Benefit-risk and cost-utility of rotavirus vaccination in Afghanistan: a modelling study informed by post-marketing surveillance data

Palwasha Anwari MD, MSc

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Department of Health Services Research and Policy

Faculty of Public Health and Policy

London School of Hygiene & Tropical Medicine

University of London

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Primary supervisor:	**Dr Andrew Clark** Associate Professor Department of Health Services Research and Policy London School of Hygiene and Tropical Medicine
Co-supervisors:	**Dr Kaja Abbas** Associate Professor Department of Infectious Disease Epidemiology London School of Hygiene and Tropical Medicine
	Dr Colin Sanderson Professor Emeritus, Operational Research in Health Care Formerly Department of Health Services Research and Policy London School of Hygiene and Tropical Medicine
Advisory committee members:	**Dr Jacqueline Tate** Senior Scientist Centers for Disease Control and Prevention United States of America
	Dr Ulla Griffiths Senior Advisor, Health Immunization UNICEF New York

Declaration

I, Palwasha Anwari, confirm that the work presented in this thesis is my own. Where information has been derived from other sources or others have contributed to the work, I confirm that this has been indicated in the thesis.

Signed:

Date: 05 February 2025

Full name: Palwasha Anwari

Abstract

Rotavirus gastroenteritis (RVGE) has an important health and economic burden, particularly in low- and middle-income countries. In response to this public health challenge, the World Health Organization recommended the implementation of rotavirus vaccination globally in 2009. The deployment of live oral rotavirus vaccines for infants has proven effective in reducing the morbidity and mortality associated with RVGE, albeit with varying degrees of effectiveness across different nations. However, concerns have arisen regarding its potential association with intussusception, a rare type of bowel obstruction, in certain contexts.

Afghanistan introduced the monovalent rotavirus vaccine, ROTARIX, in January 2018, targeting infants at six and ten weeks of age. Following its rollout, active post-licensure hospital-based surveillance was initiated from May 2018 to June 2022, focusing on monitoring the safety and effectiveness of ROTARIX among Afghan children <5 years old. This surveillance endeavour presented an opportune moment to evaluate whether the benefits of rotavirus vaccination outweigh the associated risks and whether the accrued advantages justified the incremental costs incurred.

This Doctor of Public Health (DrPH) thesis aims to assess the real-world benefit-risk and cost-utility of monovalent rotavirus vaccination in Afghanistan. Leveraging the UNIVAC decision-support model, a static proportionate outcomes cohort model, vaccine benefits (numbers of averted RVGE cases, clinic visits, hospital admissions, and fatalities among children aged <5 years), vaccine risks (potential numbers of excess intussusception hospital admissions and deaths) and associated costs, were calculated with and without rotavirus vaccination, from 2018 to 2024. Primary outcomes were the cost-utility ratio (US$ per DALY averted) and benefit-risk ratio (excess intussusception deaths per RVGE death averted). To inform future decision-making regarding rotavirus vaccination strategies, a separate analysis compared the cost-utility of four alternative rotavirus vaccine options – ROTARIX® (1 dose vial), ROTASIIL (1 dose vial), ROTASIIL (2 dose vial), and ROTAVAC (5 dose vial) – over a decade-long period (2025-2034).

Data regarding vaccine effectiveness and safety were derived from post-marketing surveillance, utilizing test-negative case-control and self-controlled case-series analyses, respectively. Supplementary inputs were drawn from a national household survey, the scientific literature, and

international databases.

This research concludes that the rotavirus vaccine is a beacon of hope in combating rotavirus diseases in Afghanistan. Its effectiveness, impact, safety, and cost-effectiveness, when considered with the contextual factors, strongly support the continuation of the rotavirus vaccination in Afghanistan. The findings from this study support the sustained implementation of rotavirus vaccination in Afghanistan. The results have been widely disseminated through various channels, such as scientific conferences, presentations, and scholarly publications.

Keywords

Rotavirus; Rotavirus vaccine; Effectiveness; Safety; Benefit-risk; Cost-utility; Surveillance; Afghanistan.

Acknowledgements

I could not have achieved what I have in the last four years without the unwavering support and guidance of my incredible supervisors, Associate Professor Andrew Clark, Associate Professor Kaja Abbas, and Professor Colin Sanderson.

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I am grateful to LSHTM for accepting me into the programme and providing a nurturing and supportive environment for growth and accomplishment. I thank you particularly Beate Kampmann and Tracey Chantler in the Vaccine Centre, and Neha Singh and Francesco Checchi in the Health in Humanitarian Crises Centre, for giving me the opportunity to contribute to the remarkable impactful work that these centres do globally.

A heartfelt thank you goes to PATH, particularly to Clint Pecenka, and the Bill and Melinda Gates Foundation, for financially supporting a significant part of my DrPH. Without this support, I would not be where I am today.

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Thank you to my family, brothers and sisters, and their families, for their love, care, and support every step of the way. Thank you for always being there for me and preventing me from succumbing to the depths of despair during my DrPH journey, and with the impact of the sudden turning upside of our lives as Afghans since August 15, 2021, as well the pandemic. Your presence in my life is genuinely a blessing. Thank you for everything.

And finally, special thanks to my parents, who are no longer with us, who I know have been there by my side throughout this process, encouraging me and cheering me on. I am sorry they are not here to celebrate this achievement together with me.

Thesis copyedited by: Steve Russell, Steve Russell Academic Editing, the Netherlands.

Dedication

This thesis is dedicated to the cherished memory of my parents:

My beloved father, retired Colonel Mohammad Anwar

My beloved mother, Nooria Bebi Hawa

Their wisdom, love, dedication to their family and nation continue to illuminate every step of my life.

Opening remarks

By Ferdowsi (فردوسی), the Persian poet who lived between 940 AD and 1020 AD, from his book "Shahnamah شهنامه"

به نام خداوند جان و خرد — کزین برتر اندیشه برنگذرد

خداوند نام و خداوند جای — خداوند روزی ده رهنمای

خداوند کیوان و گردان سپهر — فروزنده‌ی ماه و ناهید و مهر

ز نام و نشان و گمان برتر است — نگارنده‌ی بر شده پیکر است

ستودن نداند کس او را چو هست — میان بندگی را ببایدت بست

خرد را و جان را همی سنجد اوی — در اندیشه‌ی سخته کی گنجد اوی

پرستنده باشی و جوینده راه — به ژرفی به فرمانش کردن نگاه

توانا بود هر که دانا بود — ز دانش دل پیر برنا بود (فردوسی)

The translation of the first and the last lines are:

"In the name of Allah, the God of life and wisdom, whose knowledge surpasses all understanding".

"Powerful who he/she is wise. With knowledge, the heart of an old man becomes young". [Laterally, knowledge is power].

Table of contents

List of Abbreviations

AEFI	Adverse Events Following Immunization
AGE	Acute Gastroenteritis
AI	Artificial Intelligence
ARTF	Afghanistan Reconstruction Trust Fund
BHS	Basic Health Center
BPHS	Basic Package of Health Services
CEA	Cost-effective Analysis
CDC	Centers for Disease Control and Prevention
CHC	Comprehensive Health Center
CHW	Community Health Worker
COVID-19	Coronavirus Infection Disease 2019
CPHL	Central Public Health Laboratory
CUA	Cost-utility Analysis
DALY	Disability Adjusted Life-Year
DH	District Hospital
DHS	Demographic and Health Survey
DTP1	Diphtheria-Tetanus-Pertussis vaccine dose 1
DTP2	Diphtheria-Tetanus-Pertussis vaccine dose 2
DTP3	Diphtheria-Tetanus-Pertussis vaccine dose 3
dsRNA	double-stranded Riboflavin Nucleic Acid
DrPH	Doctor of Public Health
EIA	Enzyme immunoassay
EPHS	Essential package of hospital services
EPI	Expanded Program on Immunization
ELCS	Emerging Leader Consulting Services
ELISA	Enzyme-linked Immunosorbent Assay
ER	Endoplasmic Reticule
EtR	Evidence to Recommendation
EU	European Union
HBGAs	Histo-blood Group Antigens

HIV	Human Immunodeficiency Virus
HP	Health Post
HPV	Human Papilloma Virus
HMIS	Health Management and Information System
HSC	Health Sub-Center
HSS	Health System Strengthening
GACVS	Global Advisory Committee on Vaccine Safety
Gavi	Global Alliance for Vaccine and Immunisation
GCMU	Grant Contracts and Management Unit
GDP	Gross Domestic Product
GNI	Gross National Income
GRSN	Global Rotavirus Surveillance Network
GSK	GlaxoSmithKline
GVAP	Global Vaccine Action Plan
ICC	Interagency Coordination Committee
IECs	Intestinal Epithelial Cells
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMCI	Integrated Management of Childhood Illness
INF	Interferons
IQR	Interquartile range
IRB	Institution Review Board
IRF	Interferon Regulator Factor
IS	Intussusception
ISS	Immunization Services Support
JICA	Japan International Cooperation Agency
JSCS	Jawid Samsor Consultancy Services
LSHTM	London School of Hygiene and Tropical Medicine
LMICs	low- and middle-income countries
MHT	Mobile Health Team
MICS	Multiple Cluster Indicator Survey
MoF	Ministry of Finance

MoPH	Ministry of Public Health
MSc	Master of Sciences
NH	National Hospital
NIH	National Institute of Health
NGO	Non-government Organizations
NHA	National Health Account
NISA	National Statistics and Information Authority
NSP	Non-Structural Protein
OOP	Out-of-Pocket
OR	Odds Ratio
ORS	Oral rehydration solutions
PCR	Polymerase chain reaction
PH	Provincial Hospital
PMO	Performance Management Office
QALY	Quality Adjusted Life Years
RCT	Randomized controlled trails
RD	Research Degree
RI	Relative Incidence
RR	Relative Risk
RR	Risk Ratio
RVGE	Rotavirus Gastroenteritis
PRR	Pattern Recognition Receptor
RS I	Research Study I
RS II	Research Study II
RV	Rotavirus
RV1	Rotavirus vaccine dose 1
RV2	Rotavirus vaccine dose 2
RVV	Rotavirus Vaccine
SA	Sialic Acids
SCCS	Self-controlled case-series
SD	Standard Deviation
SDI	Socio-demographic index
RD	Research Degree

THE	Total Health Expenditure
UHC	Universal Health Coverage
UN	United Nations
UNAMA	United Nations Assistance Mission in Afghanistan
UNICEF	United Nations Children's Fund
UNOCHA	United Nations Office for the Coordination of Humanitarian Affairs
UNFPA	United Nations Population Fund
UNDP	United Nations Development Programme
UNPOP	United Nations Population Division
USAID	United States Agency for International Development
VP	Viral Protein
WASH	Water, Sanitation, and Hygiene
WB	World Bank
WHO	World Health Organization
WUENIC	WHO and UNICEF Estimates of National Immunization Coverage

Glossary table

Low- and middle-income countries (LMICs)	The World Bank categorized countries based on their "Gross National Income (GNI) per capita". As of 2024, 137 countries fall into the LMIC categories, representing 63% of all countries. The most recent classification is as follows: **Low-income countries**: GNI per capita of US$ 1,135 or less. **Lower-middle-income countries**: GNI per capita between US$ 1,136 and US$ 4,465. **Upper-middle-income countries**: GNI per capita between US$ 4,466 and US$ 13,845.[1]
Economic evaluation	Compares the costs and outcomes of at least two alternative programmes. There are four different types of economic evaluation: "cost-minimization analysis", "cost-effectiveness analysis", 'cost-utility analysis", and "cost-benefit analysis".[2]
Deterministic model	Is a mathematical model in which there is no inclusion of chance or "random variation" in the modelled process. Deterministic models can be solved by "numerical analysis" or "computer simulation" and give a fixed and exactly "reproducible result".[2]
Static model	Is a mathematical model in which the "force of infection- which represents how diseases spread" is assumed to be constant and "independent of the proportion of infectious people at each time point". Essentially this type of model assumes that vaccination does not infer "herd immunity".[2-4] Static models assume that key parameters (such as "population size", "disease prevalence", and "transmission rates") remain fixed. Static models are commonly employed in economic evaluations of vaccination programmes, where the focus is on "comparing costs, benefits, and health outcomes under specific assumptions".[2-4]
Dynamic model	Dynamic models, which consider "changes over time", offer a more "comprehensive perspective" but are often more complex. In these mathematical models, the "force of infection" is a "function of the proportion" of "infectious individuals" in the population at each time point. The "force of infection" can thus "change over time" in this type of model.[2]

Cost-utility analysis (CUA)	Cost-utility prices outcomes using “measures of utility” that reflect “quality- or disability-adjusted life years (QALYs or DALYs)”. For instance, it compares vaccines for rotavirus in terms of which vaccine averts a DALY most cheaply.[2]
Cost-effectiveness analysis (CEA)	In cost-effectiveness analysis, “the outcomes of measure(s)” are presented in “tangible or natural units”, such as “number of deaths averted”, “number of life-year gained”, or “number of clinic visits” or “hospitalizations prevented”. The lines between “cost-effectiveness analysis (CEA)” and “cost-utility analysis (CUA)” have become less distinct, with the latter often viewed as an expansion of the former. Usually, literature on “cost-effectiveness” frequently includes both of these approaches.[2]
Cost-benefit analysis (CBA)	Expresses” health outcomes” in terms of “monetary units” and “budgetary implication”. It helps to identify which intervention generates the greatest return on investment.[2]
Benefit-risk analysis	Assesses the “risks” associated with a situation relative to its “corresponding benefits” and evaluates the” acceptability of these risks”.[5, 6]
Disability-adjusted life year (DALY)	A measure to “adjust life years lived for disease related disability, age and time preference”.[2]
Discount rate	The rate at which “costs and outcomes are discounted to account for time preference”.[2]

Glossary references

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CHAPTER ONE: INTRODUCTION

Chapter 1: Introduction

1.1 Background

Rotavirus gastroenteritis (RVGE) is a leading cause of diarrhoeal morbidity and mortality in low- and middle-income countries (LMICs).[1,2] Live oral rotavirus vaccines effectively prevent severe RVGE morbidity and mortality but have been associated with a rare bowel disorder, intussusception, in some settings.[3,4] In 2009, the World Health Organization (WHO) recommended that all countries with high child mortality due to diarrhoea introduce rotavirus vaccination into their national immunization schedules.

In January 2018, the Afghanistan Ministry of Public Health (MoPH) introduced a monovalent rotavirus vaccine (ROTARIX) administered at six and ten weeks of age.[5] Active post-licensure hospital-based surveillance was conducted in four regions of the country (from May 2018 to June 2022) to monitor real-world safety and effectiveness of the vaccine. These data provided an opportunity to assess whether the benefits of rotavirus vaccination have outweighed the harms and whether the observed net benefits have been worth the incremental costs.

1.2 Thesis aim

The aim of this thesis is to evaluate the real-world benefit-risk and cost-utility of ROTARIX, a monovalent rotavirus vaccination, among children under the age of five in Afghanistan. The study encompasses the period from the national introduction of the vaccine in January 2018 to December 2024, and compares ROTARIX introduction to a scenario with no rotavirus vaccination. Additionally, it includes a separate prospective analysis comparing the potential cost-effectiveness of various rotavirus vaccines– ROTARIX® (1 dose vial), ROTASIIL (1 dose vial), ROTASIIL (2 dose vial), and ROTAVAC (5 dose vial) – over a decade-long period (2025-2034), aiming to inform future decision-making regarding rotavirus vaccination strategies.

1.3 Thesis objectives

The thesis has the following 8 specific objectives:

Objective 1: Employ epidemiological design, specifically the test-negative case-control design embedded into post-licensure surveillance, to assess the effectiveness of the rotavirus vaccine.

Objective 2: Compare pre- and post-vaccine introduction rotavirus gastroenteritis (RVGE) surveillance data to evaluate vaccination impact.

Objective 3: Perform a trend analysis using administrative data from the Health Management Information System (HMIS) on acute gastroenteritis (AGE) among children <5 years of age.

Objective 4: Utilize a self-controlled case-series analysis study design to assess vaccine safety within specified risk windows following each vaccine dose.

Objective 5: Examine the cost-utility of oral monovalent rotavirus vaccine retrospectively using real-world data (2018-2024).

Objective 6: Conduct both retrospective and prospective evaluation of the benefit-risk ratio of monovalent rotavirus vaccination.

Objective 7: Compare the cost-utility of different oral rotavirus vaccine products prospectively (2025-2035).

Objective 8: Gather evidence on cross-cutting issues and other criteria required to make an overall appraisal on whether rotavirus vaccination should continue to be used in Afghanistan.

1.4 Style and structure of thesis

This thesis is structured using a research paper style, with each chapter designed as a standalone piece of work that can be read independently, except for Chapter 1 (Introduction) and Chapter 7 (Discussion).

The thesis component consists of THREE published papers and SEVEN chapters. The chapters are organized as follows (see also **Figure 1-1**).

Chapter 1 introduces the readers to the thesis. I offer a succinct overview of the subject matter and the rationale or reasons for conducting this study. I delineate the main aim of the thesis and the EIGHT objectives that I have pursued, and provide an overview of the organization and

content of the SEVEN chapters comprising the thesis.

Chapter 2, the literature review, presents a comprehensive exploration and contextualization of existing literature on rotavirus, mainly on rotavirus pathophysiology and immune response, rotavirus gastroenteritis, and rotavirus vaccines and the potential adverse effects associated with rotavirus vaccination. I specify the significance of post-licensure surveillance and real-world data in modelling studies. Furthermore, this chapter sheds light on Afghanistan's country profile and healthcare system, highlighting routine immunization programmes.

The main body of the thesis **(Chapters 3 to 6)** encompasses three published peer-reviewed journal articles and a dedicated chapter on cross-cutting issues and some selected decision-making criteria that influence vaccination programmes in the country.

Chapter 3, research paper 1, addresses study objectives 1 to 3, which evaluate the effectiveness and impact of monovalent rotavirus vaccination in Afghanistan using a test-negative case-control study design, and comparing pre- and post-vaccine introduction active and passive surveillance data.

Research paper-1 citation

Anwari P, Burnett E, Safi N, Samsor A, Safi H, Chavers TP, Parashar UD, Clark AD, Tate JE. Effectiveness and impact of monovalent rotavirus vaccination in Afghanistan: a test-negative case-control analysis. Lancet Glob Health. 2024 Sep;12(9):e1517-e1525. doi: 10.1016/S2214-109X(24)00237-7 PMID: 39151986.

Chapter 4, research paper 2, addresses study objective 4, evaluating post-marketing rotavirus vaccination safety in Afghanistan, utilizing a self-control case-series study design.

Research paper-2 citation

Anwari P, Burnett E, Chavers TP, Samsor A, Safi H, Safi N, Clark AD, Parashar UD, Tate JE. Post-marketing surveillance of intussusception after ROTARIX administration in Afghanistan, 2018-2022. Vaccine. 2024 Mar 19;42(8):2059-2064. doi: 10.1016/j.vaccine.2024.02.057. Epub 2024 Feb 26.

In **Chapter 5**, the third paper, and the core analysis of this thesis, I utilized the results of Chapters 3 and 4 to populate the mathematical model, UNIVAC, to analyse the benefit-risk and cost-effectiveness of rotavirus vaccination in Afghanistan, addressing study objectives 5-7.

Research paper-3 citation

Anwari P, Debellut F, Parwiz S, Pecenka C, Clark A, Benefit-risk and cost-effectiveness of

rotavirus vaccination in Afghanistan: a modelling analysis informed by post-licensure surveillance **(submitted paper)**

Chapter 6, addressing study objective 8, delves into the unique factors specific to the country's context that influence the decision-making for rotavirus vaccination and other childhood immunizations. These factors include security concerns, armed conflict, equity issues primarily from a gender inequality and geographical perspective, financial sustainability, and the impact of the COVID-19 pandemic, all considered within the scope of available secondary data.

Chapter 7, the final chapter, synthesizes the evidence gathered and aligns it with the recommendations of the Organizational or/and Policy Analysis (OPA) (or Research Study 1) which was conducted as part of this degree. This chapter offers an opportunity for an in-depth discussion about the study's limitations, provides reflections on contextual factors, and makes suggestions for future research.

Each of the three chapters dedicated to a peer-reviewed research paper starts with a preamble section outlining the paper's contribution to the overarching goals and objectives of the thesis. Additionally, I have detailed my individual academic contributions to each paper, which is crucial for clarity as all papers involve contributions from multiple authors. Relevant funding and ethical approvals are also outlined.

Appendices for Chapters 2 to 4 are provided at the end of each respective chapter for convenient reference. The research ethics course completion certificate, ethical approval letters obtained for the thesis and specific studies included in this thesis are appended at the end of the thesis in the Annexes section.

1.5 Ethical clearance

Ethical approval for the studies included in this thesis was granted by the LSHTM Observational Ethics Committee. The reference number for the thesis REF:29622 is conditional on ethical approval from local ethical approval authorities if required. The reference numbers for the studies reported in Chapters 3 and 4 from the local ethical institution were REF:444510 and REF:444509, respectively.

1.6 Chapter 1 references

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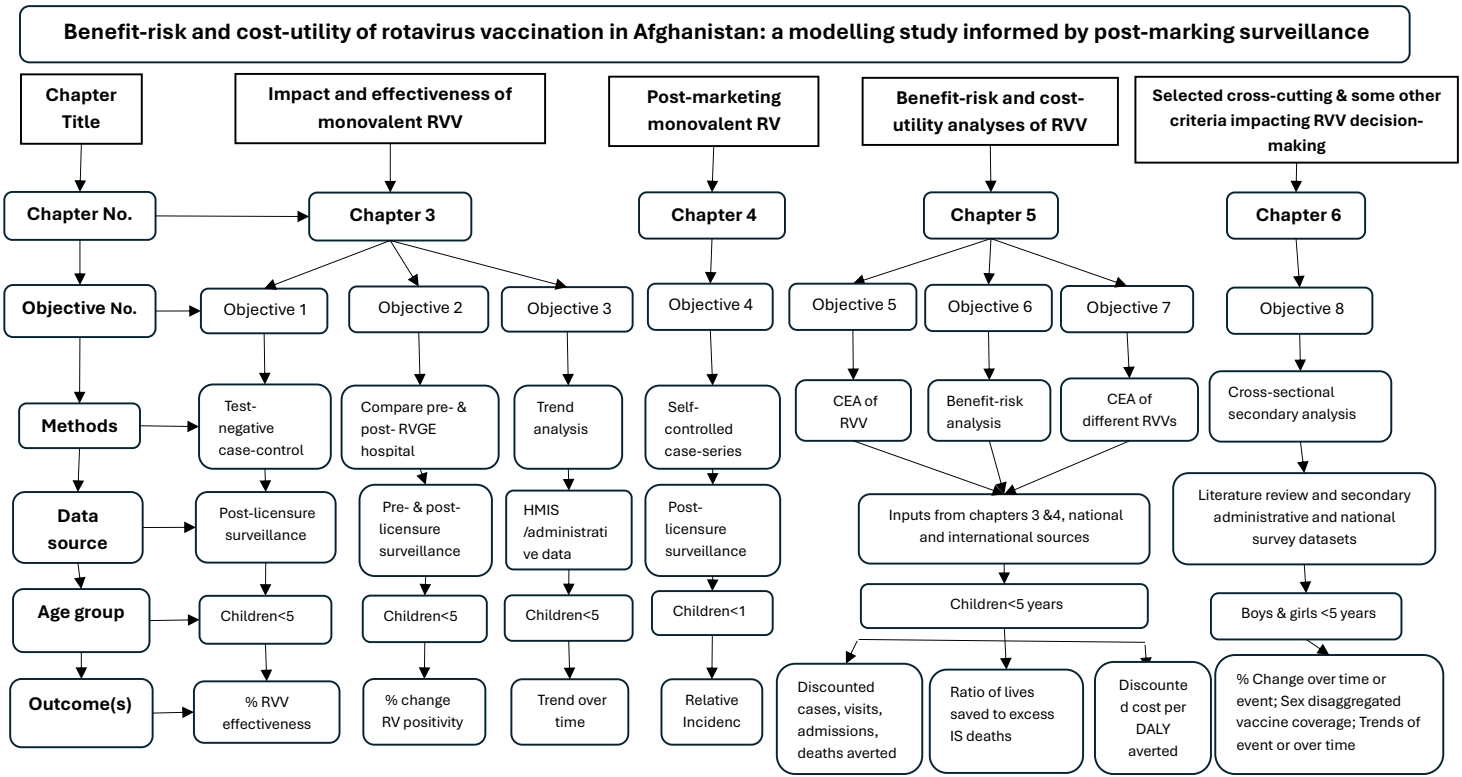
Figure 1-1 Thesis main analyses/chapters flowchart



RVV: Rotavirus vaccine; RVGE: Rotavirus gastroenteritis; HMIS: Health Management Information System; DALY: Disability adjusted life year; CEA: Cost-effectiveness analysis; IS: intussusception; COVID-19: Coronavirus disease 2019.

CHAPTER TWO: LITERATURE REVIEW

Chapter 2: Background and literature review

2.1 Rotavirus (RV)

Rotavirus (RV) is one of the main pathogens causing gastroenteritis and is a public health concern worldwide. In 1973, Ruth Bishop, Geoffrey Davidson, Ian Holmes, and Brian Ruck first discovered it in children with acute diarrhoea through intestine biopsy and stool samples in Melbourne, Australia.[1-3] RVs belong to the Reoviridae family.[4,5] "Rota" is derived from the Latin word for "wheel". The name "rotavirus" is attributed to its resemblance, as observed under an electron microscope, to a wheel with a hub, spokes, and rim.[6]

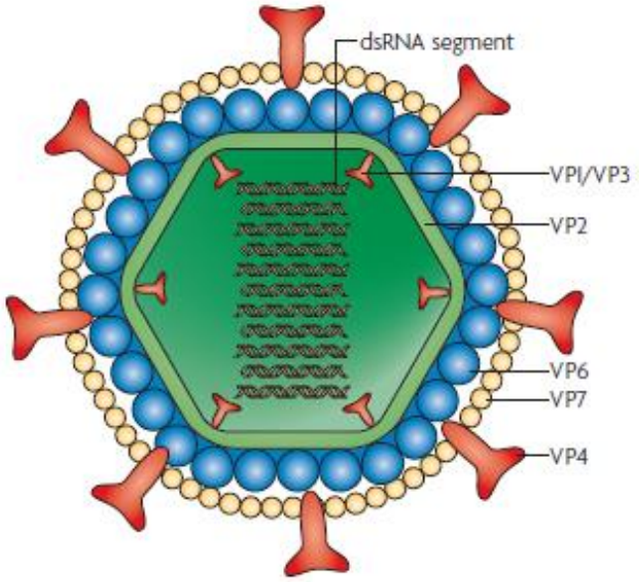
Rotaviruses, viral particles with three layers, are genetically composed of 11 double-stranded ribonucleic acid (dsRNA) genomes. Each of these helices corresponds to a gene, numbered 1 to 11, which encodes six structural viral proteins (VP1, VP2, VP3, VP4, VP6, and VP7) and six non-structural proteins (NSP1-6). Each gene codes one protein, apart from genes 9 and 11, which code for two proteins. Surrounding the RNA spiral is a three-layer icosahedral protein capsid **(Figure 2-1)**. The viral particles are unenveloped and have a diameter of up to 76.5 nm.[7-9] The external viral layer is composed of two proteins, namely viral protein VP7 and VP4, while the internal capsid is formed by three proteins, VP6, VP1, and VP2.[5] The VP7 protein undergoes glycosylation, and the serotypes determined by this protein are called G serotypes.

VP4 serotypes are additionally categorized using neutralization and sequencing tests. However, discrepancies may arise between the results obtained from these methods, leading to a dual system for P typing. Serotype numbers, such as P1 and P2, are used to refer to P serotypes, while P genotypes are indicated within brackets, like P[6] and P[2]. So far, approximately 32 distinct G and 47 P genotypes have been identified.[4] The diversity of RVs is related to gene segments carrying the G and P proteins, and at least 42 virus strains have been identified based on P-G serotype combinations.[7,10,11]

VP3 is the source of infectivity and is thought to cause asymptomatic or mild rotavirus infection. Rotaviruses are classified into alphabetic groups, such as A, B, C, etc. Group A is the predominant cause of disease in humans, whereas groups B and C are more commonly associated with diseases in animals such as bovine and porcine species. Group A is then subclassified into subgroups I, II, and III based on antigen differences in VP6. Subgroup II infection was reported to be more prevalent than subgroups I and III, but this varies with

geographical location.[7,10] Before rotavirus vaccination, 5 G and P combinations, G1P[8], G2P[4], G3P[8], G4P[8], and G9P[8], typically constituted a large portion of infections (nearly 90% of all human infectivity) worldwide.[12-14] Several less common strains circulate in Asia and Africa at lower frequencies. The overall distribution of strains varies geographically and temporally and exhibits significant variations in strain composition across different countries and seasons.

Figure 2-1 Schematic representation of rotavirus virion



Source: Angel, J., M. A. Franco, and H. B. Greenberg. 2007. Rotavirus vaccines: recent developments and future considerations. Nat. Rev. Microbiol. **5**:529–539.[7]

2.2 Burden of rotavirus gastroenteritis

Before RV vaccine development, rotaviruses caused severe gastroenteritis among children <5 years of age worldwide and were responsible for approximately 111 million episodes of gastroenteritis that required home care, 25 million hospital visits, 2 million hospitalisations and around 611,000 (range 454,000–705,000) rotavirus-related deaths among children in this age group annually. [15-18] Even in European countries, there were 3.6 million recorded cases of rotavirus gastroenteritis annually before the introduction of rotavirus vaccination.[19,20] In sub-Saharan Africa, rotavirus was responsible for nearly 40% of diarrhoea-related hospitalizations among children <5 in 2013.[21] In Afghanistan, pre-vaccine introduction hospital-based surveillance data indicated that rotavirus accounted for 51% of all

gastroenteritis hospitalizations among children <5 years, with 93% of those cases occurring in children aged <2 years. Rotavirus resulted in approximately 1,200 deaths per year among children <5 years old in Afghanistan.[22] Rotavirus transmission occurs year-round, particularly in tropical regions, and Afghanistan is among the top ten countries with the highest global rotavirus-related death rates.[16,23]

2.3 Pathogenesis and Pathophysiology of RVs

Rotavirus infection is highly contagious and causes millions of episodes of gastroenteritis per year, and approximately 95% of children aged <5 years old develop rotavirus gastroenteritis. Gastroenteritis due to rotavirus is more severe than other forms of gastroenteritis.[24] The molecular studies suggest that prostaglandins, the inflammatory agents, and nitric oxide become active due to changes in phosphorylation, mitogen-activated kinase, and myosin light chain. Rotaviruses target the specialized absorptive intestinal epithelial cells (IECs) of the small intestine. As a result of villus atrophy, disruption in haemostasis in IECs happens, with heightened turnover of epithelial cells, increased apoptosis, and the formation of sizable vacuoles within enterocytes.[25] The occurrence of diarrhoea is attributed to the loss of absorptive villus cells and the secretion of fluid into the intestinal lumen, resulting from the disturbance of mucosal cells.

The microvilli and villus size reduction interfere with sodium (Na+), glucose, and water absorption. Infants affected by rotavirus diarrhoea experience a significant loss of sodium (Na+) and chlorine (Cl-) in their stool but not potassium (K+). Infants with rotavirus diarrhoea may develop severe dehydration, shock, and potentially fatal consequences without adequate replacement of electrolyte solutions.

2.4 Rotavirus replication cycle

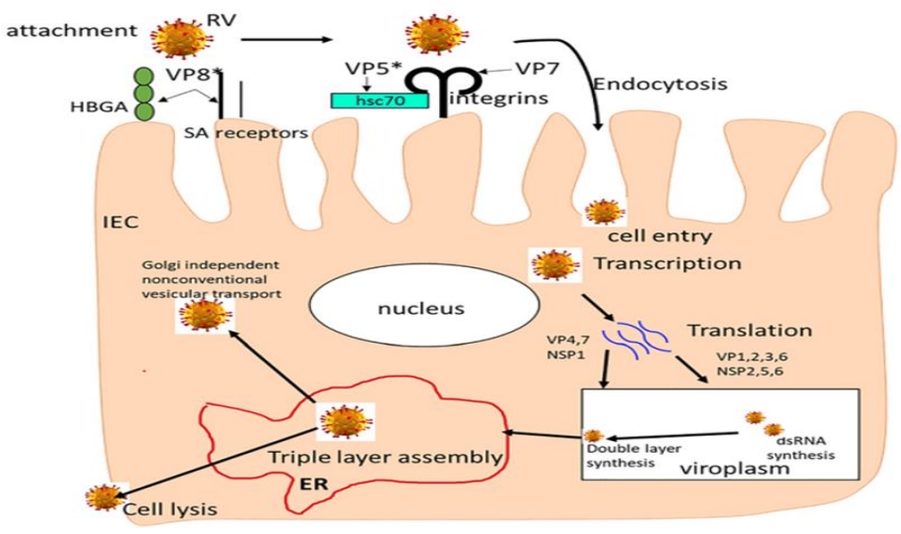
Joshua O. Amimo et al. (2021) explained the RV interaction with host intestinal epithelial cells and its replication in the gut.[25] RV is transmitted through the faecal-oral route and can spread via contact with contaminated objects. The virus can survive on surfaces such as toys, faucets, nappy (diaper) changing areas, handwashing areas, and surfaces used for food preparation.[26] The rapid development of anti-rotavirus antibodies within the first three years

of life, irrespective of hygiene and sanitation levels, has led to speculation about rotavirus transmission through airborne droplets. However, this hypothesis remains unverified.[11]

When viruses get to the gut, they attack the mucosal epithelial cells. Viruses have two primary methods of entering cells: direct entry at the epithelial plasma membrane or through epithelial endocytosis. The processes involved in cell entry include proteolytic priming, attachment to the cell, digestion of the external capsid, and subsequent internalization into the cytoplasm. The entry process begins with interactions between VP7 and cleaved VP4. The VP5 and VP8 (also denoted as VP5* and VP8*) have critical roles for VP4 protein to enter the cell.[27](**Figure 2-2)**

The ileum and jejunum are targeted explicitly by rotavirus (RV). In the initial stage of infection, RV attaches itself to cell surface molecules such as sialic acids (SA), histo-blood group antigens (HBGAs), Hsc70, and integrins, which act as receptors or co-receptors for the virus to facilitate attachment and entry into the cells.[28] The subsequent step involves the interaction between RV and mucins, which are large molecules produced by epithelial cells. Mucins are a chemical barrier and bind pathogens as an innate immune system. Studies reported that RV mainly binds with mucin structures. RV may stimulate mucin production. The disruption of mucin structure results in the dissolving of the intestine's physical barrier and more chance of entry of RV into cells. The viruses then replicate in the cell cytosol.[25]

Figure 2-2 The rotavirus replication cycle



Caption: The schematic depiction of the virus replication cycle- a work from Amimo JO, Raev SA, Chepngeno J, Saif L and Vlasova AN (December 2021), Rotavirus interactions with host intestinal epithelial cells, review: Frontiers in Immunology, **12**:793841.[25]

2.5 Clinical features of rotavirus gastroenteritis

Rotavirus gastroenteritis (RVGE) is known to affect individuals of all ages.[29,30] While the peak incidence of the disease is observed mainly between the ages of six months and two years, in low-income countries, this peak may manifest earlier.[31] The incubation period for rotavirus infection ranges from one to seven days, although some studies suggest a shorter duration of one to three days, with symptoms often emerging in less than 48 hours.[32] These symptoms, resembling those of gastroenteritis caused by other pathogens, tend to be severe. Vomiting is a prominent feature, observed in 90-100% of cases and lasting between 4 to 8 days. Fever, a common symptom, occurs in 30-100% of patients, usually remaining mild with temperatures rarely exceeding 39°C and often accompanied by malaise.

Following vomiting and fever, patients may experience transient loose stools progressing to severe watery diarrhoea, occasionally with blood or mucus. The frequency of defecation can reach up to 10 watery or loose episodes per 24 hours. Dehydration is a frequent complication, reported in approximately 80% of cases. RVGE initially presents as mild to moderate, but if left untreated, it can lead to severe dehydration and electrolyte imbalance, particularly in children under one year of age who lack access to rehydration therapy, resulting in high mortality rates.[14]

Malnutrition can develop as a secondary consequence of micronutrient malabsorption and persistent vomiting. Abdominal cramps and dehydration symptoms, such as lethargy, dry and cool skin, absence of tears, dry mouth, sunken eyes, extreme thirst, tachycardia, and reduced urine output, are also characteristic signs. The illness typically persists for 3 to 7 days from onset to symptom resolution but may endure for up to 2 to 3 weeks in some cases.[33-35]

2.6 Diagnosis of the disease

Clinically, RV gastroenteritis cannot be differentiated from other forms of diarrhoeal disease caused by other pathogens. Thus, examining the stool to detect rotavirus antigens remains the best diagnostic test. Laboratory rotavirus detection methods encompass several techniques described below.[36]

Electron microscopy offers high specificity but is labour-intensive and impractical for routine

use due to its costly equipment and specialized personnel requirement.

Antigen detection methods, widely utilized, include enzyme immunoassay (EIA), latex agglutination, and lateral-flow immunoassays. EIA, in particular, is favoured for large-scale surveillance studies due to its sensitivity and specificity in detecting protein antigens on rotavirus particles in stool specimens. Latex agglutination and rapid immunochromatographic tests serve as alternative methods to EIA, and latex particles coated with anti-rotavirus antibodies are used. It offers a convenient method for near-patient testing, usually in consulting rooms.[36]

Organizations like the United States Centres for Disease Control and Prevention (CDC) and WHO have recommended many commercial antigen detection kits for rotavirus gastroenteritis surveillances.[36]

Nucleic acid detection and nucleic acid amplification. The detection and amplification of nucleic acids play a crucial role in identifying viral infections. Visualizing the viral nucleic acid segments can be achieved through electrophoresis on acrylamide gels, followed by staining with silver nitrate. In some cases, the sensitivity of silver nitrate staining for viral nucleic acid is similar to that of EIA methods. Polymerase chain reaction (PCR) techniques provide sensitive detection of rotavirus genes, which is particularly useful for analyzing extra-intestinal tissue and studying viral shedding and disease severity correlation. However, PCR's high cost and labour-intensive nature present limitations despite its greater sensitivity and ability to isolate virus genotypes. PCR is commonly used for epidemiological studies.[36]

Serologic methods are used to determine rotavirus infections by detecting serum immunoglobulin G (IgG) and immunoglobulin A (IgA) antibodies.[37,38] Studies have reported concentrations as high as approximately 10 viruses per gram accumulated in the stools of children with gastroenteritis.[37]

2.7 Rotavirus gastroenteritis management

Currently, there are no specific antiviral medications targeting rotaviruses. The main treatment, like other childhood diarrhoeal illnesses, involves fluid replacement to prevent or address dehydration, and zinc supplementation to reduce the duration and intensity of diarrhoeal episodes, decrease stool volume. Low-osmolarity oral rehydration salts (ORS) solutions have shown superior efficacy in replenishing fluids than earlier ORS formulations.[15] When ORS is

unavailable, home-made suitable fluids can be substituted. Continuing feeding and breastfeeding are highly recommended as an additional treatment measure during the diarrhoeal episode.[39,40]

2.8 Immune response

Most of the knowledge on immune response to RVs is based on animal models (mostly neonatal and adult mice). Rotaviruses activate the antiviral innate immune response.[41,42] Like other viruses, RVs co-evolved with their hosts' defensive response, adapting various mechanisms to survive and spread, including interrupting IEC interference-mediated response. The innate immune response interacts with RVs in different ways:

- The surface of epithelial cells is coated with a protective mucus layer that contains glycoproteins known as mucins, which serve as both physical and chemical barriers against viral entry. The composition of the microbiome affects the production of mucins, and certain microbiomes may even possess antiviral components.
- Immediate activation: an innate immune response is rapidly triggered by induction of type I and type III interferons (IFNs) and other cytokines. They play important roles in limiting viral replication.
- Pattern recognition receptors (PRRs) in enterocytes or immune system cells such as macrophages and dendritic cells for adaptive B or T cells.
- Viral attachment and host range: RV replication occurs predominantly in the mature villus tip cells of the small intestine. Viral attachment to target intestinal epithelial cells also regulates host range restriction, which is determined by interferon (IFN) signalling. The interplay between innate immune factors and viral strategies impacts RV replication and pathogenesis.[42]

Acquired immunity against rotavirus typically develops in children after multiple exposures to different strains of the infection. Additionally, many newborns receive some degree of protection from maternal rotavirus antibodies transferred through the placenta or breast milk.[2,7,38,43] Consequently, their infections tend to be either asymptomatic or mild. During the acute phase of rotavirus diarrhoea, there is a robust secretion of immunoglobulin M (IgM) and IgG from the duodenal cells, which gradually diminishes by the age of 6 to 12 months. Local immunity in the gut becomes activated during this phase, leading to detectable levels of

IgA in stools. An increase in serum antibody levels during convalescence indicates an active infection.[25] Serum IgA antibodies against rotavirus serve as a gauge for the immunogenicity of all approved live attenuated rotavirus vaccines.[44]

2.9 Rotavirus vaccines

The substantial global burden of rotavirus gastroenteritis mortality and morbidity, particularly in low-resource settings, prompted international organizations to prioritize vaccine development. Understanding innate immune responses to specific RV strains informs the development of safe and effective RV vaccines.

The first generation of the live attenuated rotavirus vaccine based on a tetravalent reassortant rhesus rotavirus strain, known as RotaShield®, received licensure in the United States in 1998. This vaccine was administered in a three-dose schedule at 2, 4, and 6 months of age. However, due to the increased risk of intussusception cases among vaccinated children, exceeding 30 times the baseline rate during the 3-7 days after the first dose, RotaShield® was withdrawn swiftly from the market in 1999.[45,46]

In 2006, the United States introduced and licensed the second generation of live attenuated rotavirus vaccines, namely ROTARIX™ and RotaTeq™.[19] WHO pre-qualified and licensed ROTARIX™ and RotaTeq™ in 2006 and recommended their use for countries with efficacy data. Then, the recommendation was expanded in 2009 to all countries particularly those with high diarrhoea burden. The recommendation was expanded in 2018 to include ROTASIIL™ and ROTAVAC™. By the end of 2021, rotavirus vaccines had been introduced in more than 120 countries.[47,48] **Figure 2-3** displays a global map of rotavirus vaccine introduction as of 2021, adapted from the International Vaccine Access Center.[48] In 2018, when Afghanistan added rotavirus vaccine to the national immunization schedule, the monovalent vaccine, ROTARIX™ (GSK Biologicals, Rixensart, Belgium),administered in two doses (at 6 and 10 weeks of age) was available and approved by the Afghanistan Ministry of Public Health.[49]

Currently, four WHO pre-qualified vaccines and some other nationally approved rotavirus vaccines are available on the market. The WHO pre-qualified products are described in **Annex Table S1** at the end of this chapter.

1- ROTATEQ™ (Merck & Co. Inc., West Point, PA, USA) was licensed in 2008.
2- ROTARIX™ (GSK Biologicals, Rixensart, Belgium) was licensed in 2009.

3- ROTAVAC ™ (Bharat Biologicals, Hyderabad, India) was licensed in 2018.

4- ROTASIIL ™ (Serum Institute of India, Pune, India) was licensed in 2018.

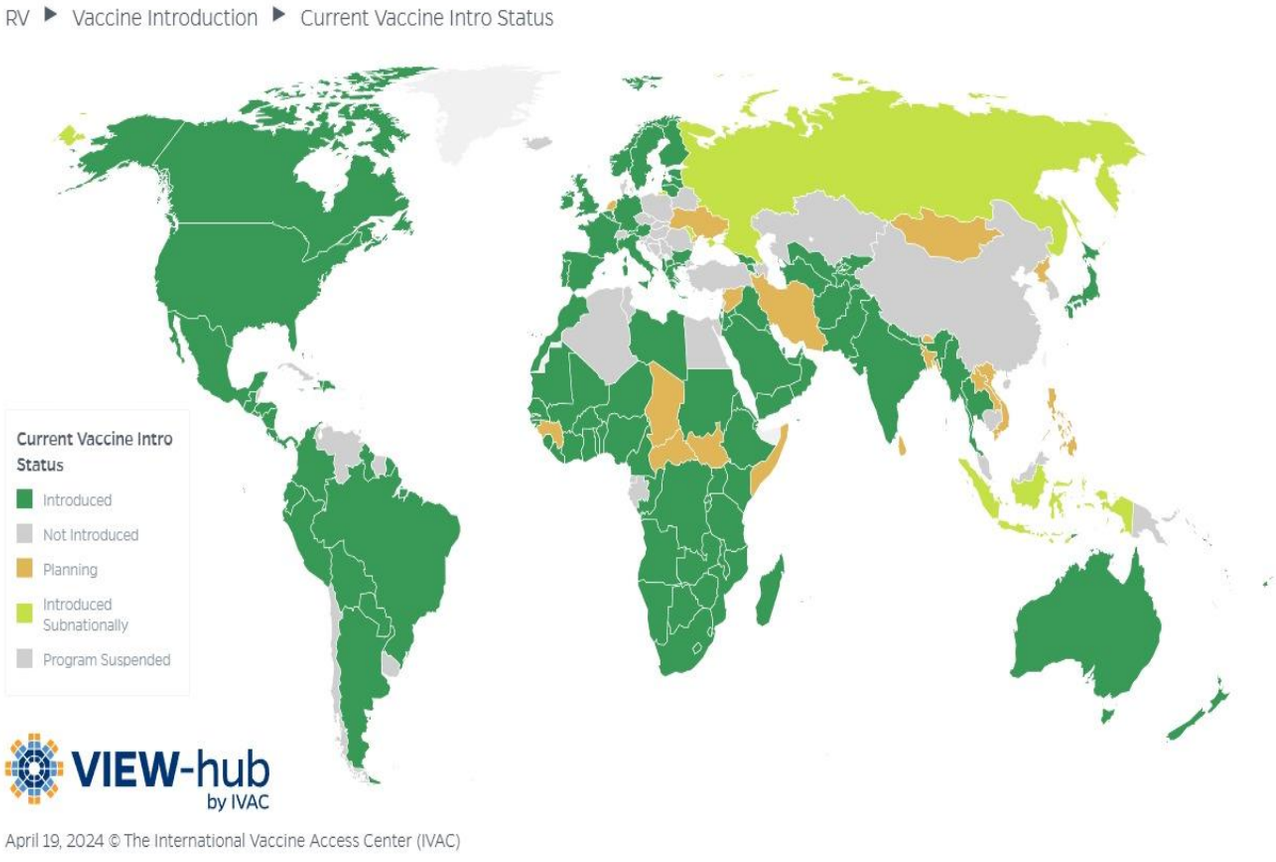
5- Other nationally available RV vaccines:

i. Rotavin-M1 (POLYVAC-USCDC, Hanoi, Vietnam), G1P[8], approved in 2012.

ii. Rotavin (POLYVAC-PATH, Vietnam), approved in 2022.

iii. Lanzhou Lamb Rotavirus (LLR) vaccine (Lanzhou Institute of Biological Products Co., Ltd., Lanzhou, China), licensed in China in 2000

Figure 2-3 Current rotavirus vaccine status, source: View Hub by IVAC



Source: View-Hub, an open access data visualization tool that displays data on vaccine introduction, use, coverage, access, impact, and disease burden for nine vaccines, including the rotavirus vaccine. The rotavirus introduction map was accessed on 19 April 2024, from https://view-hub.org/vaccine/rota

2.10 Rotavirus vaccine benefits

The benefits of the rotavirus vaccines are severalfold. Some key gains are summarized in the following sub-sections.

2.10.1 RV vaccine efficacy and effectiveness

The pre-licensure studies, including a Cochrane Review of four WHO pre-qualified RV vaccines, reported that in high- and middle-income countries with low-child mortality, vaccine efficacy is high and has had a protective effect of up to 90%-95% against severe RVGE.[50,51] However, in low-income and high-child mortality settings, it had a moderate to low protection effect of 44%-70%.[52-54] The post-licensure studies in high-mortality settings in Africa and Asia revealed that all four vaccines demonstrated similar effectiveness in preventing severe RVGE after one year of monitoring, with effectiveness ranging from 48% to 57%.[50]

A meta-analysis examining the real-world effectiveness of ROTARIX and RotaTeq revealed that the vaccine effectiveness of these two vaccines against laboratory-confirmed severe RVGE among children under 12 months old was 86%, 77%, and 63% in low-mortality, medium-mortality, and high-mortality countries, respectively. For ROTARIX only, among children aged 12 to 23 months, the vaccine effectiveness against laboratory-confirmed rotavirus was 86%, 58%, and 54% in low-mortality, medium-mortality, and high-mortality countries, respectively. [55] No observational studies assessed the effectiveness of ROTASIIL or ROTAVAC on laboratory-confirmed rotavirus or RVGE-related healthcare encounters.[50]

2.10.2 Global impact – reduced disease burden

Multiple studies have consistently shown a substantial decrease in cases of RVGE and acute gastroenteritis (AGE) over the past decade. As of 2019, RV mortality globally has dropped from over 450,000 in 2008 to 151,514 in 2019.[56-58] Projected estimates suggest that RV vaccines prevented 15% of deaths from rotavirus gastroenteritis (RVGE) in 2019, averting 139,000 RVGE deaths among children <5 years old from 2006 to 2019.[59] This improves individual health outcomes and reduces the strain on healthcare systems.

A systematic review of observational studies across 47 countries revealed substantial reductions in hospitalizations for rotavirus gastroenteritis (RVGE) and acute gastroenteritis (AGE) following the introduction of rotavirus vaccines. The review reported a median relative reduction of 59% (interquartile range [IQR], 46-74%) in RVGE hospitalizations and 36% (IQR,

23-47%) in hospitalizations due to AGE, regardless of the child mortality rates in these countries. Additionally, a reduction of 36% (IQR, 28-46%) in mortality from AGE among children < 5 years of age was observed post-introduction of rotavirus vaccination.[55]

The findings of the Global Rotavirus Surveillance Network (GRSN) indicated a significant decline in the percentage of stool samples testing positivity for rotavirus among children < 5 years old, dropping from approximately 40% to 20% following the introduction of rotavirus vaccination.[60] Furthermore, these data indicated that rotavirus vaccination has had a notable effect on the timing and intensity of seasonal outbreaks, leading to delayed onset and reduced severity in various geographical locations.[60]

A meta-regression analysis of randomized controlled trials (RCTs) examined a pooled efficacy of vaccine doses against severe RVGE at two time points: 2 weeks and 12 months after the final vaccine dose. In regions with low and medium mortality child rates, the pooled efficacy estimates were notably high at the 2-week time point (82% to 98%) and maintained strong protection at 12 months (77% to 94%). Conversely, in regions with high mortality rates, the pooled efficacy was lower at 2 weeks (66%) and declined more rapidly to 44% by the 12-month time point.[61]

2.10.3 Herd immunity

Rotavirus vaccination contributes to herd immunity, wherein a large proportion of the population becomes immune to the virus, thereby reducing its transmission. This indirect protection benefits even those who are not vaccinated, including vulnerable populations such as newborns and individuals with weakened immune systems. Some studies that included different age groups, including vaccine-eligible children, young adults, and older individuals, presented compelling evidence of the vaccine's effectiveness.[29,30,62,63] A metanalysis of studies conducted from 2008 to 2014 revealed that herd immunity contributed to a 22-25% reduction in rotavirus specific and overall gastroenteritis cases, in addition to the direct effects of the vaccine, mostly in high and middle-income settings.[64] While modelling studies in India and Niger found that indirect effects had only a minor contribution to overall estimates of the reduction in severe RVGE aged <5 years, highlighting the need for ongoing assessment of indirect benefits of rotavirus vaccine in low-income, high-mortality regions.[65,66]

2.10.4 Cost-effectiveness

Vaccination against rotavirus is considered cost-effective, as it prevents illness, reduces healthcare costs associated with hospitalizations and medical treatments for severe diarrhoea, and improves overall productivity by keeping children healthy and parents at work. A cost-effectiveness study of 73 Gavi, the Vaccine Alliance, eligible countries indicated that over 10 years period (2018-2027) the rotavirus vaccine could prevent 600,000 deaths, saving an estimated US$480 million from a governmental perspective and more than double that from the societal standpoint.[67]

2.10.5 Long-term benefits

By preventing rotavirus infections early in life, the vaccine offers long-term benefits, including reducing the use of healthcare resources and associated expenses related to cost of illness, reducing the risk of subsequent gastrointestinal illnesses, malnutrition, and developmental delays associated with recurrent or severe diarrhoeal diseases.[20,68]

2.11 Rotavirus vaccine risks

Vaccines, while highly successful and cost-effective public health interventions, prioritize safety. Even slight side effects can shake public confidence, particularly when administered to young children. Hence, any reported adverse events following immunization (AEFI) must be thoroughly investigated based on scientific evidence to uphold public trust.[69]

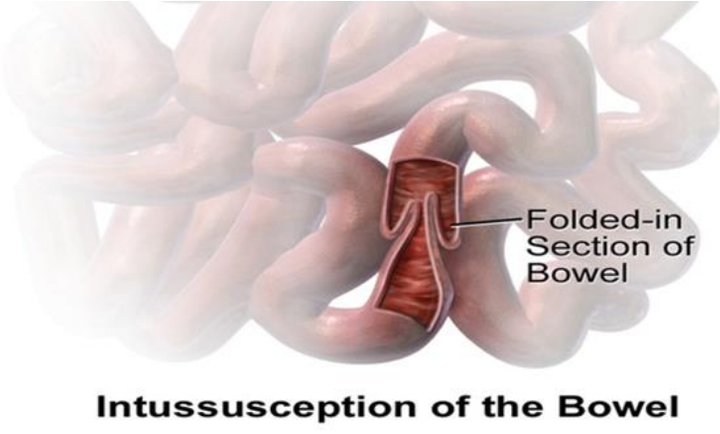
Infant vaccination with RV vaccines is an important enhancement to childhood immunization programmes, subject to vigilant safety monitoring, particularly due to potential variations in factors such as age at immunization and the characteristics of infants receiving the vaccine in routine use compared to those enrolled in clinical trials. Concerns about a low-level, short-term risk of intussusception have been identified in some settings, such as Mexico and Australia. In response, WHO advises countries to conduct post-marketing intussusception surveillance after introducing rotavirus vaccines.[14] This proactive approach ensures that any potential risks associated with vaccination are promptly identified and addressed, safeguarding the health and well-being of vaccinated individuals.

2.12 Intussusception

Intussusception is a pathologic condition that usually requires immediate medical attention. It involves the invagination of one segment of the bowel into another, leading to potential blockage and compromise of blood supply, which can result in ischemia and, if untreated, bowel perforation. **(Figure 2-4)** While some cases of intussusception may resolve spontaneously, most require hospitalization and medical intervention. This condition typically affects the small intestine and is most commonly observed in infants and young children.[70,71] The cause of intussusception in children <5 years old is not known. It is idiopathic; the cause is unknown in 90% of cases. Some other possible causes may include infections, anatomical factors, altered motility, or Micheal's diverticulum.[72] The mortality rates vary significantly based on the timely availability of appropriate treatment, ranging from less than 1% in developed nations to as high as 10% in low-income settings.[73]

The first generation of the RV vaccine was thought to cause intussusception three times the background occurrence of intussusception, so it was removed from the market rapidly after introduction. The currently pre-qualified RV vaccines, the second generation, have been linked to a small risk of intussusception in some settings in the world.[74-77] The strength of the association between the current RV vaccines and intussusception is unclear and may vary by setting.

Figure 2-4 Diagram of intussusception of the bowel



Source: Diagram of intussusception of the bowel. Created by Wiki Commons user Bruce Blaus, used under Creative Commons Attribution-Share Alike 4.0, https://creativecommons.org/licenses/by-sa/4.0 Copyright © 2022, StatPearls Publishing LLC.

2.13 Role of post-licensure surveillance and economic evaluations

Post-introduction surveillance plays a critical role in monitoring changes in disease epidemiology and evaluating the impact of vaccines. It offers valuable insights into vaccine performance under real-world conditions, facilitating an understanding of their public health implications, detection of adverse events, and guidance for policy decisions.[78] This monitoring is particularly important as RV vaccines are integrated into national immunization programmes, ensuring their real-world effectiveness aligns with pre-approval trial findings, especially in low- and lower-income countries. [9,79-81] Past experiences with other oral vaccines like polio and cholera highlight potential factors affecting vaccine performance, such as countries' socio-economic settings, maternal antibody interference, concurrency with other oral vaccine administration, breastfeeding, viral and bacterial gut infections, and malnutrition.[82,83] Furthermore, it is important to note that these vaccines may not offer uniform protection against all rotavirus strains, and their efficacy might differ in regions where the prevalence of strains varies from that observed in clinical trials.[79,83-86]

Post-licensure surveillance and economic evaluations ensure effective vaccination programmes' success, safety, and economic sustainability. Economic evaluations of vaccination programmes compare the costs of immunization with the monetary benefits derived from prevented cases of disease, healthcare savings, and gains in productivity. They provide decision-makers with essential information to optimize resource allocation, prioritize immunization strategies, and maximize public health outcomes. Moreover, benefit-risk assessments quantify the anticipated benefits of vaccination, such as reductions in morbidity and mortality, and potential risks, including adverse events following immunization.[87]

2.14 Country Profile

2.14.1 Landscape and climate

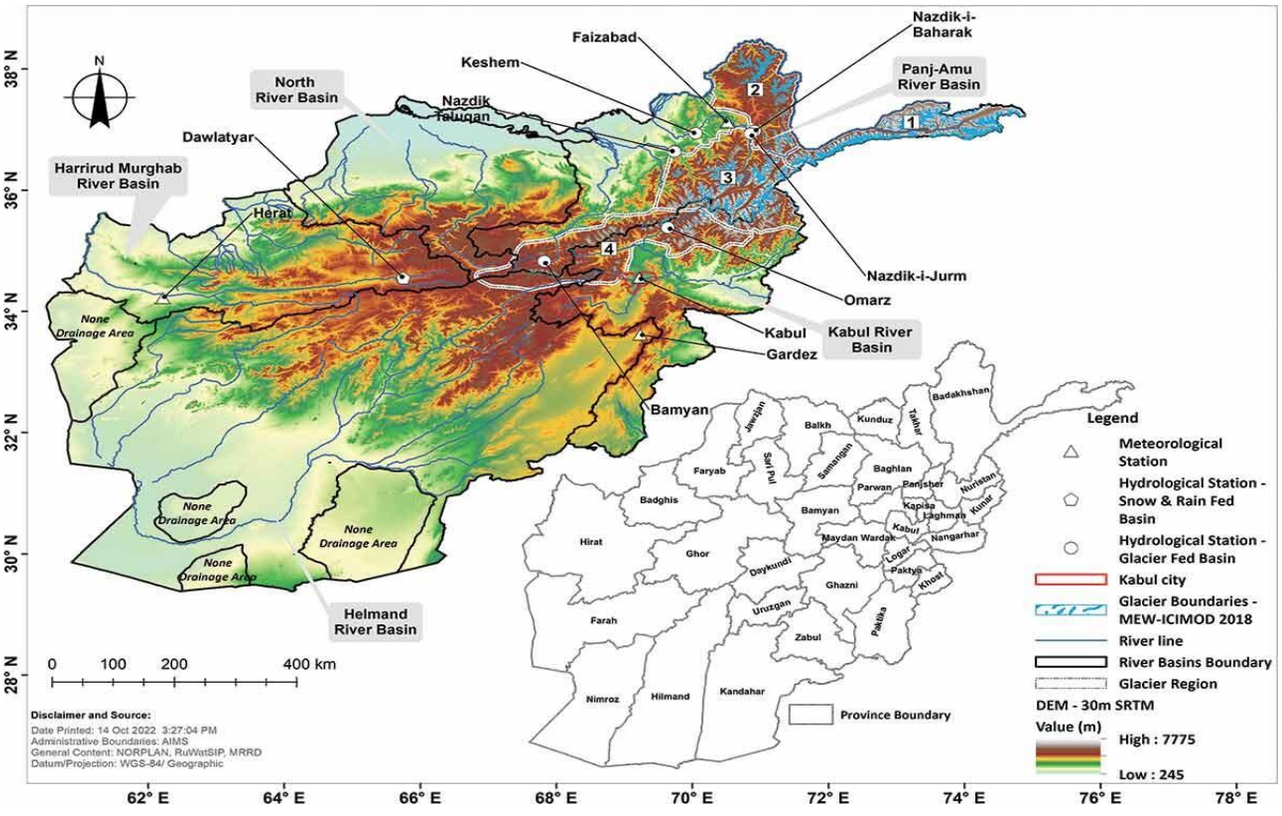
Afghanistan, located in Central Asia, shares borders with Turkmenistan, Uzbekistan, and Tajikistan to the north, China to the far northeast, Pakistan to the east and south, and Iran to the west, covering 652,000 km^2, ranking as the 41st largest country globally. It is a landlocked country renowned for its diverse geography, featuring rugged mountains, vast deserts, fertile valleys, and river basins with plains in the north and southeast. The Hindu Kush Mountains, with peaks as high as 7,000 meters above sea level, running northeast to southwest, separate the northern provinces from the rest of the country. Afghanistan's geographical diversity significantly influences its cultural, economic, and political landscape, presenting opportunities and challenges for its inhabitants. **(Map 2-1)** The terrain shapes various aspects of life from agriculture and transportation to security and development efforts. Since 1979, with the invasion of the then Soviet Union into Afghanistan, the country has gone through complex emergencies and humanitarian crises, as military and civil conflicts have combined with natural disasters, destroying the country's infrastructure, including the health system.

The country experiences four distinct seasons: spring, summer, autumn, and winter. Most areas have a dry continental climate, with hot summers reaching 40^0C in lowlands and cold winters dropping to around -25^0C in mountainous regions. Extensive snowfall occurs in mountainous areas during winter, isolating communities for up to 4 months. Irrigated agriculture heavily relies on snowmelt in spring. Rainfall primarily occurs in autumn and spring; spring rains are vital for agriculture, particularly in the northern region.

Afghanistan is ranked as the fifth most at-risk country due to climate change in the INFORM 2019 Index and confronts some of the most severe natural hazard risks globally.[88] Since the 1990s, Afghanistan has grappled with recurrent and chronic droughts, significantly impacting northern and western parts of the country and central highlands. The drought of 2002 was particularly devastating, surpassing the impact of two decades of warfare, resulting in the displacement of 700,000 individuals to neighbouring countries. As a result of the drought in 2011, millions of people were pushed into food insecurity and poverty.[89] Additionally, Afghanistan has a long history of exposure to floods, the country's most prevalent natural hazards. On average, floods affect over 300,000 people each year, with underestimated and underreported estimates, causing at least 100 deaths yearly and costing over $54 million

annually. In May 2014, floods ravaged 14 northern provinces, resulting in damage exceeding $100 million.[88,89]

Map 2-1 Geographical map of Afghanistan



Caption: Geographical map of Afghanistan, showing elevation, river lines, hydro-meteorological stations, and glacier coverage. The secondary map shows the boundaries of the 34 provinces of Afghanistan. Source and copyright Jamal A. N. Sholory, Bettina Schaefli and Stuart N. Lane: February 2023: https://doi.org/10.1080/02626667.2022.2159411.[89]

2.14.2 Demographic characteristics

Afghanistan, located at the crossroads of Central and South Asia, has a diverse population with a rich cultural heritage shaped by centuries of history, migration, and conquests. Due to the absence of an official census since 1979, different sources provide varying population estimates. For instance, the National Statistics and Information Authority (NISA) estimated the population to be 37 million in 2022, with a population growth rate of 2.14%. United Nations' estimates reported the total population of Afghanistan in 2023 to be 42 million. The population pyramid reveals that 49% of the population falls within the 0-14 age group and 53% in the 0-17 age group, indicating a significant proportion of young individuals, with approximately 68%

below 25 years old. The country exhibits a high fertility rate of 5.3 per woman and a family size of 8.2 individuals.[90] Life expectancy at birth is approximately 64 years for men and 67 years for women.[91] Some key indicators are presented in **Table 2-1**.

Afghanistan is home to various ethnic groups, with the largest being the Pashtuns, who constitute the majority of the population, making up roughly 40-45%. Other significant ethnic groups include the Tajiks, Hazaras, Uzbeks, Aimaqs, Turkmen, Baloch, and Nuristanis, among others.

The official languages of Afghanistan are Pashto and Dari /Persian. Pashto is spoken primarily in the southeastern and eastern regions, while Dari is spoken mainly in the central and northern areas. Additionally, several other languages and dialects are spoken throughout the country, reflecting its ethnic diversity.

Most of Afghanistan's population, 75%, reside in rural areas and engage in agriculture and livestock farming.[90,92] Over the past few years, urbanization has been increasing steadily, particularly in major cities such as Kabul, Herat, Mazar-i-Sharif, and Kandahar, driven by factors such as conflict-induced displacement, economic opportunities, and access to services, which has contributed to the expansion of urban slum dwelling.

2.14.3 Economy

Afghanistan ranks among the poorest countries globally. The economic downturn associated with the change of the government in mid-August 2021 led to a significant decline in income per capita. The economy shrank by 20.70% in 2021, followed by an additional 3.60% contraction in 2022. With a population growth rate of approximately 2 percent, it is estimated that income per capita will decrease by a substantial 30% between 2020 and 2022. The United Nations Development Program (UNDP) projected real gross domestic product (GDP) growth of 1.30% in 2023 and 0.40% in 2024, with GDP per capita expected to decline from US$359 in 2022 to US$345 in 2024.[93]

With the power shift to the Taliban in August 2021, over 90% of the population are now living below the poverty line, equalling approximately 34 million individuals in 2023.[94]

2.14.4 Governance

Following the overthrow of the initial Taliban regime in 2001 and with the intervention of international coalitions led by the United States, Afghanistan underwent significant political changes. According to the 2004 Constitution, the country transitioned into a parliamentary

Islamic Republic, with power and responsibilities divided among the executive, legislative, and judiciary branches.

The governance structure of Afghanistan encompasses multiple levels, including the central government, 34 provinces, around 400 districts (rural sub-units of provinces), and municipalities (urban sub-units of provinces).[95,96] This decentralized administrative system, in principle, allows for effective governance and decision-making at various levels, ensuring that rural and urban areas are adequately represented and governed. Since 2002, the number of districts has increased from 325 to 421 in 2021, mostly due to the influence of politicians and local commanders. This expansion poses significant challenges for the healthcare system, as it requires additional trained human resources, financial support, and logistics, all of which are already limited.

2.15 Healthcare system

2.15.1 Overview of the healthcare system

Article 52 of Afghanistan's 2004 Constitution establishes a comprehensive guiding principle for the state's provision of healthcare services.

"The state shall provide free preventive healthcare and treatment of diseases as well as medical facilities to all citizens by the provisions of the law." [97]

The Ministry of Public Health (MoPH) mission statement under the constitutional obligation is to:

"Improve the health of the people through quality health care services provision and the promotion of healthy lifestyles equitably and sustainably." [97]

The MoPH introduced various health policies and strategies to re-establish the health system between 2002 and 2021. One of them was the introduction of the Basic Package of Health Services (BPHS) in 2003 as a framework for providing primary healthcare. Later, in 2005, an essential package of hospital services (EPHS) was introduced with two main strategic objectives:

i. Provide standardized primary and secondary healthcare services across all primary healthcare centres.

ii. Foster equitable distribution of health services by ensuring universal access, particularly in

underserved areas and regions with limited service availability.

Both packages, including routine immunization services, have achieved significant health sector gains over the last 20 years.[98]

Healthcare service delivery happens at three levels (primary, secondary, and tertiary health service delivery) and has ten types of facility **(Figure 2-6).**

Primary care services are provided through Health Posts, Health Sub-Centers, Basic Health Centers, Comprehensive Health Center and District Hospital:

1. The **Health Post (HP)** is the first point of contact for a patient seeking healthcare at the community level. Each is run by a couple of male and female volunteer community health workers (CHWs), covering 1000-1500 people, equivalent to 100-150 families.
2. The first level of formal healthcare services is the **Basic Health Center (BHC)**, offering outpatient care, immunization, antenatal and postnatal care, family planning, and health education. It covers a population of 15,000-30,000 people and is staffed with a nurse, a midwife, a community health supervisor, and two vaccinators. The BHC supervises the activities of HPs and their catchment areas.
3. In some geographic areas, for a small and remote population group (3,000-7,000 people), a **Health Sub-Centre (HSC)**, run by a male nurse and a community midwife, has been established instead of a BHC. Not all HSCs provide immunization services.
4. The **Comprehensive Health Center (CHC)** covers a catchment area of about 30,000-60,000 people. It offers a wider range of services than does the BHC. The facility usually has limited space for inpatient care but has a laboratory. The staff includes both male and female doctors, male and female nurses, midwives, laboratory technicians and vaccinators.
5. In some communities, in addition to outpatient services, the Comprehensive Health Center (CHC) provides inpatient services, and is called a **CHC+**, with a capacity of up to 10 beds.
6. The **District Hospital (DH)** is the highest level of primary healthcare offered at the district level with a capacity of 35-75 beds. It covers up to 100,000-300,000 people. It is run by a female obstetrician/gynaecologist, a surgeon, an anaesthetist, a paediatrician, midwives, x-ray technicians, a pharmacist, and a dentist and dental technician.[99]
7. In response to emerging health priorities and to improve the BPHS reach, the package was revised in 2010. As part of that revision, a **Mobile Health Team (MHT)** was added to increase

access to primary healthcare in remote, hard-to-reach, and small-population areas with a catchment population of 1,000-7,000 people. An MHT ideally is staffed with a male health provider (doctor or nurse), a female health provider (community midwife or nurse), a vaccinator, and a driver.

Secondary care services are offered through provincial and regional hospitals.

8. The **Provincial Hospital (PH)** is a 100-200 bed hospital that provides all clinical and support services provided at district hospitals, plus rehabilitation services and infectious disease control services.
9. The **Regional Hospital (RH)** is a 200-400 bed hospital that provides all of the above plus surgery for ear, nose and throat (ENT), urology, neurology, orthopaedics, etc.

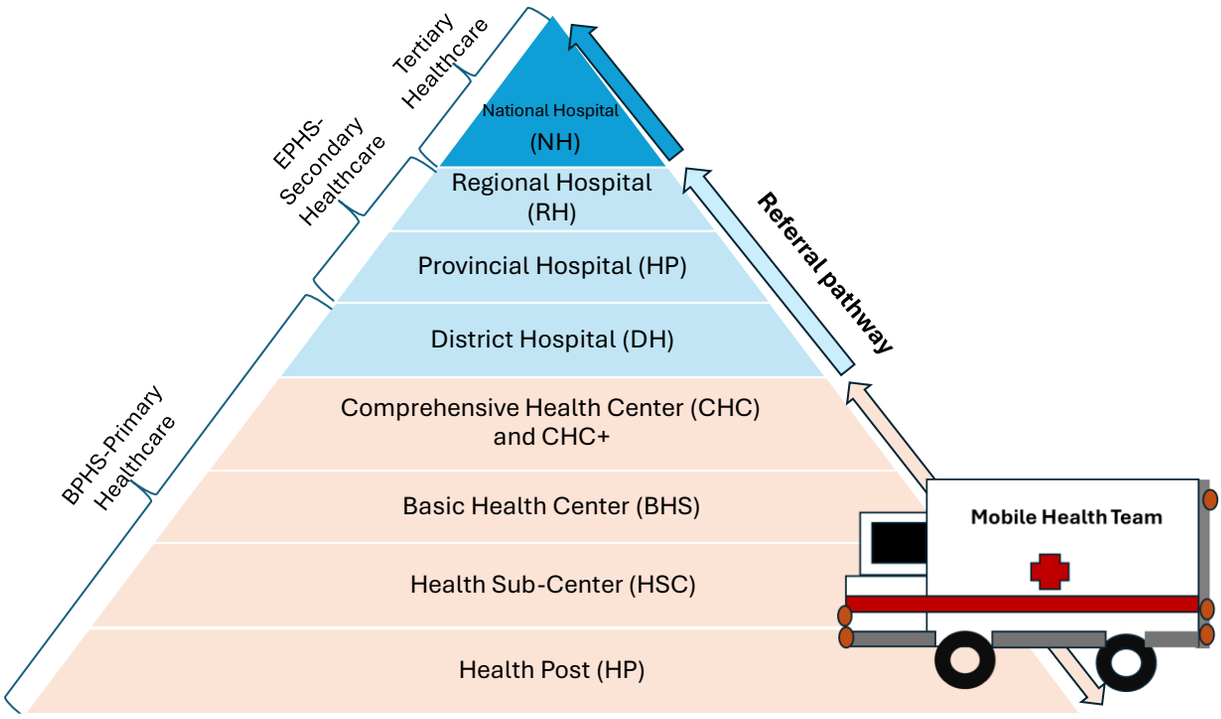
   Tertiary care services operate in the national capital, Kabul, and are teaching hospitals.
10. **National or Specialty hospitals** are specialty or super-specialty hospitals and serve as referral sites nationwide.

    The health system is designed so that clear referral pathways are established among all levels. **(Figure 2-5)** Apart from the array of health centres situated within the country's healthcare system, there are also various specialized centres focusing on diseases like tuberculosis, malaria, leishmaniasis, HIV, and facilities for treating drug users. These centres operate independently but contribute to the overall complexity of the country's healthcare framework.

    National and Regional hospitals are financed by the government's ordinary budget and managed directly by the MoPH. The rest of the healthcare services are outsourced to non-government organizations (NGOs) in 31 out of 34 provinces, while the remaining three provinces are managed directly by the MoPH through a mechanism known as "strengthen mechanism (SM) or contract-in".[100] These health facilities are financed by the Afghanistan Reconstruction Trust Fund (ARTF), a pool fund of donor organizations managed by the World Bank, also known as the development budget. Until mid-August 2021, the MoPH oversaw these contracts through the Grant Contracts and Management Unit (GCMU) from 2002 to 2018 and then by the Performance Management Office (PMO) from 2019 to 2021. Following the political upheaval in August 2021 and after a temporary pause of ARTF, the WB rearranged the modality, transferred the contract and granted management authority to the United Nations Children's Fund (UNICEF) Afghanistan Country Office in 2022. The BPHS has seven

components presented in **Box 2-1.**[101]

Figure 2-5 The healthcare structure and referral schematic diagram (source: BPHS and EPHS manuals)



A summary of BPHS services that categorized under seven elements is provided in Box1.

Box 2-1 Basic Package of Health Care (BPHS) main elements (Source: BPHS manual)

- Maternal and New-born Health
  - Provision of antenatal care
  - Delivery care services
  - Postpartum care support
  - Family planning services
  - New-born care assistance
- Child Health and Immunization
  - Expanded Programme on Immunization (EPI), including fixed sites and outreach activities.
  - Implementation of Integrated Management of Childhood Illness (IMCI) approach
- Public Nutrition
  - Initiatives for the prevention of malnutrition
  - Assessment and monitoring of malnutrition cases
- Communicable Disease Treatment and Control
  - Control measures for tuberculosis.
  - Malaria control strategies
  - HIV and AIDS prevention efforts
- Mental Health

Awareness campaigns and education on mental health Identification, diagnosis, and treatment of mental health conditions Disability and Physical Rehabilitation Services Awareness programmes and prevention measures for disabilities Provision of physical rehabilitation services Identification, referral, and follow-up support for individuals with disabilities Regular Supply of Essential Drugs Establishment of a comprehensive list of essential medicines and supplies to ensure consistent availability

2.15.2 Afghanistan's immunization programme

Routine immunization services are a key component of the BPHS under child health. The national paediatric schedule includes 11 cost-free antigens, which are administered in Basic Health Centers (BHC) and higher-level healthcare facilities. In the past several years, under the Gavi HSS grant, most of the Health Sub-Centers (HSCs) were upgraded with cold chains and offer vaccination services. Three strategies are currently implemented for delivering immunization services:

1- Fixed services, which offer daily immunizations within health facilities.

2- Outreach services, which are conducted weekly or monthly at non-health facility locations, allowing vaccinators to travel and return on the same day.

3- Mobile sessions, which are scheduled monthly or less frequently, and involve vaccinators traveling to distant locations requiring overnight stays.

The immunization programme structure, immunization schedule and decision-making for new vaccine introduction are thoroughly studied in the Organizational and Policy Analysis / Research Study 1 (RSI) [102], which is an appendix to this thesis. Some key maternal and child health indicators comparing them with neighboring and regional countries are provided **in Table 2-1.**

2.15.3 Afghanistan's Health System Financing

The Ministry of Finance (MoF) is tasked with managing and implementing the yearly budget, revenue collection, oversight of public expenditure, and government payment administration.

Until August 15, 2021, there were three primary funding sources for the health sector.

Donor's development funding (external) is the funding that comes from the United States Agency for International Aid (USAID), the European Union (EU), the World Bank (WB), and the

Japan International Cooperation Agency (JICA). The funds were provided under the Afghanistan Reconstruction Trust Fund (ARTF), managed by the WB and channelled through the Ministry of Finance (MoF), known as the on-budget or development funds. The primary funding sources for the BPHS and EPHS were estimated to be USAID (37%), the World Bank (32%), and the European Commission (29%).[103] In addition, Gavi, Global Fund, UN agencies such as WHO, UNICEF, UNFPA UNDP, and other international NGOs directly finance and top up some health programmes such as nutrition, immunization, HIV/AIDS, malaria, and tuberculosis. It is called off-budget funding, and it does not pass through the government processes. Despite the substantial support external donors provide to the healthcare sector, their contribution represents just 16.4% of the overall health expenditure.[104]

Public funding, or the ordinary budget, is the Afghanistan government fund that comes from national revenue.

Private funding comes from individuals and investors.

The National Health Account reported that the Total Health Expenditure (THE) in 2021 was 3.6 billion (US$100 per capita). Afghan households contribute 77.2% of THE in the form of out-of-pocket expenditure, followed by foreign direct fund transfers (19.3%) and only 3.3% from domestic revenue.[104,105] Government spending on health remains as low as US$5 per Afghan, while total expenditure on routine immunization per surviving infant is US$2 in public health facilities [106]. Total outlays of vaccine-preventable diseases, including expenses for polio eradication, are US$17.89 million.[107]

Table 2-1 Afghanistan demographic and child health indicators

	Indicators	Afghanistan	Pakistan	Iran	Tajikistan	Bangladesh	Nepal	Djibouti	Yemen
Demographic	Total population (persons in million)	42.2	240.5	89.2	10.6	172.9	30.9	1.2	34.4
	Average household size (person)	8.2	6.8	3.5	6.0	4.3	4.3	5.9	6.7
	Gross domestic product (GDP) per capita (2023)	$345	$1,407	$4,502	$1,189	$2,529	$1,324	$3,606	$533
Child survival & protection	Infant mortality rate (per 1000 live birth)	45	51	10	27	24	23	44	41
	Under-five mortality rate (per 1000 live birth)	58	61	12	30	29	27	52	33
	Children (aged 1-14 years) experienced any physical punishment and/or psychological aggression by caregivers	88%	NA	NA	69%	89%	82%	NA	86%
	Children < 5 whose births have been officially recorded by a civil authority	42%	42%	99%	96%	56%	77%	92%	31%
child nutrition	Early initiation of breastfeeding (Per cent)	63%	20%	69%	62%	47%	42%	52%	53%
	% Stunting (Height by Weight/-2SD)* (0-59 months)	45%	34%	5%	13%	26%	27%	19%	35%
	% Underweight (Weight for age/-2SD)* (0-59 months)	18%	11%	3%	10%	11%	11%	15%	24%
	%Wasting (Weight by Height/ -2SD*) (0-59 months)	4%	7%	4%	6%	10%	8%	11%	NA
Maternal and child	Antenatal care 4+ visits– women (aged 15-49 years	28%	52%	94%	64%	37%	78%	23%	25%

	Indicators	Afghanistan	Pakistan	Iran	Tajikistan	Bangladesh	Nepal	Djibouti	Yemen
	Skilled birth attendant by female skilled health personnel	62%	68%	99%	95%	59%	77%	87%	45%
	Diarrhoea treatment-children < 5 years with diarrhoea who received ORS*	38%	37%	61%	62%	72%	60%	94%	25%
	Surviving infants who received the 3rd dose of DTP vaccine	60%	86%	99%	96%	98%	82%	72%	46%
	Children who received the 2nd dose of measles vaccine	42%	80%	99%	96%	93%	92%	64%	45%
Education	Completion rate for children of primary school age	54%	60%	NA	98%	83%	94%	NA	63%
	Youth literacy rate for 15-24 years	56%	73%	NA	NA	94%	89%	NA	NA
WASH	% population using safely managed drinking water	30%	51%	94%	55%	59%	16%	NA	NA
	% population using at least basic drinking water	82%	91%	98%	82%	98%	91%	76%	62%
	% population using least basic sanitation services	56%	71%	90%	97%	59%	80%	67%	55%

*SD: standard deviation; ORS: oral rehydration soluble; DTP: Diphtheria, Tetanus, and Pertussis

Data source: UNICEF MICS report by country, accessed from: https://data.unicef.org/country/afg/, retrieved on August 22, 2024

Table 2-1 presents data on demographic, maternal and child health, child survival, child education, and WASH (Water, Sanitation, and Hygiene) indicators for Afghanistan and seven other countries: Pakistan, Iran, Tajikistan, Nepal, Bangladesh, Yemen, and Djibouti. Afghanistan is classified by the UN as part of South Asia and by the WHO as part of the Eastern Mediterranean Region (EMRO). The countries selected for comparison were chosen based on their geographic proximity to Afghanistan and their relatively similar socio-economic status.

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Annex for Chapter 2

Table S 2-1 Rotavirus vaccine product profile

Vaccine trade name	Rotarix TM		RotaTeq	RotaVac				Rotasiil					
Manufacturer	GlaxoSmithKline Biologicals SA (GSK)		Merck Sharp & Dohme LLC	Bharat Biotech International				Serum Institute of India Pvt Ltd					
Country of manufacturer	Belgium		United States of America	India				India					
Vaccine type	Monovalent human rotavirus vaccine		Pentavalnet human-bovine vaccine	Monovalent human rotavirus				Pentavalanet humna-bovine rotavirus vaccines					
Serotypes	RIX4414		WC3, a G6P[5]	116E				G1, G2, G3, G4, G9					
Package presentation				RotaVac (Live, attenuated)		RotaVac 5D		Rotasiil		Rotasiil-Liquid		Rotasiil Thermo	
WHO recommonded vaccine schedule	Administered at the time of DTP1, DTP2 with an interval of at least 4		Administred at the time DPT1, DTP2, and DTP3,	Administered at the time of DTP1, DTP2 and DTP3 with an interval of at least 4 weeks between doses (3 doses)				Administered at the time of DTP1, DTP2 and DTP3 with an interval of at least 4 weeks between doses (3 doses)					
Doses for fully immunized child	2	2	3	3	3	3	3	3	3	3	3	3	3
Presentation (doses per container, pharmaceutical form)	1 dose/plastic tube, liquid	multi-monodose presenttation with 5 single tubes connnected by a bar	a single-dose squeezable plastic tube	RV1, 5 doses/vial, frozen	RV1, 10 doses/vial, frozen	RV1, 1 dose/vial, liquid	RV1, 5 doses/vial, liquid	RV5, 1 dose/vial, lyophilised11	RV5, 2 doses/vial, lyophilised	RV5, 1 dose/plastic tube, liquid (strip of 5 tubes)	RV5, 2 doses/vial, liquid	RV5, 1 dose/vial, lyophilised (VVM+ 250)13	RV5, 2 dose/vial, lyophilised (VVM+ 250)13
WHO pre-qualified date	3/12/2009	2/14/2019	7/10/2008	1/5/2018	1/5/2018	6/18/2021	6/18/2021	9/21/2018	9/21/2018	2/18/2021	10/8/2021	1/28/2020	1/28/2020
WHO pre-qualified link	https://extranet.who.int/prequal/vaccines/p/rotarix	https://extranet.who.int/prequal/vaccines/p/rotarix-1	https://extranet.who.int/prequal/vaccines/p/rotateq	https://extranet.who.int/prequal/vaccines/p/rotavac	https://extranet.who.int/prequal/vaccines/p/rotavac-0	https://extranet.who.int/prequal/vaccines/p/rotavac-5dr	https://extranet.who.int/prequal/vaccines/	https://extranet.who.int/prequal/vaccines/p/rotasi	https://extranet.who.int/prequal/vaccines/	https://extranet.who.int/prequal/vaccines/p/rotasiil	https://extranet.who.int/prequal/vaccines/p/rotasii	https://extranet.who.int/prequal/vaccines/p/r	https://extranet.who.int/prequal/vaccines/p/
Adminstration	Oral	Oral	Oral	Oral	Oral	Oral	Oral	Oral	Oral	Oral	Oral	Oral	Oral
Shelf-life	24 months at 2-8OC	24 months at 2-8OC	24 months at 2-8OC	24 months at -20 °C, 6 months at 2-8 °C post thaw	24 months at -20 °C, 6 months at 2-8 °C post thaw	24 months at 2-8°C	24 months at 2-8°C	30 months at 2-8 °C	30 months at 2-8 °C	24 months at 2-8 °C	24 months at 2-8 °C	30 months at 25°C	30 months at 25°C

CHAPTER THREE: PAPER ONE

Chapter 3: Effectiveness and Impact of Monovalent Rotavirus Vaccination in Afghanistan

3.1 Preamble to Research Paper 1

The paper presented in this chapter examines the performance of ROTARIX, a monovalent rotavirus vaccine, under routine health service conditions in Afghanistan. This chapter addresses the first three objectives of the thesis.

Objective 1: Utilize an epidemiological design – specifically, the test-negative case-control design embedded within post-licensure surveillance – to assess the effectiveness of the rotavirus vaccine.

Objective 2: Analyse pre- and post-vaccine introduction surveillance data on rotavirus gastroenteritis (RVGE) to evaluate the impact of the vaccination programme.

Objective 3: Perform a trend analysis using administrative data from the Health Management Information System (HMIS) on acute gastroenteritis (AGE) among children under five years of age.

This chapter also contributes to the main thesis chapter (Chapter 5) by providing inputs such as RVGE admission rate, rotavirus vaccine coverage, impact of the rotavirus vaccine and relating these to percentage reductions in AGE and RVGE admissions, and to RV vaccine effectiveness.

3.1.1 Data Sources

The data for this paper were derived from:

1. Post-licensure surveillance, which was conducted in four hospitals from 2018 to 2021, covering approximately 27% hospital beds for children younger than 5 and 32% of the population of children <5.
2. Hospital-based active surveillance of pre-vaccine gastroenteritis from 2013 to 2015, which was conducted in two out of four post-licensure surveillance sites.
3. Routine administrative data collected by the Health Management Information System (HMIS) from 2013 to 2022, covering all inpatient admissions and outpatient visits attending at public health facilities, consistently reported for at least 11 months each year.

As the lead investigator, I oversaw the surveillance activities from March 2018, from before the inception of my research degree programme at LSHTM, until closure of the surveillance activities in

2022.

3.1.2 Independent academic contribution

As the first author, I conducted data processing, analysis, drafted the initial manuscript, shared the draft manuscript with the collaborators, compiled their feedback and finalized the manuscript accordingly. I submitted the manuscript to a peer-reviewed journal and addressed the reviewers' and journal's comments. This work was done in collaboration with the United States Centers for Disease Control and Prevention (US CDC), the Ministry of Public Health in Afghanistan, the World Health Organization Afghanistan Country Office, and a research firm managing surveillance activities. This paper was published in collaboration with these partners.

3.1.3 Ethical approval

This evaluation received approval from the Institutional Review Board (ID: 444510, April 2018) of the Ministry of Public Health, Afghanistan. The investigation was reviewed by the Human Research Protections Office at the CDC and was conducted in accordance with applicable federal laws and CDC policy. The work has also obtained ethics approval from LSHTM under the thesis protocol. The ethics approval letters issued for this manuscript are appended **(Annexes 3-1 and 3-2).**

3.1.4 Word counts

Abstract: 299 words
Manuscript: 3438 words without tables and references
Number of tables: 2
Number of figures: 3
Number of references: 30

Supplementary file: 6 tables and 3 figures, and abstract in Dari, one of the two national languages of Afghanistan.

3.1.5 Published Journal

3.1.6 Citation

Anwari P, Burnett E, Safi N, Samsor A, Safi H, Chavers TP, Parashar UD, Clark AD, Tate JE. Effectiveness and impact of monovalent rotavirus vaccination in Afghanistan: a test-negative case-control analysis. Lancet Glob Health. 2024 Sep;12(9):e1517-e1525. doi: 10.1016/S2214-109X(24)00237-7 PMID: 39151986

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	2005091	**Title**	Dr
First Name(s)	Palwasha		
Surname/Family Name	Anwari		
Thesis Title	Benefit-risk and cost-utility of rotavirus vaccination in Afghanistan: a modelling study informed by post-marketing surveillance data		
Primary Supervisor	Dr Andrew Clark		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	The Lancet Global Health		
When was the work published?	Accepted on May 31, 2024 Published on August 14, 2024 as open access		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	

Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I carried out data processing on post-licensure surveillance data and developed a data analysis plan. I coordinated with the Health Management Information System (HMIS) Department of Health to access over a decade outpatient and inpatient acute diarrhea disease data among children <5 years old. Following this, I conducted data analysis, produced tables and graphs, and wrote the initial draft of the manuscript. I compiled inputs and revised the manuscript based on the co-authors' feedback. Next, I submitted it to a peer-reviewed journal, crafted responses to the journal reviewers, and addressed editorial requirements.

SECTION E

Student Signature	Palwash Anwari [redacted]
Date	12 August 2024

Supervisor Signature	
Date	

Effectiveness and impact of monovalent rotavirus vaccination in Afghanistan: a test-negative case–control analysis

Palwasha Anwari, Eleanor Burnett, Najibullah Safi, Akmal Samsor, Helah Safi, Tyler P Chavers, Umesh D Parashar, Andrew D Clark, Jacqueline E Tate

Summary

Background Afghanistan introduced monovalent rotavirus vaccine (Rotarix) into its national immunisation schedule in January, 2018. While post-licensure studies have shown substantial declines in rotavirus gastroenteritis cases and deaths globally, there is little evidence of rotavirus vaccine effectiveness and impact from low-income countries in Asia. We aimed to evaluate the effectiveness of the Rotarix vaccine and the impact of Rotarix vaccine on rotavirus gastroenteritis hospitalisations (ie, hospital admissions) among children younger than 5 years in Afghanistan.

Methods We used a test-negative case–control design embedded in an active sentinel surveillance platform to evaluate vaccine effectiveness. Children born on or after Jan 1, 2018, who had documentation of their rotavirus vaccination status and who were admitted for acute gastroenteritis at one of four sentinel hospitals from May, 2018 to December, 2021 were eligible to be included. We used an unconditional logistic regression model to estimate vaccine effectiveness and 95% CIs for a complete series of doses compared with no rotavirus vaccine doses among patients admitted with acute gastroenteritis. Vaccine effectiveness against hospitalisation was calculated as (1−[odds of being vaccinated in cases]/[odds of being vaccinated in controls])×100%. We compared pre-vaccine (2013–15) and post-vaccine (2019–21) surveillance data from two sites to calculate vaccine impact.

Findings The vaccine effectiveness analysis included 1172 cases and 2173 controls. Approximately 2108 (63·0%) of 3345 cases and controls were male, 1237 (37·0%) were female, and 2171 (65·0%) were aged 6–11 months. Two doses of Rotarix were 45% (95% CI 22–62) effective against rotavirus hospitalisation in children aged 6–59 months, adjusting for age, severity, admission year, and rotavirus season. Rotavirus positivity decreased from 51% pre-vaccine to 39% post-vaccine, resulting in a 39% adjusted reduction in rotavirus positivity among children younger than 5 years admitted with acute gastroenteritis.

Interpretation Rotarix showed moderate effectiveness in preventing rotavirus gastroenteritis hospitalisations, consistent with findings in other low-income countries. These findings support the continued administration of the rotavirus vaccine in Afghanistan.

Funding Gavi, the Vaccine Alliance.

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See **Comment** page e1383

For the Dari translation of the abstract see **Online** for appendix 1

London School of Hygiene and Tropical Medicine, London, UK (P Anwari MSc, A D Clark PhD); **Division of Viral Disease, NCIRD, CDC, Atlanta, GA, USA** (E Burnett MPH, T P Chavers MPH, U D Parashar MD, J E Tate PhD); **JS Consultancy, Kabul, Afghanistan** (N Safi MSc, A Samsor MPH, H Safi MPH)

Correspondence to: Dr Palwasha Anwari, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK **palwasha.anwari@lshtm.ac.uk**

Introduction

Acute gastroenteritis causes an estimated one in ten deaths among children aged younger than 5 years globally.[1] A substantial proportion of severe acute gastroenteritis in children is caused by rotavirus; most rotavirus gastroenteritis deaths occur in low-income settings.[2] In 2009, rotavirus vaccines were recommended for routine use in all countries by WHO, and they are routinely administered to infants in more than 120 countries.[3]

In January, 2018, Afghanistan introduced a two-dose live, attenuated, human monovalent G1P[8], oral rotavirus vaccine (Rotarix) into the national immunisation schedule. Rotarix is co-administered with poliovirus, pneumococcal, and pentavalent (*Haemophilus influenzae* [Hib], diphtheria-tetanus-pertussis, and hepatitis B) vaccines at 6 and 10 weeks of age. Before the introduction of rotavirus vaccination, Afghanistan was estimated to have around 2000 rotavirus gastroenteritis deaths annually, which was one of the highest rates of rotavirus gastroenteritis mortality globally.[4]

While post-licensure studies in middle-income and high-income countries have shown substantial declines in rotavirus gastroenteritis after introducing rotavirus vaccines, there is little evidence of the impact of rotavirus vaccines in low-income Asian countries.[5,6] Estimates of the real-world effectiveness and impact of rotavirus vaccination in Afghanistan are therefore important for both national and regional decision making.[7,8]

In Afghanistan, active hospital surveillance data were collected during the pre-vaccine (2013–15) and post-vaccine (2019–21) periods. In this Article, we aimed to estimate the vaccine effectiveness and impact of Rotarix

Research in context

Evidence before this study

Acute gastroenteritis is estimated to cause one in ten deaths among children aged younger than 5 years globally. A substantial proportion of severe acute gastroenteritis in children is caused by rotavirus; most of the rotavirus gastroenteritis deaths occur in low-income countries. Post-licensure studies of rotavirus vaccine in middle-income and high-income countries have shown substantial effectiveness of the vaccine. We searched Embase and PubMed from database inception to Oct 30, 2023, without language restriction, for previously published studies evaluating rotavirus effectiveness and impact using the following search terms: ("effectiveness" [title] or "impact" [title], and "rotavirus vaccin*" [title], "gastroenteritis" or diarrhea" or "rota or rotavirus infection" or "acute gastroenteritis" [title], "watery diarrhea". We also reviewed references from retrieved articles to identify additional studies. Rotavirus vaccine effectiveness is lower in low-income and middle-income countries (58–66%) relative to that in high-income countries (84–86%), although effectiveness data in Asia are sparse. Despite lower vaccine effectiveness, the vaccine's impact on hospitalisations and deaths is substantial in these settings. Before the introduction of rotavirus vaccination, an estimated 51% of acute gastroenteritis admissions among Afghan children younger than 5 years were attributable to rotavirus, with more than 20 000 rotavirus gastroenteritis admissions occurring annually.

Added value of this study

In January, 2018, Afghanistan introduced rotavirus vaccination into the national immunisation schedule at 6 and 10 weeks of age. We estimated the effectiveness and impact of Rotarix vaccination under conditions of routine use in Afghan children aged younger than 5 years. This assessment provides key data on rotavirus vaccine performance that are important not only for Afghanistan but also for Asia, where rotavirus vaccine use remains low. These data are distinct from estimates in other low-income settings given the context of substantial political and health system transformations that occurred during the study period. The evaluation shows continued effectiveness of the vaccine in a highly politically unstable environment, emphasising its importance amid challenging circumstances.

Implications of all the available evidence

Rotarix showed moderate effectiveness in preventing rotavirus gastroenteritis hospitalisations among Afghan children, consistent with findings in other low-income countries. These results support the continued administration of the rotavirus vaccine in Afghanistan. This evaluation underscores the need to enhance the tracking and verification of vaccination status to enable more robust analyses. Continued surveillance and increased genotype testing will be crucial to monitor strain variations and adjust vaccination strategies accordingly.

vaccination under conditions of routine use in Afghan children younger than 5 years.

Methods

Study design

We assessed the impact of rotavirus vaccine by comparing surveillance before and after its introduction and by using a time-series method with inpatient and outpatient data from Afghanistan's national Health Management and Information System (HMIS). We conducted a test-negative case–control study embedded in an active surveillance platform to estimate vaccine effectiveness.

Data sources

The data for our analyses came from two sources: active sentinel hospital-based surveillance for rotavirus and the HMIS database.

Rotavirus gastroenteritis active hospital-based surveillance was conducted from Jan 1, 2013 to Dec 31, 2015 across two sites: Indira Gandhi Children's Hospital, a specialty hospital in Kabul Province, and the paediatrics ward of Herat Regional Hospital in Herat province. Surveillance system details have been published previously.[9]

Post-vaccine rotavirus gastroenteritis surveillance conducted from May 14, 2018 to Dec 30, 2021 included two additional referral hospitals, Mazar Regional Hospital, in north Afghanistan, and Nangarhar Regional Hospital, in the eastern part of the country. These hospitals cover four regions of the country (ie, central, west, north, and east) and represent 27% of national hospital beds for children. They serve as referral hospitals to around 32% of the total population of Afghan children younger than 5 years.[10] No regular surveillance occurred in 2016 and 2017. Pre-vaccine and post-vaccine surveillance protocols were adapted from the WHO generic protocol.[11]

All sites captured hospital admissions among children younger 5 years with acute gastroenteritis (defined as ≥3 episodes of loose, watery stools within a 24-h period lasting <7 days before admission). Stool specimens were collected within 48 h of admission and tested for rotavirus by ProSpecT rotavirus test (Basingstoke, UK).[12] All collected specimens were transported to the Central Public Health Laboratory and stored at –20°C. A randomly selected subset of the samples was sent to the Pakistan National Institute of Health for genotyping using PCR. We completed a case report form for each enrolled child, detailing their demographics, clinical and laboratory information, and socioeconomic indicators. Vaccination cards were collected to determine the rotavirus vaccination status. This evaluation obtained approval from the Institutional Review Board (ID 444510; April 2018) of the Ministry of Public Health. This investigation was reviewed by the Human Research Protections Office at the US Centers for Disease Control

and Prevention and was conducted to be consistent with applicable federal law and Centers for Disease Control and Prevention policy. We obtained informed written consent from the parents and guardians of all enrolled children in the surveillance programme.

Established in 2003, HMIS collects, stores, and analyses the monthly aggregated outpatient and inpatient health data from public health facilities in 34 provinces. For this evaluation, we analysed all-cause acute gastroenteritis among children younger than 5 years admitted to hospital or seen in outpatient public health facilities that reported data for at least 11 months of the year between Jan 1, 2013 and Dec 30, 2022.

Data analysis

We conducted three primary analyses: a vaccine effectiveness evaluation using a test-negative case–control study design, a vaccine impact analysis using a pre-vaccine versus post-vaccine design, and an interrupted time-series analysis of HMIS data.

A test-negative case–control study was used to evaluate Rotarix vaccine effectiveness against rotavirus gastroenteritis hospital admissions. Cases were children whose stool specimens tested positive for rotavirus, and controls were children whose stool specimens tested negative. Children included in the vaccine effectiveness evaluation were born on or after Jan 1, 2018, and were aged 6 months or older to ensure that they were age-eligible to receive the full vaccine series. This accounted for real-world delays in the timeliness of vaccination and the potential presence of maternal immunoglobulin through transplacental transmission or breastfeeding.[13,14] A fully vaccinated child was defined as receiving two Rotarix doses at least 2 weeks before the onset of acute gastroenteritis symptoms regardless of timing or interval between doses. We excluded children whose vaccination status was not verified by a vaccine card or who had incongruous dates of vaccination. We calculated a sample size of 2646 was needed to have 80% power at a 5% significance level with more than 40% vaccine effectiveness, 80% or less full-series vaccination coverage for controls, and a 1:2 ratio of cases to controls.[11] Including more cases and controls enabled us to conduct sub-group analyses. We used the χ^2 test to compare the distribution of categorical variables and the *t*-test and Wilcoxon rank-sum test to compare continuous variables.

We used an unconditional logistic regression model to estimate vaccine effectiveness and 95% CIs for one and two rotavirus vaccine doses compared with zero dose among patients hospitalised for acute gastroenteritis. Vaccine effectiveness was calculated as (1−[odds of being vaccinated in cases]/[odds of being vaccinated in controls])×100% for children aged 6–11, 12–23, and 6–59 months. Our analysis used a forward selection strategy to assess age, sex, surveillance site, wealth quantile, rotavirus seasonal activity, year of admission, and nutrition status as potential confounders. Any variable that resulted in a 10% or greater change in the primary analysis was considered a confounder and included in the adjusted model. Severe rotavirus gastroenteritis was defined using a modified Vesikari score of 11 or higher.[15] The peak months for rotavirus activity were defined according to the distribution of rotavirus positivity over the 4-year post-vaccine introduction surveillance period. We used the Demographic and Household Survey method to calculate the wealth quintile of each child's household based on the ownership of specific household assets (eg, mattress, radio, television, electricity, refrigerator, mobile phone, bicycle, motorcycle, computer, and car) and other criteria (eg, source of drinking water, number of people living in the household, mother's marital status, and mother's and father's education).[16]

We also stratified our vaccine effectiveness estimates by malnourishment status and rotavirus genotype. Stunting,

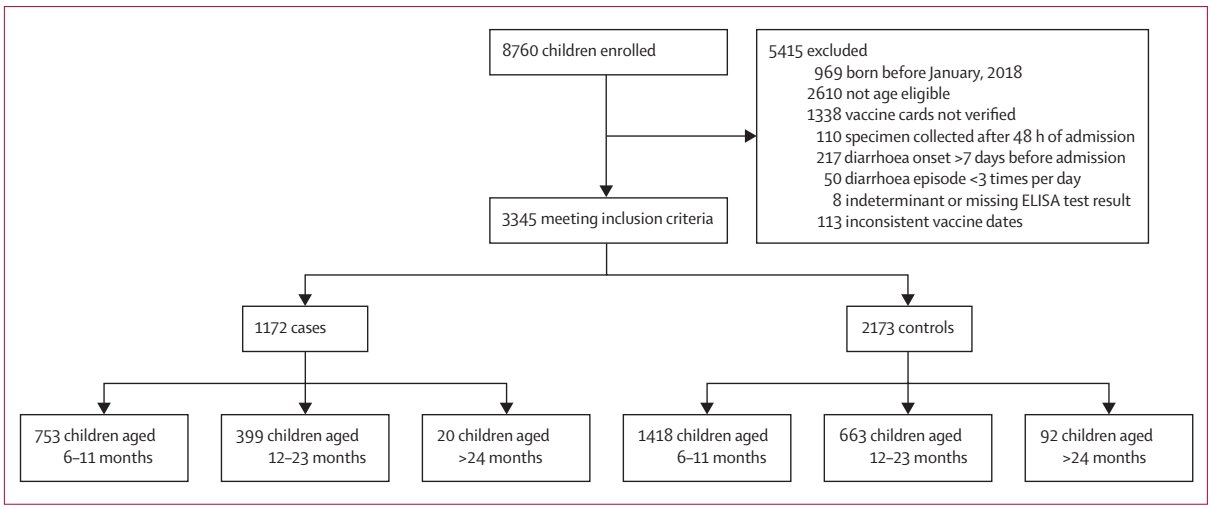

Figure 1: **Study profile**
Enrolment of children aged 0–59 months evaluated for acute gastroenteritis at four hospitals and those included in test-negative case-control analysis.

	Rotavirus positive (n=1172)	Rotavirus negative (n=2173)	p value
Sex	..	..	0·68
Female	428 (36·5%)	809 (37·2%)	..
Male	744 (63·5%)	1364 (62·8%)	..
Age, months	10 (7–13)	9 (7–14)	0·38*
Enrolment hospital	..	..	<0·0001
Indira Gandhi Children's Hospital	500 (42·7%)	493 (22·7%)	..
Herat Regional Hospital	133 (11·3%)	350 (16·1%)	..
Mazar Regional Hospital	183 (15·6%)	517 (23·8%)	..
Nangarhar Regional Hospital	356 (30·4%)	813 (37·4%)	..
Admission year	..	..	<0·0001
2018	66 (5·6%)	165 (7·6%)	..
2019	277 (23·6%)	519 (23·9%)	..
2020	481 (41·1%)	720 (33·1%)	..
2021	348 (29·7%)	769 (35·4%)	..
Peak rotavirus activity months (June–October)	768 (65·5%)	1167 (53·5%)	<0·0001
Vaccination profile, rotavirus			
0 dose	67 (6·1%)	72 (3·6%)	<0·0001
1 dose	185 (17·0%)	350 (17·4%)	..
2 doses	841/1093 (76·9%)	1590/2012 (79·0%)	..
Vaccination profile, pentavalent			
1 dose	138 (11·8%)	237 (10·9%)	0·42
2 doses	140 (11·9%)	300 (13·8%)	..
3 doses	812 (69·3%)	1477 (68·0%)	..
Vaccination profile, pneumococcal			
1 dose	141 (12·0%)	256 (11·8%)	0·13
2 doses	150 (12·8%)	338 (15·5%)	..
3 doses	793 (67·7%)	1403 (64·6%)	..
Vaccination profile, oral poliovirus			
Birth dose	955 (81·5%)	1823 (84·0%)	0·08
1 dose	136 (11·6%)	236 (10·9%)	0·55
2 doses	144 (12·3%)	302 (13·9%)	..
3 doses	811 (69·2%)	1478 (68·0%)	..
Measles vaccine	436 (37·2%)	757 (34·8%)	0·16
Outcome (recovered)	1125 (96·0%)	2083 (96·0%)	0·41
Vesikari score ≥11	1036 (88·4%)	1700 (78·2%)	<0·0001
Stunted (≤2 Z score)†	54 (41·5%)	115 (33·4%)	0·10
Wealth quintile‡			
Poorest	179 (15·3%)	447 (20·6%)	<0·0001
Poor	201 (17·1%)	390 (18·0%)	..
Middle	205 (17·5%)	390 (18·0%)	..
Rich	351 (30·0%)	579 (27·5%)	..
Richest	236 (20·1%)	349 (16·1%)	..
Genotypes			
Homotypic	39/99 (39·4%)	..	..
Partly homotypic	19/99 (19·2%)	..	..
Heterotypic	41/99 (41·4%)	..	..

Data are n (%) and median (IQR). *Obtained from Wilcoxon test. †Among enrolled patients in the Herat Regional Hospital (data from 2019–21). ‡Wealth quintile is calculated based on the ownership of mattress, radio, television, electricity, refrigerator, mobile phone, bicycle, motorcycle, and car, and other criteria such as source of drinking water, the number of people in the household, and mother and father's education level.

Table 1: **Comparison of characteristics of patients who were positive for rotavirus and controls who were rotavirus-negative with acute gastroenteritis, aged 6–59 months, 2018–21**

an indicator of chronic malnutrition, was defined as more than 2 SDs below the median height for age and was calculated using the WHO Anthro macro for SAS.[17] The stunting analysis was limited to children enrolled at the Herat Regional Hospital site because of reliability and completeness of the anthropometric data available compared with a high level of implausible values at the other sites. To assess vaccine effectiveness against specific rotavirus genotypes, we created three distinct groups similar to previous systematic reviews and meta-analyses.[18,19] The homotypic group included only the G1P[8] strain, which matches the Rotarix vaccine strain. The partially heterotypic strains included either G1 or P[8]. The fully heterotypic strains included neither G1 nor P[8].

We used data from two sites, Indira Gandhi Children's Hospital (Kabul Province) and Herat Regional Hospital (Herat Province), to compare trends in rotavirus hospitalisations pre-vaccine and post-vaccine introduction. We pooled data from all three pre-vaccination years (ie, 2013, 2014, and 2015) to calculate baseline estimates. We also pooled the three post-vaccination years (ie, 2019, 2020, and 2021). The year of introduction (2018) was excluded as this was a transition year. We adjusted our estimates of vaccine impact to ensure stability in the rate of acute gastroenteritis admissions over time using a method described in detail elsewhere.[20]

The following equation was used to calculate the adjusted average annual number of rotavirus gastroenteritis admissions in the post-vaccine period:

$$g2 \times ((g1-r1)/(g2-r2)) \times (r2/g2)$$

where r1 and r2 are the pre-vaccination and post-vaccination rotavirus gastroenteritis admissions and g1 and g2 are the pre-vaccination and post-vaccination acute gastroenteritis admissions. $g2 \times ((g1-r1)/(g2-r2))$ gives the acute gastroenteritis admissions (adjusted average annual count post-vaccination) and $(r2/g2)$ gives the unadjusted rotavirus positivity in the pooled post-vaccination period.

To assess the validity of our vaccine impact estimates for 2019–21, we calculated the reduction in rotavirus gastroenteritis hospital admissions in those younger than 5 years that would be expected had we multiplied our estimates of vaccine effectiveness by the estimated two-dose rotavirus vaccine coverage of 85%. More details on the estimation of vaccine coverage are in appendix 2 (pp 6–7).

We conducted an interrupted time-series analysis using a negative binomial model on HMIS aggregated acute gastroenteritis hospital admissions and outpatient public health facility visits to forecast the expected monthly counts in the absence of rotavirus vaccine during the post-vaccine introduction period (January, 2018–December, 2022). Seasonal variations were adjusted by including calendar month, while secular trends were factored in by including the year of admission in the

model. Model fit was assessed using the Pearson χ^2 statistic, where p>0·05 indicates an acceptable model fit. A negative binomial model was selected due to possible overdispersion of the data. We used Microsoft Excel, SAS (version 9.4), and R (version 4.2.3) for statistical analysis and producing graphs.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of 8760 children enrolled in surveillance following rotavirus vaccine introduction, 1172 cases and 2173 controls were included in the vaccine effectiveness analysis (figure 1). The most common reasons for exclusion were that the child was born before Jan 1, 2018 (969 [17·9%] of 5415), the child was younger than 6 months (2610 [48·2%]), or the vaccination status could not be verified (1338 [24·7%]; figure 1; appendix 2 p 2). Rotavirus positivity was slightly lower among children who were ineligible for the vaccine effectiveness analysis compared with children who were eligible (1690 [31·2%] of 5415 *vs* 1172 [35·0%] of 3345). More children who were eligible presented with severe acute gastroenteritis than children who were ineligible (2736 [81·8%] *vs* 3929 [72·6%]).

Rotavirus positivity was lower among individuals with verified vaccination status (1172 [35·0%] of 3345) compared to those ineligible due to unverified vaccination status (355 [39·0%] of 910; appendix 2 p 3). However, acute gastroenteritis severity and sex were not different between the two groups.

2108 (63·0%) cases and controls were male and 2171 (65·0%) were aged 6–11 months (table 1; appendix 2 pp 3–4). 768 (65·5%) cases were enrolled during the high rotavirus activity months (June–October). 76·9% (841/1093) of cases and 79·0% (1590/2012) of controls received two doses of rotavirus vaccine, while 6·1% (n=67) of cases and 3·6% (n=72) of controls were unvaccinated. The coverage of pentavalent, pneumococcal, measles, and oral poliovirus vaccines was similar among cases and controls (table 1). Cases primarily presented with severe acute gastroenteritis (1036 [88·4%] of 1172). The severity of acute gastroenteritis varied during the surveillance period, with more severe cases enrolled in 2020 (425 [41·0%] of 1036), followed by 2021 (306 [29·5%]), and 2019 (248 [23·9%]; appendix 2 pp 3–4). Based on the household wealth index, 380 (32·4%) of 172 case patients' families and 837 (38·5%) of 2173 of control patients' families fell into poor and poorest quantiles (table 1).

Genotype results were available for only 280 specimens, of which 99 were eligible to be included in the vaccine effectiveness analysis (appendix 2 p 5). The predominant strains were G1P[8] (39 [39·4%]) followed by G9P[4] (32 [32·3%]).

	Cases	Controls	Crude vaccine effectiveness (95% CI)	Adjusted vaccine effectiveness (95% CI)
Rotarix doses, patients aged 6–59 months				
0 doses	67	72	Ref	..
1 dose	185	350	43% (17 to 61)	45%* (19 to 63)
2 doses	841	1593	43% (20 to 60)	45%* (22 to 62)
Rotarix doses, patients aged 6–11 months				
0 doses	45	40	Ref	..
1 dose	127	254	56% (28 to 72)	58%* (31 to 74)
2 doses	524	1014	54% (29 to 70)	57%* (33 to 73)
Rotarix doses, patients aged 12–23 months				
0 doses	21	30	Ref	..
1 dose	57	87	6% (–79 to 51)	14%* (–69 to 56)
2 doses	301	504	15% (–52 to 52)	18%* (–49 to 55)
Vesikari score ≥11, patients aged 6–59 months				
0 doses	56	62	Ref	..
1 dose	167	273	32% (–2 to 55)	36%† (2 to 58)
2 doses	741	1238	34% (4 to 54)	37%† (7 to 57)
Vesikari score ≥11, patients aged 6–11 months				
0 doses	36	34	Ref	..
1 dose	112	201	47% (11 to 69)	50%† (13 to 71)
2 doses	466	763	42% (6 to 64)	46%† (11 to 67)
Vesikari score ≥11, patients aged 12–23 months				
0 doses	19	26	Ref	..
1 dose	54	66	–12% (–124 to 44)	2%† (–102 to 52)
2 doses	260	413	14% (–59 to 53)	20%† (–51 to 58)
Stunted (<–2 *Z* score) Herat Regional Hospital site only, 2019–21 data, patients aged 6–59 months				
0 doses	1	2	Ref	..
1 dose	3	14	33% (–802 to 95)	27%† (–998 to 95)
2 doses	43	90	6% (–960 to 92)	6%† (–1094 to 93)
Stunted (<–2 *Z* score) Herat Regional Hospital site only, 2019–21 data, patients aged 6–11 months				
0 doses	1	2	Ref	..
1 dose	2	10	64% (–519 to 98)	53%† (–826 to 98)
2 doses	26	56	4% (–1011 to 92)	15%† (–1088 to 94)
Stunted (<–2 *Z* score) Herat Regional Hospital site only, 2019–21 data, patients aged 12–23 months‡				
0 doses	..	..	..	..
1 dose	..	..	..	..
2 doses	..	..	..	..
Not stunted (≥ –2 *Z* score) Herat Regional Hospital site only, 2019–21 data, patients aged 6–59 months				
0 doses	6	5	Ref	..
1 dose	9	24	69% (–28 to 92)	65%† (–78 to 93)
2 doses	54	171	74% (10 to 92)	81%† (20 to 95)
Not stunted (≥ –2 *Z* score) Herat Regional Hospital site only, 2019–21 data, patients aged 6–11 months				
0 doses	3	3	Ref	..
1 dose	5	21	76% (–55 to 96)	86%† (–31 to 98)
2 doses	33	127	74% (–35 to 95)	87%† (5 to 98)
Not stunted (≥ –2 *Z* score) Herat Regional Hospital site only, 2019–21 data, patients aged 12–23 months‡				
0 doses	..	..	..	..
1 dose	..	..	..	..
2 doses	..	..	..	..

(Table 2 continues on next page)

	Cases	Controls	Crude vaccine effectiveness (95% CI)	Adjusted vaccine effectiveness (95% CI)
(Continued from previous page)				
Genotyping, patients aged 6–59 months (n=107)				
Homotypic	39	..	60% (–269 to 96)	..
Partly homotypic	19	..	–21% (–1466 to 91)	..
Heterotypic	41	..	48% (–385 to 95)	..

*Adjusted for age, severity of acute gastroenteritis, year of admission, and rotavirus activity season. †Adjusted for age, year of admission, and rotavirus activity season. ‡Not enough data.

Table 2: **Effectiveness of Rotarix against hospitalisation for rotavirus gastroenteritis, stratified by age group, acute gastroenteritis severity, stunting, and genotype, Afghanistan, 2018–21**

See Online for appendix 2

Adjusting for age, severity of acute gastroenteritis, year of admission, and rotavirus season, we found that among children aged 6–59 months, two doses of Rotarix were 45% (95% CI 22–62) and one dose of Rotarix was 45% (19–63) effective against hospital admission (table 2). Adjusted two-dose vaccine effectiveness against hospitalisation with rotavirus gastroenteritis among children aged 6–11 months was 57% (95% CI 33–73) and one-dose vaccine effectiveness was 58% (31–74).

In a sub-group analysis among stunted children aged 6–59 months enrolled at the Herat Regional Hospital site, the effectiveness of two doses of Rotarix was 6% (95% CI –1094 to 93; table 2). Among non-stunted children, the vaccine effectiveness for two doses of Rotarix was 81% (95% CI 20 to 95). Rotarix vaccine effectiveness against homotypic and heterotypic strains was 60% (95% CI –269 to 96) and 48% (–385 to 95), respectively. Due to the small sample size, the vaccine effectiveness estimates stratified by genotype are unadjusted.

There were 2737 and 3049 acute gastroenteritis patients aged younger than 5 years enrolled during the pre-vaccine and post-vaccine periods, respectively. There was a total of 12 months without case enrolment at the sites between 2013–15 (1 month in Indira Gandhi Children's Hospital and 11 months in Herat Regional Hospital) and 1 month without enrolment in both sites in 2020.

Rotavirus positivity declined from 51% in the pre-vaccine period (2013–15) to 39% in the post-vaccine period (2019–21); an overall reduction in rotavirus positivity of 24%. There was a 24% and 31% reduction in rotavirus gastroenteritis admissions at Indira Gandhi Children's Hospital and Herat Regional Hospital, respectively (appendix 2 pp 10–11). After adjusting for stability in the rate of test-negative acute gastroenteritis admissions, Rotarix was estimated to decrease rotavirus gastroenteritis admissions in children younger than 5 years by 39% (figure 2). Before rotavirus vaccine introduction, rotavirus cases were reported throughout the year, with the highest proportion of positive tests for rotavirus during May–July. However, after vaccine introduction, the rotavirus gastroenteritis admission peak shifted to June–October. During the pre-vaccine and post-vaccine surveillances children aged 6–11 months were the largest proportion (pre-vaccine 42·4% [1159/2737] and post-vaccine 38·6% [1177/3049]; appendix 2 pp 8–9).

To verify the validity of our impact and vaccine effectiveness estimates, we divided our estimate of a 39% reduction in hospitalisations by our estimate of 45% vaccine effectiveness to assess whether this generated a plausible estimate of rotavirus vaccination coverage. Using this method, the expected rotavirus vaccination coverage was 85%, which was consistent with Demographic and Household Survey (Kabul=80% and Herat=77%) and sentinel surveillance sites (Kabul=83% and Herat=90%; appendix 2 pp 6–7).

Only 4% (n=13) of health facilities consistently reported acute gastroenteritis hospital admissions and 43% (n=1174) of health facilities consistently reported acute gastroenteritis outpatient visits to HMIS. In each year following rotavirus vaccine introduction, the expected number of acute gastroenteritis hospital admissions during the peak rotavirus activity month exceeds the highest observed cases in any month (model fit p=0·14) indicating a substantial reduction in acute gastroenteritis hospital admissions following rotavirus vaccine introduction (figure 3). The expected and observed acute gastroenteritis outpatient visits are similar, and the observed visits overlap with the expected visits' CIs, but with a shift in seasonality (model fit p=0·10; figure 3).

Discussion

We found that two doses of Rotarix provided 45% vaccine effectiveness against rotavirus gastroenteritis hospitalisations among children aged 6–59 months. Notably, among children aged 6–11 months, in whom the disease burden is greatest, vaccine effectiveness was higher (57%). The introduction of rotavirus vaccine reduced acute gastroenteritis admissions by 39%. These vaccine effectiveness and impact findings are congruous with expected vaccine effectiveness and impact given vaccination coverage estimated by Demographic and Household Surveys. Our vaccine effectiveness estimates are also similar to results of a meta-analysis of 21 high-mortality countries (65%, 95% CI 54–74).[6,21] The observed vaccine effectiveness in Afghanistan is within the range of pre-vaccine efficacity observed in low-income settings and several other studies assessing vaccine effectiveness after vaccine introduction such as Uzbekistan (51%), Tanzania (57%), Zimbabwe (61%), and Botswana (52%).[22–24] Our estimate of the ratio of one-dose to two-dose rotavirus vaccine effectiveness was 1·00 but this is higher than the ratio reported in other low-income and middle-income countries and warrants further investigation. In a recent random effects meta-analysis of 11 low-income and middle-income countries, the ratio of one-dose to last-dose rotavirus vaccine effectiveness was estimated to be 75% (95% CI 55–96).[20,21]

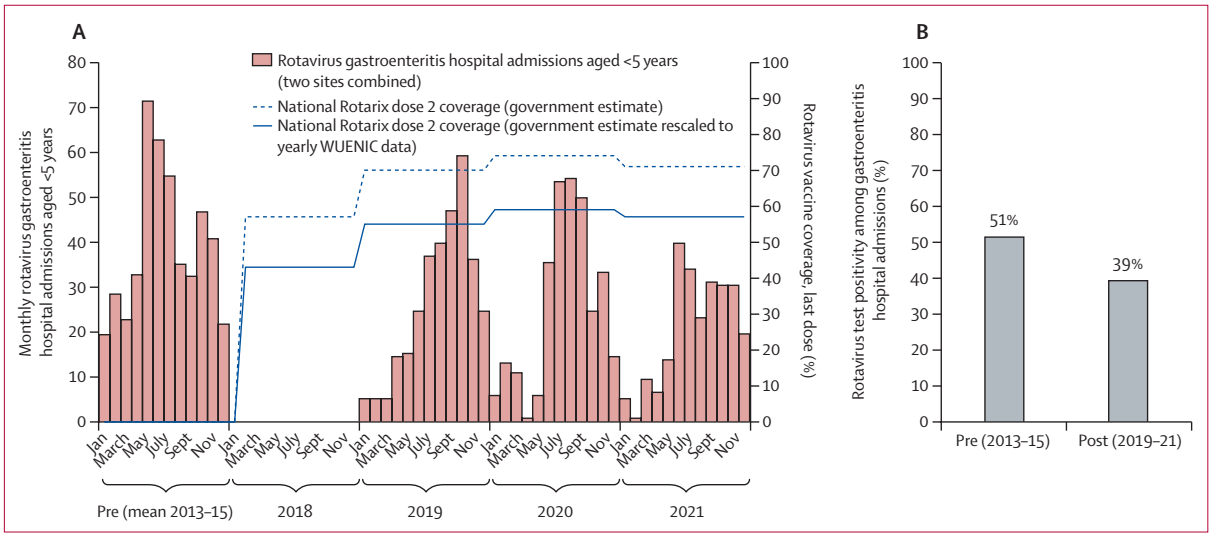

Figure 2: **Number (A) and proportion (B) of children admitted to Indira Gandhi Children's Hospital and and Herat Regional Hospital with rotavirus-positive tests, post-vaccine data compared with median pre-vaccine data and with the rotavirus vaccine coverage, 2013–21**
Data are in those aged 0–59 months.

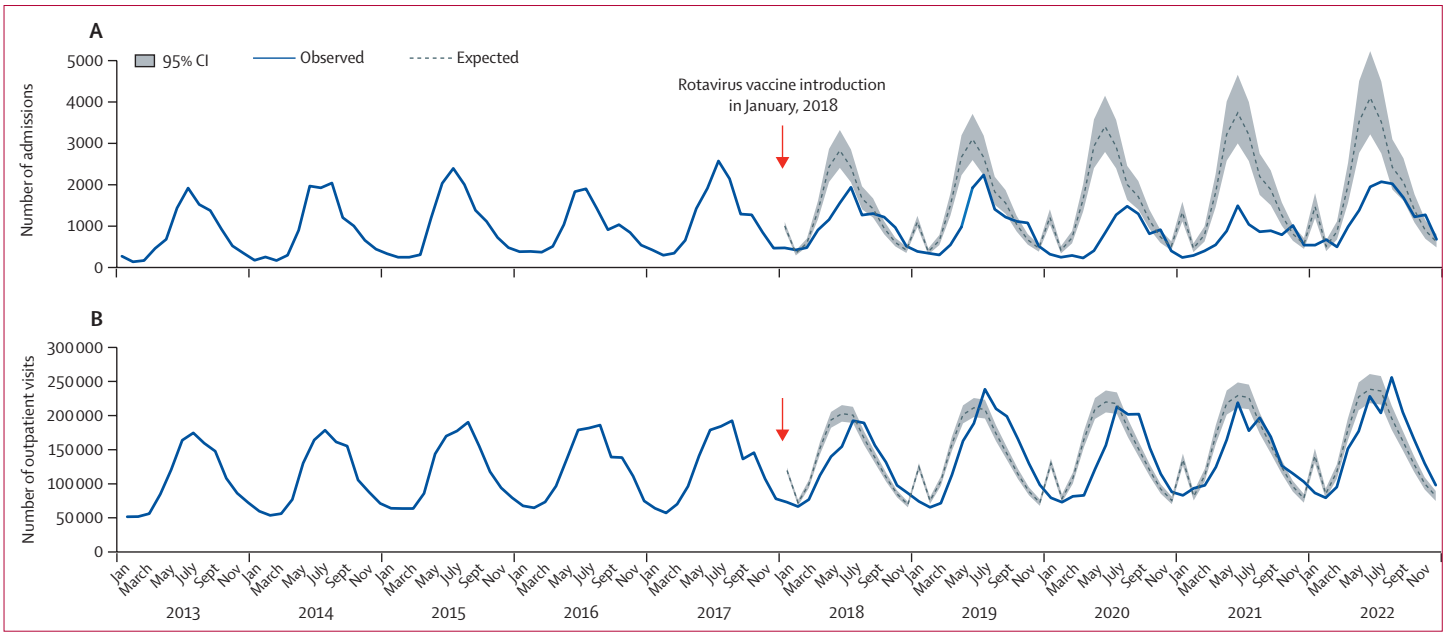

Figure 3: **All-cause acute gastroenteritis hospital admissions (A) and outpatient visits (B) before (2013–17) and after rotavirus vaccine introduction (2018–22)**
(A) Model fit, p=0·14. (B) Model fit, p=0·10.

Our surveillance identified that 33% of control patients in Herat Regional Hospital were stunted. A similar national stunting prevalence (35%) was reported by a multiple indicator cluster survey in 2022–23.[25] In our case–control analysis, the vaccine effectiveness point estimate was more than 18 times higher in non-stunted children than stunted children; however, the CIs are broad. A similar result was reported among stunted children in Mozambique, and in a literature review of 11 analyses.[26,27] The high prevalence of malnutrition in Afghanistan could account for some of the observed low vaccine effectiveness and impact compared with high-income, low-child mortality settings.[25]

In the complex landscape of health-care delivery in Afghanistan, the COVID-19 pandemic in 2020–21 and the sudden change in the Afghan Government in August 2021, presented additional challenges. There were fewer acute gastroenteritis admissions in public health facilities in 2020–21 compared with previous years followed by an increase in acute gastroenteritis admissions in 2022. Without the adjustment for this instability, we would have underestimated the impact of

vaccination (24% *vs* 39%). The reported rotavirus vaccination coverage estimates for 2020 and 2021 were very similar to the estimate for 2019, possibly due to the efforts of the Ministry of Public Health and partners to ensure continuity of coverage and increased access to children in some regions that were previously difficult to reach after the change in government. Our estimates of rotavirus vaccine coverage among test-negative control patients were based entirely on children with vaccination cards, so we might have overestimated rotavirus vaccination coverage. The 2015 Demographic and Household Survey estimates (and diphtheria-tetanus-pertussis dose 2 coverage as a proxy for the last dose of Rotarix) might offer a more accurate estimate.[16] Consistent vaccination coverage during this time underscores the significance of health-care system resilience and the improvement of vaccination services. High rotavirus vaccine coverage is an important tool in reducing the burden of acute gastroenteritis among Afghan children.

We did not observe a change in the number of acute gastroenteritis outpatient visits, which could be explained by less severe disease among outpatients than those admitted to hospital for rotavirus. Since the vaccine is more effective against severe rotavirus disease it is not unexpected that the number of outpatients would remain unchanged. However, the outpatient data helped us track the uniform seasonality of acute gastroenteritis and other contextual factors. For instance, in 2020, all-cause acute gastroenteritis outpatient visits during the peak season of acute gastroenteritis declined while the occurrence of acute gastroenteritis remained the same as previous years. In 2022, acute gastroenteritis outpatient visits showed a wider and two peak; this finding could explain the rise in acute gastroenteritis, due to other pathogens or a shift in rotavirus season like that observed in Zimbabwe, Mexico, Japan, and the USA following rotavirus vaccine introduction.[23] Further research is needed to explain if that shift in rotavirus seasonality is due to the impact of vaccine.

Our evaluation has several strengths. First, we used a test-negative case–control design to estimate vaccine effectiveness, which ensures that case and control patients have similar health-seeking behaviour. This was also financially and logistically advantageous.[28–30] Second, while the sentinel surveillance sites might not represent the entire country, they were strategically chosen based on various factors, including a high number of children's beds, extensive catchment areas, and geographical diversity. The multiyear surveillance covered an extended period and spanned various sub-national locations, using standard testing and case enrolment procedures. Third, we adjusted our estimates of vaccine impact to account for instability in the number of acute gastroenteritis admissions reported over time, which was especially important in the context of COVID-19 and governmental change. Finally, throughout the surveillance period, rigorous quality control measures were implemented. Site supervisors conducted daily checks of entries on-site, while quality officers reviewed entries on a monthly basis at the central level to check for completeness and inconsistencies in vaccination dates.

Our evaluation had some limitations. First, to provide wider representation across the country, surveillance was initially planned for a site in the south region but given the high risk of compromised data quality due to the persistent conflict and challenging security situation, we decided against it. Second, the high burden of rotavirus disease among younger children limited our power to estimate vaccine effectiveness in older age groups. Due to the small number of children in the 24 months and older age group, we were not able to calculate vaccine effectiveness for this age group. Third, only a small subset of samples was genotyped, which limited our ability to identify the circulating genotypes and estimate strain-specific vaccine effectiveness. Finally, we were limited in the HMIS data that could be included due to data quality issues and substantial missing values; however, the HMIS hospital admissions findings were consistent with sentinel surveillance findings.

Our estimates represent rotavirus vaccine effectiveness and impact in a low-income setting with high child mortality and several other challenges (eg, reduced access to safe drinking water, volatile security resulting in internally displaced populations, natural disasters such as drought and flash floods, and increased poverty and stunting prevalence among children aged <5 years). It is crucial to emphasise the importance of maintaining high vaccination coverage nationwide, especially in the face of changing situations. This evaluation showed that rotavirus vaccination has had a moderate but important health impact in Afghanistan, consistent with the vaccine effectiveness and vaccine impact reported in other low-income settings with high child mortality.

The evaluation underscores the need to enhance the tracking and verification of vaccination status to enable more robust analyses. Further research with a larger sample size is needed to establish a more conclusive understanding of the relationship between nutritional status and vaccine effectiveness. Continued surveillance and increased genotype testing will be crucial to monitor strain variations and adjust vaccination strategies accordingly.

Contributors

PA, NS, JET, and UDP developed the evaluation concept and methods. PA tailored and contextualised the generic WHO protocol. PA translated the questionnaire and consent form into two national languages, Dari and Pashto. NS, PA, AS, HS, EB, and TPC carried out primary data collection, data validation, and data processing. PA and NS secured secondary data. PA conducted data analysis and produced tables and figures. EB, JET, and ADC have accessed and verified the data. NS, AS, PA, and HS managed project administration and logistic and operation of the evaluation activity. PA wrote the draft manuscript. ADC, EB, and JET revised the manuscript and provided scientific inputs. All authors reviewed, edited, and approved the final manuscript for submission. All authors had access to the data.

Equitable partnership declaration

The authors of this paper have submitted an equitable partnership declaration (appendix 3). This statement allows researchers to describe how their work engages with researchers, communities, and environments in the countries of study. This statement is part of *The Lancet Global Health*'s broader goal to decolonise global health.

Declaration of interests

We declare no competing interests.

Data sharing

Afghanistan post-licensure surveillance data will be available on request to the corresponding author by providing a research proposal.

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See **Online** for appendix 3

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Supplementary appendix 1

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«این ترجمه به زبان دری توسط نویسنده گان ارسال شده و ما آن را به همان شکل نشر مینمایم. این ترجمه مورد بازبینی همتا قرار نگرفته است. پروسه های ویرایشی و ادیت لانست تنها بر روی نسخه اصلی زبان انگلیسی اعمال شده است، که باید به عنوان مرجع برای این دست نوشته مورد استفاده قرار گیرد.»

Supplement to: Anwari P, Burnett E, Safi N, et al. Effectiveness and impact of monovalent rotavirus vaccination in Afghanistan: a test-negative case–control analysis. *Lancet Glob Health* 2024; **12:** e1517–25.

خلاصه مقاله موثریت و تاثیر واکسین تک ظرفیتی ویروس روتا در افغانستان

پس زمینه

افغانستان در ماه جدی سال ۱۳۹۶ مطابق جنوری ۲۰۱۸ واکسین روتا ریکس یکی از واکسین های موجود ویروس روتا را در پروگرام معافیت کتلوی خود شامل کرد. مطالعات پس از مجوز نشان دهنده کاهش قابل توجهی درموارد مرگ و میر ناشی از امراض حاد معدی معایی در سطح جهان را نشان میدهد، ولی شواهد کافی از موثریت این واکسین در ممالک کم درآمد بخصوص در آسیا وجود ندارد. هدف این ارزیابی مطالعه موثریت و تاثیر واکسین روتا در میان اطفال زیر پنج سال در افغانستان است.

روش

ما از یک طرح کیس-کنترول تست منفی تعبیه شده در ضم یک سرویلانس فعال برای ارزیابی موثریت واکسین ویروس روتا استفاده کردیم. اطفالی که در تاریخ ۱۱ جدی ۱۳۹۶ مطابق اول جنوری ۲۰۱۸ و یا بعد از آن متولد شده اند، وضعیت اخذ واکسین روتا شان تایید شده باشد و در یکی از چهار شفاخانه شامل در سرویلانس به دلیل امراض حاد معایی بستر شده بودند شامل این تحلیل گردیدند. سرویلانس به مدت چهار سال بین ماه ثور ۱۳۹۷ تا جدی ۱۴۰۰ (می ۲۰۱۸ تا دسمبر ۲۰۲۱) ادامه داشت. ما از مودل لاجستک رگریشتن بدون قید برای تخمین موثریت واکسین با فاصله اطمینان ۹۵٪ استفاده کردیم. موثریت واکسین توسط فورمل ذیل محاسبه شد.

(۱- [احتمال واکسین شدن در کیس ها] تقسیم بر [احتمال واکسین شدن در کنترول ها]) ضرب ۱۰۰٪

ما ارقام سرویلانس قبل از معرفی (۱۳۹۱-۱۳۹۳) و بعد از معرفی (۱۳۹۶-۱۳۹۹) واکسین روتا دو شفاخانه شامل سرویلانس روتا را برای محاسبه تاثیرب واکسین مقایسه کردیم.

نتایج

در تحلیل موثریت واکسین روتا ۱۱۷۲ کیس و ۲۱۷۳ کنترول شامل بود. تقریبی۲۱۷۳(۶۳٪) از کیس ها و کنترول ها پسر بوده و ۲۱۷۱ (۶۵٪) شان در کتگوری سنی ۶-۱۱ ماه قرار داشتند. دو دوز روتا ریکس موثریت ۴۵٪ با فاصله اطمینان (۲۲٪-۶۲٪) در برابر بستر شدن از باعث امراض حاد معایی ناشی از ویروس روتا در بین اطفال ۶ تا ۵۹ ماه را نشان داد البته زمانیکه ما به عواملی مانند سن در زمان شروع اعراض، وخامت مرض، سال بستری شدن و موسم جهشی ویروس روتا در معادل تحلیلی خود کنترول کردیم.

مثبت بودن ویروس روتا درنزد مریضان حاد معایی از ۵۱٪ قبل از معرفی واکسین به ۳۹٪ کاهش یافته ، که این منجر به کاهش ۳۹٪ بستری شدن از باعث امراض حاد معایی در میان اطفال کمتر از ۵ سال شده است. واکسین ویروس روتا یک تاثیر متوسط را در میان اطفال افغان نشان داده که در مطابقت به دریافت های سایر کشورهای کم درآمد میباشد. نتایج این ارزیابی به ادامه تطبیق واکسین ویروس روتا در افغانستان را تایید میکند.

کلمات کلیدی: امراض حاد معایی؛ واکسین ویروس روتا ؛ موثریت واکسین؛ افغانستان

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Supplementary appendix 2

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Supplement to: Anwari P, Burnett E, Safi N, et al. Effectiveness and impact of monovalent rotavirus vaccination in Afghanistan: a test-negative case–control analysis. *Lancet Glob Health* 2024; **12:** e1517–25.

Appendix 2

Supplement file

Effectiveness and impact of monovalent rotavirus vaccination in Afghanistan: a test-negative case-control analysis

Palwasha Anwari, Eleanor Burnett, Najibullah Safi, Akmal Samsor, Helah Safi, Tyler P Chavers, Umesh D Parashar, Andrew D Clark, Jacqueline E Tate

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Table S 1 Comparison of eligibles and ineligibles for vaccine effectiveness analysis, Afghanistan 2018-21

Characteristics	Eligible (6-59 months)	Ineligible (0-59 months)	P-value
	3345 (38.2%)	**5415 (61.8%)**	
Rotavirus positive	1172 (35.0)	1690 (31.3)	0.01
Sex	2108 (63.0)	3366 (62.0)	0.42
Male	1237 (37.0)	2049 (38.0)	
Female			
Enrolment hospital			
Indira Gandhi children hospital (IGCH)	993 (29.7)	1227 (22.7)	<0.01
Herat regional children's hospital (HRH)	483 (14.4)	1005 (18.6)	
Mazar regional hospital (MRH)	700 (20.9)	1809 (33.4)	
Nangarhar regional hospital (NRH)	1169 (34.9)	1374 (25.4)	
Admission year			
2018	231 (6.9)	1695 (31.3)	<0.01
2019	796 (23.8)	1515 (28.0)	
2020	1201 (35.9)	1093 (20.2)	
2021	1117 (33.4)	1112 (20.5)	
Admission month			<0.01
January	145 (4.3)	310 (5.7)	
February	108 (3.2)	228 (4.2)	
March	180 (5.4)	228 (4.2)	
April	157 (4.7)	256 (4.7)	
May	191 (5.7)	395 (7.3)	
June	317 (9.5)	607 (11.2)	
July	367 (11.0)	638 (11.8)	
August	392 (11.7)	562 (10.4)	
September	390 (11.7)	672 (12.4)	
October	465 (13.9)	579 (10.7)	
November	396 (11.8)	459 (8.5)	
December	237 (7.1)	481 (8.9)	
Age			
0-5 months	0 (0.0)	3254 (60.1)	<0.01
6-11 months	2171 (64.9)	1003 (18.5)	
12-17 months	842 (25.2)	620 (11.5)	
18-23 months	220 (6.6)	238 (4.4)	
≥24 months	112 (3.4)	300 (5.5)	
Outcome (Recovered)	3208 (95.9)	5017 (92.6)	<0.01
Acute gastroenteritis severity (Vesikari score >=11)	2736 (81.8)	3929 (72.6)	<0.01

Table S 2 Additional characteristics of case-patients and test-negative controls, Afghanistan 2018-21

Characteristics	Rotavirus positive n=1172 (35.0%)	Rotavirus Negative n=2173 (65.0%)	P value
Vesikari score ≥11 by age group*			<0.01
6-11 months	**665 (64.2)**	**1086 (63.9)**	
12-17 months	293 (28.3)	422 (24.8)	
18-23 months	59 (6.7)	118 (6.9)	
≥24 months	19 (1.8)	74 (4.3)	
Vesikari score≥11 by months of year			0.23
January	27 (2.6)	85 (5.0)	
February	17 (1.6)	65 (3.8)	
March	38 (3.7)	107 (6.3)	
April	25 (2.4)	108 (6.4)	
May	30 (2.9)	134 (7.9)	
June	95 (9.2)	183 (10.8)	
July	130 (12.6)	148 (8.7)	
August	123 (11.9)	202 (11.9)	
September	134 (12.9)	181 (10.6)	
October	188 (18.1)	208 (12.2)	
November	157 (15.1)	170 (10.0)	
December	72 (7.0)	109 (6.4)	
Vesikari score≥11 by rotavirus activity season			
High season (January-October)	670 (64.7)	922 (54.2)	<0.01
Vesikari score≥11 by year of enrollment			<0.01
2018	57 (5.5)	118 (6.9)	
2019	248 (23.9)	386 (22.7)	
2020	425 (41.0)	560 (32.9)	
2021	306 (29.6)	636 (37.4)	
Socioeconomic parameters			
Maternal age, year, median (IQR)	28 (24-30)	28 (25-32)	<0.01¥
Maternal education			
None	862 (73.5)	1645 (75.7)	0.20
Primary school	105 (9.0)	199 (9.2)	
Secondary school	94 (8.0)	162 (7.4)	
Postsecondary school	81 (6.9)	107 (4.9)	
University	30 (2.6)	60 (2.8)	
Father's education			
None	602 (51.4)	1251 (57.6)	0.01
Primary school	98 (8.4)	204 (9.4)	
Secondary school	142 (12.1)	205 (9.4)	
Postsecondary school	202 (17.2)	354 (16.3)	
University	128 (10.9)	159 (7.3)	
Maternal Status (married)	1168 (99.7)	2149 (98.9)	0.19
Number of children in the household (Median, IQR)	2 (2.0-3.0)	2 (2.0-3.0)	0.29¥
Number of people in the household	7 (5.0-9.0)	7 (5.0-9.0)	0.17¥
Source of Drinking water			
Tap to house	244 (20.8)	392 (18.0)	<0.01
Shared community tap	209 (17.8)	538 (24.8)	
Bore hole	417 (35.6)	641 (29.5)	
Covered well	233 (19.9)	489 (22.5)	
Open well	44 (3.8)	68 (3.1)	

Lake/river/spring	25 (2.1)	45 (2.1)	
Having one of these assets at home			
Mattress	1160 (99.0)	2132 (98.1)	<0.06
Electricity	1016 (86.7)	1758 (80.9)	<0.01
Television	691 (59.0)	1167 (53.7)	0. 03
Refrigerator	389 (33.2)	639 (29.4)	0.02
Radio	419 (35.7)	833 (38.3)	0.14
Bicycle	351 (29.9)	627 (28.8)	0.51
Motorcycle	217 (19.5)	378 (17.4)	0.42
Car in home	228 (19.5)	302(13.9)	<0. 01
Mobile phone	1110 (94.7)	2002 (92.1)	<0.01
Computer	142 (12.1)	176 (8.1)	<0.01
Not stunted (≥ -2 z-score) **	71 (57.3)	208 (64.0)	0.19
Stunted (<-2 z-score) by age group**			<0.01
6-11 months	33(62.3)	723(63.4)	0.5
12-17 months	16 (30.2)	28 (24.0)	
18-23 months	4 (7.5)	13 (11.1)	
≥24 months	0 (0.0)	3 (2.6)	

¥ Obtained from Wilcoxon test.

*n=2738 (cases=1036 and controls=1700)

** Among enrolled patients in HRH site (data of 2019, 2020, and 2021), n=449.

Table S 3 Distribution of genotypes among vaccine effectiveness analysis eligibles and ineligibles, Afghanistan 2018-21

Genotypes	**VE Eligibles**		**VE Ineligibles**	
	N=99	**%**	**N=180**	**%**
G1P[4]	1	1.0	1	0.6
G1P[6]	1	1.0	3	1.7
G1P[8] (Homotypic)	**39**	**39.4**	**50**	**27.8**
G1G2G9P[4][8]	1	1.0	-	-
G2G9P[4]	1	1.0	2	1.1
G2G9P[4][6]	-	-	1	0.6
G2G12P[6]	-	-	1	0.6
G2P[4]	1	1.0	1	0.6
G2P[6][8]	2	2.0	8	4.4
G2P[8]	-	-	1	0.6
G3G9P[8]	-	-	3	1.7
G3P[4]	-	-	1	0.6
G3P[6]	-	-	1	0.6
G3P[8]	10	10.1	3	1.7
G9P[4]	32	32.3	63	35.0
G9P[6]	1	1.0	1	0.6
G9P[8]	2	2.0	9	5.0
G9P[4][6]	2	2.0	1	0.6
G9P[4][8]	2	2.0	1	0.6
G9P [8][6]	-	-	1	0.6
G9G12P[6]	-	-	14	7.8
G12P[4]	-	-	1	0.6
G12P[6]	4	4.0	10	5.6
G12P[8]	-	-	3	1.7
Sub total	**99**	**35.5%**	**180**	**64.5%**
Homotypic	39	39.4	50	27.8
Partly homotypic	19	19.2	36	20.0
Heterotopic	41	41.4	94	52.2

Vaccine coverage

To rescale observed Rotarix coverage in the post-licensure surveillance, we assumed that rotavirus dose1 and dose 2 are administered concurrently with Diphtheria, Tetanus, and Pertussis (DTP)1 and DTP-2 and have similar coverage. Using data from post-licensure surveillance sites for 2019-21, we estimated the percentage of test-negative acute gastroenteritis admissions (aged 12-23 months) receiving 2 doses of rotavirus vaccination. We compared this with reported DTP-2 coverage in the 2015 Demographic and Health Survey (DHS) for Herat and Kabul, and the WHO/UNICEF Estimates of National Immunization Coverage (WUENIC) average of DTP-1 and DTP-3 coverages. These coverages were rescaled using the WUENIC 2022 estimates.

To validate our vaccine effectiveness and impact calculations we used the 2015 DHS estimated DTP2 coverage of 77% in Herat and 80% in Kabul, which may be a more reliable proxy for rotavirus 2-dose vaccination coverage, particularly as WHO-UNICEF Estimate of National Immunisation Coverage (WUENIC) estimates of DTP1 and DTP3 coverage indicate relatively stable national vaccination coverage between the year of the survey (2015) and the first year of post-vaccine surveillance (2019).

Table S 4 Rotarix coverage among vaccine age-eligible admitted acute gastroenteritis at the two active surveillance sites in Kabul and Herat, 2019-21

Surveillance sites	**Total Number**	**%**	**Controls**	**%**	**Cases**	**%**
Indira Gandhi Children hospital (6-11 months)	560					
2 doses	410	73.2	200	76.3	210	70.5
1 dose	125	22.3	56	21.4	69	23.1
0 dose	25	4.5	6	2.3	19	6.4
Herat Regional Hospital (6-11 months)	325					
2 doses	265	81.5	202	82.4	63	78.7
1 dose	48	14.8	37	15.1	11	13.7
0 dose	12	3.7	6	2.4	6	7.5
Indira Gandhi Children hospital (12-23 months)	308					
2 doses	243	78.9	126	82. 9	117	75.0
1 dose	48	15.6	21	13.8	27	17.3
0 dose	17	5.5	5	3.3	12	7.7
Herat Regional Hospital (12-23 months)	128					
2 doses	110	85.9	76	90.5	34	77.3
1 dose	13	10.2	6	7.1	7	15.9
0 dose	5	3.9	2	2.4	3	6.8

We also plotted the full series of Rotarix coverage from different sources from the year of introduction through 2022.

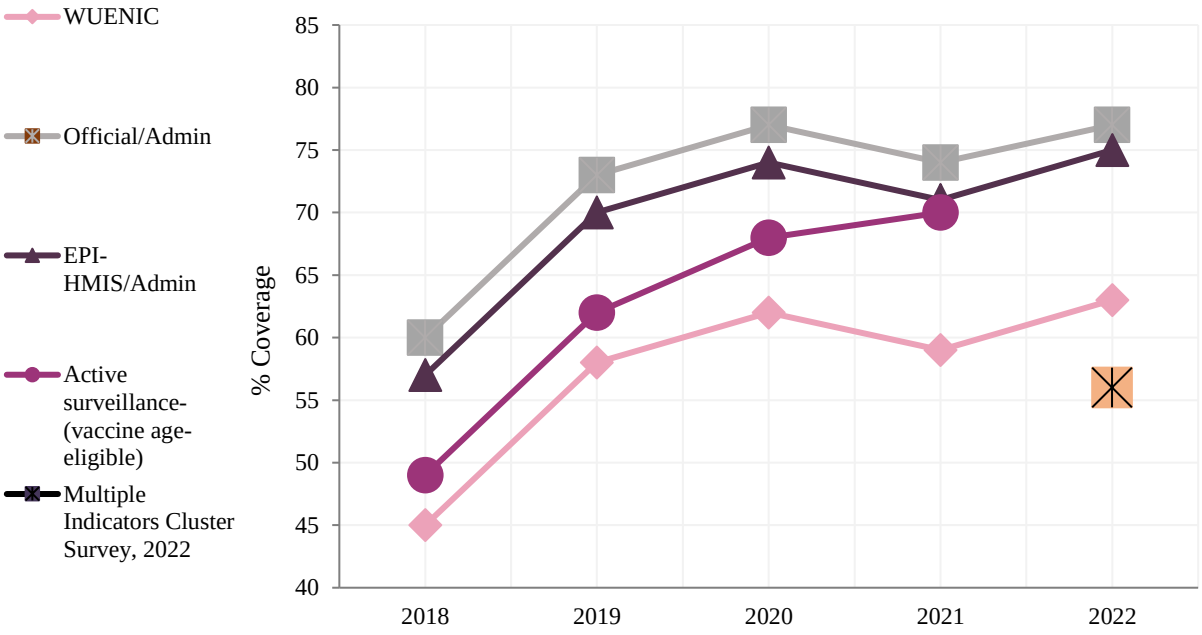

Figure S 1 comparison of complete series of Rotarix doses coverage among children 12-23 months old, 2018-22

Table S 5 Characteristics children enrolled in surveillance pre- and post-rotavirus vaccine introduction (2013-15 and 2019-21)

Variables	**Pre-vaccine surveillance (2013- 2015) (N=2,737)**			**Post-vaccine surveillance (2019- 2021) (N=3,049)**		
	Indira Gandhi Children Hospital (IGCH)	Herat regional hospital (HRH)	Both sites	Indira Gandhi Children Hospital	Herat regional hospital	Both sites
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Enrolled children	1,618 (59.1)	1,119 (40.9)	2737 (100.0)	1894 (62.1)	1155 (37.9)	3049 (100.0)
Year of admission						
2013	536 (33.2)	267 (23.9)	803 (29.3)	NA	NA	NA
2014	457 (28.2)	484 (43.2)	941 (34.4)	NA	NA	NA
2015	625 (38.6)	368 (32.9)	993 (36.3)	NA	NA	NA
2019	NA	NA	NA	626 (33.0)	514 (44.5)	1140 (37.4)
2020	NA	NA	NA	661 (34.9)	316 (27.4)	977 (32.0)
2021	NA	NA	NA	607 (32.1)	325 (28.1)	932 (30.6)
Month of admission						
January	76 (4.7)	54 (4.8)	130 (4.7)	50 (2.6)	106 (9.2)	156 (5.1)
February	130 (8.0)	0 (0)	130 (4.7)	39 (2.1)	87 (7.5)	126 (4.1)
March	99 (6.1)	41 (3.7)	140 (5.1)	71 (3.7)	80 (6.9)	151 (4.9)
April	118 (7.3)	108 (9.7)	226 (8.3)	58 (3.1)	55 (4.8)	113 (3.7)
May	130 (8.0)	356 (31.8)	486 (17.8)	85 (4.5)	93 (8.0)	178 (5.8)
June	230 (14.2)	106 (9.5)	336 (12.3)	222 (11.7)	106 (9.2)	328 (10.8)
July	175 (10.8)	149 (13.3)	324 (11.8)	245 (12.9)	156 (13.5)	401 (13.1)
August	187 (11.6)	59 (5 .3)	246 (9.0)	282 (14.9)	147 (12.7)	429 (14.1)
September	131 (8.1)	34 (3.0)	165 (6.0)	275 (14.5)	103 (8.9)	378 (12.4)
October	154 (9.5)	85 (7.6)	239 (8.7)	217 (11.5)	100 (8.7)	317 (10.4)
November	122 (7.5)	82 (7.3)	204 (7.4)	205 (10.8)	71 (6.1)	276 (9.0)
December	66 (4.1)	45 (40.5)	111 (4.1)	145 (7.7)	51 (4.4)	196 (6.4)
Age group						
0-5 months	342 (21.1)	399 (35.7)	741 (27.1)	478 (25.2)	607 (52.5)	1085 (35.6)
6-11 months	667 (41.2)	492 (44.0)	1159 (42.3)	833 (44.0)	344 (29.8)	1177 (38.6)
12-17 months	323 (20.0)	138 (12.3)	461 (16.8)	373 (19.7)	116 (10.0)	489 (16.0)
18-23 months	131 (8.1)	49 (4.4)	180 (6.6)	99 (5.2)	43 (3.7)	142 (4.7)
24> months	155 (9.6)	41 (3.6)	196 (7.2)	111 (5.9)	45 (3.9)	156 (5.1)
Male %	1021 (63.1)	725 (64.8)	1746 (63.8)	1188(62.7)	705 (61.0)	1893 (62.1)
Vaccine Card Reviewed (%)	NA	NA	NA	1378 (87.1)	1020 (92. 6)	2398 (89.3)
Rotavirus Positive (%)	1018 (62.9)	395 (35.3)	1413 (51.6)	914 (48.4)	275 (23.8)	1189 (39.1)
Outcome (recovered)	1585 (98.0)	379 (33.9)*	1964 (71.8)	1884(99.5)	1134 (98.2)	3018 (99.0)
Vaccine age-eligible**						
Rotarix 0 dose	NA***	NA	NA	77(6.2)	79 (8.4)	156 (7.1)
Rotarix 1 dose	NA	NA	NA	319 (25.6)	248 (26.3)	567 (26.0)
Rotarix 2 doses	NA	NA	NA	848 (68.2)	614 (65.3)	1462 (67.0)
DTP§ 0 dose	NC****	NC	NC	167 (11.8)	171 (15.5)	338 (13.4)
DTP 1dose	NC	NC	NC	251 (17.8)	237 (21.4)	488 (19.4)

DTP 2 doses	NC	NC	NC	231 (16.4)	192 (17.4)	423 (16.81)
DTP 3 doses	NC	NC	NC	262 (54.0)	506 (45.7)	1268 (50.4)
Pneumococcal 0 dose	NC	NC	NC	172 (12.2)	173 (15.7)	345 (13.7)
Pneumococcal 1 dose	NC	NC	NC	254 (18.0)	238 (21.5)	492 (19.5)
Pneumococcal 2 doses	NC	NC	NC	235 (16.6)	197 (17.8)	432 (17.2)
Pneumococcal 3 doses	NC	NC	NC	750 (53.2)	498 (45.0)	1248 (49.6)
Poliovirus birth dose	NC	NC	NC	1187 (84.1)	958 (86.6)	2145 (85.2)
Poliovirus 0 dose	NC	NC	NC	168 (11.9)	165 (15.0)	333 (12.2)
Poliovirus 1 dose	NC	NC	NC	250 (17.7)	238 (21.5)	488 (19.4)
Poliovirus 2 doses	NC	NC	NC	227 (16.1)	195 (17.6)	422 (16.8)
Poliovirus 3 doses	NC	NC	NC	766 (54.3)	508 (46.0)	1274 (50.6)
Measles	NC	NC	NC	370 (26.2)	177 (16.0)	547 (21.7)

*****in the HRH site, outcome for 399 (35.7%) of children was unknown- the child left the hospital without medical advice, and for another 341 children was missing.

****** Vaccine coverage is reported among rotavirus vaccine eligible children.

§ Diphtheria, Tetanus, and Pertussis

***NA-not applicable

***** NC- not collected

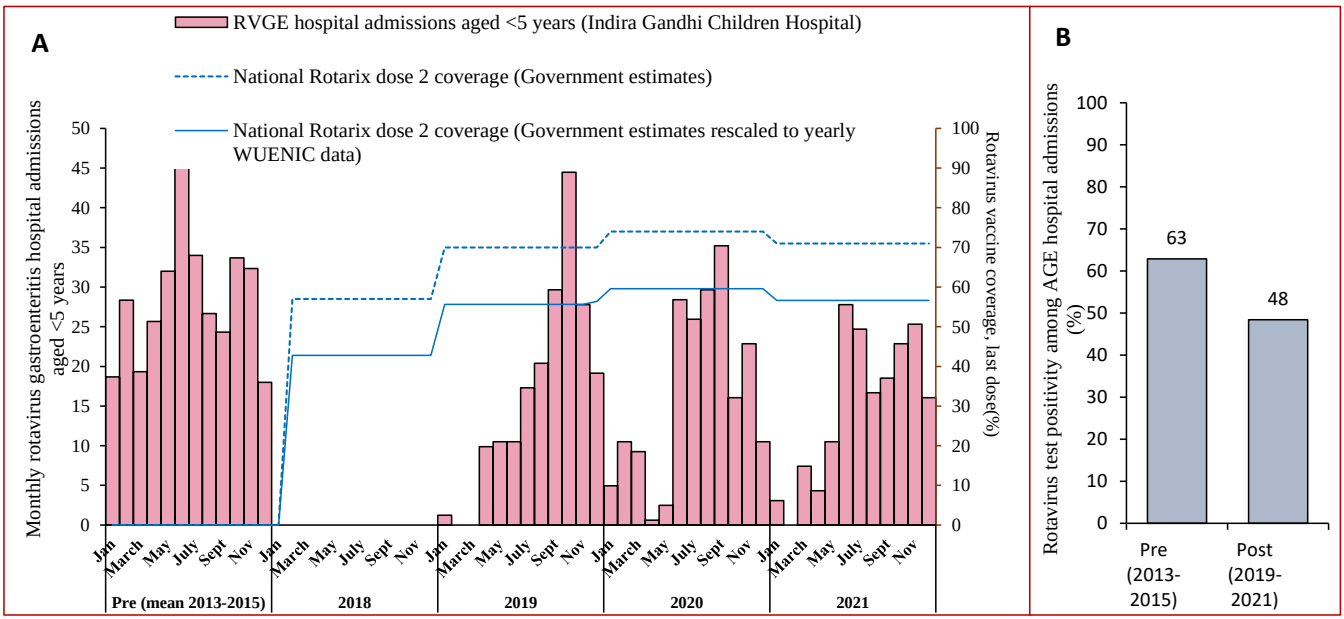

Figure S 2 Number (A) and proportion (B) of children admitted to Indira Gandhi Children Hospital with rotavirus-positive tests, compared post-vaccine data with median of pre-vaccine data and with the rotavirus vaccine coverage, 2013-21

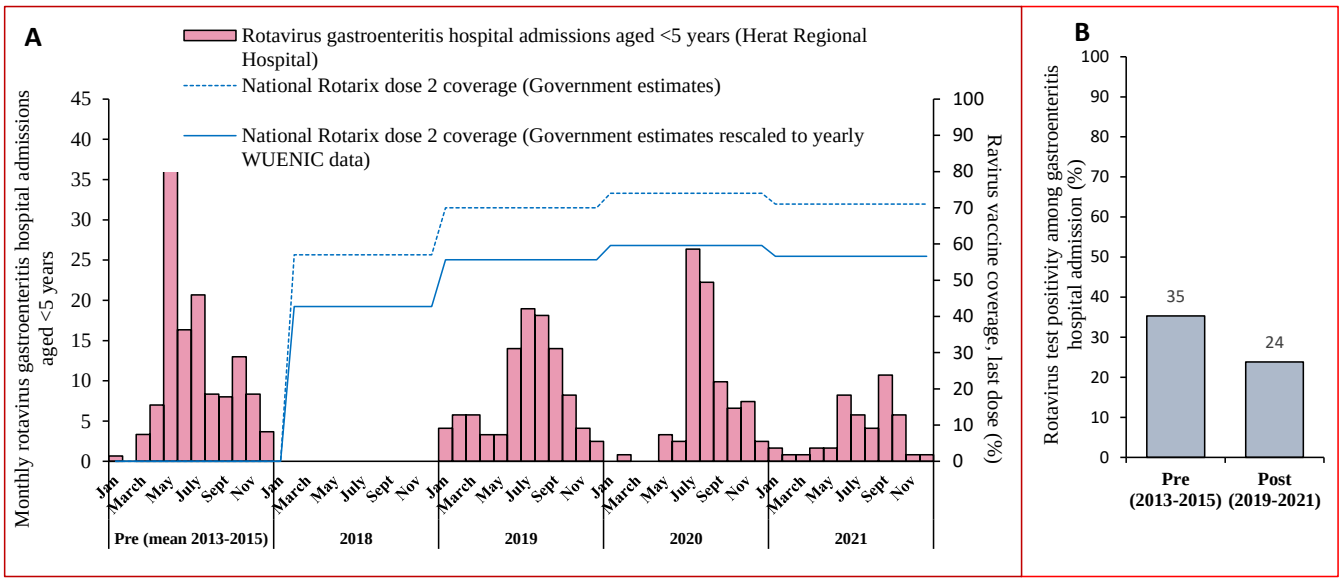

Figure S 3 Number (A) and proportion (B) of children admitted to Herat Regional Hospital with rotavirus-positive tests, compared post-vaccine data with median of pre-vaccine data and with the rotavirus vaccine coverage, 2013-21

CHAPTER FOUR: PAPER TWO

Chapter 4: Post-marketing surveillance of intussusception after ROTARIX administration in Afghanistan, 2018-2022

4.1 Preamble to Research Paper 2

The paper presented in this chapter is an analysis of post-marketing safety of ROTARIX, a monovalent rotavirus vaccine, under routine health service conditions in Afghanistan. It addresses study objective 4 under aim 2 of the thesis:

Objective 4: A self-controlled case-series analysis study design is used to assess monovalent rotavirus vaccine safety within specified risk windows following each vaccine dose.

This chapter contributes to the main chapter (Chapter 5) through providing figures on intussusception age distribution, admission rate, mortality rate and incidence ratio during specific risk windows (1-7 and 8-21 days) following each vaccine dose.

4.1.1 Data Sources

The data utilized in this paper were collected from post-marketing surveillance at four major hospitals in Afghanistan between May 2018 and March 2022.

As the lead investigator for the country, I took responsibility for establishing surveillance sites, overseeing data collection, processing, and conducting periodic analyses. The post-marketing surveillance for intussusception was part of the South Asia Intussusception Network, which included Afghanistan, Pakistan and Myanmar. I presented Afghanistan's progress at three Network meetings between 2019 and 2022.

4.1.2 Independent academic contribution

As part of my research degree programme, I completed data cleaning, processed and conducted data analysis, drafted the initial manuscript, and coordinated the finalization of the manuscript with contributors. I also managed the submission to a peer-reviewed journal and addressed feedback from reviewers and the journal.

This research was a collaborative effort involving the United States Centers for Disease Control and Prevention (CDC), the Ministry of Public Health in Afghanistan, the World Health Organization Afghanistan Country Office, and a research firm managing post-surveillance activities. In addition

to being the first author of this manuscript, I contributed to a joint paper by the Network in 2023, which is cited in the references.

4.1.3 Ethical approval

This evaluation received approval from the Institutional Review Board (ID: 444509, April 14, 2018) of the Ministry of Public Health, Afghanistan. The investigation was reviewed by the Human Research Protections Office at the CDC and was conducted in accordance with applicable federal laws and CDC policy. The work also obtained ethics approval from LSHTM under the collective thesis protocol. The ethics approval letters issued for this manuscript are appended to this thesis **(Annexes 4-1 and 4-2).**

4.1.4 Word counts

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London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	2005091	**Title**	Dr
First Name(s)	Palwasha		
Surname/Family Name	Anwari		
Thesis Title	Benefit-risk and cost-utility of rotavirus vaccination in Afghanistan: a modelling study informed by post-marketing surveillance data		
Primary Supervisor	Dr Andrew Clark		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Vaccine		
When was the work published?	19 March 2024		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	

Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I carried out data processing on post-marketing surveillance data, developed data analysis plan, produced tables and graphs, and wrote the first draft of manuscript. I compiled inputs and revised the manuscript based on the co-authors' feedback. Next, I submitted it to a peer-reviewed journal, crafted responses to the journal reviewers, and addressed editorial requirements.

SECTION E

Student Signature	Palwasha Anwari [redacted]
Date	June 25, 2024

Supervisor Signature	
Date	

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Post-marketing surveillance of intussusception after Rotarix administration in Afghanistan, 2018–2022

Palwasha Anwari [a,*], Eleanor Burnett [b], Tyler P. Chavers [b], Akmal Samsor [c], Helah Safi [c], Najibullah Safi [c], Andrew D Clark [a], Umesh D. Parashar [b], Jacqueline E. Tate [b]

[a] London School of Hygiene and Tropical Medicine, London, United Kingdom
[b] Division of Viral Diseases, NCIRD, CDC, Atlanta, United States of America
[c] JS Consultancy, Kabul, Afghanistan

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ABSTRACT

Background: In January 2018, Afghanistan introduced the monovalent oral rotavirus vaccine (Rotarix) nationwide, administered as a 2-dose series at six and ten weeks of age. We describe characteristics of intussusception cases and assess potential intussusception risk associated with Rotarix vaccination in Afghan infants.
Methods: Multi-center prospective active hospital-based surveillance for intussusception was conducted from May 2018 to March 2022 in four sentinel sites in Afghanistan. We applied the Brighton Level 1 criteria for intussusception and verified vaccination status by reviewing vaccine cards. We used the self-controlled case series (SCCS) methodology to compare intussusception incidence in the 1 to 21 days after each dose of Rotarix vaccination against non-risk periods.
Results: A total of 468 intussusception cases were identified in infants under 12 months, with 264 cases aged between 28 and 245 days having confirmed vaccination status contributing to the SCCS analysis. Most case-patients (98 %) required surgery for treatment, and over half (59 %) of those who underwent surgery required intestinal resection. Nineteen (7 %) case-patients died. Eighty-six percent of case-patients received the first dose of Rotarix, and 69 % received the second dose before intussusception symptom onset. There was no increased risk of intussusception in the 1–7 days (relative incidence: 0.9, 95 % CI: 0.1, 7.5), 8–21 days (1.3, 95 % CI: 0.4, 4.2), or 1–21 days (1.1, 95 % CI: 0.4, 3.4) following receipt of the first dose or in the 1–7 days (0.2, 95 % CI: 0.3, 1.8), 8–21 days (0.7, 95 % CI: 0.3, 1.5), or 1–21 days (0.6, 95 % CI: 0.3, 1.2) following the second dose.
Conclusion: Rotarix vaccination was not associated with an increased intussusception risk, supporting its continued use in Afghanistan's immunization program. However, there was a high level of death and resection due to intussusception among Afghan infants.

1. Introduction

In 2009, the World Health Organization (WHO) recommended that all countries introduce rotavirus vaccines, and to date, they have been introduced in over 115 countries nationally or sub-nationally, resulting in a substantial reduction in morbidity and mortality from rotavirus acute gastroenteritis among children under 5 years. [1,2] This achievement, however, was not without challenges. RotaShield, a first-generation rotavirus vaccine based on a rhesus tetravalent rotavirus strain, was licensed for use in the United States in 1998 but was swiftly recalled in 1999 due to an increased risk of intussusception (>30 times above the baseline rate during the 3–7 days after the first dose). [3–5] Intussusception, characterized by the infolding of a bowel segment, is the leading cause of blockage of the intestine in infants and young children. While rare, it is treatable but requires urgent medical intervention, typically through surgical intervention or enema reduction. [6] Left untreated, it can be fatal. [1,6,7].

The second generation of live-attenuated oral rotavirus vaccines, including Rotarix™, RotaTeq™, RotaVac™, and RotaSiil™, have been pre-qualified by the WHO for global use. [7–9] WHO recommends monitoring of intussusception risk when introducing rotavirus vaccines into new populations. Numerous post-licensure evaluations of Rotarix in seven sub-Saharan African countries, RotaTeq in South Africa and five other African countries, and RotaVac in India have shown no significant

* Corresponding author.
E-mail address: palwasha.anwari@lshtm.ac.uk (P. Anwari).

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increased risk of intussusception following rotavirus vaccination. [10–13] However, the risk of intussusception associated with the rotavirus vaccine varies by setting as a small risk has been identified in some high- and middle-income countries. [14–17] A systematic review and *meta*-analysis of 25 randomized clinical trials have reported a relative incidence of intussusception between 0.3 and 5.0, while observational studies reported a short-term increased risk of intussusception of 1.1 to 4.3 excess cases per 100,000 vaccinated infants observed within 1–7 days following the first rotavirus vaccine dose. [18,19].

An added layer of complexity stems from the natural increase in the incidence of intussusception in infants that occurs around the same age as the vaccine's administration, 2–6 months of age. [20] This overlap underscores the importance of a robust safety monitoring system. Passive vaccine safety reports, while invaluable, have their limitations and determining any excess risk following rotavirus vaccination requires a comprehensive reporting system. A pre- and post-vaccine introduction comparison is not recommended because intussusception is rare and susceptible to changes in quality and diligence of surveillance. [21].

In January 2018, the Afghanistan Ministry of Public Health (MoPH) introduced the monovalent oral rotavirus vaccine (Rotarix) nationally, as a 2-dose series administered at six and ten weeks of age. Afghanistan was a member of the Asian Intussusception Surveillance Network from May 2018 through March 2022. The details on the network are published elsewhere [22]. The pooled analysis of the network reported no increased risk of intussusception with rotavirus vaccine doses in three South Asian countries including Afghanistan. [22].

In this study, we aim to have a more in-depth look at the data from Afghanistan, assess the potential risk of intussusception associated with the first and second doses of Rotarix vaccine in Afghan infants, and provide a comprehensive view of its safety profile in the country's unique context.

2. Methods

2.1. Study setting

We conducted multi-centric prospective active hospital-based surveillance for intussusception from May 2018 to March 2022 in four sentinel sites. Indira Gandhi Children Hospital (IGCH) and Ataturk Children Hospital (ATCH) are specialty children's hospitals in Kabul province, with a catchment population of over 5 million. Nangarhar Hospital (NRH) and Herat Hospital (HRH) are regional hospitals with a catchment population of over three million. Together, the surveillance sites' catchment populations represent around 25 % of the total population of Afghanistan. [23] The study adopted the WHO generic protocol for monitoring intussusception risk after rotavirus vaccination. [21] We applied predefined inclusion criteria across all four sites. Cases were included if they were < 12 months old (i.e. admitted before the child's first birthday) and met the Level 1 Brighton Collaboration criteria for intussusception. Level 1 represents a high level of diagnostic certainty, requiring confirmation during surgical or radiological enema reduction, or autopsy verification of the intussusception. [24,25] Children admitted to the surveillance sites who were older than 12 months or did not meet Level 1 Brighton criteria were excluded from our surveillance. Besides verifying vaccination status by reviewing immunization cards, we collected demographic and clinical features and disease outcomes through a standardized questionnaire. To comply with the assumptions of the self-controlled case series (SCCS) methodology, children who were < 8 months of age at the time of hospital admission were followed-up at 8 months of age to determine vital status of the child, whether additional doses of rotavirus vaccine had been administered, and if intussusception had reoccurred. Cases were enrolled on a continuous basis and independent of their vaccination status. Informed consent was obtained from the child's caregiver/guardian. The study obtained ethics approval from the Afghanistan Institutional Review Board (IRB) (ID 444509-April 2018) which categorized it as routine disease surveillance activity and non-research activity. This investigation was also reviewed by the US CDC's Human Research Protection Office and conducted consistent with applicable federal law and CDC policy.

2.2. Study design

We used the SCCS methodology, an epidemiological study design in which case-patients serve as their own controls to calculate the risk of intussusception in different fixed time intervals. [26] This involved comparing the intussusception incidence of individual infant cases during the risk period against the incidence during non-risk periods, defined as the period before and > 21 days after each dose of Rotarix. Case-patients aged 1–8 months whose vaccination status was verified were included in the SCCS analysis. A sample of 224 cases would provide an 80 % power to detect a 2.5 relative incidence of intussusception within 7 days receiving any the two doses of Rotarix at a 5 % level of significance during observation period of 28–245 days.

2.3. Statistical analysis

We described the overall enrolled population by hospital site and described the population that met the inclusion criteria for the SCCS analysis. We used numbers and proportions to describe categorical variables and medians with interquartile range (IQR) to describe continuous variables.

We employed the pseudolikelihood method of SCCS analysis to account for the multiple doses of vaccine included in the primary series. [27,28] Using information from published studies to identify the period of peak replication of the vaccine virus in the child's gut, we calculated the relative incidence of intussusception in three periods following each Rotarix dose administration: 1–7 days, 8–21 days and 1–21 days, considering the vaccination day as day zero. [28] The observation period was between day 28 and day 245 (1–8 months) of life. In our evaluation, we included both vaccinated and unvaccinated individuals to capture a comprehensive picture of intussusception occurrences within the population. By doing so, we were able to account for the natural occurrence (background rate) of intussusception, irrespective of vaccination as intussusception incidence varies based on age. To accurately understand this variation, age was controlled for using two-week intervals. It allowed us to better understand when and at what age intussusception cases were most likely to occur.

We computed dose-specific relative incidence (RI) values for intussusception using conditional Poisson regression. The confidence intervals were calculated by bootstrapping with 1000 iterations. Data analyses were conducted using SAS^{R} 9.4 (SAS institute Inc.) and SCCS package in R 3.5.1 (R Foundation for Statistical Computing). [26].

3. Results

We identified 468 intussusception cases in infants aged < 12 months admitted to the four surveillance sites from May 2018 to March 2022, and of whom, 264 were included in the SCCS analysis (Fig. 1).

A description of the complete population is shown in Table 1. When comparing between sites, Ataturk Children's Hospital in Kabul was noticeably different than the other three sites; it had a higher proportion of children transferred from another facility (89 %), a higher proportion of children with card confirmation of their vaccination status (91 %), a higher proportion of children living in a household with at least 1 employed person (99 %), and lower mortality than 2 of the other 3 sites (6 %). Herat Regional Hospital had the highest proportion of children who died during their hospitalization (15 %). Other factors, including male sex (64 %), median transfer time to the facility (1 day; IQR 1–2), and household having a mobile phone (96 %), were similar among all sites.

Table 2 outlines the characteristics of children included in the SCCS analysis and offers a comparison between age-eligible children with and

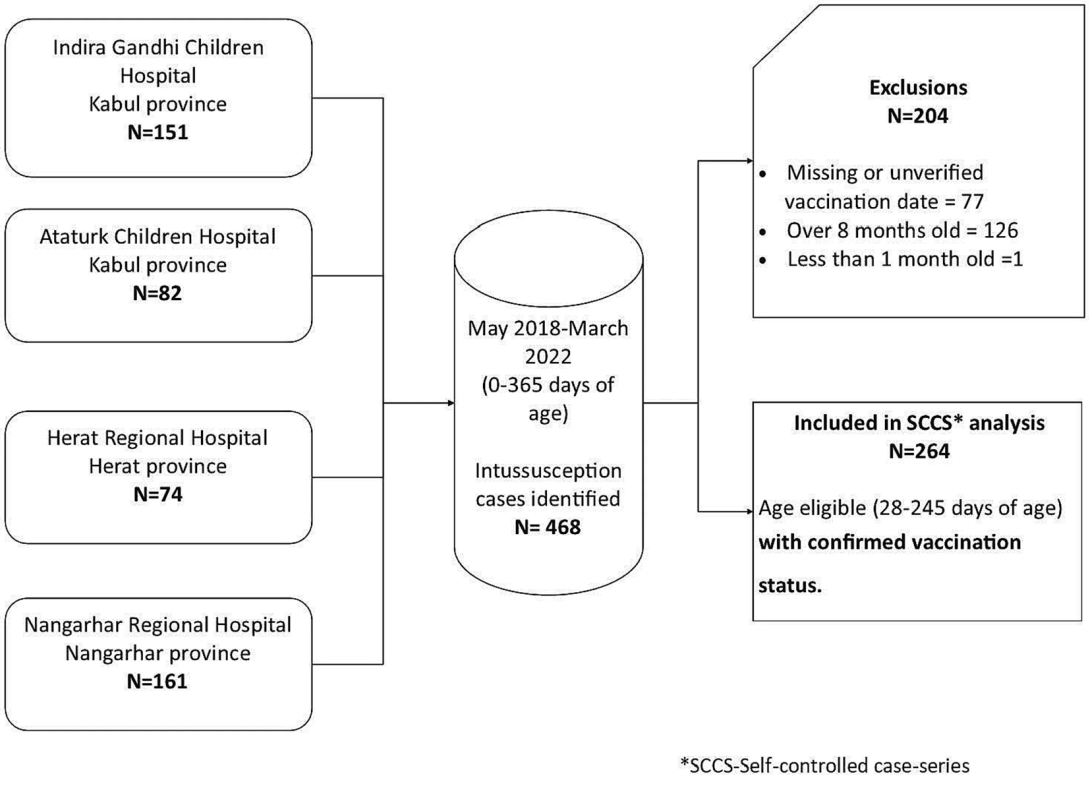

Fig. 1. Self-controlled case-series (SCCS) evaluation recruitment flow diagram, May 2018-March 2022, Afghanistan. Case-enrollment of intussusception admitted infants in four active sentinel sites between May 2028-June 2022. Of 468 admitted cases, 264 were included in the final Self-Controlled Case-Series analysis.

Table 1
Characteristics of multisite prospective intussusception surveillance, May 2018–Mar 2022, Afghanistan.

Variables	**All sites** n = 468 (100 %)	**Ataturk Children Hospital** n = 82 (17.5 %)	**Herat Regional Hospital** n = 74 (15.8 %)	**Indira Gandhi Children Hospital** n = 151 (32.3 %)	**Nangarhar Regional Hospital** n = 161 (34.4 %)
City, Province		Kabul, Kabul	Herat, Herat	Kabul, Kabul	Jalalabad, Nangarhar
Sex (Male)	299 (63.9)	55 (67.1)	43 (58.1)	90 (59.6)	111 (68.9)
Case age in week (Median, IQR)	29 (21, 38)	32 (24, 39)	27 (20, 32)	29 (21, 37)	30 (21, 38)
Child transferred from another health facility	211 (43.4)	73 (89.0)	23 (31.1)	56 (37.1)	59 (36.6)
Transfer time (Median, IQR)	1 (1, 2)	1 (1,2)	1 (1, 3)	1 (0, 2)	1 (0,2)
Outcome (Died)	39 (8.3)	5 (6.1)	11 (14.9)	14 (9.3)	9 (6.0)
Confirmed source of vaccination	385 (82.3)	75 (91.5)	54 (73.0)	119 (78.8)	137 (85.1)
Socioeconomic					
No. of People the household	8 (6, 13)	6 (5, 9)	7 (6,10)	8 (6,11)	12 (8,18)
Employment	190 (40.6)	81 (98.8)	9 (12.2)	49 (32.5)	51 (31.7)
Electricity	133 (28.4)	51 (62.2)	39 (52.7)	24 (15.9)	19 (11.8)
Mobile phone	450 (96.1)	79 (96.3)	66 (89.2)	147 (97.3)	158 (98.1)

without verified vaccination status. All children with unverified vaccination status (n = 77) underwent surgical treatment, with an intussusception fatality rate of 22 %. In terms of socioeconomic status, age-eligible children with unverified vaccination status exhibited lower levels of parental employment and were less likely to live in a household with access to television.

Median age of SCCS eligible cases at time of admission was 5 months (IQR: 4–6). Almost all cases (n = 259; 98 %) were managed surgically, and intestinal resection was performed in over half of the cases requiring surgery (n = 154; 59 %). Half of the cases (n = 133) were transferred from another health facility to one of the sentinel hospitals with a median transfer time of a day (IQR: 1–2 and range: 0–13). The hospital stay duration had a median of five days (IQR: 4–7). The intussusception case fatality rate was 7 % (n = 19). (Table 2).

In total, before the onset of intussusception symptoms, 211 (80 %) case patients received the first dose of Rotarix and 171 (65 %) received the second dose. The median time between birth and receipt of rotavirus dose 1 and 2 was 52 days (IQR:45, 64) and 94 days (IQR: 81, 112), respectively. The median number of days between rotavirus vaccination and onset of intussusception symptoms was 121 days (IQR: 88, 153) for dose 1 and 84 days (IQR: 51, 116) for dose 2. (Figs. 2 and 3).

Within the initial 1 to 7 days after the first dose, only one child began experiencing intussusception symptoms, with a relative incidence of 0.94 (95 %CI: 0.1, 7.5). In the 8 to 21 days post the first dose, symptoms arose in 4 additional children, resulting in a relative incidence of 1.3 (95 %CI: 0.4, 4.2). In the first three weeks following the first dose, the relative incidence of intussusception was 1.1 (95 %CI: 0.4, 3.4). (Table 3).

In the initial 1 to 7 days after the second dose, only one child had onset of intussusception symptoms, with a relative incidence of 0.2 (95 %CI: 0.3, 1.8). Eight children began to experience symptoms in the 8 to 21 days following the second dose, with a relative incidence of 0.7 (95 %

Table 2
Characteristics of intussusception cases included in the self-controlled case-series analysis, May 2018-March 2022, Afghanistan.

Variables	Characteristics	Age eligible for SCCS	
		With verified vaccination status **included in SCCS analysis N = 264**	With unverified vaccination status **Excluded from SCCS analysis N = 77**
Sex	Male	158 (59.9)	52 (67.5)
Age	Age in months (Median, IQR)	5 (4, 6)	6 (4, 8)
Intussusception management	Surgery	259 (98.1)	77 (100)
	Enema air or liquid contrast	5 (1.9)	0
	Intestinal resection among those treated with surgery	154 (59.5)	43 (55.8)
Outcome/ Disposition	Discharged home	236 (89.4)	59 (76.6)
	Transferred	3 (1.1)	1 (1.3)
	Died	19 (7.2)	17 (22.1)
	Abandoned	6 (2.3)	0 (0)
Referred from another facility		133 (50.4)	29 (37.7)
Transfer interval	Days (median, IQR) Days (range)	1 (1, 2) 0–13	1 (0, 2) 0–6
Length of stay in the hospital	Days (Median, IQR)	5 (4, 7)	5 (3, 7)
Vaccination history before onset IS symptoms			
Rotarix	Dose 1	211 (79.9)	NA*
	Dose 2	171 (64.8)	NA
Oral polio vaccine	Birth dose	206 (78.0)	NA
	Dose 1	230 (87.1)	NA
	Dose 2	194 (73.5)	NA
	Dose 3	126 (47.7)	NA
Intervals	**(Median, IQR) in days**		
Date of birth to vaccination	RV dose 1	52 (45, 64)	NA
	RV dose 2	94 (81, 112)	NA
With the precedent dose	RV dose 2 and dose 1	37 (32, 51)	NA
Vaccine doses to IS symptom onset	RV dose 1	121 (88.5, 153.5)	NA
	RV dose2	84 (51,116)	NA
Socioeconomic			
No. of people in the household	Median (IQR)	4 (3, 6)	4 (3, 5)
Employment	At least one parent was employed	123 (46.6)	11 (14.3)
Electricity	Yes, but usually just for some hours of the day	143 (54.2)	40 (51.9)
Mobile phone	Number (%)	258 (97.7)	68 (88.3)
Radio	Number (%)	123 (46.6)	32 (41.6)
Television	Number (%)	141 (53.4)	18 (23.4)

*Not available (NA): vaccination history was not available for children with unverified vaccination status.

CI: 0.3, 1.5). Within the first 21 days post the second dose, 9 children exhibited intussusception symptoms resulting in a relative incidence of 0.6 (95 %CI: 0.3, 1.2). (Table 3).

4. Discussion

This evaluation did not detect any significant association between intussusception and receipt of the first and second doses of monovalent rotavirus vaccine in Afghan infants. Only one case of intussusception was identified during the first 7 days after first dose of vaccine and another 4 cases identified during the 8 to 21 days after the first dose. Similarly, 1 and 8 cases occurred in the first 7 days and 8 to 21 days following the second dose, respectively. The risk of intussusception in the 1 to 7 days and 8 to 21 days after each dose of vaccine was similar to the risk of intussusception in all other risk periods after controlling for age. The Afghanistan post-marketing intussusception surveillance was part of a regional intussusception network and contributed to the pooled results of all countries participating countries in the network. Our evaluation results reflect the pooled results of Asian Intussusception Surveillance Network which showed that Rotarix did not increase the risk of intussusception in the 1 to 7 days following dose 1 with an incidence risk of 1.0 (95 %CI: 0.4, 2.6). Our findings also agree with the results that found no association between intussusception and Rotarix reported in a pooled analysis in seven sub–Saharan Africa countries and an analysis in South Africa.

The surveillance of intussusception among Afghan infants also highlighted significant variations in the outcomes of treatment, vaccine card verification, and socioeconomic status both within and among provinces. Ataturk Children Hospital, located in the eastern part of Kabul city, reported a higher number of referred cases with a lower fatality rate compared to other sites. The socioeconomic indicators, including access to job employment, home electricity, and smaller family size at this hospital, were markedly different compared to other sites within Kabul and elsewhere. This underscores the broader issue of inequality in access to essential services, which is crucial to address for improving overall health outcomes. A notable contrast emerged between children who received vaccinations and those who had unverified vaccination status, revealing disparities in both health outcomes and socioeconomic status. Notably, children with unverified vaccination status had much higher mortality and reported reduced access to parental job opportunities and had limited access to television, which is a medium for disseminating health information to families. These findings underscore the potential impact of routine health services, emphasizing the importance of vaccination services in fostering improved health and well-being among children.

The strength of this evaluation is that it was multicentric and was conducted for four years following vaccine introduction. Throughout the study, several quality control measures were implemented. Quality control officers conducted frequent, monthly visits to the study sites and cross-checked the enrolled cases with the hospital registry to ensure that case-patients were not missed. Similarly, cases-patient forms were routinely checked for completeness and vaccination cards were consulted for inconsistent vaccination dates. The evaluation happened during the COVID-19 pandemic and political change in the country in mid-August 2021 which subsequently impacted health service delivery. Because intussusception requires immediate surgical attention, there was no interruption in surveillance. The study sites represent three of five regions in the country and one-fourth of total population of the country. Furthermore, we evaluated three distinct lengths of the risk windows following each vaccine dose, 1–7 days, 8–21 days and 1–21 days, enhancing the robustness of our findings.

Our evaluation is subject to certain limitations. We focused on only government-run hospitals. Pediatric surgery accessibility across the entire country is constrained, requiring parents to undertake long journeys to reach specialized pediatric centers. It is conceivable that some cases of intussusception were not captured due to the child being treated in a private health facility or to fatalities occurring before reaching the hospital. It is important to note the coincidental timing of our surveillance with the COVID-19 pandemic. A potential association of SARS-CoV-2 and bowel inflammation with a subsequent intussusception [29] has been reported; we lacked information on SARS-CoV-2 positivity among cases. We do not think either would have introduced systematic bias using the SCCS method.

This evaluation provides further evidence in support of rotavirus vaccine safety in a high burden child mortality setting. Our findings provide robust evidence in favor of continuing the administration of the Rotarix vaccine to children. Moreover, our results are consistent with observations from other studies in various low-income countries, suggesting a broader consensus on the vaccine's safety in these settings.

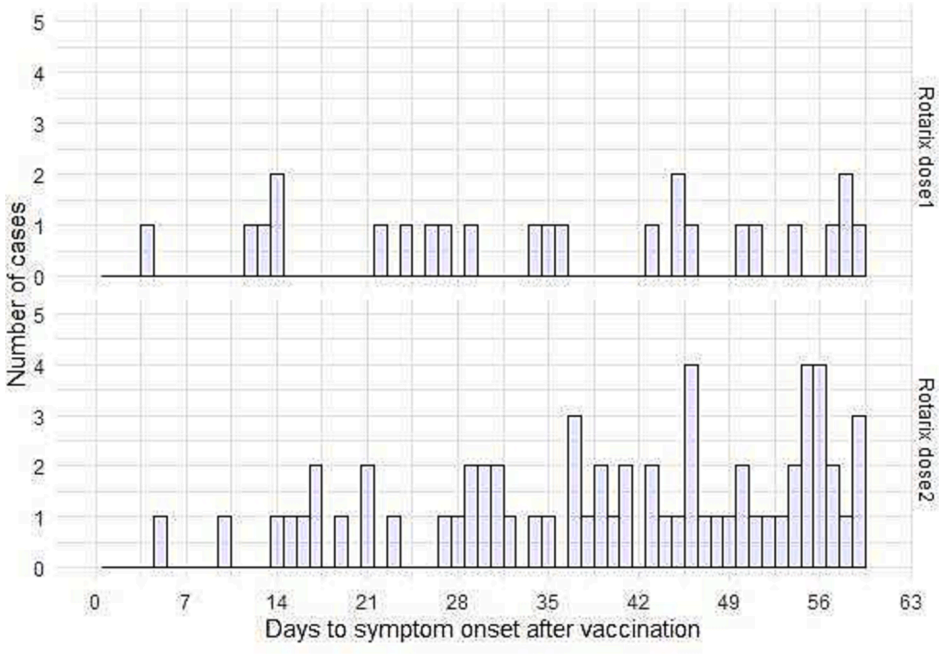

Fig. 2. Onset of intussusception after Rotarix dose 1 and 2, May 2018-March 2022, Afghanistan. Shown are the distribution of cases of intussusception cased during the 60 days after the second doses of Rotarix. An additional 192 cases occurred more than 60 days after dose 1 and an additional 116 cases occurred more than 60 days after dose 2.

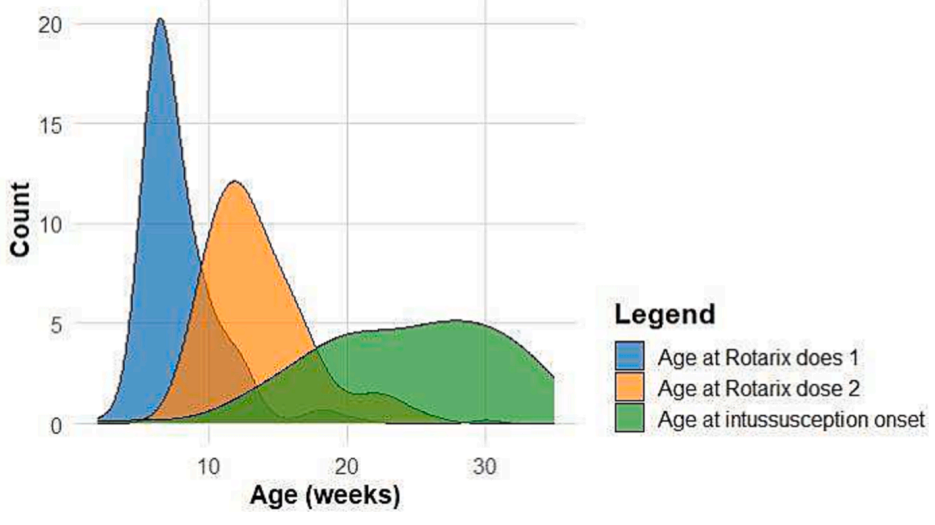

Fig. 3. Age in weeks of first and second doses of rotavirus vaccine administration and symptom onset among intussusception cases in self-controlled case series analysis, May 2018-March 2022, Afghanistan. Infants aged 28–245 days with verified vaccination status.

Table 3
Relative incidence of intussusception in the 1–7, 8–21 and 1–21 days following the first and second doses of Rotarix in Afghanistan, May 2018 through March 2022.

Dose and risk window	No. of cases	Relative incidence (95 %CI) (28–245 days observation period)
Dose 1		
1–7 days	1	0.9 (0.1, 7.5)
8–21 days	4	1.3 (0.4, 4.2)
1–21 days	5	1.1 (0.4, 3.4)
Dose 2		
1–7 days	1	0.2 (0.3, 1.8)
8–21 days	8	0.7 (0.3, 1.5)
1–21 days	9	0.6 (0.3, 1.2)

Funding source

Gavi, the global alliance.

Disclaimer

The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the United States Centers for Disease Control and Prevention.

CRediT authorship contribution statement

Palwasha Anwari: Writing – review & editing, Writing – original draft, Visualization, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Eleanor Burnett:** Writing – review &

editing, Validation, Methodology, Funding acquisition, Data curation, Conceptualization. **Tyler P. Chavers:** Writing – review & editing, Data curation, Conceptualization. **Akmal Samsor:** Writing – review & editing, Project administration, Funding acquisition, Data curation, Conceptualization. **Helah Safi:** Writing – review & editing, Project administration, Investigation, Data curation. **Najibullah Safi:** Writing – review & editing, Resources, Methodology, Conceptualization. **Andrew D Clark:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Umesh D. Parashar:** Writing – review & editing, Validation, Methodology, Conceptualization. **Jacqueline E. Tate:** Writing – review & editing, Validation, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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CHAPTER FIVE: PAPER THREE

Chapter 5: Cost-effectiveness and benefit-risk of rotavirus vaccination in Afghanistan: a modelling analysis informed by post-licensure surveillance

5.1 Preamble to Paper 5

In this paper, I utilized the main findings of Chapters 3 and 4 to populate a mathematical model, UNIVAC, to analyse the cost-effectiveness and benefit-risk of rotavirus vaccination in Afghanistan.

This analysis addresses study objective 5-7 under aim 3 of the thesis.

Objective 5: Examine the cost-utility of oral monovalent rotavirus vaccine retrospectively using real-world data (2018-2024).

Objective 6: Conduct both retrospective and prospective evaluation of the benefit-risk of monovalent rotavirus vaccination.

Objective 7: Compare the cost-utility of different oral rotavirus vaccine products prospectively (2025-2035).

5.1.1 Data Sources

The data utilized in this paper were collected from post-marketing surveillance at five major hospitals in Afghanistan between May 2018 and March 2022.

5.1.2 Independent academic contribution

As the first author of this paper, I collected input data for the UNIVAC model used in this study, validated the model by consulting e national experts in individual and group sessions. I ran cost-utility and benefit-risk analyses, constructed the tables and figures, and wrote the first draft of the paper. I compiled feedback from co-authors, finalized the paper, and submitted it to the journal for publication.

I also presented the study findings to the Afghan immunization programme and experts through a virtual workshop.

5.1.3 Word counts

Abstract: 373 words
Manuscript: 4045 words without tables and references

Number of tables: 4
Number of figures: 2
Number of references: 46

5.1.4 Published journal:

The manuscript is submitted to BMC Health Services Research Journal. It will be published as an open access article under the CC BY license (http://creativecommos.org/licenses/by/4.0/)

5.1.5 Citations

Anwari P, Debellut F, Parwiz S, Penecka C, Clark A, Cost-effectiveness and benefit-risk of rotavirus vaccination in Afghanistan: a modelling analysis informed by post-licensure surveillance (**submitted paper/under review**).

5.2 Research paper 3: Cost-effectiveness and benefit-risk of rotavirus vaccination in Afghanistan: a modelling analysis informed by post-licensure surveillance

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

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Student ID Number	2005091	**Title**	Dr
First Name(s)	Palwasha		
Surname/Family Name	Anwari		
Thesis Title	Benefit-risk and cost-utility of rotavirus vaccination in Afghanistan: a modelling study informed by post-marketing surveillance data		
Primary Supervisor	Andrew Clark		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
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Where is the work intended to be published?	BMC Health Services Research
Please list the paper's authors in the intended authorship order:	Palwasha Anwari, Fredric Debellut, Sardar Parwiz, Clint Pecenka, Andrew Clark

Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I searched for and collected epidemiological and economic input data for the study model parameters. I developed a data analysis plan, produced tables and graphs, and wrote the first draft of the manuscript. Additionally, I conducted a comprehensive literature review to ensure the accuracy of the model inputs, which I validated with national experts and through consultation sessions. I compiled the inputs and revised the manuscript based on co-authors' feedback. Next, I will submit it to a peer-reviewed journal and address the reviewers' and editorial comments

SECTION E

Student Signature	[redacted]
Date	25 August 2024

Supervisor Signature	
Date	

Benefit-risk and cost-effectiveness of rotavirus vaccination in Afghanistan: a modelling analysis informed by post-licensure surveillance

Authors

Palwasha Anwari a*

Frédéric Debellut b

Sardar Parwiz c

Clint Pecenka d

Andrew Clark a

Affiliations

a London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, England, UK

b PATH, Rue De Varembe 7, 1202 Geneva, Switzerland

C EMPHNET, Abdullah Ben Abbas St 42, Amman, Jorden

d PATH, 2201 Westlake Ave, Suite 200, Seattle, WA 98121, USA

Corresponding author: Palwasha Anwari, palwasha.anwari@lshtm.ac.uk, +1 613 293 8072

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Abstract

Introduction

Afghanistan added ROTARIX to the routine national immunization programme in 2018. We aimed to estimate the cost-effectiveness and benefit-risk of ROTARIX and compare its continued use with alternative rotavirus vaccines that could be used in the future.

Methods

We used a static cohort model with a finely disaggregated age structure (weeks of age <5 years) to assess the use of ROTARIX (1-dose vial) over a seven-year period (2018-2024) in Afghanistan. The primary outcome measure was the discounted cost (2022 US$) per Disability Adjusted Life Year (DALY) averted (from government and societal perspectives) compared to no vaccination. We also calculated the benefit-risk ratio i.e., the number of RVGE deaths prevented per one excess intussusception death. Model inputs were informed by pre- and post-licensure surveillance data, new analyses of household survey data, and updated estimates from the international literature. We ran a separate analysis to compare the potential cost-effectiveness and benefit-risk of ROTARIX (1-dose vial), ROTASIIL (1-dose vial), ROTASIIL (2-dose vial), and ROTAVAC (5-dose vial) over a ten-year period (2025-2034). Each product was compared to no rotavirus vaccination and each other. We ran deterministic and probabilistic uncertainty analyses and interpreted our results over a range of cost-effectiveness thresholds.

Findings

We estimated that routine use of ROTARIX between 2018 and 2024 has prevented 4,600 RVGE deaths (a 41% reduction), 86,400 hospital admissions, and 1.72 million outpatient visits. For every 1,493 RVGE deaths prevented by the vaccine, we estimated one potential excess intussusception death. With a heavily reduced vaccine dose cost (Gavi's support) the net cost to the Afghanistan government vaccine programme was estimated to be US$ 4.4 million per year. The cost per DALY averted was US$ 125 (0.25 times the national GDP per capita) when using a Gavi-subsidised vaccine cost and including household costs averted by vaccination. This increased to US$ 471 (0.94 times the national GDP per capita) when incorporating the full vaccine price without Gavi's subsidy and excluding household costs averted by vaccination. When assuming continued Gavi support over the period 2025-2034, the dominant product

would be ROTARIX. Without Gavi support, ROTASIIL (2-dose vial) dominates.

Conclusion

Our study supports the sustained use of rotavirus vaccination in Afghanistan. The rotavirus vaccine is cost-effective, and its health benefits greatly exceed its potential health risks.

Keywords: Rotavirus vaccine; Cost-utility; Cost-effectiveness; Benefit-risk; Afghanistan

Introduction

Acute gastroenteritis (AGE) continues to be a leading cause of mortality in children <5 years old, accounting for over half a million deaths annually and 10% of all fatalities in this age group.[1,2] Rotavirus gastroenteritis (RVGE) is estimated to be responsible for 24-37% of AGE deaths.[3,4] Following the World Health Organisation (WHO) recommendation for universal rotavirus (RV) vaccination in 2009, more than 120 countries have incorporated the vaccine into their national immunization programmes.[5,6] Gavi, the vaccine alliance, has played a pivotal role by offering financial assistance to facilitate the introduction of the RV vaccine in low-income countries.[6] At the global level, RVGE deaths in children aged <5 years have decreased from around 450,000 in 2008 to around 150,000 in 2019.[3,7,8] Recent estimates suggest that RV vaccines prevented 139,000 RVGE deaths in children <5 years old from 2006-2019.[4] RVGE also imposes an important economic burden; a cost-effectiveness study of 73 Gavi-eligible countries indicated that RV vaccines could avert an estimated US$ 878 million in healthcare costs from the societal perspective over the period 2018-2027.[9]

In January 2018, Afghanistan added ROTARIX (GlaxoSmithKline, Belgium), one of the two pre-qualified rotavirus vaccines available at that time, to the national routine immunization programme, with financial support from Gavi, the vaccine alliance. ROTARIX is an oral vaccine administered to infants in a two-dose schedule at 6 and 10 weeks of age.[10] The decision to introduce the vaccine was informed by a modelling study led by members of the Afghanistan National Immunization Technical Advisory Group (NITAG) and the Ministry of Public Health (MoPH). This study estimated that ROTARIX could prevent 25% of RVGE deaths aged <5 years at a cost of <$100 per DALY averted.[11]

Following the introduction of ROTARIX, post-licensure surveillance was established at five sites (Indira Gandhi Children Hospital, Herat Regional Hospital, Nangarhar Regional Hospital, Mazar Regional Hospital, and Ataturk Children Hospital) to monitor the effectiveness and safety of ROTARIX. Moderate vaccine effectiveness (VE) (45%; 95% CI: 22, 62) was demonstrated against RVGE hospital admissions aged 6-59 months old, and overall vaccine impact (percent reduction in RVGE admissions aged <5 years) was 39%.[12] Importantly, no substantial increased risk of intussusception (a rare type of bowel blockage) was observed except a possible slight increase in risk of intussusception 8-21 days after receiving the first dose.[13,14]

There are several reasons why the original economic evaluation of rotavirus vaccination in Afghanistan should be updated. First, the collapse of the Afghan government in mid-August 2021 led to a cessation of financial support from international donors who had previously provided crucial assistance to the

healthcare system in Afghanistan. While financial aid resumed in October 2021, it remains at a minimum and is focused on the humanitarian response. This situation underscores the critical need to rationalise health investments and re-assess cost-effectiveness. Second, post-licensure surveillance data on the real-world effectiveness of ROTARIX are now available, together with updated estimates of pre-vaccination rotavirus mortality, rotavirus vaccine coverage, and vaccine timeliness. Third, new post-licensure data on vaccine safety provides an opportunity to assess benefit-risk. Finally, four rotavirus vaccines are now available, and an updated analysis provides an opportunity to compare the cost-effectiveness of other available products on the global market.[15] ROTARIX is administered as a two-dose course, while the other three (ROTATEQ [Merck & Co., USA], ROTASIIL [Serum Institute of India Pvt. Ltd. India], and ROTAVAC [Bharat Biotech, India]) require three doses. Each vaccine has different cost characteristics, and some have experienced supply shortages, prompting a number of countries to switch to a different product.[16,17]

This study aims to estimate the cost-effectiveness and benefit-risk ratio for ROTARIX, and to compare its continued use with other rotavirus vaccines.

Methods

Study design and model

We used version 1.7.01 of the UNIVAC (Universal Vaccine) decision-support model. UNIVAC is a static cohort model with a finely disaggregated age structure (weeks of age <5 years) and can be used to assess the impact, cost-effectiveness, and benefit-risk of a range of different vaccines. It features a standardised and user-friendly Excel-based interface with a standard set of input steps and outputs. The model has been widely used by low- and middle-income countries (LMICs) to support decision-making for new vaccine introductions, including RV vaccines.[18]

We ran two types of analysis:

i. cost-effectiveness and benefit-risk analysis of ROTARIX (1-dose vial) over a seven-year period (2018-2024) compared to no vaccination; and,

ii. cost-effectiveness and benefit-risk analysis of ROTARIX (1-dose vial), ROTASIIL (1-dose vial), ROTASIIL (2-dose vial), and ROTAVAC (5-dose vial) over a ten-year period (2025-2034). ROTATEQ was excluded from the comparison as it is not covered under Gavi's financial support. Each product was compared to no rotavirus vaccination and each other.

In both analyses, we estimated the numbers of RVGE cases, outpatient visits, admissions, and deaths

with and without RV vaccination. We also estimated potential excess intussusception cases and deaths using previously described methods.[19] Vaccine programme costs and healthcare costs were estimated throughout the first five years of life, and disability-adjusted life-years (DALYs) were calculated over the lifetimes of the target birth cohorts. The primary outcome measure was the discounted cost per DALY averted (from government and societal perspectives) compared to no vaccination. The benefit-risk of vaccination was represented by the estimated number of RVGE deaths prevented per one excess intussusception death.

Since 2018, the estimated annual gross domestic product (GDP) per capita in Afghanistan has rarely exceeded US$ 500, so we compared our estimates of the cost per DALY averted to a range of potential cost-effectiveness thresholds (CETs) between US$ 0 and US$ 500.[20,21] In compliance with WHO vaccine economic evaluation guidelines, we considered both government and societal perspectives, and all future costs and health benefits were presented at a discounted rate of 3% per year, and expressed in 2022 United States Dollars (US$).[22]

Data collection and consensus building

All disease input parameters are shown in **table 1**. We estimated the incidence of severe RVGE cases in children by multiplying the WHO Eastern Mediterranean region estimate of the rate of severe AGE (5,972 per 100,000 per year, aged <5 years) by the rotavirus fraction among severe AGE cases (29.74%).[23] The rotavirus fraction was estimated using the mean of three estimates provided by Maternal and Child Epidemiology Estimation (MCEE), WHO/Centres for Disease Control and Prevention (WHO/CDC), and Global Burden of Disease (GBD).[4] The incidence of non-severe RVGE cases was estimated by subtracting the severe RVGE rate from the overall RVGE case rate (10,000 per 100,000 per year, aged <5 years) estimated in a global systematic review and meta-analysis by Bilcke et al.[24] The rate of RVGE outpatient visits was calculated by multiplying the number of non-severe and severe RVGE cases by the proportion of children with diarrhoea seeking care (53.10%), as estimated from the Afghanistan Multiple Indicator Cluster Survey (MICS) 2022-2023.[25] The rate of RVGE hospital admissions was estimated using pre-vaccination RVGE surveillance in two regions of Afghanistan, Central and Western.[26] To estimate the RVGE mortality rate we used the mean of estimates by MCEE, WHO/CDC and GBD.[27]

The age distribution of severe RVGE (community cases, outpatient visits, admissions, and deaths) was estimated by week of age <5 years using a parametric (Burr) distribution fitted to data from Afghanistan pre-vaccine surveillance (2013-2015).[28] **(Figure S1- panel a)** In the absence of national data on the age distribution of non-severe RVGE (community cases and outpatient visits), we used estimates for

Pakistan from a study by Hasso-Agopsowicz and colleagues.[28] **(Table 1)**

For calculating DALYs, we used disability weights from Salomon et al.[29] and for duration of illness, we assumed 7 days for severe RVGE cases and 3 days for non-severe RVGE cases.[30]

RVGE healthcare cost

The cost per RVGE inpatient admission was taken from a systematic review of LMICs by Baral et al. (2020), which estimated the cost per gastroenteritis (GE) admission. The same source was used to estimate the cost per outpatient visit.[31] For the base case analysis, we included direct medical costs in the government perspective and the sum of direct medical, direct non-medical, and indirect costs in the societal perspective. We assumed that the cost per outpatient visit would be the same for severe and non-severe cases. Our analysis did not include costs for treatment given at home or through the informal sector. **(Table 2)**

Vaccination coverage, timeliness, and effectiveness

Observed RV vaccine coverage from post-licensure surveillance was very similar to the national administrative coverage reported in the WHO/UNICEF Estimates of National Immunization Coverage (WUENIC) for DTP1 and DTP3. Despite disruptions caused by the COVID-19 pandemic and political changes, the official administrative rotavirus vaccination coverage was reported to be stable from 2020 to 2022. We therefore used 2022 WUENIC estimates of DTP1 and DTP3 vaccine coverage as a proxy for RV1 and RV2 (average DTP1 and DTP3) vaccine coverage and assumed this would remain consistent throughout our evaluation period.[32] We included real-world vaccine delays and vaccine timeliness (coverage by week of age) using an analysis of data from a recent nationally representative survey, MICS 2022.[25,33](**Table 1)**

We used estimates from a recent test-negative case-control study to approximate VE by time since dose administration using follow-up durations of 8 and 16 months for dose 1, and 7 and 15 months for dose 2.[12] We fitted a parametric gamma curve to each dose, assuming VE would be very high shortly after dose administration and then fall to very low levels after around 18 months of follow-up (**Figure S2**). Estimates of VE and waning were very similar for doses 1 and 2, so we assumed the same waning rate for both.

Consistent with our previous analysis, we did not account for the indirect benefits of rotavirus

vaccination, such as herd immunity, nor did we apply age restrictions to the vaccination schedule.

Vaccine price and delivery cost

According to Gavi's eligibility and transition policy version 4 (effective from January 2023) Afghanistan is classified as being in the initial self-financing phase.[34] In our base-case scenario, we applied a co-financing contribution of US$ 0.20 per dose for ROTARIX (2-doses) and US$ 0.13 per dose for ROTAVAC (3-doses) and ROTASIIL (3-doses). In scenario analysis, we ran a separate analysis assuming the government would pay the full price for ROTARIX (US$2.36 per dose for the 1-dose vial presentation), ROTASIIL (US$ 0.80 per dose for the 2-dose vial presentation, and US$ 1.05 per dose for the 1-dose vial presentation) and ROTAVAC ($US 1.15 per dose for the 5-dose vial presentation).[15] We assumed prices would remain unchanged over the evaluation period. **(Table 1)**

We applied wastage rates of 5%, 9%, and 15% for 1-dose, 2-dose and 5-dose vaccine presentations, respectively. These values were informed by reviewing the Comprehensive Multi-Year Plan (CMYP) 2021-2025.[[35]& Afghanistan EPI experts] A relatively high wastage rate of 15% for the 5-dose vaccine presentation has been derived from the current high wastage rates of the 1-dose and 2-dose vaccine presentations in the country. To calculate the cost of international handling and delivery, we applied 3% and 5% of the vaccine price, respectively.[35] The per dose cost of a safety bag with a capacity of 100 doses was estimated to be US$ 0.56.[35] No updated national data were available to estimate the health system delivery costs of rotavirus vaccination, so we used estimates for LMICs by Portnoy et, al (US$2.18 per dose in US$2022).[36] **(Table 1)** Due to limited data on the cost of switching products, we applied the average switching costs, which primarily cover the expenses of training, social mobilization, IEC materials, and stakeholder engagement, as reported by Palestine and Ghana, to the year of switching (2025).[17,37] We calculated the mid-range cost between Palestine and Ghana and divided it by the number of doses to be delivered in the first year with the 3-dose products. **(Table 1)**

Intussusception burden, risk, and costs

Intussusception (IS), invagination of a bowel segment causing blockage, is a rare but fatal medical condition if left untreated.[5,38] In some (mostly high-income) settings rotavirus vaccination has been associated with a small excess risk of IS.[5] We estimated the potential number of excess IS cases, hospital admissions and deaths to account for the potential excess risk of IS in the 1-7 and 8-21 days following the first and second dose of RV vaccination. The post-licensure self-controlled case series (SCCS) study for ROTARIX in Afghanistan reported a small relative risk (RR=1.3) in the 8-21 day period

following administration of the first dose, so we included this risk in the base analysis.[13]

Our estimates of the background rate of IS cases, hospital admissions, and mortality were obtained from post-licensure surveillance of children aged <12 months. This was the best available data source given that no IS surveillance existed pre-vaccine, and the RR of vaccination was very minor and restricted to specific age windows post-vaccination. The admission rate <12 months was rescaled to age <5 years using estimates from a systematic review of the proportion of <5 years IS hospital admissions that occurred by age 1 year in the WHO Eastern Mediterranean region.[4,13,39] The incidence rate of IS cases was derived by inflating the IS hospital admission rate to account for the percentage of children without access to care, using WUENIC estimates of the coverage of DTP1 in the year 2022 as a proxy for the maximum possible access to healthcare for severe conditions.[13,32] (**Table 1**) Estimates of the background rate of IS mortality were based on observed fatality rates among children <1 year from post-licensure surveillance. These were rescaled to represent children <5 years and inflated by DTP1 coverage to account for the percentage of children without access to care.[13,19] The age distribution of all intussusception outcomes was calculated by week of age <5 years using a parametric (Burr) distribution fitted to post-licensure surveillance data. (2018-2022).[13] **(FigureS1-panel b)**

Direct healthcare costs associated with intussusception treatment were included in the government perspective. These were estimated using the average cost per bed day in the National Hospitals Cost Analysis report, considering the average number of 5 days required for IS treatment.[40] From the societal perspective, we also included direct non-medical cost and indirect cost estimates from Baral's study without accounting for any allowance for the cost of surgery.[31] **(Table 2)**

Uncertainty analysis

We conducted deterministic scenario analyses to assess the sensitivity of the cost-effectiveness results to changes in different combinations of parameter values. We applied -/+15% to lower and higher bound of base values.[41] We considered the reported switch cost per dose of each country, Palestine and Ghana, to determine the lower and upper bounds of the vaccine delivery cost in the first year of the switch for the sensitivity analysis. We ran a scenario unfavourable to RV vaccination using the upper bound of the vaccine delivery cost per dose, a vaccine price without Gavi's subsidy, the lower bounds of the disease burden rate, and the lower bounds of the healthcare costs. We also ran scenarios favourable to RV vaccination by assuming "on-time" vaccine administration and using the upper bounds of the disease burden rates and healthcare costs, and lower bound of vaccine delivery cost, and upper bounds

of RVGE burden. Lastly, in one of the one-way sensitivity analyses, we assumed no vaccine impact on non-sever RVGE.

We ran a probabilistic sensitivity analysis (PSA) with 1000 Monte Carlo simulation runs. Within each run of the model, all parameters were simultaneously varied within their specified ranges. This was done to generate a 95% uncertainty interval around the central estimates of the cost per DALY averted. It was also done to determine the proportion of probabilistic runs with a cost-effectiveness ratio falling below CETs ranging from US$ 0 to US$ 500.

Role of the funding source

The funder of the study had no involvement in the study design, data collection, data analysis, data interpretation, or report writing. The authors had full access to all the data in the study and had final responsibility for the decision in submit for publication.

Results

Results

We estimated that seven years (2018-2024) of ROTARIX use in Afghanistan prevented 1.72 million RVGE cases, 911,337 outpatient visits, 86,444 RVGE hospital admissions and 4,644 RVGE deaths (a 41% reduction), compared to a scenario with no RV vaccination. We estimated 1,493 RVGE deaths prevented for every one potential excess intussusception death. **(Table 3)**

With a heavily reduced vaccine dose cost (due to external donor support from Gavi) the estimated vaccine programme cost was US$31.11 million over seven years. Without Gavi support, this increased to US$ 62.76 million. We estimate that the cost of vaccination could be offset by US$ $5.31 million in RVGE treatment costs from the government perspective (or US$ 15.89 million from the societal perspective) **(Table 3).**

In the base case analysis, factoring in Gavi's subsidy, the discounted cost per DALY averted was US$212 (0.42 times the national GDP per capita) from the government perspective and US$125 (0.25 times the national GDP per capita) from the societal perspective. However, when incorporating the full vaccine price without Gavi's subsidy, the discounted cost per DALY averted increased to US$472 (0.94 times the national GDP per capita) from the government perspective and US$386 (0.67 times the national GDP per capita) from the societal perspective.

Scenario analysis showed that the cost-effectiveness results were most sensitive to the price per dose (i.e. whether or not Gavi financial support was included), the burden of RVGE disease and the vaccine

delivery costs. With a reduced dose price (due to Gavi support), low vaccine delivery costs and high healthcare costs, the discounted cost per DALY averted was US$ 170 from the government's perspective and US$ 71 from a societal perspective. The assumption that the vaccine has no impact on non-severe RVGE is fairly influential. Additional details on various scenarios are provided in **supplement figure S3.**

ROTARIX had a 95% probability of being cost-effective when using a CET of US$250 (half the national GDP per capita). The full results of the probabilistic sensitivity analysis, including the cost-effectiveness plane and cost-effectiveness acceptability curve, are presented in **figure 1 and supplement figure S4 (panel a, b).**

Over the period 2025-2034, ROTARIX dominated the other three products when Gavi-subsidised prices were used. **(Table 4, Figures S5 and S6)** The estimated cost per DALY averted for continued use of ROTARIX was US$259 per DALY averted from a government perspective (and US$ 152 from a societal perspective). **(Table 4)** Without Gavi support, ROTASIIL (2-dose vial) dominates **(Table 4, Figure 2)** and there is 35% probability that three-dose vaccines could be cost-effective at a CET of US$ 500 per DALY averted from a government without Gavi's support. (**Figure S6 panel a)** With Gavi's support from societal perspective this probability increases to 95%. **(Figure S6 panel b)**

In scenario analysis, the choice of product (product with the lowest cost per DALY averted) was most sensitive to the dose price, wastage rate, health system delivery cost, and assumptions about whether 3-dose vaccines would have the same or slightly higher impact than the 2-dose vaccine (ROTARIX). **(Table 4)**

Discussion

We have updated our previous estimates of cost-effectiveness using real-world post-licensure national data and updated global estimates. Our updated analysis shows that over a seven-year period (2018-2024), ROTARIX had an important public health impact, preventing around 12,000 hospital admissions and 650 deaths each year. Our analysis also estimates a favourable ratio of benefits to risks. We estimated important economic benefits, with ROTARIX averting up to US$5.31 million and US$15.89 million in RVGE treatment costs from government and societal perspectives, respectively. Assuming a heavily discounted dose price due to support from Gavi, we estimated that it cost US$212 and US$125 to prevent each DALY, from a government and societal perspective, respectively. This is less favourable than our previous analysis (US$31 and US$29 respectively), primarily because our previous analysis assumed higher rates of RVGE mortality in the absence of vaccination. Additionally, cost values were adjusted to reflect US dollars as of 2022, a period of significant inflation since 2018. Despite these

increases, our current figures are consistent with existing literature; a meta-regression analysis reported a mean incremental cost-effectiveness ratio (ICER) of US$225 per DALY for Gavi-eligible countries.[9]

Afghanistan has faced significant economic hurdles since the Taliban's takeover of the government in August 2021. This economic downturn reduces the population and government's ability to fund health interventions. The country's ranking has declined from 153 in 2022 to 181 in 2023-2024 out of 193 countries, based on composite human development indices.[42] Additionally, the GDP per capita, often used as a basis for interpreting CETs, has seen a 12% to 62% decline from US$ 562 in 2017 to date. To address the instability in the GDP per capita, we used CETs ranging from $0-US$ 500. Our most favourable analysis suggests a cost-effectiveness ratio of 0.25 times the national GDP per capita, increasing to 0.94 times under assumptions least favourable to vaccination. Pichon-Rivere and colleagues recently recommended a CET of 0.65 time the national GDP per capita in Afghanistan using a method based on current levels of healthcare expenditure.[42] This suggests that RV vaccination is likely to remain cost-effective from a government perspective while it continues to benefit from the favourable assumption of Gavi subsidised prices. This seems probable given the recent political and economic disruption and increased need for donor assistance in Afghanistan. Looking ahead to the period 2025-2034, ROTARIX is projected to remain the dominant product, assuming continued Gavi support.

Affordability is an important consideration. With substantial external financial support from Gavi, the net cost to the Afghan government's vaccine programme was estimated to be US$ 4.44 million annually, accounting for 5.5% of the annual EPI programme budget and around 0.13% of the total national health expenditure. Without Gavi support, the vaccine programme cost would surpass US$ 8.96 million per year.

We estimated a substantial health and economic impact of vaccination. Similar findings have been reported in other low-income countries from both government and societal perspectives.[17,37,43-46] We estimated a 41% in RVGE hospitalisations and mortality per birth cohort from 2018-2024, closely replicating the 39% reduction in RVGE hospital admissions observed in the post-licensure evaluation.[47] Historically, rotavirus vaccination has shown a lower performance in LMICs compared to high-income countries. Opportunities to increase impact might involve introducing an additional dose to mitigate the effects of waning vaccine protection. We estimate this has the potential to increase health impact by around 8% (41% for 2-dose vs 49% for 3-dose vaccines).

Our analysis reaffirms the substantial benefits of RV vaccination compared to the potential excess risk of intussusception. We estimated 1,493 RVGE deaths prevented for every one potential excess

intussusception death. Recent modelled estimates of benefit-risk for 135 LMICs reported a ratio of 1,503:1.[46] We also ran a scenario with age restrictions applied (first dose <15 weeks, last dose <32 weeks). This adjustment reduced the vaccine's impact to 25%, but the benefit-risk ratio subsequently improved (to 2,790:1) because fewer doses were administered during the peak age of intussusception. More favourable benefit-risk ratio was reported in another modelled study when age restrictions were applied 2,385:1.[19]

Our analysis has some limitations. Our estimates of the burden of RVGE, vaccine effectiveness, and intussusception are uncertain. One challenge is the ambiguity surrounding the catchment population size. The last official census in the country was conducted in 1979, leaving a wide range of possible population estimates. To address this, we applied lower and upper bounds and used international estimates for some of the inputs. We also varied the rates in uncertainty analysis. Our estimates of the benefits of rotavirus vaccination may be underestimated because the UNIVAC model does not capture possible herd immunity effects. However, in this study we were able to use real-world data on VE from post-licensure surveillance and using a dynamic model in this context would introduce its own challenges e.g. it would require uncertain input parameters including social contact patterns and the duration of immunity from natural infections. The primary aim of this study is to support vaccine decision-making. While using a dynamic model is unlikely to significantly alter the conclusions, our estimates may be underestimated compared to those from a dynamic model. CEA studies using dynamic models have reported lower costs per DALY gained due to accounting for herd immunity compared to the static model.[48,49]

Conclusion

Our study underscores the importance of sustaining the use of rotavirus vaccination in Afghanistan. Future research should focus on enhancing vaccine delivery efficiency and addressing barriers to vaccine uptake, thereby increasing the public health impact of rotavirus vaccination.

Data availability

This manuscript does not report data generation.

Contributors

PA, AC developed the evaluation concept and methods. PA carried out data collection, expert consultation, data validation, data analysis, produced tables and figures, and wrote the first draft of the

manuscript. All authors have read, provided scientific inputs, contributed to, and approved the final version of the manuscript for submission.

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Declaration of interests

All authors declare no competing interests.

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Tables

Table 1. Input parameters for estimating the burden of rotavirus gastroenteritis (RVGE) in Afghanistan-2018-2027

Parameter	Mid-point value	Low bound	High bound	Sources
Annual rate per 100,000 < 5 children				
RVGE non-severe cases	8224	6990	9458	[24]
RVGE non-severe RVGE visits	4367	3712	5022	[24, 25] *53.1% diarrhoea disease health seeking <5yrs
RVGE severe cases	1776	1510	2042	[23, 4]
RVGE severe visits	943	802	1085	[23, 25] * 53.1% diarrhoea disease health seeking
RVGE hospital admissions	444	377	511	[26] inflated by DTP 1 coverage in 2022 (73% as proxy of getting healthcare)
RVGE deaths	26	22	30	[27]
Intussusception cases	30	26	35	[4,13,40] inflated to account for those without access, using 2022 DTP 1 coverage (77%)
Intussusception hospital admissions	23	20	26	[13, 32]
Intussusception deaths	7	6	8	[13, 32]
Relative risk of intussusception				
After 1-7 days				
Dose 1	1.00	1.00	1.00	[13]
Dose 2	1.00	1.00	1.00	
After 8-21 days				
Dose 1	1.30	1.11	1.50	
Dose 2	1.00	1.00	1.00	
Age distribution of non-severe RVGE (%)				
<1 month	1%			[28] (Pakistan RVGE visits age distribution) Burr shape1 (c)= 2.51 Burr shape2 (k)= 1.29 Burr scale (a)= 42.33
<2 months	2%			
<3 months	8%			
<6 months	28%			
< 12 months	73%			
<24 months	95%			
<36 months	98%			
<48 months	99%			
<60 months	100%			
Age distribution of severe RVGE (%)				[28] Age distribution fitting:
<1 month	0%			

Parameter	Mid-point value	Low bound	High bound	Sources
<2 months	5%			Burr shape1 (c)= 2.59 Burr shape2 (k)= 1 Burr scale (a)= 36.19
<3 months	8%			
<6 months	28%			
< 12 months	73%			
<24 months	95%			
<36 months	98%			
<48 months	99%			
<60 months	100%			
Intussusception age distribution				
<1 month	0%			[13] Age distribution fitting: Burr shape1 (c)= 7.19 Burr shape2 (k)= 0.15 Burr scale (a)= 19.52
<2 months	1%			
<3 months	2%			
<6 months	22%			
< 12 months	75%			
<24 months	85%			
<36 months	90%			
<48 months	95%			
<60 months	100%			
DALY calculation				
Non-severe RVGE				
DALY weight	0.19	0.19	0.26	[29] (proxy: Moderate diarrhoea)
Duration of illness (days)	3	3	7	[30] and EPI assumption
Severe RVGE				
DALY weight	0.25	0.25	0.36	[29] (proxy: Severe diarrhoea)
Duration of illness (days)	7	6	8	[30] and EPI assumption
Intussusception				
DALY weight	0.32	0.32	0.44	[29] (Abdominopelvic problem, severe)
Duration of illness (days)	7	5	9	[13]
Vaccine effectiveness				
dose 1, initial VE	100%	45%*	100%	[12] VE and 95%CI Assume efficacy of 3 doses equal to 2 doses Fitted the observed effectiveness of each dose and time of administration to the post-licensure surveillance data
dose 2, initial VE	100%	45%*	100%	
dose 3, initial VE	100%	45%*	100%	
Mean duration of VE after each dose (in months)	10	10	10	
Parameter 2 (alpha or shape)/standard error	3	3	3	
Vaccine coverage				
Dose 1				

Parameter	Mid-point value	Low bound	High bound	Sources
2018	81%	69%	93%	[32], DTP1 as proxy for RV dose1 It was aligned with observed coverage in post-licensure surveillance.
2019	75%	64%	86%	
2020	78%	66%	90%	
2021	74%	63%	85%	
2022	77%	65%	89%	
2023-2034	77%	65%	89%	
Dose 2				
2018	77%	65%	88%	[32] Average DTP 1 and 3, proxy for RV dose 2 It was aligned with observed coverage in post-licensure surveillance.
2019	74%	62%	85%	
2020	74%	63%	85%	
2021	70%	60%	81%	
2022	73%	62%	84%	
2023-2034	73%	62%	84%	
Dose 3				
2018	72%	61%	83%	[32] 2022, DTP3, proxy for RV dose 2 It was aligned with observed coverage in post-licensure surveillance.
2019	72%	61%	83%	
2020	70%	60%	81%	
2021	66%	56%	76%	
2022	69%	59%	79%	
2023-2034	69%	59%	79%	
Coverage timeliness				
Median age at dose 1, in weeks (IQR)	7	6	12	[25, 33]
Median age at dose 2, in weeks (IQR)	20	16	25	
Median age at dose 3, in weeks (IQR)	29	19	43	
Dose 1				
<1 month	0%	0%	0%	[33] Scale: 12.89 (7.25, 22, 94) Shape: 1.91
<2 months	53%	45%	61%	
<3 months	63%	54%	72%	
<6 months	71%	60%	82%	
< 12 months	75%	64%	86%	
<24 months	77%	65%	89%	
<36 months	77%	65%	89%	
<48 months	77%	65%	89%	
<60 months	77%	65%	89%	
Dose 2				
<1 month	1%	1%	1%	[33] Scale: 16.96 (11.72, 24.55) Shape: 2.97
<2 months	3%	3%	3%	
<3 months	31%	26%	36%	
<6 months	61%	52%	70%	

Parameter	Mid-point value	Low bound	High bound	Sources
< 12 months	70%	60%	81%	
<24 months	73%	62%	84%	
<36 months	73%	62%	84%	
<48 months	73%	62%	84%	
<60 months	73%	62%	84%	
Dose 3				
<1 month	0%	0%	0%	[33] Scale: 28.93 (19.39, 443.15) Shape: 2.75
<2 months	0%	0%	0%	
<3 months	5%	4%	6%	
<6 months	53%	45%	61%	
< 12 months	66%	56%	76%	
<24 months	69%	59%	79%	
<36 months	69%	59%	79%	
<48 months	69%	59%	79%	
<60 months	69%	59%	79%	
Vaccine price per dose (US$) with Gavi subsidy				
ROTARIX, 1-dose per vial, Liquid	$0.20			[15]
ROTASIIL, 1-dose per vial, liquid	$0.13			
ROTASIIL, 2-dose per vial, liquid	$0.13			
ROTAVAC, 5-dose per vial, liquid	$0.13			
Vaccine price per dose (US$) without Gavi subsidy				
ROTARIX, 1-dose per vial, Liquid	$ 2.36			
ROTASIIL, 1-dose per vial, liquid	$ 1.05			
ROTASIIL, 2-dose per vial, liquid	$ 0.80			
ROTAVAC, 5-dose per vial, liquid	$ 1.15			
International handling (% of vaccine price)	3.00%	2.55%	4.50%	[36]
International delivery (% of vaccine price)	5.00%	4.00%	7.50%	
Vaccine wastage rate				
ROTARIX, 1-dose, Liquid	5%	4%	8%	[35] and expert consensus
ROTASIIL, 1-dose, liquid	5%	4%	8%	
ROTASIIL, 2-dose, liquid	9%	8%	14%	
ROTAVAC, 5-dose, Liquid	15%	13%	23%	
Syringes wastage rate	5%	4%	8%	[35] and expert consensus (the same as vaccine wastage rate)
Health system delivery cost per dose (US$) for 2018 onward	2.18	1.09	4.36	[38]

Parameter	Mid-point value	Low bound	High bound	Sources
Additional health system cost per dose in the first year (2025) associated with switching from ROTARIX to ROTAVAC / ROTASIIL (US$)[§]	0.80	0.68	0.92	[17, 38] Average of switching cost reported in Palestine and Ghana studies Lower bound: Ghana: US$0.68 per dose Higher bound: Palestine: US$0.92 per dose

[§] We used the mid-range between the switching costs reported by Palestine's and Ghana's studies divided by the number of doses to deliver in year 1. We used the low and high values for sensitivity analysis.

Table 2. Input parameters for estimating health service costs in 2022 US$, Afghanistan

Parameter	Mid-point value	Low bound	High bound	Sources
Healthcare costs of RVGE				
Government perspective				
Non-severe outpatient visit (US$ 2022)	$5.04	$2.52	$10.08	[31]
Severe outpatient visit (US$ 2022)	$5.04	$2.52	$10.08	
Severe hospitalization (US$ 2022)	$17.56	$8.78	$35.12	
Societal perspective				
Non-Severe outpatient visit (US$ 2022)	$15.42	$7.71	$30.84	
Severe outpatient visit (US$ 2022)	$15.42	$7.71	$26.46	
Severe hospitalization (US$ 2022)	$38.05	$19.03	$76.10	
Healthcare costs of intussusception (IS)				
Government cost of IS hospitalization (US$ 2022)	$214.75	107.38	$429.50	[41,31]
Societal cost of IS hospitalization (US$ 2022)	$234.38	117.19	$468.76	

Table 3. Projected impact and cost-effectiveness of rotavirus vaccination in cohort vaccinated over period of 2018-2024 (DALY and costs discounted), government and society perspectives.

Parameter	No vaccine	ROTARIX	
		With Gavi Support	Without Gavi support
Lifetime costs and effects			
Non-Severe RVGE cases <5yrs	3,886,826	2,516,352	2,516,352
Non-RVGE clinic visits <5yrs	2,063,904	1,336,183	1,336,183
Severe RVGE cases <5yrs	839,407	493,616	493,616
Severe RVGE clinic visits <5yrs	445,725	262,110	262,110
Severe RVGE hospital admission <5yrs	209,843	123,399	123,399
Severe RVGE deaths <5yrs	11,270	6,626	6,626
Intussusception cases <5yrs	14,179	14,193	14,193
Intussusception deaths <5yrs	3,034	3,037	3,037
DALY averted (discounted*)	372,654	250,689	250,689
Vaccine programme costs (discounted*)	$0	$31,110,501	$62,760,329
Government healthcare costs (discounted*)	$16,257,205	$10,947,422	$10,947,422
Societal healthcare costs (discounted*)	$44,795,458	$28,900,879	$28,900,879
Differences (comparator = no vaccine)			
Non-Severe RVGE cases <5yrs	-	1,370,474	1,370,474
Non-RVGE clinic visits <5yrs	-	727,721	727,721
Severe RVGE cases <5yrs	-	345,791	345,791
Severe RVGE clinic visits <5yrs	-	183,615	183,615
Severe RVGE hospital admission <5yrs	-	86,444	86,444
Severe RVGE deaths <5yrs	-	4,644	4,644
Intussusception cases <5yrs	-	15¥	15¥
Intussusception deaths <5yrs	-	-3¥	-3¥
Percent reduction in severe RVGE deaths <5yrs	-	41%	41%
Percent increase in Intussusception deaths <5yrs	-	-0.10%	-0.10%
DALYs (discounted*)	-	121,965	121,965
Vaccine programme costs (discounted*)	-	$31,110,501	$62,760,329
Government healthcare costs (discounted*)		-$5,309,783	-$5,309,783
Societal healthcare costs (discounted*)	-	-$15,894,579	-$15,894,579
Cost (US$) per DALY averted (comparator = no vaccine)			
Governmental perspective			
Cost (discounted*)	-	$25,800,718	$57,450,546
DALYs averted (discounted*)	-	121,965	121,965
Cost per DALY averted (discounted*)	-	$212	$472
GDP per capital (2018)	-	$500	$500

Cost per DALY averted (discounted*) - % of GDP/capita	-	42.31	94.21
Societal perspective	-		
Cost (discounted*)	-	$15,215,921	$46,865,749
DALYs averted (discounted*)	-	121,965	121,965
Cost per DALY averted (discounted*) - % of GDP/capita	-	$125	$386
GDP per capital (2018)	-	$500	$500
Cost per DALY averted (discounted*) - % of GDP/capita	-	24.95	76.85
*Future costs/effects were discounted at a rate of 3% per year. ¥ Negative values indicate more cases or deaths with vaccination.			

Table 4. Economic evaluation of rotavirus vaccine products with and without Gavi subsidy in Afghanistan over the period 2025-2034[§]

		With Gavi subsidy				Without Gavi Subsidy			
	No vaccine	**ROTARIX, 1 dose vial, Liquid**	**ROTASIIL, 1 dose vial, Liquid**	**ROTASIIL, 2 dose vial, Liquid**	**ROTAVAC, 5 dose, liquid**	**ROTARIX, 1 dose vial, Liquid**	**ROTASIIL, 1 dose vial, Liquid**	**ROTASIIL, 2 dose vial, Liquid**	**ROTAVAC, 5 dose, liquid**
Lifetime costs and effects									
Non-Severe RVGE cases <5yrs	5,982,804	3,870,487	3,468,324	3,468,324	3,468,324	3,870,487	3,468,324	3,468,324	3,468,324
Non-RVGE clinic visits <5yrs	3,176,869	2,055,229	1,841,680	1,841,680	1,841,680	2,055,229	1,841,680	1,841,680	1,841,680
Severe RVGE cases <5yrs	1,292,059	759,107	661,324	661,324	661,324	759,107	661,324	661,324	661,324
Severe RVGE visits <5yrs	686,083	403,086	351,163	351,163	351,163	403,086	351,163	351,163	351,163
Severe RVGE hospital admission <5yrs	323,002	189,769	165,324	165,324	165,324	189,769	165,324	165,324	165,324
Severe RVGE deaths <5yrs	13,813	8,116	7,070	7,070	7,070	8,116	7,070	7,070	7,070
Intussusception cases <5yrs	21,824	21,847	21,847	21,847	21,847	21,847	21,847	21,847	21,847
Intussusception deaths <5yrs	3,719	3,723	3,723	3,723	3,723	3,723	3,723	3,723	3,723
DALY averted (discounted*)	447,553	300,865	273,727	273,727	273,727	300,865	273,727	273,727	273,727
Vaccine programme costs (discounted)	$0	$45,789,790	$66,814,597	$67,002,040	$67,927,617	$92,373,387	$95,746,701	$88,998,319	$103,166,934
Government healthcare costs (discounted*)	$23,992,598	$16,150,212	$14,668,045	$14,668,045	$14,668,045	$16,150,212	$14,668,045	$14,668,045	$14,668,045
Societal healthcare costs (discounted)	$66,109,732	$42,633,813	$38,195,960	$38,195,960	$38,195,960	$42,633,813	$38,195,960	$38,195,960	$38,195,960
Differences (comparator = no vaccine)									
Non-Severe RVGE cases <5yrs	..	2,112,317	2,514,480	2,514,480	2,514,480	2,112,317	2,514,480	2,514,480	2,514,480
Non-RVGE clinic visits <5yrs	..	1,121,640	1,335,189	1,335,189	1,335,189	1,121,640	1,335,189	1,335,189	1,335,189
Severe RVGE cases <5yrs	..	532,953	630,736	630,736	630,736	532,953	630,736	630,736	630,736
Severe RVGE visits <5yrs	..	282,998	334,921	334,921	334,921	282,998	334,921	334,921	334,921
Severe RVGE hospital admission <5yrs	..	133,233	157,677	157,677	157,677	133,233	157,677	157,677	157,677
Severe RVGE deaths <5yrs	..	5,698	6,743	6,743	6,743	5,698	6,743	6,743	6,743
Intussusception cases <5yrs	..	-23[¥]	-23[¥]	-23[¥]	-23[¥]	-23[¥]	-23[¥]	-23[¥]	-23[¥]
Intussusception deaths <5yrs	..	-4[¥]	-4[¥]	-4[¥]	-4[¥]	-4[¥]	-4[¥]	-4[¥]	-4[¥]
Percent reduction in severe RVGE deaths <5yrs	..	41.25%	48.82%	48.82%	48.82%	41.25%	48.82%	48.82%	48.82%

Percent increase in Intussusception deaths <5yrs	..	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%
DALYs (discounted*)	..	146,689	173,826	173,826	173,826	146,689	173,826	173,826	173,826
Vaccine programme costs (discounted*)	..	$45,789,790	$66,814,597	$67,002,040	$67,927,617	$92,373,387	$95,746,701	$88,998,319	$103,166,934
Government healthcare costs (discounted*)	..	$7,842,387	$9,324,553	$9,324,553	$9,324,553	$7,842,387	$9,324,553	$9,324,553	$9,324,553
Societal healthcare costs (discounted*)	..	$23,475,918	$27,903,782	$27,903,782	27,903,782	$23,475,918	$27,903,782	$27,903,782	$27,903,782
Cost (US$) per DALY averted (comparator = no vaccine) (Government perspective)									
Governmental perspective									
Cost (discounted*)	..	$37,947,404	$57,490,044	$57,677,487	$58,603,063	$84,531,000	$86,422,147	$79,673,765	$93,842,381
DALYs averted (discounted*)	..	$146,689	$173,826	$173,826	$173,826	$146,689	$173,826	$173,826	$173,826
Cost per DALY averted (discounted*)	..	$259	$331	$332	$337	$576	$497	$458	$540
Proportion of the GDP per capita (US$348) (%)		52%	66%	66%	67%	115%	99%	92%	108%
Societal perspective									
Cost (discounted*)	..	$22,313,872	$38,900,825	$39,088,268	$40,013,845	$68,897,468	$67,832,929	$61,084,547	75,253,163
DALYs averted (discounted*)	..	146,689	173,826	173,826	173,826	146,689	$173,826	$173,826	$173,826
Cost per DALY averted (discounted*)	..	$152	$224	$225	$230	$470	$390	$351	$433
Proportion of the GDP per capita (US$348) (%)	..	30%	45%	45%	45%	94%	78%	70%	87%
		ROTARIX 1st option	**ROTASIIL1 2nd option**	**ROTASIIL2 3rd option**	**ROTAVAC 4th option**	**ROTARIX 2nd option**	**ROTASIIL1 3rd option**	**ROTASIIL2 1st option**	**ROTAVAC 4th option**
Cost (US$) per DALY averted (comparator=next least costly non-dominated option)									
Government perspective (US$)	..								
Costs (discounted*)	..		-$16,586,953	-$16,774,397	-$17,699,973	$4,857,235	-$6,748,382		-$14,168,616
DALY averted (discounted*)	..		-27,138	-27,138	-27,138	-27,138	0		0
Cost per DALY averted (discounted*)	..		$611	$618	$652	-$179			
Societal perspective (US$)									
Costs (discounted*)	..		-$16,586,953	-$16,774,397	-$17,699,973	$7,812,922	-$6,748,382		-$14,168,616
DALY averted (discounted*)	..		-27,138	-27,138	-27,138	-27,138	0		**0**

Cost per DALY averted (discounted*)	..		$611	$618	$652	-$288			

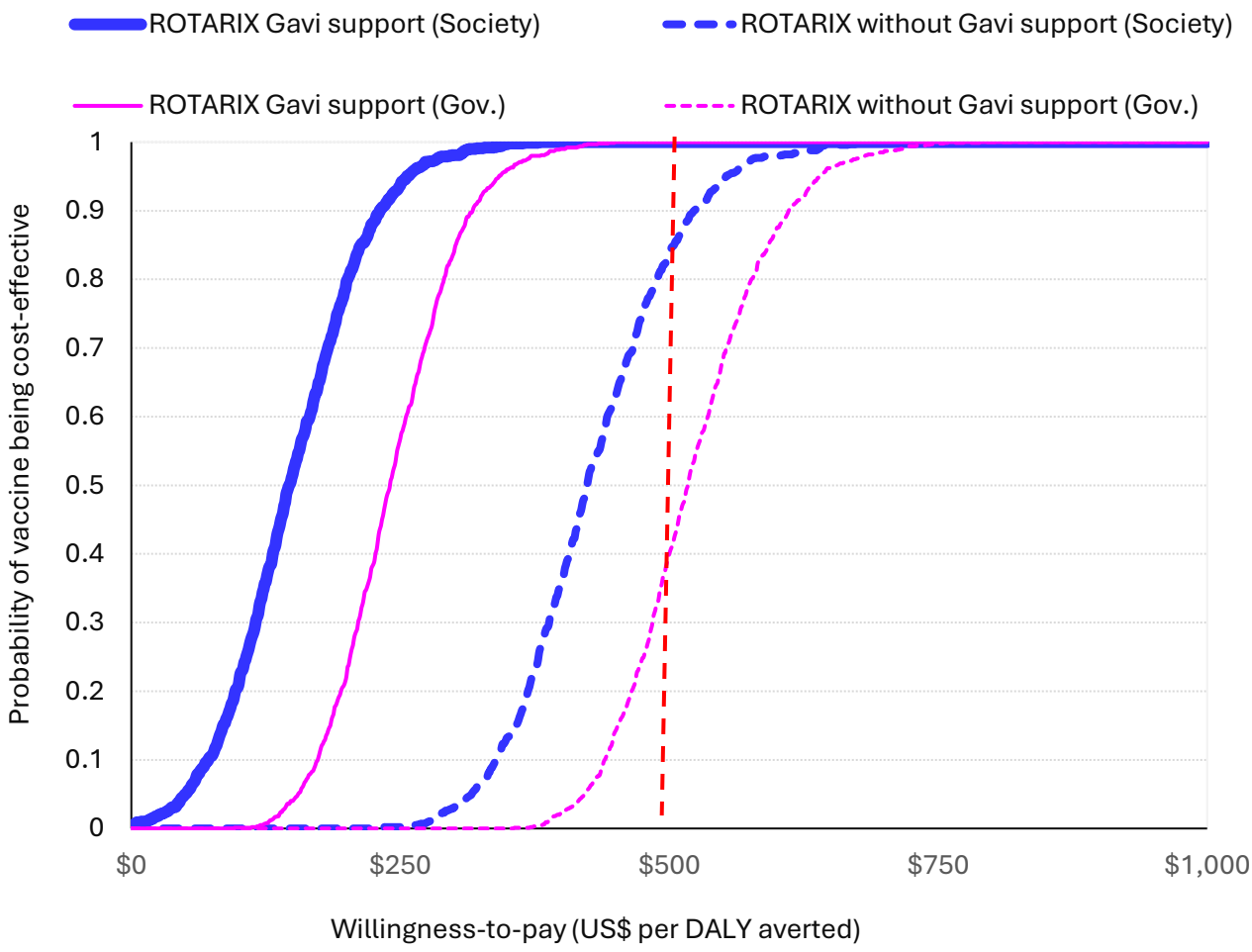
§Under the assumption of all products (3 doses vs 2 doses) have the same vaccine effectiveness.

*Future costs/effects were discounted at a rate of 3% per year.

¥ negative values indicate more cases or deaths with vaccination.

Figures

Figure 1 Probability that vaccination with ROTARIX is cost-effective at different level of willingness-to-pay (2018-2024)



Caption Figure 1. Probability that vaccination with ROTARIX is cost-effective at different willingness-to-pay thresholds from government and societal perspectives. The dashed vertical line is 1x GDP per capita (US$500)

Figure 2. ROTARIX and ROTASIIL, 2-dose per vial without Gavi's support and from government perspective

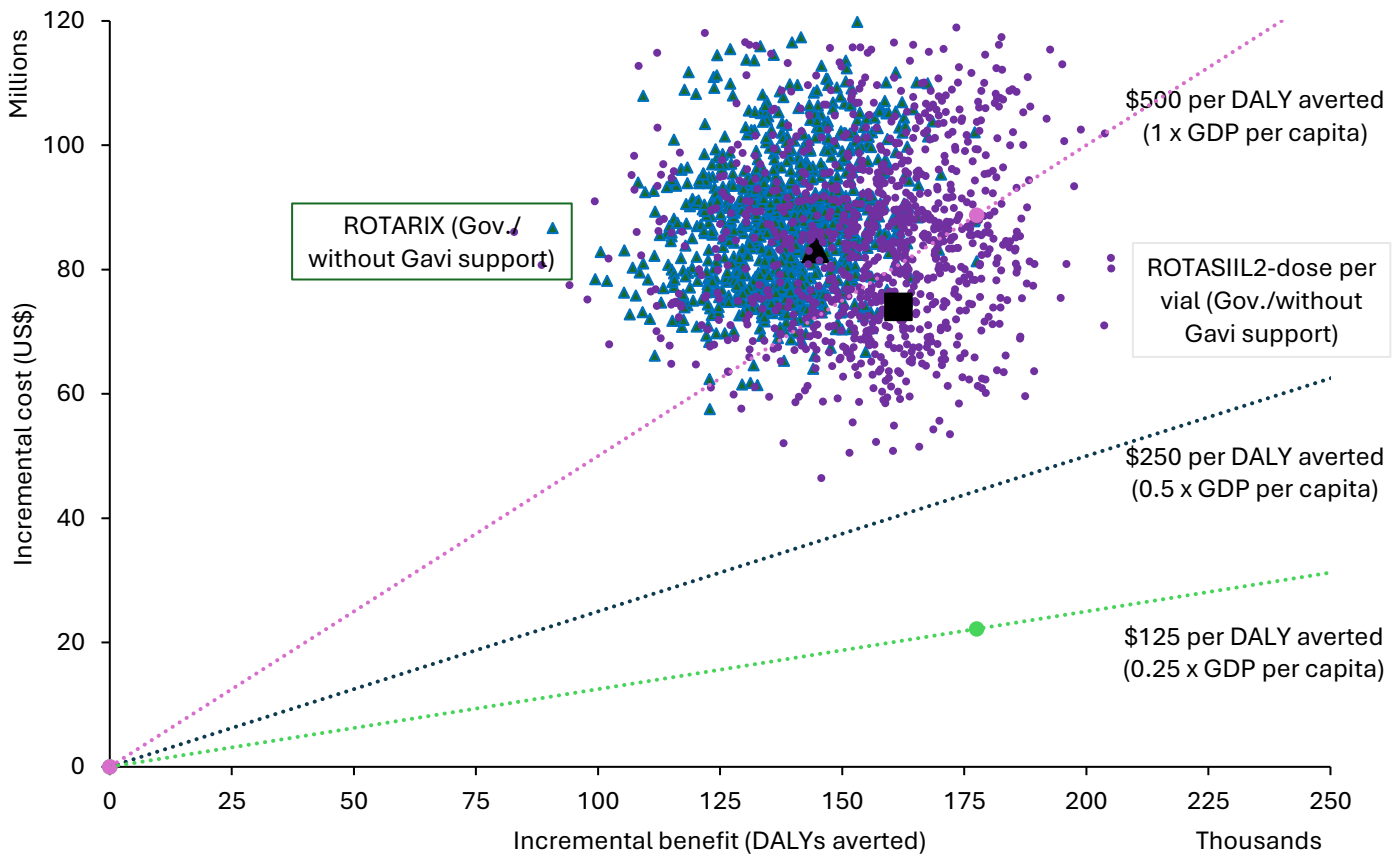
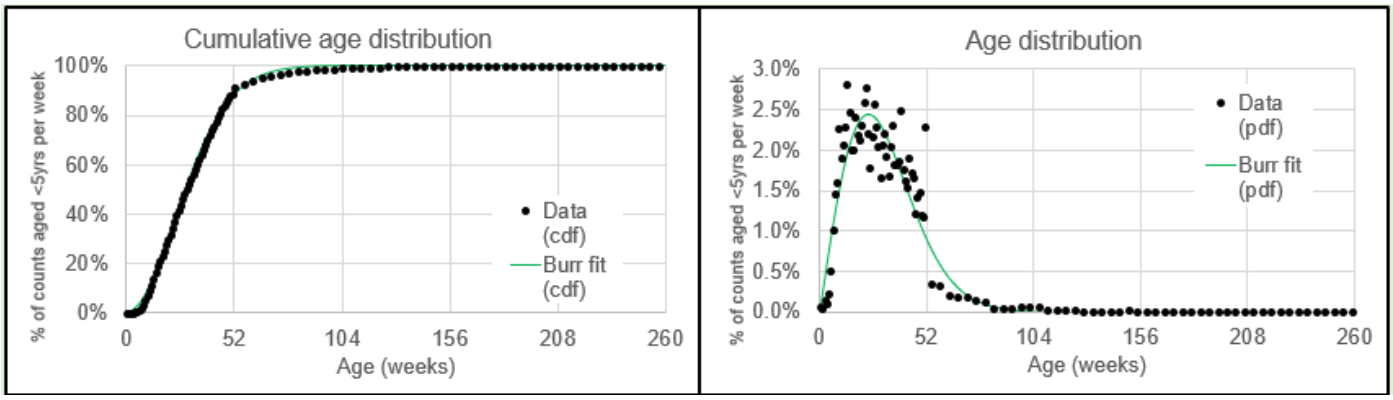


Figure 2 Caption. Probabilistic clouds showing the incremental cost (US$) and benefits (DALY averted) of rotavirus vaccine products compared to no vaccine, and each other without Gavi's financial support in Afghanistan from *government* perspective, 2025-2034. ROTASIIL 2-dose per vial (in purple) without Gavi support had the most favourable cost-effectiveness (below 1x GDP per capita). The other three products namely ROTARIX 1-dose ROTASIIL 1-dose per vial, ROTAVAC 5-dose per vial had quite similar cost-effectiveness with higher incremental benefit but at the higher incremental costs compared to ROTASIIL 2-dose per vial. Their clouds overlapped, thus we presented only ROTASIIL 2-dose and ROTARIX on the plane. Under the probabilistic sensitivity analyses, we assumed a fixed *vaccine* price over the evaluation period. Thus, the probabilistic clouds would be very sensitive to changes in vaccine *price*.

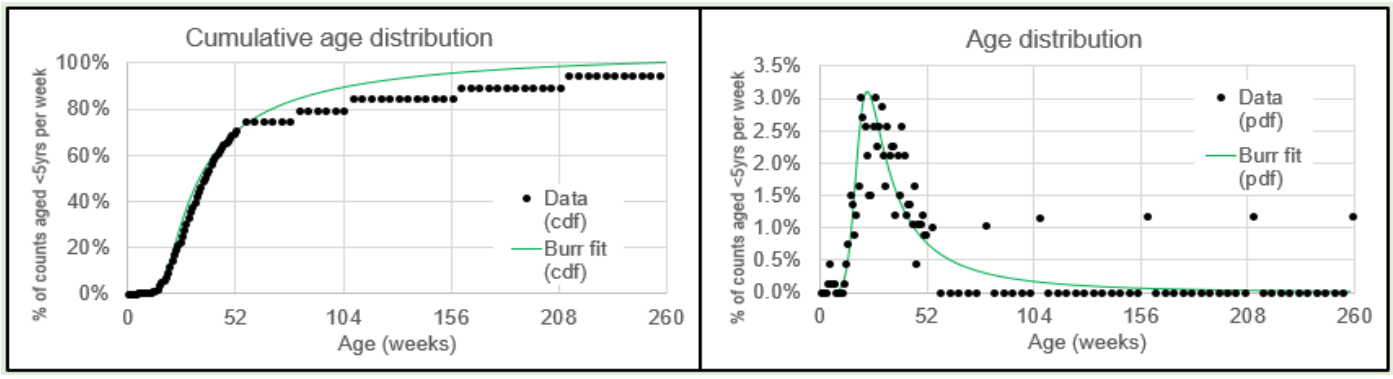
Supplements tables and figures

Figure S1 panel a. Age fitting (to weekly age bands), RVGE cases pre-licensure surveillance, Afghanistan 2013-2015



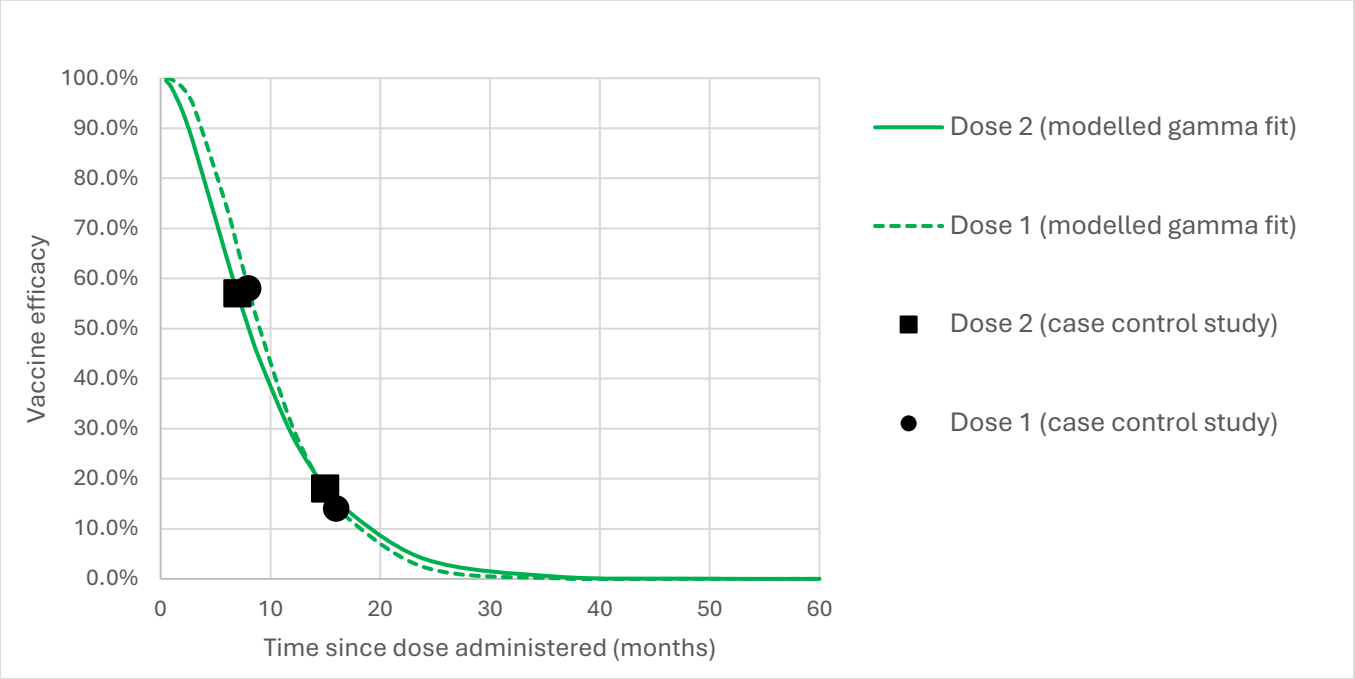
Caption: The left graph shows the cumulative age distribution of RVGE admission cases from pre-vaccine surveillance from two sites between 2013 and 2015. The right graph presents the Burr fitted age distribution curve of RVGE admission cases.

Figure S1 panel b. Age fitting (to weekly age bands), Intussusception cases, post-licensure surveillance, Afghanistan 2018-2022



Caption: The left graph shows the cumulative age distribution of intussusception cases from post-vaccine surveillance from four sites between 2018 and 2022. The right graph presents Burr fitted age distribution curve of intussusception cases.

Figure S2 Approximating efficacy of rotavirus vaccination by time since dose administration in Afghanistan using data from a test-negative case control study*



*VE=100%; Mean efficacy duration= 10 months; Alpha or shape= 3

Figure S3 Deterministic scenario analysis incremental cost-effectiveness ratio (US$ per DALY averted) of ROTARIX

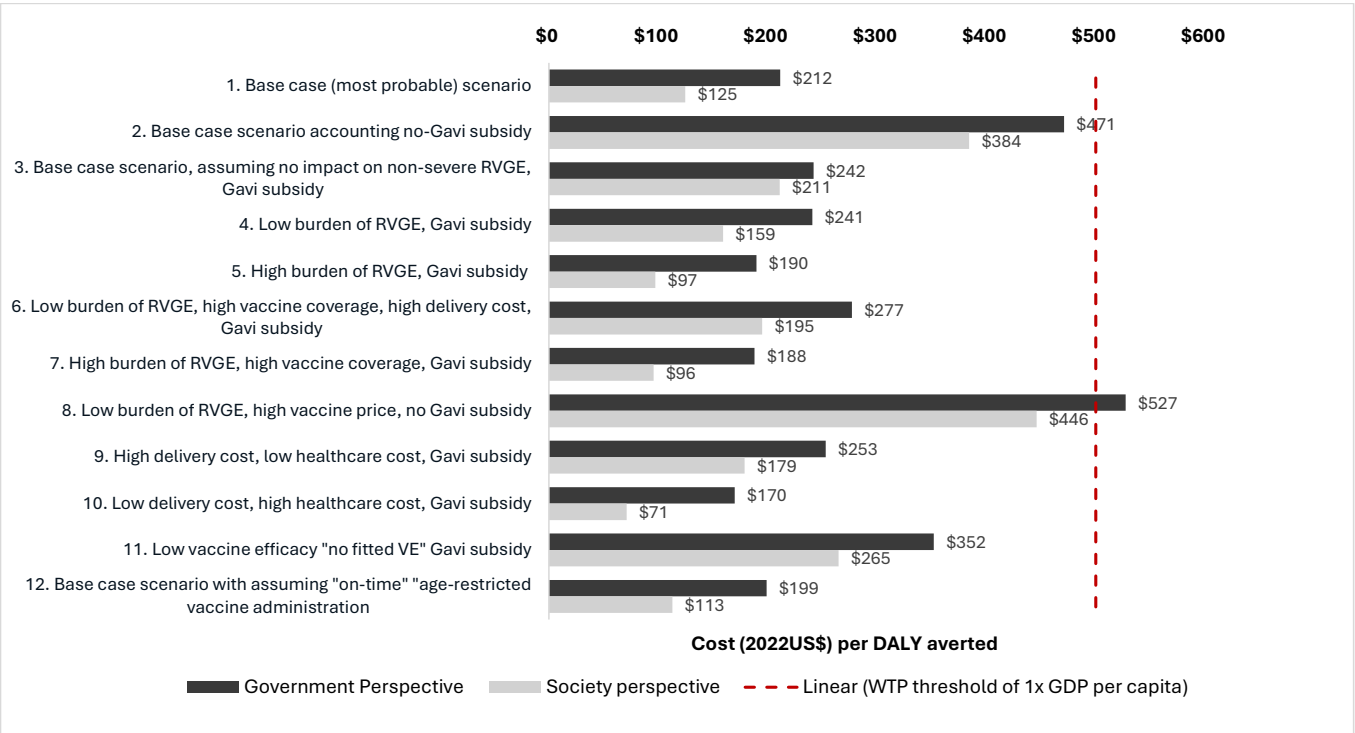
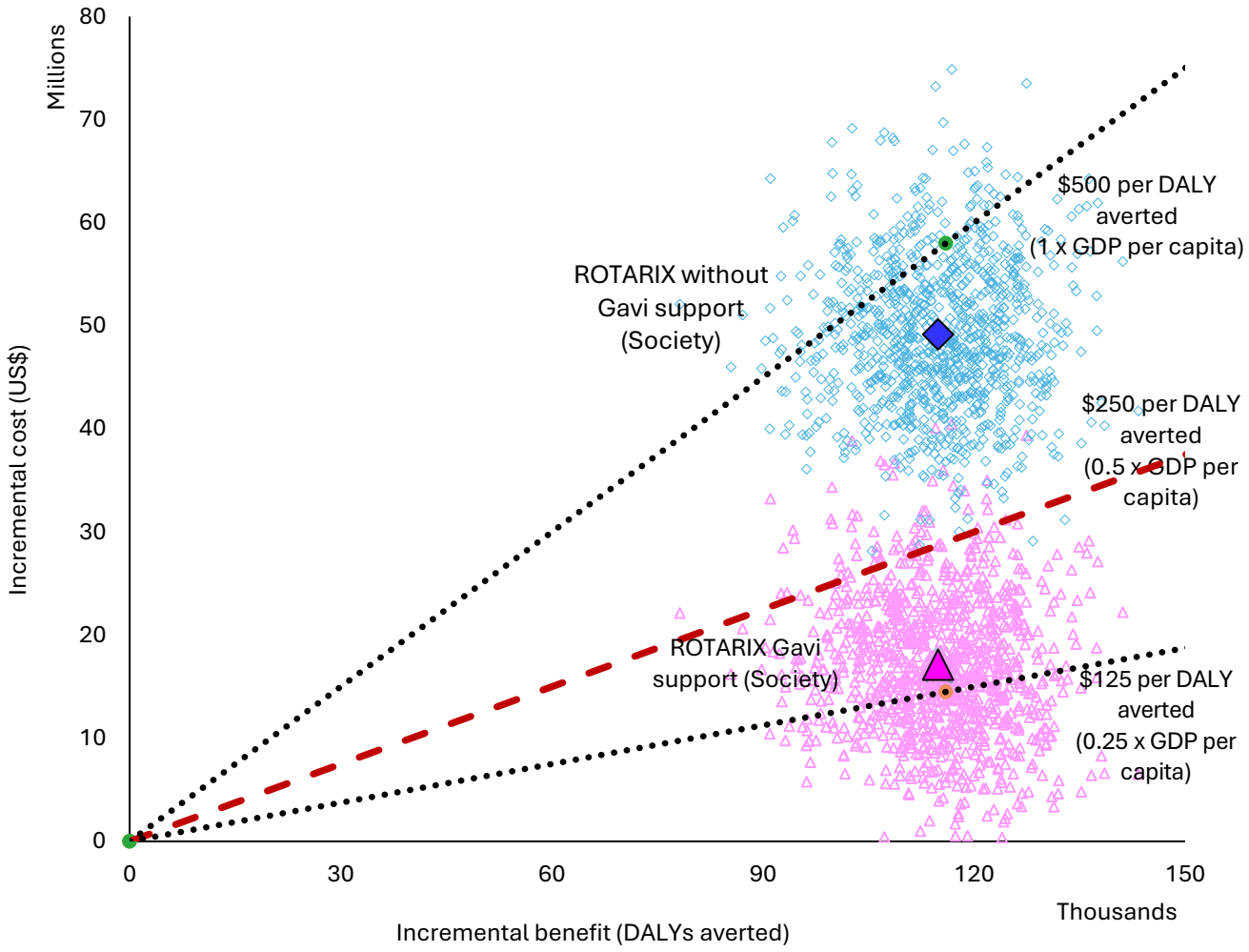


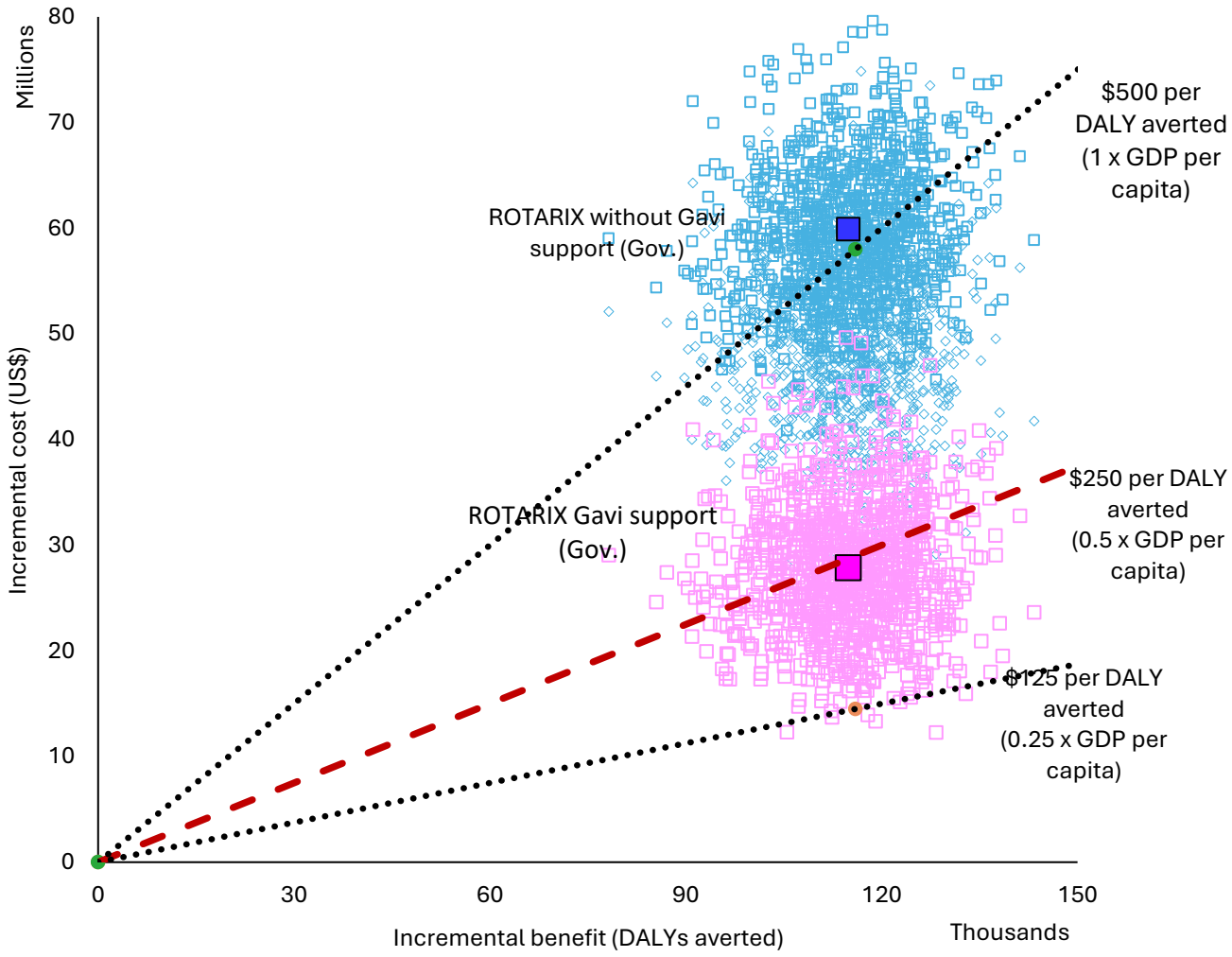
Figure S3 Caption. Deterministic scenario analysis incremental cost-effectiveness ratio (US$ per DALY averted) of ROTARIX, compared to no vaccination. Discounted cost per DALY averted (US$) for various scenarios plotted against Gross Domestic Products (GDP) per capita of US$ 500 for the period 2018-2024. This series of analyses enabled us to pinpoint the most influential economic parameters. The lowest projected discounted cost per DALY averted was observed when Gavi provided financial support, maintaining low vaccine delivery costs while healthcare costs were at the upper bound.

Figure S4 panel a. Probabilistic clouds of the incremental cost (US$) and benefits (DALY averted) of ROTARIX compared to no vaccine from societal perspectives, 2018-2024



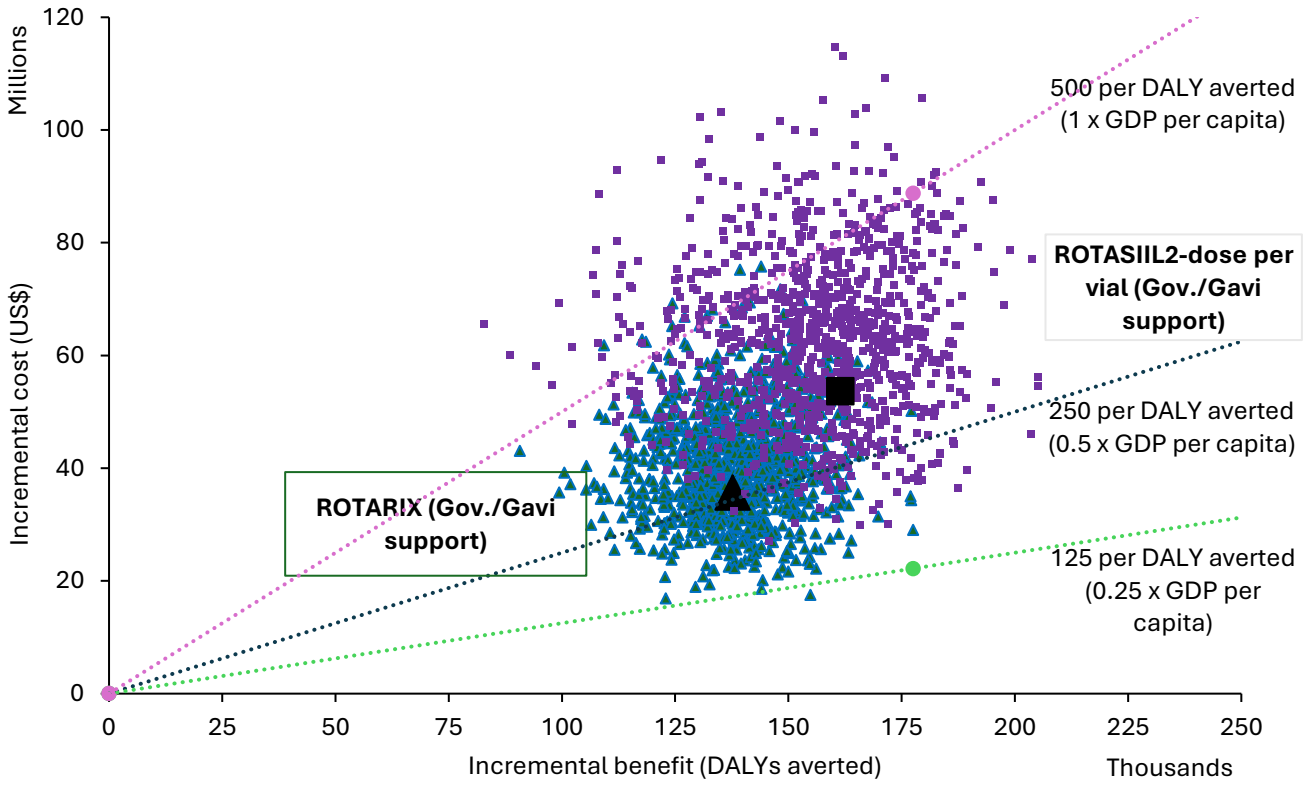
Caption Figure S4 Panel a. Probabilistic clouds showing the incremental cost (US$) and benefits (DALY averted) of ROTARIX compared to no vaccine with and without Gavi's financial support in Afghanistan from societal perspectives, 2018-2024. ROTARIX with Gavi support [purple] and ROTARIX without Gavi support [blue]. ROTARIX with Gavi's support would be cost-effective at the threshold of 1 x GDP per capita (US$500) from societal perspective. under the probabilistic sensitivity analyses we assumed a fixed price vaccine over the evaluation period. Thus, the probabilistic clouds would be very sensitive to changes in vaccine price.

Figure S4 panel b. Probabilistic clouds of the incremental cost (US$) and benefits (DALY averted) of ROTARIX compared to no vaccine from government perspectives, 2018-2024



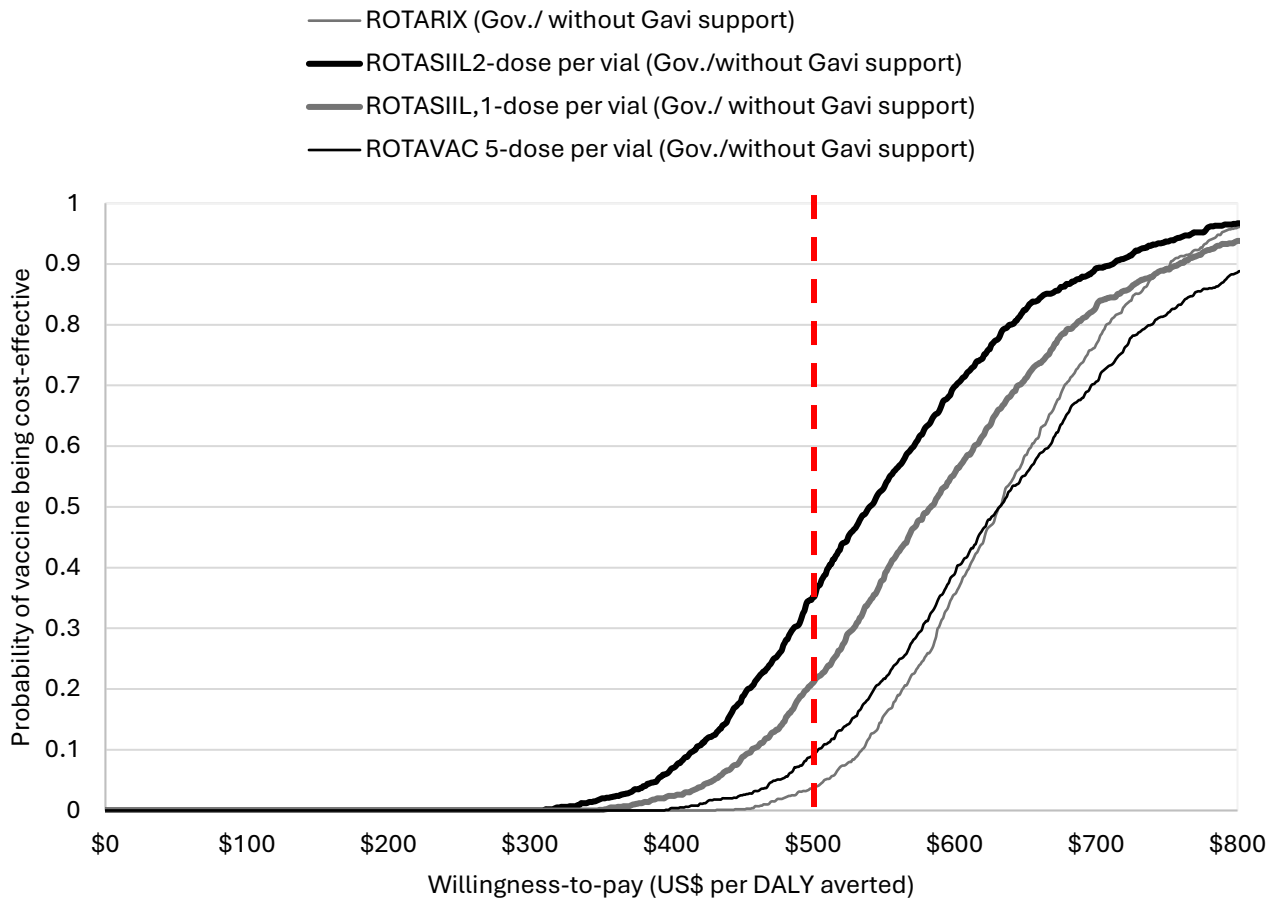
Caption figure S4 panel b. Probabilistic clouds showing the incremental cost (US$) and benefits (DALY averted) of ROTARIX compared to no vaccine with and without Gavi's financial support in Afghanistan from government perspectives, 2018-2024. ROTARIX with Gavi support [purple] and ROTARIX without Gavi support [blue]. ROTARIX with Gavi's support would be cost-effective at the threshold of slightly at 1 x GDP per capita (US$500) from government perspective. Under the probabilistic sensitivity analyses we assumed a fixed price vaccine over the evaluation period. Thus, the probabilistic clouds would be very sensitive to changes in vaccine price.

Figure S5 ROTARIX and ROTASIIL, 2-dose per vial, with Gavi's support and from government perspective



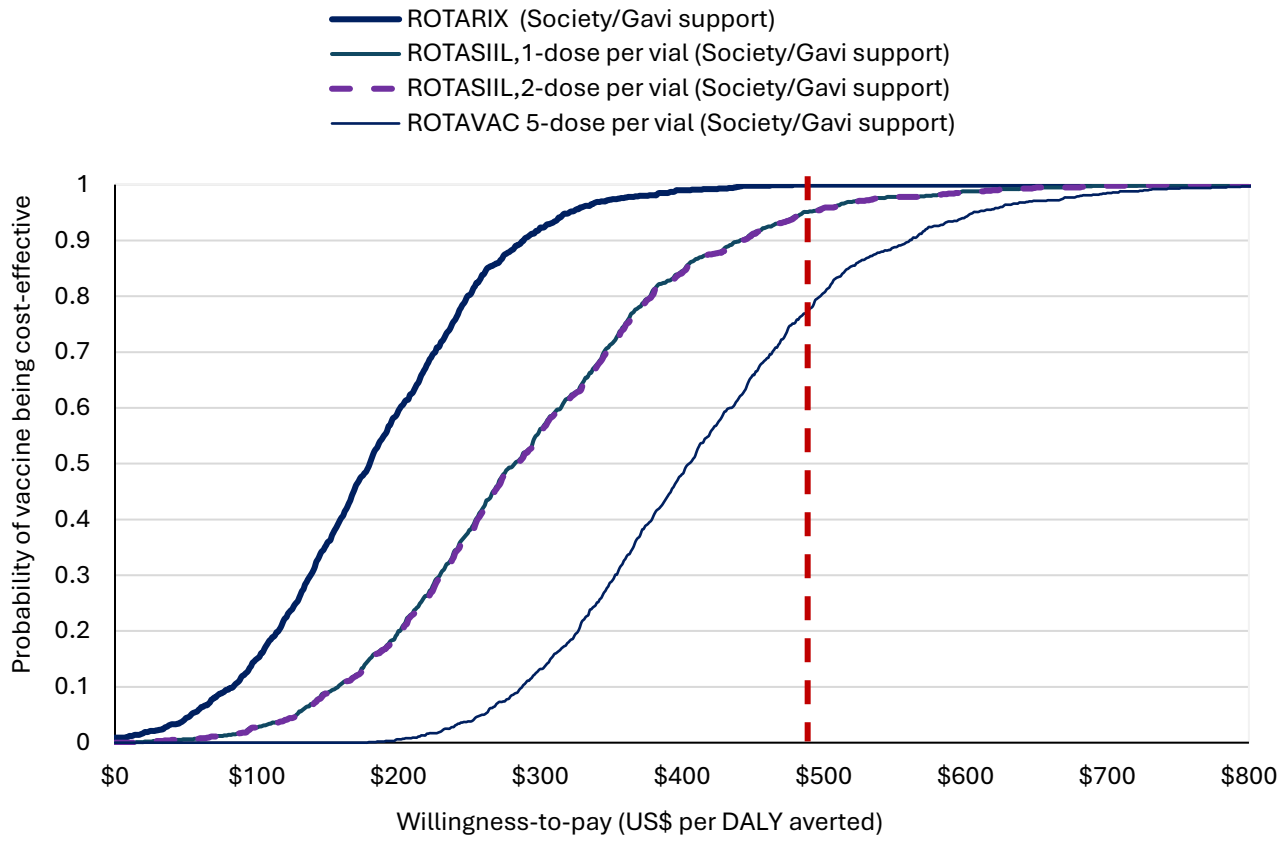
Caption figure S5. Probabilistic clouds showing the incremental cost (US$) and benefits (DALY averted) of rotavirus vaccine products compared to no vaccine, and each other with Gavi's financial support in Afghanistan from *societal* perspective, 2025-2034. ROTARIX (in blue) with Gavi support had the most favourable cost-effectiveness (at 0.5x GDP per capita. The other three products namely ROTASIIL 1-dose ROTASIIL 2-dose per vial, ROTAVAC 5-dose per vial had quite similar cost-effectiveness with higher incremental benefit at the higher incremental costs compared to ROTARIX. Their clouds overlapped, only ROTASIIL 2-dose per vial is shown and the others were dominated. Under the probabilistic sensitivity analyses, we assumed a fixed *vaccine* price over the evaluation period. Thus, the probabilistic clouds would be very sensitive to changes in vaccine *price*.

Figure S6 panel a. Willingness to pay plot of rotavirus vaccine products from government perspective without Gavi support



Caption figure 6S *panel a*. Probability that vaccination with four rotavirus vaccine products, ROTARIX, ROTASIIL (1-dose per vial and 2-dose per vial), and ROTAVAC would be cost-effective at different willingness-to-pay thresholds from societal perspective without Gavi's subsidy. The dotted vertical line is 1x GDP per capita (US$*500*)

Figure S6 panel b. Willingness to pay plot of rotavirus vaccine products from societal perspective, with Gavi support



Caption figure 6S panel b. Probability that vaccination with four rotavirus vaccine products, ROTARIX, ROTASIIL (1-dose per vial and 2-dose per vial), and ROTAVAC that would be cost-effective at different willingness-to-pay thresholds from societal perspective with Gavi's subsidy. The dotted vertical line is 1x GDP per capita (US$*500*)

CHAPTER SIX: CROSS-CUTTING ISSUES AND OTHER CRITERIA FOR ROTAVIRUS VACCINE DECISION-MAKING

Chapter 6: Cross-cutting issues and other criteria for rotavirus vaccine decision-making

6.1 Introduction

This chapter briefly introduces a decision-making framework (DMF) for vaccine decision-making in Afghanistan. It then outlines a specific rotavirus vaccine policy question: should Afghanistan continue to use rotavirus vaccination as part of the Expanded Programme on Immunization (EPI)? It also examines the evidence that is currently available for each of the recommended decision-making criteria. More details on the recommended framework can be found in the Research Study 1 (RS1) report. For several of the decision-making criteria, the evidence is summarized in the earlier chapters of this thesis. This chapter will therefore focus on cross-cutting issues and other criteria that may be important to consider when making an overall appraisal of the policy question.

6.2 Brief summay of OPA/RSI and recommended framework for appraising vaccine policy questions in Afghanistan

The Doctor of Public Health (DrPH) degree is structured around three main pillars. In the first semester, students complete two mandatory taught modules: Understanding Leadership and Management in Organization (ULMO) and Evidence-Based Public Health and Policy (EBPHP). These modules, along with other transferable skills training and workshops, prepare DrPH students for two research projects: a small-scale, focused study on Organizational and/or Policy Analysis (OPA), also known as Research Study 1 (RSI), and the main thesis, known as Research Study 2 (RSII). Each of these three pillars is a stand-alone deliverable and a prerequisite for the next stage. The DrPH degree is awarded upon completion of all three milestones.

Given my research interest in immunization in Afghanistan, I focused my OPA/RSI on studying the vaccine decision-making process in the country. Conducted between February 2021 and March 2022, the OPA aimed to document the vaccine decision-making architecture and processes in Afghanistan. This included assessing the relationships and roles of key stakeholders, as well as the sources, scope, and quality of evidence considered. One of the objectives was to provide practical

recommendations for strengthening vaccine policy decision-making in Afghanistan.

I employed a mixed-method approach, including a desk review, key informant interviews, and stakeholder analysis. The study identified three primary platforms for vaccine decision-making (VDM): the Expanded Programme on Immunization (EPI) Taskforce at programme level, the Interagency Coordination Committee (ICC) at the policy level, and the National Immunization Technical Advisory Group (NITAG), an independent technical entity. The study also identified 10 institutions with 22 existing communication lines, with the most regular and frequent information exchange occurring between the Ministry of Public Health (MoPH), WHO, UNICEF, and Gavi, the Vaccine Alliance. The MoPH was central to VDM, but Gavi along with WHO and UNICEF, due to their financial influence, had substantial influence. The role of domestic stakeholders was diminished by complex stakeholder dynamics and varying levels of engagement by national committee members.

OPA findings suggested that the decision-making process could be enhanced by strengthening the capacity of Afghanistan's NITAG as an independent technical body to formulate VDM recommendations. Among all the strategies proposed for strengthening the NITAG, the study highly recommended the use of a contextualized vaccine decision-making framework (VDMF), alongside enhancing the capacity of NITAG members in evidence generation, interrogation, and synthesis of national and international evidence.

The VDMF proposed by the OPA was derived from insights gathered through 18 national and international key informant interviews, a systematic review of national and international literature, and a comprehensive assessment of over 13 generic frameworks and guidelines for VDM. The systematic review method complied with the PRISMA guidelines and comprised a systematic search of five databases (Medline, Embase, Global Health, Cochran, and CINAHL), several specific websites of VDM platforms, and a search of grey literature. Two systematic reviews identified and covered around 200 papers from February 2000 to March 2020, and 48 additional papers identified from March 2020 - February 2022; Both contributed to the findings of the systematic review.

Of all the existing frameworks, 'Evidence to Recommendation (EtR) framework, the WHO guideline 2022' was identified as particularly suitable for adaptation for the Afghanistan context due to its flexible and adaptable nature. Figure 6-1 presents the VDMF developed for Afghanistan. This framework is supplemented with an operational checklist framed around seven main criteria: (1) problem; 2) benefits and harms; 3) values and preferences; 4) acceptability; 5) resource use; 6) equity; and 7) feasibility, and several sub-elements. For further detail, please refer to the attached

OPA/RSI report.

Afghanistan introduced ROTARIX, a monovalent RV, nationally in January 2018. However, with the regime change in mid-August 2021, the health sector has faced a severe reduction in international development funding and has been limited to humanitarian aid. Despite these challenges, post-licensure surveillance data on the effectiveness, impact, and safety of the ROTARIX vaccine were available. Furthermore, while only two vaccine types were available at the time of introduction, four WHO pre-qualified rotavirus vaccines are now available. Additionally, a global shortage of certain vaccine types has prompted many countries to switch to alternatives.

6.3 Policy question

Given context the policy question that arises is: "***Should Afghanistan continue to use rotavirus vaccination as part of the EPI?"*** The PICO framework for this policy question is as follows:

Population (p): Children <5 years of age in Afghanistan

Intervention (I): Rotavirus vaccination as part of the Expanded Programme on Immunization (EPI)

Comparison (C): No rotavirus vaccination (ROTARIX) or alternative rotavirus vaccine product

Outcome (O): Incidence and severity of rotavirus gastroenteritis (RVGE), hospitalization rates, mortality rates, and overall public health impact.

6.4 Decision criteria

Addressing this policy question involves considering several criteria that are outlined in the VDMF **(figure 6-1),** which are as follows:

1- Problem (burden of disease)

2- Benefits and harms (including vaccine efficacy/effectiveness; vaccine safety/risk; and

benefit-risk)

3- Values and preferences (acceptability of schedule; culturally and religiously preferences)

4- Acceptability (stakeholders' perception; financial, ethical and programmatic consideration)

5- Resource use (direct cost; cost-effectiveness ratio)

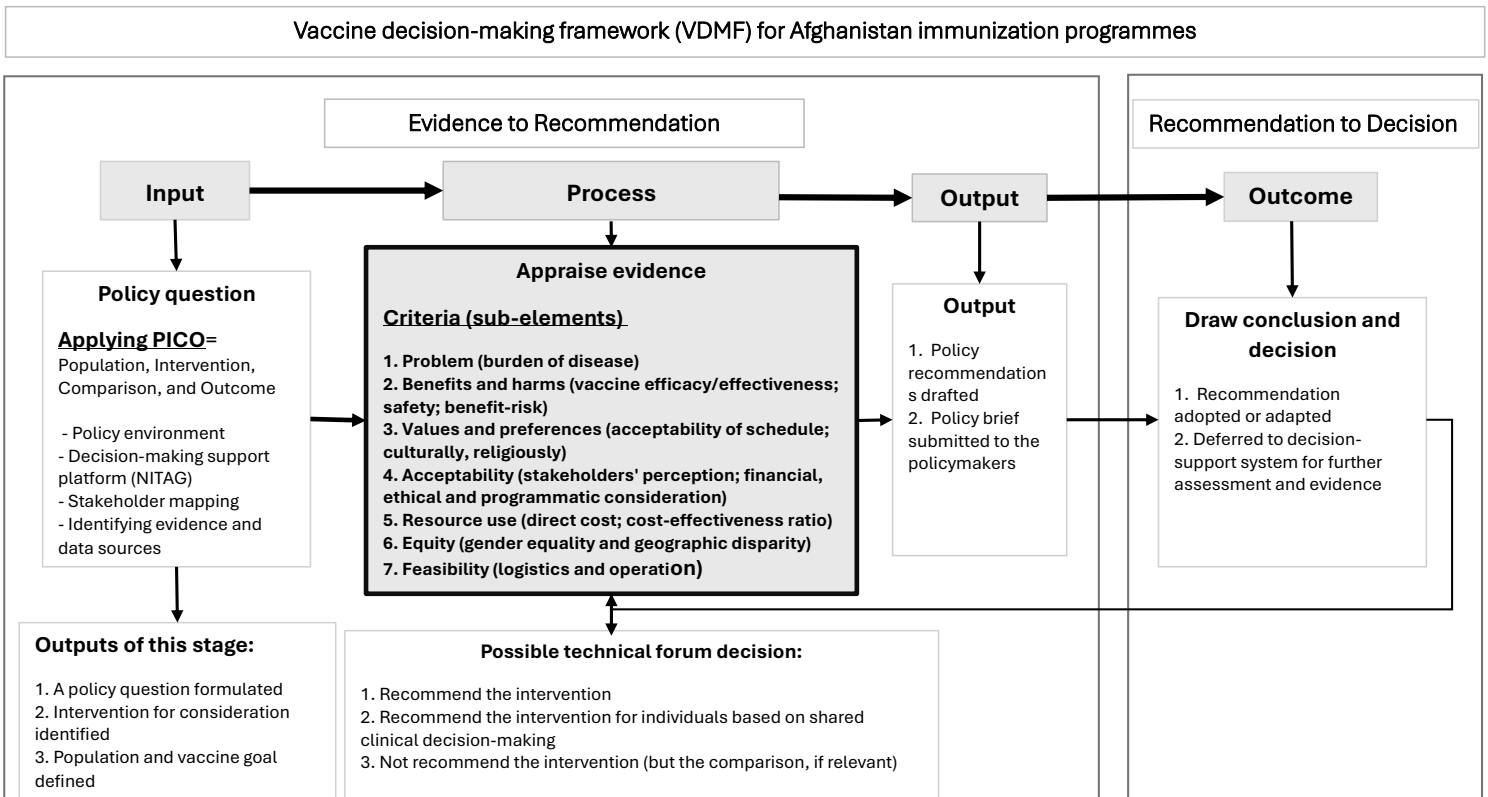
6- Equity (gender equality and geographic disparity)

7- Feasibility (logistics and operation)

The previous three chapters (Chapters 3-5) of this thesis generated evidence for these sub-elements: burden of disease; vaccine effectiveness, vaccine safety, benefit-risk; direct programme cost.

The objective of this chapter was to gather evidence on cross-cutting issues and other criteria required to make an overall appraisal on whether rotavirus vaccination should continue to be used in Afghanistan. I will therefore mainly concentrate on issues such as insecurity and armed conflict, equity with respect to gender equality and geographical disparity, financial sustainability, and the COVID-19 pandemic. Under cross-cutting issues and other criteria, we have also identified the need for exploring the impact of political influences on vaccine decision-making, as well as transparency and accountability in immunization programme management.

Figure 6-1 Vaccine decision-making framework for Afghanistan immunization programmes



6.5 Methods

This section details the methodology used to collect and analyse data. I applied an integrated approach of desk review and secondary data analysis sourced from the Health Management Information System (HMIS) and Multiple Indicators Cluster Survey (MICS) 2022-2023.

I extracted rotavirus vaccine doses 1 and 2 (RV1, RV2) and DTP 1-3 data for children <5 year from HMIS between 2019 and 2023. The rotavirus vaccine is a recent addition to the childhood immunization schedule compared to DTP1-3. However, it is co-administered with DTP1-2. Therefore, I included this vaccine in my analyses to create a better profile on status of these two vaccines. Coverage estimates are based on children of 12-23 months of age, applying a 3% annual growth rate. I calculated the percentage change of these two vaccines' coverage while considering 2019 as a reference year.

For the impact of political regime change, I compared March to October 2021 (escalation of fighting across the country, culminating in the fall of Kabul and the collapse of the government in mid-August 2021) with the same months of 2019, 2022, and 2023. To assess the impact of long-lasting security issues, I identified historical trends of childhood immunization from 1997 to date based on available survey data.

To assess the COVID-19 pandemic impact, I compared April to July 2020 (lockdown months – called the COVID period) with the same months in 2019 (pre-COVID) and 2021 (post-COVID). Since 2021, the political situation has been unstable; we also compared the COVID period with the same months of 2022 and 2023.

I calculated the percentage change in vaccine coverage using the following formula:

Percentage Change= [(New Value−Old Value)/ (Old value)] ×100

I also extracted reported routine immunization coverage from published national survey reports from 1997 to 2023 and plotted them to illustrate the trend of main childhood immunization coverage over the years. To illustrate geographical disparities, I produced country maps depicting the distribution of children aged 12-23 months who have been fully immunized and those who have ever received the rotavirus vaccine, as reported by the MICS 2022-2023.

In terms of financial sustainability for the immunization programme, Gavi, the Vaccine Alliance,

defines it as a country's ability to consistently mobilize and effectively utilize both domestic and additional external funds to achieve current and future immunization objectives in terms of access, usage, quality, safety, and equity.[1] I retrospectively assessed routine immunization expenditures as a percentage of total health expenditure, one of the WHO's global health expenditure indicators, and related budgetary issues from nationally available sources.[2] I identified trends over the past 5-10 years.

For the gender equality analysis:

1) I assessed the sex distribution of DPT 1-3 doses and RV1-2 between 2019-2023 using HMIS data.

2) Using the MICS 2022-2023 dataset, I used mothers' reported primary education as a proxy for measuring gender equality. Then, I categorized the 34 provinces into five groups (from very conservative to progressive in terms of mothers' primary education) based on mothers' attainment of primary education, where group 1 had the lowest percentage and group 5 had the highest reported percentage of primary education attainment. The classification of 34 provinces was done as follows:

    1) Very conservative (0.0 - 0.9%, N =10 provinces)
    2) Conservative (1.0 -1.9%, N =13 provinces)
    3) Transitioning (2.0 - 3.9%, N= 4 provinces)
    4) Relatively progressive (4.0 -10.0%, N= 5 provinces)
    5) Progressive (>10% N= 2 provinces)

3) I conducted gender analysis on post-licensure surveillance data (2018 and 2021).
4) Finally, I conducted content analysis of the EPI programme, training manuals, and health promotion materials from a gender perspective.

I generated maps using ArcGIS Pro 3.1.0 (Copyright© 2023 Esri Inc.). All other analyses, along with the creation of graphs and tables, were performed using either SAS 9.4 (SAS Institute Inc.) or Microsoft Excel.

6.6 Findings

6.6.1 Political influences on vaccine decision-making

As highlighted in Research Study I (OPA), vaccine decision-making in Afghanistan is influenced by a complex interplay of key stakeholders, including government, international and non-governmental organizations. In that study, we primarily focused on formal political dynamics prior to regime change in mid-August 2021. Here we aim to broaden that discussion by examining the role and interaction of both formal and informal political entities and their influence on vaccine decision-making processes.

6.6.1.1 Formal political structure

Government Institutions: Before the Taliban takeover in August 2021, the Ministry of Public Health (MoPH) played a central role in setting immunization policies in collaboration with global partners like WHO, GAVI, and UNICEF. Decision-making processes relied on technical advisory groups, such as the National Immunization Technical Advisory Group (NITAG), which evaluated evidence-based recommendations for vaccines.

Post-2021 shift in power: Since the Taliban regained control, formal governance structures have dramatically shifted. The Taliban's Ministry of Public Health now governs vaccine programmes, while international community navigate cautiously in such political circumstance where the Taliban de-facto government has not been recognized by any countries since they took power.

6.6.1.2 Informal political structure

Community leaders: Afghanistan's decentralized power dynamics mean that local actors, including tribal elders, warlords, and religious leaders, hold significant influence. Their support or opposition to vaccination campaigns determines programme success in certain parts of the country. For example, local leaders' endorsement can improve vaccine uptake, while their resistance—often fuelled by misinformation or distrust of government initiatives—can hinder progress.

Taliban ideology and influence: Historically, the Taliban opposed vaccination campaigns, particularly polio programmes, perceiving them as Western-driven initiatives or tools for their intelligence. While they have since softened their stance, especially under international pressure,

vaccine campaigns remain vulnerable to political and ideological scrutiny. Before the regime change, Taliban-ruled areas often impose restrictions on female health workers, complicating access to immunization for women and children.

6.6.2.3 Interplay between formal and informal influences

in Afghanistan, the relationship between formal and informal entities is often intertwined. Informal actors may mediate between communities and formal institutions, facilitating vaccine acceptance or, conversely, fostering resistance due to political or ideological concerns. Understanding this dynamic is crucial for designing effective and inclusive vaccination strategies.

On other hand, vaccination programmes in Afghanistan have, at times, been used as political tools by various entities. The vaccination programmes can be leveraged to gain public support, assert control over regions and resources, or as a demonstration of governmental legitimacy. Conversely, they may also become points of contention, particularly in areas with competing political or ideological interests. Recognizing these nuances is vital to ensure that vaccination efforts remain focused on public health objectives rather than being undermined by political agendas.

6.6.2 Transparency and accountability in immunization programme management

Afghanistan consistently ranks among the most corrupt countries in the world, as reflected in the Corruption Perceptions Index (CPI) published annually by Transparency International.[3]In 2023, Afghanistan has been positioned at the bottom of the CPI (162^{th} among 180 countries and territories with 4 points improvement since 2022) highlighting pervasive corruption across various sectors, including government institutions, judiciary, law enforcement, and public service delivery. Transparency and accountability are critical pillars for the effective delivery and sustainability of any public services including the immunization programmes. One of the areas of corruption is lack of transference in resource allocation and funding. Afghanistan's immunization programme is heavily reliant on international donors, mainly, Gavi, UNICEF, WHO. At the operational level, service delivery is conducted by NGOs through contracts. The lack of transparency in how funds are allocated and spent at the national and subnational levels creates inefficiencies. Likewise, information about vaccine procurement, distribution plans, resource utilizations is often unavailable to stakeholders and the public. This practice makes it difficult to track progress, identify gaps and hold responsible actors accountable. In some instance, during vaccine campaign, vaccines for public immunization campaigns have been destroyed and dumped under trees for not

going to rural areas, but then, reported those dumped vaccine dosages as number of children vaccinated. Such situation is linked with weak monitoring and limited oversight of immunization programmes and resulted in inaccurate and falsified reporting of immunization coverage rates in some districts and localities, shortage of supplies, and high wastage rate.

A lack of transparency and visible accountability undermines public confidence in immunization programme. Misinformation and rumours often thrive in such environments, discouraging vaccine uptake.

6.6.3 Insecurity and armed conflict

Afghanistan's geopolitical situation has led to severe conflicts. Here I focus on the years after the ex-Soviet Union's invasion in 1979, up to the present date. More than four decades of war and conflict can be described as follows:

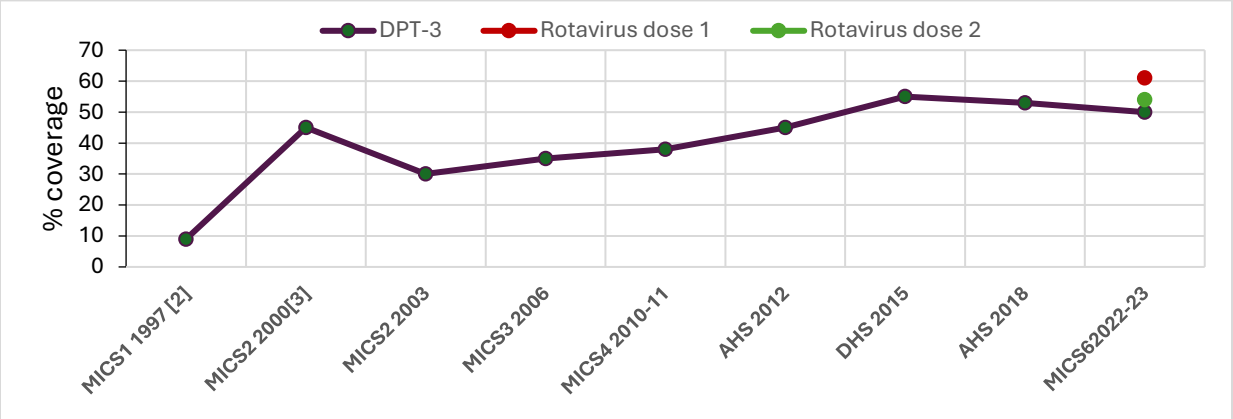
1. **1979-1992:** The Soviet Union's invasion of Afghanistan occurred in 1979 and continued until the fall of the Soviet Union-supported government in 1992 to Mujaheddin groups.
2. **1992-2001:** Dreadful internal war among the Mujaheddin groups occurred between1992 and 1995. The situation continued with the first round of Taliban rule (1995-2001).
3. **2002-2021:** The United States (US) and its allies established and supported the Afghan government under the so named "War Against Terrorism". During this period, the Taliban group reorganized and continued fighting against the US-supported government and its allies. The country experienced escalation of insecurity and conflict over these years. With the rapid withdrawal of the US and its allies, the Afghan government fell on August 15, 2021, and the Taliban took power.
4. **2021-present (2024):** The second phase of Taliban rule. Under this regime there have been no major armed conflicts, and access to all parts of the country has been granted. However, the Taliban regime has not been recognized by any country, development foreign aid has been entirely shifted to humanitarian aid, and the country's economy has been brought to the brink of collapse, with unemployment, poverty, and food insecurity growing to crisis levels.

Long-term conflict and insecurity have resulted in the disruption of basic services, including healthcare services. Despite efforts to expand healthcare service provision with the introduction and implementation of the Basic Package of Health Services (BPHS) and the Essential Package of Hospital Services (EPHS) [4] from 2002-2021, ongoing insecurity has impeded progress. As reported in household surveys, nearly half of respondents cited insecurity as the primary obstacle to accessing healthcare in 2016 [5, 6], In 2019, the Global Burden of Disease (GBD) ranked conflict and terror as the second cause of deaths in Afghanistan with a 219% increase from 2009.[7] Map 6-1 illustrates the widespread conflict across the country in February 2021, with over half of the districts being highly inaccessible due to security concerns. The majority of these districts were located along the border of Pakistan and Iran, extending from the east to the north-west of the country.[8] The long-term effects of this persistent insecurity are evident when examining the vaccination coverage reported in the MICS 2022-2023 survey. Map 6-2 underscores this impact, showing that provinces with low coverage of fully vaccinated children aged 12-23 months were predominantly those areas most affected by conflict over many years. Another example of the direct impact of insecurity on immunization was in December 2015, when 30% of vaccine eligible children, primarily in the eastern and southern provinces, could not receive a polio vaccine during National Immunization Days (NID).[6] In 2019, Grundy J. and Biggs BA reported that Afghanistan, one of the 16 high-risk and conflict-affected countries supported by Gavi, the Vaccine Alliance, had a DPT-3 coverage lower the global average (75% vs. 85%).[9]

Figure 6-1 illustrates the percentage coverage for DPT-3 over different periods reported by multiple surveys. The data points correspond to the Multiple Indicator Cluster Surveys (MICS), Afghanistan Health Surveys (AHS), and Demographic and Health Surveys (DHS) conducted between 1997 and 2022. Over the years, the coverage DTP-3 improved from <10% in 1997 to 55% in 2015. But later, it declined to 50% in 2022. National survey data for rotavirus was only available for 2022, reflecting challenges in achieving and maintaining immunization coverage. Coverage of rotavirus doses were

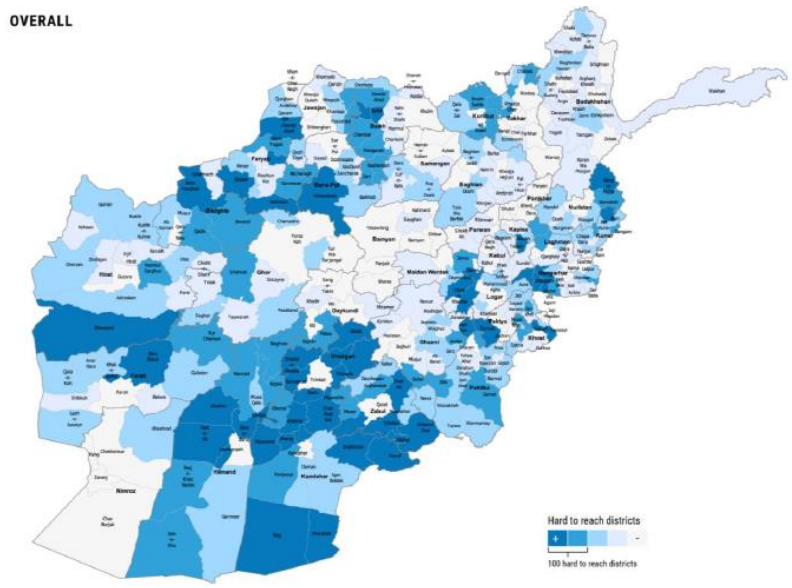
only reported on the last national survey conducted in 2022.

Figure 6-1 Child immunization trends (1997-2022) based on data extracted from various survey reports in Afghanistan[1]



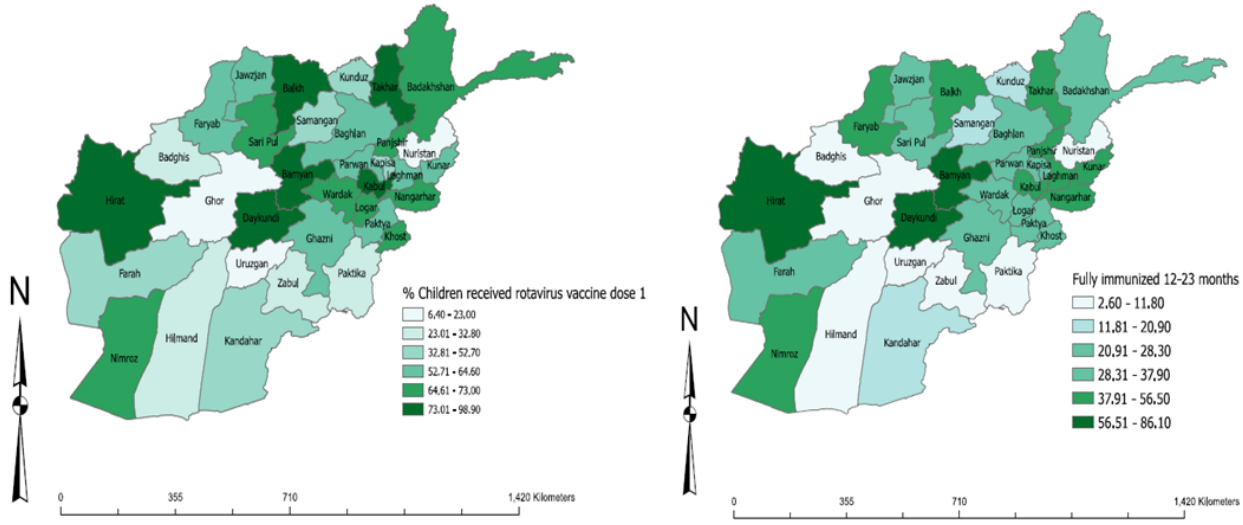
[1] [1] DPT - diphtheria, pertussis, and tetanus;
[2] MICS1 data were collected from 5 out of 32 provinces in 1997.
[3] MICS2 data were collected from only selected regions of the eastern part of the country in 2003.

Map 6-1 Hard-to-reach districts due to conflict intensity and physical restrictions imposed by Humanitarian Access Group, United Nations Office for Coordination of Humanitarian Affairs (UNOCHA), February 2021



Map 6-1: The dark blue shaded districts represent inaccessibility to health and other essential services due to insecurity and geographical difficulties in 2021. The majority of those districts were situated in the east to north-west along the Pakistan and Iran borders.

Map 6-2 Maps showing the proportion of children ever given rotavirus vaccination, and proportion of children aged 12-23 months fully vaccinated, Afghanistan MICS 2022-2023



The first few months of 2021 were marked by an unstable security situation, with the Taliban taking over provinces one after another in a few months. With the collapse of the government, the international community stopped health funding, but then in late October 2021 health sector funds were resumed. By comparing the coverage of rotavirus vaccine (RV1) before and after the government collapse with the same months in 2019, we see a10% decline in March 2021 (before the collapse) and 17% decline in October 2021 (after the collapse)**.** Further analysis for DPT1-3 and RV2 is presented in **Table 6-1.**

Table 6-1 Change in rotavirus vaccine coverages between 2019 and 2023, HMIS data, Afghanistan

	Comparison 1: 2020 vs. 2019					**Comparison 2: 2021 vs. 2019**					**Comparison 3: 2022 vs. 2019**					**Comparison 4: 2023vs. 2019**				
	DTP1	**DTP2**	**DTP3**	**RV1**	**RV2**	**DTP1**	**DTP2**	**DTP3**	**RV1**	**RV2**	**DTP1**	**DTP2**	**DTP3**	**RV1**	**RV2**	**DTP1**	**DTP2**	**DTP3**	**RV1**	**RV2**
Jan	-9%	-7%	-4%	-7%	-5%	0%	-2%	2%	3%	5%	2%	1%	1%	7%	7%	-13%	-12%	-10%	-9%	-7%
Feb	1%	-3%	0%	4%	1%	8%	3%	5%	11%	8%	8%	4%	1%	16%	10%	-2%	-4%	-5%	3%	2%
Mar	-2%	-6%	-3%	-1%	-3%	-10%	-11%	-14%	-10%	-8%	1%	1%	-5%	3%	4%	-3%	-5%	-9%	-1%	-1%
Apr	-13%	-12%	-15%	-10%	-10%	-5%	-8%	-11%	-6%	-5%	-8%	-5%	-11%	0%	4%	-12%	-6%	-8%	-7%	-1%
May	-6%	-10%	-10%	-6%	-7%	-17%	-20%	-16%	-16%	16%	-26%	-27%	-28%	-11%	-8%	-2%	-2%	-2%	0%	2%
Jun	6%	2%	-3%	13%	9%	12%	6%	1%	19%	13%	21%	11%	6%	25%	19%	7%	8%	4%	15%	17%
Jul	-2%	-1%	-4%	9%	11%	-26%	-21%	-22%	-17%	-9%	-23%	-15%	-20%	-13%	-2%	-21%	-10%	-13%	-12%	1%
Aug	5%	6%	5%	8%	10%	-5%	-7%	-6%	0%	-1%	13%	11%	10%	14%	13%	2%	0%	5%	8%	6%
Sep	8%	9%	9%	16%	20%	-18%	-21%	-23%	-13%	13%	0%	4%	2%	1%	6%	-2%	0%	0%	7%	11%
Oct	-5%	-3%	-6%	-1%	2%	-21%	-21%	-24%	-17%	15%	-7%	-5%	-7%	-21%	-19%	-12%	-11%	-14%	-7%	-6%
Nov	-9%	-6%	-6%	-7%	-5%	-7%	-12%	-13%	-4%	-7%	-10%	-11%	-11%	-8%	-9%	-12%	-10%	-13%	-8%	-6%
Dec	1%	-2%	-2%	3%	2%	14%	6%	2%	16%	8%	1%	-2%	-4%	3%	0%	-5%	-8%	-10%	-2%	-3%
Ave.	-15%	-26%	-32%	-4%	-10%	-11%	-13%	-14%	-7%	-7%	-4%	-4%	-7%	-1%	1%	-6%	-4%	-6%	-1%	3%

Legend: Cells highlighted in light red fill indicate more than 10% decrease from the baseline.

6.6.4 Equity (gender and geographic equality)

Afghanistan's diverse and challenging geographical terrain, coupled with deeply rooted tribal and gender norms, significantly influence accessibility and quality of healthcare services for men and women. Healthcare facilities are scarce and hard to reach in many remote and rural areas, while in urban areas, they may be more accessible but still face issues of quality and affordability. Gender disparities further complicate this landscape. Women, especially in rural areas, encounter numerous barriers to healthcare, including cultural norms, lack of female healthcare providers, and limited personal freedom. Gender equality is not only a fundamental human right but also a key

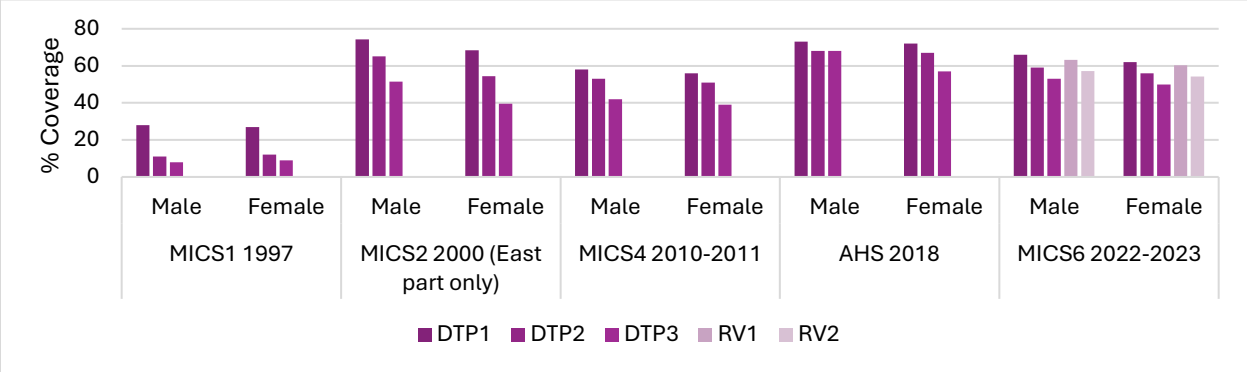
determinant of health outcomes. Gender inequality affects access to healthcare services, particularly in low- and middle-income countries (LMICs).[10] Studies have demonstrated that gender discrimination impacts health outcomes, including higher mortality rates among girls and limited access to medical treatment for women.[11-13] Empowering women has been shown to increase the likelihood of immunizing children.[14] The World Health Organization (WHO) emphasizes the need to understand the intersection of gender dynamics and vaccine uptake to design effective immunization strategies.[15]

The Afghanistan Living Condition Survey (ALCS) 2016-2017 reported that all gender equality indices consistently revealed the disadvantaged positions and limited development opportunities faced by women and girls in comparison to boys and men.[16] Women's participation in the labour market was 0.33 of that of men, while the unemployment rate, youth unemployment rate, and the proportion of young women not engaged in education, employment, or training (NEET) were higher at 1.55, 1.49, and 1.76 times higher, respectively, relative to the corresponding indicators for men.[16]

Figure 6-2 presents the sex-disaggregated national immunization coverage across different time periods reported by various national surveys. The notable trends include a general increase in vaccination coverage over time. However, significant gender disparities were observed in earlier surveys such MICS2 (2000), which showed higher coverage of DPT-3 for males compared to females. In the MICS 2022-2023 survey, the reported coverage for fully immunized children was 37.9% for boys and 35.3% for girls aged 12-23 months. The coverage trends for rotavirus vaccine doses followed a similar pattern. When we assessed the sex distribution of the rotavirus vaccine reported to HMIS between 2019-2023, a 6% difference between boys and girls in the uptake of rotavirus vaccine dose 1 was observed, with degrees of variations over the years and months. (Figure 6-3).

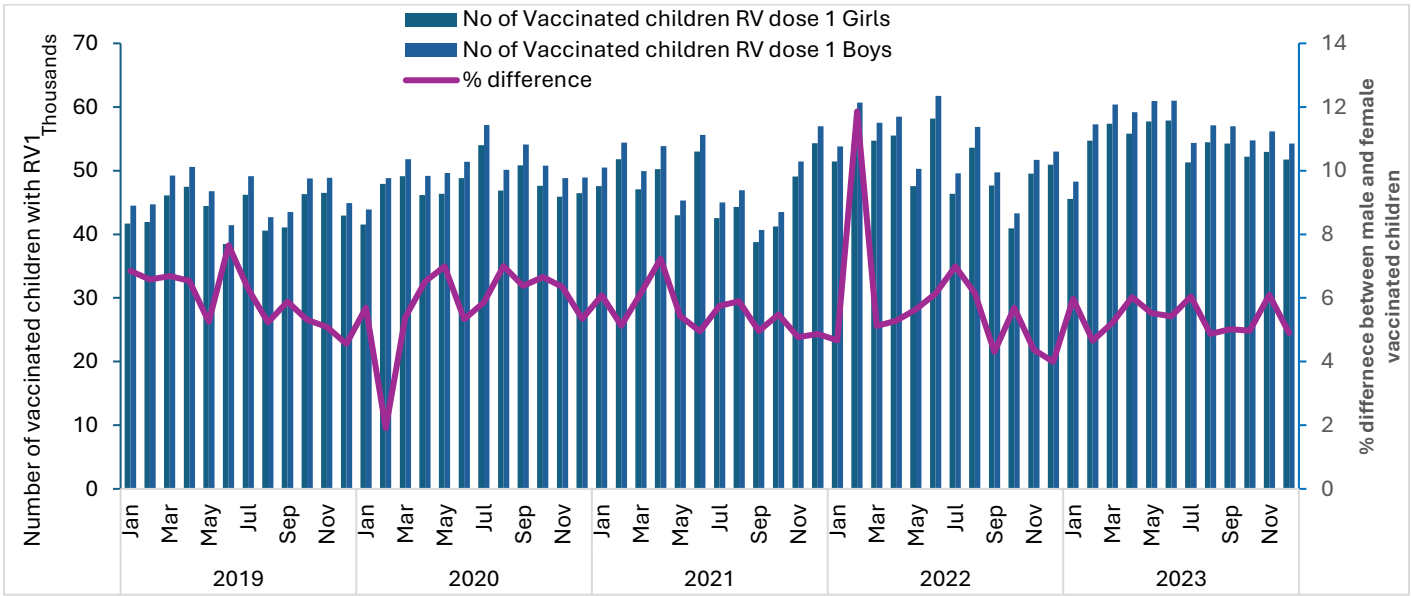
MICS data also reported on geographic disparities in immunization coverage within the country. Provinces like Uruzgan and Nuristan show the lowest immunization rates, whereas Bamyan leads with the highest coverage rates, achieving 98.9% for the rotavirus dose and 86.1% for full immunization (Map 6-2 and Figure 6-4). Similarly, wide geographic disparities for fully immunized children exist between rural and urban areas, with coverage rates of 32.5% and 49.6%, respectively.

Figure 6-2 Sex-disaggregated national immunization coverage across various time periods



Caption figure 6-2: This bar chart displays the percentage coverage for DTP1-3, and Rota1-2 vaccinations for male and female children across different survey periods. Data points are drawn from the Multiple Indicator Cluster Surveys (MICS) and the Afghanistan Health Surveys (AHS). Notable trends include a general increase in vaccination coverage over time, with visibly substantial gender disparities observed in earlier surveys, such as MICS2 (2000), e.g., DTP-3 shows higher coverage for males compared to females in 2000. These disparities appear to decrease in more recent surveys, such as AHS 2018 and MICS6 (2022-2023), indicating progress towards gender parity in immunization coverage.

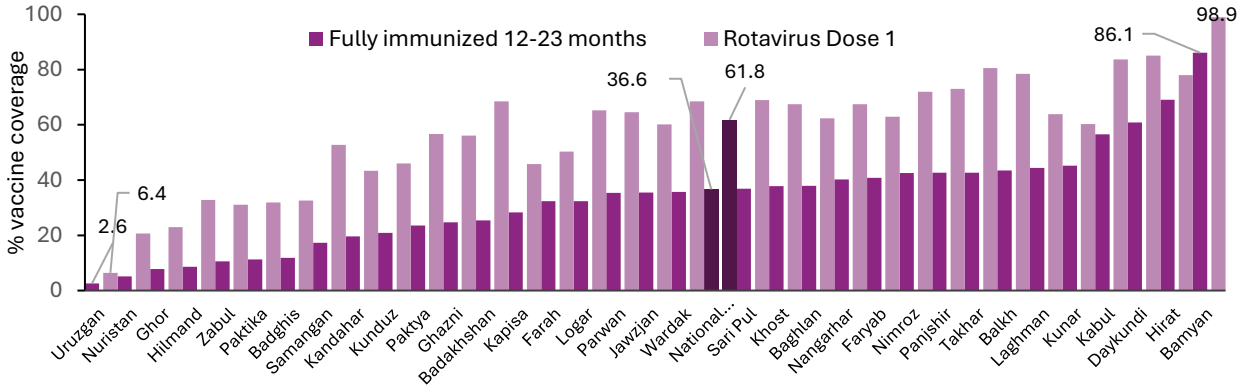
Figure 6-3 Sex-disaggregated rotavirus vaccine dose 1 coverage reported by HMIS between 2019-2023, Afghanistan



Caption figure 6-3: The bar chart displays the number of vaccinated children (in thousands) for girls and boys (blue bars) each month over the five-year period (2019-2023). The pink line represents the percentage difference between male and female vaccinated children. The data highlights fluctuations

in vaccination coverage over time, with certain months showing higher disparities between genders. On average boys have 5 percentage points higher coverage than girls.

Figure 6-4 Proportion of fully immunized children and rotavirus vaccine dose 1 among aged 12-23 months by provinces and national average, MICS 2022-2023



Post-licensure surveillance in Afghanistan (2018-2021) provided another avenue to assess data with a gender lens, with detailed findings reported elsewhere.[17, 18] Among all admitted acute gastroenteritis cases, male children accounted for 62% of all 8760 cases (P <0.0001). The two sexes had no significant difference in rotavirus positivity (male=31.40%; Female=32.40%; P = 0.42). We found no difference in rotavirus vaccine coverage between admitted boys and girls, when examining among those children with verified and unverified vaccination status.[19] Among admitted children, mothers with some levels of formal education were found to be more inclined to vaccinate their children compared to those with no education. Furthermore, maternal education level showed a significant difference (p<0.0001) between children with verified vaccination status and those with unverified status **(see Table 6-2).** When comparing survival rates in post-marketing intussusception surveillance, we found that female infants had a higher likelihood of mortality (OR: 2.79, 95% CI: 1.43, 5.44) due to intussusception (14% vs. 5%; P<0.002), as shown in **Table 6-2**. Further analysis revealed higher mortality rates at Herat Regional Hospital, with an overall rate of 15%, and a sizable disparity between females (23%) and males (9%). Indira Gandhi Children Hospital followed with an overall mortality rate of 9%, again showing higher rates among females (15%) compared to males (6%). Nangarhar Regional Hospital and Ataturk Children Hospital both reported around 6% overall mortality, with Nangarhar showing 11% for females versus 4% for males, and Ataturk reporting 8% for females versus 5% for males.

Table 6-2 Gender analysis of post-licensure rotavirus vaccine surveillance, 2018-2021, Afghanistan

Variables	Levels	Female	Male	P-value
		No. (%)	No. (%)	
Acute gastroenteritis (AGE)	Among all enrolled in the surveillance (N=8760)	3286 (37.51)	5474 (62.49)	<0.0001
Rotavirus gastroenteritis		697 (31.40)	1210 (32.40)	0.42
Rotavirus vaccine among children with verified vaccination status N=5955) *	0- dose	130 (6.98)	235 (7.42)	0.29
	1- dose	549 (29.48)	870 (27.45)	
	2- Dose	1183 (63.53)	2064 (65.13)	
Children with unverified vaccination status		498/3286 (15.15)	840/5474 (15.34)	0.49
Severity of AGE ≥ 11 vesikari score	Among all enrolled in the surveillance	2483 (75.56)	4182 (76.40)	0.37
Severity of AGE ≥11 vesikari score	Among those with verified vaccination status	1681(75.72)	2866 (76.73)	0.37
Severity of AGE ≥11 vesikari score	Among those unverified vaccination status	393 (78.92)	644 (76.67)	0.34
		Verified vaccination status	Unverified vaccination status	
Mother's education status	None	4432(74.42)	1096 (81.91)	<0.0001
	Primary school	584 (9.81)	79 (5.90)	
	Secondary school	433 (7.27)	83 (6.20)	
	Post secondary school	346 (5.81)	49 (3.66)	
	University and above	16 (0.69)	31 (2.32)	
Outcome **(death)** of IS by site	39/468 (8.33%)	23 (13.61)	16 (5.35)	0.002
Ataturk Children Hospital (Kabul)	5/82 (6.10%)	3 (11.11%)	2 (3.64%)	0.18
Indira Gandhi Children Hospital (Kabul)	14/151 (9.27%)	9 (14.75)	5 (5.56)	0.06
Herat Regional Hospital (Herat)	11/74 (14.86%)	7 (22.58)	4 (9.30)	0.11
Nangarhar Regional Hospital (Nangarhar)	9/161 (5.59%)	4 (8.00)	5 (4.50)	0.37

*N=924 were missing values.

From gender analysis of MICS 2022-2023 data, we found that mothers who attained secondary and upper secondary education were 1.8 times more likely (95% CI: 1.39, 2.22) to vaccinate their children with RVV than those mothers with no education or only primary education. Moreover,

children to mothers with higher education levels beyond secondary education were 2.6 times more likely (95% CI: 1.76, 3.83) to receive the rotavirus vaccine than those with no or some primary education.

In provinces classified as “progressive”, where ≥10% of mothers have received primary education, children were 5.0 times more likely (95% CI: 3.99, 6.14) to have received the rotavirus vaccine compared to those in “very conservative” provinces, where <1% of mothers have attained primary education.

Even in “transitioning” provinces, where 2-4% of mothers have received primary education, the likelihood of rotavirus vaccine uptake was 3.15 times higher (95% CI: 2.57, 3.86) compared to very conservative provinces. There was no significant difference in rotavirus vaccine uptake between conservative and very conservative provinces.

As part of content analysis, we found that at the management level, even before the Taliban regime took over in August 2021, only one female, as head of the training department, was part of the national management team. Across all 34 provincial and eight regional teams, EPI managers and supervisors were exclusively men. The number of female vaccinators was as low as 21% (745 out of 3499 vaccinators) until 2019. Under the Gavi’s support, training of additional new female vaccinators had begun after 2019.[20] No update data were available to report on new male and female vaccinator ratios.

Neither the EPI and the community health worker (CHW) training manuals, nor the promotion material, was gender sensitive. **Figure 6-5a** displays a gallery of illustrations printed in the EPI and CHW training manuals. The pictorial materials in those documents mainly featured boy child pictures. For example, in materials emphasizing the importance of polio vaccination, the pictorial representation feature was a boy child with crutches. Furthermore, some of the images of vaccinators administering vaccines, sourced from other countries, which were not aligned with the local dress code, could be wrongly conveying the message that vaccination is a foreign-imposed intervention. The information sheet and promotion of polio vaccine campaigns were featured with male child photos. Exceptionally, the health promotion materials for rotavirus vaccine introduction showed a baby girl published in both national languages, Dari and Pashto **(Figure 6-5b).**

Figure 6-5a Pictorial material of EPI and community health worker (CHW) training manuals

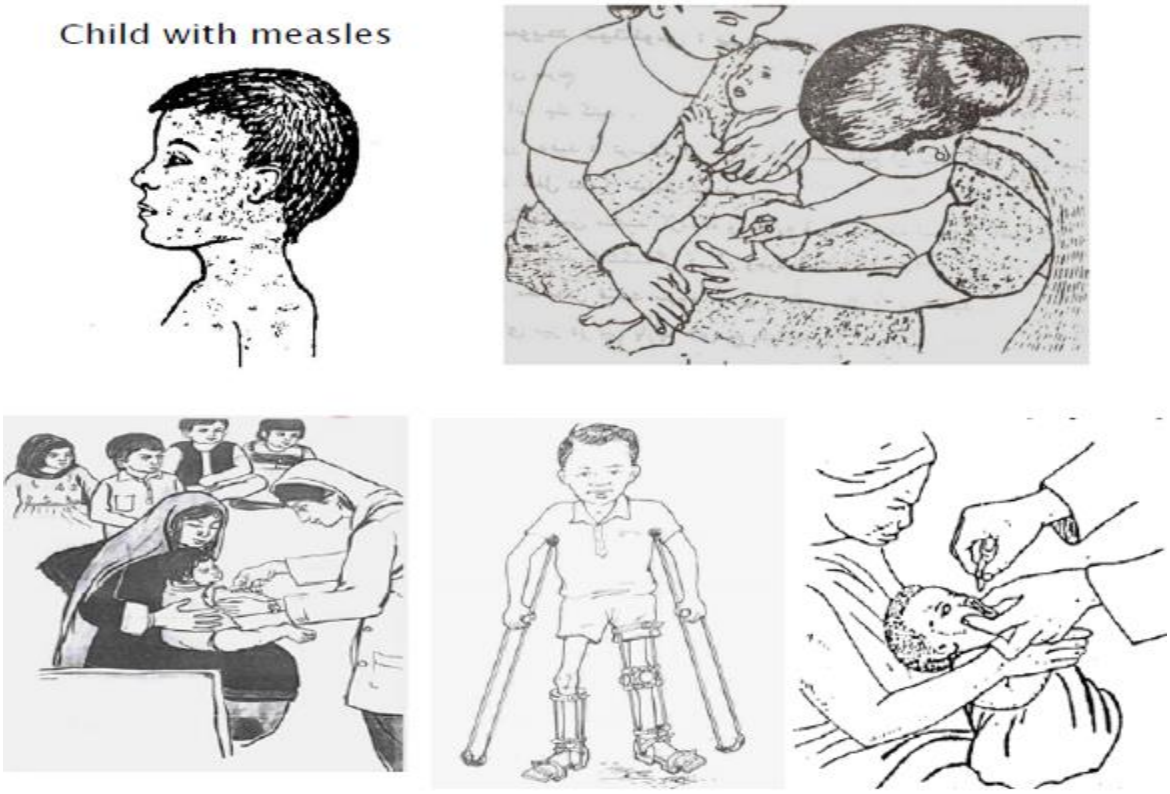


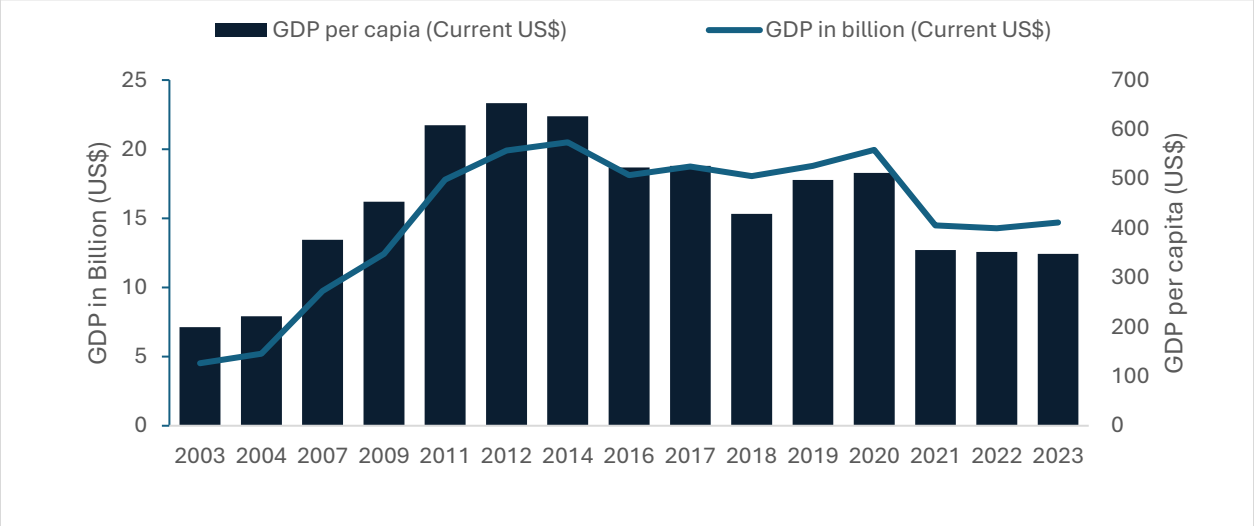
Figure 6.5b Rotavirus vaccine introduction promotional material 2017-2018; BCG vaccine parents information sheet; promotion material of polio eradication campaign

6.6.5 Financial sustainability

Afghanistan's high fertility rate of 5.3 and an annual population growth of approximately 1 million increases the financial burden on the healthcare system while the national health budget is constant or declined over the years. This financial strain is exacerbated by the fading foreign aid over recent years, particularly following the fall of the US-supported government to the Taliban in August 2021.

The nation's Gross Domestic Product (GDP) and per capita GDP have experienced significant fluctuation over the last 20 years due to economic fragility and unstable security. As such GDP contracted by 25.7% during 2021-2022 and has shown almost no growth in 2023.[21, 22] Figure 6-6 depicts trends of GDP and GDP per capita over time. All of these factors indicate that Afghanistan faces major issues with the financial sustainability of its immunization programme.

Figure 6-6 GDP and GDP per capita over time, source (World Bank accessed April 2024)



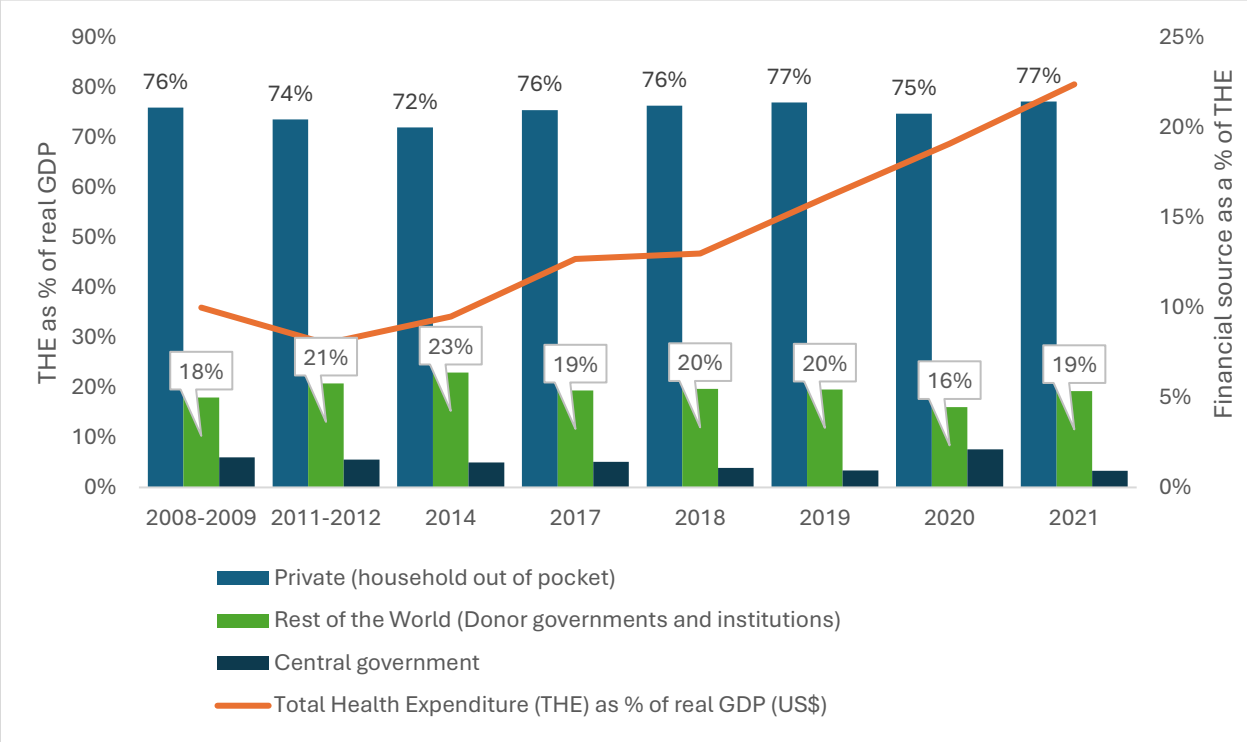
Afghanistan's National Health Account (NHA) reports have been available since 2008. Afghanistan's Total Health Expenditure (THE) has shown a threefold increase since 2008-2009, from US$1.04 billion to US$ 3.36 billion in 2021. When calculating THE as percentage of real GDP it has increased from 10% in 2008-2009 to 22% (US$100) in 2021.[23] The largest share of THE is borne by households through out-of-pocket (OOP) payments, which were 77% of THE in 2021 due to the absence of any social protection or private health insurance scheme. The lowest share of OOP (72%) was reported in 2014 when donor contributions were the highest (23%) **(Figure 6-7).**

Government domestic revenue was at its lowest at 3% in 2019 but later increased to 8% in 2020,

the highest value since 2008. However, even before the government fell to the Taliban in 2021, it had dropped back to 3%. Data for the last 2 years (2022 and 2023) under the Taliban regime were not available. **Figure 6-7** presents the trend of the share of THE as a percentage of real GDP and share of different financial sources to THE. The THE distribution by gender has shown a great shift since 2019 from 63% spent by females to 51% in 2021.

The NHA 2023 reported that vaccine preventable diseases accounted for 4.60% of THE in 2021 compared to 4.90% in 2019. The highest share of THE 2021 went to infectious and parasitic diseases (30%), followed by reproductive health (28%) and non-specific diseases including injuries (16%). Children <5 years of age consumed one quarter of THE in 2023.

Figure 6-7 trend of share of Total Health Expenditure (THE) as percentage of real GDP and share of different financial sources to THE



In 2013, the comprehensive Multi-Year Plan (cMYP) estimated that Afghanistan's immunization programme cost totalled US$ 52.6 million. Financial contributions for the immunization programme in 2013 were sourced as follows: 1% from the Afghan government, 16% from Gavi's grants (13% from its Immunization Services Support (ISS) and 3% from the Health System Strengthening (HSS) fund), and the rest from various donors. Of that budget, 42% was dedicated to procurement of traditional, underused, and new vaccines, including BCG, oral poliovirus vaccine (OPV), measles,

and tetanus toxoid, with newer vaccines like pneumococcal conjugate vaccine (PCV-13) and inactivated poliovirus vaccine (IPV) being procured in anticipation of their 2014 introductions. Approximately 26% was allocated to Supplementary Immunization Activities (SIAs), which included vaccine and operational expenses. The remaining costs were distributed among programme management (12%), service delivery (19%), and disease surveillance, advocacy, and communication (1%).[20]

When the rotavirus vaccine was introduced in January 2018, it was estimated that its introduction would account for 2.8% of the total immunization budget in 2017 and 0.1% of THE for that year.[24] Since the vaccine was projected to be highly cost-effective, the government agreed to co-finance it. According to reports, the government regularly paid its share until 2021.[25] Since then, with the imposed restriction on financial aid by donor organizations and the economic constraints facing the country, the de facto government has been unable to fulfil its co-financing obligation. As the co-financing is designated for antigen procurement, Gavi waived the Afghanistan co-financing payment which amounted to US$1.91 million per year in 2021 and 2022. Afghanistan is one of the few countries for which their traditional vaccines are procured by a donor country. Still, there is uncertainty about securing funding sources from the government of Japan for procurement of those antigens for the coming years. The cost-effectiveness analysis conducted in **Chapter 5** of this thesis provided a new budget estimate for rotavirus vaccination (i.e. assuming a heavily subsidised price due to Gavi donor support). The co-financing share for the Afghanistan government will be **US$4.4 million** per year. This seems to be the critical piece of evidence for decision-makers i.e. even if Gavi continue to cover the bulk of the cost of the vaccine, Afghanistan will still need to find $4.4m every year to fund their required contribution ($0.13 per dose plus wastage and other related health system delivery costs). Where will this money come from in the coming years?

The subsequent withdrawal of health donors following the collapse of the previous Afghan government pushed Afghanistan's health system to the verge of collapse, with many primary health facilities being closed, health personnel not being paid, and medical supplies and commodities in short supply. The impact of this funding hiatus was particularly severe in the first four months (August-November 2021) until the donors resumed support for the health sector, bypassing the Taliban government. An analysis looking at outcomes in 2021 after the suspension of donor funding to the healthcare system and comparing this with 2019 outcomes, reported that there was a 29% decrease in DPT-3 vaccination and around a 17% increase in child deaths due to vaccine

preventable diseases in 2021 compared to 2019.[26] Similar results to those reported in African countries following decreases in donor funding.[27, 28]

6.6.6 COVID-19

The COVID-19 pandemic has had widespread impacts on Afghan society. Unlike other respiratory or infectious diseases, COVID-19 often presented as asymptomatic or mild in infants and young children <5 years of age.[27] Lockdowns that were a feature of the COVID-19 pandemic affected rates of AGE incidence and vaccine coverage. It is important to understand if both factors have returned to pre-pandemic levels as this may affect rotavirus vaccine decision-making. Early in the pandemic, WHO estimated that 80 million children were at risk of vaccine-preventable diseases due to disrupted immunization services.[28] In Afghanistan, the situation was worsened by armed conflict and political instability. The government's strict lockdown measures, extended between late March to end of July 2020, coupled with shortages of healthcare personnel and supplies, led to decreased access to immunization services. Public reluctance to seek healthcare during the pandemic further undermined the system.[29]

Routine immunization services were affected by COVID-19 due to losing health facility staff and the suspension of outreach services and mobile immunization sessions, which are the two main strategies for delivery of childhood immunization in the country.[30]

When comparing the lockdown months (March-July 2020), with the same months of 2019, DPT-1 coverage declined by 15% and this decline was double that for DPT2 and DPT3 (26% and 32%), respectively. A drop in RV2 coverage (10%) was also reported in those lockdown months. Further detail is provided in **Table 6-1**. Another study, which assessed the impact of COVID-19 in one province of Afghanistan during the same months, reported a 56% decline in vaccine coverage through outreach and a 13% decline at fixed facilities, resulting in an average of 325 children per day being prevented from accessing life-saving vaccines during that period.[29]

When comparing the COVID-19 lockdown months (April-July 2020), the peak of the pandemic, with the same months in pre-COVID (April-July 2019) and post-COVID years (April-July 2021), using the post-licensure acute gastroenteritis (AGE) surveillance, we observed several significant trends presented in **Table 6-3**. During the lockdown months, a smaller proportion of cases (23%) were enrolled in surveillance compared to the pre-COVID (47%) and post-COVID (30%) periods with some variation among the sites. Among the enrolled cases, a slightly higher proportion of severe

AGE cases (77%) were observed during the COVID months compared to the pre-COVID period (74%), but this was lower than in the post-COVID era (82%). The recovery rate among admitted AGE patients was slightly lower during the COVID months (91%) compared to both the pre- and post-COVID months, 94% and 96%, respectively. Interestingly, during the COVID months, a higher proportion of AGE patients (9%) left the hospital against medical advice compared to the pre- and post-COVID months (4% during both periods). (**Table 6-3)**

During the lockdown period, there was a higher representation of AGE patients from the lowest wealth quintile compared to the high end (rich and richest) compared to the pre-COVID period. The distributions of wealth quintiles among admitted patients during the COVID and post-COVID months were not significantly different. (**Table 6-3)**

The decision-making process surrounding the introduction and implementation of the rotavirus vaccine in Afghanistan may have been significantly influenced by the changes in social dynamics during the COVID-19 pandemic. The pandemic led to closer living conditions and increased within-household mixing, which probably heightened the transmission of rotavirus within homes. At the same time, reduced community mixing may have lessened the overall exposure to the virus, potentially leading to lower levels of natural immunity among the population. This situation underscored the importance of vaccinating infants, as those not vaccinated would have faced a higher risk of severe disease in a context of diminished herd immunity. Furthermore, disruptions caused by the pandemic may have also impacted vaccine coverage, possibly leading to lower protection levels among infants and contributing to fluctuations in acute gastroenteritis (AGE) incidence.

***Table 6-3 Comparison of AGE cases and outcomes during COVID-19 lockdown months (2020) with the same months of pre-covid (2019) and post-covid (2021)* months**

	Total	April-July			P-value
		During COVID 2020	Pre-COVID 2019	Post-COVID 2021	
Enrolment hospital	2928 (100)	689 (23.53)	1361 (46.48)	878 (29.99)	<0.0001
Indira Gandhi Children Hospital	744 (25.41)	210 (29.17)	297 (21.82)	246 (28.02)	
Herat Regional Hospital	520 (17.76)	111 (16.11)	285 (20.94)	124 (14.12)	
Nangarhar Regional Hospital	860 (29.37)	176 (25.54)	480 (35.27)	204 (23.23)	
Mazar Reginal Hospital	804 (27.46)	201 (29.17)	299 (21.97)	304 (34.62)	
Sex (male) %	1848 (63.11)	443 (64.30)	837 (61.50)	568 (64.69)	0.24
Age in months (Median, IQR)	8 (4, 12)	7 (4,12)	7 (4, 12)	8 (4,12)	0.13
Rotavirus positivity	932 (31.92)	229 (33.24)	456 (33.68)	247 (28.16)	0.02
Gastroenteritis severity (Vesikari score>=11)	2265 (77.36)	532 (77.21)	1014 (74.50)	719 (81.89)	0.0001
Outcome					
Recovered	2750 (93.92)	628 (91.15)	1278 (93.90)	844 (96.13)	<0.0001
Died	6 (0.20)	0 (0.00)	6 (0.44)	0 (0.00)	
Transferred to another hospital	19 (0.65)	0 (0.00)	**19 (1.40)**	0 (0.00)	
Left hospital against medical advice	151 (5.16)	60 (8.71)	57 (4.19)	34 (3.87)	
Wealth quintile					
Poorest	723 (24.69)	174 (25.25)	326 (23.95)	223 (24.40)	<0.0001
Poor	637 (21.76)	179 (25.98)	254 (18.66)	204 (23.23)	
Middle	628 (21.45)	157 (22.79)	281 (20.65)	190 (21.64)	
Rich	504 (12.21)	106 (15.38)	250 (18.37)	148 (16.86)	
Richest	436 (14.89)	73 (10.63)	250 (18.37)	113 (12.87)	

6.7 Discussion

This chapter gathered evidence on cross-cutting issues and other criteria required to make an overall appraisal of whether Afghanistan should continue to use rotavirus vaccination as part of its national immunization programme. The chapter began with the introduction of a proposed Vaccine Decision-Making Framework (VDMF) developed as part of this DrPH's Organizational and Policy Analysis (RSI) recommendations.

Since the previous chapters of the thesis have already addressed key criteria around costs, benefits and risks, this chapter mainly focused on insecurity and armed conflict, equity in terms of gender equality and geographical disparity, financial sustainability, and the COVID-19 pandemic. The findings from assessments of these four areas highlighted the importance of each of them being thoroughly evaluated and considered when a vaccine policy recommendation is being developed.

Children are the most vulnerable group suffering from direct and indirect impacts of armed conflict and insecurity. Although EPI programmes at the global level have had substantial achievements [29], approximately 17 million children worldwide remain unvaccinated, failing to receive their first dose of DPT, constituting 10% of children born annually. Nearly 9.6 million (57%) of these unvaccinated children reside in conflict-affected areas.[30] The trend analysis in this chapter underscores the need for tailor-made and innovative approaches to maintain vaccine delivery in conflict-affected areas, such as advocacy with local traditional and religious leaders, engaging and negotiating with the armed groups, provision of mobile vaccination clinics, and leveraging community health workers.[31, 32] However, during the last 20 years, when the Taliban were fighting against the Afghan government, the International Committee of the Red Cross (ICRC), Afghan Red Cross, and some other international humanitarian organizations invested extensive time and resources to maintain engagement and negotiations with all sides. These efforts had some success, but were mainly concentrated in the south of the country, where the Taliban had more presence, and focused more on access to polio vaccine campaigns.[32] The work demonstrated that it is critical to maintain continued implementation and balance in programmes, for example, to eradicate polio, and continuity and acceptance of all routine immunization programmes should also be given importance. In any vaccine related policy decision, a holistic and integrated approach should be considered.[33]

The gender-related statistics in this chapter provide valuable insights into the dynamics of rotavirus

vaccine coverage and its acceptance across different populations. The fact that females have a slightly lower burden of RVGE relative to males, along with slightly lower vaccine coverage, is noteworthy, but it does not appear to significantly skew decision-making in a way that would discourage the continued use of the rotavirus vaccine. The data suggest that the rotavirus vaccine is broadly accepted and utilized across both genders, with coverage rates that are relatively balanced. This indicates that the vaccine is not contributing to gender-based disparities in healthcare access, which is crucial in a context like Afghanistan where gender equity in health services is a significant concern. The role of maternal education, however, appears to be a crucial factor for higher and overall immunization coverage. Mothers with some formal educations were more likely to vaccinate their children. This finding is aligned with similar findings from Kenya, where mothers who have completed primary education were 1.5 times more likely to take their children to get the oral polio vaccine, or in Eritrea, where children to mothers with primary education were 2 times more likely to be fully immunized.[34, 35] Overall, there is established evidence that maternal education correlates with child health outcomes and reduces <5 child mortality by 7-9%.[36, 37] Historically, vaccinators in Afghanistan have often had limited education, with many being hired after completing only grade 6. This, combined with underdeveloped interpersonal communication skills, has hindered the effective delivery of immunization services. The predominance of male vaccinators in a traditionally conservative society like Afghanistan further complicates the situation, as children are typically brought to health facilities by their mothers or female caregivers, who already face significant cultural barriers to seeking care—such as needing permission from and being accompanied by a male family member. Given this context, it becomes imperative to prioritize investments in girls' education and actively promote the recruitment of female vaccinators to improve immunization coverage and ultimately child health. Policymakers can be reassured that, based on the current data, sustaining the rotavirus vaccine programme is aligned with promoting gender equity in health. However, continuous monitoring is essential to ensure that as the programme continues, it does not unintentionally create or exacerbate gender-based disparities.

Referencing Map 6-2, which illustrates the distribution of full immunization coverage by provinces in Afghanistan, this analysis highlights the persistent geographic disparities in access to primary healthcare services across the country. The data underscore significant variations in childhood immunization rates across different regions, bringing to light the uneven distribution of healthcare resources and services. This disparity suggests that certain provinces may face more challenges in

providing comprehensive immunization coverage, which could be due to factors such as infrastructure, healthcare workforce distribution, and socio-economic conditions, and geography.

The implications of inequitable vaccine distribution by geography and economic status are profound. Geographic disparities often reflect broader systemic inequities, where provinces with limited infrastructure or security challenges are left underserved. These regions are disproportionately affected by preventable diseases, perpetuating cycles of poor health outcomes and economic hardship. Similarly, economic disparities exacerbate the issue, as families in lower socio-economic brackets may struggle to access vaccination services due to costs, distance to healthcare facilities, or a lack of awareness about the importance of immunization.

This disparity by geography may contribute to lower vaccine effectiveness in many low-income countries, including Afghanistan. Inequitable access to vaccination can result in inconsistent immunization schedules and lower overall vaccine coverage, which in turn reduces the overall impact of vaccination programmes, particularly if the same children are at increased risk of vaccine-preventable diseases and/or have a less optimal response to vaccination.

Such inequities in vaccine access can undermine national immunization efforts and the broader goal of achieving universal healthcare. Addressing these disparities is crucial for ensuring equitable access to essential healthcare services, including rotavirus vaccination for all children in Afghanistan. Targeted interventions, such as strengthening healthcare infrastructure, expanding outreach programmes, multisectoral collaboration, and addressing socio-economic barriers, are necessary to bridge these gaps and achieve equitable vaccine coverage.

The high stunting rate of 41%—a chronic form of malnutrition—among children younger than five years reflects significant socio-economic disparities and inequitable access to health and nutrition services. In reference to vaccine effectiveness (VE) discussed in Chapter 3, we observed substantial differences in VE between stunted and non-stunted children (6% vs. 81%). We could not report statistical significance due to the small sample size. However, it is biologically plausible that stunting may impair immune responses and reduce the overall benefits of vaccination, further exacerbating the challenges faced by vulnerable populations. This underscores the critical need to address malnutrition alongside immunization efforts to maximize the public health impact of vaccines. It also emphasizes the importance of a multisectoral approach and collaboration to effectively tackle these interconnected issues. In principle, a lack of access to nutrition services is likely to be correlated with a lack of access to immunization services; this means that stunted

children could have both lower coverage and lower efficacy, despite being at a potentially higher risk of severe outcomes from rotavirus disease. These effects could have important implications for the estimated impact of rotavirus vaccination, particularly on the most severe outcomes e.g. deaths.[38] A future analysis could help to inform the scale of these effects but would require more information on both the risk of rotavirus disease and the expected coverage among children with different nutritional characteristics. Higher efficacy vaccines may also be needed for these children. Furthermore, an important gender and geographic disparity was reported in the survival rates among infants admitted at post-marketing surveillance sites. Notably, more female infants died to intussusception compared to their male counterparts. These findings underscore significant gender disparities and raise critical questions about timely access to healthcare, the quality of care provided, and the underlying inequalities that may contribute to these differences among sites. The data suggests that female infants may face additional barriers in receiving timely and effective treatment, which could be influenced by socio-cultural factors, healthcare-seeking behaviour, and potential biases within families. Furthermore, the geographic disparities indicate that certain regions may lack the necessary resources and infrastructure to provide adequate care, exacerbating the survival outcomes for infants.

Since the re-establishment of the health system in Afghanistan in 2002-2003, there has been a notable increase in the demand for and supply of health services, particularly immunization. This can be attributed to several factors, including an increase in the number of health facilities and staff, an expansion in the number of childhood antigens available, and a rise in healthcare beneficiaries due to a high growth rate, a decrease in child mortality, an influx of returnees from neighbouring countries such as Iran and Pakistan, and an increase in life expectancy. However, financial sustainability remains a critical concern for Afghanistan's immunization programme. Over the years, total health expenditure has grown relative to GDP. When the two main sources of health sector financing – the government and external donors – have however remained constant or reduced, households have had to shoulder an increasing share of health expenditure in the form of out-of-pocket (OOP) payments. This has led to a budgetary crisis for many households, pushing them further into poverty. Strengthening the financial capacity of the health system is crucial to ensure the sustainability of immunization programmes and the delivery of vaccines to all children. Given the current political landscape in the country, sustained donor funding is vital to maintain

and improve childhood immunization coverage, particularly for the rotavirus vaccine, a recent addition to the national immunization programme.

The COVID-19 pandemic posed additional challenges to routine immunization in Afghanistan, leading to a decline in vaccine coverage and timeliness.[39, 40] The pandemic underscored the need for resilient health systems capable of adapting to emergencies while maintaining routine healthcare services.[41] As lockdown measures eased, vaccine coverage improved, highlighting the importance of flexible and mobile immunization strategies in response to crises.[42] A scoping review reported a decline of 10% to 38% in routine childhood immunization coverage in LMICs between 2019 to 2021.[40] Similarly, the number of vaccine doses administered also saw a significant decrease, with declines ranging from 25% to 51%, and the timeliness of vaccinations was affected with declines ranging from 6.2% to 34%.[40, 43] This analysis further highlighted the importance of anticipating and allocating resources for unexpected events such as disease outbreaks, natural disasters, conflicts, or similar situations hindering immunization programmes. Most importantly, a recovery and catch-up plan particularly for childhood immunization is critical.

Overall, the findings of this chapter have provided an in-depth understanding of contextual cross-cutting factors that can contribute to informing the VDMF. Chapter 7, the final chapter, will bring all findings from Chapter 3-6 to the proposed VDMF.

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CHAPTER SEVEN: SYNTHESIS AND REFLECTIONS ON THE THESIS RESEARCH

Chapter 7: Synthesis and reflections on the thesis research

In this final chapter, I summarize, synthesize and reflect on the key findings from the research studies incorporated in this thesis (Chapters 3-6). I begin in section 7.1 with a summary and synthesis of the findings structured around the eight research objectives. Under each objective, I summarize how the evidence or information contribute to the 7 criteria of the proposed Vaccine Decision-Making Framework (VDMF) which was presented in Research Study 1 (RSI). Under each objective, policy implications are summarized in terms of the question of whether rotavirus vaccination should be continued through the national immunization programme. Section 7.2 then discusses the limitations of the work presented in this thesis. Finally, I consider areas for further research, contextualize this work within the broader landscape of vaccine decision sciences and policy, and emphasize its role in informing future public health research and decision-making.

7.1 Summary of findings

This thesis has offered a comprehensive exploration and analysis of rotavirus vaccination in Afghanistan and generated evidence for a proposed Vaccine Decision-Making Framework (VDMF), scrutinizing it from the perspectives of post-licensure impact, effectiveness (Chapter 3), and post-marketing safety (Chapter 4). These evaluations laid the groundwork for the main foci of my thesis, which were the benefit-risk and cost-utility analyses of rotavirus vaccination in Afghanistan using real-world data (Chapter 5).

Given Afghanistan's distinctive context in relation to childhood immunization, in Chapter 6 I also carried out a cross-sectional assessment of the influence and interplay of factors such as armed conflict and security, equity from the standpoints of gender equality and geographic disparity, financial sustainability, and COVID-19, on childhood immunization broadly, and on rotavirus vaccination in particular.

The primary aim of the thesis was to evaluate the real-world benefit-risk and cost-utility of ROTARIX, a monovalent rotavirus vaccination, among children <5 years in Afghanistan. To accomplish this, I devised eight objectives that steered the research and analysis throughout the thesis. These objectives offered a structured approach for addressing the multifaceted aspects of rotavirus vaccination and its real-world implications. **Table 7-1** provides a summary of the findings from the studies underpinning this thesis, in relation to the seven main criteria of VDMF namely: 1) problem

(assess the importance); 2) benefits and harms; 3) values and preferences; 4) acceptability; 5) resource use; 6) equity; and 7) feasibility.

The first two columns of **Table 7-1** present the seven main criteria and related sub-elements of the VDMF. The only evidence on any criteria prior to January 2020 was a previous CEA study done in 2017 and pre-vaccine surveillance reported on RVGE hospital burden.[1,2] The last three columns summarize the findings of studies conducted under this thesis from 2020 to 2024. The highlights of the findings obtained under each objective and their contribution to the VDMF are set out below.

7.1.1 Summary and synthesis for objectives 1-3; Chapter 3, Research paper 1

Objective 1 involved an evaluation of rotavirus vaccine effectiveness (VE) under routine public health practices. This was achieved through an epidemiological study using a test-negative case-control design (TND), embedded into post-licensure surveillance conducted from May 2018 to December 2021.

The study found that ROTARIX had a moderate effectiveness of 45% (95%CI: 22, 62) for two doses among children aged 6-59 months. A rotavirus mortality peak occurs around 6-10 months.[3] Encouragingly, our study found a higher VE of 57% (95%CI: 33,73) in this age group, an indication of better effectiveness of RV vaccine given the current RVGE age distribution (2/3 of our sample were aged 6-11 months). Our findings are consistent with previously reported lower VE in low- and middle-income countries (LMICs) than high-income settings with low child mortality, suggesting a need for continued research and scientific explanation. Notably, VE was found to substantially vary by a child's nutritional status, with much lower VE among children with stunting, or low height for age ratio. Due to the small sample size when stratification was applied, we did not find statistical significance. This observation prompts future research (see section 7.3.1), specifically designed to test this hypothesis, and especially for malnutrition, particularly chronic malnutrition (stunting), as this is more prevalent in Afghanistan. The findings under this objective directly contributed to objectives 5 and 7 of the thesis, as they provided inputs for the modelling analysis.

Contribution to VDMF. The study provided empirical evidence on the effectiveness of rotavirus vaccination, and so to a sub-element of the VDMF criterion 2, **“Benefits and harms”**, and partially to criterion 4, **“Acceptability”,** sub element “financial, ethical and programmatic” aspects. However, vaccine acceptability was not directly studied under this thesis but can be inferred from relatively high coverage of RV vaccination among vaccine eligible-age children who were admitted to the surveillance sites.

Ideally, for the VDMF, it is crucial that all evidence concerning the advantages and disadvantages of a new vaccine (or any other intervention) are effectively communicated to the end-user beneficiaries. A public poll or qualitative studies are ideal to gather information on acceptability. In the context of childhood immunization. This would involve engaging with guardians and caregivers/parents to ensure their perspectives are considered **(Table 7-1)**

For **Objective 2**, I evaluated the impact of rotavirus vaccination by comparing surveillance data from pre- (2013-2015) and post- (2019-2021) vaccine introduction. After adjusting for the stability in the rate of test-negative acute gastroenteritis (AGE) admission, at 85% vaccine coverage, we estimated that RV could reduce RVGE admissions in children <5 years by 39%. There was a variation in vaccine impact across the surveillance sites, and we also reported wide geographic disparity among provinces. **(Map 6-2)** This suggests the need for further studies to explain this geographical variation (see section 7.3.2).

Contribution to VDMF. The study provided evidence on the impact of rotavirus vaccination at certain vaccination coverage levels, and so contributes to a sub-element of VDMF criterion 2, **"Benefits and harms" (Table 7-1).**

Policy implications. While a reduction in RVGE admissions of 39% (impact) might seem modest, it is significant considering the large baseline burden of RVGE among children <5 years in Afghanistan. This level of impact translates into a substantial number of children being protected from RVGE-related hospitalisation and morbidity. The findings under this objective further strengthen the case for the continuation of RV vaccination in Afghanistan. Policymakers can use these findings to advocate for sustained and increased funding for RV vaccination programmes. The data can also inform the design and implementation of targeted interventions to improve vaccination uptake and coverage (see section 7.3.7).

For **Objective 3** I conducted an interrupted time-series analysis using administrative data from the Heath Management Information System (HMIS) to assess change in AGE admissions and clinic visits over time between 2013 and 2022. The Ministry of Public Health (MoPH) routinely collects extensive data on childhood illnesses and immunizations, providing a valuable opportunity to infer vaccine impact and vaccine coverage.

Cleaning and processing of the HMIS data were challenging and time-consuming tasks due to the high volume of missing values. I applied strict criteria and limited the analysis to health facilities

that consistently reported AGE among children <5 for at least 11 months annually between 2013 and 2022. As a result, only 4% of 342 health facilities reporting AGE admissions and 43% of 2,730 health facilities reporting AGE clinical visits met the criteria and were included in the analysis.[4]

I ran a negative binomial model due to potential overdispersion in the data. This analysis also demonstrated a positive impact of RV vaccination in reducing AGE admissions. However, the impact on AGE clinic visits was less pronounced, probably because less severe AGE cases are managed in outpatient departments. Previous observational and meta-analysis studies suggested lower VE for moderate to mild RVGE, potentially due to factors such as vaccine performance, host factors, and variations in virus strains.[5] This observation prompts further research to explore explanations for the lower vaccine performance on mild to moderate RVGE. Additionally, the analysis revealed seasonality in RVGE and a slight shift in RVGE patterns following vaccine introduction.[6]

Contribution to VDMF. The study provided evidence on the impact of rotavirus vaccination, and so contributes to a sub-element of the VDMF criterion 2 "**Benefits and harms**". It also provided information about RVGE seasonality, with implications for a sub-element of the VDMF criterion 7, "**Feasibility**" ("*programme operation*") (**Table7-1**).

Policy implications. This analysis underscores the importance of HMIS data in monitoring changes over time for any health intervention, without incurring additional costs or efforts. Health programmes, including the immunization programme, can leverage routine data to identify facilities with low performance or localities with lower coverage and devise tailor-made interventions to address the specific issues observed (see section 7.3.3). Our analysis also reveals a considerable gap in the quality of routine data collected by HMIS. The quality of HMIS data can be improved by ensuring data completeness through digitization of the system to flag missing values or inconsistent or implausible inputs. Regular data cleaning, periodic data analysis and reporting, and information dissemination with the programmes can further improve healthcare service delivery.

Overall, the evaluations carried out in Chapter 3 represent the first comprehensive analysis of the impact and effectiveness of a vaccine following its introduction in Afghanistan. In addition to providing evidence that supports the continued use of the rotavirus vaccine in the country, this research contributes to the global literature on rotavirus vaccine performance in low-income

countries. These countries often face similar challenges.

7.1.2 Summary and synthesis for objective 4; Chapter 4, Research paper 2

To address **Objective 4,** I evaluated the safety of ROTARIX by utilizing post-marketing intussusception surveillance conducted in four hospital-based sentinel sites in Afghanistan from May 2018 to June 2022 (Chapter 4). Utilizing a self-controlled case-series (SCCS) design, I calculated the relative incidence (RI) rate in pre-identified risk windows (1-7 days, 8-21 days, and 1-21 days) following each RV vaccine dose compared to non-risk windows. The results indicated no evidence for increased risk with ROTARIX following each vaccine dose, except for 8-21 days following dose 1, where there was a slight, but not statistically significant, excess risk (IR:1.3; 95%CI: 0.4, 4.2). This study provides some reassurance about the safety of ROTARIX among vaccine-eligible children and supports the continued use of the rotavirus vaccine in Afghanistan. This assessment also reported a higher fatality rate among admitted infants with intussusception compared with the existing literature (8% versus <6% for LMICs).[7]

Contribution to VDMF. This evaluation provided empirical evidence on the safety of rotavirus vaccination, and so contributes to a sub-element of the VDMF criterion 2, "**Benefits and harms**".

Policy implications. The findings on rotavirus safety increase confidence in the continued use of RV vaccination in Afghanistan. A question prompted by the findings of this evaluation suggestion further exploration of the high fatality rate among admitted infants, particularly among female infants, with intussusception. This chapter (Chapter 4) has already contributed to the global literature on the safety of the RV vaccine.

The novel contribution of Chapter 4 lies in its focus on post-marketing intussusception surveillance enabling the timely detection and investigation of adverse events following immunization. While clinical trials provide crucial safety data, rare or unexpected adverse events may only emerge once vaccines are widely administered in the population. The findings provide empirical evidence on vaccine safety through robust epidemiological study design. The policy implications of these findings extend beyond the country where the study was conducted. By identifying potential risks, it enables policymakers to develop strategies to ensure vaccine safety and maintain public confidence.

Afghanistan's post-marketing surveillance was a component of the South Asia Intussusception Network, which also included Pakistan and Myanmar. As a result, I contributed as a co-author to a

joint publication of this network, further enhancing the regional and global understanding of RV safety. This underscores the importance of cross-country efforts in monitoring vaccine safety and contributes to the broader scientific community.

7.1.3 Summary and synthesis for objectives 5-7; Chapter 5, Research paper 3

Objective 5 focused on the economic evaluation of ROTARIX vaccination versus no vaccination in Afghanistan. I utilized the UNIVAC (Universal Vaccine) decision-support model, an open-access Excel-based tool. To support the continued use of RV vaccination, I retrospectively assessed health benefits and costs over a seven-year period from 2018 to 2024, from both governmental and societal perspectives, using a 3% discount rate. The strength of the model lies in its input parameters derived from real-world pre- and post-vaccine introduction surveillance data, epidemiological TND and SCCS studies under Objective 1 and Objectives 3 and 4, the most updated available national survey data, and updated global literature on disease burden.

The model estimated that ROTARIX vaccination could avert around 50,000 severe cases, and 30,000 severe clinic visits; 13,000 hospital admissions, and 700 deaths, due to RVGE per year. Additionally, it could avert over 18,000 DALYs per year.

Although Afghanistan is still in the initial phase of Gavi's eligibility for receiving financial support, I calculated all costs with and without Gavi's support for a comprehensive assessment. To run the RV vaccination programme nationally, it will cost government an annual budget of US$4.4 million per year, with the cost of averting one DALY being US$212 under Gavi's subsidy. We compared incremental cost-effectiveness ratios (ICER) with a range of willingness-to-pay thresholds ($ 0-US$ 500, equivalent to 1xGDP per capita) finding that ICER was less than 42% of 1xGDP per capita (US$ 500). Given the low likelihood of Afghanistan graduating from Gavi support in the near future, the vaccine represents good value for money from the government's perspective when using a heavily discounted dose price. UNIVAC is a static model and does not allow for herd immunity, so is expected to under-estimate the benefits by 22-25% additional indirect effects of rotavirus vaccination, according to a meta-analysis.[8]

Contribution to VDMF. The study contributes information to the following criteria of the VDMF:

criterion 1, "**Burden of disease**", in both sub-elements, "*burden of disease*", outlining the size of the problem without vaccination, and "*economic burden*"; and criterion 5, "**Resource use**", sub-element "*direct cost*" (the study provides figures for programme cost per year and as a proportion of

total vaccine programme budget and total health expenditure), and sub-element "*cost-effectiveness ratio*" (the study presents this in terms of cost per DALY averted from government and societal perspectives).

Policy implications. The CEA study reported that two doses of ROTARIX have a 41% impact in reducing RVGE hospital admissions and mortality, closely replicating the 39% impact reported under Objective 2. The CEA translates the impact of rotavirus vaccination into figures that policymakers can easily understand, such as the number of lives saved, clinical visits averted, and hospitalizations prevented. Additionally, it quantifies the intervention in monetary terms, illustrating how much a one-year programme will cost the government and the financial benefits due to the reduced burden on the healthcare system. The study findings underscore the cost-effectiveness of ROTARIX in Afghanistan, particularly considering the financial constraints faced by the current de facto government.

Objective 6 was specifically focused on the benefit-risk analysis. Building on the findings from Objective 4 and post-marketing surveillance, the mathematical modelling using the UNIVAC tool reported that for every 1493 lives saved from RVGE mortality among children <5, there is one excess death due to intussusception at a 41% vaccine impact. The study aligns with existing literature, indicating that the benefit of saving 1500 lives from RVGE among children <5 years outweighs the risk of one excess death due to intussusception. The study reconfirms the safety of the vaccine and supports continuing rotavirus vaccination in Afghanistan.

Contribution to VDMF. The study contributes data to the VDMF criterion 2, "**Benefits and harms**", sub-element "*benefit-risk*".

Policy implications. The epidemiological study under Objective 6 provides empirical evidence of the vaccine's safety among Afghan infants aged <12 months. Building on this finding, the mathematical modelling provides an opportunity to make estimations at the population level and among children < 5 years old. The results are encouraging, leaning towards health gain versus life risk.

Objective 7 aimed to provide a comprehensive CEA profile of pre-qualified rotavirus vaccines available under Gavi's support for Afghanistan. This analysis identified ROTARIX as the primary option, followed by ROTASIIL (1-dose per vial presentation) when the country is benefiting from Gavi's support. Under the assumption of no Gavi's support, ROTASIIL (2-dose per vial presentation)

emerged as the first option, followed by ROTARIX. Greater detail is provided in Chapter 5.

Contribution to VDMF. The study contributes information to the VDMF criterion 7, "**Feasibility**", and to the sub-element "*continuity of the intervention*".

Policy implications. The shortage of certain rotavirus vaccines in the global market has prompted many countries to switch to another vaccine type, posing a question to policymakers about which vaccine type is most cost-effective for them. This thesis objective specifically answers that question for Afghan policymakers in the years to come. Therefore, the timeframe for the analysis is 10 years from now (2025-2034), both with and without Gavi's support at the discount rate of 3%. This was a valuable addition to my analysis, generating evidence on each available RV vaccine and a comparison profile for future decision-making.

Chapter 5 highlights the significant potential of cost-effectiveness (CEA) and benefit-risk analyses in generating robust evidence for decision-making in vaccination programmes, such as determining the inclusion or continuation of rotavirus vaccination in national immunization schedules. As outlined in **Table 7-1**, the inputs and outputs of these models contribute substantially to most criteria and sub-elements of the proposed VDMF for Afghanistan.

This chapter underscores the importance of CEA in providing essential evidence for informed policy recommendations. Post-licensure economic and benefit-risk assessments support the continuation of the vaccination programme by demonstrating substantial health gain over perceived risk, and also economic gains. Additionally, these assessments contribute to the global literature, facilitating international comparisons and the formulation of global recommendations for rotavirus vaccination.

The study emphasizes the crucial role of Health Technology Assessment (HTA) bodies, such as the NITAG, in determining the benefit levels and acceptable risks of vaccination interventions.

7.1.4 Summary and synthesis for objective 8; Chapter 6

Chapter 6, which addresses **Objective 8**, focused on cross-cutting issues and other criteria not previously assessed in the thesis, including equity, insecurity, and financial sustainability. I also revisited the decision-making framework recommended in the OPA and reflected on the current status of the evidence available for each of the appraisal criteria.

I conducted a web search, and supplemented this with a more manual search of programme reports and other documentations, and secondary data analysis of open-access national datasets

including administrative and survey datasets.

Insecurity and armed conflict have had drastic effects on access to and utilization of immunization services. The analyses conducted in this thesis highlighted the importance of strength and resilience in health systems so they can function in and respond to changing environment and facilities. **Equity** in health and healthcare services is a core value of human rights. Equity has several dimensions, but under this thesis, I only focused on two dimensions: gender inequality and geographic disparity. **Gender inequality** has long existed in Afghanistan but becomes a more concerning issue in the current context under the rule of the women-oppressive regime of the Taliban. Women's access to health and other social services has been restricted more than ever since August 2021. However, even before that, in parts of the country where the Taliban and other combatant groups dominated, women's access to healthcare services was limited. I admit the gender analysis under this objective is not comprehensive, but there were some noteworthy findings. The gender statistics provide a positive indication that the rotavirus vaccine is being accepted and utilized similarly across genders, making it a viable candidate for sustained use. However, ongoing assessment will be necessary to ensure that gender balance is maintained, and that the vaccine continues to contribute positively to overall public health.

Regarding **geographic inequality**, the national level aggregated data usually masks the underlying inequalities at lower administrative divisions such as districts, and villages. Therefore, decisions aimed at improving the immunization programme should prioritize micro-geographic data rather than relying solely on national or provincial statistics.

The COVID-19 pandemic universally impacted all aspects of life, including child immunization. Our analyses showed that despite the severe security concerns, the childhood immunization coverage recovered from the COVID-19 impact. These recovering trends continued into 2022 and 2023, indicating of Afghanistan’s resilient health system to external shocks.

Finally, financial sustainability in health is a driving force for preventive healthcare including vaccine introduction and continuation of vaccination in Afghanistan, where the government contribution in the health sector is less than 3%. Afghanistan has a fragile economy, and GDP per capita has fallen by more than 25% since 2018 (US$562). Since Gavi’s initial self-financing is set at the threshold of U$995, Afghanistan will continue to benefit from Gavi’s financial support for immunization.

Contribution to VDMF. Analyses under this objective contributed information to VDMF criterion 4,

"**Acceptability**", sub element "*financial consideration*"; VDMF criterion 6, "**Equity**", sub-element of "*gender equality*" and "*geographic disparity*", and VDMF criterion 7, "**Feasibility**", sub-element "*security and other consideration (e.g., COVID-19)*".

Policy implications. It is important to strengthen the health system alongside continuing rotavirus vaccine use, so that it is more resilient to shocks (political events, pandemics) and more able to reach zero dose and hard to reach children (in areas geographically inaccessible or with security concerns). Finally, the evidence from this study could form the basis for an investment case to promote continued donor support for rotavirus vaccination, both from Gavi and other donors.

Table 7-1 Summary of thesis findings (2023-2024) feeding into the proposed vaccine decision-making framework adapted from the WHO evidence to recommendation (EtR) framework.

Generic criteria	Sub-elements	DrPH Thesis Objective	Study design	Main Findings of the Thesis
1- Problem (assess importance)	Burden of disease and economic burden **(Rotavirus disease)**	Obj. #5 Paper #1 Chapter #3	Mathematical modelling	**Without vaccination: Number of RVGE:** non-severe cases/year = 555,000 non-severe clinic visits/year = 295,000 severe cases/year = 120,000 severe admissions/year = 30,000 deaths per year = 16,000 DALY (discounted) = 53,000
2- Benefits and harms	Benefit (Efficacy/Effectiveness) **(RVV)**	Obj. #1, #2, #3 Paper #1 Chapter #3	Test-negative case-controlled analysis, Trend analysis, Impact analysis	**RV vaccine effectiveness of two doses:** Children 6-59 months = 45% (95% CI: 22, 62) Children 6-11 months = 58% (95% CI: 33, 73) **Impact** % of RVGE positivity among AGE admissions = 39% (2019-2021 post-vaccine period at 85% RV coverage) **Trend analysis:** Substantial reduction in AGE hospital admission following RV vaccine introduction (Model fit: p=0.14) No change in AGE clinic visits following RV vaccine introduction but a shift in seasonality observed (model fit: p=0.10)
	Safety/Risk **(RVV)**	Obj. #2 Paper #2 Chapter #3	Self-controlled case-series analysis	**Relative incidence following dose 1:** 1-7 days: 0.9 (95%CI: 0.1, 7.5) 8-21 days: 1.3 (95%CI: 0.4, 4.2) 1-21 days: 1.1 (95%CI: 0.4, 3.4) **Relative incidence following dose 2:** 1-7 days: 0.2 (95%CI: 0.3, 1.8) 8-21 days: 0.7 (95%CI: 0.3, 1.5) 1-21 days: 0.6 (95%CI:0.3, 1.2)
	Benefit-risk **(RVV)**	Obj. # 6 Paper #3 Chapter #5	Mathematical modelling	**No age restriction on vaccine dose administration** RVGE deaths prevented: excess IS deaths = 1493:1 At impact of 41% **Age restriction on vaccine dose administration** RVGE deaths prevented: excess IS deaths = 2790:1 At impact of 25%
3- Values and preferences	Acceptability of schedule (e.g., multiple injection)		Indirectly can be inferred from findings under OPA Obj. #1, #4, & # 8	The RSI, assessing the vaccine decision-making framework, identified that introduction of rotavirus vaccine was relatively inclusive and was introduced based on favourable recommendations from public health practitioners, clinicians, academia, and civil society reps though the NITAG platform. However, the general public representative was not included in the NITAG recommendation, but the rotavirus coverage disaggregated by sex in chapter 6 of the thesis indicates the acceptability of rotavirus vaccine by parents/caregivers.
	Culturally and religiously	Not studied	Not within the scope of this thesis	
4- Acceptability	Stakeholders' perception	Not studied	covered under OPA/RSI	

Generic criteria	Sub-elements	DrPH Thesis Objective	Study design	Main Findings of the Thesis
	Financial, ethical, and programmatic consideration **(RVV)**	Obj #5 &#7 Paper 3 Chapter #5	Mathematical modelling	**Economic cost of disease per child with RVGE From government perspective in 2022 US$ (discounted)** Cost per non-severe RVGE visit = $5.4 ($2.52, $10.08) Cost per severe RVGE visit = 5.04 ($2.52, $10.08) Cost per hospitalization = $17.56 ($8.78, $35.12) **From societal perspective in 2022 US$ (discounted)** Cost per non-severe RVGE visit = $15.42 ($7.71, $30.84) Cost per severe RVGE visit = $15.42 ($7.71, $30.84) Cost per RVGE admission = $38.05 ($19.03, $76.10)
5- Resource use	Direct cost (budget) **(RVV)**	Obj. # 5 Paper 3 Chapter#5	Mathematical modelling	**Vaccine programme cost per year in 2022 US$ (Discounted)** With Gavi's financial support = $4.4 million % of annual vaccine programme budget = 5.5% % of Total Health Expenditure (THE) = 0.13% Without Gavi's financial support = $9 million % of annual vaccine programme budget =11.1% % of Total Health Expenditure (THE) = 0.27% **Healthcare cost without RV vaccination per year in 2022 US$ (discounted)** from government perspective = $2.3 million From societal perspective = $6.4 million **Healthcare cost with RV vaccination per year in 2022 US$ (discounted)** From government perspective = $1.6 million **From societal perspective = $4.1 million**
	Cost-effectiveness ratio **(RVV)**	Obj. #5 Paper 3 Chapter #5	Mathematical modelling	With Gavi's financial support in 2022 US$ discounted: Cost per DALY averted from Gov. perspective = $212 (42%GDP per capita) Cost per DALY averted from societal perspective = $125 (25% GDP per capita) Without Gavi's financial support in 2022 US$ discounted: Cost per DALY averted from Gov. perspective = $471 (94% per capita) Cost per DALY averted from societal perspective = $386 (77% GDP per capita)
6- Equity	Access to intervention (Gender equality and geographic disparity) **(childhood immunization/RVV)**	Obj. #8 Chapter#6	Point/period cross-sectional study design/secondary analysis	Fully immunized child basic antigen: (12-23 months old) Source MICS2022 Male:37.9%; Female: 35.3% Rotavirus vaccine: RV1- Male: 63.2%; Female: 60.3% RV2- Male: 57.2%; Female: 54.2% Geographic disparity: basic antigen, 12-23 months old: source MICS 2022 Urban: 49.6%; Rural: 32.5% RV1: Urban: 74.3%; Rural: 57.9% RV2: Urban: 68.3%; Rural: 51.8% Figure 6-3 Chapter 6 and Map 6-2 show over half of the provinces are below the national average (36.6%): Urozgan, Nuristan, Ghor, Hilmand, Zabul, Paktika, Badghis, Samangan, Kandahar, Kunduz, Paktya, Ghazni, Badakhshan, Kapisa, Frah, Logar, Parwan Jawzjan, Wardak.

Generic criteria	Sub-elements	DrPH Thesis Objective	Study design	Main Findings of the Thesis
7- Feasibility	Logistics and operation (cold chain capacity and adaptability)	Obj #3 Paper 1 Chapter#3	Not within the scope of the thesis	Observed RVGE seasonality provides insight; this has operation and programme implication. Findings under RSI indicated that logistics and operation aspects of rotavirus vaccination were well-considered and aligned with the capacity of the national EPI cold chain.
	Continuity of the intervention **(Comparison of different rotavirus vaccine types and budget impact analysis)**	Obj. #7 Paper 3 Chapter #5	Mathematical modelling	**With Gavi's financial support cost per DALY averted in 2022 US$ (discounted):** 1st option: Rotarix = $259 (gov.) ; $152 (societal) 2nd option: ROTASIIL 1-dose vial = $331 (gov.); $224 (societal) 3rd option: ROTASIIL 2-dose vial = $332 (gov.); $225 (societal) 4th option: ROTAVAC 5-dose vial = $337 (gov.); $230 (social) **Without Gavi's financial support:** 1st option: ROTASIIL 2-dose vial = $458 (gov.); $351 (social) 2nd option: ROTASII 1-dose vial = $497 (gov.); $390 (societal) 3rd option: ROTARIX = $576 (gov.); $470 (societal) 4th option: ROTAVAC 5-dose vial = $540 (gov.); $433(societal)
	Security (coverage) **(Childhood immunization/RVV)**	Obj. #8 Chapter #6	Retrospective trend of vaccine coverage over different time periods	Maps 6-1 & 6-2 in Chapter 6 visually illustrate the long-term impact of security on the coverage of fully immunized children and rotavirus vaccine among children aged 12-23 months of age. Table 6-1, Chapter 6, presents a comparison impact of regime change in August 2021 with 2019. Average drop in coverage as follows: DPT-1: 11% DTP-2: 13% DTP-3: 14% RV1: 7% RV2:7%
	Other consideration/particular circumstances e.g., COVID-19 **(Childhood immunization/RVV)**	Obj. #8 Chapter #6	Retrospective trend of vaccine coverage over different time periods	Table 6-1, Chapter 6, presents a comparison of impact of lockdown months during the peak of the COVID-19 pandemic with the same period before the pandemic. Average drop in coverage as follows: DTP-1: 15% DTP-2:26% DTP-3: 32% RV1: 4% RV2: 10%

7.2 Thesis limitations and future research

While the thesis provides insights into the effectiveness, impact, and economic evaluation of the RV vaccination programme in Afghanistan, there are several limitations that need to be acknowledged. First, I highlight the limitations that affected all the research undertaken for this

thesis, along with their effects on my overall conclusions. Each chapter also had its own set of specific limitations, which were set out in the discussions of each paper or chapter. However, in the subsequent specific sub-sections, I revisit and examine in more detail some of the key limitations.

7.2.1 Sample size and generalizability

The VE evaluation had a relatively small sample size for sub-group analysis and stratification. For instance, we were unable to calculate VE among children >24 months due to the small sample size for this age group. Additionally, identifying circulating genotypes and estimating strain-specific VE was not possible due to the small samples for these sub-analyses. Moreover, association between stunting and VE was not statistically significant. Around 24% of the participants were excluded from the analysis because their vaccination status could not be ascertained. However, we did not observe significant differences in socio-demographic characteristics between those included and excluded from the study.

Given these limitations, our findings should be interpreted with caution. We recommend additional research to address these limitations.

7.2.2 Data quality and completeness

Some analyses in this research study relied heavily on routine data from the Health Management Information System (HMIS). While HMIS is a valuable tool for tracking healthcare indicators, it has inherent limitations related to data reliability, accuracy, and completeness. These limitations can introduce biases, potentially affecting the accuracy of trend analyses for acute gastroenteritis (AGE) admissions, clinic visits, and vaccine coverage. Such biases may result in under- or over-estimations, thereby influencing the reliability of the conclusions drawn from these analyses. Thus, we have taken below steps and well-documented while addressing data quality issues. In each chapter we explicitly acknowledged the potential biases and limitations inherent in the data and described how the use of multiple sources and triangulation helped mitigate these concerns. Our approaches to address data quality issues can be summarized as follows:

1. **Use of multiple data sources**

We incorporated data from multiple sources, including facility-level records, programme-specific reports, and independent survey data. This multi-source approach helped cross-verify the findings, reducing the potential impact of errors or gaps in HMIS data.

2. **Identification of reliable institutions**

Priority was given to data from institutions like UNICEF and WHO, recognized for their robust technical expertise and stringent quality assurance mechanisms. Additionally, analyses focused on data from health facilities that demonstrated consistent reporting for at least 11 months in a year, ensuring reliability and excluding facilities with implausible or irregular figures. This approach helped enhance the accuracy and credibility of the findings by prioritizing high-quality, dependable data sources.

3. **Data triangulation**

Triangulation was employed to validate the findings by cross-referencing data from various sources, including administrative records, household surveys such as the Demographic and Health Survey (DHS), Multiple indicator Cluster Surveys (MICSs), and the Afghanistan Health Survey (AHS), vaccine coverage estimations produced by WUNEIC, and hospital-based surveillance data. Where discrepancies were identified, additional scrutiny was applied during data processing to understand and reconcile the differences. This approach enhanced confidence in the trends and patterns observed in the data.

4. **Regular data quality assessments (DQAs)**

We conduced routine data quality assessments (DQAs) for our hospital-based surveillance data to identify and correct inconsistencies or gaps in the collected data. However, for HMIS data, as we used retrospective data, we had no control on DQAs. However, we mitigate HMIS quality date issues inherent in HMIS data, we employed the first three steps outlined above.

Based on our lessons learned, we strongly recommend implementing standardized training programmes for HMIS officers across the country, complemented by on-the-job support and mentoring. Additionally, the provision of technological tools and support, along with the adoption of robust digitalization systems, is essential. With the increasing use of Artificial Intelligence (AI), it is timely for HMIS to integrate new technologies and leverage AI features to enhance the quality, accuracy, and efficiency of administrative data systems.

7.2.3 Temporal limitations of routine data

The study covered a specific time frame (2013-2022) during which Afghanistan experienced significant events, such as the escalation of armed conflict, the COVID-19 pandemic, and regime

change. These events have influenced the vaccination programme and healthcare access, potentially confounding the results and limiting the ability to isolate the impact of the RV vaccination alone. In our cross-cutting issues section (Chapter 6), we provided a detailed analysis of the context and circumstances under which the rotavirus vaccination programme was implemented. This contextual analysis allows readers to interpret the results with an understanding of the underlying contextual factors which might have influenced the results.

7.2.4 Economic evaluation assumptions

The benefit-risk and cost-effectiveness analyses were based on many assumptions, including disease burden, healthcare costs, vaccine coverage, vaccine costs, vaccine wastage rate, etc. Variations in these assumptions could lead to different outcomes, and the results may not fully capture real-world complexities and uncertainties. We ran sensitivity and probabilistic analyses as ways to address those uncertainties.

7.2.5 Contextual factors

The unique context of Afghanistan, characterized by long-lasting armed conflict, insecurity, widespread malnutrition, limited access to water, hygiene, and sanitation (WASH) facilities, the co-existence of other infectious diseases, and financial constraints, affects the rotavirus vaccination programme and its continuation. Consequently, I dedicated a specific chapter to addressing some of these factors (Chapter 6), despite the analyses being retrospective and limited to secondary data. I made great efforts to collect data from various sources, but I was unable to obtain updated information or to cross-validate some of the information with the national EPI despite several attempts. Officials who had previously worked on the national EPI had been displaced due to regime change and did not have current information. Additionally, those currently leading the EPI programme were not cooperative.

7.3 Areas for extending this research and programmatic recommendations

While this thesis has bridged knowledge gaps and produced evidence to guide policy decisions on the continuation of rotavirus vaccination in Afghanistan, there exist a multitude of avenues through which the research can be extended to tackle further research questions.

7.3.1 Operational strategies to minimize inequitable vaccination and heterogeneous vaccine efficacy

Considering the findings of heterogenous effectiveness of rotavirus vaccine and significant geographic disparity of vaccination coverage across the country, the follow practical approaches would minimize the observed inequality in access to vaccination services.

1. Enhance vaccine coverage in underserved populations
    - Conduct targeted vaccination campaigns in marginalized and hard-to-reach areas, ensuring equitable access.
    - Deploy mobile clinics and outreach teams to provide vaccination in geographically isolated regions.
    - Partner with local organizations and community leaders to address cultural and logistical barriers to vaccination.
2. Strengthen cold chain and logistic systems
    - Improve cold chain infrastructure, especially in remote and resource-limited areas, to maintain vaccine efficacy.
    - Implement solar-powered refrigeration systems in regions with limited electricity access.
    - Optimize vaccine delivery routes using geographic information systems (GIS) for efficient resource allocation.
3. Address geographic disparities in access
    - Develop region-specific vaccination strategies tailored to the unique challenges of rural, urban, and conflict-affected areas.
    - Provide transportation subsidies or mobile immunization units to ensure children in distant areas can access vaccines.
    - Leverage digital health platforms to map coverage gaps and track immunization progress geographically.

4. Promote integrated health and nutrition services
    - Combine rotavirus vaccination efforts with maternal and child health programmes, including nutrition interventions.
    - Address malnutrition in vulnerable populations as part of immunization strategies to enhance vaccine responsiveness.
5. Implement enhanced surveillance systems:
    - Establish regional sentinel sites to monitor vaccine coverage, efficacy, and circulating genotypes.
    - Use geographic data to identify disparities in vaccine uptake and effectiveness, adapting strategies accordingly.

7.3.2 Research strategies to reduce uncertainties in vaccine performance

Historically, resource limitations have often constrained research and surveys to the national level, focusing on aggregated data that provide an overall picture of the situation. While this approach is valuable for understanding broader trends and informing national policies, it tends to obscure significant sub-national disparities. Variations in health outcomes, access to services, and resource allocation at regional, provincial, or community levels are often overlooked, leading to a lack of tailored interventions for underserved or marginalized populations.

1. Investigate geographic disparities in vaccine efficacy and impact
    - Further studies are needed to examine how geographic factors, such as climate, access to safe drinking water, sanitation, and population density, influence vaccine performance.
    - We need to design studies across diverse regions to identify disparities and adapt vaccine strategies accordingly.
    - Use advanced statistical models to analyze regional variations and predict outcomes under different scenarios.
2. Study rotavirus genotype distribution and across regions/provinces
    - We may consider establishing surveillance system to monitor regional variations in circulating rotavirus genotypes and evaluate how this impact vaccine effectiveness. Such findings should inform or adjust policies for regions with unique genotype profiles.
3. Evaluate strain-specific and population-specific vaccine efficacy (VE)

- Further studies are needed to assess how vaccine efficacy varies among different demographic groups, such as malnourished children or those in high-burden areas.

4. Develop approaches for populations with unverified vaccination status
    - Use serological studies and other diagnostic tools to assess VE in children without documented vaccination records may be considered.
    - Further studies would help to find an answer for how varying vaccination schedules or incomplete doses affect overall vaccine impact.

7.3.3 Addressing transparency and accountability in immunization programme

A lack of transparency and accountability significantly undermines immunization coverage, erodes public trust in vaccination programmes, and disrupts equitable vaccine delivery. To strengthen the sustainability of these programmes, enhance public acceptability, and achieve better immunization outcomes, the Ministry of Public Health, in collaboration with its partners, should adopt the following measures:

1. **Strengthened monitoring systems:** Implement independent third-party monitoring and evaluation frameworks to track vaccine delivery, resource utilization, and coverage rates. Leverage innovative digital tools and technologies, such as real-time dashboards and geospatial mapping to enhance monitoring efficiency and accuracy.
2. **Public disclosure**: Implement transparent reporting mechanisms that regularly share immunization programme data with stakeholders, healthcare workers, and communities.
3. **Anti-corruption measures**: Enforce stricter oversight protocols to prevent vaccine diversion, mismanagement, and fraudulent activities.
4. **Community engagement:** Build trust and strengthen programme credibility through clear, consistent communication, and transparent decision-making processes. Establish local accountability mechanisms, involving community leaders, civil society organizations, and stakeholders in programme oversight and feedback loops.

7.3.4 Impact of armed conflict and security on vaccination

Conduct in-depth studies on how armed conflict and security issues affect vaccination coverage and access to healthcare services.

Rationale: Understanding the specific challenges posed by conflict can help design targeted

interventions to maintain and improve immunization coverage in inaccessible regions.

7.3.5 Post-marketing vaccine safety surveillance

Expand post-marketing surveillance to include other potential adverse events following immunization and validate findings across different populations.

Rationale: Continuous monitoring of vaccine safety is crucial to maintain public confidence and ensure timely detection and management of any risks.

7.3.6 Interventions for enhancing vaccine uptake

Investigate interventions that can improve vaccine uptake in regions with low coverage, including community engagement, health education and health promotion, and infrastructure improvements.

Rationale: Enhancing vaccine uptake is essential to achieve high coverage and ensure the success of immunization programmes in preventing and eliminating the viruses/infections attributable to mortality and morbidity in children <5 years.

7.3.7 Strengthening the existing NITAG and national capacity

Strengthening the existing National Immunization Technical Advisory Group (NITAG) and building national capacity is crucial for future immunization programmes. This section serves more as a recommendation than a proposal for further research. The VDMF proposed under RS1/OPA has been practically pilot tested using the findings of analyses conducted in this thesis, summarized in **Table 7-1.** It demonstrates how the VDMF can operate in the real world. However, the necessity for a robust NITAGs or similar body, and the capacity building needed in relation to national experts for collecting, analysing, and synthesizing evidence, is becoming increasingly evident. Detailed recommendations for strengthening NITAG were provided in the OPA report attached to this thesis. Here are a few key highlights:

- Establish a clear vision and mission statement: define a well-articulated vision and mission statement to guide NITAG's activities and objectives.
- Enhance transparency and accountability: this includes creating a dedicated webpage to publish NITAG members' biographies, affiliations, conflicts of interest, and meeting minutes, and publishing proposed recommendations.
- Recruit a committed, diverse and multidisciplinary team: bring together a diverse and

multidisciplinary group of members, including epidemiologists, paediatricians, immunologists, microbiologists, health economists and social scientists. Additionally, include at least two laypersons (one from each gender) to represent public interests. Provide initial and periodic refresher training for all members and facilitate exchange visits among regional NITAG members to build capacity and motivation.

- Implement fair and transparent processes: this covers the processes for the appointment of the chair and members, prioritization of topics/questions, and stakeholder identification. A customized version of the generic WHO Evidence to Decision (EtD) framework, to suit the criteria for the Afghan context, could serve as a framework for standardizing vaccine-policy recommendations and vaccine-policy decision-making.

7.3.8 Translation evidence into policy: Lessons from Afghanistan's evolving governance context

Under Afghanistan's former government, translating evidence into policy was influenced by a relatively robust framework of technical bodies and international development partners. Theoretically, the National Immunization Technical Advisory Group (NITAG) played a role in evaluating evidence, providing independent recommendations, and guiding immunization policies. Development partners, including WHO, UNICEF, and Gavi, significantly supported the process by providing technical assistance, funding, and global best practices, fostering a collaborative environment for evidence-based policymaking. However, challenges such as bureaucratic inefficiencies, political instability, and reliance on external support often slowed the process. By leveraging technical expertise and fostering partnerships, the former government was able to make strides in immunization and other health interventions.

Contrary, under the Taliban de facto government, interpreting cost-effectiveness studies and other scientific evidence and translating them into policy face unique challenges shaped by ideological priorities, governance structures, and resource constraints. Unlike previous administrations, where international frameworks and donor-driven agendas heavily influenced health policy, the Taliban's governance emphasizes local sociopolitical and religious values, which may diverge from conventional evidence-based policymaking norms. Furthermore, the limited capacity of the current health system and reduced engagement with international partners complicate the integration of global evidence into national policies.

7.4 Final reflections and conclusion

Despite the limitations highlighted earlier, this thesis significantly contributes to knowledge and understanding about the rotavirus vaccination programme in a complex setting like Afghanistan. This research concludes that the rotavirus vaccine is a beacon of hope in combating rotavirus diseases. Its effectiveness, impact, safety, and cost-effectiveness, when considered with the contextual factors, strongly support the continuation of the rotavirus vaccination in Afghanistan. Additionally, the thesis identified areas for future research and provides policy-level and programmatic recommendations for enhancing the inclusiveness and effectiveness of the RV vaccination programme.

The responsibility for securing financial resources for immunization lies firmly with those in power, who are accountable for the population's health and well-being. This is not only a call to the authorities in Afghanistan but also to the international community to ensure that no Afghan infant is left behind, deprived of the protective effects of the rotavirus vaccine against RVGE mortality and morbidity.

The importance of girls' education transcends its immediate benefits. It is a powerful tool that directly influences child health and survival, making it a critical component of our collective efforts towards a healthier future.

To effectively advocate for health interventions like vaccination programmes, it is essential to present evidence in culturally resonant terms, emphasizing their potential to reduce suffering and enhance community resilience. Bridging these gaps requires sustained dialogue, culturally sensitive advocacy, and innovative approaches to evidence translation that align with local governance dynamics while ensuring public health goals remain paramount.

In essence, this thesis underscores the undeniable truth that the rotavirus vaccine, financial investment in immunization, critical attention to geographic disparity, and girls' education are not separate entities, but interconnected pieces of a larger puzzle aimed at improving global health outcomes.

7.5 Chapter 7 references

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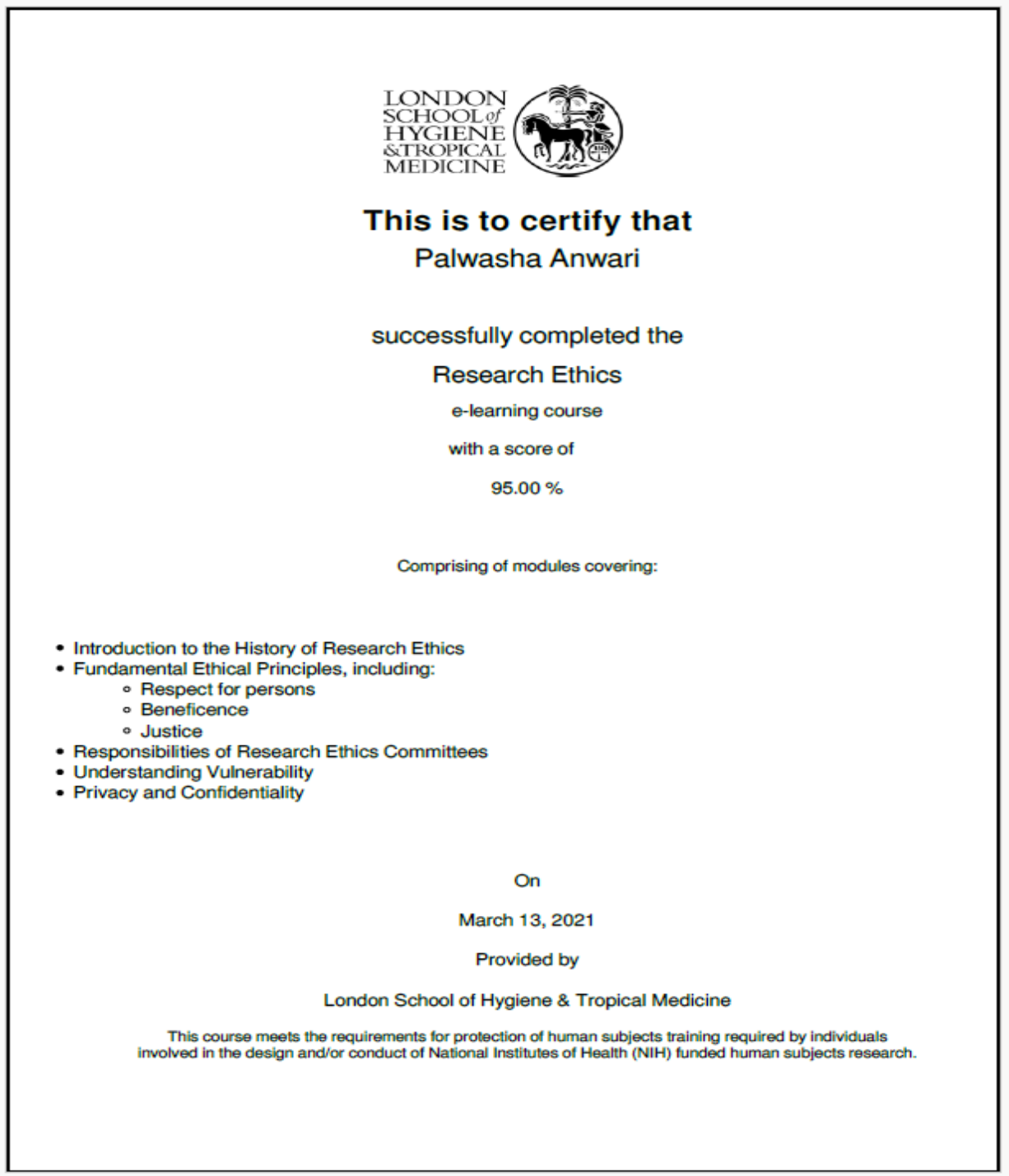
ANNEXES

Chapter 1 Annex 1: Annex 1: Reserch ethics e-course completing certificate



LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

This is to certify that

Palwasha Anwari

successfully completed the

Research Ethics

e-learning course

with a score of

95.00 %

Comprising of modules covering:

- Introduction to the History of Research Ethics
- Fundamental Ethical Principles, including:
  - Respect for persons
  - Beneficence
  - Justice
- Responsibilities of Research Ethics Committees
- Understanding Vulnerability
- Privacy and Confidentiality

On

March 13, 2021

Provided by

London School of Hygiene & Tropical Medicine

This course meets the requirements for protection of human subjects training required by individuals involved in the design and/or conduct of National Institutes of Health (NIH) funded human subjects research.

Chapter 1 Annex 2: London School of Hygiene and Tropical Medicine (LSHTM) research ethics committee approval for the thesis, all components

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636
www.lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Observational / Interventions Research Ethics Committee

Dr Palwasha Anwari
LSHTM

10 July 2023

Dear Dr Palwasha Anwari

Study Title: Benefit-risk and cost-utility of rotavirus vaccination in Afghanistan: a modelling study informed by post-marketing surveillance data

LSHTM Ethics Ref: 29622

Thank you for your application for the above research project which has now been considered by the Observational Committee via Chair's Action.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved is as follows:

Document Type	File Name	Date	Version
Other	Research_Ethics_online_training_certificate	13/05/2021	
Local Approval	CDC approval letter for Impact evaluation of RV vaccine	09/06/2023	1
Investigator CV	Palwasha Anwari-CV March 2023	09/06/2023	1
Local Approval	CDC Approval for Generic protocol-Post-marketing Intussusception Monitoring	09/06/2023	1
Local Approval	2018-04-14_IRB letter-VE	09/06/2023	1
Local Approval	2018-04-14_IRB letter_IS	09/06/2023	1
Protocol / Proposal	2023_06_08 DrPH_PA_RS2_Review_Report	13/06/2023	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study. The date the first annual report is due is 10/07/2024

At the end of the study, the CI or delegate must notify the committee using the End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk.

Further information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

[redacted]

Page 1 of 2

[redacted]

Professor David Leon and Professor Clare Gilbert

Co-Chairs

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

Chapter 1 Annex 3: London School of Hygiene and Tropical Medicine (LSHTM) research ethics committee approval letter for continuation of thesis for another year

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Observational / Interventions Research Ethics Committee

Dr Palwasha Anwari

LSHTM

14 June 2024

Dear Palwasha,

Project Title: Benefit-risk and cost-utility of rotavirus vaccination in Afghanistan: a modelling study informed by post-marketing surveillance data

Project ID: 29622

Thank you for your annual report application for the continuation of your research dated 10/06/2024 17:19 , which has now been considered by the Chair on behalf of the Ethics Committee.

Confirmation of ethical opinion

This application is approved by the committee for a further year from the date of this letter.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

After ethical review

Any changes to the application must be submitted to the committee via an Amendment form.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reaction (SUSARs) which occur during the project by submitting a SUSAR and Protocol Violation form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at http://leo.lshtm.ac.uk.

Additional information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

[redacted]

Professor David Leon and Professor Daniel Chandramohan
Co-Chairs

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

Chapter 3 Annex 1: Afghanistan Ministry of Public Health ethical approvals for hospital-based active surveillance (2018)

Islamic Republic of Afghanistan
Ministry of Public Health
Afghanistan National Public Health Institute
Institutional Review Board

د افغانستان اسلامي جمهوريت
د عامې روغتيا وزارت
د افغانستان ملي روغتيا عامې انستيتوت

Date: April 14, 2018 No. 444510

To: Dr. Palwasha Anwari
Research Consultant
Emerging Leaders Consulting Services

Subject: Exempt of proposal entitled **"Evaluation of the Impact and Effectiveness of Monovalent Rotavirus Vaccine in Afghanistan".**

Dear Dr. Anwari,

The research proposal entitled **"Evaluation of the Impact and Effectiveness of Monovalent Rotavirus Vaccine in Afghanistan"** is exempted from Institutional Review Board examination since it has been approved by NCIRD, we are pleased to accept your request for exemption and approve the study.

We reserve to the rights to monitor and audit your study and any violation of ethical norms during the course of study shall lead to withdrawal of given approval.

The duration of approval for a study to begin the research project is valid for six months and the exact date of research project implementation (start and end) should be informed to IRB secretary.

You are bound to share the result of your study with MoPH prior any dissemination plan.

Sincerely,

[redacted]

Bashir Noormal *MD.*
Director General
Afghanistan National Public Health Institute (ANPHI) &
Chairman, Institutional Review Board (IRB)
Ministry of Public Health

[redacted]

Telephone No.: +93 (0) 700 28 11 34
Email Address: dganphi.moph@gmail.com
Website: www.anphi.moph.gov.af
Postal Address: 5th & 6th floors of the Central Blood Bank Building
Behind Central Polyclinic, Cinema Pamir Area, Kabul-Afghanistan

Islamic Republic of Afghanistan
Ministry of Public Health
Afghanistan National Public Health Institute
Institutional Review Board

د افغانستان اسلامی جمهوریت
د عامی روغتیا وزارت
د افغانستان ملی روغتیا ملی انستیتوت

۴۴۵۶۲
۲۲/۲/۱۳۹۷

به ریاست محترم خدمات تشخیصیه!

محترمه داکتر پلوشه انوری، تحقیق علمی را تحت عنوان "Evaluation of the Impact and Effectiveness of Monovalent Rotavirus Vaccine in Afghanistan" انجام دهد و پروتوکول تحقیق خویش را با بورد اخلاقیات وزارت صحت عامه شریک ساخته و اجازه نامه اخذ نموده و مطابق پروتوکول تحقیق متذکره پروسه جمع آوری ارقام را آغاز مینماید و امید با ایشان از طریق لابراتوار های مرکزی همکاری نمائید.

کاپی اجازه نامه بورد اخلاقیات به زبان انگلیسی ضم مکتوب هذا گنجیل است.

[redacted]
پوهندوی دوکتور بشیر نورمل
رئیس عمومی انستیتوت ملی صحت عامه افغانستان
و رئیس بورد اخلاقیات وزارت صحت عامه

[redacted]

Telephone No.: +93 (0) 700 28 11 34
Email Address: dgaphi.nmrb@gmail.com
Website: www.moph.gov.af
Postal Address: 5th & 6th floors of the Central Blood Bank Building
Behind Central Polyclinic, Cinema Pamir Area, Kabul-Afghanistan

Note: This letter was issued in Dari language. Here is the translation in English:

To Directorate of Diagnostic Services,

Dr. Palwasha Anwari plans to conduct an evaluation titled: "Evaluation of impact and effectiveness of monovalent rotavirus vaccine in Afghanistan". She has shared her study protocol with the Ministry of Public Health Institutional Review Board and has secured ethics approval to begin data collection. We kindly request your office assistance through National Public Health Laboratories.

A copy of IRB approval in English language attached to this letter.

With regards,

Dr. Bashir Noormal

1397-2-22 (in solar national calendar)

Converted date: 2018- May-12

Chapter 3 Annex 2: United States CDC ethical approval for vaccine effectiveness study protocol adapted in Afghanistan (2017)

From: SharePoint Alert (CDC)
To: Chavers, Tyler (CDC/OID/NCIRD); Tate, Jacqueline E. (CDC/OID/NCIRD)
Subject: New Project Determination Request P_2017_DVD_Tate_324 titled Evaluation of the Impact and Effectiveness of Rotavirus Vaccine in Vaccine-Adopting Countries has been Approved.
Date: Thursday, August 31, 2017 3:06:19 PM

Workflow Notification

New Project Determination titled **Evaluation of the Impact and Effectiveness of Rotavirus Vaccine in Vaccine-Adopting Countries** has been approved by NCIRD as of August 31, 2017. The Center reference ID is P_2017_DVD_Tate_324

Below are the Determinations and Expiration of Approval (if applicable):
Human Research Protections Determination Category:

HR Not Engaged - **CDC HRPO Protocol #/Exp**: New Determination
Paperwork Reduction Act Determination:

Information Collection Request Not Required
Privacy Act Determination:

Not Applicable
Information Security Determination:

No Additional Requirements
Animal Care and Use Determination:

- CDC ACUPO Protocol #/Exp:

Data Management Plan Last Updated Date:

8/18/2017

The project has been approved as proposed by NCIRD. If additional Human Subjects, Paperwork Reduction Act, or Privacy Act review is indicated by the Determinations above, the project cannot begin until final approval is obtained from CDC's Human Research Protection Office (HRPO), the Office of Management and Budget (OMB), or the CDC Privacy Officer. If there is the need to change or modify any aspects of the proposed project, those changes must be re-reviewed and approved prior to implementation.

If you have any questions, please contact your Division ADS or the Center points of contacts:

NCIRD Points of Contact
Human Research Protections Reviewer:

Legardy-Williams, Jennifer (CDC/OID/NCIRD)
OMB Paperwork Reduction Act Reviewer:

Hynes, Ansley (CDC/OID/NCIRD)
Privacy Act Reviewer:

Chapter 4 Annex 1: Afghanistan Ministry of Public Health (MoPH) ethical approval for post-marketing intussusception monitoring in Afghanistan

Islamic Republic of Afghanistan
Ministry of Public Health
Afghanistan National Public Health Institute
Institutional Review Board

د افغانستان اسلامی جمهوریت
د عامی روغتیا وزارت
د افغانستان دعامی روغتیا ملی انستیتوت

Date: April 14, 2018

No. 444509

To: Dr. Palwasha Anwari
Research Consultant
Emerging Leaders Consulting Services

Subject: Exempt of proposal entitled **"Post-marketing Intussusception Monitoring in Afghanistan after Introduction of Oral Rotavirus Vaccine: Self-Controlled Case-Series".**

Dear Dr. Anwari,

The research proposal entitled **"Post-marketing Intussusception Monitoring in Afghanistan after Introduction of Oral Rotavirus Vaccine: Self-Controlled Case-Series"** is exempted from Institutional Review Board examination since it has been approved by NCIRD, we are pleased to accept your request for exemption and approve the study.

We reserve to the rights to monitor and audit your study and any violation of ethical norms during the course of study shall lead to withdrawal of given approval.

The duration of approval for a study to begin the research project is valid for six months and the exact date of research project implementation (start and end) should be informed to IRB secretary.

You are bound to share the result of your study with MoPH prior any dissemination plan.

Sincerely,

[redacted]

Bashir Noormal *MD, MPH*
Director General
Afghanistan National Public Health Institute (ANPHI) &
Chairman, Institutional Review Board (IRB)
Ministry of Public Health

[redacted]

Telephone No.: +93 (0) 700 28 11 34
Email Address: dganphi.moph@gmail.com
Website : www.anphi.moph.gov.af
Postal Address: 5th & 6th floors of the Central Blood Bank Building
Behind Central Polyclinic, Cinema Pamir Area, Kabul-Afghanistan

Chapter 4 Annex 2: United States CDC ethical approval for post-marketing intussusception monitoring in Afghanistan

From: SharePoint Alert (CDC)
To: Chavers, Tyler (CDC/OID/NCIRD); Tate, Jacqueline E. (CDC/OID/NCIRD)
Subject: New Project Determination Request P_2017_DVD_Tate_331 titled Post-marketing Intussusception Monitoring in Vaccine-Adopting Countries after Introduction of Oral Rotavirus Vaccine: Self-Controlled Case-Series has been Approved.
Date: Tuesday, August 29, 2017 4:12:07 PM

Workflow Notification

New Project Determination titled **Post-marketing Intussusception Monitoring in Vaccine-Adopting Countries after Introduction of Oral Rotavirus Vaccine: Self-Controlled Case-Series** has been approved by NCIRD as of August 29, 2017. The Center reference ID is P_2017_DVD_Tate_331

Below are the Determinations and Expiration of Approval (if applicable):
Human Research Protections Determination Category:

HR Not Engaged - **CDC HRPO Protocol #/Exp**: New Determination
Paperwork Reduction Act Determination:

Information Collection Request Not Required
Privacy Act Determination:

Not Applicable
Information Security Determination:

No Additional Requirements
Animal Care and Use Determination:

- CDC ACUPO Protocol #/Exp:

Data Management Plan Last Updated Date:

8/18/2017

The project has been approved as proposed by NCIRD. If additional Human Subjects, Paperwork Reduction Act, or Privacy Act review is indicated by the Determinations above, the project cannot begin until final approval is obtained from CDC's Human Research Protection Office (HRPO), the Office of Management and Budget (OMB), or the CDC Privacy Officer. If there is the need to change or modify any aspects of the proposed project, those changes must be re-reviewed and approved prior to implementation.

If you have any questions, please contact your Division ADS or the Center points of contacts:

NCIRD Points of Contact
Human Research Protections Reviewer:

Legardy-Williams, Jennifer (CDC/OID/NCIRD)
OMB Paperwork Reduction Act Reviewer: