the treatment costs of patients, and interviews were conducted during discharge from the hospital. Patients' records drawn from the above Hospital Records Departments (HRD) were reviewed for the use of resources for diarrheal patients. Resource utilisation data were abstracted from the registers for inpatients or outpatients. At the central level, several offices such as finance, procurement and supply and maintenance unit were contacted to validate the cost information. A research assistant reviewed the record of patients, and data abstraction forms were updated daily until the discharge of the patient. Finally, a telephone interview was conducted for taking necessary information within one week after discharge from hospital. Caregivers were also interviewed in their language of preference with the use of a standardised interview schedule on admission or soon thereafter. Questions were asked regarding transportation, consultation before the hospital visit, medicine brought, expenses during the hospitalization, and losses of wages resulting from absence from work.

5.2.5 Data analysis

Completed questionnaires were developed by a qualified supervisor with both numerical and logical checks to minimise errors. Before analysis, missing answers and outliers were systematically verified for accuracy of data. Patient-specific cost of illness borne by the household and provider costs are reported separately. The data were analysed using a spreadsheet in Microsoft Excel and Stata/SE 13.0 (StataCorp. College Station, TX, USA). Proportion, frequencies, rates and ratio of treatment cost were presented with a standard deviation in local currency, i.e., Bangladeshi Taka (BDT) and US dollars (US$) applying the exchange rate (US$1 = 78.5 BDT) during the year of the survey mid 2014- mid 2015 (GOB 2016). Like the earlier study of Javanbakht and colleague, to test the robustness of the assumption, a sensitivity analysis

was conducted to examine the impact of outlier on the total cost of illness (Javanbakht et al. 2011). It was observed that, the cost of caregivers of households had a higher level of uncertainty (Coduras et al. 2010a). We tested the effect of changes of 20% in the parameter values of both direct and indirect cost of households and 20% change of both medical and non-medical cost of the provider as performed in other studies (Sarker et al. 2013; Coduras et al. 2010b).

5.2.6 Ethics approval

The research protocol of this study was approved by the Institutional Review Board of the International Centre for Diarrheal Disease Research, Bangladesh (icddr,b). Informed consent was obtained from all respondents before data collection

5.3 RESULTS

5.3.1 Background characteristics

A total of 801 patients participated in the study from selected public district hospitals, among whom 402 and 399 patients were inpatients and outpatients respectively. All respondents participating in this survey were provided with information about the study, and none withheld consent. The average age of the patients were 15.46 years (SD=21.08 years) while 57.43% of them were <5 children. The highest percentage of patients were homemakers (38.12%), students (23.75%), self-employed (14.37%) and only 9.09% of the patients were salaried employees. Approximately, 31% of the patients had up to secondary grade education folloed by primary grade (29.64%). Only 4.19% of the patients had higher level education whereas 18.56% had no formal education, and 11.08% had no education (Table 5-1). Diarrheal occurrence was higher among households with lower parental levels of educational attainment (Table 1). It was also higher among households with up to 4 to 5 members (43.32%) followed by more than five members (38.83%), and the average patient's household size was 3.20 (SD=0.74) (Table 1). The average monthly income and expenditure of the household were BDT 19,603 (US$ 249.72) and BDT 15,470 (US$ 197.07) respectively while the average household healthcare expenditure in the previous three months was BDT 5,191 (US$ 66.13) (Table 5-1).

Table 5-1 Background characteristics of the study participants for public tertiary level hospital (N = 801)

Variables	Description	n (%) / mean ± SD	95% CI (% or mean)
Number of patients	N	801	
	Inpatient	402 (50.19)	(46.72 , 53.65)
	Outpatient	399 (49.81)	(46.35 , 53.28)
Patient age (%)	Up to 4	460 (57.43)	(53.09 , 59.96)
	5 to 14	55 (6.87)	(6.08 , 9.81)
	15 to 45	195 (24.34)	(21.49 , 27.44)
	46 to 60	62 (7.74)	(6.08 , 9.81)
	60+	29 (3.62)	(2.53 , 5.17)
Patient age yrs (mean ± SD)	Up to 4	1.41 ± 0.96	(1.32 , 1.50)
	5 to 14	8.12 ± 2.76	(7.38 , 8.87)
	15 to 45	29.08 ± 9.43	(27.74 , 30.41)
	46 to 60	55.47 ± 4.3	(54.38 , 56.56)
	60+	75.03 ± 11.99	(70.47 , 79.6)
	Overall	15.46 ± 21.08	(13.99 , 16.92)
Gender (%)	Male	404 (50.44)	(46.97 , 53.9)
	Female	397 (49.56)	(46.1 , 53.03)
Patient Occupation (%)	House wife	130 (38.12)	(33.09 , 43.42)
	Students	81 (23.75)	(19.51 , 28.59)
	Self-employment	49 (14.37)	(11.02 , 18.53)
	Unemployed	7 (2.05)	(0.98 , 4.26)
	Salaried employee	31 (9.09)	(6.45 , 12.66)
	Business	18 (5.28)	(3.34 , 8.24)
	Others	25 (7.33)	(4.99 , 10.64)
Patient education level (%)	Illiterate	37 (11.08)	(8.17 , 15.03)
	No formal education	62 (18.56)	(14.82 , 23.26)
	Up to primary	99 (29.64)	(24.55 , 34.36)
	Secondary	103 (30.84)	(26.26 , 36.23)
	Higher secondary	19 (5.69)	(3.67 , 8.82)
	Higher	14 (4.19)	(2.51 , 7.01)
Mother education level (%)	Illiterate	156 (19.48)	(16.87 , 22.37)
	formal education	114 (14.23)	(11.98 , 16.83)
	Up to primary	199 (24.84)	(21.97 , 27.96)
	Secondary	274 (34.21)	(30.99 , 37.57)
	Higher secondary	37 (4.62)	(3.36 , 6.31)
	Higher	21 (2.62)	(1.71 , 3.99)
Father education level (%)	Illiterate	139 (17.35)	(14.88 , 20.14)
	No formal education	139 (17.35)	(14.88 , 20.14)
	Up to primary	191 (23.85)	(21.01 , 26.93)
	Secondary	241 (30.09)	(27 , 33.36)
	Higher secondary	49 (6.12)	(4.65 , 8.01)
	Higher	42 (5.24)	(3.9 , 7.02)
Household size (%)	Less than 2	6 (0.75)	(0.34 , 1.66)
	2 to 3	137 (17.1)	(14.65 , 19.88)

	4 to 5	347 (43.32)	(39.92 , 46.79)
	More than 5	311 (38.83)	(35.5 , 42.26)
Household size		3.20 ± 0.74	(3.15 , 3.25)
Patient monthly income, BDT (n=411)		3,976.78 ± 8,397.02	(2974.40 , 4979.16)
Monthly income of household (BDT)		19,603.37 ± 26,641.74	(17,755.58 , 21451.16)
Monthly expenditure of household (BDT)		15,469.69 ± 10,702	(14,727.43 , 16,211.94)
Overall healthcare expenditure last 3 months (BDT)		5191.43 ± 17745.43	(3960.66 , 6422.20)
Income quintile (BDT)			
Poorest quintile (≤10,000)		7,963.77 ± 2,025.22	(7723.785 , 8203.75)
2nd quintile (10,001- 12,000)		11,920.73 ± 266.08	(11862.27 , 11979.20)
3rd quintile (12,001-18,000)		15,227.71 ± 1,253.44	(15035.63 , 15419.80)
4th quintile (18,001-30,000)		23,540.11 ± 4,014.05	(22961.02 , 24119.20)
Upper quintile (30,000+)		62,188.89 ± 62,881.18	(49018.68 , 75359.10)

5.3.2 Distribution of average household cost of illness

Table 5-2 shows the average cost of illness per diarrheal episode from the household's perspective. The average total costs per episode for treating the diarrhea patients were BDT 4,178.68 (US$ 53.23). The average total out-of-pocket (OOP) cost was BDT 1,688.17 (US$ 21.51) which represented 40% of the total household cost; where 28% was the direct medical and 12.41% was the direct non-medical cost. For OOP costs, medicine was the highest cost driver (BDT 1,064.19 or US$13.56) followed by transportation cost (BDT 246.58 or US$ 3.14). Among the direct medical costs, diagnostic costs (BDT 37.63 or US$ 0.48) and consultation fee (BDT 26.37 or US$ 0.34) were the two most significant cost driver during the episode. Caregivers expenditure (BDT 127.87 or US $1.63) was the critical cost component of direct non-medical costs, which included transportation, food, mobile bill and other related expenses borne by the caregivers during the episodes of diarrhea. For the indirect costs per episode (BDT 2,490 or US$ 31.72) caregivers income loss was the highest (BDT 2, 179.50 or US$ 27.76), higher than patient's productivity loss (BDT 310.51 or US$ 3.96).

Table 5-2 Distribution of mean household cost of diarrheal treatment for tertiary level hospital (N=801) BDT (US$) *

Cost	Parameter	Overall cost of treatment		Proportion of total cost
		Average	SD	
Direct Medical	Diagnostic	37.63 (0.48)	189.71 (2.42)	28
	Medicine	1064.19 (13.56)	1427.04 (18.18)	
	Consultant fee	26.37 (0.34)	121.38 (1.55)	
	Registration/admission fee	14.54 (0.19)	11.42 (0.15)	
	Medical materials (syringe/cannula etc)	27.32 (0.35)	62.43 (0.80)	
	Bed/ Cabin charge	0.28 (0.00)	7.95 (0.10)	
Direct Non-Medical	Transportation cost	246.58 (3.14)	427.76 (5.45)	12.41
	Food items	113.82 (1.45)	239.77 (3.05)	
	Informal payment	7.40 (0.09)	22.65 (0.29)	
	Caregiver's payment	0.01 (0.00)	0.35 (0.00)	
	Materials (mug/glass etc.)	22.65 (0.29)	70.59 (0.90)	
	Lodging	0.00 (0.00)	0.01 (0.00)	
	Caregivers expenditure	127.87 (1.63)	456.80 (5.820	
Total direct cost		**1688.17 (21.51)**	**2010.95 (25.62)**	**40.4**
In-direct cost	Patient income loss	310.51 (3.96)	1,374.40 (17.51)	
	Caregiver's income loss	2,179.50 (27.76)	3,445.12 (43.89)	
Total indirect cost		**2,490.01 (31.72)**	**3,881.48 (49.45)**	**59.6**
Total cost		**4,178.68 (53.23)**	**5,166.20 (65.81)**	**100**

5.3.3 Household cost and associated variable

Table 5-3 shows the association between the cost of illness and the variables of interest. The average cost of illness (BDT 8,407.58 or US$ 107.1) for an elderly person was comparatively higher than any other age group. However, the average cost of treating <5 children was significantly lower (BDT 3,440.66 or US$ 43.83) than those aged more than five years (BDT 5,173.09 or US$ 65.90) (*P <0.001*). The average cost of illness for male patients (BDT 4,441.82 or US$ 56.58) was higher than that of females (BDT 3,909.9 or US$ 49.81) and was not statistically significant (*P=0.505*). The cost of illness for inpatient care was significantly (*P<0.001*) higher (BDT 6,570 or US$ 83.7) than that of outpatient care (BDT 1,767.58 or US$ 22.52).

Table 5-3 Association between household cost and other variables

Variables	Number of patients (N)	Household cost, BDT (US$)		t / F-statistic	P-value
		Average	SD		
Age group (years)					
Up to 4	460	3,440.66 (43.83)	4,549.87 (57.96)		
5 to 14	55	2,483.17 (31.63)	3,113.52 (39.66)		
15 to 45	195	4,963.35 (63.23)	4,766.65 (60.72)	14.43[1)]	<0.0001
46 to 60	62	6,706.05 (85.43)	8,555.34 (108.99)		
60+	29	8,407.58 (107.10)	5,987.61 (76.28)		
Age group under five and others					
Under five years old patients	460	3,440.66 (43.83)	4,549.87 (57.96)		
More than five years old patients	341	5,173.09 (65.90)	5,753.68 (73.30)	4.60[2)]	<0.0001
Sex					
Male	404	4,441.82 (56.58)	5,581.65 (71.10)	1.46[2)]	0.14
Female	397	3,909.90 (49.81)	4,696.13 (59.82)		
Type of care					
Inpatient care	402	6,570.79 (83.70)	5457.71 (69.52)	14.88[2)]	<0.0001
Outpatient care	399	1,767.58 (22.52)	3,465.92 (44.15)		
Income quintile					
Poorest quintile (≤10,000)	276	3,689.3 (47.00)	4,412.93 (56.22)		
2nd quintile (10,001- 12,000)	82	4,037.95 (51.44)	4,785.6 (60.96)		
3rd quintile (12,001-18,000)	166	4,202.38 (53.53)	4,866.93 (62.00)	0.28[1)]	0.89
4th quintile (18,001-30,000)	187	4,453.03 (56.73)	5,789.56 (73.75)		
Upper quintile (30,000+)	90	5,189.48 (66.11)	6,549.86 (83.44)		
For under five years old patients					
Sex					
Male	248	3,571.68 (45.50)	4,566.33 (58.17)	0.67[2)]	0.505
Female	212	3,287.38 (41.88)	4,536.52 (57.79)		
Type of care					
Inpatient care	142	6,770.96 (86.25)	4,376.74 (55.75)	11.36[2)]	<0.0001
Outpatient care	318	1,953.54 (24.89)	3,777.22 (48.12)		
Income quintile					
Poorest quintile (≤10,000)	167	3,499.31 (44.58)	4,596.37 (58.55)		
2nd quintile (10,001- 12,000)	48	3,835.03 (48.85)	5,304.53 (67.57)		
3rd quintile (12,001-18,000)	94	3,076.29 (39.19)	3,794.47 (48.34)	0.28[1)]	0.8919
4th quintile (18,001-30,000)	111	3,554.23 (45.28)	5,024.53 (64.01)		
Upper quintile (30,000+)	40	3,263.63 (41.57)	3,697.33 (47.10)		

Note: [1)] One-way analysis of variance (ANOVA) was performed to derive significance level
[2)] Independent two samples t-test was performed to derive significance level.

5.3.4 Cost burden and coping strategies

The cost burden of diarrheal illness is presented in Table 5-4 and the 'total out of pocket costs' during treatment is shown as a percentage of the monthly earnings of the households. The OOP

payment as a proportion of household monthly income differed significantly among the income groups (P<0.0001). It was observed that during the treatment course, the most common coping strategies were regular income (85.63%) borrowing from others (15.63%) and savings (9.38%) (Figure 5-1).

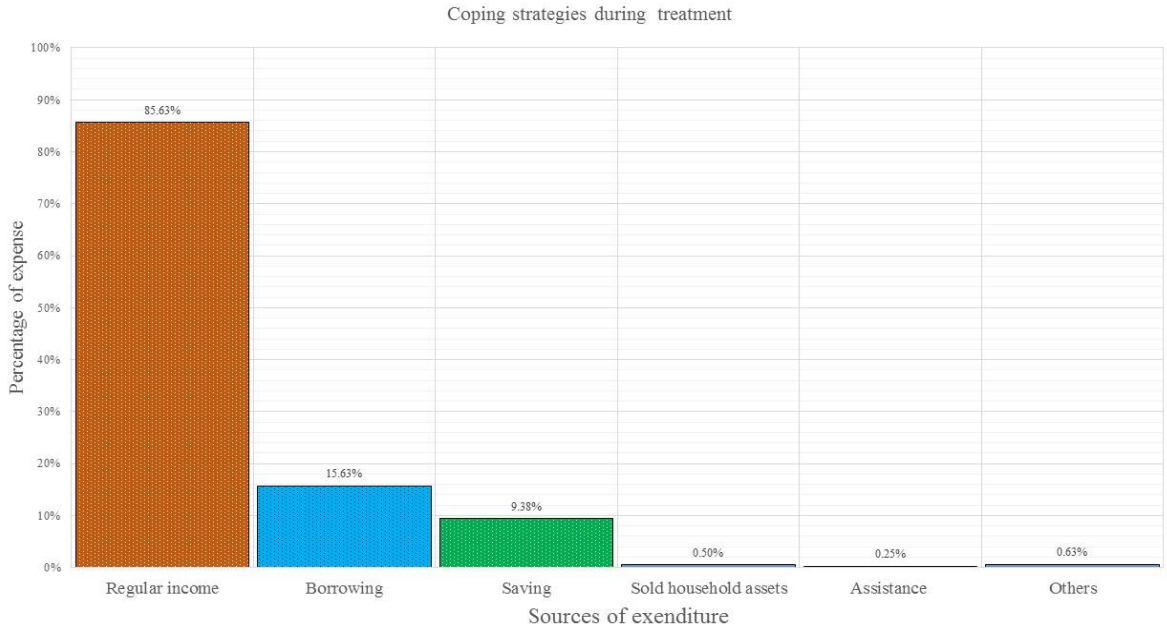

Figure 5-1 Coping mechanisms during diarrheal treatment

The overall OOP expenditure due to diarrheal treatment was 11.75% of monthly household income. However, in the poorest quintile, it exceeded 17% of the total household income. The richest (5th) quintile only spent 4.21% of their household income. Considering a 10% threshold of income level, approximately 32% households suffered from catastrophic expenditure while the poorest quintile suffered more (49%). Even at the highest threshold level of 25%, the poorest 27% of households suffered from catastrophic expenditure due to diarrheal diseases (Table 5-4).

Table 5-4 Cost burden and health expenditure in different socioeconomic condition

Income group	Direct cost as percentage of monthly household income	Percentage of household spending for healthcare expenditure as a share of monthly household income			
		10%	15%	20%	25%
Poorest quintile (≤10,000)	21.45% (17.32%-25.58%)	49.20% (43.66%-54.75%)	40.51% (35.18% - 46.08%)	31.83% (26.88% - 37.23%)	27.01% (22.35% - 32.23%)
2nd quintile (10,001-12,000)	11.60% (9.18%-14.02%)	39.64% (30.94% - 49.05%)	26.13% (18.77% - 35.12%)	16.22% (10.43% - 24.33%)	9.91% (5.55% - 17.06%)
3rd quintile (12,001-18,000)	9.35% (7.92%-10.79%)	31.84% (26.04%-38.26%)	16.14% (11.86%-21.59%)	10.31% (6.94% - 15.06%)	7.17% (4.43% - 11.41%)
4th quintile (18,001-30,000)	6.45% (5.27%-7.64%)	20.62% (16.10%-26.02%)	10.12% (6.97% - 14.46%)	5.84% (3.54% - 9.47%)	2.33% (1.05% - 5.11%)
Upper quintile (30,000+)	4.21% (3.34%-5.08%)	8.22% (4.71%-13.95%)	4.79% (2.29% - 9.75%)	4.11% (1.85% - 8.87%)	1.37% (0.34% - 5.34%)
Overall	11.75% (10.37%-13.14%)	31.77% (29.02% - 34.66%)	21.37% (18.99% - 23.97%)	15.36% (13.30% - 17.68%)	11.35% (9.57% - 13.43%)
Rich–poor ratio	0.196	0.167	0.118	0.129	0.051
Rich–poor difference	-17.24	-40.98	-35.72	-27.72	-25.64

5.3.5 Waiting and travel time

Before coming to the selected public hospitals, most patients received treatment from other formal and informal care providers (Figure 5-2). However, in LMI countries like Bangladesh, diarrheal patients are often inadequately treated at home. Homecare is associated with poor outcomes and timely medical treatment minimizes the length of each episode and reduce mortality (Carl Forsberg 2007). The average travel time to the public hospital was nearly 2 hours while at least 30 minutes were required as waiting time.

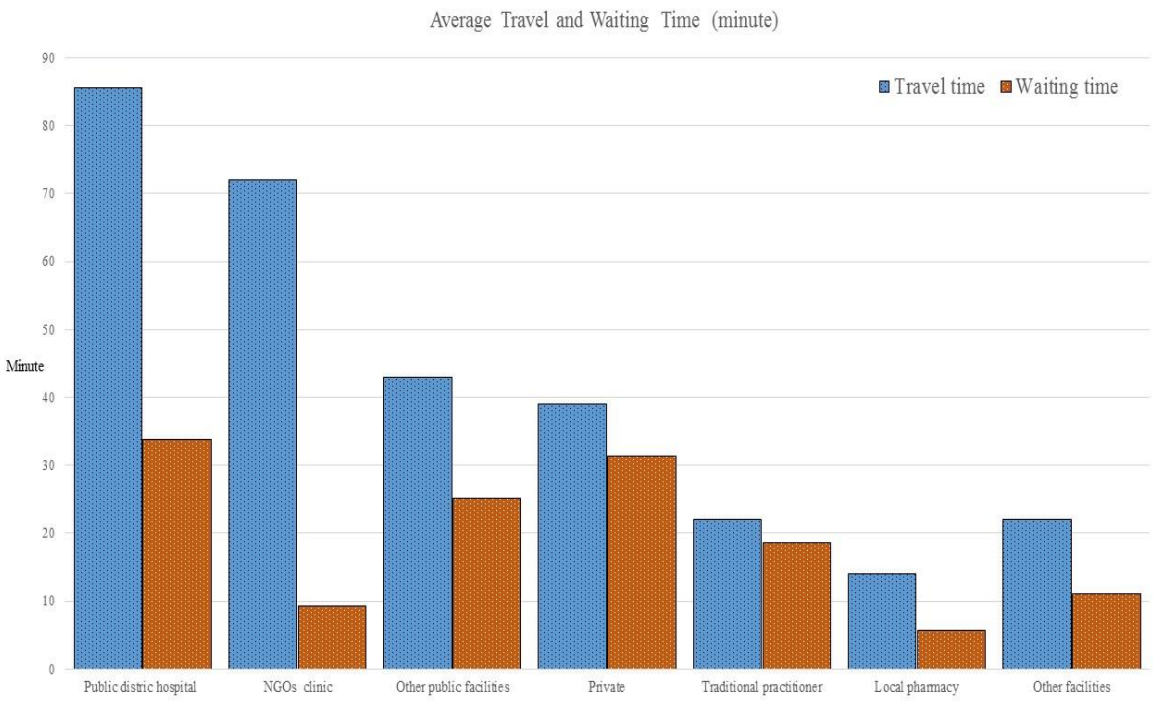

Figure 5-2 Average travel and waiting time for receiving care

5.3.6 Inpatient and outpatient cost: hospital perspective

Table 5 shows the average total inpatient and outpatient treatment cost due to diarrheal disease. The average inpatient treatment cost per patient was BDT 2,104.09 or US$ 26.80 whereas direct medical costs constituted only 4.18%. The total direct medical cost per diarrheal episode was BDT 88.27 or US$ 1.12, and medicine cost was the largest (BDT 83.23 or US$ 1.06). Among the direct non-medical costs staff salaries was a major cost driver (BDT 836.38 or US$ 10.65) followed by capital costs (BDT 456.31 or US$ 5.81). The other two larger cost components were food costs (BDT 323.25 or US$ 4.12) and space for providing patient services (BDT 321.74 or 4.10).

Table 5-5 Distribution of provider costs: average inpatient vs outpatient's cost, BDT (US $)

Cost	Parameters	Inpatient (N=402)		Outpatient (N=399)	
		Amount	% of total cost	Amount	% of total cost
Direct Medical	Medicines	83.23 (1.06)	-	28.16 (0.36)	-
	Diagnosis	-	-	-	-
	Disposable items	5.03 (0.06)	-	-	-

Total Direct Medical		88.27 (1.12)	4.18%	28.16 (0.36)	32.56%
Direct Non-Medical	Staff salaries	836.38 (10.65)	-	25.49 (0.32)	-
	Transport	31.39 (0.4)	-	-	-
	Food	323.25 (4.12)	-	-	-
	Stationery	3.44 (0.04)	-	0.1 (-)	-
	Window shade	1.21 (0.02)	-	0.03 (-)	-
	Electricity	9.96 (0.13)	-	0.27 (-)	-
	Gas bill	0.33 (-)	-	0.01 (-)	-
	Water bill	0.01 (-)	-	-	-
	Telephone bill	0.14 (-)	-	-	-
	Other Misallocations	31.66 (0.4)	-	0.85 (0.01)	-
	Capital items	456.31 (5.81)	-	4.84 (0.06)	-
	Building	321.74 (4.1)	-	26.2 (0.33)	-
Total Direct Non-Medical		2,015.82 (25.68)	95.82%	57.8 (0.74)	67.44%
Average cost per Patient		2,104.09 (26.80)	100%	85.97 (1.1)	100%

The average total outpatient cost was BDT 85.97 or US$ 1.10 where medical and non-medical costs constituted 32.56% and 67.44 % respectively. Medicine cost (BDT 28.16 or US$ 0.36) was the main cost driver followed by the cost of space (BDT 26.20 or US$ 0.33) and staff salaries (BDT 25.49 or US $ 0.32). A lump-sum amount of capital cost (BDT 4.84 or US$ 0.06) was also incurred during the treatment course of outpatients (Table 5-5).

5.3.7 Societal cost of illness

The average total societal cost of illness per episode was BDT 5,274.02 (US$ 67.18) whereas average inpatient and outpatient costs were BDT 8,675.09 (US$ 110.51) and BDT 1,853.96 (US$ 23.62) respectively (Table 5-6). Among all the cost segments, households cost contributed a larger portion (80% of the total costs) and OOP contributed 32% of the total societal cost of illness. Considering the provider actual treatment cost, the non-medical cost (19.66%) was the main cost driver. However, among all of the cost components, the indirect cost of patients and caregivers (BDT 2,490 or US$ 31.72) was the main cost driver of all types of care which is not apparent if only provider costs are measured.

Table 5-6 Societal cost of illness due to diarrheal disease, BDT (US$)

Type of care	Perspective	Types of cost	Amount BDT (US$)	Proportion of total cost (patients)
Inpatient Care (n=402)	Provider	Direct medical	88.27 (1.12)	1.02
		Direct non-medical	2,015.82 (25.68)	23.24
	Household	Out of pocket payment	2,760 (35.36)	31.82
		Indirect cost	3,811 (48.55)	43.93
	Societal	All costs	8,675.09 (110.51)	100%
Outpatient Care (n=399)	Provider	Direct medical	28.16 (0.36)	1.52
		Direct non-medical	57.8 (0.74)	3.12
	Household	Out of pocket payment	609 (7.76)	32.85
		Indirect cost	1,159 (14.76)	62.51
	Societal	All costs	1,853.96 (23.62)	100%
All- patient Care (N=801)	Provider	Direct medical	58.21 (0.74)	1.1
		Direct non-medical	1,036.81 (13.21)	19.66
	Household	Out of pocket payment	1,689 (21.51)	32.02
		Indirect cost	2,490 (31.72)	47.21
	Societal	All costs	5,274.02 (67.18)	100%

5.3.8 Annual economic burden

In the light of the earlier findings this section expresses the overall economic burden of diarrhea in Bangladesh. According to the latest national health bulletin, approximately 2.56 million diarrheal cases and 24 deaths were reported in 2015 in various health facilities in Bangladesh (MOHFW 2016). During the hospital-based survey, approximately 44% of the diarrheal patients received inpatient hospital care, and 66% had outpatient services. The total annual cost of treatment was US$ 172.02 million for societal perspective while US$ 35.72 million was incurred by the health facilities.

5.4 DISCUSSION

Diarrheal disease is a major public health concern associated with significant morbidity and mortality and economic loss in many societies. While the cost of illness for other infectious diseases in Bangladesh has been investigated (Sarker et al. 2013; Alamgir et al. 2010), knowledge of the cost of illness of diarrheal disease considering the broader societal perspective is limited. The current standards for cost-effectiveness analysis recommend to use a broader societal perspective considering both the provider and household perspective (Gold et al. 1996).

We found the average length of the diarrheal episode is five days (results not presented here), and the average treatment cost is BDT 5,274.02 (US$ 67.18) that could be saved if the diarrheal disease

was prevented. More than 52% of the total costs are the direct costs borne by the households (31%) and hospitals (21%) as the public hospitals are highly subsidised in Bangladesh (Andaleeb 2000). In early 2001, Ali et al found that the provider cost per day for the management of inpatient and outpatient in a district hospital (Manikgonj) near Dhaka city was BDT 317.27 or US$ 4.04 and BDT 53.74 or US$ 0.69 respectively (Ali 2001). Das et el estimated that the average inflation adjusted diarrheal treatment cost for under five year old children in rural Bangladesh was US$ 6.99 though they did not consider the laboratory cost borne by the hospitals as well as the income loss of the household (Das et al. 2015). From a multi-country analysis, Rheingans et al. found that the average household treatment cost for childhood diarrhoa was US$ 1.82 where direct cost and indirect costs constituted US$ 1.19 and US$ 0.63 respectively in Bangladesh. The limitations of this study was the relatively small sample size and therefore was not representative of the country and that the study was conducted in a surveillance area (Rheingans, Kukla, et al. 2012). An urban slum based study carried out in Bangladesh where the incidence of diarrhea is high and found that the cost of childhood diarrhea per episode ranged from BDT 124 (US$ 1.81) to BDT 276 (US$ 4.00) with an average duration of 3.76 days of diarrhea (Jahangir 2009). However, all of these studies did not consider the societal perspective and our study expresses a more complete accounting of all the relevant costs associated with an episode of diarrhea.

The current study found that the societal cost of illness per episode was US$ 110.51 for inpatients and US$ 23.6 for outpatients respectively. Recently, similar findings have been observed in a number of LMI countries. Aikins et al. in northern Ghana found that from the health sector perspectives, the average inpatient and outpatient treatment costs were US$ 97.40 and the US$ 4.10 respectively (Aikins et al. 2010). In Rwanda, the treatment cost per diarrheal hospitalization was US$ 101 and 65% of this cost was borne by households (Ngabo et al. 2016). Another study conducted in several hospitals in Vietnam found that the average treatment cost per episode was US$ 106.9 whereas indirect costs made up the largest share (51.3%) followed by the direct medical costs (33.8%) and direct non-medical costs (14.9%) (Hoang et al. 2015). The current study estimated the possible costs of providers (both medical and non-medical) and costs borne by the patients and their caregivers (both direct and productivity loss) in a standard hospital-based survey of six district hospitals of each six divisions in Bangladesh.

The study showed that the treatment cost for outpatients is lower than for inpatients. Among all patients, adults with diarrhea consumed significantly more resources than the young which is consistent with earlier findings that high healthcare expenditure is associated with increase in age

(Sarker et al. 2014). Diarrheal cost burden was significantly higher for the poorest than richest households. The main treatment coping mechanisms was the income of the households' head. The highest cost burden was observed for poorest quintile (21.45%) than richest quintile (4.21%). Considering the provider cost of treatment, the main cost driver was staff salaries (operating expenditure) and the cost of building (investment cost). Some of those investment costs occurred at the beginning of the program and are often not listed in accounts or budget of the hospitals but nevertheless we consider that they are real costs and should be accounted for (Drummond et al. 2005).

We estimate that, using our results, the annual economic burden of diarrheal diseases to be US$ 172.02 million which was 12.28% of the total health expenditure in Bangladesh (MOHFW 2015a). However, the estimation is based on the reported cases from health facilities although it is very common that diarrhea is inadequately managed at household level and is associated with high morbidity and mortality. In that sense, we underestimated the actual burden of diarrheal disease in Bangladesh. A literature review of economic burden of rotavirus disease study in Asian settings showed that the annual economic burden of rotavirus illness laid between US$ 0.41 million (Uzbekistan) up to US$ 365 million in China (Kawai et al. 2012), while the annual economic burden of rotavirus exceeds US$ 72 million in India (Tate et al. 2009). An unpublished estimation showed that approximately US$ 7.06 million could be saved by preventing rotavirus diseases in Bangladesh (Sarker et al. 2017). The latest estimate of the annual GDP per capita in Bangladesh (2016) was US$ 1,466 which indicated that approximately 4.58% of GDP per capita spent on treating each diarrheal episode which might be a critical concern as it is the prime cause of hospital admission in Bangladesh (Independent Online Desk 2016; Sultana et al. 2015). Therefore, by controlling diarrheal diseases huge amounts of resources would be saved. Consequently, with reduced number of patients, hospitals could save extra resources like hospital bed, space, doctor's time, and other resources that could be channeled for other purposes. During the treatment, reliance on OOP expenditures leads to catastrophic economic burden for many households. Further, many poor and vulnerable people cannot afford healthcare as currently there are no social health protection schemes in Bangladesh. To reduce financial barriers to healthcare for the needy and to avoid catastrophic health expenditures, social health protection might be an option which is the core theme of universal health coverage.

The limitations to this study include the design; as a cross-sectional study, it was not possible to estimate the cost variation in light of seasonality such as the incidence of usual peaks during the hot and winter seasons in Bangladesh (S. K. Das et al. 2014). The treatment of diarrheal disease

relies heavily on households' treatment patterns and resources which are not covered in this study (Aikins et al. 2010). The current study was conducted among hospitalized patients, but many diarrheal episodes occurred in the community which is not captured in this study. The other limitation was the sample size as only selected hospitals were considered, albeit on a randomised basis, and therefore the study might not be representative of the whole country. We did not collect the information about severity of diarrheal illness directly, though patients with severe disease are more likely to be inpatients than outpatients (Das et al. 2013).

5.5 CONCLUSIONS

In LMI countries like Bangladesh, diarrheal diseases continue to be an overwhelming problem. Cost analysis of diarrheal diseases is required for estimating resources for managing and preventing diarrheal disease. Therefore, the economic impact of any public health interventions (either preventive or promotive) that can reduce the prevalence of diarrheal infections can be estimated from the economic data generated from this study.

Competing interests: The authors declare that they have no competing interests.
Funding: The project is a part of the SIDA young investigator award.
Acknowledgements: icddr,b acknowledges with gratitude the commitment of the SIDA unrestricted fund to its research efforts. icddr,b is thankful to the Governments of Australia, Bangladesh, Canada, Sweden, and the UK for providing core/ unrestricted support. The authors gratefully acknowledge the University of Strathclyde PhD scholarship for its research effort. The authors would also like to thank the health economics and financing research groups for their comments on an earlier draft of the manuscript.

6 COST OF ILLNESS FOR CHOLERA DISEASE

Study - **III**

Published: ***BMC Infectious Disease***

Publisher: **BMC Publication**

Volume: (2013); 13:518

https://doi.org/10.1186/1471-2334-13-518

Title of the paper: Cost of illness for cholera in a high-risk urban area in Bangladesh: an analysis from the household perspective

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Abstract

Background: Cholera poses a substantial health burden to developing countries such as Bangladesh. In this study, the objective is to estimate the economic burden of cholera treatments incurred by households. The study was carried out in the context of a large vaccine trial in an urban area of Bangladesh.

Methods: The study used a combination of prospective and retrospective incidence-based cost analyses of cholera illness per episode per household. A total of 394 confirmed cholera hospitalized cases were identified and treated in the study area during June–October 2011. Households with cholera patients were interviewed within 15 days after discharge from hospitals or clinics. To estimate the total cost of cholera illness a structured questionnaire was used, which included questions on direct medical costs, non-medical costs, and the indirect costs of patients and caregivers.

Results: The average total household cost of treatment for an episode of cholera was US$ 30.40. Total direct and indirect costs constituted 24.6% (US$ 7.40) and 75.4% (US$ 23.00) of the average total cost, respectively. The cost for children under 5 years of age (US$ 21.50) was higher than that of children aged 5–14 years (US$ 17.50). The direct cost of treatment was similar for male and female patients, but the indirect cost was higher for males.

Conclusion: Our study suggests that by preventing one cholera episode (3 days on an average), we can avert a total cost of BDT 2,278.50 (US$ 30.40) per household. Among medical components, medicines are the largest cost driver. No clear socioeconomic gradient emerged from our study, but limited demographic patterns were observed in the cost of illness.

Keywords: Cost of illness, cholera, urban Bangladesh

6.1 BACKGROUND

Cholera presents a substantial health burden in the developing world and is endemic in Africa and Asia and has recently spread many parts of the world. An estimated 1.4 billion people worldwide are at risk of cholera; India and Bangladesh jointly constitute the largest share of this population (Ali et al. 2012). Cholera is a waterborne disease and is closely linked to inadequate environmental management. It is responsible for 100,000–120,000 deaths per annum globally, which constitutes an estimated 3–5million cholera cases every year (WHO 2012b). However, the World Health Organization acknowledges that only 5%–10% of cholera cases are actually reported and it is likely that their data on cholera rates are a gross underestimation of the real burden of the disease (Ali et al. 2012). In Bangladesh, there is no accurate data on the actual number of cholera cases but estimates by experts suggest an incidence of approximately 450,000 cases each year (WHO 2009b; icddrb 2011).

Cholera cases have increased in Bangladesh, especially in urban settings such as in the capital of Dhaka, where the number of hospitalized patients with severe cases has significantly increased (Chowdhury et al. 2011). Looking at diarrheal epidemics in Dhaka in 1998, 2004, and 2007, it is apparent that the number of cases of severe dehydration due to cholera is increasing with each epidemic: 22% in 1998, 25% in 2003, and 35% in 2007 (Chowdhury et al. 2011; Harris et al. 2008). Although cholera is one of the most prevalent diseases in the country, studies on its economic impact are limited. The Diseases of the Most Impoverished (DOMI), a cholera cost study group, carried out a multi-country cost-of-illness study in Matlab (rural Bangladesh), Beira (urban neighborhood in Mozambique), Kolkata (middle-class and slum neighborhood in India), and North-Jakarta (middle-class and slum neighborhood in Indonesia). While DOMI studied the cost of illness in the rural context in Bangladesh, it did not include any information regarding urban Bangladesh. This current study, therefore, aims to calculate the cost of illness for households due to cholera treatment in an urban area with high cholera prevalence. By addressing the information gap on the cost of illness for households in urban Bangladesh due to cholera treatment, this study offers a more complete economic perspective of the cost of cholera for health policy making in general and for prevention strategies in Bangladesh.

6.2 METHODS

6.2.1 Study site and population

The "Introduction of Cholera Vaccine in Bangladesh" (ICVB) project is currently being conducted in six wards (lowest administrative units) in Mirpur (an urban area), Dhaka, Bangladesh. The Mirpur area is densely populated (approximately 2.5 million people) with a high proportion of high-risk populations prone to cholera and other diarrheal diseases. The wards in Mirpur were selected based on reports of a higher influx of diarrheal patients to Dhaka hospital, an International Centre for Diarrheal Disease Research, Bangladesh (icddr,b) hospital, over the last 5 years. The estimated rate of hospitalization due to cholera is 2–6 per 1,000 people in these selected wards (Chowdhury et al. 2011). Patients of all ages residing in Mirpur's six wards who were confirmed by stool culture to have *V. cholerae* O1 and hospitalized for diarrhea were eligible to participate in this study. It is worth noting that non-hospitalized patients were not included because there is no scope for cholera confirmation without laboratory testing.

6.2.2 Study perspective

An incidence-based approach was applied to estimate the cost of illness of cholera treatment per episode from a household perspective. In the study, household members in the ICVB surveillance area who sought care at any health facilities and were laboratory confirmed as cholera cases by icddr,b hospitals were included. A structured questionnaire was developed to collect data on all possible cost components, including direct medical and non-medical costs as well as indirect costs incurred by the households.

6.2.3 Sample size

All confirmed cholera hospitalized cases, hospitalized in one of the six wards in Mirpur during June–October 2011, were included in the study. A total of 394 confirmed cholera cases were identified and interviewed.

6.2.4 Patient enrollment

Information (name, address, cell phone number) on confirmed cholera patients was collected from health facility databases and interviews were conducted within 15 days after receiving the treatment care. We interviewed the household head or the person who was most familiar with the costs incurred during the cholera treatment of the patient. The interviews were conducted at the respondent's residence. Written informed consent was obtained from all respondents. Structured

questionnaires with both open-ended and closed questions were used by trained data collectors to obtain data.

6.2.5 Measuring household costs of cholera

Household costs of cholera episodes include out-of-pocket payments made by the households for the treatment of cholera and the opportunity costs for time used by the patients and/or caregivers during the entire cholera episode. Out-of-pocket payments consisted of direct medical and non-medical costs. Direct medical costs included hospital outpatient fees, admission or registration fees, physician fees, consultant fees, payments to paramedics during home visits for intravenous infusions, medicine costs, oral rehydrating solution, laboratory tests, diagnostic fees, and any other associated medical supplies. The direct non-medical costs include transportation, lodging, food items, tips (informal payment), payment to caregiver for loss of regular work or payment for attending patient, expenditure for materials such as utensils and other items such as mosquito coils and lighters for patients and also the cost of caregivers during the treatment.

Indirect costs were those related to income or productivity loss and were measured by applying the human capital approach. Income loss for paid workers was measured by multiplying the number of lost working hours due to a cholera episode with the actual wage rate of the patient. Self-reported wage rates have been used in this study. The productivity loss due to forgone non-market activities including school, household chores, childcare, and leisure time were captured. The value of daily productivity was measured on the basis of either an assumed age-specific wage or an occupation-specific wage as used in other studies (Poulos et al. 2012). Few studies monetized the loss associated with children (Asenso-okyere & Dzator 1997) who have been considered to make important economic contributions to the household (Chima et al. 2003). We assumed age-specific wages for three groups: adults, teenagers, and children aged 5 to 14 years. The average daily wages of the patients were used for adult patients, while one half and three-quarters of that wage were applied to teenagers and children, respectively. Half the average wage was assigned to unpaid home workers, taking their age group into consideration (Poulos et al. 2012). Intangible costs, i.e., costs related to suffering and grief, have been included as an additional cost category in other studies. However, such costs are not generally valued and no tangible economic impact is implied (Chima et al. 2003). In this study, the intangible cost due to cholera was not considered.

6.2.6 Data analysis

Data were entered into Microsoft Excel 2007. All entries were manually double-checked and verified by the investigators. Subsequently, statistical analysis was performed using STATA-11.1. An equivalence scale was applied to adjust for household size when calculating household income per equivalent adult (Marks 2007). Data were presented as a total and as an average with a standard deviation in local currency, i.e., Bangladeshi Taka (BDT) and US dollars (US$) applying the exchange rate (US$1 = 75 BDT) during the mid-point of the data collection year (2011).

A sensitivity analysis was conducted on direct and indirect costs to test the robustness of the assumptions and to examine the impact of potential outliers in the database (Javanbakht et al. 2011). Costs of informal caregivers had a higher level of uncertainty and could be different (Coduras et al. 2010a). We tested the effects of a change of 20% in the parameters of both direct costs and indirect costs as performed in an earlier study (Javanbakht et al. 2011).

6.2.7 Ethical Approval

The research protocol of this study was approved by the Institutional Review Board of the icddr,b.

6.3 RESULTS

A total of 394 patients participated in the study, of which 53% were male and 47% were female, and 36% were younger than 5 years of age. All households that were approached to participate in the survey gave written consent, thus, no household refused to partake.

The average total cost of treating one episode of cholera was found to be BDT 2278.50 (US$ 30.40). The direct cost was BDT 559.50 (US$ 7.40), which represented 24.6% of the total cost. Direct costs made up 24.6% of the average total cost, of which 8.9% and 15.6% were medical and non-medical cost components, respectively. Medicine costs made up the largest share among all direct medical cost components, followed by registration or admission fees (Table 6-1). Among the direct non-medical cost components, transportation constituted the largest (BDT 140 or US$ 1.90) followed by caregiver costs (BDT 113.25 or US$ 1.50). Food items (BDT 63 or US$ 0.80) represented a significant proportion of direct non-medical cost as well. A wide range in cost per episode was observed in the standard deviation from the average value. For a better understanding of such a spread in cost, the median, and the 5th and 95th percentiles were calculated for each cost item. The median of the total cost was BDT 1,306.50 (US$ 17.40) and the distribution as 5th and 95th percentiles was BDT 285 (US$ 3.80) and BDT 5,822 (US$ 77.60), respectively. Median direct and indirect costs were BDT 392.50 (US$ 5.20) and BDT 807.50 (US$ 10.80), respectively.

The 5th and 95th percentiles for direct costs were BDT 80 (US$ 1.10) and BDT 1,430 (US$ 19.10) and the corresponding values for indirect costs were BDT 95.60 (US$ 1.30) and BDT 3,774 (US$ 50.30), respectively.

Table 6-1 Average household cost of cholera treatment, BDT (US$*)

Costs	Parameters	Average cost	Standard deviation	Proportion of total cost
Direct Medical	Diagnostic	9.6 (0.1)	75.7 (1)	9
	Medicine	148.7 (2)	246 (3.)	
	Registration fee	26.1 (0.3)	130.6 (1.7)	
	Paramedics home visit fee	2.8 (-)	21.5 (0.3)	
	Bed/ Cabin charge	16.9 (0.2)	130.7 (1.7)	
Direct Non-Medical	Transportation cost	140 (1.9)	122 (1.6)	15.6
	food items	63(0.8)	85 (1.1)	
	Informal payment	0.7 (-)	9 (0.1)	
	Caregivers payment	0.1 (-)	1 (-)	
	Materials (e.g., mug /glass/ coil)	10.6(0.1)	17 (0.2)	
	Lodging	28 (0.4)	101 (1.3)	
	Caregivers expenditure	113.2 (1.5)	172 (2.3)	
Total direct cost		559.5 (7.4)	641.7 (8.5)	24.6
In-direct	Patients income loss	811 (11)	4,301 (57)	
	Caregivers income loss	908 (12.2)	3,701 (49)	
Total indirect cost		1,719 (23)	5,656 (75.4)	75.4
Total cost of illness of household		**2,278.5 (30.4)**	**5,668 (75.6)**	**100**

* 1 US dollar (US$) = 75 Bangladeshi Taka (BDT) in mid-2011.

Indirect costs were BDT 1,719 (US$ 23) per episode per household, which represented 75.4% of the average total cost (Table 6-1). We also observed that the average caregiver's production loss (BDT 908 or US$ 12.20) was higher than that of the patient's (BDT 811 or US$ 11). A one-way sensitivity analysis with a 20% increase in the parameters of direct and indirect costs showed that the total cost increased by 4.9% and 15%, respectively.

6.3.1 Costs across income groups

The average total cost of the poorest (1st) quintile was BDT 1,894.50 (US$ 25.30) while that of the richest was BDT 2,335.60 (US$ 31.10) per episode. Households in the second quintile incurred the largest average total cost (BDT 2,993 or US$ 40). No socioeconomic gradient was observed. Direct costs represented approximately 29% of total cost in the poorest, middle, and richest quintiles. The corresponding shares in the second and fourth quintiles were 15.5% and 23.3%, respectively.

Table 6-2 Household average cost of cholera treatment by income quintile, BDT (US$)

Income quintile (equivalent per adult income, BDT)	Number of households	Average direct cost	Average Indirect cost	Average total cost
1 (≤1647)	82	562 (7.5)	1,332.5 (17.8)	1,894.5 (25.3)
2 (1,648-2,500)	78	474 (6.3)	2,519 (33.6)	2,993 (39.9)
3 (2,501-3,529)	80	482.9 (6.4)	1,197 (16)	1,680 (22.4)
4 (3,530 -5,333)	83	583.4 (7.8)	1,927 (25.7)	2,510.4 (33.5)
5 (5,334+)	77	696.4 (9.3)	1,639.2 (22)	2,335.6 (31.1)

6.3.2 Costs across age groups

The average total costs ranged between BDT 1,314 (US$ 17.50) and BDT 6,214 (US$ 82.60). The largest cost was observed among patients aged 60 years and older. The direct costs ranged between BDT 345 (US$ 4.60) and BDT 635 (US$ 8.50) and the highest cost was observed among patients under 5 years of age. While indirect costs increased for older patients, the direct costs did not show significant disparity across age groups.

Table 6-3 Household average cost of cholera treatment by age group, BDT (US$)

Age group (years)	Number of patients	Average direct cost	Average indirect cost	Average total cost
Up to 4	131	635 (8.5)	980 (13)	1,615 (21.5)
5 to 14	34	537 (7)	778 (10)	1,314 (17.5)
15 to 45	178	529 (7)	1,733 (23)	2,261 (30)
46 to 60	39	532 (7)	3,682 (49)	4,214 (56.2)
60+	12	345 (4.6)	5,870 (78)	6,214 (82.6)

6.3.3 Costs by gender

The average total costs for males and females were BDT 2,526 (US$ 33.80) and BDT 1,995 (US$ 26.50), respectively. The average direct costs were slightly more for males than females. The difference in average total cost can be explained by associated indirect costs, as a greater number of males are in the labor market. We found that the difference in indirect costs was higher for males.

Table 6-4 Cost of cholera treatment by sex

Sex	Number of patients	Average cost, BDT (US$)		
		Direct cost	Indirect cost	Total cost
Male	210	556 (7.5)	1,970 (26.3)	2,526 (33.8)
Female	184	563 (7.4)	1,432 (19.1)	1,995 (26.5)
Total	394	559 (7.4)	1,719 (23)	2,286 (30.4)

Among children under 5 years of age, males have a higher average total cost (BDT 1,763.40 or US$ 23.50) than females (BDT 1,321.40 or US$ 17.70). Both direct and indirect costs were higher for male children.

Table 6-5 Gender differential in average cost of cholera treatment among under-five children

Sex	Number of patients	Average cost, BDT (US$)		
		Direct cost	Indirect cost	Total cost
Male	87	642.4 (8.6)	1,121 (15)	1,763.4 (23.5)
Female	54	564.4 (7.7)	756 (10)	1,321.4(17.7)
Total	141	612.5 (8.2)	982 (13)	1,594.2 (21.2)

6.4 DISCUSSION

This study found that both the average and median length of a cholera episode was 3 days and the 5th and 95th percentiles of the episode were 1 and 6 days, respectively. This costing study was carried out in the Mirpur area of Dhaka, in which vaccination trial was also carried out. In the target area, 123,661 people had received their full vaccinations. The data for this study were collected when the vaccine trial had just started, and the vaccine effect may not have been achieved that time.

While the cost of illness for cholera in rural Bangladesh had been investigated in an earlier study, such information was lacking for urban areas in the country. In a multi-country study, previous researchers applied hospital-based data collection techniques in rural Bangladesh to estimate the cost of illness due to endemic cholera (Poulos et al. 2012). That study also included India, Mozambique, and Indonesia. It was found that the average cost of illness for a Bangladeshi household was US$ 12.40. The corresponding costs in Beria (Mozambique), Kolkata (India), and North Jakarta (Indonesia) were US$ 18.80, US$ 17.90, and US$ 134.00, respectively (Poulos et al. 2012). The current study, however, found that the average total cost per episode of cholera illness for households is BDT 2,278.50 (US$ 30.40).

Medicine, transportation, caregiver costs, and opportunity costs (indirect costs) were the largest cost components in the study. Some of the costs varied across socioeconomic and demographic groups. The total indirect cost was more than three times higher than the total direct cost. Among the direct costs, medical related costs constituted 36.4% of the total, representing the largest share. Among the non-medical components, transportation costs were the highest, followed by caregiver costs, which included food, lodging, and cell phone costs. It was found that the average total cost

of illness was greater for adult patients than child patients (Table 6-3). The variation in average total costs across age groups can be explained by indirect costs because the direct costs do not differ greatly across groups. While the indirect costs of adult patients can be influenced by their wage level and length of cholera episode, such costs for children are also influenced by these factors (wage and length of episode) in terms of their caregiver. The data from this study show that the health-seeking behavior of adults and children differs to some extent. For instance, children are often taken to local private practitioners before hospitalization, while adult patients generally seek care directly from hospitals. However, we did not capture the treatment seeking patter for those who did not seek care. A disaggregation of costs into components provides a better understanding of the cost drivers. In the two icddr,b hospitals (Dhaka and Mirpur hospitals), all diagnostic tests and medicines were provided free of charge to the patients. Although the patients received their required medicine in hospital, some patients still purchased extra medicine from nearby pharmacies. In addition, private hospitals also charged registration fees that are not charged in icddr,b hospitals. In some cases, out-of-pocket payments were incurred by households (Table 6-1), e.g., fees for home visits from paramedics who offer various services including intravenous saline solution and providing advice.

The high costs of transportation can be explained by travel time on highly congested roads in Dhaka. The approximate travel time to private facilities was 60 minutes, whereas it took on average 80 and 48 minutes to reach the icddr,b Dhaka hospital and Mirpur hospital, respectively. It was also observed that waiting time in private hospitals was longer (16 minutes) than in the icddr,b hospitals (4.2 minutes on average). The highest waiting times (the longest was 34 minutes) were observed in private clinics and hospitals outside the cholera surveillance area.

Table 6-6 Reported travel and waiting time for cholera treatment

Facility	**Number of visit[1]**	**Average time spent (minute)**		
		travel time	**waiting time**	**Total time**
Local pharmacy	291	11.6	1.5	13.1
Local MBBS physicians	25	25.1	13.2	38.3
icddr,b Mirpur hospital	266	48.4	4.3	52.7
icddr,b Dhaka hospital	137	80	4	84
Private clinics (ten other health facilities)[2]	33	56	16	72
Traditional practitioner	4	12.3	0	12.3
Other private clinic[3]	10	27.3	34	61.3

1) Multiple visits applied; [2)] Patients frequently visit these hospitals; [3)] Located outside ICVB surveillance area.

6.5 LIMITATIONS

This study does have some limitations. There may be some recall bias as data were collected after receiving treatment. However, to minimize the bias, we conducted all interviews within 15 days of after receiving treatment. Outpatients were excluded in this study as no confirmed cholera outpatient cases were identified during the data collection period. The patients enrolled in this study were from a high-risk cholera area (Asenso-okyere & Dzator 1997) and all cases were hospitalized, who may have some specific healthcare seeking behavior. This study did not address this issue.

6.6 CONCLUSIONS

Our study suggests that by preventing one cholera episode (3 days on an average), we can avert approximately BDT 2,278.50 (US$30.40) per household. At the same time, public and not-for-profit private providers can be benefited by avoiding treatment cost due to cholera infections. This finding has implications regarding policy decisions about investment for cholera prevention programs.

Acknowledgements: icddr,b acknowledges with gratitude the commitment of the Bill and Melinda Gates Foundation to its research efforts. The authors would also like to thank Sayem Ahmed, Marufa Sultana, Mary MacLennan, Dr. Louis Niessen and Andrew Mirelman for their comments on an earlier draft of the manuscript.

7 COST OF CHOLERA VACCINATION IN URBAN BANGLADESH

Study - **IV**

Published: ***Vaccine***

Publisher: **Elsevier Publication**

Volume: (2015); 33: 4916–4921

https://doi.org/10.1016/j.vaccine.2015.07.042

Title of the paper: Estimating the cost of cholera-vaccine delivery from the societal point of view: a case of introduction of cholera vaccine in Bangladesh

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Abstract

Cholera is a major global public health problem that causes both epidemic and endemic disease. The World Health Organization recommends oral cholera vaccines as a public health tool in addition to traditional prevention practices and treatments in both epidemic and endemic settings. In many developing countries like Bangladesh, the major issue concerns the affordability of this vaccine. In February 2011, a feasibility study entitled, "Introduction of Cholera Vaccine in Bangladesh (ICVB)", was conducted for a vaccination campaign using inactivated whole-cell cholera vaccine (Shanchol) in a high-risk area of Mirpur, Dhaka. Empirical data obtained from this trial was used to determine the vaccination cost for a fully immunized person from the societal perspective. A total of 123,661 people was fully vaccinated receiving two doses of the vaccine, while 18,178 people received one dose of the same vaccine. The total cost for vaccine delivery was US$ 492,238 giving a total vaccination cost per fully–vaccinated individual of US$ 3.98. The purchase cost of the vaccine accounted for 58% of the overall cost of vaccination. Attempts to reduce the per-dose cost of the vaccine are likely to have a large impact on the cost of similar vaccination campaigns in the future.

Keywords: Cholera, Vaccine, Cost, Health economics, Bangladesh

7.1 INTRODUCTION

Cholera represents a substantial health burden in the developing world and is endemic in Africa, Asia, South America and Central America. It is a highly infectious disease, which is transmitted through the faecal-oral route and can lead to outbreaks within a short period of time through contaminated water and food. Cholera affects all ages and if it is not addressed properly, can lead to death within a very short time. In Bangladesh, there is no well-documented data on the actual number of cholera cases but expert estimates suggest an incidence of approximately 450,000-1,000,000 cases each year, and at least 300,000 severe cholera cases which indicates the importance of vaccines as in severe cholera, as large inoculums are usually required in several cholera (Jeuland, Lucas, et al. 2009; Ahmed 2009; WHO 2009b; icddrb 2011). During a cholera outbreak, the major response should focus on case detection, rehydration-based treatment and provision of safe water, in conjunction with adequate sanitation, hand washing and safe food preparation (WHO 2011b). Cholera control through vaccination has recently received increased attention from public health officials (Schaetti et al. 2012) and the WHO recommends oral cholera vaccines as an added public health tool to traditional methods for prevention and treatment in both endemic and epidemic settings (WHO 2010). Additionally, international donors have recently advocated for expanded vaccination programs to combat cholera and other diseases (Jeuland & Whittington 2009) although in most developing countries affordability remains the key issue. Shanchol and Dukoral are two types of WHO-prequalified, safe and effective oral cholera vaccines currently available in the market (WHO 2012b).

The Expanded Program on Immunization (EPI) in Bangladesh is one of the most successful programs in health sector. EPI started in 1979 with six conventional vaccines against six diseases and introduced later hepatitis B vaccine, pentavalent vaccine, measles second dose and MR (measles and rubella) vaccine in 2012. It has been planned to introduce pneumococcal vaccine in 2014 for prevention of some forms of childhood pneumonia and meningitis. Additionally, other vaccine options in the coming years including cholera and rotavirus vaccines (DGHS 2013). Cost analyses of cholera vaccine delivery may provide useful information regarding actual resource needs and/or inputs required for introducing a new vaccine in future immunization programs. Such information is required for health policy maker, and also used for investing resources and agreements with development partners and donors. The aim of this paper is to estimate the total cost of vaccination, the cost per fully-vaccinated individual, and to identify the related cost drivers. Cost analysis was based on empirical data using a societal-cost perspective.

7.2 SETTING OF THE STUDY

This study was conducted under the feasibility study entitled, "Introduction of Cholera Vaccine in Bangladesh (ICVB)" that was carried out between 17th February and 30th April 2011. The project was in joint collaboration between the government of Bangladesh and icddr,b and examined the effectiveness of using an oral cholera vaccine (two doses) in reducing incidence of cholera in an urban setting, in this case, Dhaka. The study was conducted in six wards (lowest administrative units) of Mirpur (an urban area), Dhaka, Bangladesh. Mirpur is a densely populated area of approximately 2.5 million people with a large proportion of the population at high risk for cholera and other diarrheal diseases (Chowdhury et al. 2011; Sarker et al. 2013). The wards from which the highest reported number of diarrheal patients came to icddr,b's Dhaka hospital over the previous five years were selected. Estimated rates of hospitalization due to cholera were 2 to 6 per 1,000 diarrheal hospitalizations in these selected wards (Chowdhury et al. 2011). According to the hospital statistics, the highest numbers of cholera patients come from Mirpur, which justifies the introduction of inoculums in that area. Participants received two doses of the oral cholera vaccine, the first on day 1 and the second at least after 14 days. A total of 141,844 people was vaccinated from the six wards with 123,661 people receiving the complete two-dose schedule (fully vaccinated) and 18,178 receiving only one dose (incomplete). Pregnant women and children under one year of age were excluded from the study. Written, informed consent by the adults and consent from parents/guardians for children, as well as ascent by children aged between 11 and 17 years of age, were given prior to vaccination.

7.3 MATERIALS AND METHODS

7.3.1 Methodology

The societal cost of any vaccination program comprises three main components: first, the cost of acquiring the vaccine from the manufacturer; secondly, the cost of delivering and administering the vaccine to the target population, and thirdly, the time and pecuniary costs incurred by household members to travel to the vaccination sites and to wait to receive the vaccine (Cook, Jeuland, Whittington, Poulos, Clemens, Sur, Anh, Agtini, et al. 2008). In this study, all resource items used for vaccine delivery activities were captured using an ingredients approach, which means listing all types of input by activity and quantity, as well as the cost of each input (Drummond et al. 2005). All fixed and variable costs were captured through a comprehensive list of activities during the time of vaccination. Fixed costs included those necessary to set up and run

the vaccination campaign no matter how many people were vaccinated. Variable costs varied with the number of people being vaccinated.

The major activities related to the ICVB were vaccinating a large population, obtaining the vaccine from abroad, cold chain and waste management, training, and social mobilization. In reality, many items (cold box, vaccine carrier, etc.) used for vaccination were supplied to the ICVB program at no cost by the Government of Bangladesh. Although actual expenditure for these items was zero, the shadow prices for each item were obtained and included in our analysis. Capital items such as all types of vaccine cold box, vaccine carrier, and dial thermometer were annualized for their respective functional lifetime and the inflation-adjusted discounting rate was applied for calculating the costs of such items. In this case, we applied a 3% discounting rate (Hoang et al. 2005). This rate was then adjusted according to the average inflation rate, which was 7.96% for the period 2008-2011 as reported by the Bangladesh Central Bank (Bangladesh Bank 2014). Using this discounting rate, the cost per year of every capital item over its estimated lifetime was calculated.

Shared cost items (cold chain storage, refrigerator) were apportioned according to the proportion of time-usage of the relevant item or activity. The vehicles (pick-ups, trucks) were rented for the vaccination periods. The rental price of the vehicles was used in the analysis. Some senior level management staff of various projects were also engaged during the vaccination campaign. We estimate their time involvement in the project (as a percentage of full-time work) during the vaccination campaign and adjusted it for final calculation. For calculating the time-cost of end-users (vaccine recipients), we considered age-specific wages (Sarker et al. 2013; Poulos et al. 2012). For this purpose, three groups were created: all children between 1 and 9 years of age, adolescents between 10 and 17 years, and adults over 18 years of age among the fully-vaccinated cohort which constitutes 23%, 17% and 60% of the total population (Khan et al. 2013). As per a previous study (Cook, Jeuland, Whittington, Poulos, Clemens, Sur, Anh, Agtini, et al. 2008), we assumed that the cost of travelling and waiting to be vaccinated was zero for the first two age groups since they were accompanied by an adult and also vaccination sessions was conducted in schools and colleges. For adults, the travel and waiting times were captured and then valued according to the hourly wage of the people (Cook, Jeuland, Whittington, Poulos, Clemens, Sur, Anh, Agtini, et al. 2008). Finally, sensitivity analyses were conducted to determine the range of cost estimates for different scenarios and delivery activities. We examined the effect of changes in the price of vaccines and salary levels of the staff as the lower salary level may be appropriate for Bangladesh rather than the project staff of icddr,b. All costs were converted into US dollars

($) using the average official government exchange rate in 2011 of 72 Bangladeshi Taka (BDT) to US$ 1 (Bangladesh Bank 2014).

7.3.2 Vaccination campaign

Vaccination, defined as the administration of a vaccine, was conducted in the six wards of urban Mirpur, Dhaka. The six wards were divided into ninety clusters with two-thirds (60 clusters) being randomized to the vaccine group and one-third of the clusters to the control group. Data from disease surveillance over the previous few years in Mirpur showed that January to March were the months when disease transmission was lowest (Chowdhury et al. 2011). Accordingly, the cholera vaccination campaign was conducted from 17th February to 16th April 2011. As a feasibility study, the ICVB had chosen the fixed outreach site vaccine delivery strategy to deliver vaccine in the selected clusters. The strategy involved the administration of two doses of the cholera vaccine at least 14 days apart allowing for 12 clusters to be covered over a three-day period.

With regards to the fixed sites at which the vaccine was administered, there were three vaccination sites for each cluster. Sites were selected to maximize accessibility for the surrounding cluster population. Sites were established in open spaces (50% of total sites), schools and colleges (16%), the ground floor of car parks or garages (14%), clubs and cooperatives (10%) and government and non-government health facilities (10%). During the vaccination sessions, the vaccination team was stationed at the selected sites in each cluster and motivated the target population to visit the site for vaccination on a prefixed date and time. Using the process of volunteer involvement on national immunization days (NIDs), volunteers were recruited for the selected sites to assist in vaccine promotion and delivery with a lump sum amount. Local health facilities, pharmacies and community residents were also involved to encourage attendance.

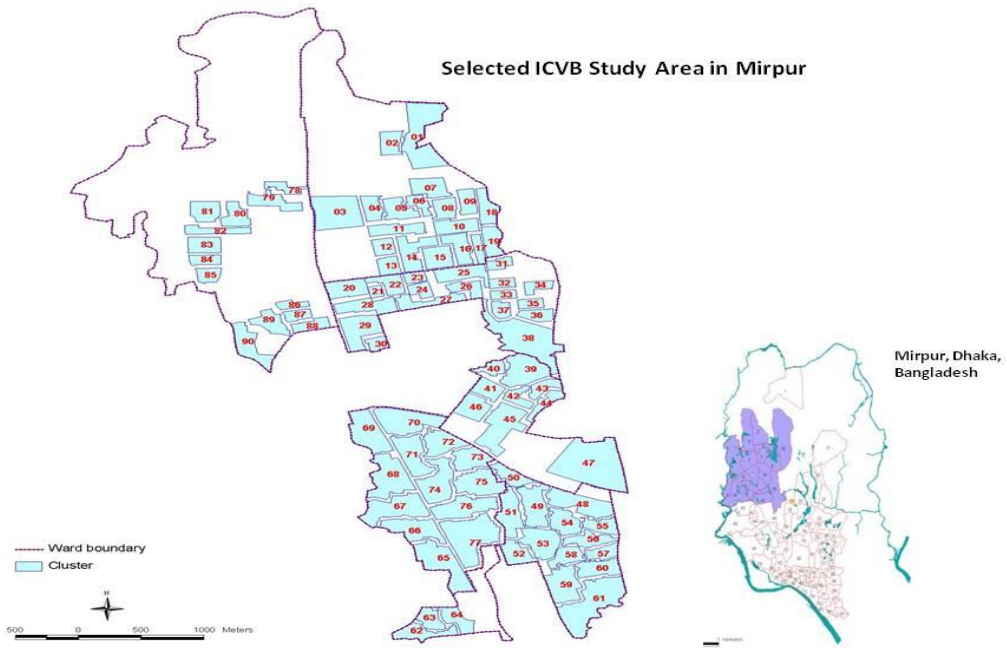

Figure 7-1 Study area of vaccination

During the pre-vaccination period, field workers and volunteers visited the targeted households in the selected clusters to inform them about the vaccination program, advise the time and place of vaccination, and receive the written consent of the participants. A cluster-wise, final master list was prepared and included in the micro plans. All eligible individuals were issued an ID card with a unique ID number. Each ID card was labeled with the name of the individual, date of birth, address, cluster information, computerized bar code and other relevant information. Cards were distributed together with information stickers about cholera and its prevention. At the time of vaccination, the individuals presented their vaccination card. At each site, a vaccination team comprised of two individuals trained in administering vaccines and 6 volunteers were deployed under supervision.

To cover the total targeted population in the clusters, each day, a total of 72 trained vaccinators, 216 volunteers along with 12 supervisors were engaged. Additionally, four reserve teams, with one individual trained in administering the vaccine and one volunteer in each, were available every day. In total, 220 volunteers and 76 trained vaccinators and 12 first line supervisors were employed over the period of the program. Under one supervisor, 7 cold chain packers organized and transported vaccine vials from the EPI center's cold store to the field area each day during the vaccination campaign. Vaccine and other logistics were also transported to the vaccination session daily. Two pickup vans carried cold boxes filled with the vaccine and delivered to all sites. One

reserve cold box with the vaccine was kept at the ICVB field office each day for emergency replenishment for the sites. During the sessions one vehicle was rented for transporting food for the workers at their respective sites. The vaccination sites were equipped with chairs, tables, benches, vaccine carrier, conditioned icepacks, forceps, water Jar, disposable glasses, pens, pencils, permanent markers, staplers, reporting forms, waste collecting boxes and bags. Surgical forceps were used to open the metal seals that encased the rubber stoppers of the outer glass vials containing the vaccine and permanent markers were used to write the date on the vaccination card. Other materials, such as pens, pencils, markers etc. were used to complete relevant information in the session reports. A water dispenser and disposable glasses were available for the vaccinated individuals to be able to drink water after taking the vaccine. After taking the vaccine, all individuals were asked to wait for half an hour at the vaccination site to address any immediate adverse events; physicians and other medical personnel were available at the field office for addressing any such events. Vaccine vials and aluminum foils were kept separate from other general waste in waste-collection bags. At the end of the session, the icepacks, along with unused vaccine vials were taken back to the central cold store by pickup truck. The pickup trucks collected the boxes and waste-collection bags from all vaccination sites and took those to the waste disposal site at icddr,b. During the vaccination campaign, a total of 268,759 vaccine vials were supplied to the field.

7.3.3 The Ethical Approval

The research protocol of this study was approved by the Institutional Review Board of icddr,b.

7.4 RESULTS

The results show the total cost of the ICVB program, separated into different fixed and variables costs. The total costs of providing vaccination were divided into six-line items, which are described below:

7.4.1 Vaccine

Shanchol™ was used for this trial. A total of 350,000 vaccines were imported for the ICVB study at a special price for research activities. The importation cost per vial was US$ 1.06, which included freight charges, insurance, international and domestic transport.

Table 7-1 Total cost of vaccination, separated into fixed-variable items

Cost Categories	Component	Amount (US$)	Percentage
Fixed cost	Stationery related (e.g., forceps and other)	360	
	Cold Chain related (e.g., cold box, vaccine carrier)	1,345	
	Designing Stationery (e.g. strategy guidelines)	1,528	
	Social Mobilization (e.g. advocacy meeting)	2,847	
	Training (e.g. volunteers, supervisors)	1,281	
Total fixed cost		7,361	1.49
Variable cost	Vaccine (vials)	284,880	
	Transport and communication	43,822	
	Salary (all types of staffs)	115,219	
	Waste Management	2,395	
	ICVB Card	5,704	
	Decoration (e.g. tent, table, chair)	6,054	
	Rent (e.g. field office)	500	
	Total travel /time cost of vaccines	3,671	
	Refreshment (e.g., food, water)	19,492	
	Stationery (e.g., pen, pencil, paper)	1,240	
	Printing (e.g., consent and other forms)	1,900	
Total Variable cost		484,887	98.51
Total Cost for Vaccination		492,238	

7.4.2 Personnel and training

During the vaccination campaign, a total of US$ 115,219 was paid as honoraria to all staff of the ICVB program including personnel responsible for administering vaccine, supervisors and volunteers (small allowance). The cold chain packers were paid US$ 1,720 during the time of vaccination. A total of US$ 1,281 was used for training-related activities for field staff and for training the trainers.

7.4.3 Social Mobilization and printing

Advocacy and social mobilization efforts are crucial for ensuring the successful introduction of a new vaccine. In the case of this program, the aim of these activities was to inform the general public and health care workers about the vaccine's introduction and likely consequences. In this regard, different types of advocacy meetings were arranged, such as meetings with local government representatives, NGOs and pediatric associations. The cost of social mobilization was US$ 2,846. In terms of designing the ICVB micro plan for the vaccination campaign, strategic guidelines and producing other manuals for managers, supervisors, those administering the vaccine, and volunteers, a total of US$ 1,528 were spent. In addition, US$ 1,250 was used to print

the participant consent forms and US$ 650 to print master lists, session reports and AEFI report forms.

7.4.4 Cold chain and waste management

After arriving in Bangladesh, the vials were unpacked and stored at the central EPI cold-storage unit. A trained management team sent the vaccines to the field. A total of US$ 1,345 was spent on cold–chain, management-related activities. For waste-management related activities, a total of US$ 2,395 was spent with US$ 1,113 being used for incineration and the remainder for buying biohazard bags, waste polythene bags and waste collecting boxes.

7.4.5 Transportation and communications

The total cost during the vaccine delivery campaign for regular conveyance to field staff, pick-up truck, rickshaw, van and fuel for transportation of the vaccines and vaccination supplies was US$ 43,821.

7.4.6 Time costs for enrollees

It took 7 minutes on an average for each participant in the study to take both doses of the vaccine, which included both travel and waiting time. The total time cost was set at US$ 3,671 for receiving both single and full doses during this vaccination campaign.

7.4.7 Supplies

The total cost of all supplies that were used to deliver the vaccines was US$ 1,240 (Table 7-1). A total of US$ 19,492 was spent on refreshments, which included water jar, disposable glasses, water and food. For decoration of the vaccination sites, a total of US$ 6,054 was used, with tents, tables and chairs being the major items. The total cost for ICVB cards was US$ 5,704.

7.4.8 Total cost during vaccine delivery

Total costs were separated into fixed costs and variable costs. In this ICVB program, total fixed costs were only US$ 7,361 while variable cost was amounted to US$ 484,877 (Table7-1). These figures give a variable cost proportion to total societal costs of 98.5%. When looking at overall total costs less the cost of the vaccine, the total was US$ 207,358 (Table 7-1) and it is approximately 42% of the total cost. In total, 268,759 vials were administered in the field. Two doses of vaccines were received by 123,661 individuals (fully vaccinated) and 18,178 individuals received only one dose of the vaccine (incomplete vaccinated). In total, 3,254 vials were wasted.

The cost of the two-dose vaccine delivery process (excluding the direct cost of the vaccine itself) was US$ 207,358 / 123,661 individuals or US$ 1.67 per fully-vaccinated individual. The cost of each vial was US$ 1.06 making the total cost of vials to be US$ 284,880, which means that for all participants, the cost per person-dose was US$ 1.83 ((US$ 207,358 + US$ 284,880) / 268,754 doses). The total societal cost per fully-vaccinated person was US$ 3.98 ((US$ 207,358 + US$284,780) / 123,661 individuals).

7.4.9 Sensitivity analysis

A sensitivity analysis was carried out to examine the cost implication of changes in some key variables such as vaccine price, staff time, staff salary and discount rate etc. (Richardson WS & Detsky AS 1995; Wallace et al. 2005). Two univariate sensitivity analyses were conducted to examine how changes in these values would affect the overall costs (Wallace et al. 2005). As in an earlier study (DoAez Domingoa et al. 1999), a 10% increment in the price of vaccines would increase the total vaccination costs by 5.8%. In this scenario, the total cost per fully vaccinated person would be US$ 4.20. When a 20% decrease in staff salary level was applied, there was a 4.6 percent reduction in total vaccination costs. The total cost per fully vaccinated individual in this latter case would be US$ 3.80.

7.5 DISCUSSION

Data used in this study was based on the practical application of a vaccination program, in contrast to many studies in this area, which employ data from a variety of sources or which are based on assumptions (Cookson et al. 1997). This project (e.g., ICVB) employed the most feasible and effective delivery strategies compatible with the EPI. In some previous studies, the cost of vaccines used in the EPI accounted for a small proportion of the total costs (Ebong & Levy 2011; Creese & Henderson 1980; Cutting 1980). In this ICVB program, we found that the vaccine cost was the main cost driver, accounting for 58% of total costs.

This suggests that for introducing a cholera vaccine into the EPI system, low-cost vaccines will be more acceptable and better, especially in resource-scarce countries, like Bangladesh. The current vaccine, Shanchol showed an overall protective efficacy of 66% against culture-confirmed cholera 3 years after administration (Sur et al. 2011). The second largest cost item was staff salary (24%). This could be attributed to the relatively high staff salary level at icddr,b compared to that of government employees and as such, government operated programs would likely see a lower staff salary cost than found in the ICVB program. The findings from this study, like those from

earlier studies, suggest that in certain settings (e.g. if personnel costs are low) and with certain vaccines, the cost-effectiveness of an immunization campaign may show greater sensitivity to the vaccine cost (Naficy et al. 1998). In an earlier study, conducted in a similar setting to that of the current ICVB program, the authors found that the total household cost of illness per episode was US$ 30.40, which is approximately 7 times more than the cost of vaccine delivery (Sarker et al. 2013). Considering cost items, in our analysis, we found that the total fixed cost was only 1.49% (Table 7-1) with the rest of the costs arising from variable items. Considering variable costs, the price of vials was highest like other immunization program (Ebong & Levy 2011). We observed that of the total costs, only 42% was used for vaccination-related activities. In the mass vaccination campaign in Zanzibar in which the Dukoral vaccine was used, the cost of vaccines alone accounted for 68% of the total costs with the remaining costs (32%) relating to vaccine-delivery related activities (Schaetti et al. 2012). In 1997, a large-scale effectiveness vaccination trial conducted in Vietnam with a locally-produced bivalent oral cholera vaccine, reported vaccine costs to be 75% of the total immunizing campaign costs (Naficy et al. 2001). Despite the observation that the fixed costs were not substantial in our analysis, the cost per fully immunized person would vary by sample size and coverage rate.

7.6 LIMITATIONS

There are several limitations of the study. We did not estimate how the vaccine coverage impact on cost of vaccination and even unable to estimate the cost of vaccination if the vaccination campaigns are conducted in other settings (e.g., rural, hard to reach are). The analysis was performed using the costs incurred during the ICVB program; and no further analysis relating to the impact of inflation or indeed reduction in vaccine costs in future years was carried out. Despite the limitations, the study emphasized on the societal cost of the cholera vaccination program including the cost of manufacturing, service providers. The results of this analysis are encouraging and demonstrate that the methodological approach for estimating costs can be applied even in rural Bangladesh as well as in the routine public health practice.

7.7 CONCLUSIONS

These results provide detailed cost information relating to vaccine activities and outlines actual resource needs and inputs that are required for introducing a new vaccine into immunization programs. The total cost of vaccination and cost per fully–vaccinated individual can be reduced substantially by introducing a low-priced vaccine, which could possibly be produced in a low-income country setting like Bangladesh.

Acknowledgement: icddr,b acknowledges with gratitude the commitment of the Bill and Melinda Gates Foundation to its research efforts. icddr,b is also thankful to the Governments of Australia, Bangladesh, Canada, Sweden and the UK for providing core/unrestricted support. We would like to thank the government of Bangladesh, International Vaccine Institute (IVI), Health Economics and Financing Research Group of icddr,b and the team member of ICVB for their continuous support during this research.

8 DEMAND FOR ORAL CHOLERA VACCINES IN URBAN BANGLADESH

Study - **V**

Submission: ***Value in Health***

Publisher: **Elsevier Publication**

Title of the paper: Willingness to pay for oral cholera vaccines in urban Bangladesh

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Abstract

Introduction: Cholera is a highly infectious disease and remains a serious public health burden in Bangladesh. The objective of the study is to measure the private demand for oral cholera vaccines (OCV) in Bangladesh and to investigate the key determinants of households' willingness to pay (WTP) for oral cholera vaccine. Findings from this study will be useful for the policy-makers to make decision on investing in future oral cholera vaccination programs in Bangladesh.

Methods: A contingent valuation method was undertaken in urban Bangladesh during December 2015 to January 2016. All respondents (N= 1051) received a description of a cholera oral vaccine (OCV) Shanchol™ which has around 60% efficacy for 2-5 years and is World Health Organization (WHO)prequalified and available in the WHO stockpile. Interviews were conducted with either the head of households or his/her spouse or a major economic contributor of the households. Respondents were asked about how much at maximum they were willing to pay for OCV for their own and their household members' protection. Results are presented as the mean and median of the reported maximum WTP of the respondents with standard deviations and 95% confidence interval. Natural log-linear regression model was employed to examine the factors influencing participants' WTP for OCV.

Results: 99% of the respondents expressed WTP for OCV with a maximum mean and median WTP per vaccination (2 doses) of US$ 2.23 and US$ 1.92 respectively. On the household level with an average number of 4.62 members, the estimated mean willingness to pay was US$10 (median: US$ 7.69) which represents the perceived demand for OCV of a household to vaccinate against cholera.

Conclusions: The demand of vaccination further indicates that there is a potential scope for recovering a certain portion of the expenditure of immunization program by introducing direct user fees for future cholera vaccination in Bangladesh. A combination of revenue from private market and pooled fund (e.g., taxes) could be considered as a sustainable way of financing oral cholera vaccine in Bangladesh to secure protection against cholera.

Keywords: cholera, contingent valuation method, Shanchol, vaccine demand, willingness to pay

8.1 INTRODUCTION

Cholera remains a serious public health burden globally and especially in regions where poverty and poor sanitation are prevalent (Cai et al. 2017). Bangladesh has one of the largest burdens of endemic cholera, with an estimated 109,052 cases each year, and approximately 66 million people are at risk of cholera (Ali et al. 2015). There are over 3,000-5,000 deaths annually and high caseloads and frequent outbreaks in the country (IVI 2013; Ali et al. 2015). The endemicity of cholera in Bangladesh is demonstrated by the predictable yearly occurrence of the disease in the country's high-risk districts and the repetitive seasonal pattern of cholera outbreaks, in spring or autumn, or both (Alam et al. 2006). To address this problem, policy makers recognized that an effective vaccine and vaccination strategy are essential for Bangladesh (IVI 2013). The World Health Organization (WHO) recommended oral cholera vaccine (OCV) for controlling cholera outbreaks in endemic regions of the world. In 2011 cholera was declared as a global priority (WHA64.15) with a specific role for introducing OCV (WHO 2004).

The prevention of disease burden and death through vaccination is one of the most cost-effective and public health achievements of the 20th century. However, introduction and sustainability of a new vaccine is still challenging in low resource countries as the costs of new vaccines are high relative to that of traditional vaccines and thus there is a need for prioritization (Levine et al. 2011; Ozawa et al. 2012). Therefore, the financing of new vaccines represents a major hurdle for immunization programs and its success depends on global commitment, internal financing mechanisms and technical and managerial capacity of those countries (Shen et al. 2016). Further, in order to scale up universal vaccination major financial commitments are often required from the public sector as well as from other related stakeholders (Bärnighausen et al. 2014). Additionally, private demand for oral cholera vaccine would provide important information about financing opportunity along with public funding.

For sustainability of immunization program, the host countries should be focused on their own financing from internal resources. Charging a private domestic contribution for this new vaccine would be an option (Shen et al. 2016). Willingness to pay is a proven tool for valuation of the private demand for future vaccines (Kim et al. 2014). The objective of the study is to capture the maximum willingness to pay for OCV and associated factors of WTP considering household's

perspectives. The demand for vaccination and its determinants is expected to be useful for the government and policy makers to adopt long term financing strategies and design future vaccination programs in a sustainable way by adding additional resources with a given public budget.

8.2 METHODS

To elicit households willingness to pay, Contingent Valuation Method (CVM) was used (Carson 2012). CVM is a standard and accepted technique for capturing maximum WTP and was originally developed in the area of valuing environmental benefits (NOAA 1993). However, in the vaccination area where the population is familiar with the potential benefit of vaccination (e.g. avoiding cases, economic costs, pains and suffering) CVM is particularly suitable (Kobelt 2013). In this analysis, we used open-ended bidding game technique, as it provide the unbiased estimates since no particular response is promoted (Drummond et al. 2005). However, there is a starting-point bias associated with the bidding game techniques (Kartman et al. 1996). In order to minimize this bias, the starting bid was taken from a pretest of the household survey and in consultation with local residents.

8.2.1 Study site and population

The study was conducted under the umbrella study of Gavi funded Vaccine Investment Strategy (VIS) learning agenda for oral cholera vaccine with the killed whole cell oral cholera vaccine, Shanchol™ (manufactured by Shantha Biotechnics, in Hyderabad, India) targeting children from 1 to 14 years in high risk urban areas (Kamrangirchar, Hazaribagh and part of Rayer bazar) of Bangladesh. This study primarily aimed to assess the preventive impact, demand, acceptability, uptake, feasibility, and cost-effectiveness of a two-dose regimen of OCV. Phase II clinical trials of the whole cell bivalent vaccine Shanchol™ in Vietnam and India and in Bangladesh have shown that this vaccine is safe and immunogenic in both adults and children (Anh et al. 2007; Mahalanabis et al. 2008; Saha et al. 2011). The latest WHO Fact sheet indicated that Shanchol™ gives approximately 65% protection against cholera for up to 5 years following vaccination in endemic areas (WHO 2016a). A cross sectional household survey was conducted from December 23, 2015 to January 16, 2016 before the cholera vaccination trial. A total of 1,051 households were randomly selected from the surveillance area and the respondents were the household head or the major economic contributor of the household.

8.2.2 Data collection tool

A paper-based survey instrument (questionnaire) was developed and implemented by the data collectors under supervision of the research team. The data collectors were pre-trained in CVM survey according to the guidelines recommended in Whittington's review of CV practices in developing countries (Whittington 2002) and the questionnaires were translated into the local language (Bangla) in order to maintain consistency. The pre-test survey of the instruments was conducted in the community before the original survey to refine the language and determine respondents' views of possible vaccine prices to offer.

8.2.3 The survey instruments

The survey instrument was approved by the Research Review Committee (RRC) and the Ethical Review Committee (ERC) of the Institutional Review Board of the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b). The instrument has seven sections relevant to the analysis (Suppl). The first section recorded the respondent's background information followed by the respondent's informed written consent and the relationship with the particular household. Section 2 gathered the demographic information of household members along with economic status (e.g., income, expenditure) of the households. Section 3 contained the questions regarding respondents' perceptions and knowledge about cholera. This section also discussed how cholera was contracted and about previous experience with cholera. The next section recorded understanding about vaccine and vaccination in general and about cholera vaccines in particular. Section 5 introduced the contingent valuation scenario, including the descriptions of the available Shanchol vaccines, its effectiveness and the duration of protection. Next some questions were administered in order to test respondents' understanding about the effectiveness of proposed vaccine (Suraratdecha et al. 2005; Canh et al. 2006). Section 6 contained the valuation questions that were used to estimate willingness to pay for oral cholera vaccine for individuals' and households protection. The seventh section recorded interviewers' observations on visible conditions of the home and opinions on the quality of the interview.

8.2.4 Data analysis

Descriptive statistics were employed to analyze and summarize the data using different variables. Data were presented as a mean and as median with a standard deviation in local currency, i.e., Bangladeshi Taka (BDT) and US dollars (US$) applying the exchange rate (US$1 = 78 BDT). Demand for OCV was constructed using the proportion of respondent stating WTP and the amount of WTP for the vaccine (Birhane et al. 2016; Whittington et al. 2002). Natural log-linear regression

model was used to examine factors influencing participants' WTP for OCV. The error normality assumption was tested graphically and heteroscedasticity was tested (Weisberg 2005). Power transformation was used to achieve the validity of the assumptions as the data violate both normality and heteroscedasticity assumptions. In order to obtain a suitable power transformation of the predicted variables Tukeys' ladder of power was used (Beyer H. Tukey 1981). The Variance Inflation Factor (VIF) was also used to check the multicollinearity among the predictors. Two econometric models were used in the analyses; model I was the respondent's WTP for oral cholera vaccine and model II for the households WTP of all household members (including respondent). All the statistical analyses were performed using Stata SE 13 version.

8.2.5 Ethics Statement

This study was approved by the Institutional Review Board of the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b). Informed written consent was taken from all interviewees, and confidentiality and anonymity were ensured.

8.3 RESULTS

8.3.1 Background Characteristics

Background statistics are summarized in Table 1. The average age of the sampled population is about 33 years, most of the respondents were female (80%) and married (93%) as in this setting it is very common that married females were mainly responsible for household decision making. The other relevant fact was that men and young single people were in search of jobs in the daytime while we conducted the survey. Most of the respondents completed primary and secondary education and approximately 24% had no formal schooling. Average household size was 4.62 persons and approximately 12% and 25 % of the households had under-five children and young children aged 5 to 14 years old respectively. The average monthly household income was BDT 16,780 (US$ 215.13). The average healthcare expenditure (last three months) was BDT 4,883 (US$ 62.60). Most of the households (59%) shared a rented house while only 17% of respondents had their own house. Most of the respondents (84%) indicated that the floor of their household was made of cement and bricks (11%). Only few of them (2%) reported lived in soil/mud-based floor.

Table 8-1 Background Characteristics

Subject	Variables	n (%)	mean ± sd (95% CI)
Respondent characteristics	**Sex of the respondent**		
	Male	203 (19.31)	(17.04 , 21.82)
	Female	848 (80.69)	(78.18 , 82.96)
	Age (years)		
	≤ 29	449 (42.72)	(39.76 , 45.74)
	30-39	339 (32.25)	(29.49 , 35.15)
	40-49	173 (16.46)	(14.34 , 18.83)
	50 and above	90 (8.56)	(7.01 , 10.42)
	Mean age (years)		32.98 ± 10.33 (32.35 , 33.60)
	Marital status		
	Married	980 (93.24)	(91.56 , 94.61)
	Others (unmarried, widow, divorce, separated)	71 (6.76)	(5.39 , 8.44)
	Educational status		
	No formal education	251 (23.88)	(21.40 , 26.56)
	Primary education	374 (35.59)	(32.74 , 38.53)
	Secondary education	352 (33.49)	(30.70 , 36.41)
	Higher secondary & above	74 (7.04)	(5.64 , 8.76)
Household characteristics	**Household size**		
	Less than 4	255 (24.26)	(21.76 , 26.95)
	4 to 5	571 (54.33)	(51.30 , 57.33)
	More than 5	225 (21.41)	(19.03 , 24.00)
	Average household size		4.62 ± 1.62 (4.52 , 4.71)
	Floor materials		
	Mud/Soil	14 (1.33)	(0.79 , 2.24)
	Cement	883 (84.02)	(81.67 , 86.11)
	Tiles	18 (1.71)	(1.08 , 2.70)
	Brick	117 (11.13)	(9.37 , 13.18)
	Others	19 (1.81)	(1.16 , 2.82)
	Types of home		
	Own house	177 (16.84)	(14.69 , 19.23)
	Rented house in slum	126 (11.99)	(10.16 , 14.10)
	Government Residence	12 (1.14)	(0.65 , 2.00)
	Individual separated house, well condition	49 (4.66)	(3.54 , 6.12)
	Rented flat/house (shared with others)	622 (59.18)	(56.18 , 62.12)
	Individual separated house, not well condition	40 (3.81)	(2.80 , 5.15)
	Others	25 (2.38)	(1.61 , 3.50)
	Any healthcare expenditure in last 3 months		
	Yes	932 (88.68)	(86.61 , 90.46)
	No	119 (11.32)	(9.54 , 13.39)
	Average healthcare expenditure (last 3 months)		4,883 ± 10,950 (4,220 , 5,545)
	Average household income		16,780 ± 15,004 (15,872 , 17,688)
	Income quintile		
	Poorest quintile (≤9,000)	245 (23.31)	6,741 ± 1,879 (6,504 , 6,977)
	2nd quintile (9,001-12,000)	209 (19.89)	10,843 ± 949 (10,713 , 10,972)
	3rd quintile (12,001-15,000)	206 (19.60)	14,404 ± 830 (14,290 , 14,518)
	4th quintile (15,001-20,000)	183 (17.41)	18,458 ± 1,577 (18,228 , 18,688)
	Upper quintile (> 20,000)	208 (19.79)	35,450 ± 24,916 (32,044 , 38,856)

8.3.2 Perception and attitude towards cholera and vaccines

Approximately 75% of the respondents mentioned that they heard about cholera infection and about 80% of the respondents believed that cholera was very serious for children <5 years of old than other. However, half of the respondents (52%) were not sure about the risk of cholera in their community. About 29% of the respondents reported that at least one of the household members had suffered from cholera previously and 1% reported a household member died due to cholera infection. Another 26 % of the respondents knew someone other than a household member who had suffered from cholera and 12% of the total respondents knew someone outside their household who died due to cholera disease. About 90% of the total respondents had taken any type of vaccines in earlier.

Considering the effectiveness of the cholera vaccine, approximately 89% of the respondents believed that cholera could be prevented by the cholera vaccine while 14% believed that the cholera vaccine could protect them from risk of death. Of all respondents, 4% of them believed that the cholera vaccine might reduce their treatment cost and avert sick days (3%) due to cholera infection. However, 6% were still not sure about the effectiveness of cholera vaccine. After being given the information and explanation of the OCV effectiveness we tested the understanding of the respondents in a structured way (Canh et al. 2006). All of the respondents understood the descriptions of the vaccine effectiveness. Approximately 92% of the respondents gave the answer correctly to the four questions designed to test the understanding of vaccine effectiveness (suppl_2). The data collectors explained the vaccine effectiveness description again and retested to 8% of the respondents who did not answer correctly. Finally, in total 97% respondents understood the effectiveness concepts after this second attempt.

8.3.3 Willingness to pay for cholera vaccine

WTP values are shown in table 8-2. The mean and median WTP for OCV per vaccination (2 doses) was estimated to BDT 174 (US$ 2.23) and BDT 150 (US$ 1.92) respectively for protection of the respondent against cholera infection. On the household level on an average number of 4.62 members, the estimated WTP was US $10 (mean) and US$ 7.69 (median) which represents the perceived private economic benefits to a household of vaccination against cholera. Among the total respondents (N=1,051), approximately 99.4% were willing to pay for the vaccines for their own protection at some price, while 99.8% reported they would purchase the vaccine for their

household members. Financial unaffordability was the main reason for those who did not agree to pay for oral cholera vaccine. The estimated mean WTP per person for under-five children was slightly higher than other age groups (table 8-2). Males had a higher WTP than females (BDT 176.98 or US$ 2.27 vs BDT 170.87 or US$ 2.19). A general socioeconomic gradient was observed in WTP, meaning that the richer socioeconomic groups were willing to pay more, with a slight exception in the 4th quintile.

Table 8-2 Background Characteristics

Willingness to pay (WTP) (n=4,713)	**Mean ± sd**	**n**	**Median**	**Interquartile range IQR**	**Range (max-min)**	**5th percentile**	**95th percentile**	**P-value**
Age groups								
<5	182.76 ± 133.89	579	150	100	1,980	50	400	
5 to 14	168.86 ± 129.53	1,200	150	100	1,990	50	400	
15 to 45	176.13 ± 135.91	2,455	150	100	2,490	50	400	0.125
46 to 64	164.62 ± 115.96	370	125	100	690	50	400	
65 and above	166.61 ± 111.94	109	150	100	565	50	400	
Gender								
Male	176.98 ± 139.33	2,392	150	120	2,490	50	400	0.056
Female	170.87 ± 124.20	2,321	150	100	1,490	50	400	
Income quintile								
Poorest quintile (≤ 9,000)	152.19 ± 92.27	949	130	100	490	40	300	
2nd quintile (9.001-12,000)	160.43 ± 158.02	1,016	128	100	2,480	50	300	
3rd quintile (12,001-15,000)	173.45 ± 111.95	867	150	120	975	50	350	0.000
4th quintile (15,001-20,000)	171.60 ± 121.85	965	150	100	690	50	500	
Upper quintile (20,000+)	214.55 ± 153.36	916	200	200	1,980	50	500	
Household size								
Less than 4	199.44 ± 181.12	759	150	150	2,490	50	400	
4 to 5	169.86 ± 121.45	2,455	150	100	1,990	50	400	0.000
More than 5	167.81 ± 117.27	1,499	125	100	680	50	400	
Household WTP, BDT	781.62 ± 631.99	1,049	600	550	6,470	190	2,000	
Per capita WTP per OCV, BDT	173.97 ± 132.12	4,713	150	100	2490	50	400	

8.3.4 Household demand for OCV

Figure 8-1 shows age-specific demand curves for OCV while 8-2 represents the household demand curve that summarize respondents' responses against WTP questions. In figure 1A, we found that the demand for cholera vaccine is slightly higher for under-five children than people at age 15 years and above. The demand curve shows the share of households at different levels of WTP for

people at different ages. The hypothetical demand for cholera vaccine falls gradually as WTP increases. Considering the variable demand for OCV across age groups, at a current market price of OCV (BDT 156 or US$ 2.00), the vaccination coverage can be increased from 60% to 68% if we target to vaccine more under-five children instead of adults (15 years and above).

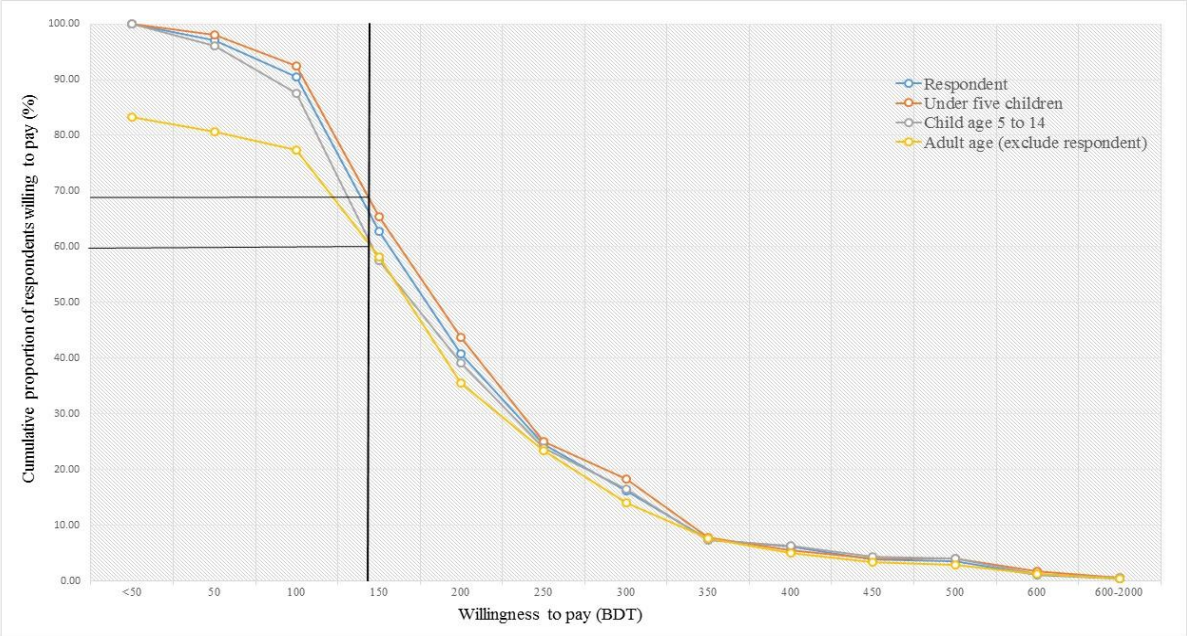

Figure 8-1 Relationship between cumulative proportions of respondents willing to pay for OCV in Dhaka, Bangladesh

Figure 8-2 shows a negative relationship between WTP and the proportion of households willing to pay those specific amounts meaning that higher proportion of households are willing to pay at lower level of payments. At the current market price of US$ 9.24 for vaccinating an entire household, 48% households would prefer to vaccinate for households protection.

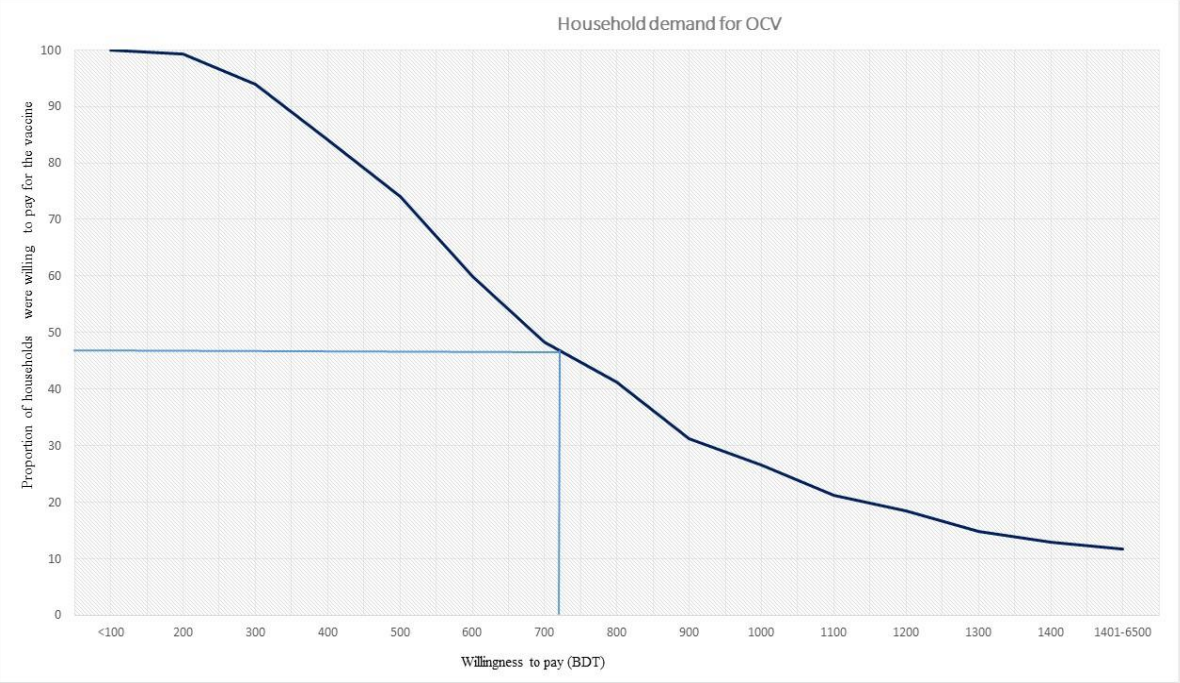

Figure 8-2 Households Inverse Demand Curve for WTP for OCV in Dhaka, Bangladesh

8.3.5 Factors associated with the willingness to pay:

In table 8-3, our natural log-linear regression model revealed that a number of factors were significantly associated with the respondent's willingness to pay for protecting him/herself and all household members from cholera infection. The factors are sex of the respondents, his/her occupation, knowledge about cholera and oral cholera vaccine, household income, size of the households and age composition of household members. Considering the sex of the respondents, males had significantly higher WTP than females and were willing to pay 15.20% more for himself and approximately 18.72 % more for their households (p-value<0.05). The employed respondents reported lower amount of WTP than unemployed and housewives. Those who had exposed cholera infections in past, intended to pay more for him/herself and for the households' protection (9.4% and 10.5% respectively). WTP was higher in the households where the number of under-five children, children aged 5 to 14 years and number of adult household members in the household increase. One under-five child will lead to 14.03% more WTP for household while 7.25% and 8.33% more WTP for children aged 5-14 years and adults (>14 years) respectively (p-value<0.001). The size of the households is one of the significant negative factors on respondents' WTP and those who belong to larger households were negatively associated with WTP. Household with 4 to 5 members had 11.63% less WTP for respondent compared with smaller household (<4 members). But such relationship was not observed regarding WTP for households.

Our model showed that household income is significantly positive associated with the both respondent's and household's WTP. Respondents from higher income households are willing to pay more compared to respondents from lower income households for their own protection as well as for their household protection. For own protection, respondents from the 3rd, 4th and 5th quintiles are willing to pay 17.53% (p-value<0.05), 15.18% (p-value<0.05), and 36.33% (p-value<0.001) more compared to respondents from lower income households (poorest quintile). Considering the household protection against future cholera cases, it was observed that the 3rd, 4th, and 5th quintile's WTP were 20.14% (p-value<0.001), 17.53% (p-value<0.05), and 38.23% (p-value<0.001) more than the poorest quintile.

Table 8-3 Factors influencing on Willingness-to-pay (WTP as a natural log form) for oral cholera vaccine

Parameters	**Descriptions**	**Co-efficient (Standard Error)**	
		Respondent WTP	**Household WTP (including respondent)**
Age of respondent (years)			
30-39	Ref: Less than 29 years	-0.01 (0.05)	0.03 (0.05)
40-49		-0.04 (0.07)	0.00 (0.07)
50 and above		-0.11 (0.09)	-0.08 (0.09)
Gender of respondent			
Male	Ref: Female	0.15** (0.07)	0.18** (0.07)
Respondent educational status			
No formal education		-0.04 (0.09)	-0.05 (0.09)
Primary education	Ref: Higher secondary & above	0.01 (0.08)	0.05 (0.09)
Secondary education		0.05 (0.08)	0.09 (0.08)
Respondent Occupation			
Employed	Ref: Housewife & Unemployed	-0.12** (0.06)	-0.12** (0.06)
Received any vaccine	=1, if respondent received any vaccine	0.01 (0.07)	-0.02 (0.07)
Someone in household has had cholera	=1, if someone in household has had cholera	0.09** (0.04)	0.10** (0.05)
Someone in household had died having cholera	=1, if someone in household died having cholera	0.29 (0.20)	0.26 (0.20)
Know someone has had cholera (outside HH)	=1, if respondent know someone who has had cholera	0.14*** (0.05)	0.16*** (0.05)
Heard about cholera	=1, if respondent heard about cholera	0.05 (0.05)	0.03 (0.05)
Cholera is common in community	=1, if respondent perceived cholera is common in community	0.01 (0.07)	-0.02 (0.07)
Child (<5 years) is more vulnerable for cholera	=1, if respondent perceived U5 is more vulnerable for cholera	-0.04 (0.07)	-0.05 (0.07)
Healthcare Utilization	=1, if utilize any healthcare in last three months	0.04 (0.06)	0.05 (0.06)
Number of U5 children	Continuous	0.03 (0.04)	0.14*** (0.04)
Number of child age 5 to 14	Continuous	-0.03 (0.03)	0.07** (0.03)
Number of adult members (>14 years)	Continuous	-0.04 (0.03)	0.08*** (0.03)

Household size			
4 to 5	Ref: Less than 4 members	-0.11* (0.06)	0.08 (0.06)
More than 5		-0.14 (0.11)	0.15 (0.11)
Income quintile (BDT)			
2nd quintile	Ref: Poorest quintile	0.05 (0.06)	0.05 (0.06)
3rd quintile		0.17**(0.06)	0.20*** (0.06)
4th quintile		0.15** (0.07)	0.17** (0.07)
5th quintile		0.36*** (0.07)	0.38*** (0.07)
Intercept	Constant	5.30*** (0.15)	6.07*** (0.15)
N		1,045	1,049
Adjusted R-square		0.054	0.164
Mean VIF		2.23	2.23
F-value, (Prob > F)		3.38***	9.20***

***significant at 1% risk level, **significant at 5% risk level, *significant at 10% risk level
*Percentage change of WTP explained by (eβ-1)*100

8.4 DISCUSSION

The study was conducted in order to assess the average WTP for future cholera vaccine and its associated determinants among the respondents and their households in an urban endemic area of Bangladesh. Our study found that the per capita WTP was approximately BDT 174 (US$ 2.23) for future OCV against cholera disease. Each household is ready to invest approximately BDT 782 (US$ 10.02) for purchasing the cholera vaccine to protect their households for future cholera cases.

The study demonstrated that most of the respondents (98%) would purchase OCV for their own and household protection. WTP was found to be higher (98%) in urban areas in comparison with rural areas of Bangladesh as found in another study, where 75% of the responded of the rural residents were interested in OCV (Islam et al. 2008). Such difference between urban and rural areas could be explained by the disparity of financial affordability between urban and rural people where the former was better-off. However, since Bangladesh has recently been upgraded as a lower- middle income country and poverty has declined substantially, we may expect more people, also in rural areas, to be interested to purchase OCV than in the past (GoB 2015). Our estimation supported that the households with members of age under five years were willing to pay more than any other age groups. Such findings were also observed in the rural context in Bangladesh (Islam et al. 2008). This makes sense in the endemic cholera prone area like Bangladesh where young children are the more vulnerable due to cholera (IVI 2013). From the experience of the earlier study conducted in this setting, it was observed that when younger children are infected with cholera, the household invested more money for seeking treatment than for adult patients (Sarker et al. 2013).

Our log-linear regression model (table 3) observed that the male respondents had significantly higher WTP than the females, which was in the same line of findings of several previous studies (Islam et al. 2008; Sauerborn et al. 2005). It was further observed that the respondents with previous experience in cholera expressed higher WTP both for self-protection and protection of the household members. This finding was supported by earlier studies which indicated that the household risk aversion is a crucial influencing factor for demand for future OCV (Lucas et al. 2007; Islam et al. 2008). However, on the contrary, there were evidence that prior awareness of disease or having a personal history of a disease did not always lead to higher willingness to pay (Dickinson et al. 2016; Harapan et al. 2017; Palanca-Tan 2008). Household income significantly positively affected both respondent's and household's WTP which was consistent with the theoretical concept of positive income elasticity that wealthier families purchase more cholera vaccines than low-income households (Lucas et al. 2007; Kim et al. 2008; Islam et al. 2008). This was crucial for Bangladesh where 63.3% of total healthcare expenditures were borne by out-of-pocket payments in absence of social health insurance and the poor people were often unable to afford adequate healthcare (MOHFW 2015a).

A free of cost supply of OCV to entire population of the country would bring a perceived economic benefit of 781.6 BDT corresponding to the average maximum WTP of the households. In an earlier study, we found that full vaccination of an individual cost BDT 165.36 (US$ 2.12) which included freight charge, transportation and imported price of vials. The individual WTP for OCV (BDT 174 or US$ 2.23), observed in this current study, exceeded the costs of vaccination, which indicated the economic viability of OCV in a market condition. It could be argued that the delivery costs of OCV would increase the vaccination costs (Sarker et al. 2015). Such additional costs could be covered by an incremental cost to the EPI program of Bangladesh, funded preferably by pooled fund (e.g. taxes).

Recently a well-known pharmaceutical company indicated that the production of the cholera vaccine might be possible at a cost below BDT 78 (US$ 1) in Bangladesh (Incepta 2017). Considering such a statement, we calculated the total costs of vaccinating a household to be BDT 720 (US$ 9.23) at which price 48% of the households of Bangladesh would be able to purchase OCV from private market. For the full coverage of OCV in the country, pooled fund (taxes) could be additionally used for subsidizing the households with lower maximum WTP. It was also observed that, even at higher prices, there was demand for OCV among wealthier. Poorer people in the same community, if do not get vaccinated, would be benefited from vaccination of wealthier populations because of herd immunity (Islam et al. 2008). It is thus necessary to introduce OCV

in private market by making those available in pharmacies or health clinics so that a share of population might get benefited from direct while some other from indirect protection from cholera (Jeuland, Lucas, et al. 2009). Based on the economic condition of the country and demand for OCV as per our current study, we recommend that a sustainable financing method could be developed where pooled fund (like, tax) and revenue from sold vaccines in private market would be used jointly.

8.5 LIMITATIONS

There are some limitations of the current study that need to be considered in interpreting results. Applying contingent valuation techniques, a possible source of bias might arise from the fact that respondents are not purchasing the vaccine in actuality (Klose 1999). Furthermore, data extraction with a paper-based questionnaire may by itself carry source risk of bias of the study. Another shortcoming arises due to resource constraints as we were not able to run multiple survey versions with different starting bids and time to think approach. However, previous study suggested that using standard practice for stated preference survey (no time to think approached) might overstate willingness to pay for the future vaccines (Cook et al. 2007). The WTP is based on the recently available Shanchol vaccine that gives protection for at least 2 years with 65% effectiveness although a recent study found the protective efficacy and duration of Shanchol is higher. Further, we did not consider the concept of herd immunity in contingent valuation scenario, so our results underestimate of true value of the particular vaccine. We did not analyze the demand for OCV using the travel cost approach where earlier studies indicated that the private demand for OCV is decreased as the households cost (i.e. transportation and time cost) due to receiving the vaccine increases (Jeuland et al. 2010). All of the above represent possible avenues for further research on this topic.

8.6 CONCLUSIONS

The study provided evidence on the perceived monetary value of oral cholera vaccine. The result showed that the per capita WTP for cholera vaccine was approximately BDT 174 (US$ 2.23); therefore, individuals should not wait for the public vaccination campaign instead can protect themselves if the vaccine is available in private market. Our study revealed that the households place more value on vaccinating under five children than older children and adults. Thus, there is a potential scope for recovering a certain portion of the financing cost of immunization program by introducing direct user fees against future cholera vaccination in Bangladesh.

9 ECONOMICS OF CHOLERA VACCINATION IN URBAN BANGLADESH

Study – **VI**

Submission (will be submitted): ***Vaccine***

Publisher: **Elsevier Publication**

Volume:

Title of the paper: Economic Burden of cholera infection and cost- effectiveness of oral cholera vaccination in urban Bangladesh

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Abstract

Introduction: Cholera is an acute diarrheal infection that remains a major global public health threat which kills within hours if the patients are untreated. Bangladesh has one of the world's highest burdens of endemic cholera, and frequent outbreaks occur both in epidemic forms. Furthermore, there appears to be the repetitive seasonal pattern of cholera outbreaks, either in spring or autumn, or both. It is important to evaluate whether the new vaccine alleviates the burden in relation to its value for money. This study aims to estimate the economic burden of cholera diseases and to measure the cost-effectiveness of using oral cholera vaccines (OCVs) in Bangladesh from a broader societal perspective.

Methods: This study used data from a cluster randomized control trial conducted in a high-risk area (Mirpur) in urban Bangladesh. The primary measurements of cost-effectiveness in the current study are: the incremental cost per disability-adjusted life year (DALY) averted, incremental cost per case averted and incremental cost per death averted. Cost of illness due to cholera infections were captured from a cross-sectional survey.

Results: The average societal cost of illness per episode was US$ 95.76, whereas the cost per fully immunized person was US$ 3.96. The study observed that the overall the incremental cost per DALY averted was US $ 3,467. The results indicated that children might be prioritized for OCV, as the cost per DALYs averted was only US$ 768, which was very cost-effective investment. Our results showed that only vaccinating adults (above 15) was not cost-effective alone. However, vaccinating the whole population in a high-risk cholera endemic area appeared as a cost-effective strategy, even during a shorter time horizon.

Conclusion: Our cost-effectiveness result was based on the practical application of an oral vaccination program in a high-risk urban area of Bangladesh. This will play a major role for policymakers in formulating rational cholera vaccination programs, especially for high-risk urban populations.

9.1 INTRODUCTION

Cholera is an acute diarrheal infection that remains a major global health problem and can rapidly to death if the patient untreated (WHO 2018). An estimated 1.4 billion of the world's population is at risk for cholera, with India and Bangladesh together constituting the greatest share of this population (Ali et al. 2012). The number of cholera cases increasing in globally, and approximately 1.3 to 4.0 million cases and 21 000 to 143 000 deaths annually due to cholera infections (Ali et al. 2015). However, the numbers of the reported cases are extensively lower than the actual burden. For instances, in 2015, WHO published that there were only 172,454 cases and 1,304 death from 42 countries (WHO 2016c). Furthermore, the World Health Organization (WHO) acknowledged that only 5%–10% of cholera cases are actually reported (WHO 2015a; Ali et al. 2012).

The Ganges River Delta and Bay of Bengal, including Bangladesh, are often considered the birthplace of cholera (Siddique & Richard 2014). However, there is no comprehensive information about the cholera-related mortality and morbidity in Bangladesh. In the absence of accurate numbers, experts suggest that approximately 66 million people are at risk of cholera and approximately 109,052 cholera cases and 3,272 deaths occur annually in Bangladesh (Ali et al. 2015). Cholera outbreaks in Bangladesh occur both in endemic and in epidemic forms, and there are repetitive seasonal pattern of cholera outbreaks, either in spring or autumn, or both (Alam et al. 2006). The transmission of cholera is often closely linked to inadequate sanitation facilities, contaminated water and poor hygiene practices (George et al. 2016). Peri-urban slums and refugee camps, where the basic infrastructures are limited and disrupted, are high-risk areas for cholera in Bangladesh (WHO 2017f). A number of literature indicated that that, various risk factors are associated with cholera infections such as floods (Schwartz et al. 2006), socio-economic status of the people (Rahman et al. 2009), living in urban area (Colombara et al. 2014b), density of population, low education level, and contaminated surface water (Ali et al. 2002; D. K. Biswas et al. 2014; You et al. 2013).

Cholera can be treated easily with an oral rehydration solution (ORS) and, in some cases, with appropriate antibiotics. However, multifaceted approaches (i.e., combination of surveillance, water, sanitation and hygiene and vaccination) are necessary for prevention of cholera infections. Recently, the WHO Position Paper on Vaccines against Cholera recommended that oral cholera vaccine (OCV) should be used for the prevention and control of cholera infections in endemic region, emergency contexts, and during cholera outbreaks (WHO 2017f; WHO 2016c; WHO

2018). There are currently three WHO pre-qualified oral cholera vaccines (Dukoral®, Shanchol™, and Euvichol®) available in globally (WHO 2016c; WHO 2018). Although vaccination through the Expanded Program on Immunization (EPI) is one of the most cost-effective health investments (WHO 2009d), various information often required regarding the decisions of new vaccines. The most common information are the health and economic burden of vaccine preventable disease, cost of vaccines, and the available resources (e.g., infrastructure, manpower) which would be justified in the decision of introducing a new vaccine (WHO 2007a; Parashar et al. 2006; WHO 2002). This is particularly crucial for resource-poor countries like Bangladesh, where resources are allocated on a priority basis and the Government and other technical personnel are convinced when they are assured about the insightful information of health burden and economic evidence of vaccine preventable diseases (Uddin et al. 2013).

Along with the burden of disease, cost-effectiveness analysis is crucial for measuring and allocating the scarce public and external resources in an most optimal manner and is often recognized as a decision making tool for vaccine introduction (Richard et al. 1999; Jamison et al. 2006). The health policy makers often use CEA for priority settings to ensure the greatest health benefits with their available budget (Bertram et al. 2016). Cost-effectiveness methods are very well established, easy to understand and have low cost implementation (Morton & Lauer 2017). Cost-effectiveness is a type of economic evaluation which is also important for any new vaccine introduction and often recommended by policymakers, international donors, and the authority of national immunisation programs (Klein 2013; GAVI 2016; Gessner et al. 2010; Uddin et al. 2013). Although the epidemiological burden of cholera is frequently discussed in published literature, the economic evidence of cholera vaccination strategies is still limited in Bangladesh context. This study aims to estimate economic burden of cholera diseases and to measure the cost-effectiveness of mass vaccination program using OCVs from the societal perspective.

9.2 METHODS

9.2.1 Study setting

A cluster randomized control trial study was conducted in a high-risk area (Mirpur) of urban Bangladesh. The trial was registered with ClinicalTrials.gov, number NCT01339845. The prime objective was to assess the overall protection against cholera diseases using “Shanchol” oral cholera vaccine (Shanta Biotechnic- Sanofi) for high-risk people of ages one year and above (except pregnant woman). The selected participants received two doses of the bivalent whole-cell

inactive vaccine within 14 days of each other. The detailed methods and randomization were reported elsewhere (Khan et al. 2013; Qadri et al. 2015). This is a follow-up study that is under the trial of "Introduction of Cholera vaccine in Bangladesh (ICVB)."

9.2.2 Cost Data Collection

9.2.2.1 Private cost of illness

An incidence-based cost of illness approach was adopted to estimate the utilisation of all resources during a cholera episode and was valued from the household's perspective. A cross-sectional survey was conducted to capture the private cost of illness. Respondents were the household heads or the economic contributors of the family, and the interview was conducted within 15 days after received the treatment services. All cholera confirmed cases that were confined in the surveillance hospitals during the period of mid-June 2011 to end of December 2012 were included in the study. A total of 1,164 cholera confirmed patients or their caregivers were interviewed and data on them was analysed. Household costs of illness included all out-of-pocket payments (direct cost) made by the households for the management of the disease and the opportunity costs (indirect cost) for time used by the patients or caregivers during the episode of illness (Sarker et al. 2013). Self-reported wages were used for estimating the income loss due to each episode. The human capital approach was applied for the measuring of the productivity costs, which reflected the value of all unpaid time devoted to the caregiving of themselves, as well as family members and friends (Rice 1966). The detailed of costing methods and estimations were described elsewhere (Sarker et al. 2018).

9.2.2.2 Provider cost of illness

The data used in this analysis were extracted from a cross-sectional survey conducted in the icddr,b Dhaka hospital located in urban Dhaka, Bangladesh. Icddr,b is non-profit tertiary level hospital, where all treatment costs, such as diagnosis, medicine, food, and lodging are provided free of charge to the patients (Sarker et al. 2013). A full economic year was considered for the estimation of the treatment cost of cholera patients that was borne by the hospital. For this purposes, a micro-costing bottom-up approach was used (Swindle et al. 1999; Wordsworth et al. 2005; Drummond et al. 2005). Resources used by the hospital and service outputs were collected from different sources of the hospitals. Data on common institutional costs were collected from finance and accounts, administration, and other relevant departments of the hospitals. Official documents were reviewed for capturing any information related to cost of the hospital.

9.2.2.3 Vaccination cost

The vaccination cost included the cost per vial and the cost per vaccination-related activities. For this aspect, all fixed and variable costs were identified through a comprehensive list of activities during the time of vaccination and valued accordingly (Drummond et al. 2005). The detailed methodology and components are described elsewhere (Sarker et al. 2015).

9.2.3 Cost-effectiveness analysis and Input parameters

The economic viability of the proposed cholera vaccination program, the societal perspective was considered, i.e., all possible cost and consequences were captured. This study employed the standards cost-effectiveness methods used by the Disease Control Priorities Project (or DCP), and WHO's CHOICE project (Tan-Torres et al. 2003; Jamison et al. 2006). The disability adjusted life year (DALY) was captured based on the standards methodology proposed by the global GBD study and compared with the WHO-GDP threshold level (WHO 2001). The DALY is a time-based measure which combines years of life lost (YLL) due to premature mortality and the years of healthy life lost to living in a state of less than perfect health (years lost to disability or YLD), in a country-specific context (McKenna et al. 2005). Therefore, DALY is the summation of YLL+YLD, and 1 DALY can be considered an equivalent to one lost year of healthy life. Recently, most of the economic evaluation of cholera vaccination programs are used WHO-GDP threshold level (Jeuland, Cook, et al. 2009; Schaetti et al. 2012; Smalley et al. 2015; Troeger et al. 2014), although the cost per case and death averted are also documented in the study (Sack 2003). The primary outcomes are: the incremental cost per DALY averted, incremental cost per case averted and incremental cost per death averted. The analyses were performed using a was done by using a spreadsheet analysis tool called VICE (Vaccine Introduction Cos-Effectiveness) calculator, as suggested by earlier study (Troeger et al. 2014). The detailed information and techniques are available in the STOP Cholera website (http://stopcholera.org). The following equations were used to estimate the results:

$$\text{DALY avoided per year}_{i,t} = \text{YLD avoided}_{i,t} + \text{YLL avoided}_{i,t} \quad \ldots\ldots\ldots\ldots (1)$$

$$\text{YLD avoided}_{i,t} = \{[(1\text{-CFR}_i) \times \text{Eff}_t \times \text{I}_i] \times \text{Duration of illness} \times \text{DW}\} \ldots\ldots\ldots\ldots (2)$$

$$\text{YLL avoided}_t = \{[(\text{CFR}_i \times \text{Eff}_t \times \text{I}_i) / 0.03] \times [1\text{-Exp}(-0.03 \times \text{LE}_i)] \ldots\ldots\ldots\ldots (3)$$

$$\text{Total DALYs avoided}_{i,t} = \sum_{t=0}^{Durration} \frac{Dalys\ avoided_{i,t}}{(1+0.03)^t} \quad \ldots\ldots\ldots\ldots (4)$$

Cost-effectiveness Ratio = Vaccination Cost / Total DALYs avoided ……..…… (5)

In the above equations, Eff is the efficacy of the vaccine, CFR is the case fatality ratio, DW means the disability weight, i.e., disability caused by cholera, I is the incidence rate, t is the time in years, and i indicates the subpopulation i.

9.2.3.1 Cholera incidence

Cholera incidence rate is context specific, i.e., the incidence is varied within the country, regions and even in seasons. Globally, the age and risk-specific cholera incidence rate ranged between 0.1 to 17.6 per 1,000 people per year (Roset et al. 1999; Cookson et al. 1997; Sack 2003; Cook et al. 2009; Jeuland, Cook, et al. 2009; Jeuland, Lucas, et al. 2009; Jeuland & Whittington 2009; Troeger et al. 2014; Smalley et al. 2015; Whittington et al. 2012). The incidence of cholera in Bangladesh ranges within 1 to 12 per 1,000 population per year, whereas the overall incidence rate of the country is 2.1 per 1000 people (IVI 2013). The children are the ones that suffer most from the cholera illness. The urban slum is often considered as a high-risk area in Bangladesh because of overpopulation, limited access to water and sanitation, unhygienic environment and other circumstantial factors (Khan et al. 2013). Over the past five years, it was estimated that, in a slum area like Mirpur, where the study located, the hospitalization rate due to cholera was 2 to 6 per 1,000 people (Chowdhury et al. 2011). However, the actual disease burden is unknown. In this model, the age-specific disease burden of the high-risk area was captured from the earlier published report with sensitivity ranged (IVI 2013).

9.2.3.2 Vaccine coverage

The vaccination coverage is subject to the nature of the vaccination strategies and the targeted population. For instance, many vaccination programs targeted among various age groups (e.g., children, adolescent, adult) and various geographical area such as (urban, rural, slums, refugee camp, hard-to-reach area) (Phares et al. 2016; Troeger et al. 2014). We observed that, globally thee cholera vaccination coverage was from 10% to 80% on various settings (Cook et al. 2009; Jeuland, Cook, et al. 2009; Jeuland, Lucas, et al. 2009; Jeuland & Whittington 2009; Smalley et al. 2015). The current cluster-randomized controlled vaccination trial reported 65% of vaccine coverage (Qadri et al. 2015), which was used for the analysis.

Table 9-1 Cost-effectiveness model parameters, with uncertainty ranges

Input Parameter	Value	Sensitivity
Fully vaccinate population	61,970 (Qadri et al. 2015)	
Age 1.0 to 4.9	9,440 (Qadri et al. 2015)	
Age 5.0 to 14.9	19,393 (Qadri et al. 2015)	
Age above 15	65,842 (Qadri et al. 2015)	
Vaccination campaign coverage (%)	65% (Qadri et al. 2015)	40 (Jeuland, Lucas, et al. 2009) to 80% (Murray et al. 1998)
Total protective effectiveness (%)		
Age 1.0 to 4.9	44% (Qadri et al. 2015)	20 - 80 (Schaetti et al. 2012; Dimitrov et al. 2014)
Age 5.0 to 14.9	33% (Qadri et al. 2015)	20 - 80 (Schaetti et al. 2012; Dimitrov et al. 2014)
Age above 15	56% (Qadri et al. 2015)	20 - 80 (Schaetti et al. 2012; Dimitrov et al. 2014)
Duration of protecton, years	2 (Qadri et al. 2015)	1-5 (Bhattacharya et al. 2013)
Incidences (cases/1000)		
Age 1.0 to 4.9	11 (IVI 2013)	3.7 (IVI 2013) to 12 (IVI 2013)
Age 5.0 to 14.9	3.5 (IVI 2013)	1.2 (IVI 2013) to 5.7 (Jeuland, Lucas, et al. 2009)
Age above 15	1.7 (IVI 2013)	0.6 (IVI 2013) -2.1 (IVI 2013)
Case Fatality Ratio (CFR)	1.5 % (IVI 2013)	0.5-3 (Jeuland, Cook, et al. 2009)
Duration of illness (days)	3 (Sarker et al. 2013)	1-6
DALY weight	0.281 (Troeger et al. 2014)	0.061 - 0.281(Salomon et al. 2012)
Life expectancy (years)		
Life Expectancy, at 3	70 (BBS 2015)	
Life Expectancy, at 10	64.1 (BBS 2015)	
Life Expectancy, at 30	45.3(BBS 2015)	
Household cost of illness (US $)	38.18	20-40 (assumption)
Provider actual cost of illness (US $)	52.23 (Sarker, Islam, et al. 2016)	30-60 (assumption)
Total cost of illness (US $)	90.41	50-100 (assumption)
Vaccine delivery cost (US $)	0.93 (Sarker et al. 2015)	0.5-1.5 (assumption)
Vaccine purchasing cost (US $)	1.06 (Sarker et al. 2015)	0.5-2 (assumption)
Total vaccination cost (US $)	3.98 (Sarker et al. 2015)	1-5 (assumption)
Discount rate (%)	3% (Jamison et al. 2006; Drummond et al. 2005)	3-10% (Jeuland, Lucas, et al. 2009)
GDP Threshold for DALYs *		
Very cost effective (per capita GDP**)	(US $) 1,466	
Cost effective (3* per capita GDP)	(US $) 4,398	

(*World Health Organization guideline, ** Bangladesh Bank)

9.2.3.3 Vaccine effectiveness and duration

A large-scale OCV trial was carried out in Kolkata with the two doses of "Shanchol" vaccines. It was found to have a 67% protective efficacy after a 3 year period of vaccine administration (Sur et al. 2011). However, after five years, the researcher investigated that the cumulative efficacy was still 65%, and their point estimation survey found that the protective efficacy remains the

same (Bhattacharya et al. 2013). The same vaccine was administrated in this cluster randomized open-label trial in Bangladesh. After a two-year period of analysis, the investigators found that the overall protective effectiveness of the vaccine was 37%, although vaccine effectiveness were varied across the age group of the population (Qadri et al. 2015). This analysis is based on the 2-year time horizon. However, most of the cholera vaccination trial applied the 3 year time horizon for cost-effectiveness estimation (Cook et al. 2009; Jeuland, Lucas, et al. 2009; Schaetti et al. 2012; Cookson et al. 1997). The sensitivity analysis is reported from a 1 to 5 year protection of different protective efficacy, as based on published literature (Bhattacharya et al. 2013).

9.2.3.4 Case fatality rate

In many studies reported case fatality rate ranged from 0.01% to up to 20% (Naficy et al. 1998; Sack 2003; Kim et al. 2011). In this analysis, we considered the average case fatality ratio to be 1.5% (ranges from 0.5 to 3) per 1,000 people, according to the latest high-risk estimation from Bangladesh. However, the case fatality might be higher up to 10% in Bangladesh (WHO 2014b; Siddique et al. 1994; IVI 2013).

9.2.3.5 Disability weights

According to the Global Burden of Diseases study, the disability weight for the diarrheal disease ranges from 0.061 to 0.281 (Salomon et al. 2012; Troeger et al. 2014). This weight indicated to understand the pain and suffering from the cholera episode, while the short duration of illness indicated that there was little effect on cost-effectiveness ratio (Jeuland, Cook, et al. 2009). The average length of the cholera infection was three days of each episode, varies from 1 to 6 days (Jeuland, Cook, et al. 2009; IVI 2013; Sarker et al. 2013).

9.2.3.6 Discount rate

The analysis is based on the findings from field level data from a 2 years' time horizon. All types of costs and associated benefits are discounted at 3% (Jamison et al. 2006; Drummond et al. 2005). A number of economic evaluation of cholera vaccination literature used the discount rate from 1 to 10%, which was used as the sensitivity test of the current study (Cook et al. 2009; Jeuland, Cook, et al. 2009; Jeuland, Lucas, et al. 2009; Naficy et al. 1998; Cookson et al. 1997).

9.2.3.7 Threshold level

To determine whether a vaccination program is represented as a 'good buy,' the cost-effectiveness threshold (CET) level is often required. The most commonly used cost-effectiveness thresholds are based on per-capita gross domestic product (GDP) of the host country, as per the report of the

Commission on Macroeconomics and Health (WHO 2001). Due to the absence of a locally established cost-effectiveness threshold level, the project adopted the World Health Organization's Choosing Intervention that are Cost Effective (WHO-CHOICE) GDP threshold level for the cost-effectiveness analysis (Tan-Torres et al. 2003; Hutubessy, Chisholm, and Edejer 2003). There is a body of OCV studies that have used the GDP threshold level as this threshold level and are able to address the concept of allocative efficiency (Jeuland, Cook, et al. 2009; Schaetti et al. 2012; Troeger et al. 2014; Smalley et al. 2015; Newall et al. 2014). According to the WHO-CHOICE threshold level, a vaccination program with an ICER less than annual GDP per capita of the reporting country (in this case, Bangladesh) is potentially 'very cost-effective', whereas ICER that is less than three times of the national annual per capita GDP is considered as a cost-effective intervention (Tan-Torres et al. 2003).

9.2.3.8 Herd protection assumption

Indirect protection from a cholera mass vaccination often protects the non-vaccinated population, a phenomenon which is called 'herd protection'. This might influence the cost-effectiveness estimates (Longini et al. 2007; Ali et al. 2005; Jeuland, Cook, et al. 2009; Troeger et al. 2014). With the stochastic cholera transmission model in rural Bangladesh, it was observed that cholera transmission could be controlled with 50% coverage of OCV as it reduces 89% of case reductions among unvaccinated people and a 93% case reduction in the overall population. It was also found that a moderate coverage (30%) would reduce 76% of cholera incidence rate (Longini et al. 2007). Like the earlier studies (Cook, Jeuland, Whittington, Poulos, Clemens, Sur, Anh, Agtinih, et al. 2008; Jit et al. 2011; Patel et al. 2013), we did not predict the herd protection as it was a high-density population in an urban slum area with a high migration rate, therefore only direct protection from the RCT trial was considered in our results (Kim et al. 2011; Naficy et al. 1998; Qadri et al. 2015). However, earlier studies reported that 0-33% cases could be averted, in addition to the direct effect of vaccine (Jeuland, Lucas, et al. 2009).

9.2.3.9 Sensitivity analysis

Cost-effectiveness analysis of vaccination programs is vastly reliant on input data variability (Bilcke & Beutels 2009) where the price of the vaccine often considered as a key variable (Constenla et al. 2009). Most of the vaccination evaluation studies found that the CEA results were highly sensitive to the disease-related mortalities and efficacy of vaccines (Rheingans et al. 2009; Podewils et al. 2005). A univariate deterministic sensitivity analysis was performed to show which parameters had the greatest impact on the cost-effectiveness of cholera vaccination (Baltussen et

al. 2002). These scenarios included vaccine price, incidence rate, vaccine coverage, vaccination protection years, discount rate, and other parameters (Cook et al. 2009; Jeuland, Lucas, et al. 2009; Naficy et al. 1998; Sack 2003; Sardar et al. 2013; Schaetti et al. 2012; Smalley et al. 2015).

9.2.3.10 Ethical approval

The study protocol was approved by the research review committee and the ethics review committee of the icddr,b, Dhaka, Bangladesh. Written informed consent was obtained from all study participants who were interviewed for the household cost of illness.

9.3 RESULTS

9.3.1 Cost of illness of cholera

As shown in Table 9-2, the average total costs of illness and its distributions from household's perspective. The average total cost of treating cholera was BDT 2,770.56 (US$ 36.94) per episode, where indirect cost was the main driver, contributing to 81% of the total cost. The average total out-of-pocket cost per episode was BDT 526.09 (US$ 7.01), where 6.20% and 12.79% were direct medical and direct non-medical cost respectively. Among the medical costs, medicine cost (BDT 131.78 or US$ 1.76) was the main cost driver, followed by admission or registration fees (BDT 18.37 or US$ 0.24). Transport costs, caregiver expenditures, and feeding costs were the largest share of direct non-medical cost. Among the indirect costs, patient's income loss was higher (BDT 1,187.15 or US$ 15.83) than that of the caregiver's income loss (BDT 1,057.32 or US$ 14.10). The median total costs were BDT 1,736 (US$ 23.15) and the distribution as 5th and 95th percentile was BDT 287 (US$ 3.83) and BDT 7,918 (US$ 105.57), respectively. Median direct and indirect costs were BDT 375 (US$ 5.00) and BDT 1,328 (US$ 17.71), respectively. The 5th and 95th percentile of direct costs were BDT 75 (US$ 1.00), and BDT 1,380 (US$ 18.40), and the indirect cost were BDT 72 (US$ 0.96), and BDT 7,010 (US$ 93.46) respectively.

Table 9-2 Average household cost of cholera treatment, BDT (US$*)

Cost	Parameter	Average cost		SD		Proportion of total cost
		BDT	US$	BDT	US$	
Direct Medical	Diagnostic	12.19	0.16	120.78	1.61	6.20
	Medicine	131.78	1.76	232.36	3.10	
	Registration/admission fee	18.37	0.24	90.04	1.20	
	Paramedics home visit fee	2.96	0.04	26.35	0.35	
	Bed/ Cabin charge	6.51	0.09	79.55	1.06	
Direct Non-Medical	Transportation cost	136.40	1.82	118.55	1.58	12.79
	Food items	83.18	1.11	116.50	1.55	

	Informal payment	0.44	0.01	7.26	0.10	
	Caregivers payment	0.66	0.01	15.82	0.21	
	Materials (mug/glass/coil etc)	9.80	0.13	14.97	0.20	
	Lodging	1.81	0.02	36.23	0.48	
	Caregivers expenditure	114.22	1.52	176.42	2.35	
	Others	7.78	0.10	28.34	0.38	
Total direct cost		526.09	7.01	578.14	7.71	18.99
In-direct cost	Patient income loss	1,187.15	15.83	2,901.30	38.68	
	Caregivers income loss	1,057.32	14.10	2,347.53	31.30	81.01
Total indirect cost		2,244.47	29.93	3,729.30	49.72	
Total household cost		2,770.56	36.94	3,944.53	52.59	100.00

From the hospital's point of view, a total of 19, 515 cholera patients utilised the hospital services during the year of 2013. The average treatment cost per patient was US$ 52.23 from the hospital's perspective. The detailed treatment cost distribution was reported elsewhere (Sarker, Islam, et al. 2016). The societal cost of illness is the summation of households cost and provider actual cost of illness. The provider actual cost of illness is the provider's cost of treatment less any fees received from the patients for hospitalization, drug, diagnostic tests, etc. Due to each cholera episode, the average societal cost of illness was US$ 95.76 (price as of 2015).

Vaccine delivery cost: The cost of vaccination was captured from empirical data during the cholera vaccination trial. The vaccination costs included the cost of vaccine delivery related activities and the cost of vials (including freight charge) from the suppliers' point of view and the cost of vaccine recipients from household points of view. The societal costs per fully immunized person were estimated by summing all of the components. The total cost per fully immunized person was US$ 3.98, whereas the cost per vial was US$ 1.06 and the vaccine administration cost per vial was US$ 0.96, respectively. The detailed breakdown of cost is reported elsewhere (Sarker et al. 2015).

9.3.2 Impacts of vaccination

According to the table 9-3 shown, the total cost and consequences of oral cholera vaccination in urban Bangladesh. All results are presented in a two years' time horizon. In this context, our results indicated that by investing US$ 257,744, at least 173 cholera cases and three deaths were averted in this period. The cost per DALY averted and cost per case averted was US$ 3,467 and US$ 1,395, respectively. A total of 70 disability-adjusted life years were averted, which indicated that the vaccination program is a cost-effective investment. The cost per fully immunized person was

US$ 3.9, our results indicated that if the price is reduced to 1.91, the vaccination will be very cost-effective holding all other parameters at the base case. The study demonstrated that OCV would be very cost-effective if we considered the long time horizon or high efficacy data, like other studies (Sur et al. 2011; Bhattacharya et al. 2013). However, the cost-effectiveness of the field vaccination trial is sensitive to cholera incidence rates, case fatality rates, and vaccine efficacy.

Table 9-3 Estimated cost-effectiveness of cholera vaccination over two years using RCT data, societal perspective

Parameter	Value (US $)
Total program cost of vaccination	257,744
Cost averted	16,558
Net cost (Total program cost - Societal averted cost)	241,186
Non-fatal cases averted	170
Deaths averted	3
Total cases averted	173
DALYs averted	70
Cost per case averted	1,395
Cost per Life Saved	92,991
Total Cost per DALY Averted	3,467
Total Vaccine Cost of Purchase & Delivery (US $)	
Cost-Effective	US $ 5.20
Very Cost-Effective	US $ 1.91
Vaccine Efficacy (%)	
Cost-Effective	36.10%
Very Cost-Effective	70.10%
Incidence (per 1,000/year)	
Cost-Effective	2.27
Very Cost-Effective	6.18
Case Fatality Ratio (%)	
Cost-Effective	1.18%
Very Cost-Effective	3.55%

Age-specific results of WHO threshold level: Figure 9-1 shown the age-specific effectiveness of vaccination program. The figure indicated that investing in the cholera vaccine for children would be cost-effective, whereas vaccinating under-five children was a very cost-effective option as the disease was more prevalent in children. In contrast, only vaccinating adults (above 15) were not cost-effective in the short-term. However, in the sensitivity analysis, we found that in the longer time horizon, the vaccination appeared to be a cost-effective investment. Furthermore, an earlier study showed that incorporating herd immunity could lead to the vaccination program being cost-effective, which was not previously established (Jeuland, Cook, et al. 2009).

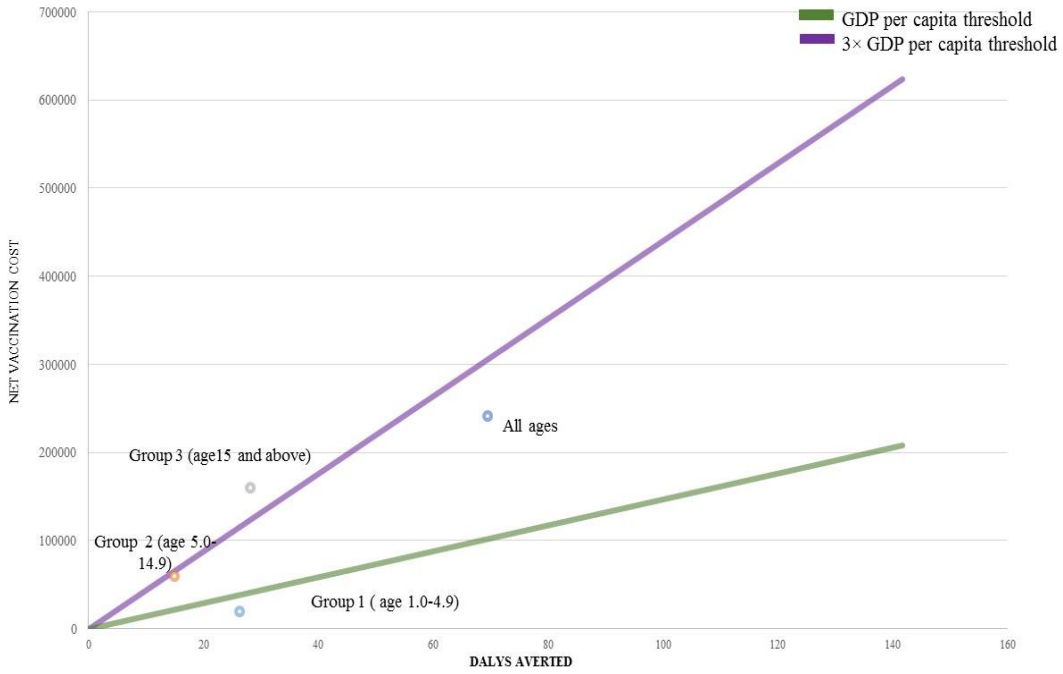

Figure 9-1 Cost-effectiveness threshold across age group using field-level data

The figure 9-2 shown that targeting oral cholera vaccination in high-risk urban area is potentially a cost-effective investment considering the current scenario. Overall, the cost per DALY averted (US$ 3,467) is within the cost-effective threshold level. This result indicated that even with a low efficacy and short duration of the vaccine, if children are prioritised, it would still be a very cost-effective option (US$ 768). In the high-risk area (e.g. hard to reach areas, urban slums, a refugee camp) where there was limited potable water, poor access to sanitation, and inadequate access to health care, vaccination might be a most cost-effective investment, as cholera incidence and case fatality rates are often higher than other setting (Sack 2003; Tan-Torres Edejer et al. 2003). The figure showed that, in a shorter duration (2 year), the cost per DALYs averted was highest for adults (US$ 5,687) which was cost-ineffective option, as the risk of infection was relatively lower than for others. However, the results demonstrated that vaccinating all ages one and above would be an appropriate vaccination strategy that also appeared as cost-effective investment. The results also indicated that limiting cholera vaccination to under-five children was a very cost-effective investment, and could be targeted easily through national immunization programs, along with other childhood vaccines.

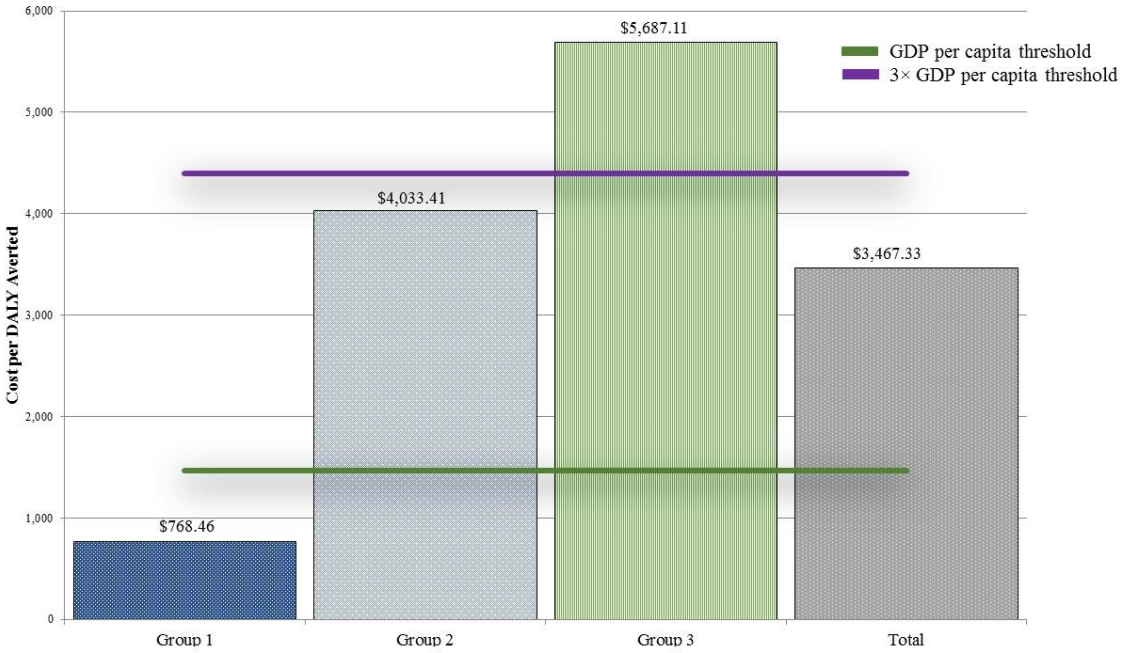

Figure 9-2 Cost-effectiveness of vaccinating different age groups over two years

Uncertainty results were incorporated in the "tornado" diagrams (Fig 9-3), which showed the largest effect on the cost-effectiveness results. The most important parameters were the price of the vaccine, case fatality ratio, the cost of vaccine, vaccine protection years, cost of delivery-related activates, effectiveness of vaccine, discounting assumption, and cholera incidence rate. If the vaccine efficacy rate is the same (field level data) but vaccine protection years are longer (e.g., 5 years, like other OCVs studies), the mass cholera vaccination program is a highly cost-effective investment in the urban settings. Although we did not consider herd immunity in this diagram, earlier studies observed that ignoring the herd immunity due to cholera vaccine led to underestimation of the cost-effectiveness of cholera vaccination programs (Jeuland, Cook, et al. 2009).

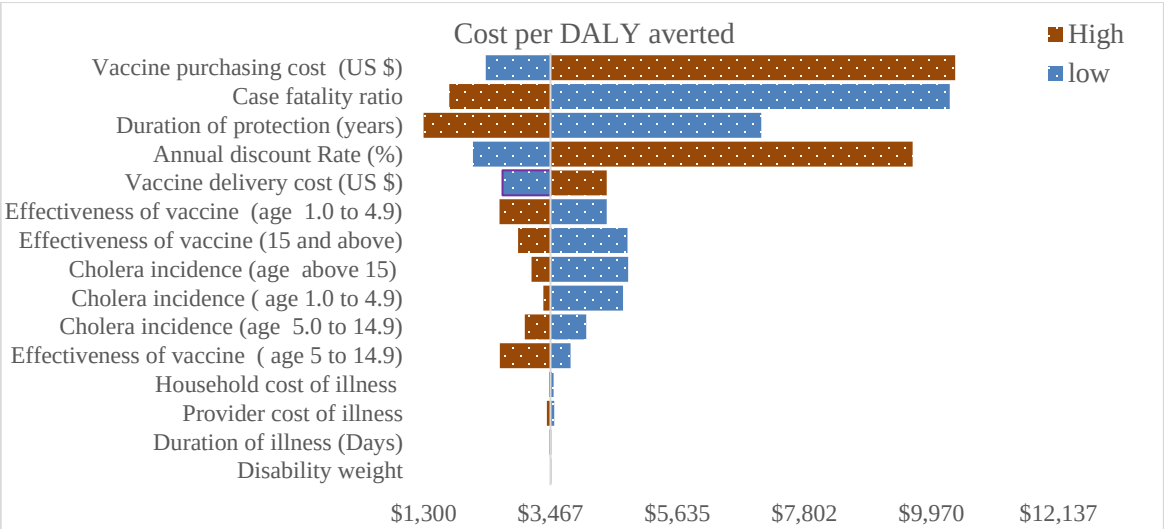

Figure 9-3 Tornado diagram showing sensitivity of cost-effectiveness of vaccination to model parameter

9.4 DISCUSSION

Cholera remains a public health problem, especially in the high-risk area of Bangladesh. According to the latest census of the country, approximately 0.23 million people are still living in a total of 13,938 urban slums, whereas 47% of those slums are located in the Dhaka division (larger administrative unit) in Bangladesh (BBS 2014). Cholera infection is still a significant concern in those endemic hotspots, especially for <5 children (37% of total population), as children typically have a higher incidence of cholera than the general population (Jeuland & Whittington 2009; IVI 2013). In recent years, many international donors have advocated for an expansion of the cholera vaccination program, and cost-effectiveness analysis is a tool for policy arguments for justifying these expanded vaccination program (Desai et al. 2016; Mahoney et al. 2007). Although successful cholera control program depends on the improvement of potable water and public sanitation system, the OCV program has already proven to be an effective component for prevention strategies, particularly for the endemic hotspot, disease outbreaks, and for the humanitarian crisis (Nogareda 2015; Desai et al. 2016). Indeed, the World Health Assembly recommends OCV as a part of an integrated cholera strategy (WHO 2011a). For this consequences, in early 2013, the GAVI Alliance supported oral cholera vaccine stockpile was created to tackle endemic cholera in emergency and non-emergency situations, and the number of doses requested for affected countries has sharply increased from 2013 to 2017 (WHO 2017b). It was roughly estimated that approximately 9.3 million doses from the OCV stockpile were used and the demand for OCVs are increasing rapidly in the endemic region and humanitarian crisis (WHO 2017b).

Despite efforts to improve water supply and sanitation, diarrhoeal-related illnesses are the leading cause of hospital admission in Bangladesh. However, there are still limited opportunities for laboratory tests confirming cholera cases. Therefore, the real health and economic burden of cholera is still unknown. This study has attempted to economics of cholera infections and effect of oral cholera vaccination in urban endemic settings. Our estimation showed that the average treatment cost per patient was US$ 95.76, while approximately US$ 3.96 was required for providing full doses (2 doses) of vaccine. The delivery of the oral cholera vaccine has already proven its feasibility and effectiveness, and this study has demonstrated the cost-effectiveness of OCV, based on two years of follow-up period of the cholera vaccination campaign (Qadri et al. 2015; Sarker et al. 2015). Our results showed that using WHO-GDP criteria, even in short time horizon (2 years after vaccination) with high migration rates, the OCV vaccination is a cost-effective investment in high-risk urban areas of Bangladesh. However, this scenario depends on several parameters, including prices of vials, coverage, and efficacy of vaccines, cholera incidence rate, as well as the duration of vaccine protection years.

Several cost-effectiveness analyses of OCV vaccination conducted in Bangladesh earlier used a model-based approach of previously published data. Troeger et al. concluded that under certain conditions, targeting high-risk populations might be a cost-effective option (Troeger et al. 2014). Jeuland and colleagues analysed the rural level data and concluded that incorporating the herd effect of OCV for the vaccination program might be a cost-effective option, something that was not possible if the herd immunity of vaccines is ignored (Jeuland, Cook, et al. 2009). However, using scenario-based approach in early 2009, a report on country investment cases of cholera vaccination in Bangladesh projected that OCV might be cost-effective depending on the price of cholera vaccine (IVI 2013). Based on recent field level data, we found that approximately 173 cholera case were averted due to oral cholera vaccinations. The total cost per cases averted was US$ 1,395 and costs per disability-adjusted life years (DALY's) were US$ 3,467, which were both within the WHO GDP threshold level. Our study suggests that even with the lower coverage and efficacy rate, the current OCV vaccination might be a cost-effective option in high risk cholera-prone area. However, it seems that (figure 9-1) immunization of the adult population is not as cost-effective (US$ 5,687 per DALY averted) as implementing it for children in a short period. Yet, our sensitivity analysis suggested that in longer time horizon (3 to 5 Years) the adult OCV vaccination is also cost-effective. However, considering the entire population, the OCV vaccination appeared as a cost-effective (US$ 3,467 per DALY averted) investment in a high-risk urban area of Bangladesh. We found that in a short time horizon with high migration rate, the

vaccination for children is a highly cost-effective option as young children are vulnerable to severe cholera cases in those endemic settings (Harris et al. 2012). The sensitivity analysis results indicated that the OCV vaccination was highly sensitive to vaccination prices, duration of protection, case fatality rates, vaccine delivery related costs, and effectiveness of vaccines. As the current vaccine was not produced in Bangladesh and the vaccine delivery costs were borne by the providers (In this case, icddr,b), who had relatively high staff salaries compared to the government employees, it can be said that government operated programs would have a lower cost than the current program (Naficy et al. 1998; Sarker et al. 2015). This would suggest that future oral cholera vaccination programs being implemented in the EPI system, the low-cost vaccine will be more acceptable as the vaccine price is the highest cost driver among the vaccination cost.

9.5 LIMITATION

There are several limitations. As this study was conducted in a high-risk urban area, this does not represent the overall scenario of the high-risk setting of the country. We used the CEA, using a DALY-based approach that used the GDP threshold. However, the DALY-based method has been criticized to some extent, as this threshold level does not consider the affordability, budget impact, sustainability of funding, feasibility of implementation, or the value of other intervention (Morton 2010; Airoldi & Morton 2009; Woods et al. 2015; Bertram et al. 2016; Newall et al. 2014; Shillcutt et al. 2009). Nevertheless, the prime intention of WHO-CHOICE GDP based thresholds was to guide the policy makers on value for money (Hutubessy et al. 2003). Therefore, other considerations relevant to country specific local context (e.g. affordability, fairness, feasibility, budget impact) should be used in the decision-making process (Bertram et al. 2016). Furthermore, relevant data is vital for such decision making process (Hutubessy et al. 2003; Newall et al. 2014; Bertram et al. 2016).

The other important limitation was that we used a static model despite the dynamic model being most useful for predicting the cost-effectiveness of the infectious disease control program. Since the dynamic transmission model is able to capture the indirect effect of reduced transmissions and the long-term effect of a vaccination programs, it thus provides a higher cost-effectiveness ratio than the static model (Lugner et al. 2010). Therefore, the current study might have underestimated the actual benefit of the oral cholera vaccination. Earlier OCV study also concluded that incorporating herd immunity makes the vaccination program more attractive from an economic perspective (Jeuland, Cook, et al. 2009). However, the dynamic model requires more detailed data, such as transmission probability, vaccine efficacy for susceptibility/infectiousness, proportion of

symptomatic infections, and seasonal boost factors, which are limited in the study context. However, many studies reported that the static model can be used if it ignored the indirect effects, as there are no particular evidence of harm, i.e. age shifts with adverse effect and without herd immunity, the vaccine appeared as a cost-effective investment (Kim & Goldie 2008; Jit & Brisson 2011; Ultsch et al. 2016). As such, many vaccination studies often excluded the concept of the 'indirect effect' of vaccine (Cook, Jeuland, Whittington, Poulos, Clemens, Sur, Anh, Agtinih, et al. 2008; Jit et al. 2011; Patel et al. 2013). Considering all of the limitations, this analysis was based on the practical application of an oral vaccination program in a high-risk urban area of Bangladesh and might be informing policymakers in formulating rational cholera vaccination programs, especially for high-risk urban populations.

9.6 CONCLUSION

This cost-effectiveness result was based on the practical application of an oral vaccination program in a high-risk urban area of Bangladesh, which will play a major role for policymakers in formulating rational cholera vaccination programs, especially for high-risk urban populations. Our results showed that only vaccinating adult (above 15) was not cost-effective in short duration. However, vaccinating the whole population in a high-risk cholera endemic area is cost-effective investment, even the shorter time horizon. These results should help inform policymakers in Bangladesh when deciding whether to include cholera vaccines in the National Immunization Program, particularly for the high-risk cholera-prone areas, or during any natural disasters or humanitarian crisis.

Funding: The project was supported from the Bill & Melinda gates Foundation.

Disclosure of potential conflicts of interest: The authors declare that they have no competing interests.

10 ROTAVIRUS VACCINATION: A DECISION ANALYSIS IN BANGLADESH

Study – **VII**

Published: ***Human Vaccines & Immunotherapeutics***

Publisher: ***Taylor & Francis***

Volume: 2018:14(1), Pages 189-198

https://doi.org/10.1080/21645515.2017.1356962

Title of the paper: **Cost-effectiveness analysis of introducing universal childhood rotavirus vaccination in Bangladesh**

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Abstract

Diarrhea is one of the world's leading killers of children, and globally, rotavirus is the most common cause of severe diarrhea among under five children. In Bangladesh, rotavirus kills nearly 6,000 under five children in each year. To reduce the burden of childhood rotavirus diseases, universal rotavirus vaccination is recommended by World Health Organization. The objective of this study is to assess the cost-effectiveness of introducing universal childhood rotavirus vaccination with the newly developed ROTAVAC vaccine in National Expanded Programme of Immunization in Bangladesh. We developed a decision model to examine the potential impact of vaccination in Bangladesh and to examine the effect if the vaccination is applied in the nationwide immunization program schedule. Introduction of childhood universal rotavirus vaccination in Bangladesh scenario appears as highly cost-effective and would offer substantial future benefits for the young population if vaccinated today. The cost per DALY averted of introducing the rotavirus vaccine compared to status quo is approximately US$ 740.27 and US$ 728.67 per DALY averted from the health system and societal perspective respectively which is "very cost-effective" using GDP threshold level according to World Health Organization definition. The results of this analysis seek to contribute to an evidence-based recommendation about the introduction of universal rotavirus vaccination in national Expanded Programme of Immunization (EPI) in Bangladesh.

Keywords: Bangladesh, childhood, cost-effective, rotavirus, vaccination

10.1 INTRODUCTION

Diarrhea is one of the world's leading killers of children, and globally, rotavirus is the most common cause of severe diarrhea among under five children and approximately 215, 000 children aged <5 years die each year due to rotavirus infections (WHO 2013c; Tate et al. 2016). It is a leading cause of infantile gastroenteritis accounting for 20% of diarrhea-associated deaths (Lundgren & Svensson 2001). The mortality burden of rotavirus diseases is greatest in Asia and Africa (Bar-Zeev et al. 2015). To tackle this public health problem, many life-saving interventions already exist, such as oral rehydration therapy and micro-nutrient supplementation that have already proven effective for preventing of diarrheal related episodes (Munos et al. 2010b). Besides, improving water quality and sanitation, food quality, and hygiene are also preventive measures for the diarrheal related diseases, although those are generally long term solutions and are linked with socioeconomic and development of communities (Diop et al. 2015). However, these strategies have not had a great impact in reducing the incidence of rotavirus diarrhea globally (WHO 2013c). Also, these interventions remain time consuming and often require a substantial amount of money. The context is crucial for a resource poor country like Bangladesh where a huge number of the population lives in urban slums and are at high risk for diarrheal diseases. It was estimated that in every year, rotavirus kills nearly 6,000 under five children in Bangladesh (CNN 2016). The symptoms of rotavirus are vomiting and fever with associated diarrhea; the average duration of illness is 6 days; and the incubation period is at least 2 to 3 days (Velazquez et al. 1996). To reduce the burden of childhood rotavirus diseases, rotavirus vaccination is highly recommended by WHO, especially for those countries where diarrheal diseases cause more than 10% of deaths (WHO 2009c).

Recently, the WHO updated its previous position papers on rotavirus vaccines and recommended that rotavirus vaccines should be included in all National Immunization Programs (NIPs) globally (WHO 2007b). However, the decision to introduce new vaccines is a quite complex issue as the new vaccines are always costly to the health system. Therefore, it is important for the policy maker to understand whether the expenditure is justifiable on epidemiological and fiscal grounds as investment in vaccine programs necessarily denies funds from competing health priorities. In addition, rotavirus vaccines are relatively expensive compared with the other childhood vaccines (Thiboonboon et al. 2016). Therefore, policy makers need to understand the expected health and economics benefit of a future rotavirus vaccination program. In 2016, approximately 81 countries have offered childhood universal rotavirus vaccination and the Global Alliance for Vaccines and Immunization (GAVI) provides financial support to certain countries for introducing rotavirus

vaccination program in their immunization programs (ROTA Council 2016). However, GAVI-supported countries are also required to make co-payments for vaccines, and understanding whether these vaccines are cost-effective is important for budgetary planning and negotiating procurement costs (Bar-Zeev et al. 2016). And these countries will eventually graduate from these programs and the support will stop. The cost-effectiveness of rotavirus vaccines has been evaluated more extensively over the past decade (Postma et al. 2011). Value for money is necessary criteria regarding new vaccination program, and cost-effectiveness analysis able to guide decision about introduction of vaccine versus other health intervention (Fischer et al. 2005). There are a number of cost-effectiveness studies of rotavirus vaccination among many lower-and middle- income settings, however, there has been no such study in the Bangladeshi context. The objective of this study is to assess the cost-effectiveness of universal childhood rotavirus vaccination with the newly developed low cost ROTAVAC vaccine in national Expanded Programme of Immunization (EPI) in Bangladesh (Bhandari et al. 2014). The analysis was based on the health system and societal points of view. In health system perspective the costs of rotavirus related medical care and the cost of vaccination program were included; whereas in the societal perspective both direct medical (e.g., medicine, diagnostic), direct non-medical cost (e.g., transportation, lodging) indirect cost (e.g., income loss) and cost of vaccination program were included.

10.2 METHODS

10.2.1 Model

A decision model was developed by using Microsoft ® Excel spreadsheet to examine the potential impact of low-cost universal oral rotavirus vaccination in Bangladesh and to examine the effect if the vaccination is applied in the nationwide immunization program schedule. We estimate the economic and health burden due to rotavirus disease and the cost-effectiveness of rotavirus vaccination in Bangladesh from the health system and societal perspective. Principal model parameters are described in Table 10-1. The primary measurements of cost-effectiveness in the current study are the incremental cost per DALY averted, incremental cost per case averted and incremental cost per death averted. Incremental cost-effectiveness ratios (ICERs) are calculated by dividing the difference in cost with and without the universal childhood rotavirus vaccination program by the difference in health outcomes with and without the intervention. For this aspect, we collected several parameters from various published papers and regional data sources. The model estimates the various health associated outcomes, health care costs averted and the

reduction in disease burden after childhood rotavirus vaccine introduction in national settings. For comparing pre and post universal rotavirus vaccination scenario, we estimated the events and possible costs to capture the baseline rotavirus disease burden and then assessed the number of rotavirus disease-associated events and possible costs that would occur after the introduction of low-cost rotavirus vaccine into the national immunization program. This is a cross-sectional static model where children aged <5 years were included (Bangladesh Bureau of Statistics 2015) and analysis was based on 2 year period with additional sensitivity analysis up to 1 to 3 year time horizon. The cost-effectiveness analysis was reported based on the health system and for societal perspective according to the Panel on Cost-Effectiveness in Health in Medicine (Gold et al. 1996). For the health system perspective, we included the costs of medical care related to rotavirus infections, and the cost of vaccination program. From the societal perspective both direct medical (e.g. medicine, diagnostic), direct non-medical cost (e.g. transportation, lodging) and indirect cost (e.g. income loss) were included in the analysis. However, intangible costs, like pain and discomfort were excluded from the analysis. In the current analysis, the costs averted by vaccination were subtracted from the costs invested in vaccination, and they then were divided by the number of DALYs or the number of deaths and cases averted due to introducing childhood rotavirus vaccination. All future costs and benefits were discounted at a rate of 3% annually (Atherly et al. 2009). For reporting the cost-effectiveness scenario we used the common cost-effectiveness threshold level proposed by the World Health Organization: an intervention is considered cost-effective if cost per DALY averted is less than three times of the national annual per capita GDP, whereas the costs less than the GDP per capita is considered highly cost-effective (Tan-Torres et al. 2003). It was observed that, DALY is the preferred choice for measuring outcomes in lower and middle-income countries rather than other methods (Thiboonboon et al. 2016).. Like earlier studies (Cook, Jeuland, Whittington, Poulos, Clemens, Sur, Anh, Agtinih, et al. 2008; Jeuland, Cook, et al. 2009) to estimate the DALY avoided due to rotavirus vaccination we applied the four equations (1-4) as described below:

$$\text{DALY avoided}_t = \text{YLD avoided}_t + \text{YLL avoided}_t \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

$$\text{YLD avoided}_t = \{[(1\text{-CFR}) \times \text{Eff}_t \times \text{Cover} \times N \times I] \times \text{Length} \times \text{DW}\} \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (2)$$

$$\text{YLL avoided}_t = \{[(\text{CFR} \times \text{Eff}_t \times \text{Cover} \times N \times I) / 0.03] \times [1\text{-Exp}(-0.03 \times \text{LE})] \quad \ldots\ldots\ldots \quad (3)$$

$$\text{Total DALYs avoided}_t = \sum_{t=0}^{Durr} \frac{Dalys\ avoided_t}{(1+0.03)^t} \quad \ldots\ldots\ldots\ldots\ldots \quad (4)$$

In the above equations, Eff_t is the effectiveness of the rotavirus vaccine in year t, Cover is the percentage of under five children that would be vaccinated if the vaccine were provided for free, CFR, I and N are the case fatality rate, incidence of rotavirus illness and number of under five children, Length is average duration of illness (i.e. number of days sick with rotavirus), DW is the disability weight, LE is the life expectancy and Durr is the duration of the vaccine effectiveness.

10.2.2 Incidence and case fatality rate

The epidemiological data comes from different studies conducted in this setting. The high burden of all diarrheal diseases, including rotavirus, was observed in the impoverished part of the population like urban slums and poor regions of the country (Chowdhury et al. 2015). The population-based incidence of hospitalization for rotavirus infections vary from 10.8 to 19.6 per 1000 children aged <5 years old (Zaman et al. 2009) and the case fatality rate of rotavirus diseases is still unknown. An earlier hospital-based study conducted in urban Bangladesh and estimated that the childhood mortality attributable to rotavirus was 2 to 3%, however, the analysis was based on the 2% sample of the diarrheal cases of the admitted person in that hospital, which might underestimate the true burden (Tanka et al. 2007). Further, the above hospital is prepared to handle the rotavirus and other diarrheal cases, hence mortality rate will be lower than the national estimation. However, recently, a nationally representative study conclude that approximately 23% under five children did not seek any of the treatment during childhood diarrhea (Sarker, Sultana, Mahumud, Sheikh, et al. 2016). Due to absence of case fatality rate in Bangladesh, we assumed that CFR may be 0.3 percent, as our health care system is prepared to handle the rotavirus cases while the uncertainty ranges goes from 0.3 to 4% (Table 10-1).

10.2.3 DALY weights

In this analysis, we used the DALY weights of 0.12 for rotavirus related illness as there is no published DALY weight specifics to rotavirus disease and this value was used for previous rotavirus study (Murray & Lopez 1996). This weight will be used to measure the pain, suffering and discomfort associated with rotavirus diseases, but the short duration means that the morbidity associated with the rotavirus had relatively a little effects on cost-effectiveness results (Jeuland, Cook, et al. 2009). Like earlier study, we considered the DALY weights 0.12 to 0.281 for sensitivity analysis to observe the possible effects of the universal rotavirus vaccination.

10.2.4 Rotavirus vaccine, cost and efficacy

Currently, there are two rotavirus vaccine RotaTeq® (RV5- 3 dose) and Rotarix® (RV1 dose) that have been licensed in many countries (WHO 2013c). These vaccines have an efficacy of 85-98%, which is already shown to reduced all-cause hospitalizations by 42 to 59% (Breuer et al. 2006; Vesikari et al. 2006). In the international private market, the price for RotaTeq® (3 dose) and Rotarix® (2 dose) per course is approximately US$ 226 and US$ 213 respectively which is relatively higher that the US$ 192 and US$ 184 paid for the same vaccines by the Vaccines for Children Program (CDC n.d.; Nelson et al. 2013). However, in GAVI-eligible countries the subsidized price ranges between US$ 0.30-US$ 0.60, which is a major concern for policy-makers for those countries that "graduate" for GAVI-eligibility and have to purchase vaccine through some other mechanism. It was observed that both of the RV1 and RV5 have similar efficacy against severe rotavirus gastroenteritis in countries where a high diversity of strains co-circulate, suggesting an important role for heterotypic protective immunity (WHO 2013c). However, the protective effectiveness of these vaccines is not the same in all regions of the world as the effectiveness is high in developed countries but decreases substantially in low and middle income countries (Linhares et al. 2008; Madhi et al. 2010; Vesikari et al. 2007; Zaman et al. 2010).

The Expanded Program on Immunization (EPI) in Bangladesh is one of the successful programs in health sector which started with six conventional vaccines against six vaccine-preventable diseases and introduced latter measles and rubella (MR) vaccine, Measles Second Dose (MSD), Pneumococal Conjugated Vaccine (PCV) and IPV vaccine. Under the Comprehensive Multi-Year Plan of the National Immunisation Programme of Bangladesh 2011-2016, EPI had aimed for introduction of rotavirus vaccine by the end of 2014 but had not yet included rotavirus vaccination in the routine immunization program. The RV1 and RV5 were available in private market and people can purchase the vaccines from pharmacies as well as from private healthcare facilities. Recently, a new rotavirus vaccine named ROTAVAC has been developed in India based on the 116E rotavirus strain and manufactured by Bharat Biotech International Limited of India. A vaccination trial in India found that ROTAVAC vaccine (3 doses) had efficacy in the first year of life was 56.3% and in second year of life was 48.9% of the severe rotavirus gastroenteritis which is encouraging for resource poor setting like Bangladesh (Bhandari et al. 2014). ROTAVAC is currently licensed only in India and planned to make the vaccine available in the public market at a price of US$ 1 per dose (Pareek 2015). However, to introduce ROTAVAC in an immunization program, additionally a vaccine delivery related cost will be incurred from the implementer's perspective. Vaccine delivery costs are associated with vaccination campaign, cold chain and

waste management, training and staffing as well as social mobilization for the particular vaccine. Vaccines and other logistics (including vaccine carrier and stationaries) need to transport from centre's cold store to field site during the vaccination campaign which are key component of delivery costs. As per the earlier study, we assume that the cost of vaccine delivery process will be US$ 0.835 per dose per individual (Sarker et al. 2015). In this analysis we estimated the cost-effectiveness using ROTAVAC vaccine with a protection up to 2 years. For simplicity of the model we ignored the indirect effect of rotavirus vaccination, although it was observed that pediatric rotavirus vaccination protects young and adults from rotavirus disease will, providing added value to the immunization program (Anderson et al. 2013). Pitzer and colleagues observed that, rotavirus vaccines would provide hard immunity but not as large as short term reduction of rotavirus infections (Pitzer et al. 2012).

Table 10-1 Input baseline parameter and sensitivity analysis

Parameters	Baseline value	Sensitivity analysis
< 5 children (all)	15,175,000 (Bangladesh Bureau of Statistics 2015)	
Life table	Country specific (WHO 2016b)	
Duration of illness (days)	6 (Bar-Zeev et al. 2015),(Diop et al. 2015)	4.7 (Ahmed, Kabir, Aminur Rahman, et al. 2009) to 10 (Cortese et al. 2013)
Price of vaccine (per vial)	US $ 1(Pareek 2015)	US $ 0.5 to US $ 10 (Author assumption)
Cost of vaccine delivery process	US $ 0.835 (Sarker et al. 2015)	US $ 0.5 to US $ 2 (Author assumption)
Vaccination coverage (%)	65% (Qadri et al. 2015)	40 % to 96% (Bhandari et al. 2014; Wilopo et al. 2009; Diop et al. 2015)
Incidence of Rotavirus (per 1000)	10.8 (Zaman et al. 2009)	8 to 19.6 (Zaman et al. 2009)
Vaccine Effectiveness	55.1% (Bhandari et al. 2014)	40 to 85% (Breuer et al. 2006; Vesikari et al. 2006).
Treatment cost for IPD	$ 84 (Arifeen et al. 2016)	US $ 51.99 to US$ 96.54 (Megiddo et al. 2014)
Treatment cost for OPD	3.88 (Tate et al. 2009)	1 to 5 (Author assumption)
Case fatality rate	0.3% (Author assumption)	0.3% to 4% (Author assumption)
Vaccine protection (years)	2 (Bhandari et al. 2014)	1 to 3 (Phua et al. 2012)
Disability weight	0.12 (Murray & Lopez 1996)	0.12 (Murray & Lopez 1996) to 0.281(Naghavi et al. 2015)
Cost-effectiveness threshold		
1× GDP per capita (2016)—WHO threshold for 'highly cost-effective' (US $)		1,466 (Independent Online Desk 2016)
3× GDP per capita (2016)—WHO threshold for 'cost-effective' (US $)		4, 398

10.2.5 Coverage of the vaccine

The Expanded Program on Immunization (EPI) is the highest priority in Bangladesh and it is recommended that children complete the schedule of immunizations during their first year of life. The current coverage rate of all vaccines is quite impressive; currently the coverage of BCG,

pentavalent vaccine (3-doses) and polio vaccine (3-doses) is above 91% according to the latest survey (NIPORT 2016). To assess the efficacy of ROTAVAC vaccine a randomized placebo-controlled trial study was conducted in India. The trial found that at least 96% of subjects received all three doses of the vaccine although it would be lower in real life universal vaccination program (Bhandari et al. 2014). However, the same vaccination coverage rate also observed in a pentavalent rotavirus vaccination trial in rural Bangladesh (Zaman et al. 2010). Recently a large oral cholera vaccine trial was conducted in urban Bangladesh where the migration rate is higher than the other parts of the country and found that the two dose vaccine coverage was at least 65% of that area (Qadri et al. 2015). In this analysis we assumed that the rotavirus vaccination will be similar to moderated coverage like the cholera vaccination coverage. However, higher migration implies greater transmission and thus possibly there might be a larger role played by herd immunity. In this model like earlier studies we used the vaccine coverage from 40% to 96% for uncertainty analysis (Bhandari et al. 2014; Wilopo et al. 2009; Diop et al. 2015) (Table 10-2).

10.2.6 Costs of illness due to childhood rotavirus

Rotavirus infection is a significant cause of childhood hospitalization and found that those who hospitalized for acute gastroenteritis, 64% of them were exposed to rotavirus infections (Satter et al. 2017; Ahmed, Kabir, Aminar Rahman, et al. 2009) Recently, a study showed that, approximately 44% of the diarrheal patients received inpatients care and remaining patients utilized the out-patient services (Sarker, Sultana, Mahumud, Meer, et al. 2016). In addition to substantial morbidity, there is growing evidence of the economic burden for households and for providers created by rotavirus. In Bangladesh, a recent study showed that the average cost of rotavirus illness was approximately US$ 84, including both direct and indirect costs (Arifeen et al. 2016). In public facilities the treatment costs were shared between public and households level while in private facilities, households bear all the treatment costs. A study conducted in a similar region showed the average inpatients and outpatients treatment cost of rotavirus illness was US$ 74.26 and US$ 3.88 respectively (Tate et al. 2009; Megiddo et al. 2014). However, it was also found that approximately 85% and 45% of the total cost of illness was incurred by the hospital for treating the rotavirus inpatients and outpatients respectively (Ahmeti et al. 2015).

10.2.7 Sensitivity analysis

We conducted one-way sensitivity analyses where we varied the value of each input according to other published and unpublished values in order to ascertain the impact of uncertainty in input values on the cost-effectiveness ratio. In scenario analyses, the cost-effectiveness ratios were

estimated using the low or the high values of selected parameters and compared with the base-case scenario i.e. no-vaccination strategy.

10.3 RESULTS

Input parameters for estimating the childhood rotavirus disease burden, service utilization and costs, vaccine coverage, efficacy duration of protection years and vaccine delivery related costs are summarized in methods section (Table 10-1). The model's results for costs and outcome for static cohorts from 2016 to 2017 for the universal childhood rotavirus vaccination are presented below.

10.3.1 Health Impact of vaccination

The outcomes presented in Table 10-2 reflect the projected health outcomes when indirect effects are ignored. We estimate that introducing rotavirus vaccination will avert approximately 1.8 million rotavirus cases over a two-year period. Once the vaccination program is fully implemented, vaccination is estimated to avert over 50 thousand outpatient admissions, 40 thousand inpatient admissions and 49.46 thousand DALYs averted and more than 2.5 thousand deaths per year.

10.3.2 Cost and healthcare utilization

Our results reveal that within the modelling time horizon, introducing universal vaccination for young population, approximately US$ 5.8 million costs could be saved from health system perspective whereas at least US$ 5.63 million costs were saved by preventing inpatient visits. The costs averted due to vaccination are higher from societal perspective (US$ 7.06 million) due to inclusion of household out-of-pocket cost and including the time costs of their caregivers.

10.3.3 Cost effectiveness estimates

A universal rotavirus vaccination in Bangladesh would cost the public approximately US$ 73.22 million for the under-five population cohort although a number of inpatient admissions and outpatient visits could be averted. The cost per DALY averted of introducing the rotavirus vaccine compared to status quo is US$ 740.27 and US$ 728.27 per DALY averted from the health system and societal perspective respectively. Both incremental cost-effectiveness ratios (ICERs) fall below the 2015-2016 fiscal year gross domestic product (GDP) per capita in Bangladesh (US$ 1,466) which is used as a threshold for determining the cost-effectiveness of an intervention.

Therefore, these results demonstrate the likely cost-effectiveness of universal childhood rotavirus program in Bangladesh according to WHO criteria (Table 10-1).

Table 10-2 Key vaccination program outcomes over 2 year's period

Parameters	Health System Perspective	Societal Perspective
Population cohort ('000)	15,175.00	15,175.00
Average costs per vaccine, US$	1	1
Average delivery costs per fully vaccinated child, US$	0.84	0.84
Total inpatients cost averted, US$ ('000)	5,673.94	6,675.23
Total outpatient cost averted, US$ ('000)	176.59	392.42
Total costs averted, US$ ('000)	5,850.53	7,067.65
Net costs of the vaccination, US$ ('000)	73,228.24	72,080.99
Total number of cases averted, ('000)	180.61	180.61
Total number of deaths averted ('000)	5.01	5.01
Total DALYs averted ('000)	98.92	98.92
Incremental cost-effectiveness ratio (ICER) per		
- DALY averted, US$	740.27	728.67
- Case averted, US$	405.46	399.1
- Life saved, US$	14,596.44	14,367.76
GDP Thresholds (for references)		
Cost-effective (3* GDP/capita)		
Very cost-effective (GDP/capita)	Yes	Yes

Costs and DALYs are discounted at 3% per year

10.3.4 Scenario analysis

Figure 10-1 and Figure 10-2 represents the results of varying select model input values on the cost-effectiveness of rotavirus vaccination from the health system perspective. The results of the deterministic sensitivity analysis showed that vaccine price, vaccine delivery cost, disease incidence, case fatality rate, vaccine coverage and vaccine efficacy were among the most important parameters that can change the ICER. These results are very conservative because we consider a simple static model and ignore the herd immunity of rotavirus vaccination. However, study indicated that in long term a significant proportion of the population might be protected against rotavirus infections due to herd effect of vaccines (Jit & Brisson 2011). In Figure 10-1, on the basis of WHO threshold, from the health system perspective, the rotavirus vaccine was highly cost effective in some of the least favorable scenarios for vaccine introduction, namely low incidence rate, low vaccine coverage, low efficacy, low healthcare utilization costs, low mortality rate and moderate price of vaccine. However, the price of the vaccine is the most influential parameter and our analysis showed that at current scenario, if the price of vaccine was at its highest (e.g. US$ 10 and above per vial i.e. market price range of currently available rotavirus vaccine was US$ 16 to US$ 25 in Bangladesh), then it appeared as a cost-ineffective option, although up

to US$ 9.40, the universal rotavirus vaccination is cost-effective in Bangladesh. Similar results were also observed for societal perspective (the figure is not presented here). This suggests that the model results are robust to changes in the value of all major variables, however, there is a need to ensure that the pricing of the vaccine is appropriate in the Bangladesh context. In figure 10-2, vaccine price, vaccine delivery related cost, incidence of disease, case fatality rate and vaccine efficacy and duration of vaccine protection are the most influential factors.

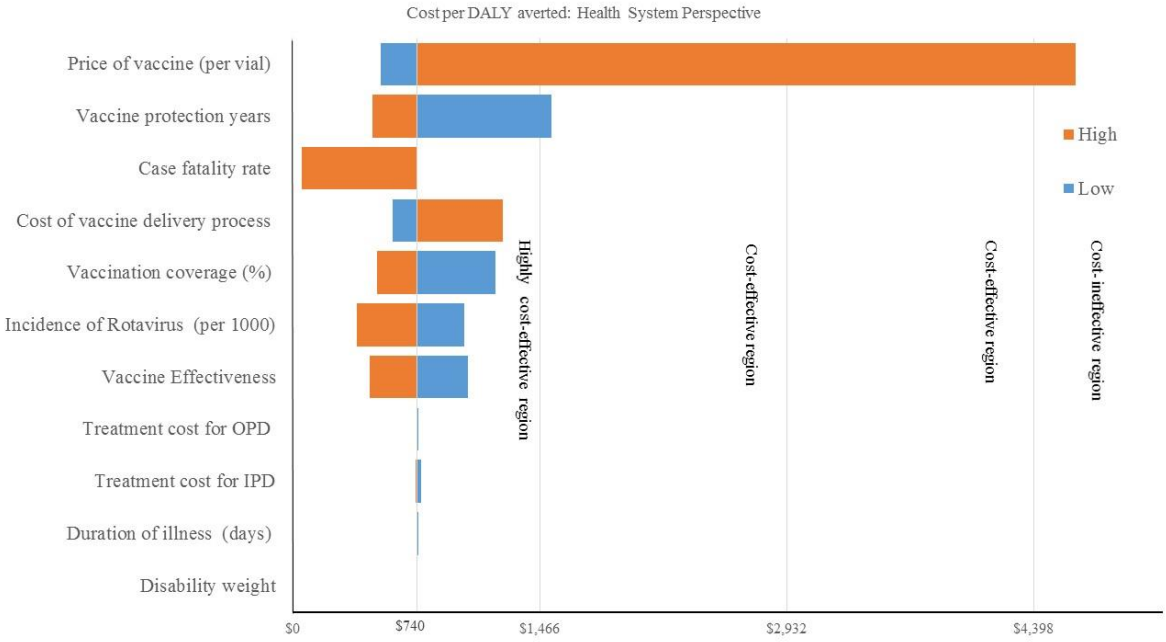

Figure 10-1 Costs per DALY averted: Health System Perspective

10.4 DISCUSSION

Several observations emerge from our analysis. The results of this evaluation suggest that universal childhood rotavirus vaccination would be highly cost-effective and would substantially reduce childhood illness and death due to rotavirus vaccination in Bangladesh. The analysis was performed using country level data where possible and relied on regional estimates LMI countries when national data were not available. Due to limited country representative data on the burden of rotavirus in Bangladesh, very limited studies are available, and this is the first cost-effectiveness analysis of rotavirus vaccination in Bangladesh. Our analysis showed that introduction of universal rotavirus vaccination would be a highly cost-effective investment from the health system (US$ 740.27 per DALY averted) and societal perspective (US$ 728.67 per DALY averted). Even in the lowest scenario the future rotavirus vaccination program will be a cost-effective option for health

system and societal perspective although we ignore the indirect effects of the vaccination. These cost-effectiveness ratios could provide a useful initial point for comparing the value for money of investments for rotavirus vaccination against the other rotavirus prevention programs such as water and sanitation interventions.

Results generated from this study are consistent with other results on the cost-effectiveness of universal rotavirus vaccination from previous studies conducted in many LMI countries in worldwide (Megiddo et al. 2014; Diop et al. 2015). A study using simulated agent-based model observed that introducing rotavirus vaccination in Indian population is a cost-effective option and which will significantly alleviate disease and financial burdens in Indian households (Megiddo et al. 2014). A country-led analysis from Senegal found that cost-effectiveness of rotavirus vaccination was US$ 92 and US$ 73 per DALY averted from the health system and societal perspective which is approximately 10 times lower than country context gross domestic product (Diop et al. 2015). In Kenya, the cost-effectiveness ratio per DALYs averted ranged between US$ 142 to US$ 288 from the societal perspective which is 15 times lower than its GDP per capita (van Hoek et al. 2012). Our results showed a cost per DALY averted relatively higher than the above studies and approximately 2 times lower than GDP per capita in Bangladesh. The short time horizon (2 years) was used in our analysis compared to the above studies which might lead for higher cost-effectiveness ratio per DALYs averted. Another reason is that we used the low case fatality, and rotavirus incidence rate is also conservative as those data comes from the estimation of rotavirus related hospitalization. Our estimation indicated that by introducing rotavirus vaccination we can prevent approximately 2500 deaths although this underestimates the real burden of rotavirus disease, as the community occurring rotavirus was not captured due to limited data. In a review study, it was observed that in LMI countries in Asia the cost per DALY averted lay between US$ 22 to US$ 2,007 due to rotavirus vaccination, however, the price of the vial ranged between US$ 1 to US$ 30 (Ozawa et al. 2012). This study found that that if the price of the ROTAVAC vaccine is 2.6 and 9.4 times higher than the current price of a vial (US$ 1), the vaccination program still a ‘very cost-effective’ and ‘cost-effective’ option. The conclusion from these findings is that the universal childhood rotavirus vaccination program remains cost-effective even at the higher price of vaccine, which is encouraging for those countries which are no longer GAVI subsidized. In Vietnam, a universal rotavirus vaccination study found that if the price per vaccine is US$ 7.26 or less then the immunization program was the cost-effective from a societal perspective (Fischer et al. 2005). In Uzbekistan, the universal rotavirus vaccination would be cost effective with the price ranges up to US$ 2, however case fatality and vaccine efficacy are the

most influential parameters which made the intervention cost-effective as our study also demonstrated (Isakbaeva et al. 2007).

Our uncertainty analysis showed (Figure 10-1) shows that from the health system perspective the future vaccination will be cost-effective even at the higher price of vaccine (up to US$ 9.4). The societal cost per DALYs averted was in line with these results. We did not consider the indirect effects from averted transmission and considered the young population which has no own indirect costs like income loss and opportunity costs which might affect the cost-effectiveness ratio. Our results showed that the cost per case and death averted were US$ 405 and US$ 14,596 from the health system perspective whereas US$ 399 and US$ 14,368 from the societal perspective. Like our study, a national rotavirus study conducted in Brazil from the health system perspective found that the cost per DALY and per life saved were US$ 643 and US$ 21,643 respectively (Constenla et al. 2008). In Thailand, from a health system perspective the cost per life saved was US$ 11,800 which is lower than Bangladesh scenario. These studies used relatively longer time horizon (5 years) compared to our study, and generally for a longer time horizon the intervention becomes increasingly cost-effective at reducing the incidence of the particular disease (Jit & Brisson 2011). Our uncertainty analysis (Figure 10-2) indicated that the cost per case and death averted ranged between US$ 210 vs US$ 2,544 and US$ 1,058 vs US$ 91,578 for the higher and lower estimation respectively.

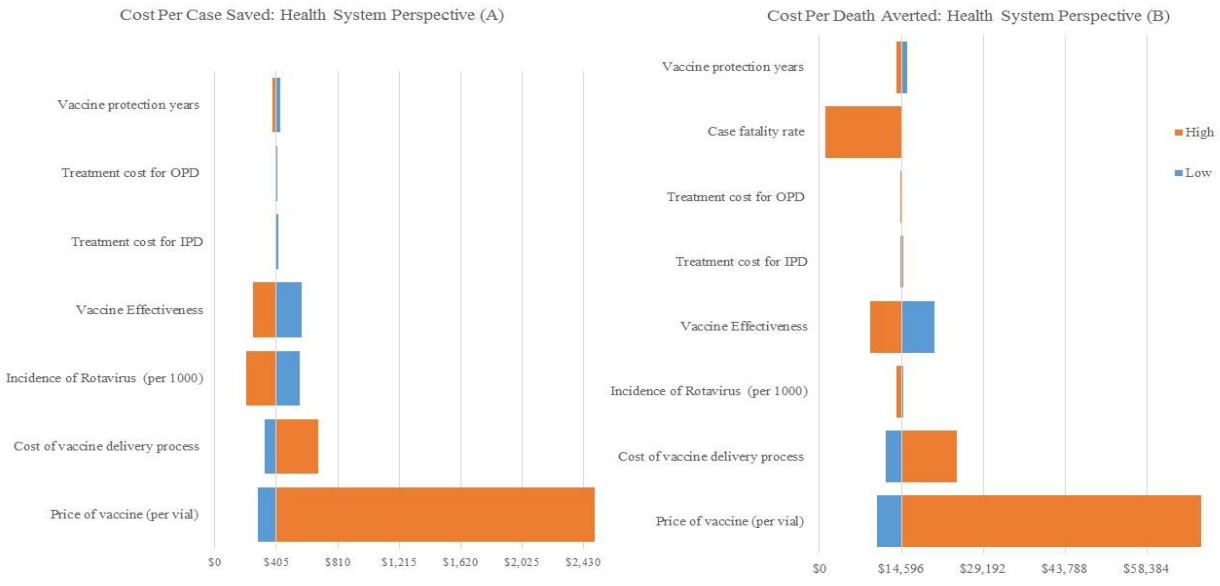

Figure 10-2 Changes in input parameter on ICER per case averted (A) and death averted (B): Health System Perspective

Our study, like most others, uses the GDP thresholds level proposed by WHO. The GDP threshold might be a useful screening tool but should not be the only consideration for vaccination investment as there are other issues such as feasibility, affordability, alternative interventions and other local consideration which are not accounted for in the threshold level decision rule. The success of vaccination programs depends on many other factors such as human resources and cold chain and logistics management (as maintaining vaccine at optimum temperature have become more complex due to nature of the vial). Further, effective and efficient vaccine delivery is also required to improve the equity of service. However, in resource-poor countries, decision-making processes need to take both of the technical and political consideration (Hipgrave et al. 2014). Many studies highlighted the importance of political factors in introducing the new vaccine in a country (Brooks et al. 1999; Bryson et al. 2010; Haas et al. 2009) and 'political rationality' was even more important for decision-making process than 'technical rationality (Lin 2003).

To inform policy makers in resource-poor settings like Bangladesh, our study demonstrated the introduction of universal rotavirus vaccines in routine childhood immunization would be a good investment with respect to health care and costs. A number of similar studies conducted in other LMICs demonstrated the childhood rotavirus vaccination is highly cost-effective and appeared 'good value of money' from the public perspective. However, those studies used various assumptions, a wide range of epidemiological, clinical, and economic parameters and also used different model and so the findings may not be directly comparable (Jit et al. 2011; Smith et al. 2011; Ortega et al. 2009; Abbott et al. 2012; Tate et al. 2009; van Hoek et al. 2012; Flem et al. 2009; Patel et al. 2013; Diop et al. 2015; Isakbaeva et al. 2007; Fischer et al. 2005). An optimum decision should be made by comparing universal rotavirus vaccination with alternative public health and healthcare interventions in Bangladesh (such as diarrheal case management strategies, other diarrheal prevention program, sanitation and hygiene related interventions and even introducing with the other vaccines). Again, cost-effectiveness results are highly dependent on input parameter, especially mortality, vaccine price and efficacy-related information. Hence, reliable estimates on childhood mortality, diseases outcome and cost estimation are important so that a standardized comparison of cost-effectiveness across a range of health interventions could be made.

Although our analysis concludes that the future rotavirus vaccination would be highly cost-effective, there are some limitations in this study as we made several assumptions which could affect the cost-effectiveness ratio. For example, uncertainty with the respect of rotavirus incidence rate, mortality, price and efficacy of vaccine. Furthermore, this analysis did not consider dynamics

or the herd protection effects, although rotavirus vaccination protects a substantial part of the young and adult population. Further, in certain endemic regions, it was observed that incorporating the herd protection made the vaccination program cost-effective which was not previously (Jeuland, Cook, et al. 2009). Again, we did not explore other rotavirus vaccines available in market which might be add depth to our study. However, sensitivity analysis showed that, despite these uncertainties, the universal childhood rotavirus vaccination will be cost-effective from the health system and societal perspective. The study based on a simple static model using the direct effect of childhood universal rotavirus vaccination has helped to contribute the knowledge generation of future rotavirus vaccination program in Bangladesh as the government of Bangladesh is committed to introducing rotavirus vaccination program in national EPI schedule (MOHFW 2010). In addition, it has helped to highlight important gaps of country representative data, especially the lack of good quality information on rotavirus incidence and mortality and the economic burden of rotavirus illness.

10.5 CONCLUSION

Introducing of childhood rotavirus vaccination in Bangladesh scenario is estimated to be highly cost-effective and would offer substantial future benefits for young population vaccinated today. Other technical, programmatic, political priority, and social issues need to be considered in the process of making the decisions on the introduction of rotavirus vaccine in Bangladesh. The results of this analysis seek to contribute to an evidence-based recommendation about the implementation of rotavirus vaccination.

Declaration of Conflicting Interests The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding: Not finding

11 DISCUSSION AND CONCLUSIONS

Diarrheal diseases remain a crucial public health concern in Bangladesh as large number of people (approximately 2.7 million) utilise the healthcare facilities annually for this illness, leading to an excessive pressure on the country's health system. However, many diarrheal cases are often managed at home inadequately. Thus, the actual scenario considering the incidence and disease related mortality with economic losses are still hidden. Due to the absence of the social health protection scheme, the economically poor and marginalized population suffer most, as the out-of-pocket payment is the primary payment strategy for accessing most healthcare services in Bangladesh, and the OOP share of total health expenditure has been increased alarmingly from 55.9% (in the year, 1997) to 67% (in the year, 2015) (MOHFW 2015b). Therefore, a considerable number of people who belong to the lower socio-economic group often deprived from receiving healthcare during diarrheal episode. This would cause a "double burden" for the poorer households as a lack of drinking water, inadequate sanitation, an unhygienic environment and living conditions are often considered the risk factors of diarrhoea, which are associated with poorer communities. Furthermore, during the term of the illness, they also face excessive treatment costs, which are unaffordable for them and therefore sometimes act as a barrier in the seeking of formal care, which may have negative health consequences. Globally, diarrhoea is the second leading cause of death among children and prevails mostly in the underdeveloped regions of the world. Therefore, broad public health interventions and socio-economic development should be prioritized for tackling the incidence of diarrhoea related illnesses. However, due to the absence of clear comprehensive diarrhoea-related economic studies, the practical and policy significance of such devastating issues are often under shaded in resource-poor settings. In this aspect, I have conducted several health economic studies related to diarrheal diseases, which provide a valuable perspective on nation-wide (e.g. rotavirus) and targeted (e.g. cholera) vaccination programs. Both have been documented in this thesis project.

This thesis began with the rationale of the project, recounting the reason of prioritizing the preventive strategies for diarrheal diseases in Bangladesh, the importance of economic analysis and rationale for vaccine introduction in Bangladesh. Study I investigated the prevalence of childhood diarrheal disease, where the most critical factors were identified and documented. The study further explored the healthcare utilisation and associated factors of care seeking behaviour that occurred during diarrheal episode. A nationwide survey data was analysed in accomplishing these objectives. The subsequent studies were related to the health and economic burden of diarrheal infections and economic evaluation related studies. Among the subsequent studies, study

II and study III were related to economic burden of treatment cost. Study II demonstrated the comprehensive cost-of-illness study of diarrheal diseases from societal perspective. Study III particularly focused on cholera infections, where the household's exhausted resources (e.g. expenditure, time) for treating cholera cases were identified and measured through a community-based survey. Study IV was related to the identification, measurement and valuation of all resources that were consumed due to the implementation of a massive cholera vaccination program in urban Bangladesh. The households' demand for cholera vaccine was explored in study V, where a contingent valuation technique (e.g., WTP) was applied during the community-based household survey. The study also provided impressions on the potential benefits of the cholera vaccination program and the potential of marketing oral cholera vaccines in Bangladesh. The last two studies were related to economic evaluation, where study VI was allied with oral cholera vaccination and study VII was related to the childhood rotavirus vaccination in Bangladesh. The former study (study VI) was based on the empirical surveillance data in a high-risk urban area of Bangladesh, while study VII was related to the hypothetical introduction of the childhood rotavirus vaccination in Bangladesh. This was as the Government planned to introduce the rotavirus vaccination in the EPI schedule. Compiling all of the empirical studies, the project has documented the actual situation of diarrhoeal diseases and the possible effects of cholera and rotavirus vaccination strategies in Bangladesh. Finally, through the data provided, it can be theorised that this research project will contribute to the health system decision making process regarding the prevention of diarrheal infections and the future health economic research aimed at the benefit of society.

This section focused on the synthesis of leading verdicts and the possible implications for policy measures, elaborating the limitations of the thesis and suggested possible future scopes of research. After of which, some concluding remarks will be offered.

11.1 Main findings and implication for policy

Bangladesh is familiar with the innovation of oral rehydration therapy for treating diarrheal patients, which has saved millions of lives globally (Rehydration Project 2014). Oral rehydration solutions are available in any health facilities, and pharmacies, along with grocery stores and local retailers at a community level in Bangladesh. Likewise, zinc has been proven as an effective treatment for diarrhoea. This is also available in the form of a tablet and syrup. Further, Diarrhoea Case Management is a part of the successful project entitled, "Integrated Management of Childhood Illness (IMCI)", as implemented by the Government of Bangladesh with assistance from WHO, UNICEF and other partners since 1998 (MOHFW 2015c). As a consequence, over the last decades diarrhoea-related mortality had declined substantially in Bangladesh (NIPORT 2016). In spite of the aforementioned successful initiatives, diarrheal diseases are the prime cause of hospitalisation, and a large number of patients receive treatment from out-door services. Furthermore, there is a significant rate of childhood related mortality associated with childhood diarrheal infections (Tanka et al. 2007; Satter et al. 2017). This sub-section summarised all of the findings associated with this thesis project which is briefly discussed below.

Table 11-1 Main findings and policy implications

Main findings	Policy implications
• The prevalence of diarrhoea is frequently observed in the first two years of life (Chapter 4, page 85,86) • The households utilized treatment services from various sources of providers (e.g. public, private and informal care) (Chapter 4, page 89) • Wealth status is a significant factor for seeking care and the household who had access to electronic media communication like radio, television, are most likely to receive treatment care from the public facilities (Chapter 4 page 90) • The average total societal cost of illness per diarrheal episode was US$ 67.18, whereas 40% of the total cost borne by out-of-pocket and cost burden was significantly highest for poorest households (Chapter 5 page 105,109) • Medicine cost was the highest cost driver and people often purchased drug/medicine from nearby pharmacies immediately without consulting doctor (Chapter 5 , page 104, Chapter 6, page 120)	• Policy makers should prioritise for initiating community based diarrheal prevention program targeting the poor and vulnerable people to overcome both communication inequalities and income related inequalities (Chapter 4, pages 92-93) • Access to treatment care can be improved through working in a partnership with local health care practitioners, pharmacies and community-based organizations (CBOs) and public facilities (Chapter 4 page 88,89; Chapter 5, page 106) • Removing financial barriers for the poorest population ; financial risk protection could be an option which is the core theme of the universal health coverage (Chapter 5, page 107)

• The average societal cost of illness per cholera episode was US$ 95.76, whereas the cost per fully immunized person was only US$ 3.96 (Chapter 9, page 164) • OCV purchasing cost was 58% of the total cost of vaccination. The cost per vial (Shanchol™) was US$ 1.06 whereas US$ 1.67 was required for vaccine delivery related activities per fully immunized person (Chapter 7, pages 132, 135) • Approximately 99% of the people had willing to pay for OCV (mean US$ 2.23, median US$ 1.92) (Chapter 8, page 146) • The OCV demand is high for under-five children (Chapter 8, page 147) • The cost of cholera vaccine could be managed from the current per capita WTP which might be attractive for local pharmaceutical companies for the production of OCVs (Chapter 8, page 147) • Household income was the crucial positive factor for OCV as the wealthier families habitually demand cholera vaccines more than for low income households (Chapter 8 , page 150) • The cholera vaccination is a very cost-effective investment for younger children in Bangladesh (Chapter 9 page 166) • Vaccinating the whole population appeared as a cost-effective investment even in the shorter time horizon and lower efficacy rate and without herd immunity of vaccine (Chapter 9 page 168) • The childhood rotavirus vaccination is a cost-effective investment in Bangladesh perspective (Chapter 10 page 183) • There were important gaps of country representative data, especially the lack of good quality information on incidence and mortality, case fatality and economic data related to rotavirus infections (Chapter 10 pages 180,189)	• The policy should be targeted for strict regulation on unauthorized medicine distribution in the pharmacies in order to control excessive OOP cost (Chapter 5, page 104; Chapter 6 page 120) • Low-cost vaccine will be more acceptable for cholera immunization program which could be reduced the cost of vaccination (Chapter 7, page 132; Chapter 8, page 145; Chapter 9, page 166; chapter 10, page 184) • OCV should be available in private market (Chapter 8, pages 146,148) • A portion of cholera vaccination cost could be managed by introducing a direct user fee (Chapter 8, pages 146,148) • The provision of partially or fully subsidized OCV will necessary for the poor and needy to ensure the high OCV coverage (Chapter 8, page 147,148) • Young children should be prioritized for OCV (Chapter 8, page 147; chapter 9 page 166) • The policy makers and the health authorities should be thinking about the introduction of OCV in high-risk urban populations and refugee camps to control cholera outbreaks (Chapter 9, pages 166-169) • Since the government is committed to introduce rotavirus vaccination in EPI, it would be necessary to introduce the rotavirus vaccination immediately, considering health and economic perspective (Chapter 10, page 183) • As a part of the cholera / rotavirus control initiatives, hospital-based surveillance system should be introduced in all hospitals/ clinics for better understanding of health and economic burden of such infections. (Chapter 9, page 169; Chapter 10 page 189)

This thesis unfolds with the prevalence and associated factors of childhood diarrheal infections. Although numerous studies focused on the risk factors of childhood diarrheal diseases in Bangladesh, most of the studies belong to the part of hospital and community-based surveillance system, such as hospital-acquired diarrhoea (Bhuiyan et al. 2014), pathogen-specific (Das et al. 2015), hospital based prevalence and severity (Ahmed, Kabir, Aminur Rahman, et al. 2009), community-based high risk population (Chowdhury et al. 2015), pathogen-specific risk factor analysis (Colombara et al. 2014a), rural hospital-based utilisation (Das et al. 2013) and urban slum (Haque et al. 2003). There are no studies regarding age-specific prevalence and determinants of childhood Diarrheal Diseases (CDDs), provider specific healthcare utilisation rate or the influencing factors of care seeking behaviour of households using nationwide survey data. For addressing the knowledge gap, study-I utilised the nationwide DHS dataset. I investigated the prevalence, healthcare utilisation pattern and associated factors of CDD so that nationwide disease burden and diarrheal case management strategies could be understood properly in order to assist the adoption of the policy and the implementation of the diarrhea related preventive program.

Recent estimation showed that diarrhea is responsible for 9% of all deaths among <5 children globally and children below 2 years are more vulnerable for diarrhoea related mortality (Fischer Walker et al. 2013; Liu et al. 2016). The current study also observed that diarrhea prevalence is common among children below 24 months of age. However, children at their second year of life are the most critical for childhood diarrhea and the prevalence is significantly higher (8.62% vs. 5.71%). The time period is crucial for certain reasons, such as the children being at a state where they become more active outside of the home, playing with whatever, and putting it into the mouth. Therefore, the unhygienic physical environment and living conditions push them to greater risk of diarrhoea (Hussain & Smith 1999). Furthermore, the prevalence of diarrhea was found higher among stunted children (7.31% vs. 4.80%), children of young mothers (6.06% vs. 3.88%), homemakers (6.40 % vs. 4.98) and users of unimproved (e.g. facility flush/pour flush not to sewer/septic tank/pit latrine) toilet (6.78% vs. 5.18%). Young mothers (aged below 20 years) often face difficulties in deal with the diseases due to the limited knowledge of preventive strategies and about exclusive breastfeeding, as it is well established that the lack of breastfeeding and malnutrition often leads to childhood diarrheal diseases (D'Souza 1997; Hussain & Smith 1999). Therefore, policies should target young mothers to improve the physical environment, as well as to acquaint them regarding the advantages of breastfeeding and to train them to handle their children during the early stage of their lives. The study also documented that geographic regions were also linked with CDDs, while prevalence varies from 1.81% to 7.10%, depending on the

regions. Urban slums, overcrowded population, poor water and sanitation system and risk of natural disasters (e.g. floods, tidal surges) were common for higher prevalence.

Though the study was unable to investigate the etiological agent across regions, such an investigation could be useful for policymakers to develop preventive and control programs. Results from the household survey also indicated that most of the young children received treatment from the formal care (75% of the total). However, 23% of mothers reported that they did not seek any treatment during the diarrheal episode. Although this study did not report the reasons of not seeking healthcare, evidence suggested that diarrheal patients are often managed inadequately by home treatment, which might be associated with its poor outcome (Chowdhury et al. 2015). Therefore, future behaviour communication program should be adequately implemented. Various factors, such as age, education and occupational status of mother, wealth status, household toilet facilities and access to electronic media (e.g. radio and television) deployed households in choosing the healthcare providers. Higher parental educational status appeared as a protective factor for preventing CDD. The reason was as such households often participated in various prevention and promotional related activities and were conscious about their hygiene. Furthermore, they contributed to improve toilet facilities, which have a potential impact in reducing the risk of such infectious diseases (Maria et al. 2011; George et al. 2014; Colombara et al. 2014b). Households having access to electronic media were more inclined to seek care from public providers, as different promotional activities, such as dramas, advertisement, and behaviour change messages were regularly broadcasted, which had a pivotal role for improving public health (Jung et al. 2015; Menon et al. 2016). Thus, massive behaviour change programs with the aim of targeting households with no access to the electronic media for controlling childhood diarrhea are recommended. The study also observed that the wealthiest households frequently utilised the private clinics and/or hospitals rather than public facilities, although poorest people are always exposed to a financial crisis, which is consequently associated with the inadequate utilisation of health care services (Navaneetham & Dharmalingam 2002; Taffa & Chepngeno 2005), or could even lead to the deprivation from the benefit of healthcare (Allen et al. 2017; Adeyanju et al. 2017). Therefore, national policymakers and donors need to set priorities for initiating community-based program for poor and vulnerable people which can help to reduce both communication and income related inequalities.

In addition, scarcity of resources is commonly recognized as a barrier for ensuring healthcare services, particularly in resource-poor settlings like Bangladesh. In addition, identifying new source of healthcare is a major political decision and usually requires a longer time for the

development of any financial strategies. Therefore, effective utilisation of available resources is crucial, which further means that the limited resources should be used optimally, so that the maximum number of people can benefit from quality healthcare services. Historically, diarrhoea is the most prevalent disease and can affect all people irrespective of age and socio-economic grades. In Bangladesh, this causes ~2.6 million diarrheal patients visiting healthcare facilities every year. Furthermore, number of cases occasionally explode during the early summer and thus additional resources like beds, doctors, nurses and medical equipment are required on an urgent basis (The Daily Star 2018).

From study I, it was observed that households utilised the healthcare services from various providers in most cases. As a follow up, study II investigated the economics of diarrheal diseases from the societal point of view. Thus, the treatment cost borne by households and public providers were analysed, as those treated in public hospitals are highly subsidized and costs are often shared among both parties, i.e. households vs. hospitals (Andaleeb 2000). The study found that average economic cost of treatment was US$ 67.18, with households contributing most of it (US$ 53.23). The OOP cost for households was US$ 21.51, which was 11.75% of their monthly income. However, among the poorest quintile, it reached up to 21.45%. This treatment costs led to an economic shock for many households as 86% of households rely on their income for mitigating this excessive cost. This is crucial for the poorest socio-economic group as they often have to sacrifice other goods and services from their livelihoods for the payment of this excessive treatment cost. Without proper social health protection, many poor and vulnerable people cannot afford care and are inadequately treated at home, which could result in negative health outcomes and even death (Carl Forsberg 2007). Therefore, to reduce financial barriers for the needy financial risk protection might be an option, which is the core theme of the universal health coverage of the recent sustainable development goals (United Nations 2016; WHO 2017e). From study I and II, it was observed that the households typically visited multiple providers for treatment care, due to the plural nature of health system in Bangladesh. Therefore, access to treatment care can be improved through working in partnership with local health care practitioners, pharmacies and community-based organizations, and public facilities. However, policy makers should focus on the diarrheal prevention program, which can reduce the cost of care for these patients. Such multi-sectorial approaches should be taken in order to cut down the excessive economic burden, as preventive measure and rapid, proper treatment strategies could minimize the diarrheal episodes, hospital days, adverse health outcomes, and even reduced the pressure of health budget (Shillcutt et al. 2016).

Study II also estimated the providers' actual cost of treatment after adjusting the payment paid by households, such as the user's fee, subsidised cost of diagnosis, and hospitalization. The average treatment cost per inpatient and outpatient were US$ 26.80 and US$ 1.12 respectively, while approximately 44% of diarrheal patients utilised hospital care. Thus, a bulk of non-medical resources (95% of the total), such as food, accommodations and staffing were required for treating these hospitalised patients. Since treatment care from private hospitals and clinics are often unaffordable, and the NGO hospitals provide limited services, many low-income people solely depend on the public hospitals for care. By adopting appropriate prevention strategies, many diarrheal cases could be averted and could be treated in out-patients ward. If this occurs, then the substantial financial resources will be saved. Consequently, physical resources, such as hospital bed, medical equipment, doctor's time, could be used for other treatment purposes, as patients often are admitted to public hospitals for various reasons.

The district public hospitals act as a secondary level referral health facility and provide care in several specialty areas, consisting of 100 to 250 beds. Although the district hospitals provides both inpatient and outpatient services, the budget allocation solely depends on the number of beds, bed days and staff, without considering the outpatient load (Ensor et al. 2003). Effective utilisation of the allocated budget in public hospitals is important for sustainable and quality care. The current resource allocation in hospitals is based on the capacity of hospital (e.g. number of beds and staffs), which suggest "need based" resource allocation goals are not considered in the system. At this nature, patients with illness of different severity levels are often considered similar and even variations in utilised treatment activities (OT, diagnostic test etc.) are yet not accounted. Thus, the system is often sometimes called an "inequitable and inefficient" health system (Ensor et al. 2003). Indeed, the distribution of patients and disease-specific treatment requirement is crucial for ensuring the efficient use of scarce resources, which are not considered in budget allocation, as seen above. This hospital based diarrheal costing study might be a starting point for discussions targeting need-based resource allocation considering treatment cost and the proportion of patients of the facility.

The next four studies (study III - VI) are related to the cholera infections; a special type of watery diarrhoea that is caused by the bacterium, *vibrio cholerae* O1 (or less frequently, O139) and is critical for all ages which can lead to death within a very short time if remain untreated or not managed properly. The epidemiological burden of cholera infection is often discussed in the published literature but the economic evidence that considers the broader societal perspective is

still limited in the context of Bangladesh. It has been well established that any severe infectious illness is associated with high medical cost and also reduces household labour supply and stopping earnings, which might be devastating, significantly influencing livelihoods and cause economic disruption and catastrophic economic burden (WHO 2014a; Khan et al. 2016; Mahumud et al. 2017; Van Doorslaer et al. 2007; Khan et al. 2017). While the cost of illness for cholera in rural Bangladesh had been investigated in an earlier study (Poulos et al. 2012), such information is limited for urban settings. Our estimation (study VI) showed that, the average household treatment cost per episode was approximately US$ 36.94, and the indirect cost (time cost of patients and caregivers) was the largest share (study III), although the average treatment cost become lower (US$ 30.4) in the off-peak cholera season. Due to limited laboratory tests for cholera confirmation, we only interviewed patients who came from the surveillance area for seeking care and laboratory confirmed as cholera cases by icddr,b hospital (in Dhaka). Thus, the OOP cost might be underestimated as icddr,b hospitals provide all diagnostic tests and medicines to the patients free of charge. Despite such limitations, the study demonstrated that the medicine and transportation costs are major cost drivers, as noted in earlier literatures (Sarker et al. 2014; Mahumud et al. 2017). Self-medication is an escalating public health problem in Bangladesh and people generally purchase medicines is used as their own judgment and without any prescription (Saha & Hossain 2017; M. Biswas et al. 2014). Although all diagnostic tests and medicines are provided free of charges at icddr,b hospital, some of patients still had to purchase extra medicines from the nearby pharmacies (study III). Previous study observed that approximately 97% of the drug-sellers recommend medicine without checking the complete history of disease, which lead to increase the OOP costs. However, the patients' request is another factor which upswings the expenditure of the household (Saha & Hossain 2017). Again, it was observed (study I and II) that pharmacies/drug retailer often acted as an important healthcare provider and people sought care from pharmacies due to its accessibility, short waiting time, affordability (because they are able to purchase the medicine in small amounts), convenient opening hours, and on occasion, even personal acquaintance with the drug sellers (Chowdhury et al. 2017; Adhikary et al. 2018) might be associated with high spending. Thus, the policy should aim at putting strict regulation on unauthorized medicine distribution in the pharmacies for controlling excessive OOP cost.

As icddr,b is a non-profit hospital, all forms of care such as diagnosis, medicine, food, and lodging are provided free of charge to all patients. The hospital-based costing study (study VI) indicated that icddr,b hospitals have to spent approximately US$ 52.23 for the treating of a cholera patient. Therefore, to recover from a cholera infection, approximately US$ 95.76 (price 2015) was

required from a societal perspective. This estimation might be higher due to the nature of icddr,b hospital as the staff salaries, as well as other maintenance activities are relatively costlier than the public hospital. However, the previous study (study II) indicated that approximately US$ 27 was spent for providing diarrhoea related inpatient care. Therefore, a huge economic loss could be saved if cholera infection could be prevented or controlled properly. As a part of the cholera control initiatives, a cholera surveillance system might be introduced in all level of hospitals so that the actual disease burden could be analysed. However, few cholera surveillance systems have been initiated recently but such surveillance are study specific (Paul et al. 2015). Although country representative cholera data is not fully available and accurate, experts assess that 0.4-1 million cholera cases occurred annually, while at least 0.3 million cases turn into severe cholera, which indicate the emergence of introducing cholera prevention initiatives (Jeuland, Lucas, et al. 2009; Ahmed 2009; WHO 2009b; icddrb 2011). The latest estimation suggested that approximately 66 million people are at risk of cholera and approximately 109,052 cholera cases and 3,272 deaths occurred annually in Bangladesh (Ali et al. 2015). Thus, huge economic costs are associated with cholera infections annually in Bangladesh.

Among the various diarrheal disease prevention program (chapter 2), immunisation has become one of the most predominant and successful health intervention and is often considered as 'best buys' (Doherty et al. 2016). As Bärnighausen and colleagues notes, the benefit of any vaccination program can be divided into two categories – 'narrow' and 'broad' benefits (Bärnighausen et al. 2014; Bärnighausen et al. 2011). In addition, Jit et al. documented the benefits of immunisation programs can be described as at least four different ways (Jit et al. 2015). The vaccinated individuals could be benefited through improving health by avoiding cases, deaths and by saving QALYs/ DALYs, which ultimately reduced the direct cost of vaccinated person, their families, as well as from public sector perspective. In addition, huge productivity-related benefits could be achieved by avoiding lost working hours due to sickness or death of a sick person, and for his/her caregivers. This is crucial for low-income people or informal workers, as they solely depend on their daily income. In this project, we found that the average household cost of treating cholera was US$ 36.94 per episode, where indirect cost contributed to 81% of the total cost. In a community survey in Mirpur, we found that most of the dwellers are labourers and are working in garments sectors. Thus, they are mostly suffered economically during illness. In additionally, approximately US$ 52.23 was consumed for treating per patient from hospital perspective which could be saved by implementing the oral cholera vaccination. The other productivity-related benefits could be potential lifetime earnings which might be increased due to improved cognition

and educational attainment, although it is difficult to measure accurately in short time and thus such benefits were excluded in this project (study VI).

The immunization program has a beneficial role in considering community and health system level impact as the unvaccinated population in a community could benefit as a result of ecological effects, such as herd immunity, eradication and avoiding antibiotic resistance (Jit et al. 2015). Vaccinations improve the equity as everyone is vaccinating equally and thus mortality could be avoided in all strata of societies, and evidence suggest that vaccination could improve the educational outcomes of children in lower income group (Bishai et al. 2003; Bärnighausen et al. 2011; Driessen et al. 2011). Thus, policymakers should adopt vaccination strategies that target poor and vulnerable people, so that equal distributional health outcome could be ensured. Furthermore, vaccination improves financial security of households by avoiding catastrophic expenditure of healthcare, as the poor often suffer during a financial crisis (Study II). Immunisation could be contributed by changing the household behaviour, as by preventing disease, household disposable incomes will increase through the reduction of healthcare expenditure and avoiding lost wages, which will lead to increases the household consumption, savings and investment. Furthermore, labour income could also rise in future (Jit et al. 2015). In addition, immunisation may have a long-term macroeconomic impact and could contribute to the increase of gross domestic products by including life time productivity and vice versa (Bärnighausen et al. 2014). Further, cholera incidence would affect the demand channel of a country (Oxford Economics 2010). For instances, a cholera epidemic would affect the tourism sector (by declining tourists) and industrial sectors (by declining in export of food, garments etc.) simultaneously. However, the association between vaccination and long-term economic behaviours of household and macroeconomic level are often expensive and time-consuming, which is beyond the scope of this project.

Study IV is related to the cost of OCV, and the study observed that the cost of one vial of vaccine (Shanchol™) itself was US$ 1.06 and approximately US$ 1.67 was required for vaccine delivery related activities per fully immunized person. The price of vials was the main cost driver, as it consumed approximately 58% of total cost. Similar observation was also made in many vaccination trial studies (Naficy et al. 2001; Schaetti et al. 2012) although the cost of vaccines used in the EPI accounted for a small proportion of the total costs (Ebong & Levy 2011; Creese & Henderson 1980; Cutting 1980). Therefore, low cost vaccine is highly preferable in reducing the cost of vaccination. Furthermore, the staff salaries and other maintenance costs (e.g. transports, logistics) are relatively expensive in setting (nature due to the international organization)

compared to that of government employees in Bangladesh. Therefore, future public operated programs would be at lower cost than those found in this study. Study IV suggested that an attempt to reduce the cost per vial is likely to have a large impact on the total cost of immunisation program. Therefore, the low-cost vaccine will be more acceptable for future cholera immunization program through EPI in Bangladesh. Although the delivered vaccine, Shanchol™, is not available in the Bangladeshi market, a local pharmaceutical company recently initiated the production of a similar cholera vaccine, named Cholvax®, with the technical support of International Vaccine Institute (IVI) for the public sector in Bangladesh (Incepta 2016).

Financing and sustainability of immunization program is a major challenge and normally depends on the global donor commitment (Shen et al. 2016). Therefore, immunisation financing policy and planning should be introduced so that a portion of cost could be managed through domestic financing (Shen, Farrell, et al. 2014). This would include the introduction of user fee ("the cost sharing option") and ensure the availability of vaccine in private markets so that households can purchase required. For identifying new resources for future OCV program or increasing domestic financing, a willingness to pay study was carried out (Study V). The study observed that the average WTP for cholera vaccines (2 doses) were US$ 2.2 and most of the respondents (99.8%) expressed their willingness to purchase it for their personal and household protection against cholera infection. Policy makers should adopt the long-term financing strategies with this finding and also contribute to design future vaccination programs in a sustainable manner allocating resources within their available budget to expand such vaccines.

The study also witnessed that the demand for OCV is comparatively higher for children under five. This finding reflects that young children are the more vulnerable to cholera (IVI 2013). From the experience of the earlier study (Study III), it was observed that when younger children were infected with cholera, the household often spent more money for seeking treatment than for adult patients. Further, household risk aversion is a crucial influencing factor for demand for future OCV (Lucas et al. 2007; Islam et al. 2008) and households that have experienced cases of cholera stated relatively higher value of OCV than non-exposed households (study V). However, prior awareness of disease or having a personal history of a disease do not always lead to higher willingness to pay (Dickinson et al. 2016; Harapan et al. 2017; Palanca-Tan 2008). This study also indicated that household income was the crucial positive factor for purchasing the vaccines, as wealthier families habitually demand cholera vaccines more than low income households (Lucas et al. 2007; Kim et al. 2008; Islam et al. 2008). Therefore, policy should ensure free or highly subsidised OCV for the poor and vulnerable people, in order to balance participation. From study

IV, it was observed that the cost of cholera vaccine could be managed from the current per capita WTP which might be attractive for local pharmaceutical companies for the production of OCVs. Since the local pharmaceutical company has already initiated the cholera vaccine production (Incepta 2016) and assured that the production cost of the cholera vaccine might be below US$ 1 in Bangladesh (Incepta 2017). In this aspect, if the vaccine is available at above mentioned price, then at least 48% of vaccination coverage will be possible by using domestic financing (study V). However, there would still be 52% of population, mostly poor, who are excluded from the potential benefit of the vaccination. Therefore, the provision of partially or fully subsidized OCV will be necessary to ensure the high OCV coverage to all the strata of society. Study V observed that if the price of vials is reduced to 50% of current price (US$ 0.5) then at least 85% people could afford the OCV from private market. And the remaining portion (15%) of population will be benefited in terms of "herd immunity" of cholera vaccines (Jeuland, Cook, et al. 2009). The demand study (study V) also indicated that even at the higher price, there could still be a market for OCVs. While these would belong to wealthier households, if the poorer households co-located with wealthier one, the poorer households would benefit from the herd immunity of the vaccines, even if poorer households do not purchase the vaccine for themselves (Islam et al. 2008). Therefore, the OCVs should be available in the private market. Further, there might be a potential scope for recovering a certain portion of the financing cost of the immunisation program by introducing direct user fees against future cholera vaccination in Bangladesh.

The last two studies (Study VI and VII) are related to the economic evaluation of vaccination program, whereas cholera vaccination trial was focused on in study VI and the possibility of future rotavirus vaccination and cost-effectiveness analysis was carried out in Study VII. Cost-effectiveness analysis, a form of economic evaluations, is a necessary tool for introduction of new vaccine (Jit et al. 2013; Lydon et al. 2014). In this aspect, study VI focused on the cost-effectiveness of cholera vaccination in urban setting, where the empirical data has been utilised to estimate the cost per unit effect after the introduction of OCV. The study demonstrated that vaccinating the whole population in a high-risk cholera endemic area is cost-effective investment even in a shorter time horizon. The cost per DALY averted (US$ 3,467) lay within the range of WHO provided threshold level. These results indicated that the vaccination decision appeared as very cost-effective investment (US$ 768 per DALY averted) for younger children, even at a lower efficacy rate of the vaccine. Therefore, children need to be prioritised for the vaccination, as young children are more vulnerable to severe cholera cases (Harris et al. 2012). However, vaccinating the adults alone (above 15) was not a cost-effective investment (study VI) in the short term, when

compared to a longer time frame (Chesson et al. 2016; Laprise et al. 2014). However, incorporating the "herd immunity" could made the cholera vaccination program economically attractive (Jeuland, Cook, et al. 2009). Practically, it is often challenging to measure the herd immunity in a short time horizon and difficult to capture the natural immunity in populations with endemic cholera, especially in urban slums and when people are highly mobile (Longini et al. 2007). The study observed that vaccination price, duration of protection, case fatality ratio, vaccine delivery related cost and vaccine effectiveness were the most sensitive parameters (study VI). The current vaccine is not produced in Bangladesh and the vaccine delivery cost was borne by the provider (here, icddr,b) which had relatively high staff salaries compared to the government employees. Thus, government operated programs would have lower cost than the current program (study IV) and so a government run program distributing a locally produced vaccine would be more cost-effective. As such, policy makers and the health authorities should think about the sustainable production of such vaccines and should introduce this vaccine in cholera endemic areas, particularly in urban slums, refugee camps, and during any natural disaster, so that massive outbreaks could be controlled in time.

The final study is about the future childhood rotavirus vaccination, which is highly recommended by WHO (WHO 2009c). Bangladesh is also committed to introduce rotavirus vaccination program in national EPI schedule by 2018 (MOHFW 2010; Bdnews24 2017a). To inform policymakers of Bangladesh, this study demonstrated that introduction of universal rotavirus vaccines in EPI would be a good investment, with respect to health care and costs (study VII). The results indicated that introducing universal vaccination for young population could save approximately US$ 5.8 million costs from health system perspective, whereas at least US$ 5.63 million costs could be averted by preventing inpatient visits. The cost per DALY averted due to introducing the rotavirus vaccine compared to the status quo was US$ 740.27 and US$ 728.27 per DALY from the health system and societal perspective respectively, which appeared as very cost-effective investment. In this study, the WHO provided GDP threshold was considered for making decisions of future nationwide rotavirus vaccination strategies although a single fixed cost-effectiveness threshold should never be used as a stand-alone criterion for the decision making process (Bertram et al. 2016). The prime intention of WHO-CHOICE GDP based thresholds, was to guide the policy makers on value for money (Hutubessy et al. 2003). Therefore, other considerations relevant to country specific local context (e.g., affordability, fairness, feasibility, budget impact) should be used in the decision-making process (Bertram et al. 2016). However, relevant data is vital for any decision making process (Hutubessy et al. 2003; Newall et al. 2014; Bertram et al. 2016). The

study also documented the important gaps of country representative data, especially the lack of good quality information on rotavirus incidence and mortality and the economics data related to rotavirus infections. Therefore, future research should be made to explore the country representative mortality, morbidity and health care utilisation related information regarding the rotavirus infection, in order to fill this knowledge gap.

11.2 Methodological consideration

The associated limitations of the studies were reported in the end of the specific study (Chapter 4 to Chapter 10). This section discusses the epistemological, contextual and methodological dimensions of the thesis and suggests further research on the highlighted topics. Various assumptions and materialities were also documented in each of the studies (study I to VII) and the main assumptions are summarised the table 11-2

Table 11-2 Assumption, Justification and likely effects on the result

Assumption	Justification and Materiality	Likely effect on the results
The recall period of DHS dataset was considered preceding two weeks of the survey	Two weeks' time period is enough to minimize the recall bias of the households (Stanton et al. 1987). To mitigate the recall bias, the interviews were conducted immediately after receiving the treatment care.	Recall bias and incorrect reporting may be underestimating or overestimating the real scenario.
Hospital administrative data were utilized for capturing provider cost of illness	The budget allocation system is quite complex in public hospital, and even the hospital authorities were unable to provide appropriated documents due to technical complexities. Therefore, several personnel (e.g. doctor, nurse, manager) were interviewed to capture the costing information. However, this can be handled by the sensitivity analysis (Study II, III, and VI).	Administrative data might be under estimated or overestimated the actual cost of illness
The surveillance data were utilised for assessing cost-effectiveness analysis of cholera vaccination	Due to unavailability of nationwide vaccine effectiveness and epidemiological data, the study adopted the data generated from the surveillance area. The country representative data (e.g. incidence rate, vaccination coverage) might be higher or lower, and can be handled via adequate sensitivity analysis.	The surveillance area was located in cholera endemic areas in urban Dhaka, the capital of Bangladesh, and had some distinct characteristics and particular healthcare seeking behaviour (e.g. health service utilization, vaccine uptake, and lifestyle). Therefore, the actual scenario might be different than the project captured.
The cost effectiveness study adopted static model and ignored	The advantage of static model is that it requires minimum data, can be built and understood easily and has a low cost. It was not possible to collect rigorous information that are essential for the dynamic model. It is	Since the dynamic transmission model was able to capture the indirect effect of reduced transmission and long-term effect of vaccination program, it provides

the indirect effect of vaccine	often laborious to capture the seasonal factors even the probability that an unvaccinated susceptible is infected either from the environment or from direct contact due to presence of a single unvaccinated infective in such populous area in urban Dhaka within such a short period of time (2-years). The static model might be used if the particular vaccine has no negative effect (directly or indirectly) and without herd immunity the vaccine appeared as cost-effective investment that we found. Furthermore, we were keen that this model should be sufficiently simple so that public policy maker, EPI manager and non-technical personnel can easily understand the findings of the cost-effectiveness analysis of introducing cholera and rotavirus vaccination. The uncertainty of the model could be captured via adequate scenario analysis.	the higher cost-effectiveness ratio than the static model. Therefore, the current study might have underestimated actual benefit of the oral cholera vaccination. Earlier OCV study also concluded that incorporating herd immunity makes the vaccination program more attractive from economic perspective. However, herd immunity might be not same as in high income countries as vaccine efficacy, coverage, demographic etc. are different. Further, epidemiological shifts in the age distribution have been observed in real world.

11.2.1 Epistemological approach

In this research project, all of the studies were linked with the economic theory, with the model grounded on the human behaviour that was reflected in the findings, as scientific theories and models are simplified depiction of reality (Box & Draper 1987; Pidd 1996). However, there were no specific guideline for choosing any particular model structure, as models depended on the objectives of the research and availability of data so that the policy question addresses appropriately in a simpler way (Drummond et al. 2005). All of the studies tried to focus the scenario in a simpler way in order to generate the new level of understanding about the overwhelming public health problem caused by diarrheal infection. As per post-positivism, a couple of structured questioners were developed and surveyed in a quantitative nature and data were collected through community-based or hospital-based surveys. Therefore, valid and reliable data sources were employed for drawn any inferences.

A series of information, like healthcare seeking behaviour, associated factors, and economic burden were documented in a simpler way from study I to study VII. The entirety of the survey was cross-sectional in nature and was thus unable to establish the causal-relationship. However, these studies were able to describe the real-life scenario during diarrheal infection, considering the prevalence, healthcare seeking behaviour, cost and determinants of such healthcare behaviour. A cross-sectional design is particularly suitable for estimating the prevalence and cost of a disease in a population, and the method is often easy, expeditious and affordable to perform and multiple

outcome can be captured (Mann 2003; Sedgwick 2014). One of the important advantages of the method was that the study participants were interviewed only once, and it was not necessary to follow-up with participants. Despite that fact, in this project (Study II), a telephone interview was conducted to capture the costs components after availing the services from the hospital. The cholera vaccination study (study VI) evolved with the randomised controlled surveillance data to generate the evidence of vaccine introduction in urban cholera endemic area in Bangladesh. There are some drawbacks of RCTs such as if the sample size is not enough, this might be problematic (Donner et al. 1990). Further, if the control group is not well defined in RCT and/or inappropriate sample size and specifically if the results are too biased due to geographical proximity of population unit, then alternative methods should be considered (Pringle & Churchill 1995). In this project the data generated from the cholera vaccination study (Study VI) was obtained from the completely randomized design study (Sanson-Fisher et al. 2007), a large sample (approximately 175,805 participants enrolled) and the control cluster was well defined (Qadri et al. 2015). This is although many studies are concerned with the lack of generalizability of RCT model, even low external validity due to atypical population (Green & Glasgow 2006; Sanson-Fisher et al. 2007). However, clinical data is more likely to be generalizable across different settings and countries (Drummond et al. 2005). The rotavirus study used a spreadsheet based decision model with available published clinical evidence that utilised country-specific resource data (Drummond et al. 2005) for assessing impact of childhood rotavirus vaccination in Bangladesh (Study VII).

Rotavirus infections are the more severe among infants aged three to twenty-four months than twenty-five to sixty months children. There is no country representative data for the incidence of rotavirus infection in Bangladesh. A hospital-based survey in Bangladesh indicated that the average annual rotavirus admission rate is 18.5 per 1000 infants 0 to 11 month while the incidence is 12.3 per 1000 among infants 12 to 13 months (Zaman et al. 2017). In this context, it seems our outcome of the study (study VII) may be overestimated as we considered all <5 children. A study in Bangladesh observed that the incidence of hospitalization for rotavirus infections vary from 10.8 to 19.6 per 1000 children aged <5 years old in Bangladesh (Zaman et al. 2009). However, many cases occurred in a community level, and therefore the actual burden is still unknown. We used the conservative incidence of rotavirus infections as per earlier study in Bangladesh (Zaman et al. 2009). Numerous RCT studies concluded that the effectiveness of rotavirus vaccine might be up to 90% against severe and moderate rotavirus infections for infants (Soares-Weiser et al. 2012b; Kawamura et al. 2011; Grant et al. 2012). However, our estimates are conservative as we have made conservative assumptions (e.g., incidence of infections, case fatality rate, vaccine effectiveness data, vaccine coverage duration of protection) due to unavailability of data which

was likely to underestimate the value of vaccines. Further, we did not include the herd immunity of rotavirus vaccines which may result conservative results compared with other studies. RCT is recognized as a gold standard for the measurement of vaccine efficacy but RCT results do not necessarily translate to measuring effectiveness of a vaccine in a population (Sanson-Fisher et al. 2007). The rotavirus vaccination study (Study VII) in this thesis project, considered the pre-post intervention of all <5 children under the real-life settings (Sanson-Fisher et al. 2007). Although our study indicated that universal childhood rotavirus vaccination is a cost-effective investment, we had considered the conservative parameters (e.g., case fatality, incidence, vaccine effectiveness, vaccine protection years) due to the unavailability of country representative data for <5 children. Therefore, our estimation is based on best available data but is nevertheless subject to some uncertainty.

Further, there is limited generalizability of using data from selected public facilities and cholera endemic area informing the nationwide policy and practices. Since a number of parameters in each setting (e.g., public facilities, urban cholera endemic area) have marked uniqueness, the nationwide estimated value can be questioned. From study II, we had estimated the annual economic burden of diarrheal diseases to be US$ 172.02 million which was 12.28% of the total health expenditure in Bangladesh. However, the estimate was based on the reported cases from public health facilities, although it is the common practise that diarrhoea is inadequately managed at household level and a large number of patients received care from private health facilities. Again, the current study was conducted among hospitalized patients, but many diarrheal episodes occurred in the community that remain unreported and could not be captured in this study. In that sense, actual burden of diarrheal disease in Bangladesh were underestimated. The economic analysis of cholera and rotavirus studies had similar limitations. In cholera studies, the parameters generated from a cholera-endemic urban area did not represent the overall country. In the rotavirus study (Study VII) we used various secondary information. For instance, we used the low case fatality and incidence rate as those data came from the estimation of rotavirus-related hospitalization cases. Our estimation indicated that by introducing rotavirus vaccination, number of cases and deaths could be prevented even though the underestimation of the real burden of rotavirus diseases, as the community occurring rotavirus was not captured due to limited data. Therefore, these results may be less generalizable due to the lack of country representative data which might alter the result that we had obtained from these studies.

All of the studies (e.g., cost of illness study, vaccination study) followed the common reporting format to ensure the transparency of the studies. Thus, the methods and analysis of results were presented in a straightforward manner so that anyone could compare similar studies in other

settings (Drummond et al. 2005). In this research project, the social perspective was considered in most of the studies (Study II, IV, VI, VIII) and followed by the proposed guidelines (Gold et al. 1996). Nevertheless, monetary valuation of outcome is still contentious in the economic evaluation guidelines (Hjelmgren et al. 2001; Drummond et al. 2005). In this project, we used human capital approaches and stated preference method for such valuation, as per economic evaluation guidelines (Drummond et al. 2005). Again, the diffusion of information is a prerequisite for any decision making policy, therefore, it is vital that methods and results of the studies should be presented in a clearer view that the project did to maximise the potential for policy impact (Coast 2004). However, there are also philosophical contentions in the use of economic evaluation (Drummond et al. 2005), classified as '*welfarist*', *'extrawelfarist'* and *'decision-maker'* approaches. According to the *welfarist* approach, the economic evaluation should be only performed based on welfare economics, as individuals optimally judges their own welfare (study V) (Drummond et al. 2005; Birch & Gafni 1996), while *extrawelfarist* based on the health sector budget perspective (Culyer 1989). Other analyst believed that economic evaluation encourages the systematically thinking about cost and consequences (Drummond et al. 2005) on the part of policy decision makers on behalf of individual beneficiaries, rather than the individuals themselves which is opposite of *welfarist* concept (Sugden & Williams 1978). This thesis is thus a combination of these three types of dimensions (study II to VII). Therefore, methodological limitations could be raised when considering one particular point of view. The generalizability of the study findings is also crucial, as various tiers of populations exist in the societies, such as such as socioeconomic groups, traditional believers, educational group, and geographic regions which might be reflected in the treatment seeking pattern. Therefore, in this project, the results were presented (Study I, II, III, V) in a simpler way, according to several dimensions. Further, the project also used the secondary source of data (Study VII) for assessing the cost-effectiveness of rotavirus vaccination in Bangladesh. Due to the dearth of the local authentic data and methodological variabilities in the economic analysis, the transferability of findings from one setting to another context is often problematic. For mitigating such variation, the study (Study VII) employed the standard method for cost-effectiveness analysis and utilized local level published data and compared with similar studies (Constenla et al. 2008; Cook, Jeuland, Whittington, Poulos, Clemens, Sur, Anh, Agtinih, et al. 2008; Jeuland, Cook, et al. 2009; van Hoek et al. 2012; Ozawa et al. 2012; Diop et al. 2015)

11.2.2 Contextual and methodological approaches:

11.2.2.1 Household Survey

The project is based on households and hospital-based survey data. There are various issues related with the household level survey data, including recall bias and incorrect reporting. Recall bias and incorrect reporting may be underestimating or overestimating the real situation. Study I is based on the national household survey data and the selected mothers' provided the information of diarrheal episode and healthcare utilization on the behalf of their young children two weeks preceding the survey. Therefore, recall bias might be associated, considering the care seeking pattern, duration of episode, cost of treatment, and even the reporting of diarrheal cases (Study I). The other studies of this research project had similar limitations. However, in the DHS survey, the recall period was considered preceding two weeks of the survey and assumed it was able to minimize the recall biased of the households (NIPORT 2016). The other research also suggested that two-week recall period of data collection from households was acceptable and no recall biased is associated during this period (Stanton et al. 1987). However, this time period often lead to an under-reporting the childhood diarrheal cases (Manesh et al. 2008). A study conducted in South India observed that there is a high risk of under-reporting of diarrheal infections if the recall period is longer, with under-reporting being raised up to 45%, particularly if the recall period is within 7-13 days (Ramakrishnan et al. 1999). In contrast, Boerma et al. indicated that if the recall period is longer than two weeks, by even just 2-3 days, there might be a risk of over reporting of the diarrheal episode (Boerma et al. 1991). To avoid such two-way discussions, my data collectors interviewed the households immediately after receiving the treatment services to avoiding a recall bias and incorrect reporting (study II, III, and VI).

Since the studies (I and II) are solely based on the household level survey, it was not possible to segregate the pathogen-specific diarrheal infections (such as rotavirus, cholera, ETEC) which might be reflected in the households' care seeking behaviours and cost. Earlier study observed that various pathogens, such as salmonella sp., shigella sp., ETEC and *V cholerae* O1/O139 and rotavirus, were typically found in the inpatient setting (A. Baqui et al. 1991; Hossain et al. 1990; Oberle et al. 1980). Further, various information on cost and service utilisation (study II, II, VI) often jeopardised the actual scenario, due to receiving care from various provider (e.g., public, private, traditional) and the cost items is often shared among household and hospitals (e.g., public or in NGOs hospital). For ensuring consistency and relevant data, the household head or economic contributor of the families were interviewed according to their local language after using the services. Further, the people were generally report their expenditure rather than the income of the

households, which was commonly observed during the pilot survey. Thus, proper training was provided by the project before collection of the data from the households.

The biased information might be pertaining to various types. For instance, in a contingent valuation study (Study V), a possible source of bias might be that the respondents will not purchase the vaccine in actuality (Klose 1999). A common tendency was also observed to express over valued of the vaccine, which was termed as hypothetical bias in the CVM technique (Cummings et al. 1986). Furthermore, it was found that hypothetical payment is always excessively high compared to the reality (Foster et al. 1997). In this context, a pilot survey was conducted before the original survey and the data collectors were trained so that they can explain the hypothetical scenario in an efficient way (see annex 4) to mitigate such issues. Furthermore, data extraction with a paper-based questionnaire in household surveys may be another risk of biased of the study as the paper-based questionnaire was editable. The project was monitored by 1st and 2nd line supervisors so that the quality data could be ensured. The other important biased associated in the household survey is the "anchor biased", which is frequently discussed in contingent valuation study (Lichtenstein et al. 1989). However, proper training on data collection process and open ended questions could easily resolve such biases (Hoevenagel 1994). This was done by the project, although evidence suggest that there is a weak relationship between the anchor bias and willingness to pay (Fudenberg et al. 2012).

The other issues that became apparent was if the eagle-eyed respondent thought that there was some actual or potential benefit for responding the questions, it might be critical if he/she thinks that reporting on particular disease and treatment makes him/her financially benefit which lead to "incorrect reporting". In this context, the data collectors explained the objectives of the study properly to all respondents and confirmed no financial benefits was associated with their responses and anyone can refuse to participate during the survey. Reporting bias might be also due to the "inaccurate report", which might be incurred due to poor understanding of particular queries (Oetting, E. & Beauvais, F. 1990). Further, self-reported diarrhoea also led to under-reporting of the actual scenario, a study in United States observed that the poor understanding of the definition of diarrheal cases led the under-reporting of the diarrhoeal diseases (Hunter & Syed 2001). Wright and colleague showed that using different definition of diarrhoea caused huge variation of diarrheal cases in Sub-Saharan Africa (Wright et al. 2006). However, under-reporting might occur if the disease was considered to be shameful - a disease that people are avoided to report which is not true in the diarrhoeal cases as it is the common event of everyday and is the part of normal life, irrespective of socio-economic class. In the DHS survey, the WHO-provided definition of

diarrhoea has been used, thus reporting bias was kept to minimum level. In hospital-based costing survey, the diarrheal patients were confirmed by the respective health personnel (e.g., doctor, nurse) and cholera patients were confirmed by icddr,b hospital.

Difficulties of understanding and language barriers were also a common phenomenon in household survey which appeared as a serious constraint in two-way communications (interviewer and respondents); it become a complex issue particularly, in rural and hard to reach areas (e.g., hilly and tribal area) and often present a key concern in the quality of the data during the household survey. In DHS surveys, significant efforts were made to translate questionnaires to local language (Study I). The diarrheal costing study (Study II) was conducted in different parts of the country. Therefore, significant training was provided to the data collectors with the local language. The other studies (Study III, IV and V) were conducted in an urban setting and the data collectors made the actual questionnaire understandable for all respondents (all socio-economic group and their skills on questioning was improved over time of the survey).

11.2.2.2 Hospital and surveillance-based survey

Hospital-based survey was carried out to capture the resource consumed due to diarrhea (Study II) or cholera infections (Study III). For this aspect, public hospitals (Study II) and not-for-profit hospitals (Study III) were selected as study sites. For assessing cost from the patients' perspective, exit interviews were conducted on the hospital grounds, followed by telephone interviews within a week of their return from the hospital. During the hospital-based survey, data collectors were actively engaged and whenever the patients were released from the hospital after receiving treatment, a face to face interview was held accordingly. Therefore, it was comparatively easier to assess the service utilization and cost precisely and there was a lower risk of recall bias compared to the cross-sectional household survey. However, such data collection strategies might hide the actual situation or disease management strategies, due to "Hawthorne" effect, in which the person observed tend to perform patient management differently and usually better than usual (Mangione-Smith et al. 2002; Holden 2001; Campbell et al. 1995). For instance, due to the presence of data collectors in hospital arena, there is a possibility to efficient allocation of resources in hospital, which led to less or more time examining the patients, and staff may be more available than usual. To mitigate this problem, the data collector conducted exit interview after availing the treatment services (Study II), and hospital data was collected through a yearly basis, after consultation with various personnel like accountants, doctors, health workers, managers, hospital superintendents and other related personnel. The studies (Study II, III, and VII) only captured the information of those who utilised the treatment care. However, many of the patients who need care but could not

receive treatment due to unaffordability issue which was not captured in these studies. Furthermore, many diarrheal cases are managed at the community level, and so are not captured by this hospital-based study. Thus, these findings were only valid for hospitalized patients, rather than the general population and future community-based household survey should be investigated to capture the situation, which is beyond our analysis. For capturing the provider treatment cost, the study solely depended on the hospital administrative data, which might be under estimated or even overestimated (Study II and study VI) as the budget allocation system was quite complex (see discussion section). Furthermore, the hospital authorities were occasionally unable to provide appropriated documents due to technical complexities in the nature of public organization. Therefore, some cost components were measured according to their statement. There sensitivity analyses (Study II, III, IV, and VI) were conducted to handle these obstacles.

The study III, V, IV and VI were based on the disease surveillance data. These surveillance studies have some limitations, particularly for assessing the costs of cholera infections (Study III). Since the surveillance area was in cholera endemic areas in urban Dhaka (the capital city), which may have some distinct characteristics and healthcare seeking behaviours, therefore, the context for the general population might be different than the project captured. Further, it was not possible to examine if the vaccination campaign had been conducted outside of the surveillance area or conducted in any different geographical location (e.g., rural, hard to reach area), which are still needed to be explored. All of the above represent possible avenues for further research on this topic.

11.3 Conclusions

Resource scarcity is commonly recognized in the healthcare sector, especially in low- and middle-income countries like Bangladesh. The thesis documented the prevalence, healthcare seeking pattern, economic cost, demand and evaluation of vaccines for preventing diarrhea related infections, along with key methodological challenges. From the findings, it can be concluded that policies for diarrheal prevention strategies should be prioritized. As cholera and rotavirus infections are life-threating conditions for high-risk population and children, the thesis point out that, vaccination programs should be introduced as such preventive programs could avert the number of cases, deaths and hospitalisations. However, an optimum decision should be made by comparing vaccination program with alternative public health and healthcare interventions in Bangladesh (e.g., diarrheal case management strategies, other diarrheal prevention program, sanitation and hygiene related interventions). The project also documented a potential scope for recovering a certain portion of the financing cost of the immunisation program in Bangladesh. However, other technical, programmatic, political priority, and social issues need to be considered in the process of making the decisions regarding the introduction of vaccination program in Bangladesh. More research on this public health problem is required before any decision to be made.

It is therefore expected that the current study will be useful for informing the policymakers with the necessary knowledge for rational investment choice in preventing diarrheal infections. Furthermore, the application methods of economic theories in a practical context (lower-middle income setting) can be useful for the implementation of the vaccination programs and the researchers who work for impact assessments.

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13 Appendix:

13.1 CHEERS Checklist

Section	Item No	Recommendation	Reported on page No/line No
Title and Abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 154 and 173
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 155 and 174
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Page 156-157 and 175-176
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analyzed, including why they were chosen.	Page 160 and 176
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 157 and 176
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 157 and 176
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 159 and 183
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 162 and 187
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 163 and 188
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 159 and 177
Measurement of effectiveness	11a 11b	*Single study-based estimates*: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data. *Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Page 159 and 176
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A

Estimating resources and costs	13a	*Single study-based economic evaluation*: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Page 165 and 180
	13b	*Model-based economic evaluation*: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Page 176
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 165 and 180
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 159 and 177
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Page 161 and 180
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Page 159,163 and 187-189
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Page 161 and 180
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Page 166 and 183
Characterizing uncertainty	20a	*Single study-based economic evaluation*: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Page 169 and 184
	20b	*Model-based economic evaluation*: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Page 169 and 184
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or	N/A

		other observed variability in effects that are not reducible by more information.	
Discussion			
Study findings, limitations, generalizability, and current knowledge	22	Summarize key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.	Page 169 and 185
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 172 and 190
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 172 and 190

13.2 Data collection tool on cost of illness due to cholera illness

Introduction of Cholera Vaccine in Bangladesh
International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b)

Cost of illness due to Cholera:

Number of Ward: _____ Card Holder_____01

Name of Area: _____ Non card Holder and Risk group_____02

Household ID: _____ Non card Holder and No Risk group_____03

PID Number_____ Receive Oral Cholera Vaccine: Yes____1

Hospital /Patient ID: _____
No____2

GIS Number: _____

Age: | | | | |

Y Y / M M

Gender:

Male _____ 1 Female _____ 2

Admission date: _____ Time: _____

Discharge date: _____ Time: _____

Name of the patient: _____

Cost data collection tool from patients

I. Direct cost

		1st Contact	2nd Contact	3rd Contact	4th Contact
101. When you affected with cholera where you get treatment (from first contact to last contact) Code 01 = Local Pharmacy 02= Local Doctor (MBBS) 03= Dhaka Child Hospital 04= Sowrawardi Hospital 05= SSF Hospital 06= Radda SSF Hospital 07= Al Helal Hospital 08= Modern Hospital 09= Marks E&T Hospital 10= Waida Hospital 11= Dr. Ajmal Hospital 12= Kalshi Child Hospital 13= Mirpur icddrb 14= Mohakhali icddrb 15= Tradition healers 16= Quack 17= Others (please specify)		----/---	------/-----	------/-----	------/-----
102. How did you went for treatment purposes Transport code 1= on foot 2= By –cycle 3= Rickshaw / Van 4= Bus 6= Private car 7= Other (specify)	Types of transport (use code)	1st 2nd 3rd 4th 5th 6th	1st 2nd 3rd 4th 5th 6th	1st 2nd 3rd 4th 5th 6th	1st 2nd 3rd 4th 5th 6th
103a. What time spend for going the treatment centre?	Money	------/-----	------/-----	------/-----	------/-----
103b. Did you spend any money for going the treatment centre?		Yes..... 1 No..... 2 Unknown..... 9	Yes..... 1 No..... 2 Unknown..... 9	Yes..... 1 No..... 2 Unknown..... 9	Yes..... 1 No..... 2 Unknown..... 9

		1st Contact	2nd Contact	3rd Contact	4th Contact
104. If yes, what is the amount of money for this purpose?	(BDT)	------/-----	------/-----	------/-----	------/-----
105. What is the waiting time for receiving this treatment purposes?	Money	------/-----	------/-----	------/-----	------/-----
106 a. Did you spend any money as a registration fee for the particular treatment centre for receiving services?		Yes..... 1 No..... 2	Yes..... 1 No..... 2	Yes..... 1 No..... 2	Yes..... 1 No..... 2
106 b. If yes, please specify the amount of money	(BDT)	------/-----	------/-----	------/-----	------/-----
107 a. Did you spend any money as a bed/cabin rent for accommodation of that centre?		Yes..... 1 No..... 2 Q.108	Yes..... 1 No..... 2 Q.108	Yes..... 1 No..... 2 Q.108	Yes..... 1 No..... 2 Q.108
107 b. If yes, please specify the amount of money	(BDT)	------/-----	------/-----	------/-----	------/-----
108. Did you spend any money for diagnostic test or other test? If yes, please specify the amount of money	Stool test (BDT)	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----
	Urine test (BDT)	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----
	Blood test (BDT)	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----
	Other test (BDT)	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 Yes..... 1 No..... 2 Unknown..... 9 ------/-----
	Total (BDT)	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----
109 a. Was the service provider come to your house for providing the service?		Yes..... 1 No..... 2	Yes..... 1 No..... 2	Yes..... 1 No..... 2	Yes..... 1 No..... 2
109 b. If the service provider come to household then what is the amount of money paid by you as a fee for this service?	(BDT)	------/-----	------/-----	------/-----	------/-----

		1st Contact	2nd Contact	3rd Contact	4th Contact
110. What is the amount of money that you spend during taking medicine purposes?	(BDT)	------/-----	------/-----	------/-----	------/-----
111 a. Did you spend any money for buying the following food items like banana, coconut, muri, chira and other?		Yes..... 1 No..... 2	Yes..... 1 No..... 2	Yes..... 1 No..... 2	Yes..... 1 No..... 2
111 b. If yes, what is amount of money for this purpose?	(BDT)	------/-----	------/-----	------/-----	------/-----
112 a. Did you spend any money as tips for your own willingness or against your willingness which consider as an informal payment?		Yes..... 1 No..... 2	Yes..... 1 No..... 2	Yes..... 1 No..... 2	Yes..... 1 No..... 2
112 b. If yes, what is amount of money for this purpose?	(BDT)	------/-----	------/-----	------/-----	------/-----
113 a. Did you bring any person to the treatment center for helping you based on payment?		Yes..... 1 No..... 2	Yes..... 1 No..... 2	Yes..... 1 No..... 2	Yes..... 1 No..... 2
113 b. If yes, what is amount of money for this purpose?	(BDT)	------/-----	------/-----	------/-----	------/-----
114 a. Did you bought any necessary things like mosquito coil, nets, mug, and jar during your stay in treatment center?		Yes..... 1 No..... 2	Yes..... 1 No..... 2	Yes..... 1 No..... 2	Yes..... 1 No..... 2
114 b. If yes, what is amount of money for this purpose?	(BDT)	------/-----	------/-----	------/-----	------/-----
115. Did you stay outside of your home for taking treatment? If yes, please specify the amount of hotel rent, food items and other expenditure during that stay?	Hotel or Seat rent (BDT)	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----
	Food items (BDT)	Yes..... 1 No..... 2 Unknown..... 9 -----/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----
	Other Expenditure (BDT)	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----

		1st Contact	2nd Contact	3rd Contact	4th Contact
	Total (BDT)	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----	Yes..... 1 No..... 2 Unknown..... 9 ------/-----
116 a. 102. How did you reached your house after taking services? Transport code 1= on foot 2= By –cycle 3= Rickshaw / Van 4= Bus 6= Private car 7= Other (specify)	Types of transport (use code)	1st 2nd 3rd 4th 5th 6th	1st 2nd 3rd 4th 5th 6th	1st 2nd 3rd 4th 5th 6th	1st 2nd 3rd 4th 5th 6th
116 b. What is the amount of time for this purpose?	Minutes	------/-----	------/-----	------/-----	------/-----
116 c. What is the amount of money for this purpose?	BDT	Yes..... 1 No..... 2 ------/-----	Yes..... 1 No..... 2 ------/-----	Yes..... 1 No..... 2 ------/-----	Yes..... 1 No..... 2 ------/-----
117 a. After reaching home, did you spend any money for various purpose like medicine, or other that associated with?		Yes..... 1 No..... 2 ------/-----	Yes..... 1 No..... 2 ------/-----	Yes..... 1 No..... 2 ------/-----	Yes..... 1 No..... 2 ------/-----
117 b. If yes, what is amount of money for this purpose?	BDT	------/-----	------/-----	------/-----	------/-----
118. After meeting the 1st contact of treatment services, how many days ago that you suffered from this disease.	Day	------/-----			
119. After meeting the last contact of treatment services, how many days suffers of your illness that you think?	Day	------/-----			

II. INDIRECT COSTS

Now I want to ask you about your occupation and absent of your work for receiving the treatment and other associated aspects.

201. How many of your (patients) family member? (Ascending order of age) Range of Age ---/--- Under 14 years ----/---- 15 to 64 Years ------/------ Above 64 Years -----/------	Total Member	-----/------
202. What is the educational qualification of the patients? Class 1 passed .....01 Class 2 passed .....02 Class 3 passed .....03 Class 4 passed .....04 Class 5 passed .....05 Class 6 passed .....06 Class 7 passed .....07 Class 8 passed .....08 Class 9 passed .....09 SSC passed .....10 HSC passed .....12 BA/ B.Com/BSc passed .....14 Honors passed ....16 Masters and higher passed.....17 No education .....66 Other (specify) .....77 N/A …….....88	Code -----/------	
203. What is the occupation of Patient? (Occupation code) Looking for a job .....01 Housewife.....02 Beggar.....03 Pensioner .....04 Home service/ Servant.....05 Motor Driver .....06 Rickshaw/van Driver.....07 Day labor.....08 Fisherman .....09 Tailor/ Berber .....10 Business .....11 Services.....12 Teacher.....13 Doctor .....14 Engineer.....15	Primary occupation -----/------ Secondary occupation -----/------	

Internship.....16 Student.....17 Hawker.....18 Germen's labor.....19 Benaroshis's labor .....20 Other (specify).....,..... 77 Unknown .....,..... 99 N/A... …….……..….88			
204. Monthly income of patients	Yes..... 1 -----/------ No..... 2 N/A 88		
205. When the person affected with cholera during that time, did he/she engaged a paying job?	Yes .....1 No ……..…….……..2		
206. How many days he/she absent from work / school/ institution	Day	-----/------	
207. Did you make any income loss due to this absent from work?	Yes .....01 No ……..……...……..02 Unwillingness to answer..... 03		
208. If Yes, please specify the amount of money	-----/------ BDT		
209. What monthly income of your family?	-----/------ BDT		
210. During illness, did anybody taking care of the patients? If yes, please specify the following information. In case of educational qualification use the previous educational code	Attendant 1	Education -------/------	Day -----/------- Hour -----/------
	Attendant 2	Education -------/------	Day -----/------- Hour -----/------
	Attendant 3	Education -------/------	Day -----/------- Hour -----/------
211. Please specify the occupation and monthly income of the attendant (use the previous occupational code)	Attendant 1	Occupation ----/----	monthly income ------/-------/------
	Attendant 2	Occupation ----/----	monthly income ------/-------/------
	Attendant 3	Occupation ----/----	monthly income ------/-------/------
212 a. Did the attendant faces any income losses due to caring the patients?	Yes…..... 1 No..... 2 N/A…….... 88		

212 b. If yes, what is amount of money for this purpose?	-----/------ BDT				
213. For this purpose, did attendants spend any money during that time? If yes, please specify the amount of hotel rent, food items and other expenditure during that stay?		1st Contact	2nd Contact	3rd Contact	4th Contact
	Hotel or Seat rent (BDT)	----/------	----/------	----/------	----/------
	Food items (BDT)	----/------	----/------	----/------	----/------
	Transport (BDT)	----/------	----/------	----/------	----/------
	Others (BDT)	----/------	----/------	----/------	----/------
	Total (BDT)	----/------	----/------	----/------	----/------

Thank you for your cooperation

Name of the field Investigator:

Signature: _____

Date:_____

Name of the field Supervisor

Signature_____

Date: _____

13.3 Data collection tool on household cost of diarrheal treatment

Section 1. Identification information

1. Name of the Hospital:_____
2. Number/Name of the ward: ___
3. Bed Number_____
4. Patient ID: _____
5. Name of the identified diseases _____
6. Type of the patient:
   Outpatient-------- (1)
   Inpatient -------- (2)

7. If Outpatient-
   Date of visiting Hospital: |__|__|-|__|__|-|__|__|__|__| (DD-MM-YY)

8. If inpatient-
   Admission date: |__|__|-|__|__|-|__|__|__|__| (DD-MM-YY)
   Discharge date: |__|__|-|__|__|-|__|__|__|__| (DD-MM-YY)

9. Name of the patients _____
10. Name of the respondent**:** _____
11. Age of the respondent (Year) _____
12. Respondent relationship to the patient (Please use code) |__|__|

Mother(1),Father(2),Brother(3),Sister (4),Grandfather/Grandmother (5),Relatives (6),Neighbor/Friend (7),patient himself (8),Spouse of patient (9) Son/Daughter of patient (10) Others---------- (77)

13. Contact Number (Mobile/Telephone): |__|__|__|__|__|__|__|__|__|__|__|
14. Address: _____
    _____
15. Interviewer ID**:** |__|__|__|__|__|__|
16. Start time of interview**:** |__|__|**:**|__|__| (hh : mm) □ AM □ PM
17. End time of interview**:** |__|__|**:**|__|__| (hh : mm) □ AM □ PM

Consent Form for data collection

Protocol No: PR-13064

Protocol title: Estimation of the burden of diarrheal disease: A study in several district hospitals and a tertiary level icddr,b hospital Bangladesh.

Organization: icddr,b

Purpose of the research:

Greetings, I am (interviewer…….) from icddr,b (Cholera Hospital), an International research institute. You may have the concern that in developing countries like Bangladesh diarrhoea and diarrhoea related complexities are one of the main reasons for health hazards. The objective of our study are to identify the cost incurred by the patient's family for the treatment of diarrhoea and diarrhoea related diseases, how do they manage the healthcare cost and moreover the socio-economic impact of diarrhoea and diarrhoea related diseases to the individuals. For this purpose I would like to ask you some questions related to your income, treatment cost incurred by you and how money is managed to pay the cost.

Why did we select you?

As you have come to this hospital for treatment and there is a project running in this hospital so by random sampling process you are selected as a respondent for this research.

Method:

If you agree to participate in this study, it would involve an interview lasting about 50 minutes. In this interview, I shall ask you some questions related to your income, time spent to receive treatment, treatment cost incurred by you and how money is managed to meet the cost. You can choose your comfortable place for interview. If you agree, I can start interview now or I can come again at your convenient time.

Privacy and confidentiality of information:

We are assuring you that information given by you will be kept strictly confidential. We also want to assure you that all paper records of the interviews will be kept in a safe and secure place for five years and will be used for only for this study. We also ensure you that your name and other identity will not be exposed while the research results will be published. So it will not be possible to trace the answers back to you.

Future use of information:

Information provided by you will be used for this research only and your name will not be exposed when the research results will be published.

Risk:

There are no physical and social risks related to your participation in this study and if you refuse to participate in this study, you or your family will not face any difficulties to get treatment or other activities.

Benefit:

You will not be directly benefited by participating in this study. However, this information will improve the efficiency and the quality of services of this research in future.

Freedom not to participate and withdraw:

It is voluntary to participate in this study. You have the right not to answer any question if you wish. Even you can withdraw yourself at any portion of the interview.

Compensation:

You will not be financially benefitted for your participation in this research. Rather your information may help you and other persons like you to get improved health care.

Whom to contact for any query:

If you have any query regarding the study, you are free to ask the interviewer. You can also contact the principal investigator of this study or IRB coordinator at the address given below.

Md. Abdur Razzaque Sarker
Principal Investigator
icddr,b
Mohakhali, Dhaka-1212
Telephone: 02-8860523-32 (Ext.2524)
Email: arazzaque@icddrb.org

M. A. Salam Khan
IRB coordinator,
Research Administration Services,
icddr,b
Mohakhali, Dhaka-1212
Telephone: 02-8860523-32 (Ext. 3206)
Email: salamk@icddrb.org

Do you agree to participate in this study?
Yes---------- (1) No---------- (2)

_____	_____
Signature/Thumb-mark of the participant	Date
_____	_____
Signature of the Interviewer	Date

Section 2. Background information		
1.Age of the Patient	Year Month Day	
2. Sex	Male----------(1) Female----------(2) Transgender----------(3)	
3. Occupationof the patient (Please use code) (Skip from question 4 to question 5 if child)		House wife (1), Student(2), Worker(3), Unemployed (4), employee(5), business(6), Others (77), Not applicable (99)
4. Monthly income of the patient	---/--/--/--/---/ BDT	
5.Patient'seducational qualification(Please use code)	Class One pass(1), Class two pass(2), Class three pass(3), Class four pass(4), Class five pass(5), Class six pass(6), Class seven pass(7), Class eight pass(8), Class nine pass(9), SSC pass(10), HSC pass(12), B.A /B.Com /B.S.C pass (15), Honor's pass (16), Masters Pass (17), Just can sign (88), Illiterate (00), Others(77)	
6.Patient's educational qualification of mother (Please use code)		
7. Patient's educational qualification of father (Please use code)		
8. Mother's occupation (Please use code)		
9. Father's occupation (Please use code)		
10. Household members	Total household members |_____| |_____| a. Number of member less than or equal 14 years |_____| b. Number of member aged 15 to 64 years|_____| c. Number of member above 64 years |_____|	
11. Monthly income of patients family	_____(BDT)	
12. Monthly expenditure of patients family	Items	Amount (BDT)
	1.Food	
	2. Electricity bill	
	3. House rent	
	4. Water bill	
	5. Gas bill	
	6. Clothing	
	7. Phone/Internet bill	
	8. Education	
	9. Health	
	10. Transportation	
	11. Others	

	12. Total Cost	
13. Health expenditure of the family in last three months.	Items	Amount (BDT)
	1. Medicines	
	2. Consultation fees	
	3. Diagnosis cost	
	4. Food cost	
	5. Transportation cost	
	6. Hospital bed fee	
	7. Others	
	8. Total Cost	

Section 3. Cost incurred before the current facility					
1. Did you treated for diarrhoea from any other facility before visiting this hospital?	Yes----------(1) No----------(2) If "No" then skip to the section 4.				
2. How many hospitals have you visited for the treatment of diarrhoea?	☐☐				
3. From which facilities did you get treatments?	1st Contact |_____| 2nd Contact |_____| 3rd Contact |_____| 4th Contact |_____|	Name:	Code		
		Public facility	1		
		Private facility	2		
		NGO treatment center	3		
		Pharmacy	4		
		Traditional healer/Homeopath	5		
		Other (Please specify)_____	6		
4. How much time spent for going these treatment centres?	Time (Hour : minute)				
	1st Visit	2nd Visit	3rd Visit	4th Visit	
	|__|__|:|__|__| (hh: mm)	|__|__|:|__|__| (hh : mm)	|__|__|:|__|__| (hh : mm)	|__|__|:|__|__| (hh : mm)	
5. How much time did you have to wait to get the treatment from the treatment center?	|__|__|:|__|__| (hh : mm)	|__|__|:|__|__| (hh : mm)	|__|__|:|__|__| (hh : mm)	|__|__|:|__|__| (hh : mm)	
6. How much money needed to get the treatment?	Items	Net total (BDT)			
		1st Visit	2nd Visit	3rd Visit	4th Visit
	Consultation fees				
	Medicine cost				

	Diagnosis				
	Food				
	Transportation				
	Hospital bed fee				
	Tips (Informal paying)				
	Others				
	Net total				

7. How many days you had to stay in the hospital? (LOS)(Length of stay)	Day (d), Hour (h) and Minute (m)			
	1st Visit	2nd Visit	3rd Visit	4th Visit
	-------- (d) -------- (h) -------- (m)	-------- (d) -------- (h) -------- (m)	-------- (d) -------- (h) -------- (m)	-------- (d) -------- (h) -------- (m)

8. Did the patient have to remain absent from job/School or institution due to illness?	Yes ----------(1) No----------(2) N/A ----------(99)
9. If yes how many days he/she was absent from work / school/ institution?	Days|__|__|__|
10. Did you (Patient) have any income loss due to this absent from work?	Yes----------(1) No----------(2) Unwilling to answer---------(3)
11. If Yes, please mention the amount of money.	|__|__|__|__|__|__| BDT

12. During illness, did anybody take care of the patients? If yes, please mention the time.	Yes ---------- **(1)** No ---------- **(2)**	
	Attendant 1	|__|__|- |__|__|-|__|__| (day : hour : minute)
	Attendant 2	|__|__|- |__|__|-|__|__| (day : hour : minute)
	Attendant 3	|__|__|- |__|__|-|__|__| (day : hour : minute)
13. What is the occupation and monthly income of the attendant? **Occupation code**: House wife(1), Student(2), Worker(3), Unemployed (4),	Attendant 1	Occupation code- |__|__| Monthly income- |__|__|__|__|__|__|
	Attendant 2	Occupation code- |__|__| Monthly income- |__|__|__|__|__|__|
		Occupation code- |__|__|

Service(5),Business(6),Other(Please Specify)----------(77)	Attendant 3	Monthly income- |__|__|__|__|__|
14. Did the attendant faces any income losses due to take caring the patients? If yes, what is amount of money for this purpose?	Yes ---------- **(1)** No ---------- **(2)**	
	Attendant 1	|__|__|__|__|__|BDT
	Attendant 2	|__|__|__|__|__|BDT
	Attendant 3	|__|__|__|__|__|BDT
15. For this purpose, did the attendants have to spend any other money during that time?(such as food, boarding etc) (If yes, please mention the amount)	Yes ---------- **(1)** No ---------- **(2)**	
	Attendant 1	|__|__|__|__|__|BDT
	Attendant 2	|__|__|__|__|__|BDT
	Attendant 3	|__|__|__|__|__|BDT

Section 4. Cost incurred during stay in the current facility		
1. How did you come to this hospital? How much time it took to come? 01 = By rickshaw/Van 02 = By bus 03 = By CNG/Taxi 04 = By private Car 05 = On foot 77 = Other (Please specify): …….	Types of transport	1. |__|__| 2.|__|__| 3. |__|__|
	Total time	|__|__|:|__|__| (hour : minute)
2. a) Did you spend any money to come to this treatment centre? If yes, how much money was spent?	Yes ---------- **(1)** No ---------- **(2)** |__|__|__|__|__| (BDT)	
2. b) If no, then why? Self-transport----------1 Did not demand money-------2 Other----------77	|__|__|	
3. How long did you have to wait to get the treatment?	Total time	|__|__|:|__|__| (hour : minute)
4. Did you spend any money as a registration fee for receiving services? If yes please mention the amount of money	Yes ---------- **(1)** No ---------- **(2)** |__|__|__|__|__| (BDT)	
5. Did you spend any money for consultation? If yes please mention the amount of money	Yes ---------- **(1)** No ---------- **(2)** |__|__|__|__|__| (BDT)	

6. For how long did the hospital staffs treated/ examined you? (Skip from question 7 to question 8 if outpatient)	Staffs	Number of visit	Time per visit (minute)
	□Doctor		
	□Nurse		
	□Ward boy		
	□Aya		
	□Other,please specify:_____ _		
7. Did you spend any money as a bed/cabin rent for accommodation of this centre? If yes please mention the amount of money	Yes ---------- **(1)** No ---------- **(2)** |__|__|__|__|__| (BDT)		
8. Did you stay in the hotel/boarding for treatment purpose? If yes please mention the amount of money	Hotel	Yes ---------**(1)** No---------- **(2)** |__|__|__|__|__| (BDT)	
	Food	Yes ---------- **(1)** No ---------- **(2)**	

9. Did it cost for buying food for the patient during stay in this hospital? If yes please mention the amount of money		|__|__|__|__|__| (BDT)
10. Besides this, was there any cost for buying diet, coconut, flattened rice, banana or others? If yes please mention the amount of money		Yes ---------- **(1)** No---------- **(2)** |__|__|__|__|__| (BDT)
11. Did you hire someone for your help in the facility? If yes how much was paid to the attendant?		Yes ---------- **(1)** No ---------- **(2)** |__|__|__|__|__| (BDT)
12. Did you bought any necessary things like, mug, mosquito coil, nets, tissue etc. during your stay in treatment centre?		Yes ---------- **(1)** No ---------- **(2)** |__|__|__|__|__| (BDT)

13. Did you have to do any diagnostic test?

Yes ---------- **(1)** No ---------- **(2)**

If yes please mention the amount of money

Name of the test	Quantity(numeric value)	Household		Hospital	
		Quantity	Total cost	Quantity	Total cost
Stool test					
Urine test					
Stool culture					
Blood test					
Other					
Total					

14. a. Did you have to buy any medicine for treatment?

Yes ---------- **(1)** No ---------- **(2)**

If yes Please mention the amount.

14. b. Total medicine cost of household

|__|__|__|__|__|__|

Drug/Saline (ph/tab/ml)	Total Quantity	Household		Hospital	
		Qty	Cost	Quantity	Cost

15. Did you spend any money as tips for your own willingness or against your willingness which consider as an informal payment?

If yes please mention the amount of money

Yes ---------- **(1)** No ---------- **(2)**

|__|__|__|__|__| (BDT)

<table>
<tr><td rowspan="8">16. Did you need any medical equipment (such as syringe, micro pore, cannula etc.) for your treatment?

Yes ---------- (1) No ---------- (2)

If yes please mention the amount of money</td><td rowspan="2">Name</td><td colspan="3">Household</td><td colspan="2">Hospital</td></tr>
<tr><td>Total Quantity</td><td>Quantity</td><td>Total BDT</td><td>Quantity</td><td>Total BDT</td></tr>
<tr><td>Syringe</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Needle</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Micro pore</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Cannula</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Others</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Total</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>17. How did you pay your health care cost? (Multiple answer is accepted)</td><td colspan="6">From regular earnings ---------- (1)
From savings ----------(2)
By lending money----------(3)
From the grant ----------(4)
By selling household things---------(5)
By selling assets----------(6)
Others (please specify) ----------(77)</td></tr>
<tr><td>18. Did the patient have to remain absent from job due to illness?</td><td colspan="6">Yes ----------(1)
No----------(2)
N/A----------(99)</td></tr>
<tr><td>19. If yes how many days he/she absent from work?</td><td colspan="6">Day|__|__|__|</td></tr>
<tr><td>20. Did you (patient) make any income loss due to this absent from work?</td><td colspan="6">Yes ----------(1)
No----------(2)
Unwilling to reply ----------(3)</td></tr>
<tr><td>21.If yes then how much income was lost?</td><td colspan="6">|__|__|__|__|__|__| BDT</td></tr>
<tr><td rowspan="4">22. During illness, did anybody take care of the patients in hospital/treatment centre?

If yes, please mention the time.</td><td colspan="6">Yes ---------- (1) No ---------- (2)</td></tr>
<tr><td>Attendant 1</td><td colspan="5">|__|__|- |__|__|-|__|__| (day : hour : minute)</td></tr>
<tr><td>Attendant 2</td><td colspan="5">|__|__|- |__|__|-|__|__| (day : hour : minute)</td></tr>
<tr><td>Attendant 3</td><td colspan="5">|__|__|- |__|__|-|__|__| (day : hour : minute)</td></tr>
<tr><td rowspan="6">23. What is the occupation and monthly income of the attendant?
Occupation code: House wife(1), Student(2), Worker(3), Unemployed (4), Service(5), Business(6), Other(Please Specify)---------- (77)</td><td rowspan="2">Attendant 1</td><td colspan="5">Occupation code- |__|__|</td></tr>
<tr><td colspan="5">Monthly income- |__|__|__|__|__|</td></tr>
<tr><td rowspan="2">Attendant 2</td><td colspan="5">Occupation code- |__|__|</td></tr>
<tr><td colspan="5">Monthly income- |__|__|__|__|__|</td></tr>
<tr><td rowspan="2">Attendant 3</td><td colspan="5">Occupation code- |__|__|</td></tr>
<tr><td colspan="5">Monthly income- |__|__|__|__|__|</td></tr>
<tr><td rowspan="3">24. Did the attendant faces any income losses due to caring the patients?

If yes, what is amount of money for this purpose?</td><td colspan="6">Yes ---------- (1) No ---------- (2)</td></tr>
<tr><td>Attendant 1</td><td colspan="5">|__|__|__|__|__|__|BDT</td></tr>
<tr><td>Attendant 2</td><td colspan="5">|__|__|__|__|__|__|BDT</td></tr>
</table>

	Attendant 3	|__|__|__|__|__|BDT
25. For this purpose, did the attendants have to spend any other money during that time? (such as food, boarding etc.) (If yes, please mention the amount)	Yes ---------- **(1)** No ---------- **(2)**	
	Attendant 1	|__|__|__|__|__|BDT
	Attendant 2	|__|__|__|__|__|BDT
	Attendant 3	|__|__|__|__|__|BDT
26. Do you think you/your child is fit at present?		Yes ---------- **(1)** No ---------- **(2)**

(After a week collect the following data by contacting with the patient)		
27. How did you returned home from this facility? How much time did it take? 01 = By rickshaw/Van 02 = By bus 03 = By CNG/Taxi 04 = By private Car 05 = On foot 77 = Other (Please specify):…….	Types of transport	1. |__|__| 2. |__|__| 3. |__|__|
	Total time	|__|__|:|__|__| (hour : minute)
28. Did you spend any money in transport purpose to return home?		Yes----------(1) No----------(2) Don't know----- (3)
29.If yes how much it cost?	st (BDT)	|__|__|__|__|__|
30. During and after returning home did you spent any money for medicine, diet or other purpose?		Yes ---------- (1) No ---------- (2)
31. If yes how much it cost?	st (BDT)	|__|__|__|__|__|
32. Did you affect by diarrhoea again after discharging from this hospital?		Yes------- (1) No---------(2)
33. If yes how many days were you affected by diarrhoea?	s	|__|__|__|
34. Did the patient have to remain absent from job/school or institution due to illness?	Yes ----------(1) No----------(2) N/A----------(99)	
35. If yes, how many days?	Days|__|__|__|	
36. Did you (patient) make any income loss due to this absent from work?	Yes ----------(1) No----------(2) Unwilling to reply --------- (3) N/A ---------- (99)	
37. If yes then how much income was lost?	|__|__|__|__|__| BDT	
38. During illness, did anybody take care of the patients in hospital/treatment centre?	Yes ---------- (1) No ---------- (2)	
	Attendant 1	|__|__|- |__|__|-|__|__| (day : hour : minute)
	Attendant 2	|__|__|- |__|__|-|__|__| (day : hour : minute)

If yes, please mention the time.	Attendant 3	|__|__|- |__|__|-|__|__| (day : hour : minute)
39. What is the occupation and monthly income of the attendant? Occupation code: House wife(1), Student(2), Worker(3), Unemployed (4), Service(5), Business(6), Other(Please Specify)---------- (77)	Attendant 1	Occupation code- |__|__|
		Monthly income- |__|__|__|__|__|
	Attendant 2	Occupation code- |__|__|
		Monthly income- |__|__|__|__|__|
	Attendant 3	Occupation code- |__|__|
		Monthly income- |__|__|__|__|__|
40. Did the attendant face any income losses due to take caring the patients? If yes, what is amount of money for this purpose?	Yes ---------- (1)	No ---------- (2)
	Attendant 1	|__|__|__|__|__|BDT
	Attendant 2	|__|__|__|__|__| BDT
	Attendant 3	|__|__|__|__|__|BDT

Thank you for your cooperation.

Name of the field Investigator:

Signature: _____

Date: _____

Name of the field Supervisor:

Signature_____

Date: _____

13.4 Data collection tool on willingness to pay for oral cholera vaccine

Consent Form
Protocol number : PR-15091
Title of the protocol: Targeted vaccination of children in the urban slums against cholera: evaluation of a potentially cost-effective and impactful strategy for deploying oral cholera vaccine against endemic cholera in Bangladesh

Sub-title of the Study: Willingness to pay for oral cholera vaccine

Principal Investigator: Dr. Firdausi Qadri

Co-Investigator: Abdur Razzaque Sarker, Dr. Ziaul Islam,

Purpose of the research:

Greetings, I am (Name of the interviewer.....) from icddr,b(Cholera Hospital), an International research institute. You are aware about that, in many developing countries like Bangladesh diarrhoea related illness is one of the major cause of public health problem. We are conducting a research on oral cholera vaccination program for children among 1 to 14 years to show the protective of the oral cholera vaccine in this area. For this purposes, we are conducting a study and the objective of this study is to find out how much households willingness to pay (WTP) for the purchasing the cholera vaccine. Now I'd like to know whether you would buy the vaccine if the vaccine is available in private market at a specified price. Please try to think carefully about what you would actually do if you had to spend your own money and you need to think that there are many other things that you need to purchase to maintaining in your family. There are no rights or wrong answers. We really want to know what you would do whether to purchase the vaccine or not.

Why did we select you?

Since this project is being conducted in your area and randomly, we consider you as a respondent of this study.

Method:

If you agree to participate in this research study, it would involve an interview lasting about 45 minutes. In this interview,I'd like to know whether you would buy the vaccine if it was available at a specified price in the market. You can choose your comfortable place for interview. If you agree I can start interview now or I can come again at your convenient time.

Privacy, anonymity and confidentiality:

We are assuring you that information given by you will be kept strictly confidential. We also want to assure you that all paper records of the interviews will be kept in a safe and secure place for five years and will not be used for any other purpose than the study. We ensure you that your name and other identity will not be exposed while the research results will be published. So it will not be possible to trace the answers back to you.

Future use of information:
Information provided by you will be used for this research only and your name will not be exposed when the research results will be published.

Risk:
There are no physical and social risks related to your participation in this study and if you refuse to participate in this study, you and your family will not faces any risk.

Benefit:
You will not be directly benefited by participating in this study. However**,** this information will improve the efficiency and quality of this service.

***Freedom not to participate and withdraw*:**

You are absolutely free to either participate or not participate in the study. You are free not to answer any question if you wish. Even you are free to withdraw at any point of the interview.

Compensation:
The study is unable to provide any financial compensation to you.

If you have any query regarding the study, you are free to ask the interviewer. You can also contact the principal investigator of this study or IRB coordinator at the address given below.

Dr. Ziaul Islam
Associate Scientist
Centre for Vaccine Sciences,
icddr,b, 68, Shaheed Tajuddin Ahmed Sarani, Mohakhali, Dhaka-1212,
Bangladesh.. Tel: 880 2 9841751, Ext. 2531;

M. A. Salam Khan
IRB coordinator,
Research Administration Services,
icddr,b
Mohakhali, Dhaka-1212
Telephone:02-8860523-32 (Ext. 3206)

Are you agree to participate in this study □ Yes □ No

_____ _____
Signature or left thumb impression of participant Date

_____ _____
Signature of the Interviewer Date

Section 1: Background Information

PID Number: |____|____|____|____|____|____|____|____|____|____|____|____|

Name of the respondent:

_____

Address: _____

_____

Age the respondent: Year |____|____| Month |____|____|

Relation: Mother (1), Father (2), Brother (3), Sister (4), Grandparents (5), Relative (6), Neighbour/ Friend (7), Other (8)

Relationship with the Household's member (insert code): |_____|

Contact no (Cell/Telephone) |____|____|____|____|____|-|____|____|____|____|____|____|

The above cell phone is belonging to you? Yes (1) No (2)

Interviewer ID: |_____|_____|_____|_____|_____|_____|

Interview start time: |__|__|:|__|__| (HH:MM) □ AM □ PM

Interview end time: |__|__|:|__|__| (HH:MM) □ AM □ PM

Interviewer, how long did you have to wait, after arriving at the respondent's home, to conduct this interview? (Please fill in below in minutes, if you didn't have to wait, please record "zero")
_____ Minute

If the survey is not completed, please indicate the reason why?

(1) Respondent seriously ill, cannot reschedule
(2) Respondent refused to be interviewed
(3) Respondent refused to sign consent
(4) Respondent decided to stop before finishing interview
(5) Respondent absent
(6) No children under 15 yrs. in the family
(99) Others, specify

201..Member ID	202. Name	203. Relationship with the household head	204. Sex Male (1), Female (2)	205. Age (actual)		206.Marital status 1 Married 2 Unmarried 3 Widow 4 Divorce 5 Separation	207. Education (complete year)	208. Occupation Code of occupation 1. Farmer 2. Rickshaw/ van driver 3. Bus/ truck/ CNG driver 4. Garments/factory worker 5. Fisherman 6. Public Job 7. Private Job 8. Business 9. Tea stall 10. Daily worker 11. Farm house 12. Fishmonger 13. Restaurant 14. Small scale 15. Homemaker 16. Domestic worker 17. Immigrant 18. Student 19. Unemployed 20. Disable person 21. Beggar 22. Retired 88. Other. 99. Not applicable	209. How many days work in last 1 month	210. Monthly income (e.g. consider last month)
				Year	Month					
1										
2										
3										
4										
5										
6										
7										
8										
9										

211. Did you/ your family member spend any money due to receiving healthcare?	Yes . . . . (1) No . . . . (2) → 213	
212. If yes, please specify	Item	Amount (BDT)
	Medicine	
	Physician fee	
	Diagnosis	
	Bed Fee	
	Food	
	Transport/ communication	
	Other (specify)	
	Total	
213. Have you heard anything about this study from your friend, neighbors, or family members?	Yes . . .(1) No . . . .(2) If yes specify _____ _	

Section -3. Perceptions and Attitude Towards Cholera

The next questions I would like to ask you are about the disease cholera.

301. Have you ever heard of the disease cholera?	Yes . . . . . .(1) No . . . . . .(2) Don't know/not sure. . (99)
302. What are the symptoms of cholera? (Spontaneous response, more than one response permitted)	*Please read the following description to all respondents:* Cholera is a disease often characterized by severe diarrhea, frequent episodes of watery diarrhea, vomiting, and weakness
Don't know/not sure	99

303. How does someone become infected by cholera? (Spontaneous response, more than one response permitted: check all that apply)

Answer	*Please mark (circle) is applicable*
drinking unboiled water	1
eating food from street vendors	2
eating unclean, uncooked vegetables	3
eating unripe fruit	4
bad weather	5
using unhygienic latrines	6
not washing hands before/after eating	7
flies touching food	8
Outdated food	9
Others (specify)	88

don't know/not sure	99		
304. How common do you think cholera is in your neighborhood? (read all responses before taking answer; one response permitted)	Not very common . . . . . (1) Common . . . . . (2) Very Common . . . . . (3) Don't know/not sure . . . (99) 306		
305. How serious is cholera for the following groups? (For each group, read all responses and mark one response	Age range	Code	Very serious (1) Serious (2) Not so serious (3) Don't know/not sure (99)
	Members aged under 5 years and		
	Members aged 6 to 10 years		
	Members aged 11to14 years		
	Members aged 15-19 years and above		
	Members aged 20 to 64 years and above		
306. Has anybody in your household (including yourself) ever had cholera?	Yes . . . . . (1) No . . . . . .(2) Don't know/not sure. (99)		
307. Has anybody in your household ever died due to cholera?	Yes . . . . . (1) No . . . . . .(2) Don't know/not sure. (99) → 309		

308. For each person in your household who died of cholera, please tell me how old they were when they died. (Spontaneous response; record total number of individuals who died of cholera in each group)

List of household member	Number
Infant less than one	
Members aged under 1 to 5 years and	
Members aged 6 to 10 years	
Members aged 11to14 years	
Members aged 15-19 years and above	
Members aged 20 to 64 years and above	
309. Have you known personally anyone (other than a household member) who has been sick due to cholera?	Yes . . . . . (1) No . . . . . .(2) Don't know/not sure. (99)
310. Have you known personally anyone (other than a household member) who has died due to cholera?	Yes . . . . . (1) No . . . . . .(2) Don't know/not sure. (99)

Section 4. Vaccines and Cholera

Next I'd like to talk about the spread and prevention of cholera. Cholera is spread primarily through eating food and drinking water contaminated by the feces of patients. You can help protect yourself from cholera by always consuming only safe, clean food and water and washing your hands thoroughly after defecation and before taking food.

Cholera is caused by a type germ. When someone becomes ill with cholera, he/she can develop severe diarrhea that can cause him or her to lose large amounts of fluids and salts. When the body loses too many fluids and salts, it can no longer work properly. The patient's kidneys can stop working, and the patient could die. The patient with cholera should drink plenty of oral saline and when severe, take intravenous saline/ cholera saline. If the patient takes Antibiotics right away, the diarrhea should not last as long.

The diarrhea caused by cholera will stop in a few days. Giving fluids works well to prevent and treat the worst problems caused by cholera, and giving fluids also makes the patient feel better. However, without treatment a person with cholera can become severely sick or die.

401. Do you have any questions or anything you are not clear about	Yes . . . (1) No . . . (2) 402

If yes, record the respondent's questions:

_____

_____

[Enumerator: If you know the answer to the respondent's questions, please answer them truthfully and briefly. If you are not sure you know the answer, please tell the respondent that you are not sure.]

I would like to ask you the following questions about vaccines.

402. Have you ever heard about vaccines?	Yes . . . (1) No . . . (2)

403. In your opinion, what is the purpose of a vaccine? (Spontaneous response, multiple response permitted)

Prevent disease for children . . . . . .(1) Prevent disease for pregnant women . . . .(2) Prevent disease for all people . . . . . .(3) Cure disease . . . . . .(4) Others (specify) . . . . . .(88) Don't know/not sure . . . . . (99)	

Read the following statement to all responded

Vaccine is for "prevention", not for treatment. You have to take a vaccine before you get sick.

404. Have you been vaccinated before?	Yes . . . . . (1) No . . . . . (2) Dont know/ Not sure . (99)
405. Has anyone in this household including you had either the any cholera vaccine?	Yes . . . . . .(1) No . . . . . (2) } 409 Dont know/ Not sure . . . (99) }
406. If yes, from where you received/ bought?	Pharmacy . . . . . .(1) Private hospital . . . .(2) Public hospital . . . .(3) Vaccination centre . . . . . .(4) Other (specify) ___(88)

407. Were you satisfied with that vaccine?	Yes . . . . . .(1) 409 No . . . . . (2) Dont know/ Not sure . . . . . (99)
408. If no, why not? (Spontaneous response, record only the most important) [Enumerator: If the respondent gave more than one reason, please ask which is the most important reason]	Did not prevent Cholera____ (1) Was not satisfied with the characteristics of vaccine (i.e. smell or color or taste)____(2) not satisfied with the method of administering the vaccine____(3) Minor side effects (i.e. diarrhea, rash, leaves scars on skin, fever, headache, loss of appetite, vomiting)____(4) Caused other major health problems _____ (5) Because the vaccine was locally produced _____(6) Other specify _____ (88) Dont know/ Not sure _____99)
409. Do you think that the vaccine will work against cholera disease?	Yes . . . . . (1) No . . . . . (2) Dont know/ Not sure . (99)
410. In your household, who would be primarily involved in making the decision whether or not to purchase cholera vaccines for your household members? (Spontaneous response, multiple responses permitted)	Myself (respondent . . . . . .(1) Spouse of respondent . . . . . (2) Parents of respondent . . . . . .(3) Parents in-law(s) of respondent . . . . . .(4) Son/ Daughter of respondent . . . . . .(5) Other (specify) . . . . . (88) Dont Know/Not sure . . . . . .(99)

Section 5. Cholera Vaccine (CV) scenario

Please explained the following topics in detailed

Doctors and scientists have developed a new vaccine that can prevent people from getting cholera. We'd like to know what you would do if the new cholera vaccine was available for sale at a convenient location like a vaccination camp or vaccination clinic or in any private clinic or pharmacy.

- This new vaccine could be given to individuals to prevent them from having cholera in the future
- This vaccine is completely safe and has no side effect and orally administrated like polio vaccine
- It could not be used to treat someone who currently has cholera.
- This vaccine cannot be used for children under 1 year and pregnant women.
- the vaccine would be required taken about 2 weeks apart
- The vaccine will upto 60% effective for 2 years duration

Vaccine Effectiveness

Now I want to explain exactly what I mean when I say the vaccine would be [60%] effective. Suppose that each of these little blue or red figures (*Enumerator: show the picture*) represents a person. (Enumerator: point out the circle). The 100 figures inside this circle represent 100 persons who have taken the vaccine, while the figures outside the circle represents those who have not taken the vaccine. The cholera vaccine is not 100% effective; that is the vaccine is only (60%) effective. Therefore, of the

100 people taking the vaccine in the circle, there will be (60%) of the people who have taken the vaccine that are protected (i.e., the vaccine works for them) for a period of 2 years. The blue figures inside this circle represent these people. The rest of the people (the red ones inside the circle) who have been vaccinated (40) will not be protected against cholera even though they have taken the vaccine, because the vaccines did not work for them. They will still be at risk of getting cholera just like they were before they got the vaccine or just like the people outside the circle who haven't received vaccines. However, even if they get cholera, their symptoms may not be quite as severe compared to someone who has not received the vaccine. The people who receive cholera vaccine will not be able to know if the vaccine works for them. Of course, we don't know who would actually get cholera. A red person outside the circle who has not taken a vaccine still has a relatively small risk of being infected.	
Assess understanding about the vaccine effectiveness Now I am going to ask you some questions to make sure that the information I told you is clear	
First round	
501. Please point to all the people who have taken the vaccine [Interviewer: put a mark into a relevant place]	Respondent did give the correct answer____(1) Respondent did not give the correct answer ___(2) Respondent did not know/not sure____(3)
502. Please point to all the people who have taken the vaccine and it work for them. [Interviewer: put a mark into a relevant place]	Respondent did give the correct answer____(1) Respondent did not give the correct answer ___(2) Respondent did not know/not sure____(3)
503. How many years would the cholera vaccine work for them?	Year_____ (1) If respondent gave incorrect answer, please correct it (2) Respondent did not know/not sure____(3)
504. How many people have taken the vaccine but can still get cholera? [*Interviewer: put a mark into a relevant place*]	Respondent did give the correct answer____(1) Respondent did not give the correct answer ___(2) Respondent did not know/not sure____(3)
505.If an unvaccinated person gets infected by cholera, can the vaccine be used to cure them?	Respondent did give the correct answer____(1) Respondent did not give the correct answer ___(2) Respondent did not know/not sure____(3) *If respondent gave incorrect answer, please correct it.*
506. Interviewer: did the respondent give the correct answer to all three effectiveness questions (501,502 and 504)	Yes . . . . . (1) 513 No. . . . . .(2) *Enumerator: If No to **CV Scenario** tell the respondent:*
"I feel that I need to explain about the effectiveness of the vaccine a little bit more." (explain the effectiveness of the vaccine again) "Now I would like to go over the questions again, to make sure that the information I told you is clear."	
Second round	

507. Please point to all the people who have taken the vaccine [Interviewer: put a mark into a relevant place]	Respondent did give the correct answer____(1) Respondent did not give the correct answer ___(2) Respondent did not know/not sure____(3)
508. Please point to all the people who have taken the vaccine and it work for them. [Interviewer: put a mark into a relevant place]	Respondent did give the correct answer____(1) Respondent did not give the correct answer ___(2) Respondent did not know/not sure____(3)
509. How many years would the cholera vaccine work for them?	Year_____ (1) If respondent gave incorrect answer, please correct it (2) Respondent did not know/not sure____(3)
510. How many people have taken the vaccine but can still get cholera? [*Interviewer: put a mark into a relevant place*]	Respondent did give the correct answer____(1) Respondent did not give the correct answer ___(2) Respondent did not know/not sure____(3)
511. If an unvaccinated person gets infected by cholera, can the vaccine be used to cure them?	Respondent did give the correct answer____(1) Respondent did not give the correct answer ___(2) Respondent did not know/not sure____(3) *If respondent gave incorrect answer, please correct it.*
512. Interviewer: did the respondent give the correct answer to all three effectiveness questions (507, 508 and 510)	Yes . . . . . (1) 513 No. . . . . .(2) *Enumerator: If No to **CV Scenario** tell the respondent:*
Note: Whether the respondents gave the correct answer or not, please skip to the next question.	
513. Please indicate what you believe to be the most important benefit of the vaccine.	
Prevent pain and suffering of cholera . . . . (1) Avoid teatment cost of cholera . . . . . (2) Prevent risk of death from cholera . . . . . .(3) Avoid income loss due to cholera . . . . . .(4) Don't know/No answer . . . . (5) Othjer (please specify) . . . . . (99)	
514. With this information, will you be willing to accept Cholera vaccine if it is offered in any immunization facility?	Yes . . . . .(1) No . . . . .(2)
515. Please rate your level of acceptance of Cholera vaccine?	Very unwilling . . . . (1) Unwilling . . . . . (2) Not sure ...(3) Willing . . . . . (4) Very willing . . . . (5)
Section 6. Willingness to pay for Cholera Vaccine	

Suppose, the government will not provide the vaccine at free. If someone wish to vaccinated, he/she must purchase the vaccine with specified price. The purchasing price of the vaccine will be uniform to all. In this situations, Now I'd like to know whether you would buy the vaccine if it was available at a specified price. Some people say they cannot afford the price of the vaccine or that they are actually not at risk of getting this disease. Other people say that would buy the vaccine because the protection is really worth it to them. Again some other people replied, "this vaccine has a great importance and I would really like as much protection from this disease as possible."

In other studies about vaccines, we have found that people sometimes say they want to buy the vaccine. They think: "I would really like as much protection from this disease as possible." However, they may forget about other things they need to spend their money on in real life. Please try to think carefully about what you would actually do if you had to spend your own money. There are no rights or wrong answers. We really want to know what you would do.

For your information, a new cholera vaccine named " Shancol" is available in india at a price ranges between 127-150 Bangladeshi taka, i.e. a total BDT 254-300 will be required for two dose. However, a study conducted in urban Bangladesh and found that, the average total household cost of treatment for an episode of cholera was up to BDT 2278 which is quite high.

Willingness to Pay (WTP) (FOR SELF)	
601. If the Cholera vaccine is not publicly funded, will you be willing to pay for it for two dose?	Yes . . . (1) → 603 No . . . (2) → 602 and 605 থেকে continue
602. If no, Why? (Spontaneous response, multiple responses permitted)	Not enough money. . . . . .(1) Too expensive. . . . . (2) I am too old a not required. . . . . (3) Not for myself but only for children. . . . . (4) Yes, only if the doctor recommends. . . . . .(5) Yes, only if many people around me get cholera illness .(6) Respondent did not know/not sure . . . (99)
603. How much will you be willing to pay for the two dose cholera vaccine?	|_____| BDT
604. If due to inflation or other uncertainties, the cost for the vaccine is higher than what you have just stated, what is the maximum amount you are very certain to pay for yourself? Bearing in mind that your entire household (both adult and children) may have to receive the vaccine about the same period?	|_____| BDT
WTP (WTP for other household member)	

605. If the Cholera vaccine is not publicly funded, will you be willing to pay for it for your household members?	Yes . . . . .(1) 607 continue No . . . . . (2) 606 & Section **7** continue
606. If no, Why? (Spontaneous response, multiple responses permitted)	Not enough money . . . . . (1) Too expensive . . . . . .(2) Not for myself but only for children . . . . . .(3) Yes, only if the doctor recommends . . . . . (4) Yes, only if many people around me get cholera illness. . (5) Other (specify) _____ . . . . . .(88) Respondent did not know/not sure . . . . . (99)

607. Please fill up the following table (ONLY FOR HOUSEHOLD MEMBERS NOT INCLUDING YOURSELF)

Relationship	Yes (1), No (2)	Age	Number of Dose	Maximum WTP
Spouse				
Mother				
Father				
Child 1				
Child 2				
Child 3				
Child 4				
Child 5				
Child 6				
Other adult 1				
Other adult 2				
Other adult 3				
Other Child 1				
Other Child 2				

608. How difficult did you find it to make your decision?	Very difficult . . . .(1) Difficult . . . . . (2) Easy . . . . . .(3) Very easy . . . . . (4)

Section 7. End of questionnaire

This is the end of the interview. Thank you very much for your participation. We'd like to state that it is necessary for you to protect yourself from contracting cholera. The objective of this survey is to learn about your willingness to pay for cholera vaccines either for yourself or your household members. We need to ask different households their willingness to purchase at different prices. Thus, don't worry if you hear that other people in your community have been asked related to this survey

701. How reliable do you think is the information you got from the respondent??	Very reliable . . . . . .(1) Reliable . . . . . (2) Fairly reliable . . . .(3) Not reliable . . . . . (4) Very unreliable. . (5)
702. Do you think the respondent understood about the vaccine efficacy scenario and the importance of the vaccination?	Did not understand . . . . .(1) Fairly understood . . . . . .(2) Understood . . . . . .(3) Don't know/not sure . . .(99)
703. *Enumerator: Please note the type of flooring material*	Mud . . . . . (1) Cement . . . . . .(2) Mosaic[floor tiles] .(3) Brick . . . . . .(4) Others (specify) . . . (88)
704. *Enumerator: Please note the type of material used in the Wall*	Thatch/ bamboos . . .. (1) Mud . . . . . (2) Corrugated tin . . ... (3) Plastic/polythene.. . (4) Bricks . . . . (5) Wood . . . . . (6) Other (specify) . . . .(77)
705. *Enumerator: Please note the type of material used in the Roof*	Thatch/bamboo/wood etc . . .(1) Plastic/polythene . . . . . (2) Corrugated tin . . . . . .(3) Concrete . . . . . .(4) Others, Specify . . . .(77)
706. What type of house does the respondent live in?	Own homestead . . . . . (1) Rented house in slum . . . . . (2) Government quarters . . . . . (3) Single-family home in good condition . . . . .(4) Flat/home shared by multiple families . . . . . (5) Single-family home in poor condition . . . . (6) Others, (specify) . . . . . .(77)
707. Other suggestions/ comments.....	