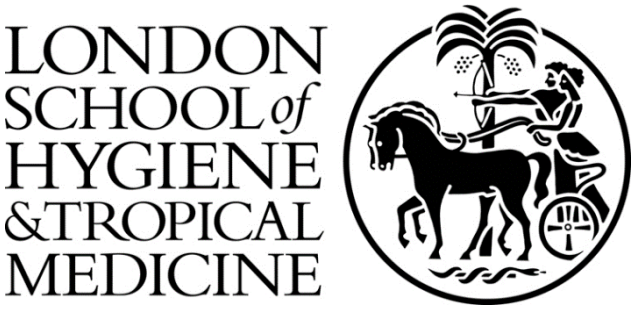

Mortality benefits and intussusception risks of rotavirus vaccination in low- and middle-income countries

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Signed Declaration

I Andrew David Clark, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Andrew David Clark

Abstract

Infant rotavirus vaccines have led to substantial reductions in rotavirus gastroenteritis (RVGE) hospital admissions and costs, but some studies have reported an elevated risk of intussusception, a rare bowel disorder, in vaccinated infants. The aim of this thesis is to quantify the potential mortality benefits and intussusception risks of alternative rotavirus vaccination schedules in 135 low- and middle-income countries (LMICs).

The thesis begins with an introduction to the topic and background to the literature and concludes with some final reflections on the research and its relevance for informing national decisions about vaccine safety and optimal scheduling of rotavirus vaccines. The main body of the thesis includes a series of research papers which address specific topics relevant to the estimation of mortality benefits and intussusception risks. These include methods for estimating: RVGE deaths <5 years of age; RVGE age distributions <5 years; vaccine coverage and timeliness; rotavirus vaccine efficacy and waning; and, intussusception incidence, age distributions, and case fatality ratios in children <5 years of age. The final research paper brings together this evidence and uses a national-level vaccine decision support model to estimate the potential rotavirus mortality benefits (averted RVGE deaths <5 years of age) and risks (excess intussusception deaths <5 years of age) of 18 possible vaccination schedules in 135 LMICs. Scenarios with and without age restrictions are evaluated.

Rotavirus vaccines are found to have a favourable benefit-risk profile in LMICs. Mortality benefits and intussusception risks are estimated to vary considerably by country and choice of rotavirus vaccination schedule. Schedules involving birth and booster doses could further increase benefits and reduce risks, but more research is needed to assess their feasibility, safety and impact.

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Table of abbreviations

AEFI	Adverse Events Following Immunization
AD	Anderson-Darling statistic
AIC	Akaike's Information Criterion
AIIMS	All India Institute of Medical Science
ATP	According-To-Protocol
BCG	Bacillus Calmette-Guérin vaccine
BCL	Brighton Collaboration Level
BIC	Bayesian Information Criterion
BMGF	Bill and Melinda Gates Foundation
BRV-PV	Bovine Rotavirus Pentavalent Vaccine
CDC	Centers for Disease Control and Prevention
CEA	Cost-Effectiveness Analysis
CFR	Case Fatality Ratio
CHERG	Child Health Epidemiology Reference Group of UNICEF and the WHO
CV	Cramer-von Mises statistic
DHS	Demographic and Health Surveys
DIC	Deviance Information Criterion
DTP1	Diphtheria-Tetanus-Pertussis vaccine dose 1
DTP2	Diphtheria-Tetanus-Pertussis vaccine dose 2
DTP3	Diphtheria-Tetanus-Pertussis vaccine dose 3
EIA	Enzyme Immunoassay
FEC	Finnish Extension Trial
FUP	Follow-up
FVI	Fully Vaccinated Infants
GAVCS	Global Advisory Committee on Vaccine Safety
GAVI	Global Alliance for Vaccines and Immunization
GBD	Global Burden of Disease Project
GE	Gastroenteritis
GEMS	Global Enteric Multicenter Study
GMC	Geometric Mean Concentration
GNI	Gross National Income
GRSN	WHO-coordinated Global Sentinel Site Rotavirus Surveillance Network
HIC	High-Income Country
ICD	International Classification of Diseases
IGME	UN Inter-agency Group for Child Mortality Estimation
IHME	Institute of Health Metrics and Evaluation
IV	Intravenous rehydration
iVE	Instantaneous Vaccine Efficacy
IVIR-AC	Immunization and Vaccines-related Implementation Research Advisory Committee
KDE	Kernel Density Estimation
KS	Kolmogorov-Smirnov statistic
LLR	Lanzhou Lamb Rotavirus vaccine
LMIC	Low- and Middle-Income Country
LSHTM	London School of Hygiene and Tropical Medicine
MAE	Mean Absolute Error

MAL-ED	Malnutrition and Enteric Disease Study
MCEE	Maternal Child Epidemiology Estimation Group
MCMC	Markov Chain Monte Carlo
MCRI	Murdoch Children's Research Institute
MCV1	Measles-Containing Vaccine dose 1
Meas1	Measles-Containing Vaccine dose 1
MICS	Multiple Indicator Cluster Surveys
MLE	Maximum Likelihood Estimation
MMR	Measles Mumps and Rubella vaccine
MSD	Moderate-to-Severe Diarrhoea
NIH	National Institutes of Health
NLS	Non-Linear Least Squares
NRSN	Indian National Hospital Rotavirus Surveillance Network
OPV	Oral Polio Vaccine
ORS	Oral Rehydration Salts/Solution
PCR	Polymerase Chain Reaction
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCH	Royal Children's Hospital, Melbourne
RCT	Randomised Controlled Trial
REST	Rotavirus Efficacy and Safety Trial
RMSE	Root Mean Squared Error
RR	Relative Risk
RV3-BB	Rotavirus Vaccine based on G3 P6 strain (Bishop and Barnes)
RVGE	Rotavirus Gastroenteritis
SAE	Severe Adverse Events
SAGE	Strategic Advisory Group of Experts
SCCS	Self-Controlled Case Series
U5	Under-five years of age
UNICEF	United Nations International Children's (Emergency) Fund
UNPOP	United Nations Population Division
USAID	United States of America International Development
VAPP	Vaccine Associated Paralytic Poliomyelitis
VIMC	Vaccine Impact Modelling Consortium
WAIFW	Who Acquires Infection From Whom
WHO	World Health Organization
WUENIC	WHO and UNICEF Estimates of National Immunization Coverage

1.0 Chapter 1 – Introduction

1.1 Benefits and risks of live oral rotavirus vaccines

Rotavirus is an important cause of gastroenteritis (GE) in children aged <5 years globally (1). Two oral rotavirus vaccines (Rotarix® - GlaxoSmithKline, and RotaTeq® - Merck & Co.) became available in 2006, and have been introduced in over half the countries of the world (2). Many have introduced with donor support from the GAVI Alliance, a public-private partnership which provides vaccine finance to the world's poorest countries (3). Post-licensure studies have shown substantial reductions in GE hospital admissions (4) but some studies have reported an elevated risk of intussusception, a rare bowel disorder, in vaccinated infants (5, 6).

In 2012, my colleagues and I estimated the potential mortality benefits and intussusception risks of introducing live oral rotavirus vaccines into the national immunization programmes of 158 countries (7). Benefits were estimated in terms of averted numbers of rotavirus gastroenteritis (RVGE) deaths aged <5 years. Risks were estimated in terms of excess numbers of vaccine-related intussusception deaths aged <5 years. This analysis provided a reassuringly favourable benefit-risk profile for rotavirus vaccines. It also informed a WHO recommendation to remove age restrictions for vaccination (first dose before age 15 weeks, last dose before age 32 weeks) given that the benefits of preventing additional rotavirus mortality from later vaccination greatly exceeded the intussusception risks (8). Since our 2012 analysis, estimates of the number of RVGE deaths aged <5 years (without vaccination) have decreased considerably from ~450,000 in 2008 to ~200,000 in 2015 (1). The evidence for several other inputs has also been significantly strengthened. Consequently, there has been a need to update the analysis so that decision makers in low- and middle-income countries (LMICs) can use the best available evidence to determine whether the benefit-risk profile in their country is still in favour of rotavirus vaccine introduction and the removal of age restrictions.

1.2 Optimising rotavirus vaccination schedules

Mortality benefits and intussusception risks will be influenced by the choice of national rotavirus vaccination schedule. For programmatic and economic reasons rotavirus vaccines are currently co-administered with Diphtheria-Tetanus-Pertussis (DTP)-containing vaccines in the first six months of life. Most countries recommend

two doses of Rotarix® with DTP1 and DTP2, or three doses of RotaTeq® with DTP1, DTP2, and DTP3 as per current WHO recommendations. The actual age of administration varies between countries due to differences in national schedules (target ages for DTP) and differences in the timeliness of vaccination (9). The standard infant schedules recommended by WHO have demonstrated high and durable efficacy in low mortality countries but modest efficacy in higher mortality settings (10). This has stimulated interest in the potential value of a booster dose given with the first dose of measles-containing vaccine (MCV1, referred to hereafter as Meas1)(11) or a birth dose given at the same time as Bacillus Calmette-Guérin (BCG)(12). A birth dose has the potential to prevent disease that occurs very early in life, while a booster dose has the potential to mitigate the effects of waning rotavirus vaccine protection, a phenomenon observed in several high mortality settings (10). Birth doses also have the potential to reduce the number of excess (vaccine-related) intussusception cases by administering the first dose earlier in life, when the background risk of intussusception is lower. The optimal number and timing of doses (concurrent with different combinations of BCG, DTP1, DTP2, DTP3 and Meas1) will depend on several criteria, including the balance of benefits to risks i.e. number of RVGE deaths averted per excess intussusception death.

1.3 Scope of the thesis

The aim of this thesis is to quantify the potential mortality benefits (averted RVGE deaths <5 years of age) and risks (excess intussusception deaths <5 years of age) of alternative rotavirus vaccination schedule options in LMICs. The World Bank defines low- and middle-income as any country with a GNI per capita below $12,236 in the 2018 fiscal year (13). The scope is LMICs because the overwhelming majority of RVGE deaths and intussusception deaths occur in these countries. In high income countries, other factors such as healthcare treatment costs and cost-effectiveness become more influential. These factors were beyond the scope of this thesis.

1.4 Style and structure of thesis

Chapter 2 provides an overview and background to the literature on rotavirus, rotavirus vaccines, intussusception and benefit-risk modelling. The main body of the thesis then includes a series of research papers which address specific topics relevant to the estimation of mortality benefits and intussusception risks. These include estimation of: RVGE deaths aged <5 years (Chapter 4); RVGE age distributions <5

years (Chapter 5); vaccine coverage and timeliness (Chapter 6); rotavirus vaccine efficacy and waning (Chapter 7); and, intussusception incidence, age distributions and case fatality ratios - CFRs (Chapter 8). The final research paper (Chapter 9) brings together this evidence and uses a national vaccine decision support model to estimate the potential rotavirus mortality benefits and intussusception risks of 18 possible rotavirus vaccination schedules in 135 LMICs. The thesis concludes with some final reflections on the research and its relevance for informing national decisions about vaccine safety and optimal scheduling of rotavirus vaccines (Chapter 10).

This is a research-paper thesis rather than the conventional book style. Six of the chapters are full research papers. Two have been published in peer-reviewed journals (Chapters 4 & 6) and the remaining four (Chapters 5, 7, 8 and 9) have been prepared for submission. For consistency between published and unpublished research papers, references are listed at the end of each chapter, and the numbering of tables and figures is restarted at the beginning of each chapter. Each research-paper chapter begins with a short section describing how the paper contributes to the overall aim and objectives of the thesis. I have also described my independent academic contribution to each paper. This is important to clarify because all papers include contributions from others. Relevant funding and ethical approvals are also described.

Appendices to Chapters 5, 8 and 9 are included at the end of each chapter for ease of referencing. Other appendices are included at the end of the thesis, either because they contain optional background material (Appendices 1-5, 10), or because they describe analyses that were primarily done by others (Appendices 6-9).

List of references (Chapter 1)

1. Clark A, Black R, Tate J, Roose A, Kotloff K, Lam D, et al. Estimating global, regional and national rotavirus deaths in children aged <5 years: Current approaches, new analyses and proposed improvements. PLoS One. 2017;12(9):e0183392.

2. ROTA Council. Country introductions of rotavirus vaccines. Available at: http://rotacouncil.org/vaccine-introduction/global-introduction-status/ [accessed 31st August 2018].

3. GAVI. Rotavirus vaccine support. Available at: https://www.gavi.org/support/nvs/rotavirus/ [Accessed 31st August 2018].

4. Burnett E, Jonesteller CL, Tate JE, Yen C, Parashar UD. Global Impact of Rotavirus Vaccination on Childhood Hospitalizations and Mortality from Diarrhea. The Journal of infectious diseases. 2017;215:1666-72.

5. Stowe J, Andrews N, Ladhani S, Miller E. The risk of intussusception following monovalent rotavirus vaccination in England: A self-controlled case-series evaluation. Vaccine. 2016;34(32):3684-9.

6. Yih WK, Lieu TA, Kulldorff M, Martin D, McMahill-Walraven CN, Platt R, et al. Intussusception risk after rotavirus vaccination in U.S. infants. N Engl J Med. 2014;370(6):503-12.

7. Patel MM, Clark AD, Sanderson CF, Tate J, Parashar UD. Removing the age restrictions for rotavirus vaccination: a benefit-risk modeling analysis. PLoS Med. 2012;9(10):e1001330.

8. WHO. WHO position paper – January 2013. Rotavirus. Weekly Epidemiological Review (WER) Available at: http://wwwwhoint/wer/2013/wer8805/en/ [Accessed 7 Feb 2018]. 2013;88(5):49–64.

9. Clark A, Sanderson C. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. Lancet. 2009;373(9674):1543-9.

10. Lopman BA, Pitzer VE. Waxing Understanding of Waning Immunity. J Infect Dis. 2018;217(6):851-3.

11. Zaman K, Fleming JA, Victor JC, Yunus M, Bari TI, Azim T, et al. Noninterference of Rotavirus Vaccine With Measles-Rubella Vaccine at 9 Months of Age and Improvements in Antirotavirus Immunity: A Randomized Trial. J Infect Dis. 2016;213(11):1686-93.

12. Bines JE, At Thobari J, Satria CD, Handley A, Watts E, Cowley D, et al. Human Neonatal Rotavirus Vaccine (RV3-BB) to Target Rotavirus from Birth. N Engl J Med. 2018;378(8):719-30.

13. Bank W. World Bank list of economies (June 2017). Available at: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups [Accessed 7th February 2018].

2.0 Chapter 2 – Review of the literature

2.1 Rotavirus gastroenteritis

Gastroenteritis (GE), characterised by diarrhoea, abdominal cramps, nausea and sometimes vomiting, is usually diagnosed when a child experiences three or more loose stools, or vomiting, within a 24-hour period (1). Without adequate fluid replenishment GE can quickly lead to dehydration, electrolyte imbalance, metabolic acidosis, shock and death (2). Descriptions of GE exist as far back as the earliest records of human civilisation (3) and its role in child mortality is well documented - described in 1940s London as "one of the most fatal diseases of infancy in our capital"(4).

In 1973 Ruth Bishop, Geoffrey Davidson, Ian Holmes and Brian Ruck identified a high volume of particles of a new virus in the faeces of children admitted to the Royal Children's Hospital (RCH) in Melbourne, Australia. The wheel-like structure seen under an electron microscope was the inspiration for the name rotavirus (*rota* is latin for wheel) (5). Prior to this discovery, the causative agents of GE were poorly understood. Rotavirus has since been detected in numerous studies around the world and is now recognised as a leading global cause of GE hospitalisations in children aged <5 years (6).

Rotavirus is detected by testing stool samples, typically with commercially available enzyme immunoassays (EIAs). EIAs have proven to be highly sensitive and specific and have been the standard test used to detect rotavirus in randomised controlled trials (RCTs). Several different strains of rotavirus can cause infection and disease in humans. The outer shell of the rotavirus particle contains two important proteins that determine the strain; a glycoprotein (G-type) and a protease-sensitive protein (P-type). G-types can be reliably identified using EIAs and are known as serotypes. EIA serotyping is less reliable for P-types, so these are often determined using a molecular technique called Polymerase Chain Reaction (PCR). P-types are also referred to as genotypes [represented in square brackets] (7). In 2010, the most common strains identified by the Rotavirus WHO surveillance network were G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8] with wide variations in strain mix across countries and seasons (8). Rotavirus has a clear seasonal pattern in most high income countries, but seasonal peaks are less evident in lower income settings, where many countries experience year-round disease (9).

Following a brief period of protection from maternal antibodies, almost every child in the world, irrespective of where they live, will be infected with rotavirus at least once before their fifth birthday. The mode of transmission is thought to be faecal-oral, and the incubation period (interval between exposure and onset of symptoms) is usually less than 48 hours (2). Natural or wild type rotavirus infections (asymptomatic or symptomatic) have been shown to provide some protection against subsequent moderate-to-severe disease. Important birth cohort studies have been conducted in Mexico and India. In Mexico, two prior infections provided complete protection against subsequent moderate-to-severe disease (10). In India however, two infections provided only 57% protection (and only 79% after three) (11). In both settings, natural infections provided limited protection against subsequent asymptomatic infections and mild disease. Thus frequent reinfections are probably very common and provide the basis for continued circulation. A study in England detected rotavirus in the stools of healthy individuals in all age groups (12).

Two point scoring systems have been used to determine the severity of RVGE in randomised controlled trials (RCTs), the 20-point 'Vesikari' system and the 24-point 'Clark' system (13). Points are awarded for the presence and severity of different symptoms e.g. duration of vomiting, duration of diarrhoea, rectal temperature, signs of dehydration etc. Nearly all RCTs of rotavirus vaccines define severe RVGE as 11-20 points on the Vesikari scale. Some older trials use a Clark score of 16-24 points. These two scores have been shown to correlate poorly with one another when estimating the proportion of RVGE episodes defined as severe (13, 14).

In the scientific literature, the most commonly reported rotavirus disease burden indicator is the rotavirus-positive proportion among GE hospital admissions aged <5 years. Some studies have also reported the rotavirus-positive proportion among cases of moderate-to-severe diarrhoea (MSD)(15). Definitions of MSD vary but typically the symptoms include three or more loose or liquid stools per day and 'some' dehydration, defined by WHO as having two or more of the following signs: restlessness/irritability; sunken eyes; and thirsty/drinks eagerly. Signs of more severe dehydration include lethargy, unconsciousness and a skin pinch that goes back very slowly (≥ 2 seconds). Rehydration treatment involves dissolving an inexpensive sachet of oral rehydration salts/solution (ORS) in drinking water or making an equivalent home preparation (six teaspoons of sugar, half a teaspoon of salt and one litre of drinking water). However, because RVGE is often associated with explosive

vomiting and diarrhoea, intravenous rehydration (IV) is required in more serious cases (16).

Estimates of the number of RVGE deaths <5 years of age vary from ~120,000 to ~215,000 in the year 2015 (6). Most of these deaths were in Sub-Saharan Africa and South Asia, where many children are not promptly or adequately rehydrated. The incidence of symptomatic RVGE episodes is thought to be similar across the world, and largely unaffected by living standards or hygiene. A meta-analysis of studies conducted between 1977 and 2003 estimated 0.24 episodes of RVGE (of any severity) per person-year of observation among children aged less than 2 years worldwide (17). Assuming most cases occur in the first two years of life, this is roughly equivalent to every child in the world having a symptomatic episode of RVGE at least once before their fifth birthday. Consequently, large numbers of children require medical attention, with potentially significant costs to both households and Governments. A study by Clark *et al* estimated a cost to the English National Health Service (NHS) of over £11 million each year (18).

2.2 Rotavirus vaccination

In 1987, Albert Kapikian and colleagues at the US National Institutes of Health (NIH) developed RotaShield® (Wyeth-Ayherst), a live attenuated, or weakened, oral vaccine based on a human-rhesus (monkey) combination of rotavirus strains. This was licensed for use in the USA in 1998 for administration in three doses at 2, 4 and 6 months of age, but withdrawn in 1999 following association with intussusception, a rare but potentially fatal bowel disorder (19).

In 2006, two second generation live attenuated oral vaccines were licensed for use in the USA following large-scale efficacy and safety trials (20, 21). The first vaccine, Rotarix ® (GlaxoSmithKline) was developed by Richard Ward and David Bernstein at the Cincinnati Children's Hospital and is based on a G1P[8] human strain (22), the most common strain in circulation globally (8). This is a two-dose vaccine administered at 2 and 4 months of age. The second vaccine, Rotateq ® (Merck), was developed at the Wistar Institute and Children's Hospital of Philadelphia by Fred Clark, Paul Offit and Stanley Plotkin. In this vaccine, four human G-types (G1, G2, G3, G4) and one human P-type (P[8]) were each combined with a bovine (cow) rotavirus strain (WC3) to produce a pentavalent vaccine with five reassorted human-bovine strains (23). This vaccine is given in three doses at 2, 4 and 6 months of age.

A good deal of pre- and post-licensure evidence has now been accumulated on the efficacy and safety of Rotarix® and RotaTeq®. Both vaccines have demonstrated >90% efficacy against severe RVGE episodes in low mortality settings. However, the combined estimate of efficacy from higher mortality countries (Bangladesh, Vietnam, Ghana, Kenya and Mali) is only around 67% in the first year of life and 34% in the second year of life (24). The reason for lower and less durable efficacy in these settings is unclear but has been linked to factors including poorer nutritional status and more frequent exposure to a wider range of enteric pathogens (25). Both vaccines have demonstrated clinical cross-protection to the major strains not included in the vaccines (26), and thus similar efficacy in different settings. It is difficult to compare the two vaccines directly as different case definitions and severity scales were used in some trials (13) and the two vaccines have never been directly compared in a head-to-head RCT within the same study population. However, the post-licensure experience of countries that have used both Rotarix® and RotaTeq® does not suggest any material difference in impact (27).

In recent years, several manufacturers have emerged from LMICs. In China, LLR® (Lanzhou lamb rotavirus vaccine - Lanzhou Institute of Biological Products) is based on a single G10P[12] lamb rotavirus strain, and has been sold in the private market since 2000. A case control study of LLR® in China reported effectiveness of 43% for a single dose administered between 2 and 35 months of age (28). In Vietnam, Rotavin® (POLYVAC-Vietnam) is based on an attenuated human G1P[8] strain isolated from a Vietnamese child. This vaccine was licensed for use after demonstrating comparable immunogenicity to Rotarix® among Vietnamese infants (29). In India, two vaccines have been developed. ROTAVAC® (Bharat Biotech International, India) was recently WHO pre-qualified for global use (30). This is based on a naturally attenuated human-bovine (cow) strain (II6E) isolated from an Indian infant by Maharaj K Bahn and colleagues at the All India Institute of Medical Sciences (AIIMS) in Delhi (31). This vaccine demonstrated 54% efficacy against severe RVGE in Indian infants and is priced at less than $3 per three-dose course. This is considerably lower than the price of Rotarix® and RotaTeq®. A bovine-human reassortant pentavalent rotavirus vaccine (BRV-PV) called ROTASIIL® (Serum Institute of India) is also licensed for use in India. This has demonstrated 38% efficacy against severe RVGE in India, and 65% efficacy in Niger (32, 33). This vaccine may also be WHO pre-qualified for global use soon.

Several others rotavirus vaccines are also in the pipeline, including neonatal and non-replicating injectable vaccines (34, 35). An oral neonatal vaccine, RV3-BB (Murdoch Children's Research Institute - MCRI, Australia) has shown to be efficacious in Indonesia when administered as a three-dose series (36). This has the potential to increase vaccination coverage and potentially reduce vaccine-related intussusception events by allowing the first dose to be administered earlier in life when the background rate of intussusception is low. Other vaccines in the pipeline include non-replicating injectable vaccines (35). These could prove to be safer and more efficacious than existing live oral vaccines, but more clinical evidence will be needed to confirm this.

2.3 Rotavirus vaccination and intussusception

Intussusception is the main cause of bowel obstruction in children aged <5 years. It occurs when a segment of the intestine telescopes or folds back on itself (43). This blocks the passage of food and liquid through the intestine and restricts the supply of blood to the affected area. Some cases of intussusception will spontaneously resolve without treatment, but delayed diagnosis can lead to perforation and infection in the lining of the abdominal cavity: peritonitis. Peritonitis can cause severe abdominal pain, fever, shock and death (44). In high income countries most children are diagnosed quickly with ultrasound or radiograph and the bowel will return to normal after injecting a liquid or gas into the rectum (enema). In more severe cases surgery is usually very successful. However, in parts of Africa and other high mortality settings, enemas are less common due to a lack of imaging equipment and expertise, and because many children will present very late to hospital in a severe condition (37). In these cases, surgery is often the primary method of diagnosis and treatment, leading to death in ~10% of African children that reach hospital (45). The cause of intussusception is usually unclear, but infections that cause swelling in the bowel wall may be associated (46).

Intussusception occurs naturally in the absence of vaccination, but the risk appears to be slightly elevated shortly after rotavirus vaccination in some studies. The first rotavirus vaccine, RotaShield® (Wyeth-Ayherst) was voluntarily withdrawn from the market in 1999 when an elevated risk of intussusception was detected among vaccinated infants in the USA (19). The risk was equivalent to one additional case in every 5,000-10,000 vaccinated infants. There is now enough accumulated evidence from post-licensure studies to suggest that both Rotarix® and RotaTeq® are also

associated with an increased risk of intussusception in some settings (38, 39). While the scale of risk associated with Rotarix® and RotaTeq® is believed to be smaller than the risk observed for RotaShield®, a true comparison is not possible because both vaccines have been administered within age windows designed to avoid the background peak age of intussusception. Many of the vaccines administered in the RotaShield® programme were administered as part of a catch-up campaign, so were administered to older infants when the background incidence of intussusception was high (40). To limit the scale of potential vaccine-related intussusception cases the two major vaccine manufacturers have recommended different age restrictions tailored to their own vaccines. The aim of these age restrictions is to ensure the vaccine is administered earlier in life, when the background incidence of intussusception is lower. The WHO harmonised the different manufacturers' age restrictions and recommended administration of the first dose before 15 weeks of age and the final dose before 32 weeks of age (24). Following a modelling analysis in 2012, the WHO revised their recommendation to allow countries to remove age restrictions in countries where the benefits of later vaccination would greatly exceed the risks (24, 41).

An excess or vaccine-related case of intussusception is defined by WHO as an adverse event following immunization (AEFI). Intussusception is a 'serious' adverse event because it has the potential to lead to hospitalisation and death. Serious adverse events are included within the wider spectrum of all severe adverse events (SAE). SAEs also include severe reactions that are not life-threatening. The distinction between 'serious' and 'severe' is important; serious is a regulatory term whereas severe is not (42).

Different study designs have been used to detect any potential relative risk of intussusception following vaccination, but because intussusception is such a rare event, these studies are often not powered for reliable detection of an increase in risk. The self-controlled case series (SCCS) methodology is considered to be relatively reliable and has been widely used (5). In this method, children with intussusception act as their own controls. The risk of intussusception is calculated for the period of hypothesised elevated risk (i.e. 21 days following vaccination) and then compared to the risk of intussusception in all other periods, with appropriate adjustment for age (43). Intussusception risk is expressed as the relative incidence (RI) or relative risk (RR) compared to the expected background incidence in the absence of vaccination. A meta-analysis of Rotarix® studies by Stowe *et al* found pooled RI estimates of 2.4

(95% confidence interval 1.5 - 3.8) and 1.8 (1.3 - 2.4) in the 21 day period after the first and second doses, respectively (44). Similar risks have also been reported for RotaTeq® in the USA (39) and Australia (38). The estimates for Rotarix® and RotaTeq® in Australia were equivalent to one additional case in every 14,000-20,000 vaccinated infants, but studies from other settings have reported a lower level of risk, and none have reported a risk as high as RotaShield® (one in every 5,000-10,000 vaccinated infants). Encouragingly, a recent SCCS study of Rotarix® in Africa found no elevated risk of intussusception in the first 1-7 days after dose 1 (RI 0.30, 95% CI 0.0 - 1.0) or dose 2 (RI 0.8, 95% CI 0.2 – 1.7) and no elevated risk 8-21 days after dose 1 (RI 1.0, 95% CI 0.3 – 2.3) or dose 2 (RI 0.7, 95% CI 0.4 – 1.2). This was a multi-site study including infants from seven countries (Ethiopia, Ghana, Kenya, Malawi, Tanzania, Zambia, and Zimbabwe) (45).

2.4 Published studies evaluating the benefits and risks of rotavirus vaccination

In 2012, Patel *et al* estimated the potential mortality benefits and intussusception risks of introducing live oral rotavirus vaccines into the 2010 birth cohort of 158 countries (24). This study updated an earlier analysis conducted in 2009 based on 117 countries (46). The 2012 study found that with full adherence to the manufacturers' age restrictions, universal introduction of rotavirus vaccination would prevent 156,000 RVGE deaths and cause 253 deaths (benefit-risk ratio of ~600:1). Without age restrictions, rotavirus vaccines were estimates to prevent 203,000deaths and cause 547 deaths (benefit-risk ratio of ~370:1). The study therefore found that removing age restrictions from a standard infant schedule co-administered with DTP would prevent an additional ~47,000 RVGE deaths and potentially cause an additional ~300 intussusception deaths each year (incremental benefit-risk ratio of 154:1)(24). This study informed a WHO recommendation to remove the manufacturers' age restrictions for vaccination given that the benefits of preventing additional rotavirus mortality from later vaccination greatly exceeded the intussusception risks (41). The 2012 publication (Appendix 1) and WHO position paper (Appendix 2) are available in the list of appendices.

Several other benefit-risk analyses have also been published. A multi-country analysis for all countries in Latin America estimated a benefit-risk ratio of 395:1 (47), while in a study in Brazil and Mexico the estimate was 260:1 (48). The benefit-risk ratio was estimated to be 88:1 in England (18), 273:1 in France (49), 77:1 in the USA (50) and 366:1 in Japan (51). Other high income countries have calculated benefits and

risks for hospitalisations, but not mortality (38). In higher income countries, mortality from both rotavirus and intussusception is very rare, and other criteria become more important. In England, Clark *et al* estimated that Rotarix® would cause one additional intussusception admission in every 18,551 vaccinated English infants (5th and 95th percentiles, 6,728 - 93,952), equivalent to 35 additional intussusception admissions each year. In contrast, it was estimated that each year the vaccine prevented three rotavirus deaths, 13,000 rotavirus admissions, 27,000 rotavirus emergency visits and 74,000 rotavirus GP consultations in children aged <5 years, with lead to annual savings of over £11 million. There were 375 fewer RVGE admissions for every additional intussusception admission (18).

All studies evaluating the benefits and risks of rotavirus vaccination have used a relatively simple and conservative modelling approach, excluding any estimation of the indirect effects of vaccination. Most of the studies have justified this on the basis that if the benefit-risk profile is favourable without herd effects, then it would only be more so if those additional benefits were included. Not all studies have captured the potential risk in the 1-7 day, 8-21 day windows following administration of both of the first doses, and not all studies have presented probabilistic uncertainty intervals around their central estimates. All studies have assumed that the relative risks do not vary with age, implying that the absolute number of excess cases is heavily dependent on the background incidence of intussusception at the time of vaccine administration.

2.5 Modelling considerations for predicting the benefits of rotavirus vaccination

There are several aspects of a model's structure or design which, if excluded, could lead to incorrect assessment of the scale of vaccination impact. Several systematic reviews have evaluated the different characteristics of rotavirus vaccine impact models in the context of economic evaluations and cost-effectiveness analysis (CEA). A review of economic evaluations by Bilcke and Beutels identified 17 unique models globally, of which only ten (59%) included a realistic RVGE age distribution, nine (53%) included partial vaccine protection, seven (41%) included waning duration of protection and none (0%) accounted for transmission dynamics, e.g. herd effects (52). A subsequent review of models in developing countries by Tu *et al* identified 15 models of which only two (13%) included partial immunity acquired from wild-type (natural) infections and none (0%) accounted for herd immunity effects (53). Another review (Aballea *et al*, Sanofi Pasteur) identified 68 studies (15 unpublished). Seasonality was included in five (7%) of the studies, but was shown to have a minimal

influence on vaccine impact estimates. In contrast, waning duration of protection was shown to have an important influence in some of the analyses. Only one (2%) of the models explicitly modelled the natural history of disease and associated herd effects (54). Postma *et al* compared estimates from three models and attributed differences in results to assumptions about dose-specific vaccine efficacy, waning duration of protection and the level of immunity acquired from natural infections (55). The timeliness of vaccination was shown to be influential in a cost-effectiveness study by Clark *et al* in Peru. This analysis showed that ignoring delays and assuming 'on-time' vaccination would over-estimate health benefits by 4% (56). An analysis of delays in 45 other countries by Clark and Sanderson showed that Peru's immunization programme is relatively timely compared to others, so this error is likely to be greater in countries with more pronounced delays (57).

Unlike static cohort models, transmission dynamic models are able to predict the number of susceptible, infectious and immune individuals over time. These models are also able to capture the interplay between immunity acquired from vaccination and immunity acquired from repeated natural (wild type) infections. Models of this kind typically require assumptions to be made about the number of individuals exposed by each infectious individual (also known as the basic reproductive number or R0), the duration of immunity acquired from natural infections, and further assumptions about who acquires infection from whom (WAIFW). Pitzer *et al* described five rotavirus transmission dynamic models that were each calibrated to the same age-specific RVGE incidence data from England and Wales (58). All five models simulated the flow of groups of individuals into different compartments (health states) over time using differential equations. A pivotal study by Velasquez *et al* was used to inform estimates of protection from 1 up to 4 natural infections against subsequent infections and disease episodes (10). Estimates of R0 varied considerably between the five models, ranging from ~1 to 26 secondary exposures per infectious individual. Discrepancies between the model predictions reflected uncertainties in the age-specific risk of RVGE infections, and the duration of natural and vaccine-induced immunity. However, over the long-term (5 years post-vaccination), all of the models predicted impact among children aged <5 years that was broadly similar to what would have been predicted by direct effects alone, based on a simple multiplication of age-specific disease, vaccine coverage and efficacy. Park *et al* subsequently evaluated the potential impact of ROTASIIL® vaccination in Niger using the same set of transmission models that were compared by Pitzer *et al*. An ensemble approach with Bayesian averaging was used to give greater weight to model structures with a

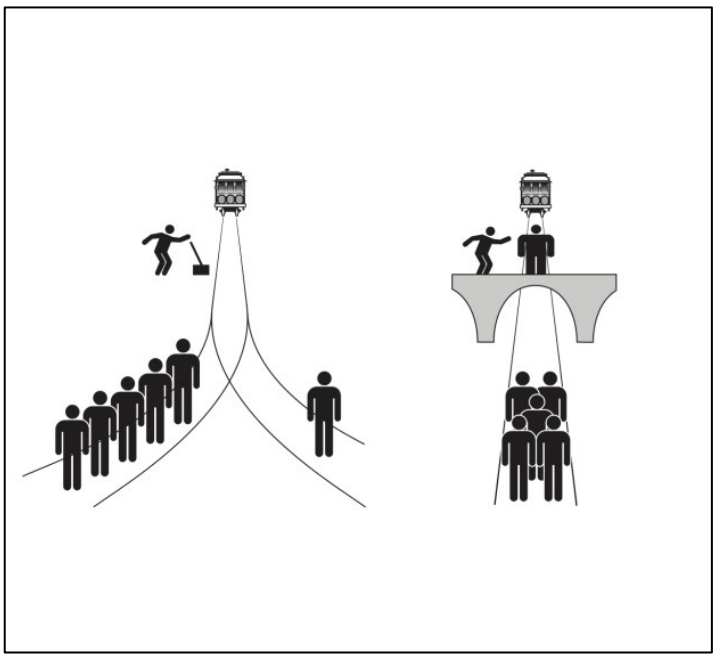
better fit to the local data. The authors found a marginal role for herd effects in explaining overall impact (~1% of the total long-term impact in children aged <5 years) (59). This is consistent with the findings of a study by Rose *et al* in India (60). In this study a sophisticated individual-based transmission dynamic model was developed, and informed by data from a pivotal birth cohort study by Gladstone *et al*. Using this data, the model accounted for protection from 1 to 4 natural infections against subsequent infections and disease episodes (11), and predicted that introduction of ROTAVAC ® would lead to a 35% reduction in rotavirus deaths aged <5 years. This was almost identical to the impact estimated by two much simpler models, leading the authors to conclude that simpler approaches would be adequate for estimating the potential impact on mortality among children aged <5 years in this setting.

Real-world post-licensure studies have produced conflicting results about the level of impact among unvaccinated children. While there is evidence of short-term herd effects in high income settings, evidence from LMICs is relatively sparse (61). Short-term decreases in RVGE hospital admissions have been observed among children too old to be vaccinated in El Salvador (62), Ghana, Moldova (63) and Rwanda (64). However, no substantial herd effect was observed in Malawi (65), South Africa (2), Tanzania (63) or Zambia (66), and even where studies have reported short-term indirect benefits, uncertainties remain about whether these will be sustained over the longer-term.

2.6 Ethical considerations in the context of rotavirus vaccination

When the first rotavirus vaccine (RotaShield®) was voluntarily removed from the market in the USA, ethicists argued that *"the future of a potentially lifesaving vaccine for developing countries has been imperilled by its recent withdrawal".* A central argument was that inaction was not a morally neutral state, and that *"if one is culpable for vaccine related deaths, then one is also culpable for deaths caused by withholding the vaccine."* (67). This concept is akin to a well-known thought experiment in ethics known as the trolley or tram problem (68). In this experiment a tram is about to kill five people, but pulling a lever can divert the tram on to another track where only one person will be killed.

Graphical depiction of the trolley problem



Source: https://i0.wp.com/moralarc.org/wp-content/uploads/2015/04/trolley-problem.jpg?w=620

Another variation is that a person is pushed from a bridge into the path of the tram, again saving five lives at the expense of one. The moral dilemma is a choice between inaction and intervention. Utilitarianism (the greatest good for the greatest number) would favour intervention (69). In the context of rotavirus vaccination this would mean favouring schedule options that maximise the net number of deaths prevented, irrespective of whether large number of intussusception deaths are caused in the process. This raises important ethical considerations and is contrary to the public health principle 'first do no harm' (67). It also fails to consider uncertain consequences that could be associated with taking action. For example, an increase in high profile legal challenges and anti-vaccine sentiment could have an adverse effect on the coverage of rotavirus vaccines, and potentially other vaccines. In England, concerns about the safety of whole-cell pertussis and MMR (measles mumps and rubella) vaccines have previously led to substantial short-term declines in coverage (65). There is also some evidence that a death caused by action/intervention may be perceived by individuals as worse than a death caused by inaction (70, 71).

Herbert Simon made a distinction between substantive rationality, choosing the outcome with the maximum mathematical utility, and procedural rationality, allowing decision makers to reject options that do not meet minimum standards (72). In terms

of rotavirus vaccination, this would imply a maximum level of acceptable risk, above which the vaccination programme would not be socially acceptable. The risk associated with RotaShield® in the USA (more than one excess intussusception cases in every 10,000 vaccinated infants) provides an important psychological benchmark for what might be considered a maximum level of acceptable risk. Fine and Clarkson have argued that the level of acceptable risk will differ depending on whether the choice is made by individuals (more likely to choose lower uptake) or public health decision-makers representing the community as a whole (more likely to choose higher uptake) (73). Another benchmark that could be used to inform a socially acceptable risk for rotavirus vaccines is the level of risk that has been accepted for other vaccines. However, combining this evidence is not straightforward. The WHO provides reported reaction rates for each vaccine formulation but the spectrum of possible adverse effects is broad and the uncertainty intervals around the risks are wide. For BCG vaccine, the risk of disseminated BCG disease (fatal in 50% of cases) is reported to be less than one in every 200,000 vaccinated infants. For the first dose of oral polio vaccine (OPV) the risk of vaccine associated paralytic poliomyelitis (VAPP) is one in every 750,000 vaccinated infants. For Measles and DTP vaccines, rates of febrile seizures are relatively common (one in every ~3000 doses) but these are rarely fatal (42, 74). Resnik has argued that the maximum level of acceptable risk should not exceed the maximum risk of death for high risk forms of paid labour, such the mortality risks among fishermen, loggers and extraction workers. He went on to suggest this as one possible approach for determining the maximum acceptable risk among paid volunteers in clinical trials. The maximum acceptable risk of a serious adverse event could then be derived by combining the maximum acceptable mortality risk with the CFR for the serious adverse event in question (75). This approach has obvious limitations if applied to the example of rotavirus vaccination because the focus is on adults and paid participation.

For rotavirus vaccination, the maximum acceptable risk will be inextricably linked to the scale of potential benefits and for this reason, it would be very difficult for national decision-making committees to set universal thresholds for maximum acceptable risk. A minimum threshold for the balance of benefits to risks (minimum benefit-risk ratio) could however be developed, and may lead to more consistent decision-making across vaccines. The Global Advisory Committee on Vaccines Safety (GACVS) and Strategic Advisory Group of Experts (SAGE) are the principal advisory groups to WHO on issues around the safety and acceptability of rotavirus vaccines, and ultimately the committee members will have to make value judgements and

recommendations informed by the best available evidence on benefits and risks, as well as other criteria including costs, cost-effectiveness and operational feasibility (76).

List of references (Chapter 2)

1. Majowicz SE, Hall G, Scallan E, Adak GK, Gauci C, Jones TF, et al. A common, symptom-based case definition for gastroenteritis. Epidemiol Infect. 2008;136(7):886-94.

2. Groome MJ, Zell ER, Solomon F, Nzenze S, Parashar UD, Izu A, et al. Temporal Association of Rotavirus Vaccine Introduction and Reduction in All-Cause Childhood Diarrheal Hospitalizations in South Africa. Clin Infect Dis. 2016;62 Suppl 2:S188-95.

3. Lim ML, Wallace MR. Infectious diarrhea in history. Infect Dis Clin North Am. 2004;18(2):261-74.

4. Gairdner P. Infantile diarrhoea: An Analysis of 216 Cases with Special Reference to Institutional Outbreaks. Arch Dis Child. 1945;20(101):22-7.

5. Bishop R. Discovery of rotavirus: Implications for child health. J Gastroenterol Hepatol. 2009;24 Suppl 3:S81-5.

6. Clark A, Black R, Tate J, Roose A, Kotloff K, Lam D, et al. Estimating global, regional and national rotavirus deaths in children aged <5 years: Current approaches, new analyses and proposed improvements. PLoS One. 2017;12(9):e0183392.

7. Greenberg HB, Estes MK. Rotaviruses: from pathogenesis to vaccination. Gastroenterology. 2009;136(6):1939-51.

8. WHO. Global rotavirus information and surveillance bulletin. Reporting period: January-December 2010. World Health Organization V, 2011. Available at: http://www.who.int/immunization/diseases/rotavirus/Final_RV_bulletin_Jan_Dec_2010_Data.pdf [accessed 24th March 2014].

9. Patel MM, Pitzer VE, Alonso WJ, Vera D, Lopman B, Tate J, et al. Global seasonality of rotavirus disease. Pediatr Infect Dis J. 2013;32(4):e134-47.

10. Velazquez FR, Matson DO, Calva JJ, Guerrero L, Morrow AL, Carter-Campbell S, et al. Rotavirus infections in infants as protection against subsequent infections. N Engl J Med. 1996;335(14):1022-8.

11. Gladstone BP, Ramani S, Mukhopadhya I, Muliyil J, Sarkar R, Rehman AM, et al. Protective effect of natural rotavirus infection in an Indian birth cohort. N Engl J Med. 2011;365(4):337-46.

12. Phillips G, Lopman B, Rodrigues LC, Tam CC. Asymptomatic rotavirus infections in England: prevalence, characteristics, and risk factors. Am J Epidemiol. 2010;171(9):1023-30.

13. Givon-Lavi N, Greenberg D, Dagan R. Comparison between two severity scoring scales commonly used in the evaluation of rotavirus gastroenteritis in children. Vaccine. 2008;26(46):5798-801.

14. Aslan A, Kurugol Z, Cetin H, Karakaslilar S, Koturoglu G. Comparison of Vesikari and Clark scales regarding the definition of severe rotavirus gastroenteritis in children. Infect Dis (Lond). 2015;47(5):332-7.

15. Kotloff KL, Blackwelder WC, Nasrin D, Nataro JP, Farag TH, van Eijk A, et al. The Global Enteric Multicenter Study (GEMS) of diarrheal disease in infants and young children in developing countries: epidemiologic and clinical methods of the case/control study. Clin Infect Dis. 2012;55 Suppl 4:S232-45.

16. WHO. World Health Organization. Diarrhoeal Disease Fact Sheet. Available at: http://www.who.int/en/news-room/fact-sheets/detail/diarrhoeal-disease [accessed 12th August 2018]. 2018.

17. Bilcke J, Van Damme P, Van Ranst M, Hens N, Aerts M, Beutels P. Estimating the incidence of symptomatic rotavirus infections: a systematic review and meta-analysis. PLoS One. 2009;4(6):e6060.

18. Clark A. JM, Andrews N., Atchison C., Edmunds J., Sanderson C., . Evaluating the potential risks and benefits of infant rotavirus vaccination in England. Vaccine. 2014.

19. Schwartz JL. The first rotavirus vaccine and the politics of acceptable risk. Milbank Q. 2012;90(2):278-310.

20. Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, Abate H, Breuer T, Clemens SC, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med. 2006;354(1):11-22.

21. Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med. 2006;354(1):23-33.

22. Ward RL, Bernstein DI. Rotarix: a rotavirus vaccine for the world. Clin Infect Dis. 2009;48(2):222-8.

23. Clark HF, Offit PA, Plotkin SA, Heaton PM. The new pentavalent rotavirus vaccine composed of bovine (strain WC3) -human rotavirus reassortants. Pediatr Infect Dis J. 2006;25(7):577-83.

24. Patel MM, Clark AD, Sanderson CF, Tate J, Parashar UD. Removing the age restrictions for rotavirus vaccination: a benefit-risk modeling analysis. PLoS Med. 2012;9(10):e1001330.

25. Bhandari N, Rongsen-Chandola T, Bavdekar A, John J, Antony K, Taneja S, et al. Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian infants: a randomised, double-blind, placebo-controlled trial. Lancet. 2014.

26. Vesikari T. Rotavirus vaccination: a concise review. Clin Microbiol Infect. 2012;18 Suppl 5:57-63.

27. Immergluck LC, Parker TC, Jain S, Laghaie E, Spandorfer P, Jerris RC, et al. Sustained Effectiveness of Monovalent and Pentavalent Rotavirus Vaccines in Children. J Pediatr. 2016;172:116-20 e1.

28. Fu C, He Q, Xu J, Xie H, Ding P, Hu W, et al. Effectiveness of the Lanzhou lamb rotavirus vaccine against gastroenteritis among children. Vaccine. 2012;31(1):154-8.

29. Dang DA, Nguyen VT, Vu DT, Nguyen TH, Nguyen DM, Yuhuan W, et al. A dose-escalation safety and immunogenicity study of a new live attenuated human rotavirus vaccine (Rotavin-M1) in Vietnamese children. Vaccine. 2012;30 Suppl 1:A114-21.

30. WHO. WHO. WHO prequalified vaccines. Last updated 8/8/2018. Available at: https://extranet.who.int/gavi/PQ_Web/ [accessed 8th August 2018]. 2018.

31. Bhan MK, Glass RI, Ella KM, Bhandari N, Boslego J, Greenberg HB, et al. Team science and the creation of a novel rotavirus vaccine in India: a new framework for vaccine development. Lancet. 2014.

32. Isanaka S, Guindo O, Langendorf C, Matar Seck A, Plikaytis BD, Sayinzoga-Makombe N, et al. Efficacy of a Low-Cost, Heat-Stable Oral Rotavirus Vaccine in Niger. N Engl J Med. 2017;376(12):1121-30.

33. Kulkarni PS, Desai S, Tewari T, Kawade A, Goyal N, Garg BS, et al. A randomized Phase III clinical trial to assess the efficacy of a bovine-human reassortant pentavalent rotavirus vaccine in Indian infants. Vaccine. 2017;35(45):6228-37.

34. Yen C, Tate JE, Hyde TB, Cortese MM, Lopman BA, Jiang B, et al. Rotavirus vaccines: Current status and future considerations. Hum Vaccin Immunother. 2014;10(6).

35. Kirkwood CD, Ma LF, Carey ME, Steele AD. The rotavirus vaccine development pipeline. Vaccine. 2017.

36. Bines JE, At Thobari J, Satria CD, Handley A, Watts E, Cowley D, et al. Human Neonatal Rotavirus Vaccine (RV3-BB) to Target Rotavirus from Birth. N Engl J Med. 2018;378(8):719-30.

37. Mpabalwani EM, Mwenda JM, Tate JE, Parashar UD. Review of Naturally Occurring Intussusception in Young Children in the WHO African Region prior to the Era of Rotavirus Vaccine Utilization in the Expanded Programme of Immunization. J Trop Pediatr. 2017;63(3):221-8.

38. Carlin JB, Macartney KK, Lee KJ, Quinn HE, Buttery J, Lopert R, et al. Intussusception risk and disease prevention associated with rotavirus vaccines in Australia's National Immunization Program. Clin Infect Dis. 2013;57(10):1427-34.

39. Yih WK, Lieu TA, Kulldorff M, Martin D, McMahill-Walraven CN, Platt R, et al. Intussusception risk after rotavirus vaccination in U.S. infants. N Engl J Med. 2014;370(6):503-12.

40. Simonsen L, Viboud C, Elixhauser A, Taylor RJ, Kapikian AZ. More on RotaShield and intussusception: the role of age at the time of vaccination. J Infect Dis. 2005;192 Suppl 1:S36-43.

41. WHO. WHO position paper – January 2013. Rotavirus. Weekly Epidemiological Review (WER) Available at: http://wwwwhoint/wer/2013/wer8805/en/ [Accessed 7 Feb 2018]. 2013;88(5):49–64.

42. WHO. Module 3. Adverse events following immunization. Available at: http://www.who.int/vaccine_safety/initiative/tech_support/Part-3.pdf [accessed 13th August 2018].

43. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. BMJ. 2016;354:i4515.

44. Stowe J, Andrews N, Ladhani S, Miller E. The risk of intussusception following monovalent rotavirus vaccination in England: A self-controlled case-series evaluation. Vaccine. 2016;34(32):3684-9.

45. Tate JE, Mwenda JM, Armah G, Jani B, Omore R, Ademe A, et al. Evaluation of Intussusception after Monovalent Rotavirus Vaccination in Africa. N Engl J Med. 2018;378(16):1521-8.

46. Patel MM, Clark AD, Glass RI, Greenberg H, Tate J, Santosham M, et al. Broadening the age restriction for initiating rotavirus vaccination in regions with high rotavirus mortality: benefits of mortality reduction versus risk of fatal intussusception. Vaccine. 2009;27(22):2916-22.

47. Desai R, Parashar UD, Lopman B, de Oliveira LH, Clark AD, Sanderson CF, et al. Potential intussusception risk versus health benefits from rotavirus vaccination in Latin America. Clin Infect Dis. 2012;54(10):1397-405.

48. Patel MM, Lopez-Collada VR, Bulhoes MM, De Oliveira LH, Bautista Marquez A, Flannery B, et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. N Engl J Med. 2011;364(24):2283-92.

49. Lamrani A, Tubert-Bitter P, Hill C, Escolano S. A benefit-risk analysis of rotavirus vaccination, France, 2015. Euro Surveill. 2017;22(50).

50. Desai R, Cortese MM, Meltzer MI, Shankar M, Tate JE, Yen C, et al. Potential intussusception risk versus benefits of rotavirus vaccination in the United States. Pediatr Infect Dis J. 2013;32(1):1-7.

51. Ledent E, Lieftucht A, Buyse H, Sugiyama K, McKenna M, Holl K. Post-Marketing Benefit-Risk Assessment of Rotavirus Vaccination in Japan: A Simulation and Modelling Analysis. Drug Saf. 2016;39(3):219-30.

52. Bilcke J, Beutels P. Reviewing the cost effectiveness of rotavirus vaccination: the importance of uncertainty in the choice of data sources. Pharmacoeconomics. 2009;27(4):281-97.

53. Postma MJ, Jit M, Rozenbaum MH, Standaert B, Tu HA, Hutubessy RC. Comparative review of three cost-effectiveness models for rotavirus vaccines in national immunization programs; a generic approach applied to various regions in the world. BMC Med. 2011;9:84.

54. Aballea S, Millier A, Quilici S, Caroll S, Petrou S, Toumi M. A critical literature review of health economic evaluations of rotavirus vaccination. Hum Vaccin Immunother. 2013;9(6):1272-88.

55. Tu HA, Woerdenbag HJ, Kane S, Rozenbaum MH, Li SC, Postma MJ. Economic evaluations of rotavirus immunization for developing countries: a review of the literature. Expert Rev Vaccines. 2011;10(7):1037-51.

56. Clark AD, Walker DG, Mosqueira NR, Penny ME, Lanata CF, Fox-Rushby J, et al. Cost-effectiveness of rotavirus vaccination in peru. J Infect Dis. 2009;200 Suppl 1:S114-24.

57. Clark A, Sanderson C. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. Lancet. 2009;373(9674):1543-9.

58. Pitzer VE, Atkins KE, de Blasio BF, Van Effelterre T, Atchison CJ, Harris JP, et al. Direct and indirect effects of rotavirus vaccination: comparing predictions from transmission dynamic models. PLoS One. 2012;7(8):e42320.

59. Park J, Goldstein J, Haran M, Ferrari M. An ensemble approach to predicting the impact of vaccination on rotavirus disease in Niger. Vaccine. 2017;35(43):5835-41.

60. Rose J, Homa L, Meropol SB, Debanne SM, Bielefeld R, Hoyen C, et al. Health impact and cost-effectiveness of a domestically-produced rotavirus vaccine in India: A model based analysis. PLoS One. 2017;12(11):e0187446.

61. Bennett A, Bar-Zeev N, Cunliffe NA. Measuring indirect effects of rotavirus vaccine in low income countries. Vaccine. 2016;34(37):4351-3.

62. Yen C, Armero Guardado JA, Alberto P, Rodriguez Araujo DS, Mena C, Cuellar E, et al. Decline in rotavirus hospitalizations and health care visits for childhood diarrhea following rotavirus vaccination in El Salvador. Pediatr Infect Dis J. 2011;30(1 Suppl):S6-S10.

63. Burnett E, Jonesteller CL, Tate JE, Yen C, Parashar UD. Global Impact of Rotavirus Vaccination on Childhood Hospitalizations and Mortality From Diarrhea. J Infect Dis. 2017;215(11):1666-72.

64. Ngabo F, Tate JE, Gatera M, Rugambwa C, Donnen P, Lepage P, et al. Effect of pentavalent rotavirus vaccine introduction on hospital admissions for diarrhoea and rotavirus in children in Rwanda: a time-series analysis. Lancet Glob Health. 2016;4(2):e129-36.

65. Bennett A, Pollock L, Jere KC, Pitzer VE, Parashar U, Tate JE, et al. Direct and possible indirect effects of vaccination on rotavirus hospitalisations among children in Malawi four years after programmatic introduction. Vaccine. 2018.

66. Mpabalwani EM, Simwaka CJ, Mwenda JM, Mubanga CP, Monze M, Matapo B, et al. Impact of Rotavirus Vaccination on Diarrheal Hospitalizations in Children Aged <5 Years in Lusaka, Zambia. Clin Infect Dis. 2016;62 Suppl 2:S183-7.

67. Weijer C. The future of research into rotavirus vaccine. Bmj. 2000;321(7260):525-6.

68. Foot P. The problem of abortion and negative and positive duty: a reply to James LeRoy Smith. J Med Philos. 1978;3(3):253-5.

69. Mill JS. Utilitarianism: Hackett Publishing Co, Inc; 2nd edition edition (1 Mar. 2002). 88 p.

70. Ball LK, Evans G, Bostrom A. Risky business: challenges in vaccine risk communication. Pediatrics. 1998;101(3 Pt 1):453-8.

71. Bauch CT, Earn DJ. Vaccination and the theory of games. Proc Natl Acad Sci U S A. 2004;101(36):13391-4.

72. Simon H. From substantive to procedural rationality, in HA Simon (ed.) Models of bounded rationality: behavioural economics and business organization. . Cambridge, MA: MIT Press; 1976.

73. Fine PE, Clarkson JA. Individual versus public priorities in the determination of optimal vaccination policies. Am J Epidemiol. 1986;124(6):1012-20.

74. WHO. Global Vaccine Safety. WHO vaccine reaction rates information sheets. Available at: http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/ [accessed 13th August 2018]. 2018.

75. Resnik D. The Ethics of Research with Human Subjects: Protecting People, Advancing Science, Promoting Trust. 1 ed: Springer International Publishing; 2018. XIII, 316 p.

76. WHO. Global Advisory Committee on Vaccine Safety (GACVS). Available at: http://www.who.int/vaccine_safety/initiative/communication/network/_gacvs/en/ [Accessed 31st August 2018].

3.0 Chapter 3 - Aim and objectives of thesis

3.1 Aim

The aim of this thesis is to estimate the potential mortality benefits (averted RVGE deaths aged <5 years of age) and risks (excess intussusception deaths <5 years of age) of alternative rotavirus vaccination schedules in LMICs.

3.2 Objectives

The objectives are:

1. To review national estimates of RVGE deaths <5 years of age, in the absence of rotavirus vaccination, in LMICs **(Chapter 4)***;*
2. To estimate the age distribution of RVGE cases, outpatient visits, hospitalisations and deaths <5 years of age in the absence of rotavirus vaccination and extrapolate to LMICs without data **(Chapter 5)**;
3. To estimate the timeliness of BCG, DTP1, DTP2, DTP3 and Meas1 vaccination in countries with household surveys, and extrapolate to LMICs without data **(Chapters 6 and 9)**;
4. To estimate the efficacy of rotavirus vaccination by duration of follow-up and type of setting **(Chapter 7)**;
5. To estimate the incidence, age distribution and case fatality of intussusception hospital admissions in children <5 years of age, and establish methods to extrapolate to LMICs without data **(Chapter 8)**;
6. To estimate the relative risk of intussusception in the 1-7 day and 8-21 day period following administration of the first two doses of rotavirus vaccination, and generate pooled estimates for use in benefit-risk analysis **(Chapter 9)**; and,
7. To develop a transparent static cohort model to simulate the experience of infants born in the 2015 birth cohort in 135 LMICs. The model will be used to estimate the number of RVGE deaths, intussusception cases and intussusception deaths in each week of age between birth and age 5.0 years, with and without rotavirus vaccination, for 18 alternative schedule options **(Chapter 9).**

4.0 Chapter 4 - Estimation of rotavirus deaths in children aged <5 years

4.1 Contribution of paper to the aim and objectives of the thesis

Estimates of the number of rotavirus deaths in the absence of vaccination are needed as a basis for predicting the potential mortality benefits of rotavirus vaccination. Three prominent research groups (WHO/CDC, CHERG/MCEE and GBD/IHME) have published global estimates of the number of RVGE deaths aged <5 years, but there are substantial differences in these estimates. The paper identifies reasons for the differences in estimates and some important limitations. In particular, acute watery diarrhoea may be responsible for a higher proportion of diarrhoeal hospital admissions than diarrhoeal deaths. Thus, applying rotavirus-positive proportions among hospitalisations to deaths could lead to over-estimates of RVGE deaths aged <5 years. Each group has subsequently shared updated estimates for the year 2015. The three updated estimates were used to calculate a mean and 95% confidence interval for each country in the benefit-risk analysis (Chapter 9).

4.2 Independent academic contribution

I was asked to chair a WHO working group to bring together the three groups, compare approaches and propose improvements for future estimates. My task was to compare the publicly available spreadsheet estimates of national, regional and global rotavirus mortality estimates, review the documented methods, explain the reasons for differences and propose improvements for future estimates. I gathered the datasets, ran the statistical analysis for the comparison exercise and wrote the first draft of the paper. In addition to my analysis, several gaps in the evidence were identified at an early stage in the process, and new analyses were done by others to help bridge these gaps. This included estimating the proportion of diarrhoea deaths and admissions due to acute watery diarrhoea, estimating the rotavirus attributable fraction among rotavirus hospitalisations, and the extent to which this varies depending on the type of diagnostic test used. The analyses done by others involved new analysis of the Global Enteric Multicenter Study (GEMS) database, the WHO Global Rotavirus Surveillance Network (GRSN) database, and other datasets.

4.3 Ethical approval

Appendix 3 (Chapter 4, S1 Table, Information about the data used for new analyses) describes the ethical approvals obtained by all collaborators/co-authors involved in this work. I did not seek LSHTM ethical approval for my contribution to the paper because my analysis was based on publicly available datasets and published papers in the public domain. I had no access to files with patient identifiable data and did not analyse or have access to any primary databases.

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RESEARCH ARTICLE

Estimating global, regional and national rotavirus deaths in children aged <5 years: Current approaches, new analyses and proposed improvements

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Abstract

Background

Rotavirus is a leading cause of diarrhoeal mortality in children but there is considerable disagreement about how many deaths occur each year.

Methods and findings

We compared CHERG, GBD and WHO/CDC estimates of age under 5 years (U5) rotavirus deaths at the global, regional and national level using a standard year (2013) and standard list of 186 countries. The global estimates were 157,398 (CHERG), 122,322 (GBD) and 215,757 (WHO/CDC). The three groups used different methods: (i) to select data points for rotavirus-positive proportions; (ii) to extrapolate data points to individual countries; (iii) to account for rotavirus vaccine coverage; (iv) to convert rotavirus-positive proportions to rotavirus attributable fractions; and (v) to calculate uncertainty ranges. We conducted new analyses to inform future estimates. We found that acute watery diarrhoea was associated with 87% (95% CI 83–90%) of U5 diarrhoea hospitalisations based on data from 84 hospital sites in 9 countries, and 65% (95% CI 57–74%) of U5 diarrhoea deaths based on verbal autopsy reports from 9 country sites. We reanalysed data from the Global Enteric Multicenter Study (GEMS) and found 44% (55% in Asia, and 32% in Africa) rotavirus-positivity among U5 acute watery diarrhoea hospitalisations, and 28% rotavirus-positivity among U5 acute

Competing interests: ML was the Principal Investigator of the Global Enteric Multicenter Study (GEMS) supported by the Bill and Melinda Gates Foundation (Grant #38874), and has previously served as a consultant to Merck Vaccines. KK has received funding from Merck, Sharp and Dohme to study the safety and effectiveness of rotavirus vaccine among African infants. This does not alter our adherence to PLOS ONE policies on sharing data and materials. All other authors declare no conflict of interest.

Abbreviations: AF, Attributable fraction; AFe, Attributable fraction in the exposed; AWD, Acute watery diarrhoea; CHERG, Child Health Epidemiology Reference Group of UNICEF and the World Health Organization (now MCEE—Maternal Child Epidemiology Estimation Group); EIA, Enzyme Immunoassay; GBD, Global Burden of Disease Study; GEMS, Global Enteric Multicenter Study; GRSN, WHO-coordinated Global Sentinel Site Rotavirus Surveillance Network; IGME, UN Inter-agency Group for Child Mortality Estimation; MAL-ED, Malnutrition and Enteric Disease Study; MSD, Moderate-to-severe diarrhoea; NRSN, Indian National Hospital Rotavirus Surveillance Network; U5, Under-five years of age; WHO/CDC, World Health Organization and Centers for Disease Control and Prevention.

watery diarrhoea deaths. 97% (95% CI 95–98%) of the U5 diarrhoea hospitalisations that tested positive for rotavirus were entirely attributable to rotavirus. For all clinical syndromes combined the rotavirus attributable fraction was 34% (95% CI 31–36%). This increased by a factor of 1.08 (95% CI 1.02–1.14) when the GEMS results were reanalysed using a more sensitive molecular test.

Conclusions

We developed consensus on seven proposals for improving the quality and transparency of future rotavirus mortality estimates.

Introduction

Rotavirus is a leading cause of diarrhoeal mortality in children less than five years old (U5), but there is considerable disagreement about how many rotavirus deaths occur each year. Recent estimates from different sources range from ~120,000 to ~215,000 [1–3]. Accurate rotavirus mortality estimates help governments and donors prioritise public health interventions and provide a basis for assessing the impact of immunization on mortality rates. Conflicting estimates from different sources create confusion and can delay the introduction of important diarrhoea mortality prevention measures, such as rotavirus vaccines.

In recent years, three groups have produced estimates of rotavirus deaths:

1. CHERG—the Child Health Epidemiology Reference Group of the World Health Organization (WHO) and UNICEF. CHERG is now referred to as MCEE—the Maternal and Child Epidemiology Estimation group;
2. GBD—the Global Burden of Disease Study, a collaboration led by the Institute for Health Metrics and Evaluation (IHME); and,
3. WHO/CDC—the WHO and Centers for Disease Control and Prevention (joint estimates).

A meeting coordinated by WHO (Geneva, March 2015) facilitated the initial discussions on the differences between the currently available rotavirus mortality estimates. This work builds on a previous assessment of differences between CHERG and GBD estimates of all-cause U5 diarrhoea deaths [4]. Several gaps in the evidence were identified at an early stage in the process, and one important task was to conduct new analyses to help bridge these gaps. First, rotavirus is not associated clinically with acute bloody (dysenteric) diarrhoea and rarely with persistent diarrhoea (of 14 days duration or more). As a result, many of the rotavirus-positive proportions reported in hospital surveillance networks, and in the literature, exclude these cases, and simply report the rotavirus-positive proportion among hospitalised children with acute watery diarrhoea. If this proportion is applied to all episodes of diarrhoea resulting in hospitalisation, it will result in overestimates. Second, there is very limited evidence to inform whether the distribution of clinical syndromes for U5 diarrhoea hospitalisations (% acute watery, % acute bloody, % persistent) is similar to, and thus a reasonable proxy for, the distribution of clinical syndromes for U5 diarrhoea deaths. Most approaches assume that rotavirus-positivity among diarrhoea hospitalisations is a reasonable proxy for rotavirus-positivity among diarrhoea deaths. However, the two proportions are rarely reported in the same study population. Third, to date there has been no explicit quantification of the rotavirus attributable

fraction among U5 diarrhoea hospitalisations, or the extent to which that varies depending on the type of diagnostic test used.

The aim of this manuscript is to compare the existing rotavirus mortality estimates, explain the reasons for differences, provide evidence to inform key areas of uncertainty, and propose improvements for future estimates.

Methods

We used a range of methods and sources of data. First, we compared existing estimates of U5 rotavirus deaths at the global, regional and national level and identified key differences in the approaches used. Second, we used data from a large number of hospitals to estimate the proportion of U5 diarrhoea hospitalisations that were acute watery, acute bloody and persistent. Third, we used data from verbal autopsy studies to estimate the proportion of U5 diarrhoea deaths that were acute watery, acute bloody and persistent. Fourth, we calculated the proportion of U5 diarrhoea hospitalisations and U5 diarrhoea deaths that were rotavirus-positive in each of the African and Asian sites included in the Global Enteric Multicenter Study (GEMS). Fifth, we used data from GEMS to estimate the proportion of rotavirus-positive U5 diarrhoea hospitalisations that were entirely attributable to rotavirus, and quantified the increase in the rotavirus attributable fraction when a more sensitive molecular test was used to determine rotavirus-positivity.

All data used in this study were anonymized prior to access and analysis. Please see supporting information (S1 Table) for details about institutional ethical approvals, and how and where the data were collected.

U5 rotavirus deaths: Comparison of estimates from GBD, CHERG and WHO/CDC

An independent reviewer (AC) compared the methods and data files published by the Global Burden of Disease 2013 Study (GBD 2013) [1, 5], CHERG [2, 6] and WHO/CDC [3, 7]. GBD provided a data file with country specific estimates of U5 rotavirus deaths [8].

We compared global, regional and national estimates of U5 deaths, U5 diarrhoea deaths and U5 rotavirus deaths for the year 2013 using a standard list of 186 countries (S1 File). CHERG did not report country estimates of U5 rotavirus deaths, so we multiplied country estimates of U5 diarrhoea deaths for the year 2013 by regional estimates of the proportion of U5 diarrhoea deaths due to rotavirus, as reported by CHERG for the year 2010. We removed two countries from the GBD list (Taiwan, Palestine) and seven from the WHO/CDC list (Cook Islands, Monaco, Nauru, Niue, Palau, St Kitts and Nevis, San Marino, Tuvalu) because they did not appear in both GBD and WHO/CDC datasets. GBD, CHERG and WHO/CDC used different classifications for grouping countries. For the purpose of this comparison exercise, all countries were grouped using the WHO classification system i.e. AFRO, AMRO, EMRO, EURO, SEARO, WPRO [9].

Clinical syndromes of U5 diarrhoea hospitalisations: Acute watery, acute bloody, persistent

To estimate the proportion of U5 diarrhoea hospitalisations that were acute watery, acute bloody and persistent, we used data from 84 hospitals in 9 countries:

1. 50 hospitals (5 in Indonesia, 42 in Rwanda and 3 in Zambia) from the WHO-coordinated Global Sentinel Site Rotavirus Surveillance Network—GRSN [10];

2. 7 hospitals from the Indian National Hospital Rotavirus Surveillance Network—NRSN (Delhi, Hyderabad, Kolenchery, Ludhiana, Tirupati, Trichy and Vellore); and;
3. 27 hospitals included in the Global Enteric Multicenter Study—GEMS (1 in Bangladesh, 4 in India, 6 in Gambia, 10 in Kenya, 6 in Mozambique). Methods for recruiting and enrolling moderate-to-severe diarrhoea (MSD) cases in GEMS have been described in detail elsewhere [11]. We included 5 of the 7 GEMS sites in this particular analysis. Mali and Pakistan were excluded because they rarely hospitalised children [12].

To be included, sites had to be major paediatric hospitals or district hospitals with ≥100 children aged <5 years hospitalised for diarrhoea. For GEMS sites, inpatients included children with inpatient status at enrolment as well as children who were admitted after enrolment. Data had to be available for the full 12 months of the year (to account for rotavirus seasonality) and obtained before the introduction of rotavirus vaccination. Diagnoses were grouped into acute watery, acute bloody and persistent diarrhoea based on coding systems in place in the country and site. Acute syndromes were <14 days in duration, and persistent were ≥14 days. All GRSN, NRSN and GEMS sites excluded patients who were defined as "persistent" at the time of enrolment, but included patients who became persistent after enrolment. Paediatric logbooks were reviewed in the Indian NRSN sites and Indonesian GRSN sites. Cases were excluded (2% in India, 8% in Indonesia) if there was not enough information in the logbook to categorise them. Electronic discharge data were used in Rwanda and Zambia so all cases had to be coded into a category.

The Stata 14 command *metaprop* was used for meta-analysis of the proportion of U5 diarrhoea hospitalisations associated with acute watery diarrhoea (AWD), with random effects and exact confidence intervals [13].

Clinical syndromes of U5 diarrhoea deaths

The clinical syndromes for U5 diarrhoea deaths were assessed using published verbal autopsy data from 5 demographic surveillance sites in Bangladesh, Ethiopia, Pakistan, Tanzania and Uganda [14] and verbal autopsy data from 4 sites in Cameroon, Malawi, Niger and Nigeria (Henry Kalter personal communication). The data came from investigation of child deaths identified in a household survey, including deaths in the community or a health facility, using the birth history method with follow-up questions to family members of the deceased child (S1 Table). All data sources included children aged <5 years and covered a period of at least 12 months, so they reflect all seasons.

The Stata 14 command *metaprop* was also used for meta-analysis of the proportion of U5 diarrhoea deaths associated with AWD, with random effects and exact confidence intervals [13].

Rotavirus-positive proportion in U5 diarrhoea hospitalisations and U5 diarrhoea deaths in GEMS

We calculated the rotavirus-positive proportions among MSD cases aged <5 years who were admitted to hospital in 6 of the 7 country sites included in GEMS, using the conventional EIA (Enzyme immunoassay) test results. We excluded Mozambique because there was an unusually high number of positive samples in healthy controls, and only 55% of the rotavirus-positive cases and 7% of the rotavirus-positive healthy controls were shown to be rotavirus-positive on retesting with a different EIA test kit.

We calculated rotavirus-positive proportions separately for acute watery diarrhoea and all clinical syndromes combined (acute watery, acute bloody and persistent cases). In GEMS, if

more than 9 children with MSD were identified in a fortnight, only the first 9 children were enrolled and tested for rotavirus; the remainder were recorded on a log and assumed to have the same rotavirus-positive proportion as enrolled cases that were identified in the same fortnight, age stratum (0-11m, 12-23m, 24-59m) and diarrhoea syndrome (acute watery, acute bloody, persistent).

We also calculated the proportion of U5 deaths that: a) tested positive for rotavirus within 7 days of death; and, b) had diarrhoea coded as the first or second cause of death on their verbal autopsy (VA) report. Rotavirus-positive children with a missing VA report (~20%) were assumed to have the same cause-of-death breakdown as rotavirus-positive children with a VA report.

For completeness, we also calculated the rotavirus-positive proportion among healthy controls as well as MSD cases that were not admitted to hospital.

Proportion of rotavirus-positive U5 diarrhoea hospitalisations attributable to rotavirus in GEMS

GEMS tested for a wide range of enteric pathogens in the stools of MSD cases and healthy community controls without diarrhoea matched to cases by age, gender, and residence; controls were enrolled within 14 days of the index case. GEMS also included information about whether MSD cases were admitted to hospital or not.

We used multiple conditional logistic regression to calculate the odds ratio of rotavirus EIA positivity in hospitalized MSD cases vs matched healthy controls adjusted for the presence of other pathogens. All syndromes of diarrhoea were included. We then calculated the attributable fraction (AF) as described by Bruzzi *et al* [15]. These methods were the same as those used to estimate attributable fractions in the main GEMS analysis [12, 16]. However, we restricted the analysis to hospitalised cases, thought to be a better proxy for estimating rotavirus-attributable mortality than all MSD cases. We excluded Mozambique from all AF analyses due to concerns about the quality of the EIA testing, and did not estimate individual AFs for Mali and Pakistan because hospitalisation for diarrhoea was very rare in these sites.

Using these attributable fractions, which represent the fraction of hospitalised MSD cases with disease attributable to rotavirus, we calculated the attributable fraction among the exposed (AF_e). The AF_e represents the fraction of rotavirus positive cases who have disease caused by rotavirus. The rotavirus-positive proportions used to derive the AF and AFe were based only on the children with MSD that were tested for rotavirus. These were age-specific (0-11m, 12-23m, 24-59m) and did not involve extrapolation to non-enrolled MSD cases.

Finally, we used previously described methods [17] to calculate the rotavirus attributable fraction based on quantitative Polymerase Chain Reaction (qPCR). We restricted the analysis to a subset of 721 hospital cases and matched controls, and calculated the AF for all country sites combined, excluding Mozambique. To quantify the test performance of EIA compared to qPCR, we repeated this analysis for EIA test results, and calculated the ratio between the two attributable fractions. All syndromes of diarrhoea were included. Confidence intervals were calculated by bootstrapping with 1000 iterations.

Results

Comparison exercise

GBD produce their own estimates of U5 deaths [18], whereas CHERG and WHO/CDC use U5 deaths from the UN Inter-agency Group for Child Mortality Estimation (IGME)[19]. Both GBD and IGME estimate approximately 6.3 million U5 deaths globally in 2013 (Table 1) but

Table 1. Comparison of CHERG, GBD and WHO/CDC estimates of U5 deaths, U5 diarrhoea deaths and U5 rotavirus deaths in the year 2013 by WHO region, and for selected large countries.

	GLOBAL	AFRO	AMRO	EMRO	EURO	SEARO	WPRO	Bangladesh	DR Congo	India	Indonesia
U5 deaths											
UN (IGME) used by CHERG	**6,282,254**	2,977,576	227,475	845,286	136,850	1,700,178	394,889	129,433	319,977	1,340,055	136,371
GBD	**6,271,643**	3,164,861	248,643	738,702	130,573	1,604,028	384,836	128,228	340,416	1,249,673	148,807
WHO/CDC	**-**	-	-	-	-	-	-	-	-	-	-
Proportion of U5 deaths due to diarrhoea											
CHERG	**0.09**	0.10	0.04	0.10	0.04	0.10	0.06	0.06	0.11	0.10	0.06
GBD	**0.08**	0.10	0.05	0.12	0.03	0.06	0.02	0.01	0.17	0.06	0.06
WHO/CDC	**-**	-	-	-	-	-	-	-	-	-	-
U5 diarrhoea deaths											
CHERG	**577,508**	293,289	9,297	84,592	5,689	162,298	22,344	8,298	33,730	140,451	7,505
GBD	**519,485**	312,297	11,923	88,071	3,694	94,574	8,926	1,715	57,344	80,188	8,694
WHO/CDC	**577,508**	293,289	9,297	84,592	5,689	162,298	22,344	8,298	33,730	140,451	7,505
Proportion of U5 diarrhoea deaths due to Rotavirus											
CHERG	**0.27**	0.27	0.23	0.31	0.26	0.26	0.33	0.26	0.27	0.26	0.26
GBD	**0.24**	0.24	0.18	0.18	0.26	0.27	0.42	0.12	0.13	0.26	0.37
WHO/CDC	**0.37**	0.39	0.26	0.36	0.31	0.35	0.43	0.33	0.40	0.34	0.50
U5 rotavirus diarrhoea deaths											
CHERG	**157,398**	78,601	2,176	26,477	1,473	41,386	7,284	2,116	9,040	35,815	1,914
GBD	**122,322**	73,758	2,178	15,984	976	25,637	3,790	202	7,523	21,205	3,176
WHO/CDC	**215,757**	115,023	2,455	30,577	1,752	56,287	9,664	2,723	13,526	47,082	3,771

Region and global estimates may differ from official WHO/CDC, CHERG and GBD estimates because a standard set of countries and regions was used and no rounding was done prior to aggregation.

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some important differences exist at country/regional levels e.g. ~739,000 (GBD) vs ~845,000 (IGME) in the Eastern Mediterranean Region (EMRO). The main methodological differences between GBD and IGME have been described in detail elsewhere and include the choice of data points selected (vital registration, census and household surveys) and fitting methods used [20].

GBD and CHERG produce their own estimates of the proportion of U5 deaths due to diarrhoea [5, 6]; WHO/CDC use the CHERG estimates. GBD and CHERG estimated that 8–9% of U5 deaths were caused by diarrhoea at the global level in the year 2013 (Table 1). Differences in GBD and CHERG estimates for the South East Asia (SEARO) region (6% vs 10%) are driven by differences in estimates for India (6% vs 10%) where U5 diarrhoea deaths are ~80,000 vs ~140,000 respectively (Table 1). In other regions there is more agreement. Estimates for the African (AFRO) region are consistent overall (10% vs 10%) but there are still large differences at country level e.g. Zimbabwe (Fig 1).

Methodological differences between GBD and CHERG have been described in detail elsewhere [4]. In brief, CHERG excluded verbal autopsy studies that only investigated a single cause of death and data points from incomplete vital registration systems in higher mortality

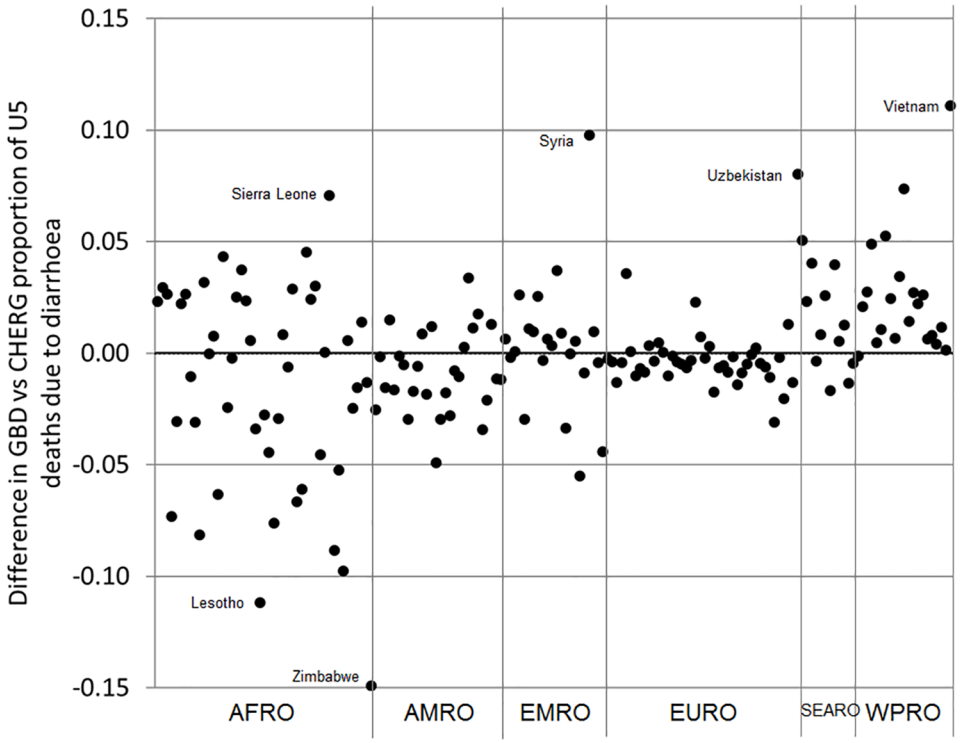

Fig 1. Country-level differences in GBD vs CHERG estimates of the proportion of U5 deaths due to diarrhoea in the year 2013 by WHO region.

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settings. GBD included these data points and adjusted for missing data. GBD also included unpublished data points obtained under third party data use agreements whereas CHERG only use publicly available data points [21].

All three groups produce their own estimates of the proportion of U5 diarrhoea deaths that are attributable to rotavirus. For the year 2013, the global proportions were 24% (GBD), 27% (CHERG) and 37% (WHO/CDC). These correspond to 122,322 (GBD), 157,398 (CHERG) and 215,757 (WHO/CDC) U5 rotavirus deaths (Table 1). Fig 2 shows the extent of variation in the fraction of diarrhoea deaths attributed to rotavirus across countries within each WHO region. There are large differences in some countries; for example, in DR Congo the proportions are 13% (GBD), 27% (CHERG) and 40% (WHO/CDC).

The three groups used different methods to:

1. select data points (rotavirus-positive proportions);
2. extrapolate data points to individual countries;
3. account for rotavirus vaccine coverage;
4. convert rotavirus-positive proportions to rotavirus attributable fractions; and,
5. calculate uncertainty ranges.

A more detailed description of these differences can be found in the supporting information (S1 Appendix).

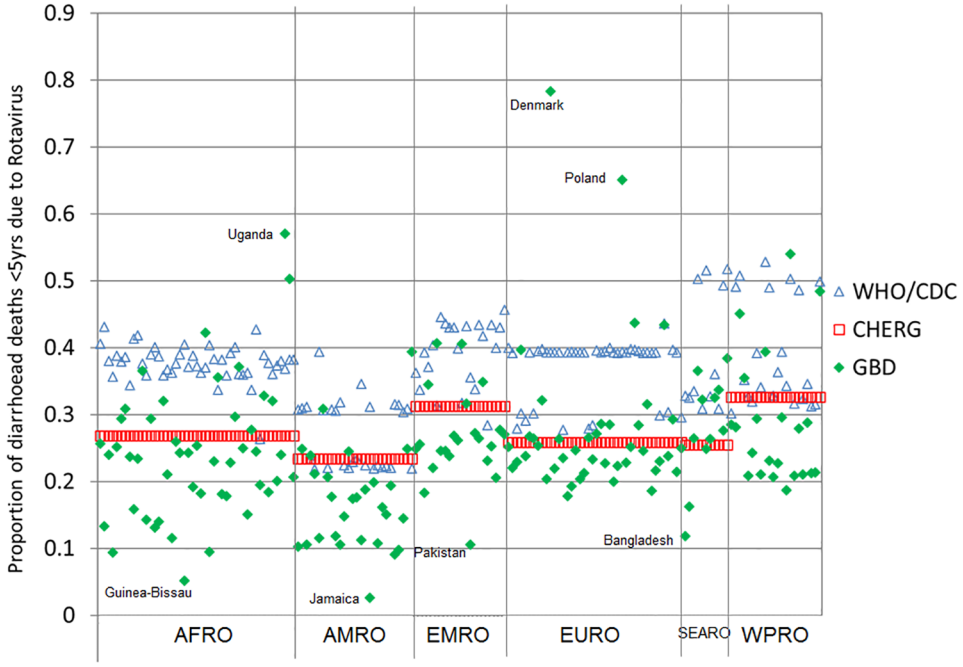

Fig 2. Country-level variation in the fraction of U5 diarrhoea deaths due to rotavirus in the year 2013 by source of estimates and by WHO region.

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Clinical syndromes for U5 diarrhoea hospitalisation

Table 2 shows the distribution of clinical syndromes for U5 diarrhoea hospitalisations for various sites in Africa and Asia. A meta-analysis including data from all GRSN, NRSN and GEMS sites suggests that acute watery diarrhoea was associated with 87% (95% CI 83–90%) of U5 diarrhoea hospitalisations (Fig 3) but there was substantial evidence for heterogeneity (I-squared 99.08%, p = 0.00) between the studies. The GEMS site in Bangladesh (Mirzapur) had a very high rate of acute bloody diarrhoea for reasons that are not clear.

Clinical syndromes for U5 diarrhoea deaths

Table 2 shows the distribution of clinical syndromes for U5 diarrhoea deaths. A meta-analysis suggests that acute watery diarrhoea was associated with 65% (95% CI 57–74%) of U5 diarrhoea deaths (Fig 4) but again there was substantial evidence for heterogeneity between the studies (I-squared 92.06%, p = 0.00). In four of the nine countries with verbal autopsy data, the clinical syndromes of diarrhoea deaths were compared for those who died in any type of health facility and those who died in the home, as reported by the family respondent. Most of deaths were in the home (Cameroon 70%, Malawi 50%, Niger 86% and Nigeria 78%) but the distribution of acute watery, acute bloody and persistent diarrhoea was similar irrespective of the place of death (Kalter, personal communication).

Rotavirus-positive proportion in U5 diarrhoea hospitalisations and U5 diarrhoea deaths in GEMS

For all GEMS sites combined (excluding Mozambique), rotavirus was detected (EIA-positive) in 44% of acute watery U5 diarrhoea hospitalisations (55% in Asia, and 32% in Africa)

Table 2. Number and proportion of acute watery, acute bloody and persistent cases among U5 diarrhoea hospitalisations and U5 diarrhoea deaths in various settings before rotavirus vaccine introduction.

Source	Study location	Study type	Study period	Diarrhoea outcome	Age	Total[Δ] n	Acute Watery n	Acute Bloody n	Persis-tent* n	Acute Watery %	Acute Bloody %	Persis-tent %
Clinical syndromes of U5 diarrhoea hospitalisations												
GRSN	Indonesia	Surveillance hospitals (n = 5)	2014–15	Inpatients	<5yrs	1840	1695	110	35	**92%**	6%	2%
	Rwanda	Surveillance hospitals (n = 42)	2012	Inpatients	<5yrs	9097	8878	199	20	**98%**	2%	0.2%
	Zambia	Surveillance hospitals (n = 3)	2009–11	Inpatients	<5yrs	4381**	3761	15	-	**86%**	0.3%	-
NRSN	India	Surveillance hospitals (n = 7)	2013–14	Inpatients	<5yrs	5156	4940	196	20	**96%**	4%	0.4%
GEMS	Bangladesh	Case control study hospitals (n = 1)	2007–10	Inpatients	<5yrs	337	171	154	11	**51%**	46%	3%
	India	Case control study hospitals (n = 4)	2007–10	Inpatients	<5yrs	437	411	17	10	**94%**	4%	2%
	Gambia	Case control study hospitals (n = 6)	2007–10	Inpatients	<5yrs	440	397	14	28	**90%**	3%	6%
	Kenya	Case control study hospitals (n = 10)	2007–10	Inpatients	<5yrs	175	129	3	44	**74%**	1%	25%
	Mozambique	Case control study hospitals (n = 6)	2007–10	Inpatients	<5yrs	633	579	6	48	**91%**	1%	8%
Clinical syndromes of U5 diarrhoea deaths												
Verbal	Bangladesh	Demographic surveillance (16)	2003–11	Deaths	1-59m	59	43	7	9	**73%**	12%	15%
autopsy studies	Pakistan	Demographic & Health Survey (16)	2006–7	Deaths	1-59m	318	213	22	83	**67%**	7%	26%
	Cameroon	Subnational household survey***	2006–10	Deaths	1-59m	166	125	20	22	**75%**	12%	13%
	Ethiopia	Demographic surveillance (16)	2003–12	Deaths	1-59m	60	19	6	35	**32%**	10%	58%
	Malawi	Subnational household survey***	2008–11	Deaths	1-59m	149	118	18	13	**79%**	12%	9%
	Niger	Demographic & Health Survey***	2006–10	Deaths	1-59m	160	104	32	24	**65%**	20%	15%
	Nigeria	Demographic & Health Survey***	2009–13	Deaths	1-59m	537	435	70	32	**81%**	13%	6%
	Tanzania	Demographic surveillance (16)	2000–11	Deaths	1-59m	80	48	13	19	**60%**	16%	24%
	Uganda	Demographic surveillance (16)	2007–10	Deaths	1-59m	77	37	9	31	**48%**	12%	40%

[Δ]Totals for GEMS sites do not sum exactly due to rounding

*GRSN, NRSN and GEMS persistent cases include only those children who progressed to 'persistent' status (14+ days duration) after acute admission

** 605 cases in Zambia were classified as 'non-infectious diarrhoea', which is likely to include persistent cases as well as other cases that could not be classified as acute watery or acute bloody diarrhoea.

*** Henry Kalter, personal communication

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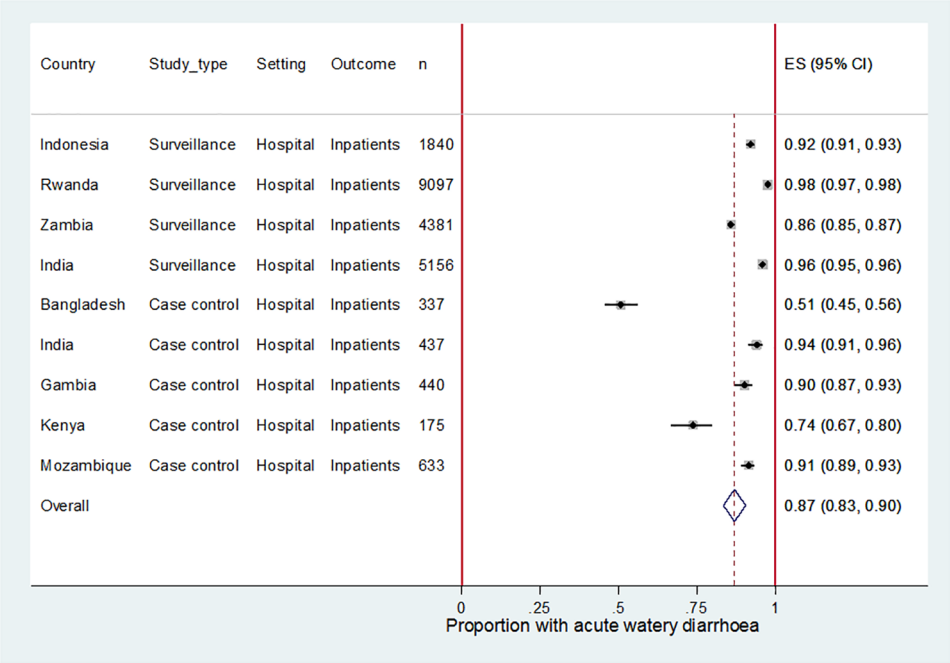

Fig 3. Meta-analysis showing the proportion of U5 diarrhoea hospitalisations associated with acute watery diarrhoea (AWD) for selected sites in Africa and Asia.

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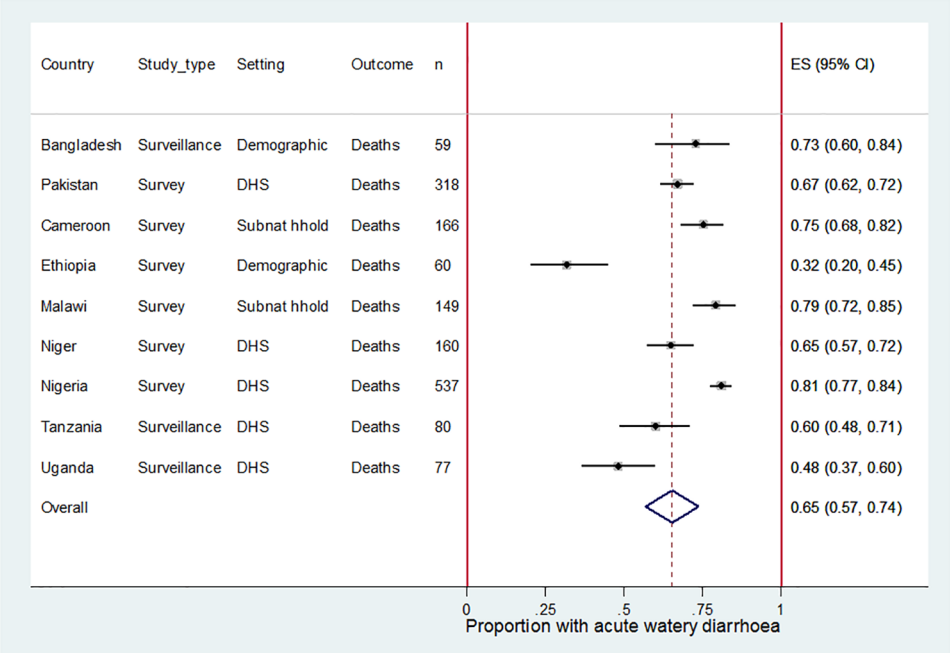

Fig 4. Meta-analysis showing the proportion of U5 diarrhoea deaths associated with acute watery diarrhoea (AWD) for selected sites in Africa and Asia.

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Table 3. Number and proportion of rotavirus infections in healthy controls and different types of diarrhoea cases aged <5yrs in GEMS.

			Bangladesh	India	Pakistan	ASIA	Gambia	Kenya	Mali	AFRICA	TOTAL
Controls		Number positive	74	42	66	**182**	42	39	43	**124**	**306**
		Number tested	2465	2014	1838	**6317**	1569	1883	2064	**5516**	**11833**
		% Positive	3%	2%	4%	**3%**	3%	2%	2%	**2%**	**3%**
All syndromes	MSD	Number positive	23	292	187	**502**	208	250	573	**1031**	**1533**
	Not hospitalised	Number tested	741	1398	902	**3041**	1038	1644	3109	**5791**	**8832**
		% Positive	3%	21%	21%	**17%**	20%	15%	18%	**18%**	**17%**
	MSD	Number positive	111	233	2	**346**	152	40	5	**197**	**543**
	Hospitalised	Number tested	337	437	8	**782**	440	175	41	**656**	**1438**
		% Positive	33%	53%	25%	**44%**	35%	23%	12%	**30%**	**38%**
Acute watery	MSD	Number positive	0	284	125	**409**	198	207	515	**920**	**1329**
	Not hospitalised	Number tested	2	1315	485	**1802**	899	1258	2657	**4814**	**6616**
		% Positive	0%	22%	26%	**23%**	22%	16%	19%	**19%**	**20%**
	MSD	Number positive	93	230	0	**323**	141	33	5	**179**	**502**
	Hospitalised	Number tested	171	411	3	**585**	397	129	35	**561**	**1146**
		% Positive	54%	56%	0%	**55%**	36%	26%	14%	**32%**	**44%**
	Deaths	Number positive	4	0	0	**4**	1	2	5	**8**	**12**
	(within 7 days of enrolment)	*Number VA adjudicated*	4	0	0	**4**	0	1	2	**3**	**7**
		Number VA confirmed as diarrhoea	4	0	0	**4**	0	0	2	**2**	**6**
		% VA confirmed as diarrhoea	100%	-	-	**100%**	-	0%	100%	**67%**	**86%**
		Number positive (adjusted for VA)	4	-	-	**4**	-	0	5	**5**	**10**
		Total deaths	5	0	1	**6**	12	12	7	**31**	**37**
		% Positive	*	*	*	*	*	*	*	*	**28%**

*proportion positive not reported at country-level due to small numbers.

VA = verbal autopsy.

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(Table 3). When all clinical syndromes of diarrhoea were included, the rotavirus-positive proportion was 38% (44% in Asia; 30% in Africa).

Rotavirus was detected (EIA-positive) in 32% (12/37) of children aged <5yrs that died within 7 days of enrolment at any type of health facility with acute watery MSD. Seven of the rotavirus-positive children that died had a VA report, and 6 of these children (86%) had diarrhoea coded as a primary or secondary cause of death. Assuming that children with rotavirus who lacked a VA report died from diarrhoea at the same rate as those with a report, the fraction of U5 diarrhoea deaths that were rotavirus-positive was estimated to be 28% (10/37) (Table 3). It was not possible to consider all syndromes because there were very few acute bloody diarrhoea deaths (n = 3) and no persistent cases were eligible for inclusion in this analysis due to the short 7-day follow-up period.

The rotavirus-positive proportion was 3% in healthy controls. The rotavirus-positive prevalence in MSD inpatients was approximately double the rotavirus-positive prevalence in MSD outpatients. 10% (147/1438) of inpatients and 20% (1782/8832) of outpatients had no detected pathogen using conventional testing methods.

Table 4. Rotavirus positive proportion, attributable fraction (AF) and attributable fraction in the exposed (AFe) for MSD cases <5yrs that were hospitalised with all syndromes of diarrhoea in GEMS*.

	Rotavirus positive proportion *(includes extrapolation to MSD cases that were not enrolled)* Value	Rotavirus positive proportion *(enrolled MSD cases only)*** Value	AF		AFe	
			Value	95% CI	Value	95% CI
Bangladesh	0.33	0.35	0.34	(0.30, 0.38)	0.96	(0.94, 0.98)
India	0.53	0.48	0.47	(0.42, 0.52)	0.99	(0.97, 1.00)
Pakistan	0.25	0.22	***	***	***	***
ASIA	**0.44**	**0.40**	**0.39**	**(0.36, 0.42)**	**0.97**	**(0.95, 0.98)**
Gambia	0.35	0.29	0.28	(0.23, 0.33)	0.98	(0.96, 1.00)
Kenya	0.23	0.21	0.19	(0.13, 0.26)	0.91	(0.82, 0.99)
Mali	0.12	0.18	***	***	***	***
AFRICA	**0.30**	**0.26**	**0.24**	**(0.20, 0.29)**	**0.95**	**(0.91, 0.99)**
ALL SITES	**0.38**	**0.35**	**0.34**	**(0.31, 0.36)**	**0.97**	**(0.95, 0.98)**

* Includes all syndromes of diarrhoea i.e. acute watery diarrhoea, acute bloody diarrhoea, and acute watery cases that became persistent after enrolment.

** These values were based on the children that were enrolled i.e. tested for rotavirus. Age-specific presentations of these values (0-11m, 12-23m, 24-59m) were used in the calculation of AF and AFe.

*** Rotavirus-positive hospitalisation was rare in Mali (n = 5) and Pakistan (n = 2) so country-specific AF and AFe are not reported. The data for these countries are included in the estimates for ASIA, AFRICA and ALL SITES.

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Proportion of rotavirus-positive U5 diarrhoea hospitalisations attributable to rotavirus in GEMS

The AFe value (equivalent to the rotavirus attributable fraction among rotavirus-positive U5 diarrhoea hospitalisations) was 0.97 (95% CI 0.95–0.98) for all included GEMS sites (Table 4) and all diarrhoea syndromes combined.

Using qPCR instead of EIA for rotavirus detection increased the AF by a factor of 1.08 (95% CI 1.02–1.14).

Proposed improvements

We propose a number of improvements for consideration by all groups involved in the development of future rotavirus mortality estimates.

Reporting a standard set of minimum variables to describe all input data points

Previous comparison exercises have stressed the need for input data points to be made available at the time estimates are published [4, 20]. Recent Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) have recommended publication of a spreadsheet table with details about the data points used to inform estimates [22]. These guidelines do not provide explicit guidance on the variables that should be reported. We suggest that the following standard set of minimum variables should be reported: (a) author/reference; (b) country; (c) sub-national location; (d) data collection period; (e) age range; (f) type of study; (g) type of diagnostic test; (h) number of enteric pathogens tested; (i) inpatient/outpatient; (j) pre/post

implementation of rotavirus vaccine in the public sector, or preferably a more precise estimate of rotavirus vaccine coverage with details about the source of sub-national or national coverage data used; (k) type of clinical syndrome e.g. acute watery, all syndromes; (l) included/excluded in final estimates; (m) justification if excluded; (n) rotavirus-positive proportion (unadjusted); (o) rotavirus-positive proportion (adjusted); and, (p) description of adjustment applied. Inclusion and exclusion criteria should be clearly documented, and any exclusions applied after data extraction should be justified using a clearly defined framework for evaluating data quality and outliers.

Annual online publication of WHO surveillance data points in spreadsheet format

A spreadsheet table should be published annually on the WHO web site to allow for potential inclusion of GRSN data by all groups in future estimates. At a minimum, rotavirus-positive proportions <5 years should be made available by country (aggregated across sub-national sites) and by calendar year. The standard set of recommended variables described above should be reported for each data point. To ensure the integrity and confidentiality of country surveillance data and to protect the ownership of those who collect the data, this and similar surveillance data should be aggregated and proper attribution should be given to countries that share this data. Data for sub-national sites should be provided where possible and where appropriate to do so. Given its importance to global estimates, efforts should also be made to routinely publish the sub-national Indian NRSN data points in an accessible spreadsheet format, with data points presented by sub-national location and data year. Other partners and networks that generate rotavirus-positive proportions are also encouraged to share their data in an accessible format, wherever possible.

Extrapolation of data points to country-level estimates using methods that appropriately capture between-country variation

Statistical regression modelling or finer levels of stratification than geographical region should be used when and where possible to extrapolate sub-national data points to different countries. The source of all sub-national, national and supranational indicators used to inform statistical regression models (e.g. GDP per capita) should be clearly defined. Care should be taken to ensure the coverage and impact of rotavirus vaccination is consistently captured at all levels of the analysis, including U5 deaths, the proportion of U5 deaths due to diarrhoea, and the proportion of U5 diarrhoea deaths due to rotavirus. Where possible, groups should extract and test the importance of other potentially influential sub-national characteristics e.g. private/public hospital, secondary/tertiary hospital, under-five mortality rate, proportion of patients from rural areas etc. If it is not feasible to collect this information from all sites, then a more detailed review of the GRSN dataset could be informative, and would allow comparison of several sub-national sites within the same countries. Input data points should be disaggregated into individual years of data collection to capture changes in the rotavirus-positive proportion over time at country level; covariates linked to period effects (e.g. GDP per capita, under-five mortality rate) should be carefully selected on the basis of their ability to reproduce observed trends in the rotavirus-positive proportion.

Separation of the clinical syndromes of U5 diarrhoea hospitalisations

Rotavirus is not associated clinically with acute bloody or persistent diarrhoea, two diarrhoeal syndromes that may also be proximal or distal causes of death. Rotavirus-positive proportions

derived exclusively from acute watery U5 diarrhoea hospitalisations should be adjusted to account for the proportion of total U5 diarrhoea hospitalisations that are acute watery. If the rotavirus-positive proportion (r) is not reported for all clinical syndromes combined, then the equation $r = ab + c(1 - b)$ can be used, where a is the rotavirus-positive proportion among acute watery U5 diarrhoea hospitalisations, b is the proportion of total U5 diarrhoea hospitalisations that are acute watery, and c is the rotavirus-positive proportion among acute bloody and persistent U5 diarrhoea hospitalisations combined. In the absence of local data to inform parameter b, our analysis shows that acute watery diarrhoea is likely to be responsible for no more than 87% (95% CI 83–90%) of U5 diarrhoea hospitalisations. The true value of b is likely to be lower because all data points included in the meta-analysis under-estimated the role of persistent diarrhoea. Given that rotavirus is not associated clinically with acute bloody or persistent diarrhoea, the value of parameter c is likely to be at least ~3% based on the rotavirus-positivity observed in healthy controls in GEMS.

Accounting for uncertainty in the steps used to convert rotavirus-positive proportions into rotavirus-attributable fractions

The frequent asymptomatic carriage of many pathogens in the stools of healthy controls necessitates the calculation of attributable fractions. To estimate the proportion of rotavirus-positive cases that are attributable only to rotavirus, the population attributable fraction estimated by the equation $r \times AFe$ can be used, where r is the rotavirus-positive proportion reported among U5 diarrhoea hospitalisations (all syndromes combined), and AFe is the rotavirus-attributable fraction among rotavirus-positive U5 diarrhoea hospitalisations (all syndromes combined). Because it is rare for diarrhoea surveillance studies to include diarrhoea-free controls, very few studies allow calculation of AFe. GEMS does include diarrhoea-free controls so permits this calculation; our new analysis of GEMS calculated the AFe to be 0.97 (95% CI 0.95–0.98). This value was relatively consistent across all GEMS sites where it could be reported (Bangladesh, India, Gambia, Kenya). This suggests that rotavirus is the attributable cause in almost all U5 rotavirus-positive diarrhoea hospitalisations. In a separate, related analysis, the rotavirus attributable fraction was shown to increase by a factor of 1.08 (95% 1.02–1.14) when the more sensitive qPCR test was used. This is similar (albeit slightly larger) than the adjustment made to r to account for AFe, so both adjustments could reasonably be excluded, and this would have a limited impact on central estimates of U5 rotavirus deaths. However, adjustments applied to some pathogens and not others, would lead to inconsistent reporting of central estimates (and uncertainty intervals) across enteric pathogens. These adjustments, and their uncertainty, should therefore be reflected in future estimates for all enteric pathogens, including rotavirus.

Further research into the clinical syndromes of U5 diarrhoea deaths, and the real-world impact of rotavirus vaccines on those deaths

To date, all groups have assumed that the proportion of U5 diarrhoea hospitalisations caused by rotavirus is a reasonable proxy for the proportion of U5 diarrhoea deaths caused by rotavirus. This approach has been taken because hospitalisation is thought to be a good proxy for diarrhoea that is sufficiently severe to lead to death. Two aspects of our analysis suggest this assumption may lead to over-estimates of the number of U5 rotavirus deaths. First, we estimate that acute watery diarrhoea is associated with 87% of diarrhoea hospitalisations but only 65% of U5 diarrhoea deaths. Higher case fatality ratios (CFR) have been reported for acute bloody and persistent diarrhoea than acute watery diarrhoea [23] but more evidence on the fatality of different syndromes is needed to corroborate this. In addition, the analysis of

diarrhoeal deaths relied on verbal autopsy reports which may be prone to recall bias, and our analysis of diarrhoea hospitalisations only included those that became persistent after admission. Second, rotavirus was detected in a higher proportion of U5 acute watery diarrhoea hospitalisations than U5 acute watery diarrhoea deaths in GEMS (44% vs 28%). Thus, among children that had access to treatment, rotavirus was estimated to be less fatal than other causes of acute watery diarrhoea. However, more evidence is needed on the effect of treatment on the proportion of acute watery diarrhoea deaths due to rotavirus; in communities without access to treatment services, rotavirus may represent a larger proportion of acute watery diarrhoea deaths. Another explanation for the lower rotavirus-positivity among U5 acute watery diarrhoea deaths, is that the number of deaths captured in the 7 days after enrolment (n = 37) were too few to make a reliable assessment. Longer follow-up periods allow more deaths to be included but it then becomes increasingly difficult to ascertain whether children who were rotavirus-positive at the time of enrolment were still rotavirus-positive at the time of death, and whether cases that were negative at enrolment had a new rotavirus episode prior to death.

Further evidence is needed from other geographical locations on the distribution of clinical syndromes among U5 diarrhoea hospitalisations and deaths. This should include a more accurate assessment of the role of persistent diarrhoea among U5 diarrhoea hospitalisations. More importantly, efforts should be made to accurately capture the real-world impact of rotavirus vaccines on U5 diarrhoea deaths in early introducing countries. This will provide critical insights into the true contribution of rotavirus to U5 diarrhoea deaths in different locations.

Presenting and incorporating the uncertainty in parameters used to derive U5 rotavirus deaths

The uncertainty interval around the central estimates of U5 rotavirus deaths should be explicitly defined (e.g. the type of confidence or prediction interval) and should incorporate uncertainty in each of the three core parameters (number of U5 deaths, % due to diarrhoea, % due

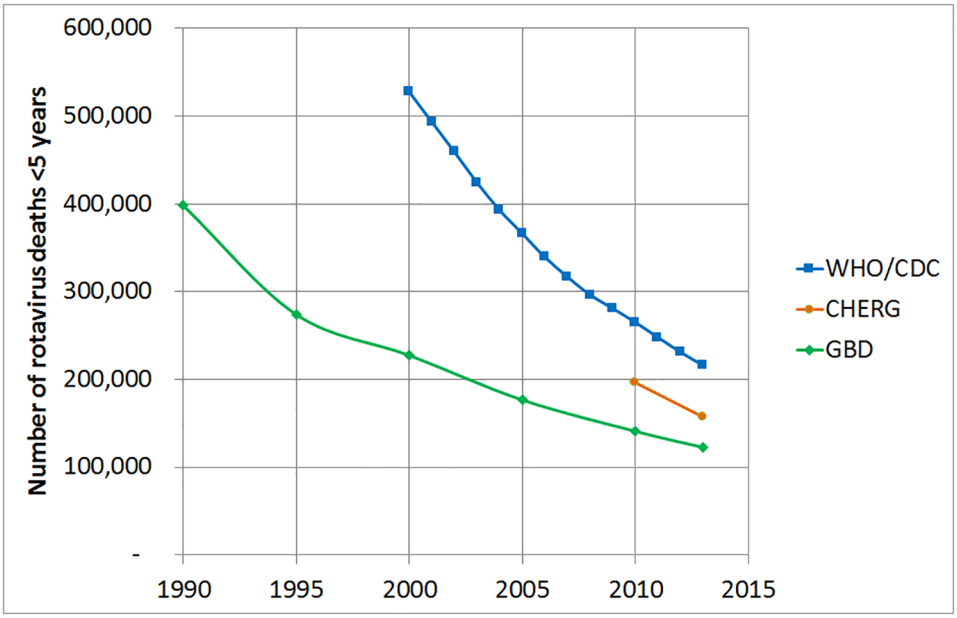

Fig 5. Global estimates of the number of rotavirus deaths <5 years in the year 2013 by source of estimates.

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to rotavirus) as well as any other parameters used to adjust the original input data points e.g. the parameters used to convert rotavirus-positive proportions into rotavirus-attributable fractions.

Conclusion

There is considerable disagreement between global estimates of U5 rotavirus deaths, but it is encouraging to note that estimates are converging over time, at least in absolute terms (Fig 5).

The aim of this analysis was not to recommend a single set of best estimates, but rather to explain the reasons for differences, provide evidence to inform key areas of uncertainty, and propose improvements for future estimates. Updates to GBD [24] and CHERG (now MCEE) estimates were already well advanced during the course of this comparison study, and further convergence is expected. The suggested improvements presented in this manuscript should be incorporated, as far as possible, into future rotavirus mortality estimates. This is likely to be an iterative and evolving process as new evidence emerges over time.

Supporting information

S1 Table. Information about the data used for new analyses.
(DOCX)

S1 Appendix. Further details on the comparison of rotavirus mortality estimates from GBD, CHERG and WHO/CDC.
(DOCX)

S1 File. Country-level dataset used to compare CHERG, GBD and WHO/CDC estimates of U5 deaths, U5 diarrhoea deaths and U5 rotavirus deaths in the year 2013.
(XLSM)

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References

1. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015; 385(9963):117–71. https://doi.org/10.1016/S0140-6736(14)61682-2 PMID: 25530442
2. Lanata CF, Fischer-Walker CL, Olascoaga AC, Torres CX, Aryee MJ, Black RE. Global causes of diarrheal disease mortality in children <5 years of age: a systematic review. PLoS One. 2013; 8(9):e72788. https://doi.org/10.1371/journal.pone.0072788 PMID: 24023773
3. Tate JE, Burton AH, Boschi-Pinto C, Parashar UD. Global, Regional, and National Estimates of Rotavirus Mortality in Children <5 Years of Age, 2000–2013. Clin Infect Dis. 2016; 62 Suppl 2:S96–S105.
4. Kovacs SD, Mullholland K, Bosch J, Campbell H, Forouzanfar MH, Khalil I, et al. Deconstructing the differences: a comparison of GBD 2010 and CHERG's approach to estimating the mortality burden of diarrhea, pneumonia, and their etiologies. BMC Infect Dis. 2015; 15:16. https://doi.org/10.1186/s12879-014-0728-4 PMID: 25592774
5. IHME. GBD 2013. CSV file [IHME_GBD_2013_AGE_SEX_SPECIFIC_ALL_CAUSE_AND_CAUSE_-SPECIFIC_MORTALITY_WEB_TABLE_31_Y2014M12D17.CSV] containing diarrhoea deaths <5yrs for 6 calendar years (1990, 1995, 2000, 2005, 2010, 2013). http://wwwhealthdataorg [accessed March 2015].
6. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet. 2015; 385(9966):430–40. https://doi.org/10.1016/S0140-6736(14)61698-6 PMID: 25280870
7. WHO/CDC estimates of Rotavirus deaths <5yrs 2000–2013. http://www.who.int/immunization/monitoring_surveillance/burden/estimates/rotavirus/en/ [accessed 26 May 2016]
8. IHME. GBD 2013. CSV file [Rota.csv] containing country-level rotavirus deaths <5yrs for 6 calendar years (1990, 1995, 2000, 2005, 2010, 2013) and 4 age groups (<6 days, 7–27 days, 28–364 days, 1–4 years). Unpublished (courtesy of Ali Mokdad—March 2015).
9. WHO region classification. http://www.who.int/about/regions/en/ [accessed 19th March 2016].
10. Agocs MM, Serhan F, Yen C, Mwenda JM, de Oliveira LH, Teleb N, et al. WHO global rotavirus surveillance network: a strategic review of the first 5 years, 2008–2012. MMWR Morb Mortal Wkly Rep. 2014; 63(29):634–7. PMID: 25055187
11. Kotloff KL, Blackwelder WC, Nasrin D, Nataro JP, Farag TH, van Eijk A, et al. The Global Enteric Multicenter Study (GEMS) of diarrheal disease in infants and young children in developing countries: epidemiologic and clinical methods of the case/control study. Clin Infect Dis. 2012; 55 Suppl 4:S232–45.
12. Kotloff KL, Nataro JP, Blackwelder WC, Nasrin D, Farag TH, Panchalingam S, et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. Lancet. 2013; 382(9888):209–22. https://doi.org/10.1016/S0140-6736(13)60844-2 PMID: 23680352
13. StataCorp. 2015. Stata Statistical Software: Release 14. College Station TSL.
14. Rahman AE, Moinuddin M, Molla M, Worku A, Hurt L, Kirkwood B, et al. Childhood diarrhoeal deaths in seven low- and middle-income countries. Bull World Health Organ. 2014; 92(9):664–71. https://doi.org/10.2471/BLT.13.134809 PMID: 25378757
15. Bruzzi P, Green SB, Byar DP, Brinton LA, Schairer C. Estimating the population attributable risk for multiple risk factors using case-control data. Am J Epidemiol. 1985; 122(5):904–14. PMID: 4050778
16. Blackwelder WC, Biswas K, Wu Y, Kotloff KL, Farag TH, Nasrin D, et al. Statistical methods in the Global Enteric Multicenter Study (GEMS). Clin Infect Dis. 2012; 55 Suppl 4:S246–53.

17. Liu J, Platts-Mills JA, Juma J, Kabir F, Nkeze J, Okoi C, et al. Use of quantitative molecular diagnostic methods to identify causes of diarrhoea in children: a reanalysis of the GEMS case-control study. Lancet. 2016; 388(10051):1291–301. https://doi.org/10.1016/S0140-6736(16)31529-X PMID: 27673470

18. IHME. Mortality estimation process. https://vizhub.healthdata.org/mortality/ [accessed 19th May 2016].

19. IGME. UN Inter-agency Group for Child Mortality Estimation. http://www.childmortality.org/ [accessed 18th March 2016].

20. Alkema L, You D. Child mortality estimation: a comparison of UN IGME and IHME estimates of levels and trends in under-five mortality rates and deaths. PLoS Med. 2012; 9(8):e1001288. https://doi.org/10.1371/journal.pmed.1001288 PMID: 22952434

21. Vos Theo B R, Phillips David E, Lopez Alan D, Murray Christopher J L. Authors Reply to Correspondence—Causes of child death: comparison of MCEE and GBD 2013 estimates. Liu Li, Black Robert E, Cousens Simon, Mathers Colin, Lawn Joy E, Hogan Daniel R. Published Online May 23, 2015 http://dx.doi.org/10.1016/S0140-6736(15)60663-8.

22. Stevens GA, Alkema L, Black RE, Boerma JT, Collins GS, Ezzati M, et al. Guidelines for Accurate and Transparent Health Estimates Reporting: the GATHER statement. Lancet. 2016.

23. Bhandari N, Bhan MK, Sazawal S. Mortality associated with acute watery diarrhea, dysentery and persistent diarrhea in rural North India. Acta Paediatr. 1992; 81 Suppl 381:3–6.

24. Mortality GBD Causes of Death C. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016; 388(10053):1459–544. https://doi.org/10.1016/S0140-6736(16)31012-1 PMID: 27733281

5.0 Chapter 5 - Estimation of rotavirus age distributions in children aged <5 years

5.1 Contribution of paper to the aim and objectives of the thesis

This analysis involved fitting parametric curves to available data on age distributions. This allows estimation of RVGE hospital admissions by week of age between birth and age 5.0 years. This level of granularity is important for assessing the potential benefits of alternative rotavirus vaccination schedules. Many country datasets are analysed, and these provide a critical input to the benefit-risk analysis (Chapter 9). For countries without data, methods of extrapolation are proposed based on under-five mortality strata. There is considerable variation between countries in the median age of RVGE hospital admission. Countries in high mortality settings have a much lower median age than countries in lower mortality settings.

5.2 Independent academic contribution

I was the LSHTM principle investigator and senior author of the paper. I was responsible for the main statistical analysis (fitting of age distributions) and worked on this independently. I wrote the R code, ran the statistical analysis and wrote the first draft of the paper. The regression models were done by Colin Sanderson. The systematic review and data gathering were done by the first two authors. I helped to develop the methodology for the systematic review and used Distiller software to resolve any conflicts between the two systematic reviewers.

5.3 Ethical approval

This study was approved by the ethical committee (Ref 14398) of the London School of Hygiene and Tropical Medicine (LSHTM).

Global review of the age distribution of rotavirus disease in children aged <5 years before the introduction of rotavirus vaccination

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Abstract

Background: The impact of live oral rotavirus vaccines could be improved by adjusting the schedules, but in published age distributions of rotavirus gastroenteritis (RVGE) the age bands are too broad to allow a detailed investigation of the potential gains.

Methods: We sought datasets that could provide age distributions of rotavirus-positive community cases, clinic visits, hospital admissions, emergency visits and deaths among children <5 years of age, before the introduction of rotavirus vaccines. We analysed the WHO Global Rotavirus Surveillance Network (GRSN) database and conducted a systematic literature review (January 1990 to February 2017) to identify other relevant datasets. We contacted study investigators to obtain more granular age distributions than were originally published. We used a robust statistical approach to fit parametric age distributions to each country dataset and mortality stratum. We calculated the median age, and cumulative proportion of RVGE events expected to occur at specific ages between birth and 5.0 years.

Findings: We identified 117 pre-vaccination datasets with rotavirus-positive events among children aged <5 years. The median age of rotavirus-positive hospital admissions was 38 weeks (inter-quartile range IQR: 25-58) in countries with very high child mortality and 65 weeks (IQR: 40-107) in countries with low/very low child mortality. In countries with very high child mortality 69% of rotavirus-positive admissions <5 years were in the first year of life, with 3% by 10 weeks, 8% by 15 weeks and 27% by 26 weeks of age.

Conclusions: The median age of rotavirus disease in children aged <5 years varies between and within countries but tends to be younger in higher mortality settings. The age distributions presented in this paper provide information that is critical for assessing the potential benefits of alternative rotavirus vaccination schedules in different countries, and for monitoring programme impact.

Introduction

Rotavirus gastroenteritis (RVGE) is estimated to cause around 200,000 child deaths each year (1). Over half of the countries in the world now include live oral rotavirus vaccines in their national immunization programmes (2). There are three vaccines licensed for global use (Rotarix® - GSK, RotaTeq® - Merck & Co., and ROTAVAC® - Bharat Biologicals), others for national use (e.g. in Vietnam, China and India) and several others in the pipeline, including neonatal and non-replicating injectable vaccines (3). Randomised controlled trials (RCTs) have reported high vaccine efficacy (~90%) against severe RVGE in low mortality countries but modest efficacy (~50%) in higher mortality settings (4). Alternative schedules are being considered to increase their impact. A neonatal vaccine has had promising results in Indonesia(5), and some studies have evaluated the potential of a booster dose given at around 9-12 months of age (6, 7). Several studies and surveillance systems have collected information on RVGE age distributions but much of it is unpublished or has been published in age bands that are too broad to allow a detailed assessment of the potential impact of alternative rotavirus vaccination schedules. More granular age distributions would also help to quantify the number of RVGE cases expected to occur at specific ages, so that changes can be monitored after vaccination. More generally, there is a need to update the global evidence on RVGE age distributions, compare them between countries and regions, and establish a reliable method for extrapolating them to countries without data. An unpublished review was conducted in 2012 (8) but this did not include the large multi-country Global Rotavirus Surveillance Network (GRSN) database (9), and several pivotal multi-country studies have also been published since (10-12).

In this paper we aim to estimate granular age distributions of rotavirus disease outcomes in children aged <5 years by type of RVGE presentation, country and mortality level, before the introduction of rotavirus vaccines.

Methods

Ethical Approval

This study was approved by the ethical committee of the London School of Hygiene and Tropical Medicine (LSHTM); ethics reference 14398. All authors and countries gave their consent to analyse and publish the data.

Search strategy and study selection

We sought country datasets containing counts of rotavirus-positive disease in children aged <5 years before the introduction of rotavirus vaccines. A country dataset is defined as a dataset derived from a single study (e.g. hospital surveillance, case-control, cohort etc.) within a single country, reporting on a single rotavirus-positive outcome/presentation (community cases, clinic visits, emergency visits, hospitalisations, deaths). If a dataset contained multiple sub-national locations and/or multiple calendar years, then these were aggregated, and any relevant exclusion criteria were applied to the aggregated dataset. When studies reported multiple rotavirus-positive presentations then each presentation was considered to be a distinct dataset. Pre-vaccine datasets only included data for years prior to rotavirus vaccine introduction.

First, we analysed the WHO GRSN database, which contains information about hospital admissions among children <5 years from surveillance sites in 69 countries (9). In these sites, rotavirus-positivity is determined by enzyme immunoassay (EIA). We applied the definition described above and aggregated sub-national locations and multiple calendar years to create unique pre-vaccine introduction GRSN country datasets. The year of rotavirus vaccine introduction was determined by WHO/UNICEF Estimates of National Immunization Coverage (WUENIC)(13). If a country dataset did not have data of hospital admissions by day of age, then we used month of age. Admissions recorded as aged zero days were removed for face validity (inconsistent with the rotavirus incubation period).

Second, we conducted a systematic literature review adhering to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to identify other relevant rotavirus studies. A full description of the search strategy is provided in the supplementary appendix (Appendix). In brief, we searched for papers published between January 1990 and February 2017 and publications in English, French, Spanish and Polish. We excluded studies in which rotavirus positivity was not determined by EIA or quantitative polymerase chain reaction (qPCR); non-human studies; nosocomial infection studies; studies without information on individuals aged less than 5 years old; special populations such as HIV-infected patients; meta-analyses and systematic reviews reporting regional or global age

distributions; and, papers without an accessible full text link. Two independent reviewers (MHA, CL) screened abstracts and any ambiguity was resolved by a third reviewer (AC). A letter was sent by email to the investigators of all studies identified in the systematic review. Investigators were asked to provide anonymised data or complete a standard data extraction table with counts by week of age up to 5.0 years. If the investigators did not respond before the end of August 2017 and no other study was available for that country, we extracted the age distribution reported in the publication. We included all country datasets that were obtained from a previously unpublished literature and database search conducted by Sanderson *et al* in 2012(8). This included articles published between 1990 and 2011.

All country datasets were combined into a central database with a standard format and list of variables and analysed together with the GRSN datasets. We cross-checked datasets identified through the literature search and GRSN to avoid data duplication. Prior to analysing the datasets, we excluded studies that included fewer than 35 RVGE events, had known concerns about EIA quality, had fewer than three age bands <1 year of age and did not capture cases from birth. We designed a tool to assess the risk of bias in RCTs and observational studies and assigned very low, low or medium risk of bias to each country dataset. The risk of bias was scored against a list of five criteria (Appendix).

Data analysis

We fit a range of parametric distributions (Gamma, Weibull, Lognormal, Log Logistic, Burr) to several GRSN datasets that were reported by day of age, and that represented the extreme range of younger and older age distributions globally. We fit age distributions using Maximum Likelihood Estimation (MLE). The best-fitting distribution was chosen by comparing goodness of fit statistics (Kolmogorov-Smirnov; Cramer-von Mises; Anderson-Darling) and goodness of fit criteria (Akaike's Information Criterion, Bayesian Information Criterion). For each country dataset, we calculated the best-fitting parameters of the chosen distribution. We generated summary tables with the median age, interquartile age range, and the cumulative proportion of RVGE cases aged <5 years that were estimated to occur at different granular ages between birth and age 5.0 years. We reported the Root Mean Squared Error (RMSE) and Mean Absolute Error (MAE) for the parametric distribution fitted to each country dataset. All analyses were conducted using *R* v.3.4.1 using the following packages: *polspline, nloptr, zoo, MASS, fitdistrplus, actuar* and *mutil.*

We assigned each of the 201 countries in the world to an under-five mortality quintile (very low, low, medium, high and very high) using 2010-2015 estimates of under-five mortality as

reported by the UNPOP 2017 Revision(14). We grouped all datasets according to the under 5 mortality quintile of the country concerned, and calculated the median age and median best-fitting parameters for each stratum. We also ran a series of regression analyses to explore which combinations of variables would best predict the median age and parameters of the chosen parametric distribution. To compare differences in rotavirus disease presentations we plotted the full set of median ages reported for a given presentation against their respective 2010-2015 under-five mortality rates. We fit a least-squares line of best fit for each presentation, reported the R-squared value and compared the best-fitting lines.

We used ArcGIS mapping software to display the median age of rotavirus hospitalisation estimated for each country in the world. If more than a single dataset was available for a country, we calculated the median age and median best-fitting parameters of all datasets for that country. If no dataset was available, we assigned the median age of the country's corresponding mortality stratum.

Results

We identified 117 pre-vaccination datasets with rotavirus-positive events among children <5 years of age (6 datasets with community cases, 12 with clinic visits, 7 with emergency visits, 92 with hospital admissions and 0 with deaths) (Table 1, Figure 1). Around half of the country datasets (51/117) were rotavirus-positive cases identified through hospital-based sentinel site surveillance from the GRSN (35 reported by day of age and 16 reported by month of age). The other half (66/117) were identified from the systematic literature review (n=61) or obtained from the previously unpublished review (n=5). The 117 pre-vaccination datasets were taken from 47 studies with very low (n=24), low (n=12) and medium (n=11) risk of bias.

Log Logistic age distributions had favourable goodness of fit statistics and criteria (Appendix Figures S1 and S2) so were used to generate summary statistics on the age distribution of hospital admissions aged <5 years (Appendix Tables S2 and S3). The median age of RVGE hospital admission was 38 weeks (inter-quartile range IQR: 25-58) in countries with very high child mortality, 43 weeks (IQR: 28-68) in countries with high child mortality, 46 weeks (IQR: 29-72) in countries with medium child mortality and 65 weeks (IQR: 40-107) in countries with low/very low child mortality (Figure 2). We collapsed the low and low child mortality strata because they had a very similar age profile (67 weeks for very low and 63 weeks for low). In countries with very high child mortality 69% of rotavirus-positive admissions in children <5 years were in the first year of life, with 3% by 10 weeks, 8% by 15 weeks and 27% by 26 weeks. There was considerable variation within each child mortality stratum. For

example, in the very high child mortality stratum, the median age ranged from 29 weeks (IQR: 19-46) in Zambia to 50 weeks in Ethiopia (IQR: 30-81). Similarly, in the low/very low mortality stratum, the median age ranged from 35 weeks (IQR: 19-64) in France to 101 weeks (IQR: 65-157) in Ukraine.

Globally, most countries with a low median age were in Africa (Figure 3). In general, the median age of rotavirus-positive hospital admissions decreased as child mortality increased (one-way ANOVA, $p<0.0001$), but there were notable outliers such as France and The Netherlands where the median age was exceptionally low (35 and 48 weeks respectively) and Mauritius and Ukraine where the median age was exceptionally high (84 and 101 weeks respectively). Regression models with more variables provided no substantive advantage over the simple stratification by under-five mortality quintile (Appendix Tables S4 and S5).

There were relatively few global datasets with age distributions for community cases, clinic visits and emergency visits, and none for RVGE deaths that met our inclusion criteria. The median age for RVGE emergency visits was around 10 weeks younger than the median age for RVGE hospital admissions. The median age for RVGE clinic visits was around 5 weeks older than the median age for RVGE hospital admissions (Appendix Tables S6-S8). This pattern was consistent across settings with different under-five mortality rates (Appendix Figure S3).

Discussion

We have gathered and synthesised a large amount of evidence on rotavirus age distributions globally. To our knowledge this is the first systematic global study to estimate granular age distributions by country, mortality stratum and level of care sought. We use statistically robust and standard methods to provide reproducible parametric age distributions for each country. We show that the median age of rotavirus disease varies between and within countries but tends to occur at a much younger age in higher mortality settings. We hypothesise that this is probably due to a higher force of infection and shorter intervals between repeat infections in these settings. There could also be important age-specific differences in the early management and treatment of RVGE in higher mortality settings. Birth cohort studies have shown a peak age of infection at around 20 months of age in Mexico (medium mortality) (15) compared to 5.5 months in India (high mortality) (16). RVGE age distributions were similar in these studies, probably because natural infections were less protective in India leading to more cases in older ages; consistent with rotavirus vaccination doses being less protective in high mortality settings (17). However, this comparison included cases that were not hospitalised.

Our analysis relies heavily on the WHO GRSN database which may include sentinel sites that are not fully representative of the country concerned. Importantly, healthcare seeking behaviour varies by country and age and this may help to explain heterogeneities observed within each mortality stratum. For example, in some settings with high rates of private healthcare, children aged <1 year may be more likely to be treated outside of the regular sentinel surveillance system. In Hungary, Slovenia and Ukraine the median age of rotavirus-positive hospital admissions was 86, 88 and 101 weeks respectively. This high median age might simply be a characteristic of rotavirus in Central and Eastern Europe or may reflect other surveillance peculiarities e.g. under-recruitment of younger patients or over-recruitment of mild RVGE cases. We analysed the very low and low mortality strata without Ukraine but that did not change the median age of 65 weeks. In other datasets, there may be a bias to younger ages. For example, we found a surprisingly low median age of hospital admission from multiple datasets in France (median age 27-41 weeks) for reasons that are not clear.

We chose to fit parametric distributions, rather than report the actual age distributions observed in each study. This required an assumption to be made about the standard functional form of the distribution. However, our parametric fitting approach: a) provides a function that can be easily reproduced by others; b) avoids the issue of *heaping* i.e. the tendency to report cases at exactly 1.0 years, 2.0 years etc., an issue that has been evident in many of the datasets because of a reporting artefact; c) smooths distributions based on small (noisy) samples; and, d) allows standard reporting of the proportion of RVGE cases that occur at specific ages e.g. the proportion of cases occurring before the first dose of rotavirus vaccine at 6 weeks, or before vaccine age restrictions are applied at 15 weeks. We also explored non-parametric smoothing approaches. We used Kernel Density Estimation (KDE), with default Gaussian smoothing. However, *heaping* was evident in some of the datasets and areas of density below zero were common. One way to avoid this is to truncate the density at zero, but this introduces a bias in the distribution and creates an implausible cliff-edge at zero in some datasets. Another way to avoid this is to use Logspline Density Estimation, with the lower bound set to zero. This worked well for some datasets but not others and required manual adjustment to the number and location of knots so was not practical as a standardised approach.

We obtained many datasets on rotavirus-positive hospital admissions but few on other presentations. No datasets with rotavirus-positive deaths met our inclusion criteria because they had fewer than 35 deaths and it was very difficult to ascertain whether the deaths were entirely attributable to rotavirus. Compared to hospital admissions, we found a higher median age for clinic visits and a younger median age for emergency visits, but this was based on very few data points.

Conclusion

The median age of rotavirus disease in children aged <5 years varies between and within countries but tends to be younger in higher mortality settings. The age distributions presented in this paper should provide information that is critical for assessing the potential benefits of alternative rotavirus vaccination schedules in different countries, and for monitoring the impact of rotavirus vaccines.

Conflicts of interest: All authors declare no conflicts of interest.

Disclaimer: The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

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Table 1. Number of country datasets containing RVGE age distributions before the introduction of rotavirus vaccination, by type of presentation and under-five mortality quintile

Quintile for 2010-2015 under-five mortality rate	Number of country datasets (Number of rotavirus-positive cases)				
	Hospital admissions	Emergency visits	Clinic visits	Community cases	Total
Very Low	13 (31,211)	3 (10,467)	3 (1,552)	0 (0)	19 (43,230)
Low	8 (10,348)	2 (179)	1 (41)	0 (0)	11 (10,568)
Medium	14 (13,990)	0 (0)	1 (224)	1 (89)	16 (14,303)
High	31 (23,557)	2 (167)	3 (461)	4 (536)	40 (24,721)
Very High	26 (26,142)	0 (0)	4 (1,066)	1 (71)	31 (27,279)
Total	**92 (105,248)**	**7 (10,813)**	**12 (3,344)**	**6 (696)**	**117 (120,101)**

Figure 1. Flowchart of the study selection process and data extraction.

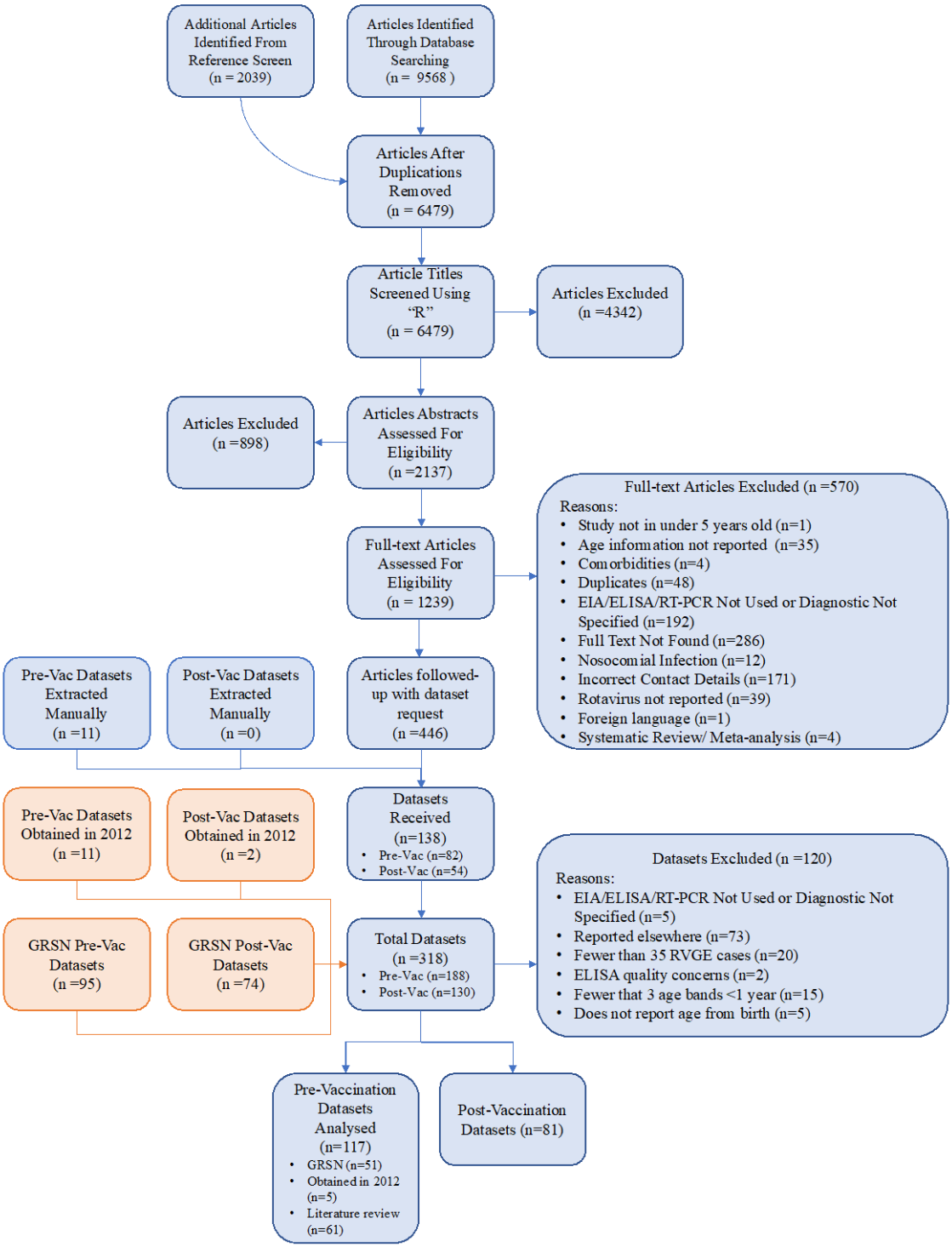


Figure 2. Age distributions of rotavirus-positive hospital admissions by under-five mortality strata

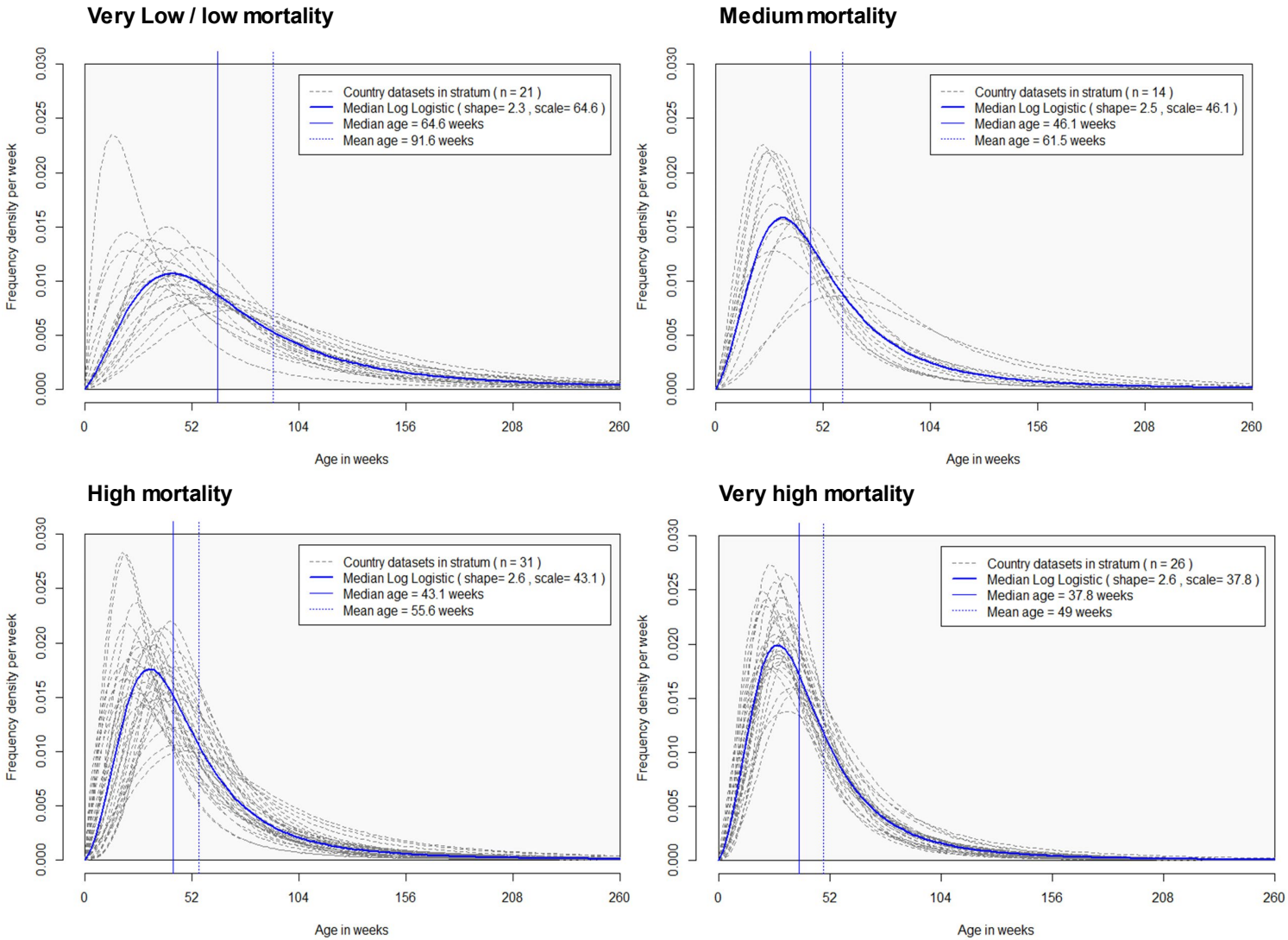
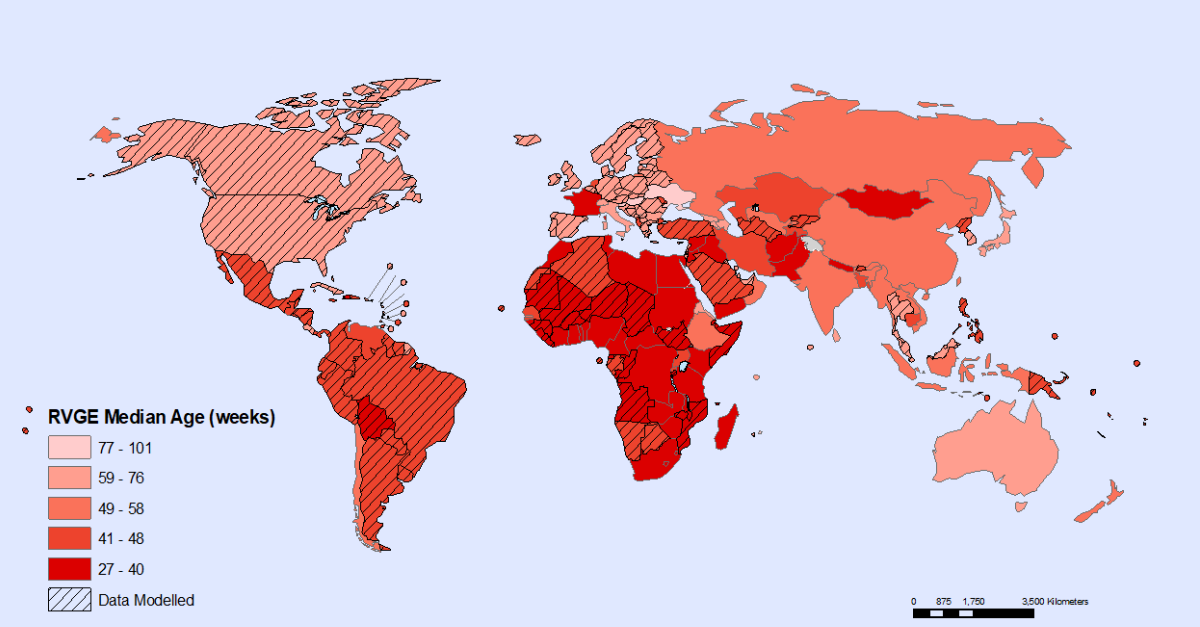


Figure 3. Estimated and extrapolated pre-vaccination median age of rotavirus-positive hospital admissions <5 years by country.



Lighter red represents younger median age and darker red represented older median age. If more than one study was conducted within a country, the median of median ages was used. If no data were available for a country, the median age was extrapolated (indicated by diagonal shading) using the median age of the under-five mortality stratum.

Appendix to:

Global review of the age distribution of rotavirus disease in children aged <5 years before the introduction of rotavirus vaccination.

Mateusz Hasso-Agopsowicz, Chandresh Nanji Ladva, Benjamin Lopman, Colin Sanderson, Adam L. Cohen, Global Rotavirus Surveillance Network, Rotavirus Age Distribution Collaborators, Jacqueline E. Tate, Ximena Riveros, Ana Maria Henao-Restrepo, Andrew Clark

Search strategy

a) Search Terms

1. rotavir*
2. Rotavirus Infections/ or Rotavirus
3. 1 or 2
4. incidence
5. hospital*
6. case*
7. visit*
8. admission*
9. death*
10. surveill*
11. Fetal Mortality/ or Child Mortality/ or Infant Mortality/ or Hospital Mortality/ or Mortality/
12. Mortalit*
13. Diarrh*
14. Diarrhea/ or Diarrhea, Infantile/
15. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 3 and 15
17. limit 16 to (humans and yr="1990 -Current" and ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)") and (english or french or polish or spanish))

b) Limits:

- English, French, Spanish, Polish,
- Humans
- Year 1990- current
- Yr 0-5

c) Search engines (with modified search terms where appropriate):

- EMBASE
- Cochrane
- Medline
- Chinese citation database

d) Exclusion Criteria

- Rotavirus Not Reported
- Age Information Not Reported
- No Cases <5 Years
- EIA/ELISA or PCR Not Used or Diagnostic Not Specified
- Hospital Acquired (Nosocomial) Infection
- Comorbidities (Other Medical Conditions) in Cases
- Systematic Review/Meta-Analysis
- In vitro or animal study
- Full-Text Not Found

Risk of bias assessment tool

When reviewing studies, we expanded the exclusion criteria to exclude highly biased studies (see Methods: Literature Review). Additionally, following a consultation with Cochrane we designed a custom tool to assess the risk of bias in the remaining observational studies. We checked each study for the following criteria:

i) whether participants were representative of the general population;
ii) whether participants' characteristics were reported;
iii) whether surveillance methods and outcomes were the same for all participants;
iv) whether study assessors were blinded at outcome assessment; and,
v) whether drop-outs, withdrawals and missing data were described?

Each answer was given a score: 0 for "No", 1 for "Unclear", and 2 for "Yes". The total score was calculated and studies with a score of 0-1 were considered to have a very low risk of bias; 2-4 low risk of bias; and 5-7 medium risk of bias (Appendix Table S1).

Appendix Table S1: Assessment criteria and scores for risk of bias in studies with rotavirus disease age distributions in children aged <5 years

	Selection Bias	Baseline Confounding	Outcome Measurement	Blinding at Outcome Assessment	Description of Missing					
Ref	Are participants representative of the general population?	Are characteristics of participants reported?	Are surveillance and measurement of outcomes the same for all participants?	Are study assessors blinded at outcome assessment?	Are drop-outs, withdrawals and missing data described?	Total "Y"	Total "U"	Total "N"	Score	Risk of Bias
(18)	Y	Y	Y	U	Y	4	1	0	1	VERY LOW
(19)	Y	Y	Y	U	Y	4	1	0	1	VERY LOW
(10)	Y	Y	N	Y	N	3	0	2	4	LOW
(20)	Y	Y	Y	U	Y	4	1	0	1	VERY LOW
(21)	Y	Y	Y	U	Y	4	1	0	1	VERY LOW
(12)	Y	Y	Y	Y	N	4	0	1	2	LOW
(22)	Y	N	Y	U	N	2	1	2	5	MEDIUM
(23)	Y	Y	Y	U	Y	4	1	0	1	VERY LOW
(11)	Y	Y	Y	U	Y	4	1	0	1	VERY LOW
(24)	Y	N	Y	U	N	2	1	2	5	MEDIUM
(25)	Y	N	Y	U	N	2	1	2	5	MEDIUM
(26)	Y	Y	Y	U	Y	4	1	0	1	VERY LOW
(27)	Y	Y	Y	U	Y	4	1	0	1	VERY LOW
(28)	Y	Y	Y	U	N	3	1	1	3	LOW
(29)	Y	Y	Y	U	N	3	1	1	3	LOW
(30)	Y	Y	Y	U	Y	4	1	0	1	VERY LOW
(31)	Y	N	Y	U	N	2	1	2	5	MEDIUM
(32)	Y	N	Y	U	N	2	1	2	5	MEDIUM
(33)	Y	Y	Y	U	Y	4	1	0	1	VERY LOW
(34)	Y	Y	Y	Y	Y	5	0	0	0	VERY LOW
(35)	Y	Y	Y	U	Y	4	1	0	1	VERY LOW
(36)	Y	Y	Y	U	N	3	1	1	3	LOW
(37)	Y	Y	Y	U	N	3	1	1	3	LOW
(38)	Y	Y	Y	U	Y	4	1	0	1	VERY LOW
(39)	Y	Y	Y	U	Y	4	1	0	1	VERY LOW
(40)	Y	Y	Y	U	Y	4	1	0	1	VERY LOW
(41)	Y	N	Y	U	Y	3	1	1	3	LOW
(42)	Y	Y	N	U	Y	3	1	1	3	LOW
(43)	Y	N	Y	U	N	2	1	2	5	MEDIUM
(44)	Y	Y	Y	U	Y	4	1	0	1	VERY LOW
(45)	Y	N	Y	U	N	2	1	2	5	MEDIUM
(46)	Y	Y	Y	U	N	3	1	1	3	LOW
(47)	Y	Y	Y	U	N	3	1	1	3	LOW
(48)	Y	Y	Y	U	N	3	1	1	3	LOW

(49)	Y	Y	Y	U	Y	4	1	0	1	VERY LOW
(50)	Y	Y	Y	U	Y	4	1	0	1	VERY LOW
(51)	Y	Y	Y	U	Y	4	1	0	1	VERY LOW
(52)	Y	N	Y	U	N	2	1	2	5	MEDIUM
(53)	Y	Y	Y	U	Y	4	1	0	1	VERY LOW
(54)	Y	N	Y	U	N	2	1	2	5	MEDIUM
(55)	Y	N	Y	U	N	2	1	2	5	MEDIUM
(56)	Y	Y	Y	U	Y	4	1	0	1	VERY LOW
(57)	Y	Y	Y	U	Y	4	1	0	1	VERY LOW
(58)	Y	Y	Y	U	N	3	1	1	3	LOW
(59)	Y	N	N	U	N	1	1	3	7	MEDIUM
(15)	Y	Y	Y	U	Y	4	1	0	1	VERY LOW
(9)	Y	Y	Y	U	Y	4	1	0	1	VERY LOW

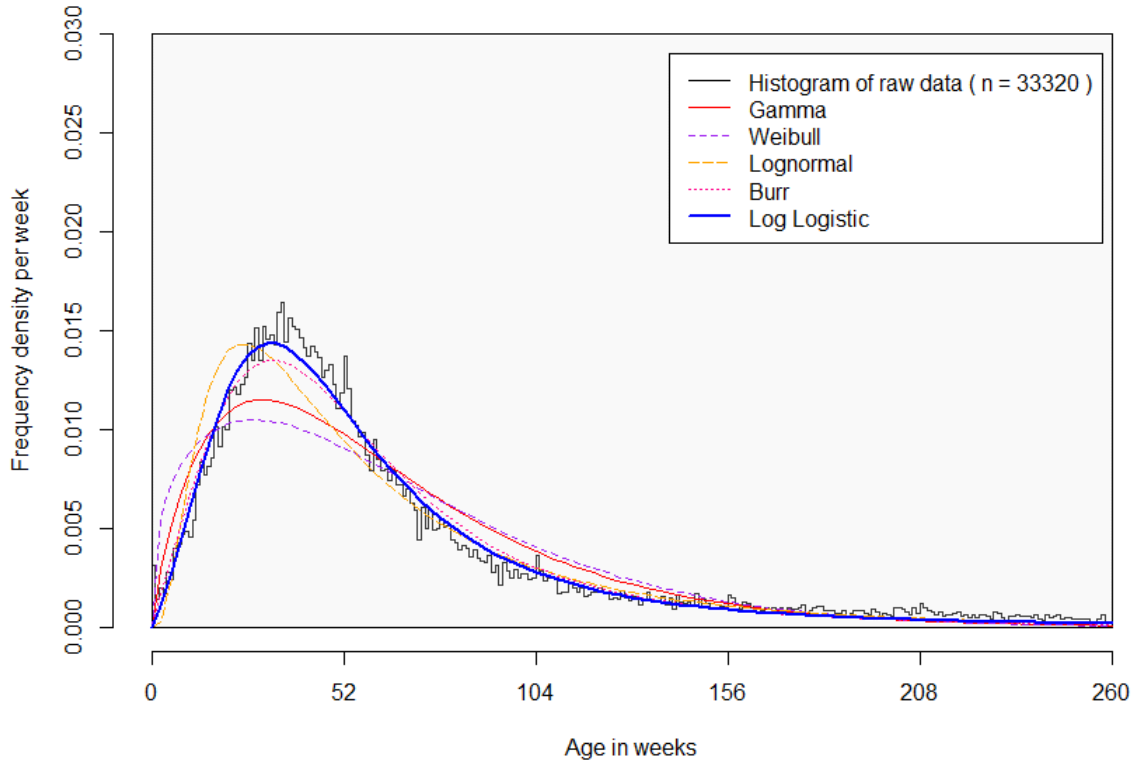
Justification for choosing the Log Logistic age distribution

We fitted a range of parametric distributions to all cases identified in the GRSN that were reported by day of age. This dataset was used to identify the best-fitting parametric distributions because it had finest age granularity and covered a wide range of countries. Importantly, it also included a country dataset very skewed to younger ages (Zambia) and a country dataset very skewed to older ages (Ukraine) and represented the full range of age distributions identified in our search. We fitted separate parametric distributions to the aggregated global dataset, each WHO region, Zambia and the Ukraine. The *Log Logistic* distribution had the lowest (most favourable) goodness of fit statistics (Kolmogorov-Smirnov, Cramer-von Mises, Anderson-Darling) for Zambia, WHO regions AFR, SEAR, WPR and the global dataset (Appendix Figures S1 & S2). The *Lognormal* distribution had marginally better goodness of fit statistics than *Log Logistic* in the Ukraine. The *Burr* distribution had marginally better goodness of fit criteria than *Log Logistic* for most datasets (Akaike's Information Criterion – AIC, Bayesian Information Criterion - BIC) but had much worse goodness of fit statistics. In the interests of using a flexible, defensible and standardised fitting approach, we used the *Log Logistic* distribution to fit curves to all datasets.

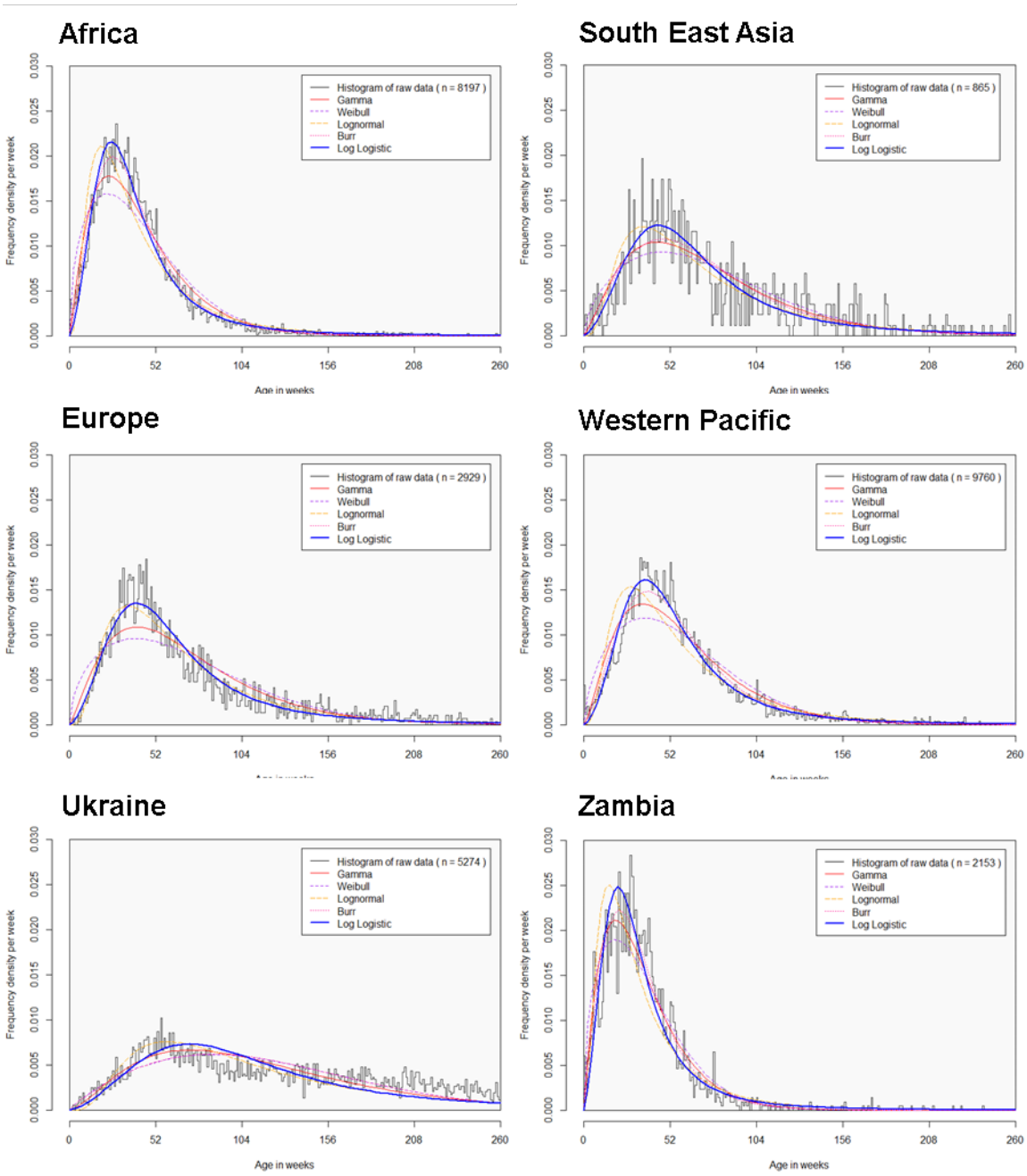
The Log Logistic age distribution is defined by a scale (α) and a shape (β) parameter. The scale parameter is conveniently the same as the median age. The proportion of rotavirus disease within each week of age is calculated by the following equation, where x represents the age at the beginning of each week of age

$$\frac{(\beta/\alpha)(x/\alpha)^{\beta-1}}{(1+(x/\alpha)^{\beta})^2}$$

Appendix Figure S1: Age distribution of rotavirus-positive hospital admissions aged <5 years for all countries included in the WHO GRSN database with data reported by day of age, before the introduction of rotavirus vaccination: comparison of alternative fitted parametric distributions



Appendix Figure S2: Age distribution of rotavirus-positive hospital admissions aged <5 years for selected countries and WHO regions included in the WHO GRSN database with data reported by day of age, before the introduction of rotavirus vaccination: comparison of fitted parametric distributions



Appendix Table S2. Age distributions for rotavirus-positive hospital admissions aged <5 years before the introduction of rotavirus vaccination: median, interquartile range and cumulative age distribution

Study characteristics			Median (IQR)			Proportion of RVGE hospital admissions expected to occur by specific ages												
Ref	Country	n	50th pc.	25th pc.	75th pc.	6w	2m	10w	14w	15w	4m	6m	9m	12m	24m	36m	48m	60m
(41)	Australia	**44**	**67**	42	108	0·4%	0·9%	1·2%	2·6%	3·1%	4·2%	10·1%	22·3%	35·9%	73·5%	87·6%	93·2%	95·8%
(57)	Bulgaria	**2197**	**65**	40	105	0·5%	1·0%	1·4%	3·0%	3·5%	4·8%	11·3%	24·1%	37·9%	74·6%	88·1%	93·4%	95·9%
(52)	Chile	**942**	**49**	29	81	1·0%	2·3%	3·1%	6·2%	7·2%	9·6%	20·3%	38·0%	53·4%	83·8%	92·6%	95·9%	97·4%
(23)	China, Hong Kong SAR	**13147**	**69**	41	116	0·5%	1·2%	1·6%	3·2%	3·6%	4·9%	10·9%	22·6%	35·1%	70·5%	85·0%	91·3%	94·4%
(42)	China, Hong Kong SAR	**123**	**84**	53	133	0·2%	0·4%	0·6%	1·3%	1·6%	2·2%	5·6%	13·6%	23·9%	62·4%	81·5%	89·8%	93·7%
(10)	France	**8035**	**43**	23	80	3·0%	5·6%	7·1%	12·2%	13·6%	16·9%	29·4%	46·0%	58·6%	82·8%	90·8%	94·2%	96·0%
(40)	France	**473**	**27**	15	49	6·1%	11·3%	14·2%	23·5%	25·9%	31·2%	48·9%	66·8%	77·3%	92·4%	96·2%	97·7%	98·5%
(9)	Georgia	**110**	**67**	42	107	0·4%	0·9%	1·2%	2·6%	3·0%	4·2%	10·1%	22·3%	35·9%	73·8%	87·8%	93·4%	95·9%
(10)	Hungary	**1820**	**86**	52	142	0·3%	0·7%	0·9%	1·8%	2·1%	2·9%	6·8%	15·1%	25·0%	60·4%	78·8%	87·5%	91·9%
(22)	Italy	**1002**	**77**	46	128	0·4%	0·9%	1·2%	2·5%	2·9%	3·9%	8·8%	18·8%	30·1%	65·7%	82·1%	89·5%	93·3%
(59)	Italy	**2434**	**62**	33	119	1·9%	3·4%	4·3%	7·4%	8·2%	10·3%	18·6%	31·2%	42·5%	70·6%	82·7%	88·6%	91·9%
(37)	Japan	**58**	**73**	48	113	0·2%	0·4%	0·6%	1·5%	1·7%	2·5%	6·7%	16·7%	29·4%	70·8%	87·2%	93·4%	96·1%
(10)	Netherlands	**710**	**48**	25	92	3·0%	5·4%	6·8%	11·3%	12·6%	15·5%	26·5%	41·6%	53·6%	78·7%	87·9%	92·2%	94·5%
(39)	New Zealand	**555**	**55**	35	87	0·4%	1·1%	1·5%	3·4%	4·0%	5·5%	13·6%	29·7%	46·1%	82·2%	92·6%	96·2%	97·7%
(9)	Oman	**728**	**53**	35	78	0·3%	0·7%	1·0%	2·5%	3·1%	4·5%	12·6%	30·5%	49·2%	86·7%	95·2%	97·8%	98·8%
(54)	Russian Federation	**819**	**58**	36	95	0·6%	1·4%	1·9%	3·9%	4·5%	6·1%	14·0%	28·8%	43·6%	78·7%	90·2%	94·6%	96·7%
(9)	Seychelles	**123**	**62**	38	102	0·6%	1·3%	1·8%	3·7%	4·3%	5·8%	13·0%	26·6%	40·5%	75·7%	88·3%	93·4%	95·9%
(10)	Slovenia	**2224**	**88**	58	134	0·1%	0·2%	0·3%	0·8%	0·9%	1·3%	3·8%	10·4%	19·8%	60·6%	81·8%	90·6%	94·5%
(9)	Sri Lanka	**153**	**65**	46	93	0·1%	0·2%	0·3%	0·8%	1·0%	1·6%	5·4%	16·8%	32·9%	80·8%	93·7%	97·3%	98·6%
(36)	Switzerland	**586**	**64**	38	107	0·6%	1·4%	1·8%	3·7%	4·3%	5·7%	12·6%	25·6%	39·0%	73·8%	87·1%	92·6%	95·3%
(9)	Ukraine	**5276**	**101**	65	157	0·1%	0·2%	0·3%	0·7%	0·8%	1·2%	3·2%	8·3%	15·8%	51·7%	74·8%	86·0%	91·5%
Very low / low mortality (median)		**728**	**65**	40	107	0·4%	1·0%	1·4%	3·0%	3·5%	4·8%	11·3%	24·1%	37·9%	73·8%	87·8%	93·4%	95·9%
(9)	Armenia	**781**	**76**	52	113	0·1%	0·2%	0·3%	0·9%	1·0%	1·5%	4·7%	13·2%	25·4%	70·4%	88·1%	94·3%	96·9%
(9)	China	**1078**	**52**	33	81	0·5%	1·2%	1·7%	3·9%	4·6%	6·4%	15·6%	33·4%	50·4%	84·8%	93·8%	96·8%	98·2%
(9)	Egypt	**666**	**34**	22	53	1·1%	2·8%	4·0%	9·0%	10·6%	14·7%	32·8%	58·1%	74·4%	94·5%	98·0%	99·0%	99·5%
(46)	Iran	**275**	**47**	30	74	0·7%	1·6%	2·3%	5·0%	5·9%	8·1%	19·1%	38·6%	55·8%	87·1%	94·8%	97·3%	98·4%
(47)	Iran	**88**	**50**	28	89	1·6%	3·2%	4·2%	7·8%	8·8%	11·3%	21·8%	38·0%	51·7%	80·4%	90·0%	94·0%	96·0%
(9)	Iran	**958**	**46**	29	72	0·7%	1·7%	2·4%	5·3%	6·2%	8·6%	20·1%	40·2%	57·5%	87·9%	95·1%	97·5%	98·5%
(9)	Jordan	**337**	**32**	21	50	1·6%	3·8%	5·3%	11·4%	13·2%	17·9%	37·1%	61·4%	76·3%	94·7%	98·0%	99·0%	99·4%
(28)	Kazakhstan	**2023**	**46**	29	72	0·7%	1·6%	2·3%	5·1%	6·0%	8·3%	19·7%	39·8%	57·2%	87·9%	95·1%	97·5%	98·6%
(9)	Mauritius	**355**	**84**	54	132	0·2%	0·4%	0·5%	1·2%	1·5%	2·1%	5·4%	13·3%	23·6%	62·8%	82·0%	90·2%	94·1%
(9)	Mongolia	**1424**	**38**	26	55	0·4%	1·3%	1·9%	5·1%	6·1%	9·1%	24·7%	52·0%	71·6%	95·1%	98·5%	99·3%	99·7%
(9)	Syria	**1157**	**35**	23	53	0·8%	2·3%	3·3%	7·8%	9·2%	13·0%	30·8%	57·1%	74·3%	94·9%	98·2%	99·2%	99·5%
(9)	Tunisia	**118**	**40**	26	61	0·8%	2·0%	2·9%	6·5%	7·6%	10·7%	25·2%	48·7%	66·4%	92·1%	97·0%	98·6%	99·2%
(27)	Venezuela	**102**	**42**	27	66	0·9%	2·2%	3·0%	6·6%	7·7%	10·5%	23·9%	45·5%	62·5%	89·9%	95·9%	97·9%	98·8%
(9)	Vietnam	**4628**	**52**	35	76	0·2%	0·6%	0·9%	2·3%	2·8%	4·1%	12·2%	30·7%	50·3%	88·1%	95·9%	98·2%	99·0%
Medium mortality (median)		**724**	**46**	29	72	0·7%	1·7%	2·4%	5·2%	6·2%	8·8%	21·0%	40·0%	57·3%	88·0%	95·5%	97·7%	98·7%
(9)	Azerbaijan	**643**	**71**	45	113	0·3%	0·7%	0·9%	2·1%	2·4%	3·4%	8·4%	19·4%	32·3%	71·2%	86·6%	92·8%	95·6%

(19)	Bangladesh	**297**	**35**	19	65	3·8%	7·2%	9·2%	15·7%	17·4%	21·5%	36·4%	54·5%	66·9%	87·7%	93·7%	96·2%	97·4%
(10)	Bangladesh	**191**	**53**	39	73	0·0%	0·2%	0·3%	0·9%	1·2%	1·9%	7·5%	25·1%	47·8%	91·2%	97·7%	99·2%	99·6%
(33)	Bangladesh	**2021**	**45**	33	61	0·1%	0·3%	0·5%	1·5%	1·9%	3·2%	12·3%	37·4%	62·5%	95·2%	98·8%	99·6%	99·8%
(56)	Bangladesh	**4787**	**48**	36	63	0·0%	0·1%	0·2%	0·8%	1·0%	1·8%	8·4%	31·2%	58·5%	95·6%	99·1%	99·7%	99·9%
(9)	Cambodia	**2094**	**48**	33	70	0·2%	0·6%	0·9%	2·4%	2·9%	4·4%	13·5%	34·5%	55·5%	90·9%	97·1%	98·8%	99·4%
(9)	Eritrea	**110**	**67**	42	107	0·4%	0·9%	1·2%	2·6%	3·0%	4·2%	10·1%	22·3%	35·9%	73·8%	87·9%	93·4%	96·0%
(24)	Guatemala	**91**	**47**	28	78	1·2%	2·7%	3·6%	7·1%	8·2%	10·8%	22·3%	40·4%	55·6%	84·5%	92·8%	96·0%	97·5%
(10)	India	**173**	**52**	38	70	0·0%	0·1%	0·2%	0·8%	1·0%	1·8%	7·4%	26·2%	50·6%	92·9%	98·3%	99·4%	99·7%
(34)	India	**704**	**43**	27	69	1·0%	2·3%	3·1%	6·6%	7·7%	10·5%	23·2%	43·9%	60·6%	88·7%	95·3%	97·5%	98·5%
(44)	India	**52**	**54**	38	78	0·1%	0·4%	0·6%	1·6%	2·0%	3·0%	9·7%	27·0%	47·0%	88·0%	96·2%	98·4%	99·2%
(48)	Indonesia	**88**	**48**	32	73	0·4%	1·1%	1·6%	3·8%	4·5%	6·4%	16·6%	36·5%	54·9%	88·2%	95·6%	97·9%	98·8%
(9)	Indonesia	**711**	**60**	39	94	0·3%	0·8%	1·1%	2·5%	3·0%	4·2%	10·8%	25·0%	40·7%	79·6%	91·5%	95·7%	97·5%
(9)	Iraq	**1786**	**32**	19	52	2·3%	5·2%	7·0%	13·8%	15·7%	20·5%	39·1%	61·5%	75·3%	93·6%	97·3%	98·6%	99·1%
(43)	Kenya	**429**	**41**	28	60	0·5%	1·3%	1·9%	4·7%	5·7%	8·3%	22·2%	47·1%	66·7%	93·4%	97·8%	99·0%	99·5%
(45)	Kenya	**232**	**26**	17	40	2·5%	6·1%	8·4%	17·6%	20·2%	26·7%	50·1%	73·4%	85·0%	97·0%	98·9%	99·4%	99·7%
(51)	Kenya	**195**	**33**	22	49	0·9%	2·4%	3·5%	8·4%	10·0%	14·2%	33·7%	60·9%	77·6%	95·9%	98·6%	99·4%	99·7%
(53)	Kenya	**587**	**42**	29	61	0·3%	0·9%	1·4%	3·8%	4·6%	6·9%	19·7%	44·9%	65·6%	93·7%	98·0%	99·1%	99·6%
(9)	Kenya	**634**	**39**	25	63	1·2%	2·8%	3·8%	8·1%	9·4%	12·7%	27·3%	49·3%	65·6%	90·6%	96·2%	98·0%	98·8%
(9)	Lao	**482**	**56**	39	81	0·1%	0·4%	0·6%	1·5%	1·9%	2·8%	9·0%	24·9%	43·9%	86·2%	95·4%	98·0%	99·0%
(9)	Libya	**717**	**38**	24	58	1·0%	2·4%	3·4%	7·6%	8·9%	12·3%	28·1%	52·1%	69·2%	92·8%	97·3%	98·7%	99·2%
(9)	Madagascar	**58**	**38**	26	55	0·4%	1·3%	2·0%	5·1%	6·2%	9·1%	25·0%	52·3%	71·9%	95·2%	98·5%	99·3%	99·7%
(25)	Morocco	**582**	**36**	22	60	2·1%	4·5%	6·0%	11·6%	13·2%	17·1%	33·1%	54·1%	68·7%	90·7%	95·9%	97·7%	98·6%
(9)	Morocco	**450**	**43**	26	73	1·6%	3·3%	4·5%	8·6%	9·9%	12·9%	25·7%	44·8%	59·8%	86·4%	93·7%	96·5%	97·8%
(9)	Myanmar	**919**	**50**	35	70	0·1%	0·4%	0·6%	1·7%	2·2%	3·4%	11·3%	31·8%	53·9%	91·5%	97·5%	99·0%	99·5%
(9)	Nepal	**536**	**38**	21	68	3·3%	6·2%	8·0%	13·9%	15·5%	19·3%	33·6%	51·7%	64·5%	86·7%	93·3%	95·9%	97·3%
(9)	Senegal	**228**	**42**	23	75	2·8%	5·3%	6·8%	11·9%	13·3%	16·7%	29·7%	47·1%	60·2%	84·5%	92·0%	95·1%	96·7%
(55)	South Africa	**216**	**27**	18	41	2·0%	5·0%	7·0%	15·4%	17·9%	24·1%	47·8%	72·5%	84·8%	97·1%	99·0%	99·5%	99·7%
(9)	Tajikistan	**1395**	**42**	30	59	0·2%	0·6%	0·9%	2·6%	3·3%	5·2%	16·9%	43·2%	66·0%	94·9%	98·6%	99·4%	99·7%
(28)	Uzbekistan	**1081**	**50**	32	77	0·5%	1·2%	1·8%	4·0%	4·7%	6·6%	16·4%	35·1%	52·7%	86·3%	94·6%	97·3%	98·4%
(9)	Yemen	**1068**	**37**	25	57	0·8%	2·2%	3·1%	7·1%	8·4%	11·8%	27·8%	52·6%	70·1%	93·5%	97·6%	98·9%	99·4%
High mortality (median)		**536**	**43**	28	68	0·5%	1·3%	1·9%	4·7%	5·7%	8·3%	22·2%	43·9%	60·6%	90·9%	97·1%	98·6%	99·2%
(9)	Afghanistan	**4628**	**36**	24	55	0·9%	2·4%	3·4%	7·9%	9·3%	12·9%	29·8%	54·8%	71·9%	93·9%	97·8%	98·9%	99·4%
(9)	Benin	**125**	**37**	28	50	0·1%	0·5%	0·8%	2·7%	3·5%	5·7%	21·2%	54·3%	77·3%	97·7%	99·5%	99·8%	99·9%
(9)	Cameroon	**1263**	**31**	20	48	1·8%	4·2%	5·9%	12·6%	14·6%	19·5%	39·7%	64·0%	78·3%	95·2%	98·2%	99·1%	99·5%
(9)	Central African Republic	**293**	**31**	21	44	0·7%	2·2%	3·4%	8·7%	10·5%	15·3%	37·9%	67·4%	83·0%	97·5%	99·3%	99·7%	99·8%
(9)	Côte d'Ivoire	**82**	**37**	26	53	0·4%	1·2%	1·9%	5·0%	6·1%	9·1%	25·6%	54·0%	73·7%	95·8%	98·7%	99·5%	99·7%
(21)	DR Congo	**272**	**36**	26	51	0·3%	1·0%	1·5%	4·4%	5·4%	8·4%	25·3%	55·5%	75·9%	96·7%	99·1%	99·6%	99·8%
(9)	DR Congo	**1750**	**33**	23	48	0·5%	1·5%	2·3%	6·3%	7·7%	11·6%	31·5%	61·8%	79·8%	97·1%	99·2%	99·7%	99·8%
(9)	Ethiopia	**518**	**50**	30	81	0·9%	2·1%	2·8%	5·7%	6·6%	8·9%	19·3%	37·0%	52·6%	83·7%	92·7%	96·0%	97·5%
(10)	Gambia	**86**	**50**	34	74	0·3%	0·7%	1·0%	2·7%	3·2%	4·8%	13·5%	32·9%	52·5%	88·6%	96·1%	98·2%	99·0%
(9)	Ghana	**1133**	**39**	25	61	1·0%	2·5%	3·5%	7·6%	8·9%	12·2%	27·3%	50·3%	67·1%	91·8%	96·8%	98·4%	99·1%
(9)	Guinea-Bissau	**443**	**40**	25	63	1·0%	2·5%	3·5%	7·5%	8·8%	11·9%	26·5%	48·8%	65·5%	91·0%	96·4%	98·2%	98·9%
(9)	Lesotho	**86**	**38**	26	57	0·5%	1·5%	2·2%	5·4%	6·5%	9·5%	24·8%	51·0%	70·1%	94·3%	98·1%	99·2%	99·6%
(31)	Malawi	**807**	**31**	21	48	1·3%	3·2%	4·7%	10·6%	12·4%	17·2%	37·7%	63·8%	79·0%	95·9%	98·6%	99·3%	99·6%
(49)	Nigeria	**49**	**40**	26	62	0·8%	2·0%	2·8%	6·4%	7·5%	10·5%	24·7%	47·8%	65·5%	91·7%	96·9%	98·5%	99·1%
(9)	Nigeria	**1336**	**39**	27	58	0·5%	1·3%	2·0%	5·0%	6·0%	8·8%	23·5%	49·2%	68·7%	94·0%	98·0%	99·1%	99·5%
(9)	Pakistan	**3276**	**37**	21	63	2·4%	5·0%	6·6%	12·3%	13·9%	17·8%	33·2%	53·3%	67·2%	89·4%	95·1%	97·2%	98·2%
(9)	Rwanda	**123**	**47**	31	72	0·5%	1·2%	1·8%	4·1%	4·9%	6·9%	17·6%	37·9%	56·2%	88·6%	95·7%	97·9%	98·8%

(9)	Sierra Leone	**74**	**39**	24	63	1·4%	3·2%	4·4%	8·9%	10·3%	13·7%	28·5%	50·0%	65·8%	90·2%	95·9%	97·8%	98·7%
(9)	Sudan	**4077**	**39**	25	59	0·8%	2·1%	3·0%	6·9%	8·1%	11·4%	26·6%	50·6%	68·1%	92·7%	97·3%	98·7%	99·2%
(9)	Swaziland	**138**	**35**	22	56	1·4%	3·4%	4·7%	10·0%	11·5%	15·6%	32·7%	56·1%	71·8%	93·0%	97·2%	98·6%	99·2%
(9)	Tanzania	**66**	**37**	26	53	0·4%	1·3%	2·0%	5·2%	6·3%	9·4%	25·9%	53·9%	73·4%	95·6%	98·7%	99·4%	99·7%
(9)	Togo	**293**	**36**	23	58	1·5%	3·4%	4·6%	9·7%	11·2%	15·0%	31·3%	54·0%	69·7%	92·1%	96·8%	98·3%	99·0%
(20)	Uganda	**263**	**41**	29	58	0·2%	0·6%	1·0%	2·9%	3·6%	5·7%	18·4%	45·6%	68·0%	95·3%	98·7%	99·5%	99·7%
(9)	Uganda	**211**	**44**	30	63	0·2%	0·7%	1·1%	3·0%	3·7%	5·6%	17·0%	41·5%	63·1%	93·4%	98·0%	99·2%	99·6%
(9)	Zambia	**2149**	**29**	19	46	1·9%	4·6%	6·5%	13·7%	15·9%	21·3%	42·5%	66·9%	80·5%	95·8%	98·4%	99·2%	99·6%
(9)	Zimbabwe	**2601**	**39**	25	60	0·9%	2·2%	3·2%	7·1%	8·4%	11·6%	26·7%	50·2%	67·5%	92·2%	97·1%	98·5%	99·2%
Very high mortality (median)		**293**	**38**	25	58	0·8%	2·1%	2·9%	6·6%	7·9%	11·5%	26·5%	52·1%	69·2%	93·7%	97·9%	99·0%	99·4%

Appendix Table S3. Goodness of fit statistics, goodness of fit criteria and best-fitting parameters of Log Logistic age distributions fitted to age distributions for rotavirus-positive hospital admissions <5 years in different countries

Study characteristics			Period		Shape			Scale			COR	Goodness of fit statistics and criteria						
Ref	Country	Age grps. (n)	From	To	Est.	L95	U95	Est.	L95	U95		RMSE	MAE	KS	CV	AD	AIC	BIC
Very low / low mortality																		
(41)	Australia	31	1984	1985	2·31	1·71	2·91	66·87	52·71	80·99	0·0953	5%	4%	0·14	0·17	1·72	468	472
(57)	Bulgaria	44	2005	2011	2·27	2·19	2·35	64·64	62·56	66·71	0·0442	2%	1%	0·06	1·17	11·61	23250	23262
(52)	Chile	95	2007	2010	2·17	2·05	2·29	48·82	46·35	51·33	0·0464	3%	2%	0·05	0·50	4·13	9530	9539
(23)	Hong Kong	60	1997	2011	2·14	2·11	2·17	69·28	68·31	70·24	0·0428	2%	2%	0·06	4·89	66·91	142364	142379
(42)	Hong Kong	56	2014	2015	2·40	2·04	2·76	84·17	73·51	94·86	0·0419	2%	2%	0·07	0·05	0·86	1357	1362
(10)	France	100	2007	2016	1·77	1·73	1·80	42·74	41·82	43·66	0·0618	3%	2%	0·05	5·88	56·62	81992	82006
(40)	France	20	1997	2000	1·83	1·70	1·97	26·65	24·38	28·92	0·0253	3%	3%	0·06	0·25	2·33	4389	4397
(9)	Georgia	74	2012	2012	2·33	1·97	2·68	66·68	57·29	76·11	0·0326	5%	3%	0·08	0·10	0·73	1170	1176
(10)	Hungary	100	2006	2016	2·19	2·11	2·28	85·82	82·69	88·93	0·0570	3%	2%	0·08	1·41	15·58	20349	20360
(22)	Italy	98	2009	2016	2·16	2·05	2·27	76·90	73·09	80·72	0·0654	2%	2%	0·07	0·85	8·84	11013	11023
(59)	Italy	99	2013	2016	1·70	1·64	1·76	62·12	59·63	64·64	0·0928	4%	3%	0·08	3·97	40·34	26657	26668
(37)	Japan	32	2004	2006	2·54	2·00	3·08	73·43	60·36	86·47	0·0360	3%	2%	0·10	0·07	0·46	620	624
(10)	Netherlands	95	2007	2016	1·68	1·57	1·78	47·72	44·16	51·28	0·0756	4%	3%	0·07	0·92	10·73	7432	7441
(39)	New Zealand	57	1998	2000	2·44	2·27	2·61	55·47	52·20	58·74	0·0410	3%	2%	0·10	0·51	5·02	5631	5640
(9)	Oman	51	2008	2010	2·75	2·59	2·92	52·59	50·20	54·99	-0·0222	5%	3%	0·10	0·64	3·46	7208	7218
(54)	Russia	98	2005	2007	2·25	2·12	2·38	58·26	55·20	61·33	0·0122	3%	2%	0·04	0·22	2·57	8540	8550
(9)	Seychelles	85	2013	2016	2·19	1·87	2·51	61·97	53·24	70·71	0·0123	3%	2%	0·06	0·06	0·45	1308	1314
(10)	Slovenia	99	2007	2016	2·64	2·55	2·73	88·33	85·94	90·72	0·0424	2%	2%	0·06	0·73	12·08	24287	24299
(9)	Sri Lanka	90	2014	2016	3·10	2·69	3·51	65·40	59·56	71·24	-0·0358	4%	3%	0·08	0·18	1·08	1548	1554
(36)	Switzerland	96	2002	2006	2·14	2·00	2·29	64·09	59·95	68·26	0·0352	1%	1%	0·05	0·17	2·85	6260	6269
(9)	Ukraine	258	2012	2016	2·52	2·46	2·57	101·17	99·26	103·08	0·0538	4%	3%	0·09	6·84	55·95	59369	59382
Medium mortality																		
(9)	Armenia	193	2012	2012	2·80	2·64	2·97	76·32	72·98	79·66	0·0056	2%	1%	0·04	0·17	1·77	8244	8254
(9)	China	180	2014	2016	2·46	2·33	2·58	51·68	49·56	53·84	0·0446	3%	2%	0·05	0·75	6·82	10792	10801
(9)	Egypt	35	2008	2010	2·57	2·41	2·74	34·36	32·60	36·11	0·0227	1%	1%	0·06	0·37	2·42	6095	6104
(46)	Iran	33	2008	2010	2·42	2·18	2·66	47·21	43·25	51·15	0·0033	1%	1%	0·05	0·12	1·07	2729	2736
(47)	Iran	34	2008	2009	1·94	1·59	2·28	50·22	41·01	59·45	0·0349	2%	2%	0·10	0·11	0·93	919	924
(9)	Iran	47	2008	2010	2·42	2·29	2·55	45·92	43·85	47·98	-0·0049	3%	2%	0·07	0·42	2·68	9466	9476
(9)	Jordan	34	2008	2012	2·45	2·23	2·67	32·26	29·84	34·69	0·0349	2%	1%	0·07	0·25	1·78	3068	3075
(28)	Kazakhstan	98	2007	2009	2·44	2·35	2·54	46·19	44·78	47·59	0·0344	2%	1%	0·05	1·21	9·24	19849	19860
(9)	Mauritius	174	2010	2014	2·44	2·24	2·66	84·02	77·80	90·25	0·0348	2%	2%	0·06	0·17	1·77	3896	3904
(9)	Mongolia	138	2013	2016	2·94	2·81	3·07	37·97	36·82	39·14	0·0433	2%	1%	0·05	0·79	6·10	12914	12925
(9)	Syria	32	2008	2013	2·70	2·56	2·83	35·09	33·79	36·38	0·0274	1%	1%	0·06	0·65	5·69	10512	10522
(9)	Tunisia	31	2008	2010	2·55	2·17	2·93	39·80	34·90	44·71	-0·0177	3%	2%	0·08	0·09	0·53	1123	1129
(27)	Venezuela	57	2003	2003	2·41	2·02	2·80	42·05	36·18	47·94	0·0125	1%	1%	0·04	0·02	0·15	990	995
(9)	Vietnam	232	2012	2016	2·87	2·80	2·94	51·80	50·91	52·70	0·0091	1%	1%	0·02	0·30	4·50	45154	45167

High mortality																		
(9)	Azerbaijan	206	2012	2016	2·37	2·22	2·52	71·04	66·96	75·09	0·0249	2%	2%	0·05	0·30	2·72	6886	6895
(19)	Bangladesh	35	2012	2012	1·82	1·64	1·99	35·35	31·58	39·12	0·0406	7%	4%	0·12	0·57	3·95	2922	2929
(10)	Bangladesh	57	2007	2010	3·50	3·08	3·92	53·32	49·61	57·02	-0·0004	1%	1%	0·05	0·06	0·40	1811	1817
(33)	Bangladesh	81	2000	2006	3·57	3·44	3·70	45·04	44·09	46·00	0·0103	1%	1%	0·05	0·67	3·80	18307	18318
(56)	Bangladesh	42	2012	2017	3·93	3·84	4·03	47·67	47·08	48·27	0·0207	1%	1%	0·07	2·64	16·03	42899	42912
(9)	Cambodia	178	2013	2016	3·00	2·89	3·10	48·31	47·11	49·50	0·0085	1%	1%	0·02	0·08	0·92	19968	19979
(9)	Eritrea	74	2013	2013	2·33	1·97	2·68	66·67	57·27	76·08	0·0333	5%	3%	0·08	0·10	0·74	1170	1175
(24)	Guatemala	46	2007	2009	2·13	1·76	2·49	46·81	38·99	54·65	0·0885	6%	4%	0·09	0·18	1·43	914	919
(10)	India	55	2007	2010	3·68	3·22	4·14	51·67	48·07	55·28	-0·0167	1%	1%	0·05	0·04	0·29	1615	1621
(34)	India	19	2005	2007	2·34	2·20	2·49	43·28	40·95	45·60	0·0438	3%	2%	0·10	0·94	7·14	6866	6875
(44)	India	28	2011	2012	3·04	2·33	3·76	54·09	46·11	62·06	0·0161	4%	3%	0·09	0·12	0·96	511	515
(48)	Indonesia	27	2013	2013	2·61	2·16	3·07	48·22	41·52	54·91	0·0020	2%	2%	0·08	0·06	0·33	867	872
(9)	Indonesia	175	2014	2016	2·51	2·35	2·66	60·43	57·34	63·50	0·0117	2%	1%	0·03	0·09	1·36	7326	7335
(9)	Iraq	48	2008	2011	2·25	2·16	2·34	31·64	30·51	32·76	0·0001	2%	2%	0·06	0·80	5·31	16585	16596
(43)	Kenya	43	2009	2014	2·81	2·59	3·04	40·63	38·31	42·95	-0·0089	3%	2%	0·08	0·36	2·46	4025	4033
(45)	Kenya	34	2009	2011	2·50	2·22	2·77	25·97	23·70	28·26	-0·0601	3%	2%	0·13	0·63	3·74	2049	2056
(51)	Kenya	61	2005	2007	2·76	2·44	3·09	33·20	30·28	36·10	0·0060	3%	2%	0·07	0·08	0·51	1756	1763
(53)	Kenya	77	2002	2004	2·96	2·76	3·16	41·81	39·84	43·79	0·0262	1%	1%	0·05	0·21	1·27	5439	5448
(9)	Kenya	148	2008	2013	2·34	2·19	2·50	39·50	37·21	41·77	-0·0082	1%	1%	0·03	0·10	0·76	6103	6111
(9)	Lao	137	2013	2016	2·99	2·77	3·21	56·44	53·49	59·40	-0·0164	2%	2%	0·04	0·18	1·26	4755	4763
(9)	Libya	38	2008	2013	2·52	2·37	2·68	37·75	35·85	39·61	0·0120	2%	1%	0·07	0·36	2·43	6732	6741
(9)	Madagascar	38	2013	2013	2·95	2·30	3·60	37·78	32·23	43·33	0·0366	3%	2%	0·09	0·07	0·63	529	533
(25)	Morocco	34	2006	2009	2·15	2·00	2·29	36·10	33·73	38·45	0·0060	3%	2%	0·06	0·26	1·85	5592	5601
(9)	Morocco	38	2008	2009	2·10	1·94	2·26	43·07	39·76	46·36	-0·0029	2%	2%	0·07	0·29	2·12	4502	4510
(9)	Myanmar	143	2014	2016	3·20	3·02	3·37	49·52	47·79	51·24	0·0160	1%	1%	0·03	0·10	0·84	8695	8705
(9)	Nepal	36	2014	2016	1·85	1·71	1·98	37·63	34·68	40·57	0·0517	4%	3%	0·08	0·50	5·21	5303	5311
(9)	Senegal	111	2009	2014	1·84	1·64	2·04	41·51	36·43	46·59	0·0638	4%	3%	0·08	0·24	2·10	2294	2301
(55)	South Africa	20	2003	2004	2·61	2·32	2·90	26·88	24·52	29·25	0·0076	4%	3%	0·08	0·18	1·07	1875	1882
(9)	Tajikistan	156	2012	2014	3·25	3·11	3·40	42·42	41·24	43·60	0·0055	1%	1%	0·03	0·25	1·41	12760	12770
(28)	Uzbekistan	92	2008	2009	2·50	2·38	2·63	49·82	47·78	51·87	0·0333	1%	1%	0·05	0·41	3·44	10716	10726
(9)	Yemen	38	2008	2011	2·61	2·47	2·74	37·48	36·00	38·96	0·0235	2%	2%	0·07	0·59	4·56	9919	9929
Very high mortality																		
(9)	Afghanistan	46	2008	2016	2·59	2·53	2·65	36·19	35·49	36·89	0·0095	3%	2%	0·08	3·12	18·70	42811	42823
(9)	Benin	56	2013	2016	3·66	3·11	4·22	37·21	34·20	40·21	-0·0311	5%	4%	0·09	0·15	1·03	1094	1100
(9)	Cameroon	132	2008	2013	2·45	2·34	2·57	30·85	29·66	32·03	0·0290	2%	1%	0·04	0·42	4·04	11374	11385
(9)	C. Afr. Rep.	74	2011	2016	3·00	2·71	3·29	30·63	28·63	32·63	0·0187	1%	1%	0·05	0·08	0·72	2532	2539
(9)	Côte d'Ivoire	52	2010	2016	3·03	2·48	3·58	37·00	32·43	41·57	0·0446	3%	2%	0·07	0·10	0·57	739	744
(21)	DR Congo	24	2012	2013	3·22	2·90	3·54	36·39	34·09	38·71	0·0433	3%	2%	0·08	0·25	1·94	2395	2402
(9)	DR Congo	123	2009	2016	3·10	2·98	3·22	33·41	32·54	34·28	0·0246	1%	1%	0·03	0·30	3·00	15253	15264
(9)	Ethiopia	49	2008	2013	2·21	2·05	2·37	49·61	46·26	52·95	0·0064	2%	2%	0·04	0·12	1·31	5267	5275
(10)	Gambia	43	2007	2010	2·82	2·31	3·32	50·19	43·73	56·64	0·0419	4%	3%	0·07	0·06	0·54	838	843
(9)	Ghana	145	2009	2011	2·45	2·33	2·57	38·83	37·23	40·42	0·0363	2%	1%	0·04	0·28	3·18	10707	10717
(9)	Guinea-Bis.	120	2010	2013	2·40	2·22	2·59	39·79	37·12	42·47	0·0393	3%	2%	0·04	0·16	1·46	4223	4231
(9)	Lesotho	51	2013	2016	2·83	2·32	3·33	38·47	33·52	43·41	0·0420	2%	2%	0·06	0·06	0·43	793	798
(31)	Malawi	58	1997	2007	2·64	2·48	2·79	31·43	30·01	32·85	0·0320	2%	1%	0·08	0·42	4·28	7169	7178
(49)	Nigeria	19	2012	2013	2·54	1·95	3·13	40·36	32·60	48·12	0·0458	4%	3%	0·11	0·06	0·49	466	470
(9)	Nigeria	152	2010	2016	2·84	2·71	2·97	39·43	38·15	40·71	0·0143	1%	1%	0·03	0·21	1·57	12343	12354

(9)	Pakistan	53	2008	2016	2·05	1·99	2·10	36·59	35·53	37·66	0·0241	1%	1%	0·05	1·40	11·92	31740	31752
(9)	Rwanda	74	2010	2011	2·59	2·20	2·98	47·20	41·78	52·64	0·0439	3%	2%	0·06	0·13	1·52	1199	1205
(9)	Sierra Leone	26	2013	2013	2·27	1·82	2·71	38·99	32·40	45·58	0·0195	6%	5%	0·12	0·14	0·89	717	722
(9)	Sudan	47	2008	2010	2·56	2·50	2·63	38·65	37·86	39·45	0·0227	2%	1%	0·07	2·49	15·96	38282	38294
(9)	Swaziland	69	2013	2014	2·39	2·05	2·73	35·18	30·95	39·41	0·0606	3%	2%	0·10	0·24	1·46	1284	1290
(9)	Tanzania	45	2009	2012	2·98	2·37	3·60	37·01	31·96	42·06	0·0078	5%	3%	0·09	0·07	0·47	601	606
(9)	Togo	97	2009	2013	2·34	2·11	2·57	36·40	33·38	39·44	0·0341	2%	2%	0·05	0·13	1·57	2759	2766
(20)	Uganda	25	2012	2012	3·24	2·91	3·57	41·19	38·53	43·83	0·0263	3%	2%	0·07	0·18	1·33	2382	2389
(9)	Uganda	84	2015	2016	3·06	2·71	3·41	43·64	40·35	46·94	0·0290	3%	2%	0·05	0·10	0·90	1961	1968
(9)	Zambia	135	2008	2013	2·48	2·39	2·57	29·35	28·49	30·21	0·0490	3%	2%	0·05	1·13	10·37	19026	19038
(9)	Zimbabwe	190	2009	2013	2·51	2·43	2·60	38·86	37·84	39·88	0·0226	1%	1%	0·03	0·37	3·68	24521	24533

COR: Correlation coefficient between fitted shape and scale parameters

Goodness of fit statistics and criteria: RMSE = Root Mean Squared Error, MAE = Mean Absolute Error, KS = Kolmogorov-Smirnov statistic; CV= Cramer-von Mises statistic; AD= Anderson-Darling statistic; AIC = Akaike's Information Criterion; BIC = Bayesian Information Criterion.

Regression models to predict scale and shape parameters of the Log Logistic distribution

Independent variables considered

- 5 mortality strata (v low, low, medium, high, v high)
- 3 mortality strata (v low and low, medium, high and v high)
- 2 mortality strata (v low/ + low; medium + high + v high)
- WHO regions (6)
- WHO Choice mortality strata/subregions (14)
- Mid-year of data collection period (1980-1999, 2000-2004, 2005-2009, 2010-2014, 2015-2018).
- Presentation: clinic visits, community cases, emergency visits, hospital admissions.
- Access to skilled delivery: 0-35%, 36-44%, 45-54%, 55-64%, 65-94%, 95-100%.
- GDP per capita in 2011

Datasets considered

A. all 117 studies
B. 110 studies excluding 7 of emergency admissions
C. 106 studies excluding 7 of emergency admissions and 4 with midyear of data collection between 1980 and 1999.
D. 103 studies excluding 7 of emergency admissions, 4 with midyear of data collection between 1980 and 1999, and 3[1] with no data on GDP

Appendix Table S4: Summary of alternative models for the Scale (median age) parameter

Model	Data	Independent variables	df	Akaike's Information Criterion	Adjusted R^2 (Scale)
1	A	14 WHO Choice mortality sub-regions	13	919.8	41.5%
2	A	5 mortality strata	4	920.7	36.8%
3	B	5 mortality strata	4	861.3	40.8%
4	C	5 mortality strata	4	815.9	47.6%
5	D	5 mortality strata	5	794.4	43.8%
6	D	6 WHO regions and 2 mortality strata	6	793.9	45.7%
7	D	6 WHO regions and 3 mortality strata	7	784.2	50.5%
8	D	6 WHO regions and 5 mortality strata	9	787.5	49.8%
9	D	6 WHO regions and 3 mortality strata, with interactions	15	777.0	56.9%
10	D	5 mortality strata and GDPpc2011	5	784.4	49.5%
11	D	6 WHO regions & 3 mortality strata with interactions, and GDPpc2011	16	765.4	61.8%

[1] 1 study from the Seychelles and 2 from Hong Kong. The Seychelles is the only country in the AFRO region in the Low or Very Low mortality strata.

By comparing models 2 to 5 in this table it can be seen that selecting less heterogeneous sets of studies for analysis resulted in better fits.

Using D, the most restricted dataset, it can then be seen that models 9 and 11 provide the best fit, in terms of both AIC and adjusted R-square. However they involve large numbers of predictors relative to the numbers of observations, including one for the mid strata and one for the high strata in each region, risking overfitting. For several combinations of stratum and region of the coefficient depends on only one data point, and for 2 combinations there is no data point.

Model 5, in which the predicted value of the scale parameter for a country is simply the mean of the scale parameters for all studies in that country's mortality stratum, provides a moderately good fit with few predictors, and is worth considering for its simplicity.

Model 7 is superior to model 5 (likelihood ratio test p = 0.1%) and so is Model 10 (LR test p = 0.05%). There is no evidence that model 10 is superior to model 7 in terms of fit (LR test p = 12%) but model 10 involves fewer predictors.

For the Shape parameter, restricting the analysis to dataset D again improved the fit for the simple mortality strata model in terms of AIC (116.9 for model 5compared to 131.2 for model 2) but not in terms of adjusted R-squared (12.8% compared to 15.0%). However none of the models tried was good. For example model 7 gave R-square 16.9% and AIC 114.8.

Appendix Table S5: Selected regression models for estimating the scale parameter of the Log Logistic age distribution

		Model 5			Model 7			Model 10		
R-Sq		46.0%			53.90%			52.00%		
adjusted R-sq		43.8%			49.8%			49.5%		
AIC		794.4			787.5			784.4		
		group n	*coeff*	*p*	*group n*	*coeff*	*p*	*group n*	*coeff*	*p*
Constant			70.16	0.000		55.53	0.000		91.09	0.000
GDP per capita									-0.0006	0.001
mortality	Very low	11	0.00					11	0.00	
	Low	8	-6.22	0.234	19	0.00		8	-21.93	0.001
	Mid	15	-22.12	0.000	15	-9.58	0.032	15	-40.15	0.000
	High	38	-25.36	0.000	69	-15.31	0.000	38	-45.17	0.000
	Very high	31	-31.39	0.000				31	-51.80	0.000
region	AFR				37	0.00				
	AMR				4	2.69	0.638			
	EMR				18	-3.92	0.240			
	EUR				19	14.99	0.001			
	SEAR				18	6.53	0.035			
	WPR				7	6.50	0.183			

			Model 11		
R-Sq			67.80%		
adjusted R-sq			61.8%		
AIC			765.4		
			group n	*coeff*	*p*
Constant				52.82	0.000
GDP				-0.0004	0.001
region/	AFR	Low	0	-	
mortality		Mid	1	34.76	0.003
		High	36	-13.23	0.052
	AMR	Low	1	1.83	0.873
		Mid	1	-6.39	0.575
		High	2	-0.62	0.947
	EMR	Low	1	9.97	0.394
		Mid	7	-10.50	0.160
		High	10	-14.58	0.044
	EUR	Low	14	29.17	0.000
		Mid	2	11.38	0.222
		High	3	2.87	0.734
	SEAR	Low	2	8.45	0.362
		Mid	0	-	
		High	16	-5.22	0.452
	WPR	Low	1	39.18	0.002
		Mid	4	-4.49	0.576
		High	2	0.00	

Appendix Table S6: Age distributions for rotavirus-positive community cases aged <5 years before the introduction of rotavirus vaccination: median, interquartile range and cumulative age distribution*

Reference	Country	n	50th pc.	25th pc.	75th pc.	6w	2m	10w	14w	15w	4m	6m	9m	12m	24m	36m	48m	60m
(12)	Bangladesh	**143**	**44**	31	61	0·2%	0·5%	0·8%	2·4%	2·9%	4·7%	15·6%	41·1%	64·1%	94·6%	98·5%	99·4%	99·7%
(12)	India	**40**	**43**	29	65	0·5%	1·3%	2·0%	4·7%	5·6%	8·0%	20·5%	43·3%	62·3%	91·4%	96·9%	98·5%	99·2%
(58)	India	**282**	**37**	19	70	4·4%	7·9%	9·8%	16·2%	17·9%	21·7%	35·6%	52·4%	64·2%	85·4%	92·1%	95·0%	96·5%
(15)	Mexico	**89**	**28**	17	46	3·1%	6·7%	9·0%	17·3%	19·6%	25·2%	45·5%	67·4%	79·8%	94·9%	97·9%	98·9%	99·3%
(12)	Nepal	**71**	**50**	35	70	0·1%	0·4%	0·6%	1·8%	2·3%	3·6%	11·6%	32·0%	53·8%	91·1%	97·4%	98·9%	99·5%
(12)	Pakistan	**71**	**37**	25	56	0·7%	2·0%	2·8%	6·7%	8·0%	11·3%	27·4%	52·7%	70·7%	93·9%	97·9%	99·0%	99·4%
	Median	**80**	**40**	27	63	0·6%	1·7%	2·4%	5·7%	6·8%	9·7%	23·9%	47·9%	64·2%	92·6%	97·6%	98·9%	99·4%

*These age distributions are likely to be biased to younger ages because all of the data used for the fitting was based on children aged <2 years.

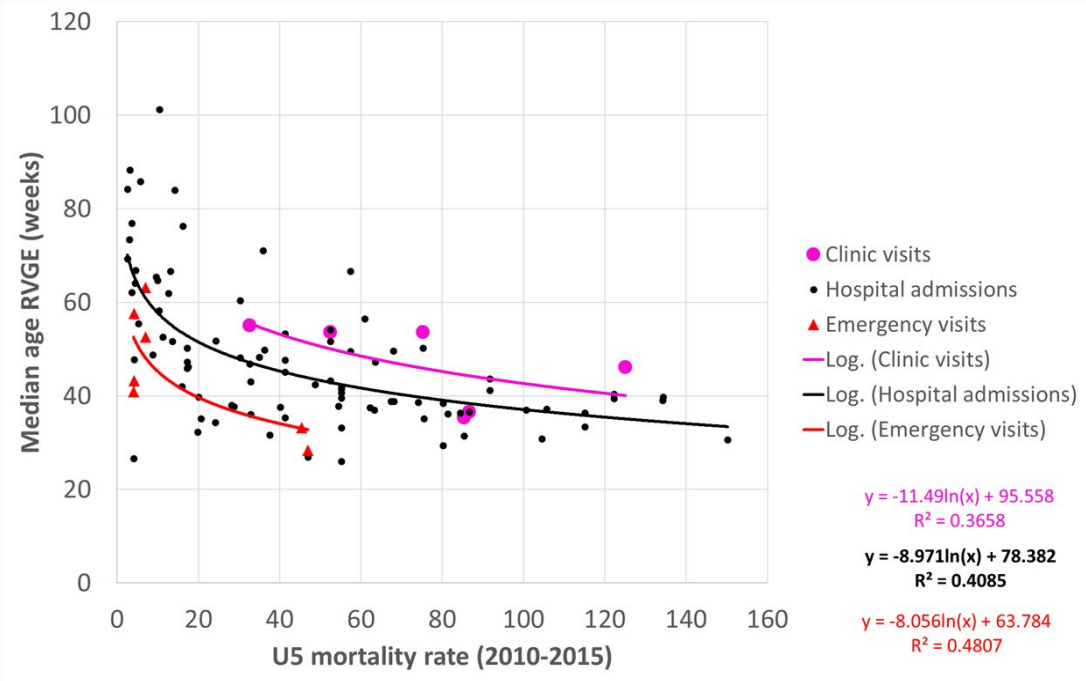
Appendix Table S7: Age distributions for rotavirus-positive clinic visits aged <5 years before the introduction of rotavirus vaccination: median, interquartile range and cumulative age distribution

Reference	Country	n	50th pc.	25th pc.	75th pc.	6w	2m	10w	14w	15w	4m	6m	9m	12m	24m	36m	48m	60m
(50)	China	**224**	**46**	29	72	0·7%	1·8%	2·5%	5·4%	6·4%	8·8%	20·4%	40·6%	57·8%	88·0%	95·1%	97·5%	98·5%
(11)	Gambia	**119**	**54**	37	78	0·2%	0·5%	0·7%	1·9%	2·4%	3·6%	10·8%	28·3%	47·8%	87·4%	95·8%	98·1%	99·0%
(35)	Germany	**1244**	**58**	33	101	1·1%	2·2%	2·9%	5·5%	6·3%	8·2%	16·8%	31·2%	44·6%	76·2%	87·8%	92·7%	95·2%
(24)	Guatemala	**56**	**55**	36	84	0·3%	0·8%	1·2%	2·8%	3·4%	4·8%	12·6%	29·1%	46·4%	83·8%	93·6%	96·9%	98·2%
(3)	Hungary	**229**	**96**	57	163	0·3%	0·6%	0·8%	1·7%	1·9%	2·6%	6·0%	12·9%	21·4%	53·9%	73·3%	83·4%	89·0%
(11)	India	**222**	**54**	36	79	0·2%	0·5%	0·8%	2·1%	2·5%	3·8%	11·2%	28·7%	47·9%	87·0%	95·5%	98·0%	98·9%
(11)	Kenya	**183**	**40**	26	61	0·8%	2·0%	2·8%	6·4%	7·6%	10·6%	25·2%	48·8%	66·6%	92·2%	97·1%	98·6%	99·2%
(31)	Malawi	**446**	**35**	25	51	0·5%	1·4%	2·2%	5·7%	7·0%	10·4%	28·3%	57·4%	76·3%	96·3%	98·9%	99·5%	99·8%
(11)	Mali	**275**	**46**	31	69	0·4%	1·0%	1·5%	3·7%	4·5%	6·5%	17·4%	38·8%	58·1%	90·1%	96·5%	98·4%	99·1%
(11)	Pakistan	**226**	**37**	25	54	0·6%	1·7%	2·5%	6·2%	7·5%	10·8%	27·6%	54·5%	72·9%	95·0%	98·4%	99·3%	99·6%
(3)	Slovenia	**79**	**76**	50	116	0·1%	0·3%	0·5%	1·2%	1·4%	2·0%	5·6%	14·7%	26·9%	69·4%	86·8%	93·3%	96·2%
(30)	Thailand	**41**	**54**	33	88	0·7%	1·7%	2·3%	4·7%	5·4%	7·3%	16·4%	32·6%	47·9%	81·2%	91·5%	95·3%	97·1%
	Median	**223**	**54**	33	78	0·4%	1·2%	1·8%	4·2%	4·9%	6·9%	16·6%	31·9%	47·9%	87·2%	95·3%	97·7%	98·7%

Appendix Table S8: Age distributions for rotavirus-positive emergency visits aged <5 years before the introduction of rotavirus vaccination: median, interquartile range and cumulative age distribution

Reference	Country	n	50th pc.	25th pc.	75th pc.	6w	2m	10w	14w	15w	4m	6m	9m	12m	24m	36m	48m	60m
(29)	France	**9127**	**41**	21	78	3·7%	6·6%	8·3%	13·9%	15·3%	18·8%	31·6%	48·0%	60·1%	83·1%	90·7%	94·1%	95·9%
(18)	Israel	**1245**	**43**	28	67	0·6%	1·6%	2·3%	5·3%	6·3%	8·9%	21·5%	43·4%	61·5%	90·3%	96·3%	98·2%	99·0%
(32)	Namibia	**119**	**33**	18	61	4·4%	8·2%	10·4%	17·5%	19·4%	23·8%	39·2%	57·2%	69·1%	88·6%	94·1%	96·4%	97·6%
(10)	Netherlands	**95**	**58**	36	92	0·5%	1·2%	1·7%	3·6%	4·2%	5·7%	13·5%	28·7%	44·0%	79·8%	91·1%	95·2%	97·1%
(55)	South Africa	**48**	**28**	16	52	5·5%	10·2%	12·8%	21·5%	23·7%	28·8%	46·0%	64·2%	75·2%	91·6%	95·8%	97·5%	98·3%
(26)	USA	**101**	**63**	41	98	0·3%	0·7%	1·0%	2·3%	2·7%	3·9%	9·9%	23·2%	38·1%	77·5%	90·4%	95·1%	97·1%
(38)	USA	**78**	**53**	32	87	0·9%	1·9%	2·6%	5·3%	6·1%	8·1%	17·7%	34·3%	49·4%	81·6%	91·5%	95·3%	97·1%
	Median	**101**	**43**	28	78	0·9%	1·9%	2·6%	5·3%	6·3%	8·9%	21·5%	43·4%	60·1%	83·1%	91·5%	95·3%	97·1%

Appendix Figure S3: Median age of rotavirus disease before the introduction of rotavirus, by type of presentation and national under-five mortality rate



We did not include community cases in this analysis because the data were only available up to two years of age, compared to five years for other presentations.

List of references (Chapter 5)

1. Clark A, Black R, Tate J, Roose A, Kotloff K, Lam D, et al. Estimating global, regional and national rotavirus deaths in children aged <5 years: Current approaches, new analyses and proposed improvements. PLOS ONE. 2017;12:e0183392.

2. Pneumonia and Diarrhea Progress Report 2017: Pushing Progress through Investment & Action. Available from: https://www.jhsph.edu/research/centers-and-institutes/ivac/resources/IVAC-2017-%0APneumonia-Diarrhea-Progress-Report.pdf. 2017.

3. Kirkwood CD, Ma L-F, Carey ME, Steele AD. The rotavirus vaccine development pipeline. Vaccine. 2017.

4. Lamberti LM, Ashraf S, Walker CLF, Black RE. A Systematic Review of the Effect of Rotavirus Vaccination on Diarrhea Outcomes Among Children Younger Than 5 Years. The Pediatric Infectious Disease Journal. 2016;35:992-8.

5. Bines JE, At Thobari J, Satria CD, Handley A, Watts E, Cowley D, et al. Human Neonatal Rotavirus Vaccine (RV3-BB) to Target Rotavirus from Birth. New England Journal of Medicine. 2018;378:719-30.

6. Burnett E, Lopman BA, Parashar UD. Potential for a booster dose of rotavirus vaccine to further reduce diarrhea mortality. Vaccine. 2017;35(51):7198-203.

7. Haidara FC, Tapia MD, Sow SO, Doumbia M, Coulibaly F, Diallo F, et al. Evaluation of a Booster Dose of Pentavalent Rotavirus Vaccine Coadministered With Measles, Yellow Fever, and Meningitis A Vaccines in 9-Month-Old Malian Infants. J Infect Dis. 2018;218(4):606-13.

8. Sanderson C, Clark A, Taylor D, Bolanos B. Global review of rotavirus morbidity and mortality data by age and region. 2012.

9. WHO. Rotavirus laboratory network. Available at: http://www.who.int/immunization/monitoring_surveillance/burden/laboratory/Rotavirus/en/ [Accessed 31st August 2018]. 2018.

10. Hungerford D, Vivancos R, Read JM, Pitzer VE, Cunliffe N, French N, et al. In-season and out-of-season variation of rotavirus genotype distribution and age of infection across 12 European countries before the introduction of routine vaccination, 2007/08 to 2012/13. Eurosurveillance. 2016;21.

11. Kotloff KL, Nataro JP, Blackwelder WC, Nasrin D, Farag TH, Panchalingam S, et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): A prospective, case-control study. The Lancet. 2013;382:209-22.

12. Platts-Mills JA, Babji S, Bodhidatta L, Gratz J, Haque R, Havt A, et al. Pathogen-specific burdens of community diarrhoea in developing countries: A multisite birth cohort study (MAL-ED). The Lancet Global Health. 2015;3.

13. WHO, UNICEF. WHO/UNICEF Estimates of National Immunization Coverage. 2017.

14. UNWPP. The 2017 Revision of the United Nations World Population Prospects. Available at: https://esa.un.org/unpd/wpp/. [Accessed 7th February 2018].

15. Velázquez FR, Matson DO, Calva JJ, Guerrero ML, Morrow AL, Carter-Campbell S, et al. Rotavirus Infection in Infants as Protection against Subsequent Infections. New England Journal of Medicine. 1996;335:1022-8.

16. Gladstone BP, Ramani S, Mukhopadhya I, Muliyil J, Sarkar R, Rehman AM, et al. Protective effect of natural rotavirus infection in an Indian birth cohort. The New England journal of medicine. 2011.

17. Patel M, Glass RI, Jiang B, Santosham M, Lopman B, Parashar U. A systematic review of anti-rotavirus serum IgA antibody titer as a potential correlate of rotavirus vaccine efficacy. Journal of Infectious Diseases. 2013.

18. Leshem E, Givon-Lavi N, Tate JE, Greenberg D, Parashar UD, Dagan R. Real-World Effectiveness of Pentavalent Rotavirus Vaccine among Bedouin and Jewish Children in Southern Israel. Clinical Infectious Diseases. 2016;62:S155-S60.

19. Arif MT, Asm NUA, Rajesh A, Belal H, Mahfuza M, Shampa S, et al. Rotavirus surveillance at a who-coordinated invasive bacterial disease surveillance site in Bangladesh: A feasibility study to integrate two surveillance systems. PLoS ONE. 2016;11.

20. Bwogi J, Malamba S, Kigozi B, Namuwulya P, Tushabe P, Kiguli S, et al. The epidemiology of rotavirus disease in under-five-year-old children hospitalized with acute diarrhea in central Uganda, 2012-2013. Arch Virol. 2016;161(4):999-1003.

21. Mayindou G, Ngokana B, Sidibé A, Moundélé V, Koukouikila-Koussounda F, Christevy Vouvoungui J, et al. Molecular epidemiology and surveillance of circulating rotavirus and adenovirus in Congolese children with gastroenteritis. Journal of Medical Virology. 2016;88:596-605.

22. De Grazia S, Bonura F, Colomba C, Cascio A, Di Bernardo F, Collura A, et al. Data mining from a 27-years rotavirus surveillance in Palermo, Italy. Infection, Genetics and Evolution. 2014;28:377-84.

23. Chiang GPK, Nelson EAS, Pang TJHS, Law SK, Goggins W, Chan JYC, et al. Rotavirus incidence in hospitalised Hong Kong children: 1 July 1997 to 31 March 2011. Vaccine. 2014;32:1700-6.

24. Estévez A, Arvelo W, Hall AJ, López MR, López B, Reyes L, et al. Prevalence and genetic diversity of norovirus among patients with acute diarrhea in Guatemala. Journal of Medical Virology. 2013;85:1293-8.

25. Benhafid M, Elomari N, Elqazoui M, Meryem AI, Rguig A, Filali-Maltouf A, et al. Diversity of rotavirus strains circulating in children under 5 years of age admitted to hospital for acute gastroenteritis in morocco, june 2006 to may 2009. Journal of Medical Virology. 2013;85:354-62.

26. Denno DM, Shaikh N, Stapp JR, Qin X, Hutter CM, Hoffman V, et al. Diarrhea etiology in a pediatric emergency department: A case control study. Clinical Infectious Diseases. 2012;55:897-904.

27. González GG, Liprandi F, Ludert JE. Molecular epidemiology of enteric viruses in children with sporadic gastroenteritis in Valencia, Venezuela. Journal of Medical Virology. 2011;83:1972-82.

28. Latipov R, Utegenova E, Kuatbayeva A, Kasymbekova K, Abdykarimov S, Juraev R, et al. Epidemiology and burden of rotavirus disease in Central Asia. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2011;15:e464-9.

29. de Rougemont A, Kaplon J, Fremy C, Legrand-Guillien MC, Minoui-Tran A, Payan C, et al. Clinical severity and molecular characteristics of circulating and emerging rotaviruses in young children attending hospital emergency departments in France. Clinical Microbiology and Infection. 2016;22:737.e9-.e15.

30. Bodhidatta L., McDaniel P., Sornsakrin S., Srijan A., Serichantalergs O. Case-control study of diarrheal disease etiology in a remote rural area in western Thailand. American Journal of Tropical Medicine and Hygiene. 2010;83:1106-9.

31. Cunliffe NA, Ngwira BM, Dove W, Thindwa BD, Turner AM, Broadhead RL, et al. Epidemiology of rotavirus infection in children in Blantyre, Malawi, 1997-2007. J Infect Dis. 2010;202 Suppl:S168-74.

32. Page N, Pager C, Steele AD. Characterization of Rotavirus Strains Detected in Windhoek, Namibia during 1998–1999. The Journal of Infectious Diseases. 2010;202:S162-S7.

33. Zaman K, Yunus M, Faruque ASG, Arifeen SE, Hossain I, Azim T, et al. Surveillance of rotavirus in a rural diarrhoea treatment centre in Bangladesh, 2000-2006. Vaccine. 2009;27.

34. Kang G, Arora R, Chitambar Shobha D, Deshpande J, Gupte MD, Kulkarni M, et al. Multicenter, Hospital-Based Surveillance of Rotavirus Disease and Strains among Indian Children Aged <5 Years. The Journal of Infectious Diseases. 2009;200:S147-S53.

35. Karsten C, Baumgarte S, Friedrich AW, Von Eiff C, Becker K, Wosniok W, et al. Incidence and risk factors for community-acquired acute gastroenteritis in north-west Germany in 2004. European Journal of Clinical Microbiology and Infectious Diseases. 2009;28:935-43.

36. Wildi-Runge S, Allemann S, Schaad UB, Heininger U. A 4-year study on clinical characteristics of children hospitalized with rotavirus gastroenteritis. European Journal of Pediatrics. 2009;168:1343-8.

37. Sugata K, Taniguchi K, Yui A, Miyake F, Suga S, Asano Y, et al. Analysis of Rotavirus Antigenemia and Extraintestinal Manifestations in Children With Rotavirus Gastroenteritis. PEDIATRICS. 2008;122:392-7.

38. Klein EJ, Boster DR, Stapp JR, Wells JG, Qin X, Clausen CR, et al. Diarrhea etiology in a Children's Hospital Emergency Department: a prospective cohort study. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2006;43:807-13.

39. Grimwood K, Huang QS, Cohet C, Gosling IA, Hook SM, Teele DW, et al. Rotavirus hospitalisation in New Zealand children under 3 years of age. Journal of Paediatrics and Child Health. 2006;42:196-203.

40. Moulin F, Marc E, Lorrot M, Coquery S, Sauve-Martin H, Ravilly S, et al. [Hospitalization for acute community-acquired rotavirus gastroenteritis: a 4-year survey]. Arch Pediatr. 2002;9:255-61.

41. Coulson BS, Grimwood K, Masendycz PJ, Lund JS, Mermelstein N, Bishop RF, et al. Comparison of rotavirus immunoglobulin A coproconversion with other indices of rotavirus

infection in a longitudinal study in childhood. Journal of Clinical Microbiology. 1990;28:1367-74.

42. Yeung KHT, Tate JE, Chan CC, Chan MCW, Chan PKS, Poon KH, et al. Rotavirus vaccine effectiveness in Hong Kong children. Vaccine. 2016.

43. Wandera EA, Mohammad S, Komoto S, Maeno Y, Nyangao J, Ide T, et al. Molecular epidemiology of rotavirus gastroenteritis in Central Kenya before vaccine introduction, 2009–2014. Journal of Medical Virology. 2017;89:809-17.

44. Kar S, Pattnaik D, Das SC, Pharveen I. Prospective hospital-based surveillance to estimate the burden of rotavirus gastroenteritis in children less than five years in Bhubaneswar. Clinical Epidemiology and Global Health. 2014;2:52-5.

45. Kiulia NM, Nyaga MM, Seheri ML, Wolfaardt M, Van Zyl WB, Esona MD, et al. Rotavirus G and P types circulating in the eastern region of Kenya: Predominance of G9 and emergence of G12 genotypes. Pediatric Infectious Disease Journal. 2014;33.

46. Motamedifar M, Amini E, Talezadeh Shirazi P. Frequency of Rotavirus and Adenovirus Gastroenteritis Among Children in Shiraz, Iran. Iranian Red Crescent Medical Journal. 2013;15:729-33.

47. Najafi A., Najafi S., Vahdat K., Kargar M., Javdani N. Importance of viral pathogens in children with acute gastroenteritis in the south of Iran. Annals of Saudi Medicine. 2013;33:124-9.

48. Sudarmo SM, Shigemura K, Athiyyah AF, Osawa K, Wardana OP, Darma A, et al. Genotyping and clinical factors in pediatric diarrhea caused by rotaviruses: One-year surveillance in Surabaya, Indonesia. Gut Pathogens. 2015;7.

49. Uzoma EB, Chukwubuikem C, Omoyibo E, Tagbo O. Rota virus genotypes and the clinical severity of Diarrhoea among children under 5 years of age. Niger Postgrad Med J. 2016;23(1):1-5.

50. Zhang S, Yin J, Yang J, Tian L, Li D, Zhang Q, et al. Epidemiology and genetic diversity of group A rotavirus in acute diarrhea patients in pre-vaccination era in southwest China. Journal of Medical Virology. 2017;89:71-8.

51. O'Reilly CE, Jaron P, Ochieng B, Nyaguara A, Tate JE, Parsons MB, et al. Risk factors for death among children less than 5 years old hospitalized with diarrhea in rural Western Kenya, 2005-2007: A cohort study. PLoS Medicine. 2012;9.

52. Díaz J, Pérez Rodríguez A, Olea A, Gonzalez C, Galeno H, Soto F, et al. Sistema de Vigilancia de Rotavirus en Hospitales Centinelas en Chile. Rev Cubana Med Trop. 2009;61:5-12.

53. Nokes DJ, Abwao J, Pamba A, Peenze I, Dewar J, Maghenda JK, et al. Incidence and clinical characteristics of group A rotavirus infections among children admitted to hospital in Kilifi, Kenya. PLoS Med. 2008;5(7):e153.

54. Podkolzin AT, Fenske EB, Abramycheva NY, Shipulin GA, Sagalova OI, Mazepa VN, et al. Hospital-Based Surveillance of Rotavirus and Other Viral Agents of Diarrhea in Children and Adults in Russia, 2005–2007. The Journal of Infectious Diseases. 2009;200:S228-S33.

55. Seheri LM, Page N, Dewar JB, Geyer A, Nemarude AL, Bos P, et al. Characterization and Molecular Epidemiology of Rotavirus Strains Recovered in Northern Pretoria, South Africa during 2003–2006. The Journal of Infectious Diseases. 2010;202:S139-S47.

56. Satter SM, Gastanaduy PA, Islam K, Rahman M, Rahman M, Luby SP, et al. Hospital-based surveillance for rotavirus gastroenteritis among young children in Bangladesh: Defining the potential impact of a rotavirus vaccine program. Pediatric Infectious Disease Journal. 2017;36:168-72.

57. Mladenova Z, Steyer A, Steyer AF, Ganesh B, Petrov P, Tchervenjakova T, et al. Aetiology of acute paediatric gastroenteritis in Bulgaria during summer months: Prevalence of viral infections. Journal of Medical Microbiology. 2015;64:272-82.

58. Mehendale S, Venkatasubramanian S, Girish Kumar CP, Kang G, Gupte MD, Arora R. Expanded Indian national rotavirus surveillance network in the context of rotavirus vaccine introduction. Indian Pediatrics. 2016;53:575-81.

59. Ianiro G, Delogu R, Fiore L, Monini M, Ruggeri FM, Pagani E, et al. Group A rotavirus genotypes in hospital-acquired gastroenteritis in Italy, 2012–14. Journal of Hospital Infection. 2017;96:262-7.

6.0 Chapter 6 - Estimation of rotavirus vaccine coverage and timeliness

6.1 Contribution of paper to the aim and objectives of the thesis

This paper was published prior to registration of the research degree but provides important background to the household survey data and survival analysis methods used to calculate coverage and timeliness of vaccination in different LMICs. The paper was published in the Lancet. As the Lancet is not an open access journal, it is included in this chapter in its final draft post-refereeing, rather than in the publisher's final format. The appendix to the paper is also included in this format, at the end of the thesis (Appendix 5).

Vaccine timeliness is required to calculate vaccine impact in each week of age. It can also be used to calculate the number of new doses administered in each week of age, and thus allows for more precise estimation of the potential intussusception risks in each week of age.

The survival analysis in the publication was done by Colin Sanderson using USAID Demographic and Health Survey (DHS) data. Since this paper was published, Colin has expanded the database to include UNICEF Multiple Indicator Cluster Surveys (MICs) and has updated the estimates periodically. For the updated benefit-risk analysis (Chapter 9), Colin shared estimates of country-specific coverage rates derived from survival analysis of 73 nationally representative household surveys. This included estimates of coverage at different ages up to age 3.0 years, for the following vaccines: BCG; DTP1; DTP2; DTP3; and, Meas1. To accommodate this data into the benefit-risk analysis, I fit parametric curves to the age-specific coverage estimates for each country/vaccine using maximum likelihood estimation (MLE). This allowed calculation of uncertainty intervals and provided a convenient basis for extrapolating timeliness curves to countries without household survey data. The methods and outputs of this analysis are described in more detail later in the chapter.

6.2 Independent academic contribution

In the published paper, I extracted the datasets, ran the first analysis, wrote the first draft and presented the work to WHO's Strategic Advisory Group of Experts (SAGE). Survival analyses were done by Colin Sanderson. For the new benefit-risk analysis (Chapter 9), Colin shared updated survival analyses, and I fit parametric curves to

these data. For the parametric fitting, I wrote the R code, tested goodness of fit for a range of distributions, and developed methods to extrapolate the curves to countries without data.

The timing of children's vaccinations in 45 low- and middle-income countries

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Summary

Background: Vaccinations are often delayed until well after the recommended ages, leaving many children exposed for longer than they should be. We estimated vaccination coverage at different ages, and delays in administration, in 45 low-income and middle-income countries.

Methods: We used data for 217 706 children from Demographic and Health Surveys between 1996 and 2005 (median 2002), which provided data for vaccination of children on the basis of events recorded on vaccination cards and interviews with mothers, with imputation of missing values and survival analysis. We devised an index combining coverage and delay.

Findings: For vaccinated children, the median of the median delays in the 45 countries was 2.3 weeks (IQR 1.4-4.6) for bacille Calmette-Guérin (BCG); 2.4 weeks (1.2-3.3) for diphtheria, tetanus, and pertussis (DTP1); 2.7 weeks (1.7-3.1) for measles-containing vaccine (MCV1); and 6.2 weeks (3.5-8.5) for DTP3. However, in the 12 countries with the longest delays for each vaccination, at least 25% of the children vaccinated were more than 10 weeks late for BCG, 8 weeks for DTP1, 11 weeks for MCV1, and 19 weeks for DTP3. Variation within countries was substantial: the median of the IQRs in the 45 countries for delay in DTP3 was 10.9 weeks, 7.9 weeks for MCV1, 5.4 weeks for BCG, and 5.3 weeks for DTP1. The median of the national coverage rates for DTP1 increased from 57% in children aged 12 weeks to 88% at 12 months, and for DTP3 from 65% at 12 months to 76% at 3 years.

Interpretation: The timeliness of children's vaccination varies widely between and particularly within countries, and published yearly estimates of national coverage do not capture these variations. Delayed vaccination could have important implications for the effect of new and established vaccines on the burden of disease.

Funding: WHO's Initiative for Vaccine Research.

Introduction

Late administration of vaccines has implications for the success of child immunisation programmes. Currently WHO/UNICEF (1) vaccination coverage estimates are based on the prevalence of vaccinated children in a given cohort (eg 12-23 months for DTP), or numbers of vaccinations in a given year divided by the number of surviving infants (or, for BCG, by the number of newborns). This throws very little light on the extent to which vaccinations are administered 'on time' (2). In practice a few children may be vaccinated early but many will be vaccinated late (3,4), and for some vaccines programme effectiveness may be reduced if children at high risk of exposure are left unprotected (5). On the other hand vaccination at older ages, or increased intervals between doses, can give more durable protection (6-9). Booster doses may offset the limitations of early doses in some respects, but at extra cost. Thus information about the actual timing of vaccination is needed to help policy makers monitor programmes and respond if need be. Two of the WHO/UNICEF Global Immunisation and Vision Strategies (GIVS) are to strengthen monitoring of coverage and strengthen the analysis of data (10), and improved surveillance of departures from 'age-appropriate' vaccination has been recommended in both low- and high-income settings (11-13).

There are also concerns about using current schedules as the basis for delivering new vaccines. For example it is uncertain whether new rotavirus vaccines will provide indirect protection to unvaccinated infants, and according to a WHO position paper, "vaccination should not be initiated for infants aged more than 12 weeks"(14), because of a potentially higher risk of intussusception, a rare bowel disorder. The implication is that the safety as well as the effectiveness of the programme may depend on timely administration.

Methods

The Demographic & Health Surveys (DHS)(15) provide representative data on vaccination of children, based on events recorded on vaccination cards and interviews with mothers. There were surveys in 52 countries between 1996 and 2005, and the most recent survey for each country was used. Seven were excluded, 4 with no data on days of the month of birth, 2 with fewer than 250 children with complete and valid data for calculating exact age at each vaccination, and 1 with non-standard recording of dates. For the remaining 45 the median survey year was 2002, and the median (IQR) national sample size of children less than 3 years old at the time of the mother's interview was 3,952 (3,012 to 6,043), with a range from 1,127 to 30,666.

At the time of these surveys 28 countries used the standard schedule for BCG (birth), Diphtheria-tetanus-pertussis vaccine and Oral polio vaccine (DTP/OPV: 6, 10, 14 weeks) and Measles-containing vaccine (MCV1: 9 months). Seven countries in South and Central America used birth, 2, 4, 6, and 12 months, and the others used local variants.

The survey data on child's month and year of birth were almost complete, but if the day of the month of birth was missing it was imputed. Vaccination cards were the primary source for vaccination dates. If the card was not available or a specific vaccination was not recorded, the mother was asked whether the child had been vaccinated. Ages at vaccination were imputed for cases in which the only evidence for vaccination was mother's recall, using separate regression analyses for each country to identify the necessary predictors. The website gives more details on imputation.

Age-specific coverage rates and delays after target ages were estimated using survival analysis methods(16,17) with sampling weights provided in the DHS datasets. Coverage at different ages and delays are closely linked, and a summary index was calculated from the area under the cumulative age-at-vaccination curve (the hatched area as a % of the rectangle CDEF in Figure 1). This is analogous to the Kaplan-Meier survival curve and indicates mean coverage between target age and 24 months, or 36 months for MCV1.

One way of improving coverage is to take opportunities to give children vaccinations that they have missed when they attend for others later in the schedule. The extent to which opportunities were being taken to give missed doses of DTP when children attend for MCV1, and vice versa, was examined. An opportunity was defined as, for a child at least 9 months old at the time, i) any dose of DTP if they had not yet had MCV1, or ii) MCV1 if they had not yet had all doses of DTP, conditional on no dose of DTP in the preceding 4 weeks. The opportunity was 'taken' if the child was given doses of DTP and MCV1 on the same date. This analysis was based on actual vaccination dates from cards, with no imputation.

Analyses were carried out using Stata version 10 (Stata Corp, College Station, Texas).

Role of the funding source

The World Health Organization's Initiative for Vaccine Research provided funding and comments on an earlier draft. They also suggested the work should be presented to the Strategic Advisory Group of Experts (SAGE) whose feedback informed this analysis.

Results

Data quality

Data quality was examined for all the children covered by the surveys. The older the children, the less likely they were to have a card record of their vaccination (Table 1). Also reported coverage (card plus mother's recall) dropped slightly as child's age at interview increased from 2 to 4 years, consistent with lower levels of reporting for more 'distant' events. Only data for children less than 36 months old when their mother was interviewed were included in the main analyses. In children aged 36 to 59 months the percentages of all vaccinations with a card date that were given after the age of 36 months were 0.7%, 1.0%, 1.5% and 3.3% for BCG, DTP1, DTP3 and MCV1 respectively.

Ages at vaccination

Figure 2 gives the distributions of ages at vaccination for the cohorts of children 18 to 35 months old at the time of the mother's interview, using card data only. This provides complete 'follow-up' to age 18 months (c 78 weeks) for all of the children. Each distribution has high peaks near or after target ages, followed by long tails to the right, indicating delays in vaccination in substantial proportions of children. The different peaks in the distributions for DTP and MCV reflect the two main target ages. The results for OPV1-3 were very similar to those for DTP1-3. These distributions should be interpreted as broad indicators of the nature rather than scale of the problem because each country's contribution is implicitly weighted by the size of its survey sample, and this is only very weakly related to population size. Also the data are from a variety of survey years.

Imputation

The predictors of delay used in the imputation were rural/urban residence, home or hospital birth, mother's years of education and age at birth, child's position in birth order and child's age at mother's interview. Gender was a significant independent predictor in only two countries and was not used.

Age-specific coverage rates

Table 2 gives medians, 25th and 75th percentiles across countries for coverage rates at different ages, and summary indices for different regions, using both card and imputed dates. Overall, the median of the country values for BCG coverage increased from 49% at 4 weeks to 89% at 12 months. Median coverage for DTP1 increased from 57% at 12 weeks to 82% at 6 months

and 91% at 3 years. Coverage for DTP3 increased from 65% at 12 months to 76% at 3 years, and MCV1 from 54% at 12 months to 82% at 3 years, so in both cases coverage at 12 months substantially underestimates final coverage. In general coverage for the 27 countries in the WHO AFRO region was lower than for the 9 countries in the AMRO region, although the highest 25% of AFRO countries were similar to the lowest 25% of the AMRO group, and much better for DTP1. In the other WHO regions the numbers of countries in the analysis were small.

Table 3 gives coverage rates for each national survey. 95% CIs are not shown but the standard errors of the percentages in the table can be summarised as follows: for BCG, mean 0.7% std 0.2%; for DTP1, mean 0.7% std 0.3%; for DTP3, mean 0.6% std 0.4%; and for MCV1, mean 0.5% std 0.5%. Thus the 95% CIs for the estimates of coverage were typically 1 to 1.5% above and below the figures given. Countries with generally very high coverage rates include Egypt, Peru, Rwanda and the Kyrgyz Republic. Countries with generally low rates include Chad, Nigeria and Yemen. Some countries had a marked drop-off in coverage between DTP1 and DTP3, including the Dominican Republic, Gabon, Guinea, Niger, Nigeria and Togo. In most countries over 30% of children were vaccinated at more than 12 weeks old, so under the existing safety guidelines would have been ineligible for rotavirus vaccine.

Delays after target ages

The website gives median, quartiles and inter-quartile ranges (IQRs) for delays for BCG, DTP1, DTP3 and MCV1 for each country. In Table 4 these parameters are summarised with median values across the 45 countries and 25th and 75th percentiles. For BCG for example, the median of the 45 country median delays was 2.3 weeks, the 25th percentile of the country medians was 1.4 weeks and the 75th percentile 4.6 weeks (so the median delay was more than this in a quarter of the countries). The distributions of median delays for DTP1 and MCV1 were broadly similar, but the delays for DTP3 were more than twice as long.

In 75% of the countries a quarter of the children were subject to delays of a week or less for DTP1 and MCV1, and just over a week for BCG, and so were vaccinated close to the scheduled ages. However the country-specific distributions of ages at vaccination had long tails. Thus for BCG the median of the 45 country-specific 75th percentile delays was 6.6 weeks compared to 2.3 weeks for the median of medians and 0.7 weeks for the median 25th percentile. The corresponding figures for DTP1 and MCV1 were broadly similar, and for DTP3 about double. For 25% of the countries surveyed, 25% of the children were at least 10, 8, 11 and 19 weeks late in being given BCG, DTP1, MCV1 and DTP3 respectively.

Opportunistic vaccination

The percentages of opportunities taken in each country to give DTP when a child was given MCV1 or vice versa are shown in the right-hand column of Table 3. These percentages tended to be higher in countries with lower coverage, which suggests that in general this strategy is making a useful contribution by giving a late boost to coverage rates that would otherwise have been even lower. However results from some countries went against this trend. For example in Gabon DTP3 coverage at 12m was 33% and opportunities taken 21%; in Nigeria, 24% and 22%.

Discussion

Variation between countries in vaccination coverage rates is widely reported. We have shown that coverage at 12 months underestimates final coverage, and that there is substantial variation within as well as between countries in adherence to the recommended schedules.

Our findings are based on survey data. How representative are they? Consistent DHS sampling methods and questionnaires were used in every country, but the survey years varied (1996-2005) so country-specific results are not strictly comparable. In terms of completeness of reporting, one problem was that there were no data on children that had died before the interview. The proportions of children affected varied from about 5% of children aged less than 1 year to about 7% of children aged less than 3 years and of course varied between countries. However it seems unlikely that the children who died will generally have had a better vaccination record that those who did not, so we may, if anything, have slightly underestimated the delays and overestimated the coverage. Incompleteness of data on surviving children is of more concern. Where possible the dates of vaccination were taken from record cards. However for 32% of vaccinations the evidence was mothers' recall, or a card with no information on the date. We imputed the missing values from the known dates of children from the same country survey who were similar in terms of local predictors of age at vaccination, in the belief that this would give a more accurate result than assuming that the vaccination experience of the children with missing dates was similar to the rest. This will not have eliminated information bias altogether, and its extent remains uncertain.

Our index attempts to capture both coverage and timeliness. The implicit weight given to the timeliness element depends on the age range covered; we chose up to 2 years for BCG and DTP, and up to 3 years for MCV1, these being the age ranges with a heavy burden of relevant mortality in low income countries. In this formulation there is no 'penalty' for vaccinating

children before target dates, but an adjustment could be made by subtracting the shaded % of the rectangle ABCF in Figure 1.

Countries as diverse as Egypt, Peru, Rwanda and the Kyrgyz Republic all have relatively high and timely coverage, and in most countries at least a quarter of the children are vaccinated close to the schedule. Prima facie this suggests that delays are not inevitable. However the scale of variation within countries is striking. There may be concerns about safety on the part of parents or care-givers or both, particularly if the child is unwell at the time the vaccination is due(18-19), but in a review of nine surveys 'lack of parental acceptance of immunisation' was given in a median of 3% of responses and 'was not an important reason for missed opportunities'. There will be accessibility, organisational and cultural factors; in almost all the countries in this study delays were more protracted in more rural areas. Coverage may have improved since the survey year in some areas, but this does not necessarily mean improvements in timeliness.

Do these delays matter? In principle, if schedules are designed to achieve a balance between effective protection at vulnerable ages, durable protection and vaccine safety, then adherence to schedules must matter too, but it is difficult to say how much. Others have made the case for more timely vaccination against pertussis (21), measles (22) and Haemophilus influenzae type b (Hib)(23). Delays may be unimportant in children protected indirectly by high and timely coverage of their contacts, but many children at high background risk of mortality and of vaccination delay will not benefit from herd effects of this kind.

Rotavirus vaccination (RV) is a topical case. It is currently scheduled with DTP, but in most of the countries in our study more than 30% of the children were past the WHO-recommended age window for RV when they were given DTP1. This may be a problem in more developed countries too, at least in some population groups (24); in a recent study from Philadelphia, Pennsylvania the figure was 23% (25). One possible scenario is strict adherence to the recommendation and no improvement in timeliness. This would compromise the impact of the RV programme. However according to the Global Advisory Committee on Vaccine Safety strict adherence would be "extremely difficult to implement in the field" in low income countries (26), and a more likely scenario is no improvement in timeliness and widespread violation of the recommended age window. This may compromise safety, although the evidence on level of risk in older children is weak. The WHO recommendation is based on experience of an earlier vaccine, *RotaShield (Wyeth-Ayerst)*, now withdrawn, which was linked to a rare bowel disorder when the first dose was administered to older infants [Rothman K, Young-Xu Y, Arellano F. Age dependence of the relation between reassortant rotavirus

vaccine (RotaShield) and intussusception. J Inf Dis 2006; 193: 898-9.]. Safety trials of the new vaccines did not address the effects of delayed vaccination, and while the authors of a recent study of post-marketing safety monitoring data from the US excluded an overall effect on the scale of RotaShield (27), it covered relatively few children with delayed first doses. Even if the new vaccines do carry an as yet undetected excess risk in older children, in high mortality settings broadening the age restriction may well represent a 'greater good' from a utilitarian perspective. The benefits and risks of decisions of this kind would have to be considered carefully and in context by policy makers, as will the implications for informing parents.

Improvement in timeliness on the other hand would improve RV programme effectiveness and reduce any residual risks to safety. Introducing RV might stimulate such improvements, and the rest of the vaccination programme would benefit. The problem is that the optimal ages for different vaccines may differ. Delays for Pneumococcal conjugate vaccine for example may be associated with more durable levels of individual protection (28), although the effect on programme effectiveness is unclear. On the other hand coverage and adherence to schedules may be improved and family as well as programme costs reduced by vaccinating against several pathogens at one visit (29). In this situation the design of the schedule should be based on a detailed assessment of a range of options.

Assessments of vaccination programmes are generally based on evidence from efficacy trials, in which children are vaccinated relatively close to the schedule. Applied to wider populations these are likely to be optimistic, and there is little evidence about the relative benefits of seeking to improve timeliness rather than say expanding final coverage. One approach might be to include different schedules in trials, but this would increase the sample sizes needed and there may be ethical issues. A second approach would be to gather data on the effectiveness of vaccines in countries (or areas within countries) with contrasting levels of delay. The challenge would be to design out or take account of the other factors involved such as differences in age-specific patterns of transmission, disease and antibody protection (30). A third approach would be to use computer simulation models. Ideally all three approaches would be used; they would inform each other and strengthen decision making on vaccine policy.

More generally, there is a need for monitoring and surveillance systems which allow for more detailed analyses of timeliness and coverage than are currently available.

Contributors

AC extracted the datasets, did the first analysis, wrote the first draft and presented the work to WHO's Strategic Advisory Group of Experts (SAGE). CS did the survival analysis and imputation, devised the coverage index, and wrote later drafts.

Conflict of interest statement

We declare that we have no conflict of interest.

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Table 1: Quality of data on DTP1, by child's age at interview, for surveys with data on children aged up to 5 years.

DTP1	*Child's age at interview (years)*					
	0	*1*	*2*	*3*	*4*	*Overall*
% with DTP1 not yet given	35.3%	14.2%	14.3%	15.4%	15.8%	19.1%
% given, recorded on card with date	46.8%	54.0%	44.9%	37.4%	33.0%	43.3%
recorded on card, no date	0.4%	0.8%	0.8%	0.9%	1.0%	0.8%
mother's recall only	12.3%	23.7%	30.9%	36.3%	39.7%	28.4%
% not known	0.2%	0.5%	0.6%	0.8%	1.0%	0.6%
No data[1]	5.0%	6.7%	8.5%	9.2%	9.5%	7.8%
Total numbers of children surveyed	69,859	67,858	66,713	67,903	66,734	339,067
% of those given DTP1 with card record of date[2]	78.7%	68.7%	58.6%	50.1%	44.8%	59.7%
Coverage among children with data	62.8%	84.7%	84.3%	82.9%	82.4%	79.10%

1. 91% of these were the children who had died before their mother's interview.
2. (number with card date)/(number with card date + card[no date] + mother's recall)

Table 2: Target ages and median, 25th and 75th percentiles for estimated coverage at different ages across 45 countries.

		BCG			*DTP1*			*DTP3*			*MCV1*		
			%iles			*%iles*			*%iles*			*%iles*	
		Median	*25th*	*75th*	*Median*	*25th*	*75th*	*Median*	*25th*	*75th*	*Median*	*25th*	*75th*
Target (weeks)		0	0	0	6	6	9	3.2	3.2	4	9	9	9
Coverage at	4w	49%	30%	70%									
	8w	69%	48%	81%	24%	8%	36%						
	12w	74%	62%	86%	57%	46%	70%						
	4m	82%	68%	90%	73%	60%	83%	10%	4%	22%			
	5m	84%	70%	90%	80%	64%	88%	27%	16%	42%			
	6m	85%	73%	91%	82%	67%	89%	36%	23%	54%			
	9m	87%	75%	92%	87%	75%	92%	59%	43%	72%	12%	10%	14%
	12m	89%	76%	93%	88%	73%	92%	65%	49%	79%	54%	37%	69%
	18m	90%	78%	94%	90%	75%	94%	72%	52%	83%	74%	58%	82%
	24m	90%	78%	94%	90%	76%	94%	74%	53%	84%	80%	62%	88%
	36m	91%	78%	95%	91%	76%	95%	76%	56%	85%	82%	66%	91%
Index	All countries	84%	73%	89%	84%	70%	89%	63%	45%	72%	74%	58%	83%
	AFRO[1]	83%	72%	86%	78%	67%	85%	58%	40%	68%	67%	56%	80%
	AMRO[2]	91%	87%	93%	91%	88%	93%	75%	55%	79%	83%	76%	87%

1. 27 countries covered by the WHO Regional Office for Africa
2. 9 countries covered by the WHO Regional Office for the Americas

Table 3: Variation between countries in estimated coverage for BCG, DTP1, DTP3 and MCV1; and in opportunities taken.

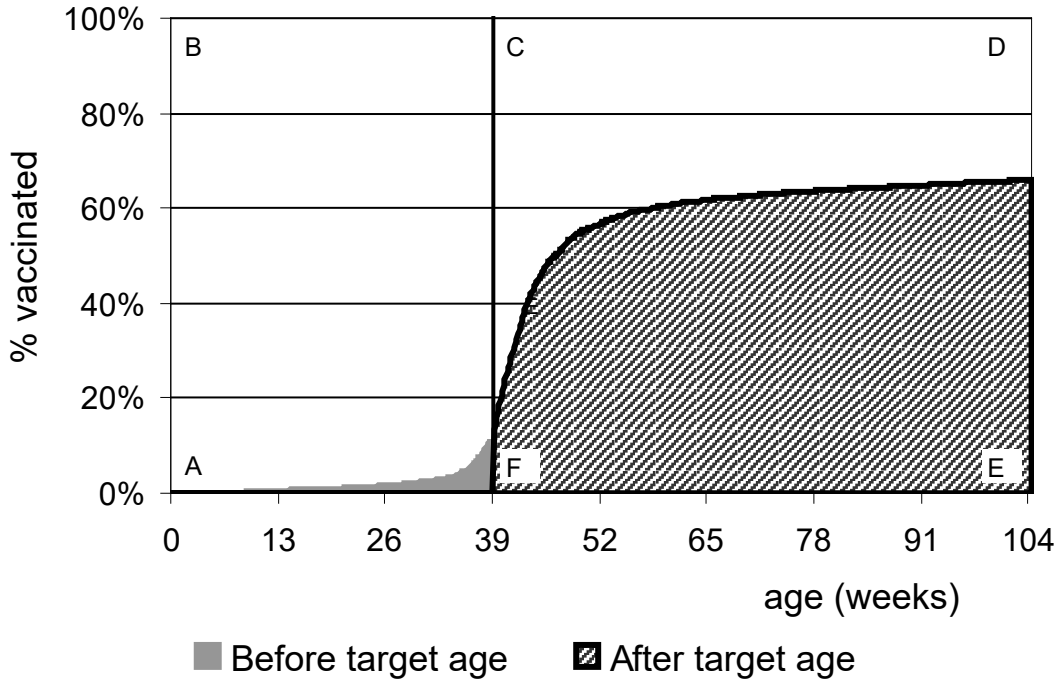
		BCG					DPT1					DPT3					MCV					Opps
		at 4w	*at 12w*	*at 6m*	*at 12m*	*Index*	*at 8w*	*at 12w*	*at 6m*	*at 12m*	*Index*	*at 6m*	*at 9m*	*at 12m*	*at 3yrs*	*Index*	*at 9m*	*at 12m*	*at 18m*	*at 3yrs*	*Index*	*taken*
Bangladesh	2004	8%	72%	90%	93%	85%	33%	71%	89%	92%	88%	57%	75%	80%	82%	72%	10%	69%	78%	80%	75%	43%
Benin	2001	75%	86%	89%	90%	89%	51%	72%	84%	87%	84%	52%	63%	69%	74%	65%	7%	60%	71%	74%	69%	66%
Bolivia	2003	59%	79%	87%	92%	88%	8%	54%	84%	92%	88%	12%	52%	65%	79%	65%	5%	15%	64%	90%	74%	22%
Brazil	1996	36%	80%	88%	91%	87%	3%	70%	89%	94%	91%	5%	68%	76%	89%	75%	9%	75%	89%	94%	87%	57%
Burkina	2003	42%	66%	72%	77%	73%	10%	43%	67%	73%	70%	30%	44%	50%	62%	48%	12%	47%	58%	67%	58%	37%
Cambodia	2000	19%	43%	56%	64%	59%	17%	35%	53%	61%	58%	23%	33%	38%	51%	38%	9%	39%	48%	62%	51%	62%
Cameroon	2004	49%	72%	80%	85%	80%	41%	61%	74%	80%	77%	48%	56%	60%	68%	57%	16%	58%	66%	71%	65%	53%
Chad	2004	13%	22%	29%	36%	33%	12%	17%	30%	39%	36%	8%	13%	16%	28%	16%	7%	15%	23%	30%	24%	65%
Colombia	2005	73%	88%	93%	96%	93%	5%	69%	92%	96%	93%	19%	72%	80%	89%	79%	44%	54%	86%	96%	89%	45%
Comoros	1996	56%	76%	85%	91%	86%	34%	57%	80%	88%	83%	34%	50%	61%	79%	58%	14%	48%	67%	85%	69%	69%
Congo	2005	65%	86%	89%	89%	87%	14%	61%	82%	84%	82%	55%	63%	66%	70%	63%	12%	59%	66%	73%	67%	20%
Côte d'Ivoire	1998	55%	71%	76%	80%	77%	30%	52%	71%	76%	73%	36%	46%	53%	66%	50%	14%	50%	67%	74%	66%	64%
Dominican Rep.	2002	71%	90%	93%	93%	91%	6%	63%	85%	91%	88%	26%	49%	54%	62%	55%	54%	74%	82%	95%	87%	27%
Egypt	2005	70%	96%	98%	98%	95%	11%	90%	98%	99%	97%	25%	93%	94%	95%	93%	25%	95%	96%	98%	96%	7%
Eritrea	2002	33%	67%	83%	89%	83%	43%	64%	82%	88%	84%	64%	74%	79%	85%	74%	24%	74%	82%	89%	83%	60%
Gabon	2000	56%	76%	84%	88%	84%	24%	41%	57%	63%	59%	23%	28%	33%	39%	30%	11%	46%	58%	66%	57%	21%
Ghana	2003	50%	78%	85%	88%	84%	37%	67%	85%	89%	85%	54%	69%	75%	81%	69%	19%	72%	83%	87%	81%	38%
Guatemala	1998	28%	55%	73%	82%	76%	7%	39%	76%	85%	81%	20%	43%	56%	81%	54%	10%	56%	75%	91%	76%	68%
Guinea	2005	61%	74%	77%	78%	76%	35%	55%	72%	74%	71%	36%	46%	49%	53%	45%	16%	46%	54%	59%	55%	50%
Haiti	2000	34%	56%	64%	69%	65%	28%	50%	66%	73%	70%	24%	35%	42%	56%	39%	10%	37%	52%	75%	57%	72%
Honduras	2005	71%	91%	97%	98%	95%	2%	83%	98%	99%	97%	8%	84%	92%	96%	88%	2%	12%	93%	97%	93%	17%
India	2005	30%	61%	73%	76%	71%	28%	54%	71%	73%	70%	40%	50%	54%	57%	50%	12%	53%	60%	64%	59%	18%
Kenya	2003	49%	77%	85%	87%	83%	48%	72%	86%	88%	86%	61%	68%	71%	74%	67%	20%	67%	74%	80%	74%	40%
Kyrgyz	1997	91%	95%	97%	98%	97%	6%	70%	93%	97%	94%	43%	83%	89%	96%	85%	1%	15%	89%	96%	90%	4%
Lesotho	2004	66%	88%	91%	92%	90%	58%	81%	89%	91%	89%	66%	76%	79%	85%	75%	7%	74%	84%	91%	84%	22%
Madagascar	2003	30%	60%	68%	72%	68%	36%	54%	67%	72%	69%	48%	57%	61%	66%	57%	12%	53%	58%	64%	58%	39%
Malawi	2004	28%	66%	84%	90%	83%	33%	64%	89%	93%	89%	52%	72%	79%	87%	72%	14%	69%	82%	88%	80%	34%
Mali	2001	33%	46%	56%	63%	60%	25%	36%	49%	57%	55%	22%	29%	34%	48%	33%	14%	37%	48%	61%	50%	65%
Mauritania	2000	30%	43%	50%	58%	55%	20%	34%	45%	53%	50%	21%	28%	31%	40%	30%	13%	35%	48%	58%	48%	30%
Morocco	2003	89%	96%	97%	98%	95%	63%	90%	95%	96%	94%	84%	90%	92%	95%	88%	14%	86%	90%	93%	89%	44%
Mozambique	2003	58%	74%	81%	84%	81%	6%	51%	78%	84%	78%	41%	59%	65%	76%	60%	16%	62%	74%	82%	74%	53%
Namibia	2000	79%	89%	90%	90%	89%	68%	82%	90%	91%	89%	65%	73%	76%	82%	72%	14%	74%	81%	89%	81%	42%
Nicaragua	2001	70%	86%	92%	94%	92%	4%	66%	89%	93%	91%	46%	66%	73%	88%	75%	4%	13%	80%	93%	83%	42%
Niger	1998	21%	36%	44%	46%	43%	14%	27%	39%	45%	42%	15%	22%	24%	28%	22%	12%	29%	37%	42%	37%	64%
Nigeria	2003	27%	41%	45%	48%	46%	18%	26%	36%	39%	38%	16%	19%	21%	25%	20%	10%	30%	36%	43%	37%	22%
Peru	2004	79%	94%	95%	96%	94%	3%	80%	95%	97%	95%	72%	80%	83%	88%	81%	1%	13%	83%	89%	83%	17%
Rwanda	2005	71%	94%	95%	96%	93%	62%	91%	95%	96%	94%	81%	86%	88%	89%	84%	10%	81%	87%	90%	85%	43%
Senegal	2005	49%	77%	87%	89%	84%	37%	67%	84%	90%	85%	56%	69%	72%	79%	68%	14%	63%	76%	80%	74%	51%
Tanzania	1999	59%	85%	91%	93%	89%	53%	75%	89%	92%	88%	60%	73%	80%	85%	72%	16%	74%	82%	84%	79%	55%
Togo	1998	48%	65%	73%	76%	73%	31%	49%	63%	69%	66%	28%	36%	42%	49%	39%	11%	36%	46%	52%	46%	55%
Turkey	1998	8%	66%	85%	87%	85%	3%	46%	81%	85%	81%	34%	53%	56%	63%	52%	11%	71%	81%	88%	80%	16%
Uganda	2000	30%	54%	69%	76%	71%	24%	44%	64%	74%	69%	27%	37%	44%	53%	41%	13%	49%	62%	68%	61%	77%
Uzbekistan	1996	90%	94%	95%	96%	95%	6%	48%	84%	94%	90%	40%	61%	73%	93%	72%	12%	63%	87%	99%	86%	19%
Yemen	1997	9%	35%	46%	50%	46%	18%	35%	47%	51%	48%	27%	35%	38%	42%	35%	14%	39%	44%	47%	44%	31%
Zambia	2001	38%	73%	86%	91%	85%	15%	51%	84%	91%	85%	43%	64%	74%	84%	67%	18%	69%	82%	92%	83%	46%

Table 4: Delay in vaccination (weeks): variation between and within countries

		BCG			*DTP1*			*DTP3*			*MCV1*		
		across 45 countries			*across 45 countries*			*across 45 countries*			*across 45 countries*		
		Median	*%iles*		*Median*	*%iles*		*Median*	*%iles*		*Median*	*%iles*	
			25th	*75th*		*25th*	*75th*		*25th*	*75th*		*25th*	*75th*
Across children in a country sample	*Median*	2.3	1.4	4.6	2.4	1.2	3.3	6.2	3.5	8.5	2.7	1.7	3.1
	25th %ile	0.7	0.3	1.3	0.6	0.3	1.0	2.7	1.4	3.5	0.1	-0.3	0.4
	75th %ile	6.6	4.3	10.3	6.3	3.7	8.3	13.5	9.0	19.1	7.6	5.3	11.0
	IQR	5.4	3.4	8.6	5.3	3.6	7.1	10.9	8.0	15.6	7.9	5.9	13.9

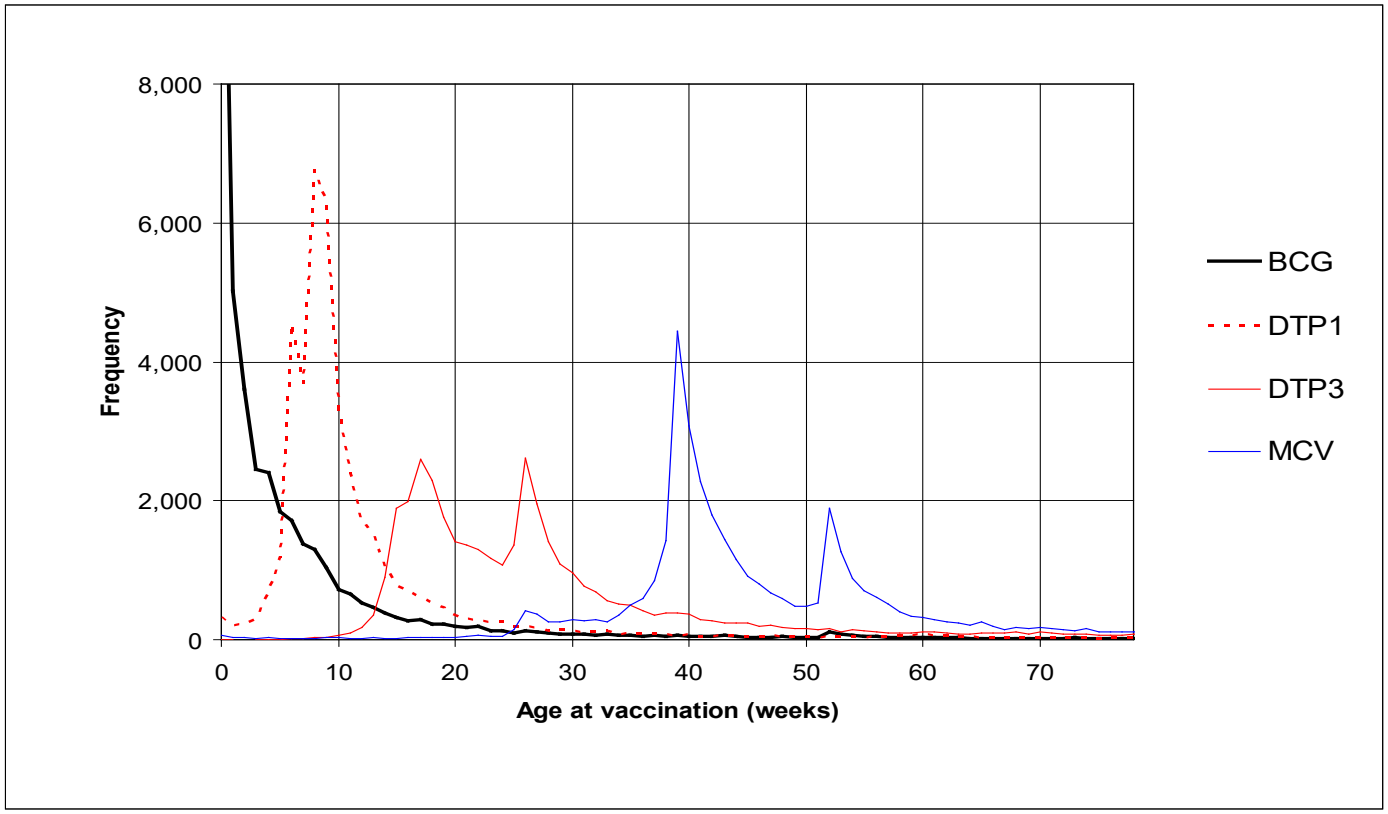
Negative values indicate vaccination before target date.

Figure 1: The plot of cumulative coverage against child's age, and calculation of the coverage index



The index is calculated from the shaded area after the target age as a % of the whole area CDEF.

Figure 2: Age distributions for administration of BCG, DTP1, DTP3 and MCV1 vaccines, based on card dates only among children aged 18-35.9m



List of references for published paper

1. WHO-UNICEF estimates of coverage, http://www.who.int/vaccines/globalsummary/immunization/timeseries/tswucoverageDTP3.htm (accessed 19 June 2008)

2. Luman E, Barker L, Shaw K, McCauley M, Buehler J, Pickering L. Timeliness of childhood vaccinations in the United States: days unvaccinated and number of vaccines delayed. JAMA 2005; 293: 1204-1211.

3. Mulholland K, Hilton S, Adegbola R, Usen S, Oparaugo A, Omosigho C et al. Randomised trial of Haemophilus influenzae type-b tetanus protein conjugate for prevention of pneumonia and meningitis in Gambian infants, The Lancet 1997; 349, 1191-1197.

4. Ndiritu M, Cowgill KD, Ismail A, Chiphatsi S, Kamau T, Fegen G et al, Immunization coverage and risk factors for failure to immunize within the Expanded Programme on Immunization in Kenya after introduction of new Haemophilus influenzae type b and hepatitis b virus antigens. BMC Public Health 2006; 6:132

5. Heiniger U, Zuberbuhler M. Immunization rates and timely administration in pre-school and school-aged children. Euro J Pediatr 2006; 165: 124-9.

6. Orenstein WA, Weisfeld JS, Halsey NA. Diphtheria and Tetanus Toxoids and Pertussis Vaccine, Combined [in Halsey NA, de Quadros CA, Recent Advances in Immunization. A Bibliographic Review. Scientific Publication No. 451, 1983]

7. Baraff LJ, Leake RD, Burstyn, DG, Payne T, Cody CL, Manclark CR, St Geme Jr, JW, Immunological Response to Early and Routine DTP Immunization in Infants, Paediatrics 1984;73: 37-42

8. Halsey NA, Galazka A. The efficacy of DTP and oral poliomyelitis immunization schedules initiated from birth to 12 weeks of age, WHO Bulletin 1985; 63: 1151-1169.

9. Belloni C, de Silvestri A, Tinelli C, Avanzini MA, Marconi M, Strano F, Rondini G, Chirico G, Immunogenicity of a Three-Component Acellular Pertussis Vaccine Administered at Birth, Paediatrics 2003;111: 1042-1045.

10. GIVS Global Immunization Vision and Strategy 2006-2015. http://www.who.int/vaccines-documents/DocsPDF05/GIVS_Final_EN.pdf (accessed 10 July 2007)

11. Domblowski KJ, Lantz PM, Freed GL. The need for surveillance of delay in age-appropriate immunization. Am J Prev Med 2002; 23: 36-42.

12. Akmatov MK, Kretzchmar, Kramer A, Mikolajczyk RT, Timeliness of vaccination and its effect on fraction of vaccinated population. Vaccine 2008; 26:3805-3811

13. Hull BP, McIntyre PB. Timeliness of childhood immunisation in Australia. Vaccine 2006; 24:4403-4408

14. Weekly epidemiological record, Rotavirus Position Paper, 2007, 82, 285-296, World Health Organisation, Geneva. http://www.who.int/wer/2007/wer8232.pdf (accessed 10th July 2007)

15. Demographic & Health Surveys, http:///www.measuredhs.com (accessed 10th July 2007)

16. Laubereau B, Hermann M, Schmitt HJ, Weil J, Von Kries R, Detection of delayed vaccinations: a new approach to visualize vaccine uptake. Epidemiol. Infect 2002; 128, 185-192

17. Dayan GH, Shaw KM, Baughman AL et al. Assessment of delay in age-appropriate vaccination using survival analysis. Am J Epidemiol 2006; 163: 561-670.

18. Abbotts B, Osborn LM. Immunization status and reasons for immunization delay among children using public health immunization clinics. Am J Dis Child 1993; 147: 965-968.

19. Kroger AT, Atkinson WL, Marcuse EK, Pickering LK, General Recommendations on Immunization, Recommendations of the Advisory Committee on Immunization Practices (ACIP), MMWR 2006; 55:1-48

20. Hutchins S, Jansen H, Robertson S. Missed opportunities for immunisation. Expanded Programme on Immunisation. WHO Geneva 1993.

21. Crowcroft NS, Stein C, Duclos P, Birmingham M. How best to estimate the global burden of pertussis? Lancet Infectious Diseases 2003; 3: 413-418

22. Dannetun E, Tegnell A, Hermansson G, Torner A, Giesecke J. Timeliness of MMR vaccination – influence on vaccination coverage. Vaccine 2004; 22: 4228-4232.

23. Von Kries R, Bohm O, Windfuhr A, Haemophilus influenzae b-vaccination: the urgency for timely vaccination. Eur J Pediatrics 1997; 156: 282-287.

24. Luman E, Barker L, McCauley M, Drews-Botch C. Timeliness of childhood immunisations: a state-specific analysis. Am J Publ Health 2005; 95 (8): 1367-74.

25. Daskalaki I, Spain CV, Long SS, Watson B, Implementation of Rotavirus Immunization in Philadelphia, Pennsylvania: High Levels of Vaccine Ineligibility and Off-Label Use. Pediatrics 2008; 122; e33-e38

26. Weekly epidemiological record, Global Advisory Committee on Vaccine Safety, 2006, 81, 13-20, World Health Organisation, Geneva. http://www.who.int/wer/2006/wer8101.pdf (accessed 10th July 2007)

27. Haber P, Patel M, Izurieta HS, et al. Postlicensure monitoring of intussusception after RotaTeq vaccination in the United States, February 1, 2006, to September 25, 2007. Pediatrics 2008;121(6):1206-12.

28. Barzilay EJ, O'Brien KL, Kwok YS, Hoekstra RM, Zell ER, Reid R, Santosham M, Whitney CG, Feikin DR, Could a single dose of pneumococcal conjugate vaccine in children be effective? Modeling the optimal age of vaccination, Vaccine 2006; 24: 904-913.

29. Kalies H, Grote V, Vestraeten T, Hessel L, Schmitt HJ, von Kries R. The use of combination vaccines has improved timeliness of vaccination in children. Pediatr Infect Dis J; 2006: 25(6): 507-12.

30. Funkhouser A, Wassilak S, Orenstein W, Hinman A, Mortimer E. Estimated effects of a delay in the recommended vaccination schedule for diphtheria and tetanus toxoids and pertussis vaccine. JAMA 1987; 257: 1341-1346.

6.3 Methods used to fit parametric vaccine timeliness curves in 135 LMICs

The research paper presented in this chapter used information from USAID Demographic and Health Surveys (DHS). This database has since been expanded to include UNICEF Multiple Indicator Cluster Surveys (MICs). The most recent database includes 73 nationally representative household surveys that were conducted in the last ten years (2009 or later) in LMICs. To accommodate this data into the benefit-risk analysis (Chapter 9), age-specific coverage estimates from survival analysis were converted into cumulative age distributions (% of final coverage at 3 years achieved at different ages) for BCG, DTP1, DTP2, DTP3 and Meas1. Parametric curves were then fitted to these cumulative age distributions using R version 3.4.0 (packages *MASS* and *fitdistrplus)*. Fitting parametric timeliness curves allowed each country/vaccine to be defined by a small number of parameters (e.g. shift, shape and scale) which could then be conveniently varied in scenario analysis e.g. to assess earlier or later target ages. It also allowed 95% confidence intervals to be calculated for each parameter and provided a convenient basis for extrapolating timeliness curves to countries without household survey data (around half of the 135 LMICs evaluated in the benefit-risk analysis).

For each country/vaccine, goodness of fit was compared for Lognormal, Gamma, Weibull and Log Logistic cumulative age distributions, using the Akaike Information Criterion (AIC). The Log Logistic distribution generally ranked the highest (had the lowest/most favourable AIC scores), so was used to calculate best-fitting shape and scale parameters, and their respective 95% confidence intervals, for all countries/vaccines (Tables 5-9)[1].

The Log Logistic age distribution is defined by a scale (α) and a shape (β) parameter. The scale parameter is the same as the median age. The proportion of children vaccinated within each week of age is calculated by the following equation, where x represents the age at the beginning of each week of age

$$\frac{(\beta/\alpha)(x/\alpha)^{\beta-1}}{(1+(x/\alpha)^{\beta})^2}$$

[1] Table numbers start at 5, and Figures at 3, for continuity with the research-paper presented earlier.

For countries without a recent household survey the target ages currently recommended for BCG, DTP1, DTP2, DTP3 and Meas1 were extracted from the official WHO schedules database (1). Parametric timeliness curves were assigned to these countries using the median of the Log Logistic scale and shape parameters for all other countries with the same schedule. This simple approach was used because the 0, 6, 10, 14 and 39-week schedule (for BCG, DTP1, DTP2, DTP3 and Meas1) tends to be used in similar (higher mortality) LMICs, whereas the 0, 2, 4, 6, 12-month schedule is more commonly used in lower mortality LMICs (Figures 3-7). This was also the most practical approach because some children are vaccinated earlier than the target age in many countries, making it difficult to standardise different timeliness curves to a common starting point, and then average them in a reliable way.

For countries with unique national schedules (target ages) and no household survey data, the median parametric timeliness curve for the closest matching target age was used for each vaccine. A shift parameter was added (difference between the target age of the country and the closest matching target age, in weeks) to ensure that extrapolated timeliness curves were aligned with the relevant national schedules.

For the benefit-risk analysis (Chapter 9), the fitted and extrapolated vaccine timeliness curves for each country were rescaled to reflect the coverage level estimated by WHO/UNICEF in the year 2015 (2).

Table 5. Median age (IQR - inter-quartile range) of BCG vaccination in 72 LMICs; fitted Log Logistic shape and scale parameters and AIC rank

Country	Survey	Target age (wks)	Sample size (n)	Shape			Scale (median age, wks)			IQR age, wks		Log Logistic AIC rank
				Mid	L95% CI	U95% CI	Mid	L95% CI	U95% CI	25th	75th	
Afghanistan	2011_MICS4	0.0	1444	**1.3**	1.2	1.4	**3.0**	2.8	3.2	1.3	7.0	2
Algeria	2013_MICS4	0.0	8230	**3.9**	3.8	3.9	**1.1**	1.1	1.2	0.9	1.5	1
Armenia	2010_DHS6	0.0	858	**7.7**	7.2	8.2	**1.0**	1.0	1.0	0.9	1.2	1
Bangladesh	2014_DHS7	0.0	3142	**2.9**	2.8	3.0	**6.6**	6.5	6.7	4.5	9.6	2
Belize	2011_MICS4	0.0	824	**1.9**	1.8	2.0	**3.2**	3.0	3.4	1.8	5.7	2
Benin	2011_DHS6	0.0	3248	**2.1**	2.1	2.2	**1.6**	1.6	1.7	1.0	2.7	1
Bosnia and Herzegovina	2012_MICS4	0.0	1059	**2.9**	2.7	3.1	**1.2**	1.2	1.2	0.8	1.8	1
Burkina Faso	2010_DHS6	0.0	3367	**2.1**	2.0	2.2	**2.1**	2.0	2.1	1.2	3.5	2
Burundi	2010_DHS6	0.0	1309	**2.4**	2.3	2.5	**2.5**	2.4	2.6	1.6	4.0	2
Cambodia	2014_DHS7	0.0	2077	**2.6**	2.5	2.7	**1.2**	1.2	1.3	0.8	1.9	1
Cameroon	2011_DHS6	0.0	1918	**1.7**	1.7	1.8	**2.8**	2.7	2.9	1.5	5.3	2
Central African Republic	2010_MICS4	0.0	1475	**1.8**	1.7	1.8	**2.1**	2.0	2.2	1.1	3.8	1
Chad	2010_MICS4	0.0	842	**1.4**	1.3	1.5	**5.8**	5.3	6.3	2.6	12.8	2
Colombia	2010_DHS6	0.0	7856	**3.6**	3.6	3.7	**1.1**	1.1	1.1	0.8	1.5	1
Comoros	2012_DHS6	0.0	1113	**2.4**	2.3	2.5	**1.4**	1.4	1.5	0.9	2.3	1
Congo	2011_DHS6	0.0	1443	**2.0**	1.9	2.1	**2.0**	1.9	2.1	1.2	3.5	2
Costa Rica	2011_MICS4	0.0	1271	**8.1**	7.6	8.5	**1.0**	1.0	1.0	0.9	1.2	1
Côte d'Ivoire	2011_DHS6	0.0	1395	**1.6**	1.5	1.7	**2.4**	2.3	2.6	1.2	4.9	1
Cuba	2014_MICS5	0.0	3214	**10.4**	10.0	10.7	**1.0**	1.0	1.0	0.9	1.1	1
Democratic Republic of the Congo	2013_DHS6	0.0	847	**1.7**	1.6	1.8	**2.2**	2.0	2.4	1.1	4.2	2
Dominican Republic	2014_MICS5	0.0	8426	**2.8**	2.7	2.8	**1.3**	1.3	1.3	0.9	1.9	1
El Salvador	2014_MICS5	0.0	3804	**5.6**	5.4	5.8	**1.1**	1.0	1.1	0.9	1.3	1
Ethiopia	2011_DHS6	0.0	1521	**1.7**	1.6	1.8	**9.3**	8.8	9.8	4.8	17.9	4
Gabon	2012_DHS6	0.0	1558	**2.0**	1.9	2.1	**2.1**	2.0	2.2	1.2	3.6	1
Gambia	2013_DHS6	0.0	1889	**2.5**	2.4	2.6	**3.1**	3.0	3.2	2.0	4.8	1
Ghana	2016_DHS7	0.0	1454	**2.1**	2.0	2.2	**1.7**	1.7	1.8	1.0	2.9	2
Guatemala	2015_DHS7	0.0	6090	**1.7**	1.7	1.8	**2.3**	2.2	2.4	1.2	4.3	2
Guinea	2012_DHS6	0.0	894	**1.9**	1.8	2.0	**2.0**	1.9	2.2	1.1	3.6	1
Guinea-Bissau	2014_MICS5	0.0	3224	**1.7**	1.6	1.7	**3.2**	3.1	3.4	1.7	6.2	2
Guyana	2014_MICS5	0.0	1718	**2.3**	2.2	2.4	**1.5**	1.5	1.6	0.9	2.5	1
Haiti	2012_DHS6	0.0	1543	**1.4**	1.3	1.4	**4.6**	4.3	4.9	2.1	10.1	2
Honduras	2011_DHS6	0.0	5662	**2.4**	2.4	2.5	**1.3**	1.3	1.3	0.8	2.1	1
Kazakhstan	2015_MICS5	0.0	324	**14.3**	12.7	15.8	**1.0**	1.0	1.0	0.9	1.1	1
Kenya	2014_DHS7	0.0	8479	**2.0**	2.0	2.0	**2.0**	1.9	2.0	1.1	3.4	2
Kyrgyzstan	2012_DHS6	0.0	2359	**5.4**	5.2	5.6	**1.1**	1.0	1.1	0.9	1.3	1
Lao People's Democratic Republic	2012_MICS4	0.0	2501	**1.3**	1.2	1.3	**3.5**	3.3	3.7	1.5	8.2	2
Lesotho	2014_DHS7	0.0	687	**2.0**	1.8	2.1	**1.7**	1.6	1.8	1.0	3.0	2

Liberia	2013_DHS6	0.0	1099	**1.8**	1.7	1.9	**2.2**	2.1	2.3	1.2	4.1	2
Madagascar	2012_MICS4	0.0	335	**1.4**	1.3	1.6	**4.1**	3.6	4.7	1.9	8.9	1
Malawi	2016_DHS7	0.0	2381	**2.0**	1.9	2.0	**2.1**	2.0	2.1	1.2	3.6	1
Mali	2012_DHS6	0.0	786	**1.6**	1.5	1.7	**4.3**	4.0	4.6	2.1	8.7	2
Mauritania	2011_MICS4	0.0	1383	**1.7**	1.7	1.8	**2.5**	2.4	2.6	1.3	4.7	1
Mexico	2015_MICS5	0.0	3662	**2.7**	2.6	2.8	**1.3**	1.3	1.4	0.9	2.0	1
Mongolia	2013_MICS5	0.0	2479	**29.7**	28.5	30.9	**1.0**	1.0	1.0	1.0	1.0	1
Mozambique	2011_DHS6	0.0	4586	**1.8**	1.8	1.9	**2.0**	1.9	2.0	1.1	3.6	1
Namibia	2013_DHS6	0.0	1011	**7.6**	7.1	8.1	**1.0**	1.0	1.0	0.9	1.2	1
Nepal	2014_MICS5	0.0	1005	**1.8**	1.7	1.9	**3.5**	3.3	3.7	2.0	6.4	1
Nigeria	2013_DHS6	0.0	4470	**1.5**	1.5	1.6	**4.0**	3.8	4.1	1.9	8.1	2
Pakistan	2011_MICS4	0.0	4401	**1.7**	1.7	1.8	**4.0**	3.9	4.1	2.1	7.5	2
Peru	2010_DHS6	0.0	11912	**2.4**	2.4	2.5	**1.5**	1.5	1.5	1.0	2.4	1
Rwanda	2015_DHS7	0.0	2086	**3.0**	2.9	3.1	**1.5**	1.5	1.6	1.1	2.2	1
Sao Tome and Principe	2014_MICS5	0.0	995	**3.7**	3.5	3.9	**1.1**	1.1	1.2	0.8	1.5	1
Senegal	2015_DHS7	0.0	2601	**2.0**	1.9	2.0	**3.0**	2.9	3.1	1.7	5.3	2
Serbia	2014_MICS5	0.0	821	**4.2**	3.9	4.5	**1.1**	1.1	1.1	0.8	1.4	1
Sierra Leone	2013_DHS6	0.0	2148	**1.9**	1.9	2.0	**1.8**	1.8	1.9	1.0	3.2	1
State of Palestine	2014_MICS5	0.0	3900	**2.8**	2.7	2.8	**2.0**	2.0	2.1	1.4	3.0	2
Sudan	2014_MICS5	0.0	2103	**1.7**	1.6	1.7	**6.3**	6.0	6.6	3.2	12.2	3
Swaziland	2014_MICS5	0.0	1349	**8.6**	8.2	9.1	**1.0**	1.0	1.0	0.9	1.2	1
TFYR Macedonia	2012_MICS4	0.0	705	**1.8**	1.7	1.9	**1.8**	1.7	1.9	1.0	3.3	1
Timor-Leste	2009_DHS6	0.0	2430	**1.6**	1.6	1.7	**3.4**	3.3	3.6	1.7	6.7	2
Togo	2013_DHS6	0.0	1380	**2.1**	2.0	2.2	**2.4**	2.3	2.5	1.4	4.1	2
Tunisia	2012_MICS4	0.0	1491	**4.2**	4.0	4.4	**1.1**	1.1	1.1	0.8	1.4	1
Uganda	2011_DHS6	0.0	804	**1.6**	1.5	1.7	**2.6**	2.3	2.8	1.3	5.1	2
United Republic of Tanzania	2016_DHS7	0.0	4523	**1.6**	1.6	1.7	**2.7**	2.6	2.8	1.4	5.3	2
Viet nam	2014_MICS5	0.0	1431	**1.8**	1.7	1.9	**3.1**	2.9	3.2	1.7	5.7	2
Yemen	2010_DHS6	0.0	2357	**1.8**	1.8	1.9	**7.3**	7.1	7.6	4.0	13.5	2
Zambia	2013_DHS6	0.0	5171	**1.6**	1.6	1.6	**3.8**	3.6	3.9	1.9	7.4	2
Zimbabwe	2015_DHS7	0.0	2423	**2.6**	2.5	2.7	**1.4**	1.3	1.4	0.9	2.1	1
Republic of Moldova	2012_MICS4	0.3	266	**6.1**	5.4	6.8	**1.1**	1.0	1.1	0.9	1.3	1
Ukraine	2012_MICS4	0.4	412	**4.1**	3.7	4.5	**1.1**	1.1	1.1	0.8	1.4	1
Tajikistan	2012_DHS6	0.5	2530	**1.8**	1.8	1.9	**1.7**	1.6	1.7	0.9	3.1	1
Egypt	2014_DHS6	1.0	4223	**2.7**	2.6	2.8	**1.8**	1.7	1.8	1.2	2.6	1
	Median	0.0		**2.00**	1.92	2.08	**2.05**	1.97	2.13	**1.2**	**3.6**	

Table 6. Median age (IQR - inter-quartile range) of DTP1 vaccination in 73 LMICs; fitted Log Logistic shape and scale parameters and AIC rank

Country	Survey	Target age (wks)	Sample size (n)	Shape			Scale (median age, wks)			IQR age, wks		Log Logistic AIC rank
				Mid	L95% CI	U95% CI	Mid	L95% CI	U95% CI	25th	75th	
Afghanistan	2011_MICS4	6.0	1286	**1.9**	1.8	2.0	**12.9**	12.2	13.5	7.2	22.9	1
Armenia	2010_DHS6	6.0	781	**3.9**	3.7	4.2	**13.8**	13.3	14.2	10.4	18.2	1
Bangladesh	2014_DHS7	6.0	3086	**6.0**	5.8	6.1	**8.9**	8.9	9.0	7.4	10.8	1
Benin	2011_DHS6	6.0	2233	**4.1**	3.9	4.2	**8.3**	8.1	8.4	6.3	10.8	1
Burundi	2010_DHS6	6.0	1292	**6.4**	6.1	6.7	**8.1**	8.0	8.2	6.8	9.6	1
Cambodia	2014_DHS7	6.0	1938	**6.3**	6.0	6.5	**7.7**	7.7	7.8	6.5	9.2	1
Cameroon	2011_DHS6	6.0	1834	**3.9**	3.8	4.1	**8.4**	8.2	8.6	6.4	11.1	1
Central African Republic	2010_MICS4	6.0	1292	**2.9**	2.8	3.1	**9.7**	9.4	10.0	6.7	14.1	1
Chad	2010_MICS4	6.0	867	**1.8**	1.7	1.9	**13.1**	12.2	14.0	7.0	24.4	1
Comoros	2012_DHS6	6.0	1045	**4.0**	3.8	4.2	**8.4**	8.2	8.6	6.4	11.0	1
Côte d'Ivoire	2011_DHS6	6.0	1274	**3.3**	3.1	3.5	**9.2**	8.9	9.4	6.6	12.8	1
Democratic Republic of the Congo	2013_DHS6	6.0	873	**3.5**	3.3	3.7	**8.9**	8.6	9.2	6.5	12.1	1
Ethiopia	2011_DHS6	6.0	1580	**2.4**	2.3	2.5	**11.2**	10.8	11.6	7.1	17.8	1
Gabon	2012_DHS6	6.0	586	**3.6**	3.3	3.8	**8.9**	8.5	9.2	6.5	12.1	1
Ghana	2016_DHS7	6.0	1423	**5.8**	5.6	6.1	**8.0**	7.9	8.2	6.7	9.7	1
Guinea	2012_DHS6	6.0	714	**3.0**	2.9	3.2	**9.6**	9.2	10.0	6.7	13.7	1
Guinea-Bissau	2014_MICS5	6.0	3222	**3.7**	3.6	3.9	**9.7**	9.6	9.9	7.3	13.0	1
Haiti	2012_DHS6	6.0	1604	**2.5**	2.4	2.6	**11.4**	11.0	11.8	7.3	17.8	1
Kenya	2014_DHS7	6.0	8275	**6.0**	5.9	6.1	**7.3**	7.3	7.3	6.1	8.8	1
Lao People's Democratic Republic	2012_MICS4	6.0	2462	**2.5**	2.4	2.5	**11.4**	11.1	11.7	7.3	17.8	1
Lesotho	2014_DHS7	6.0	692	**8.0**	7.5	8.5	**7.6**	7.5	7.7	6.6	8.7	1
Liberia	2013_DHS6	6.0	1069	**3.9**	3.7	4.1	**8.8**	8.5	9.0	6.6	11.6	1
Madagascar	2012_MICS4	6.0	437	**2.6**	2.4	2.8	**11.5**	10.7	12.2	7.5	17.6	1
Malawi	2016_DHS7	6.0	2284	**6.2**	6.0	6.5	**8.2**	8.1	8.3	6.9	9.8	1
Mali	2012_DHS6	6.0	715	**2.5**	2.3	2.6	**10.3**	9.8	10.9	6.6	16.1	1
Mauritania	2011_MICS4	6.0	428	**2.7**	2.5	2.9	**10.2**	9.5	10.8	6.8	15.2	1
Mozambique	2011_DHS6	6.0	4396	**3.9**	3.8	4.0	**11.5**	11.3	11.6	8.7	15.2	1
Namibia	2013_DHS6	6.0	929	**6.6**	6.2	7.0	**7.3**	7.2	7.4	6.2	8.6	1
Nepal	2014_MICS5	6.0	977	**5.4**	5.1	5.7	**8.8**	8.7	9.0	7.2	10.8	1
Nigeria	2013_DHS6	6.0	4229	**2.7**	2.6	2.7	**9.8**	9.6	9.9	6.4	14.7	1
Pakistan	2011_MICS4	6.0	4402	**3.5**	3.4	3.6	**10.2**	10.1	10.4	7.5	13.9	1
Rwanda	2015_DHS7	6.0	2016	**9.6**	9.2	10.0	**7.5**	7.5	7.6	6.7	8.4	1
Sao Tome and Principe	2014_MICS5	6.0	954	**9.2**	8.7	9.8	**7.4**	7.4	7.5	6.6	8.4	1
Senegal	2015_DHS7	6.0	2561	**4.2**	4.1	4.4	**9.2**	9.1	9.3	7.1	11.9	1
Sierra Leone	2013_DHS6	6.0	2007	**3.4**	3.3	3.6	**8.2**	8.1	8.4	6.0	11.3	1
Sudan	2014_MICS5	6.0	2161	**3.3**	3.2	3.4	**8.6**	8.4	8.7	6.1	12.0	1
Swaziland	2014_MICS5	6.0	1316	**12.9**	12.2	13.5	**7.1**	7.0	7.1	6.5	7.7	1

Timor-Leste	2009_DHS6	6.0	2408	**3.2**	3.1	3.3	**9.5**	9.3	9.7	6.7	13.4	1
Togo	2013_DHS6	6.0	1309	**5.5**	5.3	5.8	**8.0**	7.9	8.1	6.6	9.8	1
Uganda	2011_DHS6	6.0	753	**4.0**	3.7	4.2	**9.3**	9.0	9.6	7.0	12.3	1
United Republic of Tanzania	2016_DHS7	6.0	4547	**5.6**	5.4	5.7	**8.0**	7.9	8.1	6.6	9.7	1
Yemen	2010_DHS6	6.0	3015	**2.9**	2.8	3.0	**9.8**	9.6	10.0	6.8	14.3	1
Zambia	2013_DHS6	6.0	5199	**3.6**	3.5	3.7	**9.1**	8.9	9.2	6.7	12.3	1
Zimbabwe	2015_DHS7	6.0	2553	**6.5**	6.3	6.7	**7.3**	7.3	7.4	6.2	8.7	1
Burkina Faso	2010_DHS6	8.0	3039	**6.2**	6.0	6.4	**10.4**	10.3	10.5	8.7	12.4	1
Congo	2011_DHS6	8.0	1059	**5.5**	5.2	5.7	**10.9**	10.7	11.1	8.9	13.3	1
Serbia	2014_MICS5	8.0	1076	**7.1**	6.7	7.5	**11.7**	11.5	11.8	10.0	13.6	1
Belize	2011_MICS4	8.7	775	**5.9**	5.5	6.3	**11.3**	11.1	11.5	9.4	13.6	1
Bosnia and Herzegovina	2012_MICS4	8.7	1021	**5.1**	4.8	5.3	**12.9**	12.6	13.1	10.4	16.0	1
Colombia	2010_DHS6	8.7	7394	**5.8**	5.6	5.9	**10.4**	10.3	10.4	8.6	12.6	1
Costa Rica	2011_MICS4	8.7	1184	**8.7**	8.3	9.2	**9.8**	9.7	9.9	8.6	11.1	1
Cuba	2014_MICS5	8.7	35	**1.7**	1.2	2.1	**18.7**	11.5	25.9	9.6	36.3	2
Dominican Republic	2014_MICS5	8.7	3028	**1.6**	1.5	1.6	**32.3**	30.9	33.6	16.2	64.4	4
Egypt	2014_DHS6	8.7	4613	**10.3**	10.1	10.6	**9.9**	9.9	9.9	8.9	11.0	1
El Salvador	2014_MICS5	8.7	3719	**11.5**	11.2	11.8	**9.7**	9.7	9.7	8.8	10.7	1
Gambia	2013_DHS6	8.7	1673	**5.5**	5.3	5.7	**11.6**	11.5	11.8	9.5	14.2	1
Guatemala	2015_DHS7	8.7	5725	**5.5**	5.4	5.6	**11.3**	11.2	11.4	9.3	13.8	1
Guyana	2014_MICS5	8.7	1685	**7.1**	6.8	7.4	**10.5**	10.4	10.6	9.0	12.2	1
Honduras	2011_DHS6	8.7	5416	**11.2**	10.9	11.4	**9.8**	9.8	9.9	8.9	10.8	1
Kazakhstan	2015_MICS5	8.7	248	**4.6**	4.1	5.1	**11.8**	11.2	12.4	9.3	15.0	1
Kyrgyzstan	2012_DHS6	8.7	2141	**5.0**	4.8	5.2	**10.1**	9.9	10.2	8.1	12.5	1
Mexico	2015_MICS5	8.7	3349	**4.1**	4.0	4.3	**10.5**	10.3	10.6	8.0	13.6	1
Mongolia	2013_MICS5	8.7	2276	**14.4**	13.9	14.9	**9.6**	9.6	9.7	8.9	10.4	1
Peru	2010_DHS6	8.7	12137	**7.5**	7.4	7.6	**10.2**	10.1	10.2	8.8	11.8	1
Republic of Moldova	2012_MICS4	8.7	179	**4.6**	4.0	5.3	**11.3**	10.7	11.9	8.9	14.3	1
State of Palestine	2014_MICS5	8.7	3750	**14.0**	13.6	14.4	**10.4**	10.3	10.4	9.6	11.2	1
Suriname	2010_MICS4	8.7	1051	**2.3**	2.2	2.5	**14.0**	13.4	14.6	8.8	22.3	1
Tajikistan	2012_DHS6	8.7	2396	**4.1**	4.0	4.2	**11.5**	11.3	11.7	8.8	15.0	1
TFYR Macedonia	2012_MICS4	8.7	699	**7.1**	6.7	7.6	**15.1**	14.9	15.4	13.0	17.7	1
Tunisia	2012_MICS4	8.7	1409	**7.4**	7.1	7.8	**10.1**	10.0	10.2	8.7	11.8	1
Ukraine	2012_MICS4	8.7	327	**4.2**	3.7	4.6	**16.4**	15.6	17.1	12.6	21.3	1
Viet nam	2014_MICS5	8.7	74	**2.0**	1.6	2.4	**17.8**	13.8	21.8	10.2	30.9	2
Algeria	2013_MICS4	13.0	7011	**7.0**	6.9	7.2	**15.9**	15.9	16.0	13.6	18.6	1
	Median	6.0		**3.9**	3.7	4.1	**8.9**	8.8	9.2	6.7	12.0	
	Median	8.0		**6.2**	6.0	6.4	**10.9**	10.7	11.1	8.9	13.3	
	Median	8.7		**5.5**	5.4	5.7	**11.3**	10.7	11.4	8.9	13.6	

Table 7. Median age (IQR - inter-quartile range) of DTP2 vaccination in 73 LMICs; fitted Log Logistic shape and scale parameters and AIC rank

Country	Survey	Target age (wks)	Sample size (n)	Shape			Scale (median age, wks)			IQR age, wks		Log Logistic AIC rank
				Mid	L95% CI	U95% CI	Mid	L95% CI	U95% CI	25th	75th	
Afghanistan	2011_MICS4	10.0	1098	**3.0**	2.8	3.1	**17.0**	16.4	17.6	11.7	24.6	1
Bangladesh	2014_DHS7	10.0	2929	**7.3**	7.0	7.5	**14.1**	14.0	14.3	12.2	16.4	1
Benin	2011_DHS6	10.0	2016	**4.8**	4.6	5.0	**13.6**	13.4	13.8	10.8	17.1	1
Burundi	2010_DHS6	10.0	1223	**8.8**	8.4	9.2	**13.1**	12.9	13.2	11.5	14.8	1
Cambodia	2014_DHS7	10.0	1789	**6.4**	6.2	6.7	**13.3**	13.1	13.4	11.2	15.7	1
Cameroon	2011_DHS6	10.0	1688	**5.5**	5.2	5.7	**13.4**	13.2	13.6	11.0	16.4	1
Central African Republic	2010_MICS4	10.0	1008	**3.7**	3.5	3.8	**16.7**	16.2	17.2	12.4	22.6	1
Chad	2010_MICS4	10.0	595	**2.4**	2.2	2.6	**22.4**	21.1	23.8	14.2	35.5	2
Comoros	2012_DHS6	10.0	963	**4.5**	4.3	4.8	**14.6**	14.2	14.9	11.4	18.6	1
Côte d'Ivoire	2011_DHS6	10.0	1108	**3.6**	3.4	3.8	**15.8**	15.4	16.3	11.7	21.5	1
Democratic Republic of the Congo	2013_DHS6	10.0	782	**3.9**	3.7	4.2	**14.4**	14.0	14.9	10.9	19.1	1
Ethiopia	2011_DHS6	10.0	1336	**2.9**	2.7	3.0	**18.4**	17.8	19.0	12.6	27.0	1
Gabon	2012_DHS6	10.0	504	**4.0**	3.7	4.3	**14.5**	14.0	15.1	11.0	19.2	1
Ghana	2016_DHS7	10.0	1346	**7.6**	7.2	7.9	**13.1**	13.0	13.3	11.3	15.2	1
Guinea	2012_DHS6	10.0	570	**4.1**	3.8	4.4	**15.4**	14.8	15.9	11.7	20.1	1
Guinea-Bissau	2014_MICS5	10.0	2880	**4.1**	3.9	4.2	**16.6**	16.3	16.9	12.7	21.8	1
Haiti	2012_DHS6	10.0	1355	**3.1**	3.0	3.2	**19.3**	18.7	19.9	13.5	27.5	1
Kenya	2014_DHS7	10.0	7852	**8.4**	8.3	8.6	**11.8**	11.8	11.9	10.4	13.5	1
Lao People's Democratic Republic	2012_MICS4	10.0	2161	**2.8**	2.7	2.9	**20.9**	20.3	21.4	14.1	30.9	2
Lesotho	2014_DHS7	10.0	655	**9.8**	9.1	10.5	**12.8**	12.6	13.0	11.4	14.3	1
Liberia	2013_DHS6	10.0	928	**4.7**	4.4	4.9	**15.2**	14.8	15.5	12.0	19.2	1
Madagascar	2012_MICS4	10.0	388	**3.8**	3.5	4.1	**18.3**	17.5	19.2	13.7	24.5	1
Malawi	2016_DHS7	10.0	2176	**6.8**	6.6	7.1	**13.4**	13.3	13.6	11.4	15.8	1
Mali	2012_DHS6	10.0	635	**3.2**	3.0	3.4	**16.6**	15.9	17.3	11.8	23.5	1
Mauritania	2011_MICS4	10.0	355	**4.0**	3.6	4.4	**14.6**	13.9	15.2	11.1	19.2	1
Mozambique	2011_DHS6	10.0	3990	**4.3**	4.2	4.4	**18.3**	18.1	18.6	14.2	23.7	1
Namibia	2013_DHS6	10.0	870	**9.8**	9.2	10.4	**11.8**	11.7	11.9	10.5	13.2	1
Nepal	2014_MICS5	10.0	894	**7.3**	6.9	7.8	**13.8**	13.5	14.0	11.8	16.0	1
Nigeria	2013_DHS6	10.0	3679	**3.3**	3.2	3.4	**16.0**	15.7	16.2	11.4	22.3	1
Pakistan	2011_MICS4	10.0	4401	**4.3**	4.2	4.4	**16.3**	16.1	16.5	12.6	21.0	1
Rwanda	2015_DHS7	10.0	1939	**12.9**	12.5	13.4	**11.9**	11.9	12.0	11.0	13.0	1
Sao Tome and Principe	2014_MICS5	10.0	905	**8.6**	8.1	9.1	**12.5**	12.4	12.7	11.0	14.2	1
Senegal	2015_DHS7	10.0	2324	**5.0**	4.9	5.2	**15.1**	14.9	15.3	12.1	18.8	1
Sierra Leone	2013_DHS6	10.0	1832	**3.7**	3.5	3.8	**14.9**	14.6	15.3	11.1	20.2	1
Sudan	2014_MICS5	10.0	1974	**3.7**	3.6	3.9	**14.7**	14.4	15.0	11.0	19.8	1
Swaziland	2014_MICS5	10.0	1278	**12.7**	12.1	13.4	**11.4**	11.4	11.5	10.5	12.5	1
Timor-Leste	2009_DHS6	10.0	2211	**4.2**	4.0	4.3	**14.9**	14.6	15.1	11.4	19.4	1

Togo	2013_DHS6	10.0	1228	**6.2**	5.9	6.5	**13.3**	13.1	13.5	11.1	15.9	1
Uganda	2011_DHS6	10.0	666	**4.5**	4.2	4.8	**15.1**	14.6	15.5	11.8	19.2	1
United Republic of Tanzania	2016_DHS7	10.0	4241	**6.6**	6.4	6.7	**13.3**	13.2	13.4	11.2	15.7	1
Yemen	2010_DHS6	10.0	2616	**3.6**	3.5	3.7	**16.3**	16.0	16.6	12.0	22.0	1
Zambia	2013_DHS6	10.0	4845	**4.4**	4.3	4.5	**15.2**	15.0	15.3	11.8	19.5	1
Zimbabwe	2015_DHS7	10.0	2415	**7.1**	6.9	7.4	**12.5**	12.3	12.6	10.7	14.5	1
Armenia	2010_DHS6	12.0	716	**4.7**	4.4	5.0	**21.9**	21.3	22.5	17.3	27.7	1
Burkina Faso	2010_DHS6	12.0	2869	**7.6**	7.4	7.9	**15.3**	15.2	15.5	13.3	17.7	1
Congo	2011_DHS6	12.0	968	**6.5**	6.1	6.8	**15.7**	15.4	15.9	13.2	18.6	1
Gambia	2013_DHS6	13.0	1571	**5.5**	5.2	5.7	**18.2**	17.9	18.5	14.9	22.2	1
Kazakhstan	2015_MICS5	13.0	219	**6.1**	5.4	6.8	**17.3**	16.7	18.0	14.5	20.7	1
Mongolia	2013_MICS5	13.0	2148	**19.8**	19.0	20.5	**14.4**	14.3	14.4	13.6	15.2	1
Tajikistan	2012_DHS6	13.0	2229	**5.2**	5.0	5.4	**17.3**	17.1	17.6	14.0	21.4	1
Tunisia	2012_MICS4	13.0	1326	**9.3**	8.9	9.7	**15.4**	15.2	15.5	13.7	17.3	1
Viet nam	2014_MICS5	13.0	57	**2.8**	2.1	3.6	**21.3**	17.5	25.1	14.5	31.4	1
Serbia	2014_MICS5	14.0	1028	**7.3**	6.9	7.7	**18.9**	18.6	19.1	16.3	21.9	1
Kyrgyzstan	2012_DHS6	15.2	1968	**7.4**	7.1	7.7	**18.1**	17.9	18.2	15.6	21.0	1
Algeria	2013_MICS4	17.3	6364	**6.9**	6.7	7.0	**22.5**	22.4	22.6	19.2	26.4	1
Belize	2011_MICS4	17.3	721	**7.0**	6.6	7.5	**20.8**	20.4	21.1	17.8	24.3	1
Bosnia and Herzegovina	2012_MICS4	17.3	973	**5.2**	4.9	5.5	**20.6**	20.1	21.0	16.6	25.4	1
Colombia	2010_DHS6	17.3	6828	**7.1**	6.9	7.2	**20.0**	19.9	20.1	17.1	23.4	1
Costa Rica	2011_MICS4	17.3	1106	**16.0**	15.2	16.9	**18.9**	18.8	19.0	17.6	20.2	1
Cuba	2014_MICS5	17.3	26	**5.3**	3.2	7.4	**20.6**	18.0	23.2	16.7	25.4	1
Dominican Republic	2014_MICS5	17.3	1395	**2.4**	2.3	2.5	**31.2**	30.0	32.4	19.8	49.1	2
Egypt	2014_DHS6	17.3	4335	**15.2**	14.8	15.6	**18.9**	18.8	19.0	17.6	20.3	1
El Salvador	2014_MICS5	17.3	3523	**16.4**	16.0	16.9	**18.8**	18.7	18.9	17.6	20.1	1
Guatemala	2015_DHS7	17.3	5059	**6.8**	6.6	6.9	**21.6**	21.4	21.7	18.4	25.4	1
Guyana	2014_MICS5	17.3	1559	**8.9**	8.5	9.3	**20.1**	19.9	20.3	17.7	22.7	1
Honduras	2011_DHS6	17.3	4967	**13.3**	12.9	13.6	**19.4**	19.3	19.4	17.8	21.0	1
Mexico	2015_MICS5	17.3	2997	**4.4**	4.2	4.5	**20.0**	19.7	20.3	15.5	25.7	1
Peru	2010_DHS6	17.3	11038	**8.1**	8.0	8.2	**20.0**	20.0	20.1	17.5	22.9	1
Republic of Moldova	2012_MICS4	17.3	160	**8.1**	7.0	9.3	**20.7**	20.0	21.4	18.0	23.7	1
State of Palestine	2014_MICS5	17.3	3503	**21.2**	20.6	21.8	**19.3**	19.2	19.3	18.3	20.3	1
Suriname	2010_MICS4	17.3	914	**6.6**	6.3	7.0	**21.5**	21.1	21.8	18.2	25.3	1
TFYR Macedonia	2012_MICS4	17.3	663	**7.2**	6.7	7.6	**22.9**	22.5	23.3	19.6	26.7	1
Ukraine	2012_MICS4	17.3	299	**3.0**	2.7	3.3	**27.6**	25.7	29.5	19.2	39.7	2
	Median	10.0		**4.4**	4.2	4.5	**14.7**	14.4	15.1	**11.4**	**19.2**	
	Median	13.0		**5.8**	5.3	6.3	**17.3**	16.9	17.8	**14.2**	**21.1**	
	Median	17.3		**7.1**	6.7	7.5	**20.6**	20.0	21.0	**17.8**	**24.3**	

Table 8. Median age (IQR - inter-quartile range) of DTP3 vaccination in 73 LMICs; fitted Log Logistic shape and scale parameters and AIC rank

Country	Survey	Target age (wks)	Sample size (n)	Shape			Scale (median age, wks)			IQR age, wks		Log Logistic AIC rank
				Mid	L95% CI	U95% CI	Mid	L95% CI	U95% CI	25th	75th	
Afghanistan	2011_MICS4	14.0	865	**2.7**	2.6	2.9	**28.9**	27.7	30.2	19.4	43.2	2
Bangladesh	2014_DHS7	14.0	2715	**7.5**	7.3	7.8	**19.4**	19.2	19.6	16.8	22.4	1
Benin	2011_DHS6	14.0	1766	**4.8**	4.6	5.0	**19.4**	19.1	19.7	15.4	24.4	1
Burundi	2010_DHS6	14.0	1140	**8.6**	8.2	9.1	**18.4**	18.2	18.6	16.2	20.9	1
Cambodia	2014_DHS7	14.0	1636	**6.5**	6.3	6.8	**18.4**	18.1	18.6	15.5	21.7	1
Cameroon	2011_DHS6	14.0	1497	**5.5**	5.2	5.7	**19.0**	18.7	19.3	15.5	23.2	1
Central African Republic	2010_MICS4	14.0	729	**3.7**	3.5	4.0	**24.7**	23.8	25.5	18.4	33.2	1
Chad	2010_MICS4	14.0	430	**3.0**	2.7	3.2	**28.1**	26.5	29.7	19.4	40.7	2
Comoros	2012_DHS6	14.0	865	**4.0**	3.8	4.3	**21.3**	20.7	22.0	16.3	28.0	1
Côte d'Ivoire	2011_DHS6	14.0	952	**4.5**	4.2	4.7	**21.4**	20.9	21.9	16.8	27.4	1
Democratic Republic of the Congo	2013_DHS6	14.0	675	**4.3**	4.0	4.6	**20.9**	20.3	21.6	16.2	27.0	1
Ethiopia	2011_DHS6	14.0	1121	**3.8**	3.6	4.0	**22.9**	22.3	23.5	17.1	30.5	2
Gabon	2012_DHS6	14.0	414	**3.8**	3.5	4.2	**19.9**	19.1	20.8	14.9	26.5	1
Ghana	2016_DHS7	14.0	1262	**7.7**	7.3	8.1	**18.2**	17.9	18.4	15.7	20.9	1
Guinea	2012_DHS6	14.0	461	**4.3**	4.0	4.7	**21.1**	20.3	21.8	16.3	27.2	1
Guinea-Bissau	2014_MICS5	14.0	2529	**4.3**	4.1	4.4	**23.6**	23.2	24.0	18.2	30.6	1
Haiti	2012_DHS6	14.0	1114	**3.0**	2.9	3.2	**28.2**	27.2	29.2	19.5	40.6	1
Kenya	2014_DHS7	14.0	7248	**8.6**	8.5	8.8	**16.6**	16.5	16.7	14.6	18.9	1
Lao People's Democratic Republic	2012_MICS4	14.0	1802	**3.0**	2.9	3.1	**29.3**	28.4	30.1	20.3	42.2	2
Lesotho	2014_DHS7	14.0	612	**8.1**	7.5	8.6	**18.2**	17.9	18.6	15.9	20.9	1
Liberia	2013_DHS6	14.0	787	**4.3**	4.1	4.6	**22.2**	21.5	22.8	17.2	28.5	1
Madagascar	2012_MICS4	14.0	313	**4.5**	4.0	4.9	**23.7**	22.6	24.8	18.5	30.3	1
Malawi	2016_DHS7	14.0	2035	**7.0**	6.7	7.2	**18.9**	18.7	19.1	16.1	22.1	1
Mali	2012_DHS6	14.0	563	**3.6**	3.4	3.9	**22.2**	21.3	23.1	16.4	30.1	1
Mauritania	2011_MICS4	14.0	294	**4.5**	4.0	4.9	**21.1**	20.1	22.0	16.5	26.9	1
Mozambique	2011_DHS6	14.0	3549	**4.3**	4.2	4.4	**25.7**	25.3	26.0	19.9	33.1	1
Namibia	2013_DHS6	14.0	810	**8.4**	7.9	8.9	**16.4**	16.2	16.6	14.4	18.7	1
Nepal	2014_MICS5	14.0	806	**7.7**	7.2	8.1	**19.0**	18.7	19.3	16.5	22.0	1
Nigeria	2013_DHS6	14.0	3065	**3.7**	3.6	3.8	**21.7**	21.3	22.1	16.1	29.2	1
Pakistan	2011_MICS4	14.0	4344	**4.7**	4.6	4.8	**22.1**	21.8	22.3	17.4	27.9	1
Rwanda	2015_DHS7	14.0	1864	**13.3**	12.8	13.8	**16.5**	16.4	16.6	15.2	17.9	1
Sao Tome and Principe	2014_MICS5	14.0	874	**9.0**	8.4	9.5	**17.6**	17.3	17.8	15.5	19.8	1
Senegal	2015_DHS7	14.0	2058	**5.4**	5.2	5.6	**21.0**	20.7	21.2	17.1	25.7	1
Sierra Leone	2013_DHS6	14.0	1596	**4.0**	3.9	4.2	**21.9**	21.4	22.3	16.6	28.7	1
Sudan	2014_MICS5	14.0	1721	**3.8**	3.7	4.0	**21.4**	20.9	21.9	16.0	28.6	1
Swaziland	2014_MICS5	14.0	1215	**10.2**	9.7	10.8	**16.1**	16.0	16.3	14.5	17.9	1
Timor-Leste	2009_DHS6	14.0	2009	**4.7**	4.5	4.8	**20.9**	20.6	21.2	16.5	26.5	1

Togo	2013_DHS6	14.0	1101	**5.8**	5.5	6.1	**18.8**	18.5	19.1	15.6	22.7	1
Uganda	2011_DHS6	14.0	581	**3.7**	3.4	4.0	**22.9**	22.0	23.8	17.0	30.9	1
United Republic of Tanzania	2016_DHS7	14.0	3919	**6.5**	6.3	6.7	**18.8**	18.6	19.0	15.9	22.3	1
Yemen	2010_DHS6	14.0	2251	**4.2**	4.1	4.3	**22.4**	22.0	22.8	17.2	29.1	1
Zambia	2013_DHS6	14.0	4384	**4.4**	4.3	4.5	**21.8**	21.5	22.0	17.0	27.9	1
Zimbabwe	2015_DHS7	14.0	2228	**6.7**	6.4	6.9	**17.7**	17.6	17.9	15.1	20.9	1
Burkina Faso	2010_DHS6	16.0	2699	**7.2**	7.0	7.4	**20.8**	20.6	21.0	17.8	24.2	1
Congo	2011_DHS6	16.0	821	**7.0**	6.6	7.4	**21.2**	20.8	21.6	18.1	24.8	1
Gambia	2013_DHS6	17.3	1441	**5.6**	5.4	5.8	**24.4**	24.0	24.8	20.0	29.7	1
Kazakhstan	2015_MICS5	17.3	190	**2.8**	2.4	3.1	**32.1**	29.1	35.2	21.7	47.7	2
Mongolia	2013_MICS5	17.3	1992	**18.1**	17.4	18.8	**19.0**	18.9	19.1	17.9	20.2	1
Tajikistan	2012_DHS6	17.3	2089	**5.0**	4.8	5.2	**23.3**	23.0	23.7	18.7	29.0	1
Viet nam	2014_MICS5	17.3	49	**3.1**	2.2	4.0	**26.2**	21.6	30.8	18.5	37.2	1
Armenia	2010_DHS6	18.0	658	**4.8**	4.5	5.1	**31.1**	30.2	32.0	24.7	39.1	1
Serbia	2014_MICS5	20.0	954	**6.9**	6.5	7.3	**26.2**	25.8	26.6	22.3	30.7	1
Algeria	2013_MICS4	21.7	5751	**6.4**	6.2	6.5	**29.3**	29.1	29.5	24.7	34.8	1
Kyrgyzstan	2012_DHS6	21.7	1863	**6.3**	6.0	6.5	**26.6**	26.3	26.9	22.3	31.7	1
Belize	2011_MICS4	26.0	641	**8.1**	7.6	8.7	**30.1**	29.6	30.5	26.3	34.4	1
Bosnia and Herzegovina	2012_MICS4	26.0	908	**5.5**	5.2	5.8	**30.1**	29.5	30.8	24.7	36.8	1
Colombia	2010_DHS6	26.0	6132	**7.4**	7.3	7.6	**29.5**	29.4	29.7	25.5	34.3	1
Costa Rica	2011_MICS4	26.0	1000	**13.6**	12.9	14.4	**28.3**	28.1	28.5	26.1	30.7	1
Cuba	2014_MICS5	26.0	24	**2.6**	1.7	3.6	**76.2**	52.8	99.6	50.2	115.7	4
Dominican Republic	2014_MICS5	26.0	1065	**3.2**	3.0	3.3	**40.3**	38.9	41.7	28.5	57.0	2
Egypt	2014_DHS6	26.0	3937	**19.2**	18.7	19.8	**27.9**	27.8	28.0	26.4	29.6	1
El Salvador	2014_MICS5	26.0	3278	**14.6**	14.1	15.0	**28.1**	28.0	28.3	26.1	30.3	1
Guatemala	2015_DHS7	26.0	4480	**7.0**	6.9	7.2	**31.8**	31.6	32.0	27.2	37.2	1
Guyana	2014_MICS5	26.0	1409	**10.0**	9.5	10.5	**29.3**	29.0	29.5	26.2	32.7	1
Honduras	2011_DHS6	26.0	4537	**12.5**	12.1	12.8	**29.0**	28.9	29.2	26.6	31.7	1
Mexico	2015_MICS5	26.0	2600	**4.2**	4.0	4.3	**30.0**	29.5	30.5	23.0	39.0	1
Peru	2010_DHS6	26.0	9830	**8.1**	8.0	8.2	**30.0**	29.8	30.1	26.2	34.3	1
Republic of Moldova	2012_MICS4	26.0	129	**11.0**	9.2	12.9	**29.4**	28.6	30.2	26.6	32.5	1
State of Palestine	2014_MICS5	26.0	3175	**25.5**	24.7	26.3	**28.3**	28.2	28.4	27.1	29.5	1
Suriname	2010_MICS4	26.0	827	**6.2**	5.8	6.6	**31.9**	31.3	32.5	26.7	38.1	1
TFYR Macedonia	2012_MICS4	26.0	611	**7.5**	7.0	8.0	**30.8**	30.3	31.4	26.6	35.7	1
Tunisia	2012_MICS4	26.0	1167	**10.1**	9.5	10.6	**28.5**	28.2	28.8	25.6	31.8	1
Ukraine	2012_MICS4	26.0	261	**3.0**	2.7	3.4	**35.0**	32.4	37.6	24.4	50.2	2
	Median	14.0		**4.5**	4.2	4.8	**21.1**	20.6	21.8	**16.4**	**27.0**	
	Median	17.3		**5.0**	4.8	5.2	**24.4**	23.0	24.8	**18.7**	**29.7**	
	Median	26.0		**8.1**	7.6	8.2	**30.0**	29.5	30.2	**26.3**	**34.3**	

Table 9. Median age (IQR - inter-quartile range) of Meas1 vaccination in 73 LMICs; fitted Log Logistic shape and scale parameters and AIC rank

Country	Survey	Target age (wks)	Sample size (n)	Shape			Scale (median age, wks)			IQR age, wks		Log Logistic AIC rank
				Mid	L95% CI	U95% CI	Mid	L95% CI	U95% CI	25th	75th	
Cambodia	2014_DHS7	26.0	1234	**9.1**	8.6	9.6	**42.7**	42.3	43.2	37.9	48.2	1
Congo	2011_DHS6	36.0	746	**11.1**	10.4	11.8	**42.5**	42.0	42.9	38.5	46.9	1
Bangladesh	2014_DHS7	38.0	2078	**14.7**	14.2	15.3	**42.7**	42.5	42.9	39.6	46.0	1
Afghanistan	2011_MICS4	39.0	453	**3.4**	3.1	3.7	**52.2**	49.7	54.7	37.7	72.3	1
Benin	2011_DHS6	39.0	1703	**8.3**	7.9	8.6	**42.8**	42.4	43.2	37.4	48.8	1
Burkina Faso	2010_DHS6	39.0	2151	**15.4**	14.8	16.0	**41.7**	41.5	41.8	38.8	44.7	1
Burundi	2010_DHS6	39.0	815	**14.4**	13.5	15.3	**42.5**	42.2	42.8	39.4	45.9	1
Cameroon	2011_DHS6	39.0	1086	**9.4**	8.9	9.9	**41.7**	41.3	42.2	37.1	46.9	1
Central African Republic	2010_MICS4	39.0	530	**5.1**	4.7	5.5	**46.1**	44.7	47.4	37.1	57.2	1
Chad	2010_MICS4	39.0	405	**2.8**	2.5	3.0	**48.3**	45.2	51.3	32.4	71.8	3
Comoros	2012_DHS6	39.0	665	**5.6**	5.2	6.0	**43.1**	42.1	44.1	35.4	52.5	1
Côte d'Ivoire	2011_DHS6	39.0	682	**5.1**	4.8	5.5	**44.7**	43.6	45.8	36.0	55.4	1
Democratic Republic of the Congo	2013_DHS6	39.0	454	**7.4**	6.8	8.0	**44.5**	43.5	45.4	38.3	51.6	1
Ethiopia	2011_DHS6	39.0	775	**6.8**	6.3	7.2	**42.7**	41.9	43.4	36.3	50.2	1
Gabon	2012_DHS6	39.0	836	**6.0**	5.6	6.4	**45.5**	44.6	46.3	37.9	54.6	1
Gambia	2013_DHS6	39.0	1142	**9.4**	8.9	9.9	**43.7**	43.2	44.1	38.9	49.1	1
Ghana	2016_DHS7	39.0	969	**14.8**	13.9	15.6	**42.7**	42.4	43.0	39.6	46.0	1
Guinea	2012_DHS6	39.0	360	**5.7**	5.2	6.3	**44.7**	43.3	46.1	36.9	54.1	1
Guinea-Bissau	2014_MICS5	39.0	1948	**6.8**	6.6	7.1	**43.9**	43.5	44.4	37.4	51.6	1
Haiti	2012_DHS6	39.0	883	**3.4**	3.3	3.6	**61.5**	59.4	63.6	44.7	84.6	1
Kenya	2014_DHS7	39.0	5026	**11.6**	11.3	11.9	**42.3**	42.2	42.5	38.5	46.5	1
Lao People's Democratic Republic	2012_MICS4	39.0	1457	**5.4**	5.2	5.7	**47.9**	47.1	48.6	39.1	58.6	1
Lesotho	2014_DHS7	39.0	470	**11.5**	10.5	12.4	**43.2**	42.6	43.7	39.2	47.5	1
Liberia	2013_DHS6	39.0	516	**7.2**	6.6	7.8	**44.0**	43.1	44.9	37.8	51.3	1
Madagascar	2012_MICS4	39.0	237	**6.1**	5.4	6.9	**44.8**	43.2	46.4	37.5	53.6	1
Malawi	2016_DHS7	39.0	1543	**10.6**	10.1	11.1	**43.3**	43.0	43.7	39.1	48.1	1
Mali	2012_DHS6	39.0	431	**5.4**	4.9	5.9	**42.3**	41.1	43.6	34.6	51.9	1
Mauritania	2011_MICS4	39.0	422	**4.0**	3.6	4.3	**44.2**	42.3	46.0	33.5	58.2	1
Mongolia	2013_MICS5	39.0	1500	**17.5**	16.7	18.4	**40.9**	40.7	41.1	38.4	43.5	1
Mozambique	2011_DHS6	39.0	3045	**6.3**	6.1	6.5	**44.3**	43.9	44.7	37.2	52.8	1
Namibia	2013_DHS6	39.0	623	**5.2**	4.8	5.6	**41.3**	40.3	42.2	33.4	50.9	1
Nepal	2014_MICS5	39.0	558	**6.9**	6.4	7.4	**45.0**	44.1	45.9	38.4	52.8	1
Nigeria	2013_DHS6	39.0	2252	**5.2**	5.0	5.4	**45.6**	45.0	46.2	37.0	56.2	1
Pakistan	2011_MICS4	39.0	4285	**7.5**	7.3	7.7	**43.3**	43.1	43.6	37.4	50.2	1
Rwanda	2015_DHS7	39.0	483	**5.6**	5.2	6.0	**57.6**	55.9	59.3	47.3	70.1	3
Sao Tome and Principe	2014_MICS5	39.0	763	**11.0**	10.2	11.7	**42.6**	42.2	43.0	38.5	47.1	1
Senegal	2015_DHS7	39.0	1434	**9.9**	9.5	10.4	**43.6**	43.3	44.0	39.1	48.8	1

Sierra Leone	2013_DHS6	39.0	1165	**6.3**	5.9	6.6	**43.2**	42.6	43.9	36.3	51.5	1
Sudan	2014_MICS5	39.0	1229	**3.8**	3.6	3.9	**38.3**	37.4	39.3	28.6	51.3	3
Swaziland	2014_MICS5	39.0	955	**11.6**	10.9	12.3	**41.8**	41.4	42.1	38.0	45.9	1
Timor-Leste	2009_DHS6	39.0	1480	**8.4**	8.0	8.8	**42.1**	41.7	42.5	37.0	48.0	1
Togo	2013_DHS6	39.0	795	**9.5**	8.9	10.1	**43.5**	42.9	44.0	38.7	48.8	1
Uganda	2011_DHS6	39.0	418	**7.0**	6.4	7.6	**44.2**	43.2	45.2	37.8	51.7	1
United Republic of Tanzania	2016_DHS7	39.0	2897	**10.8**	10.5	11.2	**43.5**	43.3	43.8	39.3	48.2	1
Viet nam	2014_MICS5	39.0	903	**10.5**	9.9	11.2	**44.5**	44.0	45.0	40.1	49.4	1
Yemen	2010_DHS6	39.0	1772	**5.0**	4.8	5.2	**46.4**	45.6	47.1	37.2	57.8	1
Zambia	2013_DHS6	39.0	3364	**7.6**	7.4	7.9	**44.5**	44.2	44.9	38.6	51.4	1
Zimbabwe	2015_DHS7	39.0	1743	**9.7**	9.3	10.1	**42.6**	42.3	42.9	38.0	47.7	1
Algeria	2013_MICS4	47.7	5296	**8.8**	8.5	9.0	**43.9**	43.7	44.1	38.7	49.8	1
Armenia	2010_DHS6	52.0	523	**13.7**	12.6	14.7	**57.6**	57.0	58.2	53.1	62.4	1
Belize	2011_MICS4	52.0	525	**7.6**	7.0	8.2	**57.7**	56.7	58.8	49.9	66.8	1
Bosnia and Herzegovina	2012_MICS4	52.0	737	**9.7**	9.0	10.3	**60.7**	59.9	61.5	54.2	68.0	1
Colombia	2010_DHS6	52.0	4622	**9.1**	8.8	9.3	**59.0**	58.7	59.3	52.3	66.6	1
Cuba	2014_MICS5	52.0	2087	**11.2**	10.8	11.7	**56.4**	56.1	56.7	51.1	62.2	1
Dominican Republic	2014_MICS5	52.0	4368	**5.3**	5.2	5.5	**57.8**	57.3	58.3	47.0	71.1	1
Egypt	2014_DHS6	52.0	233	**7.1**	6.3	7.9	**46.7**	45.1	48.2	39.9	54.5	1
El Salvador	2014_MICS5	52.0	2559	**21.6**	20.8	22.3	**55.9**	55.7	56.0	53.1	58.8	1
Guatemala	2015_DHS7	52.0	3490	**11.7**	11.4	12.1	**58.8**	58.5	59.1	53.5	64.6	1
Guyana	2014_MICS5	52.0	1113	**16.9**	16.0	17.9	**57.0**	56.7	57.3	53.4	60.8	1
Honduras	2011_DHS6	52.0	3565	**17.6**	17.0	18.1	**56.4**	56.2	56.6	53.0	60.0	1
Kazakhstan	2015_MICS5	52.0	149	**4.0**	3.4	4.6	**53.9**	50.2	57.5	40.9	70.9	2
Kyrgyzstan	2012_DHS6	52.0	1351	**8.6**	8.1	9.0	**56.5**	56.0	57.1	49.7	64.3	1
Mexico	2015_MICS5	52.0	2013	**6.6**	6.3	6.8	**61.0**	60.3	61.7	51.6	72.1	1
Peru	2010_DHS6	52.0	7308	**10.4**	10.2	10.7	**59.3**	59.1	59.5	53.4	65.9	1
Republic of Moldova	2012_MICS4	52.0	100	**4.8**	3.9	5.8	**54.6**	50.9	58.4	43.5	68.6	1
Serbia	2014_MICS5	52.0	627	**7.7**	7.1	8.2	**62.4**	61.4	63.4	54.1	72.0	1
State of Palestine	2014_MICS5	52.0	2513	**37.1**	35.8	38.4	**55.8**	55.7	55.9	54.2	57.5	1
Suriname	2010_MICS4	52.0	853	**10.3**	9.7	11.0	**59.2**	58.5	59.8	53.2	65.8	1
Tajikistan	2012_DHS6	52.0	1634	**6.2**	5.9	6.5	**55.7**	55.0	56.4	46.6	66.5	2
TFYR Macedonia	2012_MICS4	52.0	552	**8.4**	7.8	9.0	**56.6**	55.7	57.6	49.7	64.5	1
Tunisia	2012_MICS4	52.0	786	**9.0**	8.4	9.6	**69.3**	68.4	70.1	61.4	78.2	1
Ukraine	2012_MICS4	52.0	185	**3.5**	3.0	3.9	**65.2**	60.8	69.6	47.5	89.5	2
Costa Rica	2011_MICS4	65.0	691	**12.6**	11.7	13.5	**69.6**	69.0	70.3	63.8	76.0	1
	Median	39.0		**7.0**	6.6	7.6	**43.6**	43.1	44.1	37.8	51.3	
	Median	52.0		**9.0**	8.4	9.3	**57.6**	56.7	58.3	52.3	65.9	

Figure 3. Distributions of the actual age at BCG vaccination in 72 LMICs with median distribution for countries with a target age at birth

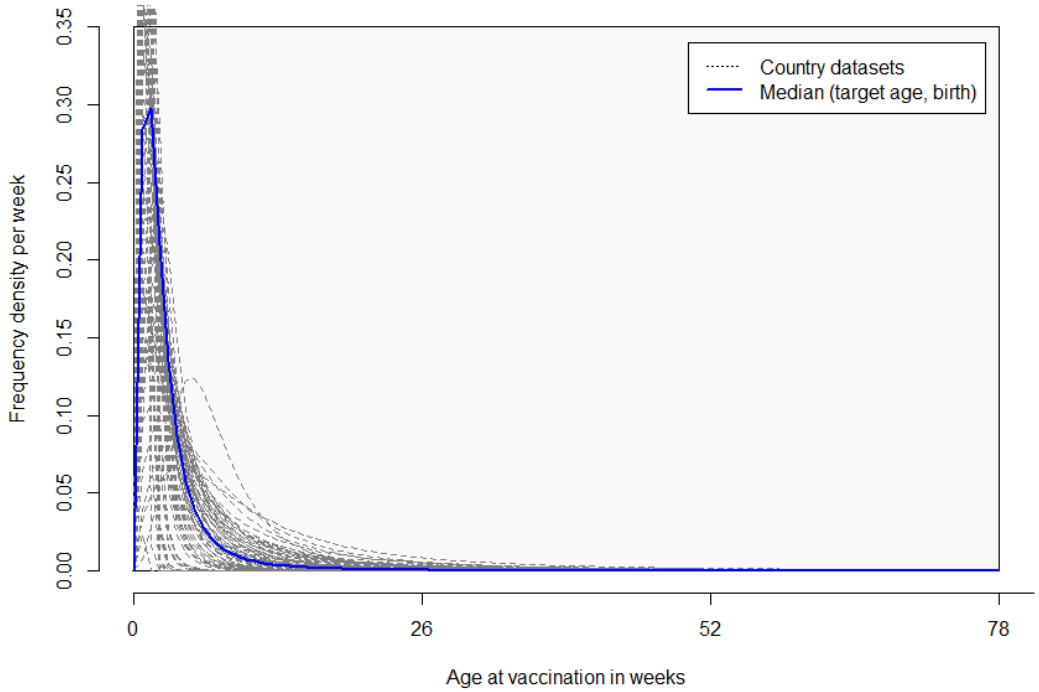


Figure 4. Distributions of the actual age at DTP1 vaccination in 73 LMICs with median distributions for countries with target ages at 6 weeks and 2 months

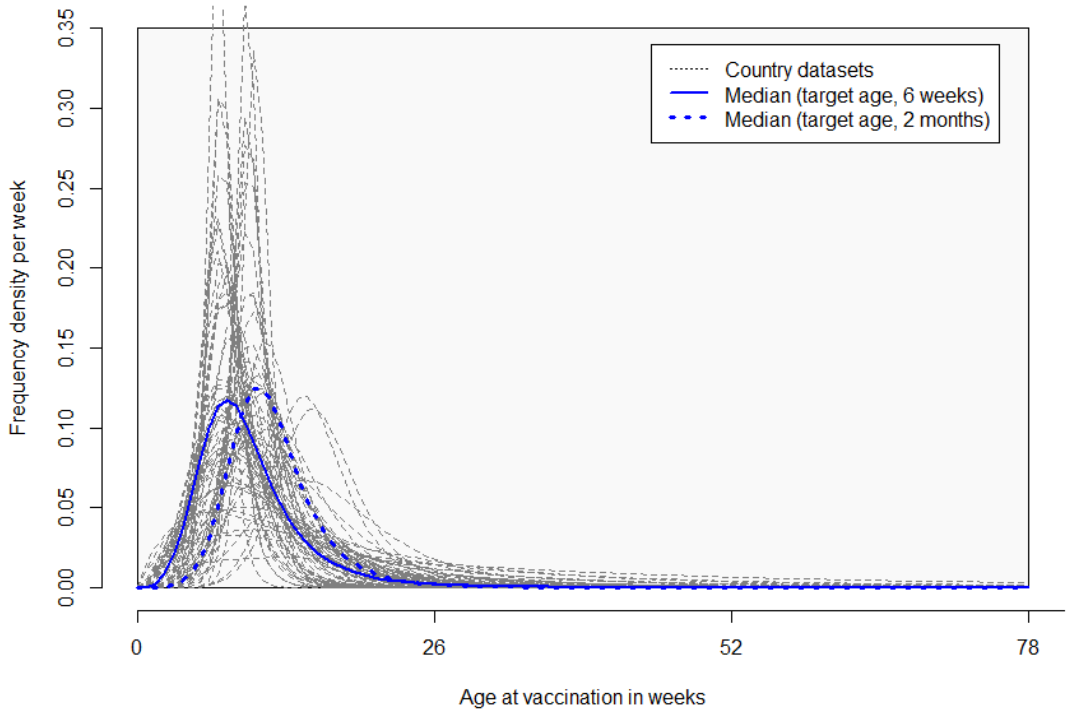


Figure 5. Distributions of the actual age at DTP2 vaccination in 73 LMICs with median distributions for countries with target ages at 10 weeks and 4 months

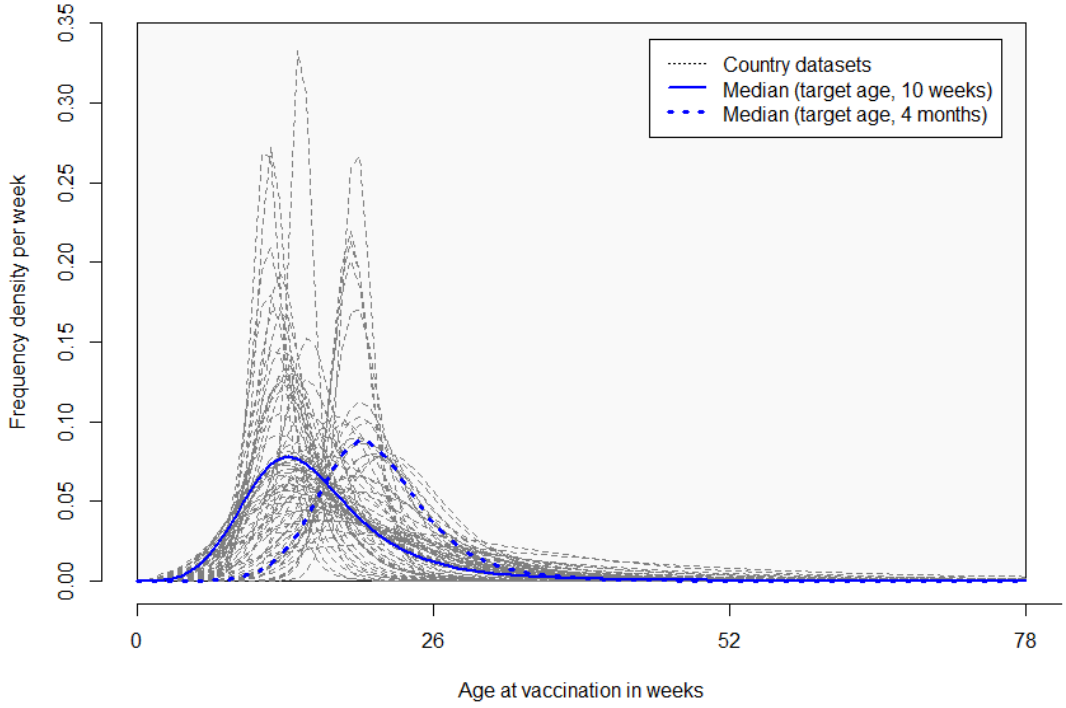


Figure 6. Distributions of the actual age at DTP3 vaccination in 73 LMICs with median distributions for countries with target ages at 14 weeks and 6 months

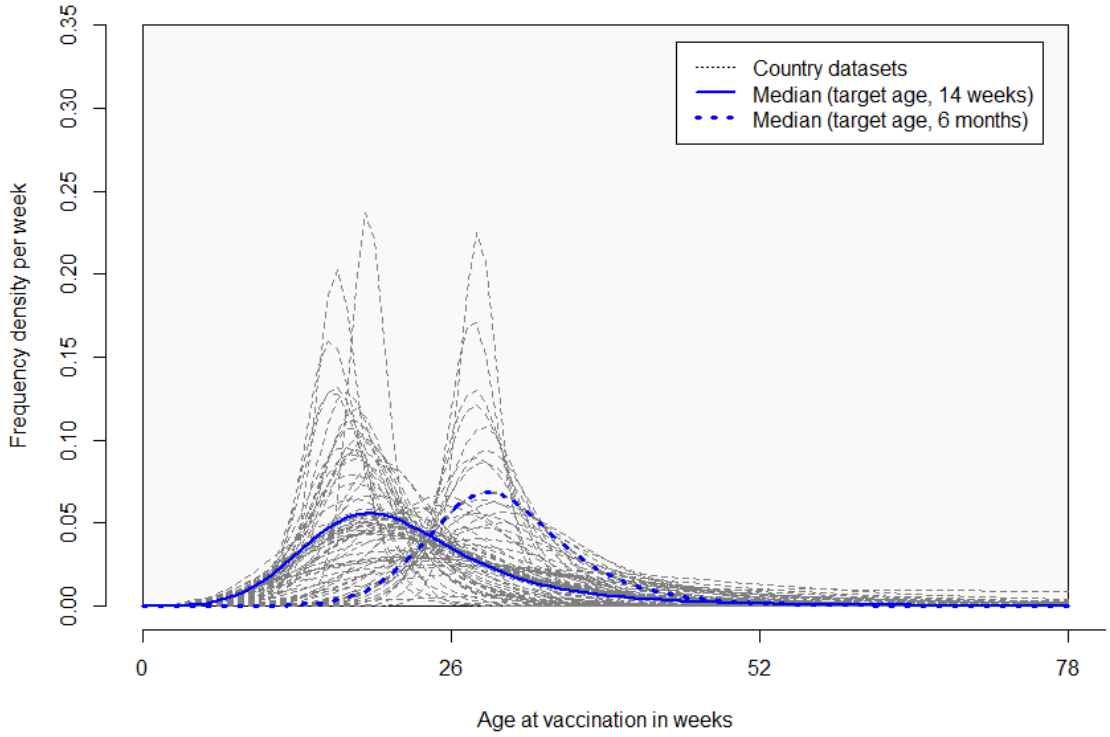
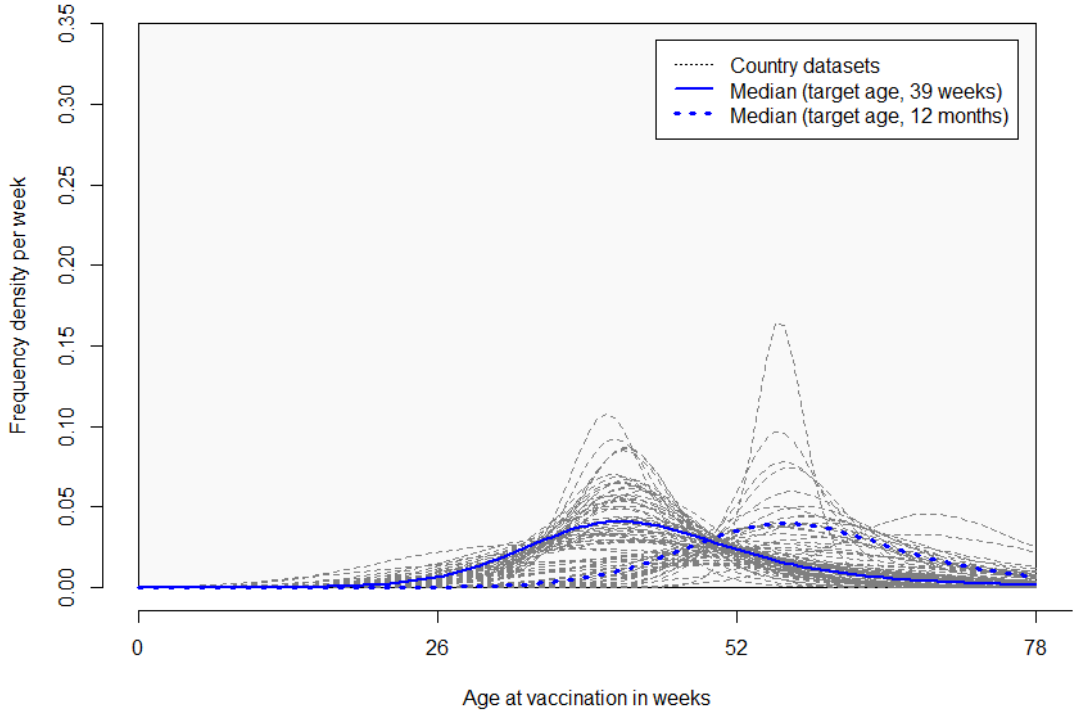


Figure 7. Distributions of the actual age at Meas1 vaccination in 73 LMICs with median distributions for countries with target ages at 39 weeks and 12 months



List of references (Chapter 6)

1. WHO. Immunization schedule data (July 2017 version). Available at: www.who.int/immunization/monitoring_surveillance/data/schedule_data.xls [Accessed 12th December 2017].

2. WHO/UNICEF. WHO/UNICEF Estimates of National Immunization Coverage (WUENIC). Version 15th July 2017. Available at: http://www.who.int/immunization/monitoring_surveillance/routine/coverage/en/index4.html [Accessed 7th Feb 2018]

7.0 Chapter 7 - Estimation of rotavirus vaccine efficacy and waning

7.1 Contribution of paper to the aim and objectives of the thesis

This paper brings together available evidence from RCTs on the efficacy of live oral rotavirus vaccines and uses the data to generate pooled estimates of efficacy by duration of follow-up and type of setting. These are essential to the estimation of rotavirus vaccine impact in each week of age. The pooled estimates from this paper are used in the benefit-risk analysis (Chapter 9). Specifically, I used the estimates for the medium mortality stratum, high mortality stratum (no India) and for India alone. Several possible waning functions were evaluated in this paper. The gamma function had the best goodness of fit in the high mortality stratum, so was used in the base case estimates of the benefit-risk analysis. However, the power function (the main function presented in this paper) estimated less rapid waning and had a better fit in the medium mortality stratum. This function was also evaluated in an alternative 'what-if' scenario to assess the impact of this choice on the benefit-risk ratios.

The paper presented in this chapter also evaluates two schedules that were compared in a head-to-head trial in Indonesia (a three-dose neonatal schedule and a three-dose infant schedule). In the analysis presented in this paper, the neonatal schedule is estimated to have twice the mean duration of protection as the infant schedule. This informed a what-if scenario evaluated in the benefit-risk analysis (Chapter 9), where all doses administered as part of a neonatal schedule were assumed to have twice the mean duration of protection as doses administered as part of an infant schedule.

7.2 Independent academic contribution

I extracted the data from the RCTs and ran initial statistical analyses using Maximum Likelihood Estimation (MLE). This involved writing the R code to fit curves to the mid-points of the reported durations of follow-up in each trial. Mid-points were used rather than the full duration of follow-up in order to approximate instantaneous efficacy at specific follow-up durations. I presented the work to the WHO IVIR-AC committee and wrote the first draft of the paper.

The analysis was subsequently improved by involving experts in Bayesian meta-regression (Kevin Van Zandvoort and Stefan Flasche) who recommended a novel method for converting cumulative vaccine efficacy into instantaneous efficacy (rather

than the crude mid-point approach). Kevin Van Zandvoort ran these subsequent analyses and authored Appendices A-D. Kevin was later included as a joint first author to recognise his important contribution. Appendices A-D are included at the end of the thesis (Appendices 6-9), rather than in the main body of this chapter because I had a minor role in their development.

7.3 Ethical approval

This study was approved by the ethical committee (Ref 15829) of the London School of Hygiene and Tropical Medicine (LSHTM).

Estimating instantaneous efficacy of live oral rotavirus vaccines by duration of follow-up

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Disclaimer

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

Summary

Background

It has become clear that the duration of protection offered by rotavirus vaccines varies across the world, and that this is important to understanding and predicting vaccine impact. There is now a large body of evidence on the efficacy of live oral rotavirus vaccines (VE) in different settings, but this has never been synthesised to obtain robust estimates of efficacy by duration of follow-up by type of setting.

Methods

We identified all RCTs of rotavirus vaccines published before March 2018. For all reported follow-up periods we extracted the mean duration of follow-up, the number of enrolled infants, and case counts for rotavirus-positive severe gastroenteritis (RVGE) in both placebo and vaccine arms. We used a Bayesian hierarchical Poisson meta-regression model to estimate pooled VE and its waning with time for three mortality strata. We then converted these cumulative VE estimates into instantaneous VE (iVE).

Findings

In settings with low-mortality (number of studies, n=10) iVE pooled for infant schedules of Rotarix® and RotaTeq® was 98% (95% credibility interval: 93-100%) two weeks following the final dose of vaccination and 94% (87-98%) after 12 months. In medium-mortality settings (n=8), equivalent estimates were 82% (74-92%) and 77% (67-84%). In settings with high-mortality (n=13), there were five vaccines with observation points for infant schedules. The pooled iVE was 66% (48-81%) after two weeks of follow-up and 44% (27-59%) after 12 months. The data points from India were influential in the high-mortality stratum; iVE pooled for ROTAVAC® and ROTASIIL® in India was 54% (-78-88%) after two weeks and 42% (-128-85%) after 12 months. For RV3-BB in Indonesia, we found more durable efficacy for the neonatal schedule than the infant schedule.

Interpretation

Rotavirus vaccine efficacy is lower and wanes more rapidly in high mortality settings but the earlier peak age of disease in these settings means that rotavirus vaccines are still likely to provide substantial benefit. Strategies to improve the level and durability of protection in high mortality settings should be explored.

Ethical approval

This study was approved by the ethical committee (Ref 15829) of the London School of Hygiene and Tropical Medicine (LSHTM).

Funding

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Strengths and limitations of this study

- We use high quality evidence from randomised placebo-controlled trials.
- We provide statistically robust and novel methods for estimating instantaneous efficacy by duration of follow-up.
- Combining data points for different brands of vaccine and different infant schedules enabled us to maximise the number of data points in each stratum.

Introduction

Rotavirus gastroenteritis (RVGE) is estimated to cause around 200,000 child deaths each year (1-3) with most deaths occurring in Sub-Saharan Africa and South Asia. Episodes of RVGE occur frequently in young children irrespective of living standards and are a major contributor to healthcare costs worldwide (4, 5).

Over half of the countries in the world have introduced rotavirus vaccines into their national immunisation programmes (6). Infants typically receive two oral doses of Rotarix® (GSK Biologicals) or three oral doses of RotaTeq® (Merck & Co.) in the first six months of life (7, 8). Both vaccines have demonstrated high and durable efficacy against episodes of severe RVGE in high income settings, but lower and less durable efficacy in Sub-Saharan Africa and South Asia (9-12). Other live oral rotavirus vaccines are becoming available (ROTAVAC® - Bharat Biotech, ROTASIIL® – Serum Institute of India, RV3-BB – MCRI) but these have also reported lower and/or less durable efficacy in high mortality settings when used as part of a standard infant schedule i.e. India, Indonesia and Niger (13-16). Alternative schedules are being considered as one way to improve efficacy in the second year of life. This may involve administering the first dose at birth (15) or administering a booster dose at 9-12 months (17).

Countries considering rotavirus vaccine introduction, global bodies such as the World Health Organization (WHO) and donors funding vaccine introduction in resource-poor settings, require accurate projections of the potential impact of vaccination. Such projections are also useful in post-introduction surveillance, to ensure that the vaccine is performing as expected, and to estimate the remaining burden of disease after the vaccine has been introduced. Mathematical models can predict the potential impact of rotavirus vaccines but require credible estimates of vaccine efficacy by duration of follow-up, in different settings. This information is also critical to the evaluation of alternative vaccination schedules. A large body of evidence now exists from high quality randomised controlled trials (RCTs) in different parts of the world but these data have never been pooled and synthesised to obtain robust estimates of vaccine efficacy over time. Combining this evidence is not straightforward. There is substantial variation in trial settings, follow-up periods, sample sizes, case definitions, and statistical methods used to calculate confidence intervals. In addition, the main outcome reported in RCTs is the cumulative efficacy (VE) over a period of many weeks, but if there is evidence of vaccine waning, then the cumulative efficacy over the entire follow-up period may greatly overestimate the actual instantaneous efficacy (iVE) at the end of the follow-up period.

Our aim is to propose statistically robust and consistent methods for estimating the instantaneous efficacy of live oral rotavirus vaccines by duration of follow-up (time since

administration of the final dose of rotavirus vaccination). We then apply these methods to the entirety of the relevant literature to generate definitive efficacy estimates by mortality setting.

Methods

Search strategy and selection criteria

We included all individually randomised placebo-controlled trials that were identified in a recent Cochrane systematic review of studies published between May 2012 and March 2018 (Soares-Weiser et al, forthcoming)(18) and cross-checked the list against the studies identified by a recent review by Lamberti et al (19). We excluded trials that were based on special populations, trials without an infant schedule and trials without clear reporting of enrolled infants and events in different periods of follow-up. The outcome measure was efficacy against episodes of severe RVGE, which is the primary endpoint reported in nearly all RCTs of rotavirus vaccines. Severe RVGE is defined as 11-20 points on the Vesikari scale (20), or for some older trials, 15-24 points on the Clark scale (21). If this outcome was not reported, we used the closest available proxy e.g. efficacy against episodes of RVGE that were admitted to hospital or the emergency department. In all RCTs rotavirus-positive episodes were detected by enzyme immunoassay (EIA).

Follow-up definition

We extracted vaccine efficacy for all reported periods of follow-up. We extracted the number of infants and number of rotavirus-positive cases in both the placebo and vaccine arms, as well as the mean duration of follow-up in months. We extracted according-to-protocol (ATP) estimates, which exclude any disease cases that are reported in the first 14 days post-vaccination and only include infants that received all recommended doses. We added 14 days to the reported mean duration of follow-up to calculate the entire period between administration of the last dose and the mean age at follow-up. If all infants were followed to a specific age (e.g. 12 months) we subtracted the mean age of administration of the final dose (or target age if the mean was not reported) from the specific follow-up age.

Stratification of studies

To account for heterogeneity between the RCT sites, we grouped all 201 countries in the world into quintiles (very low mortality, low, medium, high, very high) using the under-five mortality rates reported for the period 2010-2015 in the 2017 Revision of the United Nations Population Division (UNPOP) database. We further collapsed the very low and low quintiles and the high and very high quintiles to give three mortality strata (low, medium, high). Each

RCT was then assigned to a specific stratum. For RCTs with multiple sites across several countries, we included each individual country as a separate observation point where this was possible. If RCT results were not disaggregated by country, we used the sample size in each site to calculate a weighted under-five mortality rate and used this to assign the trial to a specific mortality stratum. We restricted the pooled analysis to infant schedules only.

Recalculating cumulative vaccine efficacy for reported periods of follow-up

There was substantial variation in the way authors estimated vaccine efficacy and 95% confidence intervals. Our pooled analyses (see section below) used case counts and numbers reported in trials to generate credible intervals, but to ensure consistent reporting of the observed data in the plots we also recalculated VE and 95% confidence intervals using the method of Daly and Altman (22, 23). VE was calculated as 1 – RR (relative risk) with zero-inflation to 0.5 for rotavirus-positive disease events in the vaccine arm (24).

Efficacy by duration of follow-up and mortality strata

We used a Bayesian hierarchical meta-regression model to estimate cumulative vaccine efficacy by duration of follow-up. We generated separate pooled estimates for RCTs in low, medium and high mortality strata. We assumed that the observed number of cases in the unvaccinated and vaccinated groups followed a Poisson distribution. The total number of cases in the unvaccinated group in study *i* and period *p*, $Y_{i,p,u}$, was estimated as:

$$\log(Y_{i,p,u}) = \lambda_{i,p} + P_{i,p,u}$$

Similarly, the total number of cases in the vaccinated group in study *i* and period *p,* $Y_{i,p,v}$, was estimated as:

$$\log(Y_{i,p,v}) = \lambda_{i,p} + P_{i,p,v} + \theta_i(t_{i,p})$$

where $\lambda_{i,p}$ is the baseline rate of becoming infected, $P_{i,p,*}$ is the total person-months of follow-up in the respective group, and $\theta_i(t_{i,p})$ is the cumulative relative risk ratio (RR) in study *i*, at *t* months of follow-up. Total person-months of follow-up was calculated as the number of participants at the beginning of the follow-up period multiplied by the mean reported duration of follow-up. The hierarchical component of the model ensured that parameter values of the study-specific RR were identical across periods in studies with more than one data point e.g. RR for period 1, RR for period 1+2 combined.

Best-fitting model parameters were estimated using Markov Chain Monte Carlo (MCMC) methods. Gibbs sampling was used to draw from posterior distributions. We used non-informative prior distributions for all parameters. We ran four parallel MCMC chains and visually assessed whether chains converged. We reported medians and 95% credible intervals

from the posterior distribution of the cumulative vaccine efficacy. In the absence of any prior knowledge about the likely shape of waning we explored several functional forms, including linear, power law, sigmoid and gamma (Appendix A). Their goodness of fit was assessed using the Deviance Information Criterion (DIC), visual assessment, and biological plausibility.

The best-fitting function of cumulative efficacy was used to estimate instantaneous vaccine efficacy (iVE) by duration of follow-up using a novel approach, based on Kaplan-Meier survival estimates. The instantaneous rate ratio at time *t*, $\sigma(t)$, is retrieved using the formula below. Here, the instantaneous rate ratio is a function of the cumulative rate ratio at time *t*, $\theta(t)$, all instantaneous rate ratios up until time *t*, $\sigma(x)$, the baseline rate or force of infection at time *t*, λ_t, and all baseline rates up until time *t*, λ_x:

$$\sigma(t) = \theta(t) + \int_{x=0}^{t} (\theta(t) - \sigma(x)) \frac{\lambda_x}{\lambda_t} dx$$

The instantaneous and cumulative rate ratios are identical at time $t=1$, i.e. $\sigma(1)= \theta(1)$. We then solve the integral using an iterative approach. If changes in baseline rates are unknown, they can be assumed to be similar over time, and $\frac{\lambda_x}{\lambda_t}$ set to 1 or omitted from the equation. iVE at time *t* is then calculated as $1 - \sigma(t)$. Extensive details and example simulations of this method are given in Appendix B. For each stratum, we reported iVE at standard follow-up times.

Analyses were done using R version 3.4.3 (25) using the *rjags* package.

Head-to-head comparison of efficacy for alternative schedules

To compare the efficacy and waning associated with different rotavirus vaccine schedules we identified RCTs that directly compared different vaccine schedules head-to-head and requested more granular unpublished information from the investigators on the number of events occurring in each week of follow-up after the last dose was administered. In sites with available data, we fitted the same models (Appendix A) as in the pooled analysis, but without the hierarchical parameters. Again, cumulative vaccine efficacy was converted to instantaneous vaccine efficacy.

Results

RCTs included in study

We included 50 observation points from 31 RCTs published before March 2018 in populations with low (n=10), medium (n=8) and high (n=13) under-five mortality (Table 1). We excluded

trials that specifically evaluated high HIV prevalence populations (26) and trials that only presented results for breastfed versus non-breastfed infants (27). We excluded the Finnish Extension Trial (FEC)(28, 29) because the results for the extension trial could not be disentangled from the European estimate reported in the REST trial. For the pooled analysis we focused on infant schedules, so excluded the neonatal RotaShield trial in Ghana (30) and the neonatal schedule arm of the RV3-BB trial in Indonesia (15). The neonatal schedule arm of the RV3-BB trial was included in a separate head-to-head comparison of the infant and neonatal schedule in Indonesia (see below).

Most of the data points (40/50) were reported using a Vesikari score of 11-20 (V11-20). There were 24 data points for Rotarix, 19 for RotaTeq, two for RV-3BB, three for ROTASIIL and two for ROTAVAC. More data points (30/50) were based on a three-dose schedule than a two-dose schedule (20/50). The mean age of administration for the first dose ranged from six to 13 weeks.

Efficacy by duration of follow-up and mortality strata

We estimated cumulative and instantaneous vaccine efficacy (median and 95% credible intervals) by duration of follow-up (Figure 1, Table 2). In settings with low-mortality iVE pooled for infant schedules of Rotarix® and RotaTeq® was 98% (95% credibility interval: 93-100%) two weeks following the final dose of vaccination and 94% (87-98%) after 12 months. Equivalent pooled estimates for medium-mortality settings were 82% (74-92%) and 77% (67-84%). In settings with high-mortality (n=13), there were five vaccines with observation points for infant schedules. The pooled iVE was 66% (48-81%) after two weeks of follow-up and 44% (27-59%) after 12 months.

The two large studies in India (ROTAVAC® and ROTASIIL®) were influential, so we ran a sensitivity analysis to calculate iVE with and without the Indian data points, and for India alone (Figure 2, Table 2). In India, iVE pooled for ROTAVAC® and ROTASIIL® was 54% (-78-88%) after two weeks and 42% (-128-85%) after 12 months. When the Indian data points were excluded from the high-mortality stratum, iVE was 81% (56-94%) after two weeks and 36% (5-60%) after 12 months. Thus without the Indian data points, there was higher initial efficacy, but more rapid waning.

A simple power function was fitted in all strata because this required the fewest assumptions/parameters and had goodness of fit (DIC scores) that were consistently favourable across all strata of interest, compared to other functions (Appendix A).

Head-to-head comparison of efficacy for alternative schedules

There were few RCTs with head-to-head comparisons of different schedules. In Indonesia, a three-dose neonatal RV3-BB schedule (0-5 days, 8-10 weeks, 14-16 weeks) was compared to a three-dose RV3-BB infant schedule (8-10 weeks, 14-16 weeks, 18-20 weeks)(15). For the neonatal schedule, the cumulative efficacy was 94% (55-99%) after ~9 months of follow-up and 75% (43-89%) after ~15 months. For the infant schedule, cumulative efficacy was 77% (32-92%) after ~8 months and 51% (7-74%) after ~14 months (Table 1). For this trial we were able to obtain the number of events in each week of follow-up to better inform estimates of instantaneous efficacy over time. For the neonatal schedule, the estimated iVE was 100% (99-100%) after 2 weeks, 77% (73-81%) after 6 months and 40% (26-53%) after 12 months of follow-up. For the standard infant schedule, instantaneous efficacy was 97% (93-99%) after 2 weeks, 51% (45-57%) after 6 months and 2% (-23-23%) after 12 months of follow-up (Table 2, Figure 3). Again, a simple power function was used because it required the minimum number of assumptions/parameters and had favourable DIC scores (Appendix A). Results for alternative functions are shown in Appendix D.

The only other trial with head-to-head comparison of schedules was a multi-country trial comparing infant schedules of Rotarix in South Africa and Malawi. We were unable to obtain the underlying dataset for this trial. In both countries, a three-dose schedule (6, 10, 14 weeks) had higher cumulative efficacy than the two-dose schedule (10, 14 weeks) but confidence intervals were wide (Table 1).

Discussion

Our analysis shows that live oral rotavirus vaccines provide high and durable protection in low and medium mortality settings. Efficacy is lower and wanes more rapidly in high mortality settings, but these settings are also associated with higher rates of severe disease and mortality earlier in life. Before the introduction of rotavirus vaccines, the median age of severe RVGE hospitalisation is estimated to be ~9 months in high mortality settings (Hasso-Agopsowicz et al, forthcoming). Thus, live oral rotavirus vaccines are still likely to provide substantial benefit in these settings, irrespective of waning.

The reasons for lower rotavirus vaccine efficacy in resource-poor settings are not well understood. Immunogenicity studies have shown much lower Geometric Mean Concentrations (GMCs) in resource-poor settings compared to high income settings (31). Hypotheses for lower immunogenicity include interference by maternal antibodies, oral polio vaccines (OPV), breastfeeding, malnutrition, other enteric co-infections, rotavirus strain

diversity and HIV infection. Competition in the gut has also been proposed as a reason for the lower performance of OPV in resource-poor settings (32, 33). Research is currently underway to assess the role of maternal antibodies and gut microbiota in the immune response to rotavirus vaccines in UK, Malawian and Indian infants (34). Two pivotal cohort studies from Mexico(35) and India (36) have reported contrasting estimates of the protection conferred by natural infections against subsequent disease. In Mexico (medium mortality), two prior infections (asymptomatic or symptomatic) conferred 100% protection against subsequent moderate/severe RVGE. In India (high mortality), the equivalent protection was 57% after two prior infections (and 79% after three prior infections). Thus, if natural infections are less likely to protect against moderate/severe RVGE in higher mortality settings, then a live oral vaccine mimicking natural infection will also have lower estimated efficacy in these children.

The reported declines in instantaneous efficacy may not be entirely caused by declining vaccine-induced antibodies. Some of the decrease could be explained by higher rates of immune-boosting asymptomatic and mild infections among placebo recipients compared to vaccine recipients. The risk of severe RVGE in vaccine recipients would then converge with, and may exceed, the risk in placebo recipients over time. Our analysis of the infant and neonatal schedules for RV3-BB in Indonesia suggested a positive protective effect of the vaccine in the first 12 months of follow-up, but extrapolation of the curves suggested a negative effect thereafter. This would be consistent with preferential natural boosting among placebo recipients, but is speculative, as it involves extrapolating beyond the observed period of follow-up in the trial. Re-analysis of RCT data from Bangladesh has allowed these effects to be partly disentangled by excluding any children that experienced an episode of non-severe RVGE. This explained some but not all of the reduction in vaccine efficacy observed over time. However, it was not possible to exclude infants that had prior asymptomatic infections, and these may also play an important role (37).

Head-to-head comparisons of vaccine schedules for the same vaccine were very rare, and more evidence is needed from more geographical locations on the relative benefits of one schedule over another. In our analysis of RV3-BB in Indonesia, the neonatal schedule provided more durable protection than the infant schedule. A neonatal schedule is also likely to result in higher and earlier coverage, and fewer vaccine-related intussusception events, so warrants serious consideration. A booster dose later in infancy (17, 38) or schedules that use injectable non-replicating vaccines (39) could be beneficial, but more evidence is needed on the safety and clinical efficacy of both of these options.

For the pooled analysis, we combined evidence for different vaccine products and different infant schedules to avoid small numbers of data points in each stratum. None of the RCTs

compared different brands of rotavirus vaccination head-to-head in the same population. There were several observations for RotaTeq and Rotarix but the Rotarix sites included data points from South Africa, which had higher efficacy and lower child mortality relative to the sites evaluated in the RotaTeq trials. Thus, in the absence of head-to-head comparisons from the same trial populations, there is currently insufficient evidence to favour one product over another in terms of vaccine efficacy and duration of protection. However, the post-licensure experience of countries that have used both Rotarix and RotaTeq does not suggest any material difference in impact (40).

Most of the data points were reported against Vesikari 11-20 but some were reported against Clark 16-24. These two scores have been shown to correlate poorly with one another when estimating the proportion of RVGE episodes defined as severe (41, 42). However, this bias is unlikely to change the conclusion that protection is high and durable in the low mortality stratum, where the Clark scale was more commonly used.

We stratified our results by mortality and presented pooled results with and without data points from influential studies. We restricted the analysis to RCTs because they represent the gold standard approach for measuring per protocol vaccine efficacy and provide accurate information about the mean duration of follow-up. Other designs, such as case controls studies, report vaccine effectiveness (1 – odds ratio) rather than vaccine efficacy (1 – relative risk) and do not permit precise estimation of the mean duration of follow-up. Some case control studies report vaccine effectiveness by age band, so could potentially be used to derive the duration of follow-up, but this approach becomes increasingly crude as the width of the age band increases. Case control studies are also at risk of bias because vaccinated infants are likely to differ from unvaccinated infants for both known and unknown reasons.

We reported the initial/peak efficacy starting at two weeks of follow-up due to uncertainty around the time it may take for antibodies to develop after vaccination. In addition, we had to extrapolate our fitted estimated of cumulative vaccine efficacy to periods without empiric data e.g. beyond two years of follow-up. The absence of empirical data from RCTs is represented by larger credible intervals in these periods. However, this makes comparison of different waning functions difficult. Evidence from RCTs with a longer duration of follow-up or high-quality observational studies is needed to overcome this knowledge gap.

We used a novel approach to convert estimates from cumulative vaccine efficacy to instantaneous vaccine efficacy. Simulations (in Appendix B) showed that this method appears to work well and is able to retrieve instantaneous vaccine efficacy by converting cumulative vaccine efficacy, and that cumulative efficacy may over-estimate instantaneous efficacy if vaccine efficacy wanes. However, there are some limitations in applying this method to the

meta-regression used in this study. First, it would be better to use relative rates than relative risks. We had to compute relative risks because most of the RCTs only reported observed numbers of cases and individuals at a limited number of time follow-up points. However, as severe RVGE is a relatively rare outcome, risk and rate ratios are expected to be numerically similar, and we assume that this bias is negligible in our study. Second, waning of vaccine efficacy (or conversely, waxing of the relative rate) may interact with changes in baseline rates. This effect would be relatively small on the estimated cumulative vaccine efficacy but may be pronounced when converted to an instantaneous vaccine efficacy. As we had no information on changes in the baseline rates in our studies, we assumed that this rate was constant over time (an assumption which is often made in survival analyses) and did not correct for it. The bias is likely to be in the direction of increasing VE since baseline rates are declining, particularly in high mortality settings. Our method should ideally be extended to control for different changing baseline-rates across different studies, as would be the case in a pooled analysis. However, even uncorrected instantaneous vaccine efficacy should still be a better approximation to true instantaneous vaccine efficacy than cumulative vaccine efficacy in the case of waning vaccine efficacy.

Conclusion

Recent reviews of the efficacy, effectiveness and impact of rotavirus vaccines (19, 43, 44) have described variation in rotavirus vaccine effects according to under-five mortality and geographical region. However, this is the first time all of the available RCT evidence has been synthesised to obtain robust estimates of instantaneous efficacy by duration of follow-up. Our analysis provides the most comprehensive evidence to date that rotavirus vaccine efficacy is lower and wanes more rapidly in high mortality settings. Strategies to improve the level and durability of protection in high mortality settings should be explored.

Table 1. Observations from published RCTs included in the pooled analysis of infant schedules: cumulative efficacy (VE) for reported periods of follow-up (FUP) after two or three doses of live oral rotavirus vaccines

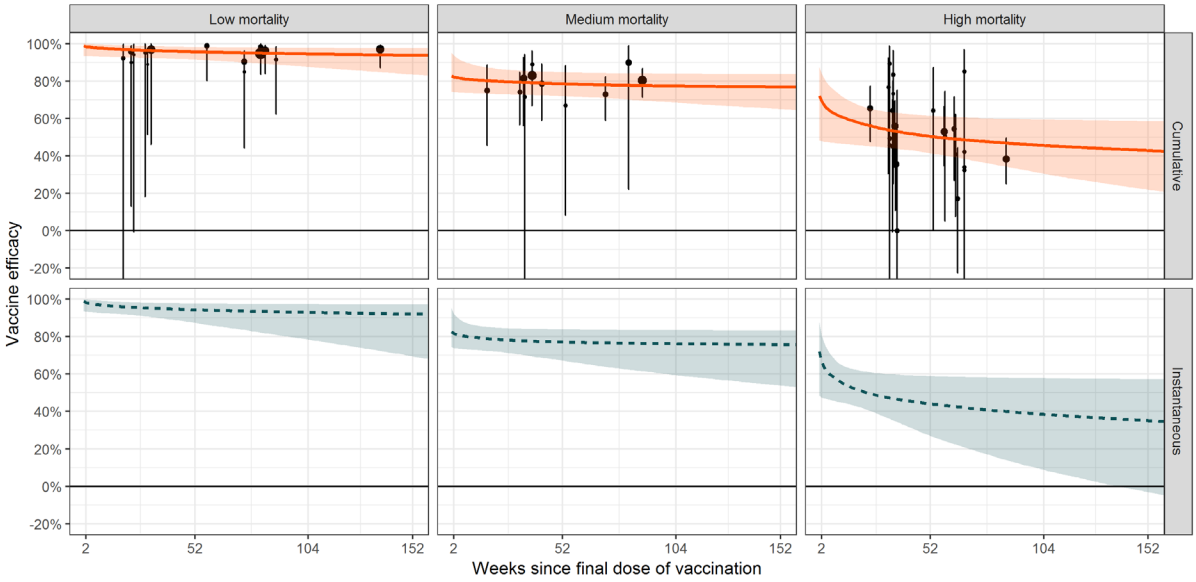
Ref	Country	Schedule			Score	FUP	Placebo		Vaccine		VE		
		d1 age (weeks)	Doses	Brand		(m)	Cases	N	Cases	N	Mid	L95	U95
High mortality													
(9)	Bangladesh	10.0	2d	Rotarix	V11-20	8.1	35	301	9	292	73%	45%	87%
(10)	Malawi	11.0	2d	Rotarix	V11-20	7.7	38	483	21	525	49%	15%	70%
(10)	Malawi	11.0	2d	Rotarix	V11-20	15.6	53	483	38	525	34%	2%	56%
(11)	South Africa*	11.0	2d	Rotarix	V11-20	7.7	9	408	5	418	46%	-60%	82%
(11)	South Africa*	11.0	2d	Rotarix	V11-20	15.6	13	408	9	418	32%	-56%	71%
(10)	Malawi	6.2	3d	Rotarix	V11-20	7.7	38	483	20	505	50%	15%	70%
(10)	Malawi	6.2	3d	Rotarix	V11-20	15.6	53	483	32	505	42%	12%	62%
(11)	South Africa*	6.2	3d	Rotarix	V11-20	7.7	9	408	1	425	89%	16%	99%
(11)	South Africa*	6.2	3d	Rotarix	V11-20	15.6	13	408	2	425	85%	35%	97%
(12)	Bangladesh	8.3	3d	RotaTeq	V11-20	8.0	31	565	17	563	45%	2%	69%
(12)	Bangladesh	8.3	3d	RotaTeq	V11-20	14.7	56	565	33	563	41%	11%	61%
(45)	Ghana	8.4	3d	RotaTeq	V11-20	8.0	42	1081	15	1081	64%	36%	80%
(45)	Ghana	8.4	3d	RotaTeq	V11-20	14.5	57	1081	26	1081	54%	28%	71%
(45)	Kenya	7.3	3d	RotaTeq	V11-20	8.1	12	611	2	610	83%	26%	96%
(45)	Kenya	7.3	3d	RotaTeq	V11-20	12.3	14	611	5	610	64%	1%	87%
(45)	Mali***	6.9	3d	RotaTeq	V11-20	8.5	4	921	4	921	0%	-299%	75%
(45)	Mali	6.9	3d	RotaTeq	V11-20	14.9	58	921	48	921	17%	-20%	43%
(14)	Niger	6.8	3d	ROTASIIL	V11-20	5.6	87	1728	31	1780	65%	48%	77%
(13)	India**	6.9	3d	ROTASIIL	V11-20	8.3	94	3498	61	3527	36%	11%	53%
(13)	India	6.9	3d	ROTASIIL	V11-20	20.0	275	3502	171	3533	38%	26%	49%
(16)	India	6.8	3d	ROTAVAC	V11-20	8.2	64	2187	56	4354	56%	37%	69%
(16)	India	6.8	3d	ROTAVAC	V11-20	13.4	76	2187	71	4354	53%	35%	66%
(15)	Indonesia[$]	9.3	3d	RV3-BB	V11-20	7.5	17	504	4	511	77%	32%	92%
(15)	Indonesia	9.3	3d	RV3-BB	V11-20	13.5	28	504	14	511	51%	7%	74%
Medium mortality													
(46)	China	9.6	2d	Rotarix	V11-20	4.0	32	1573	8	1575	75%	46%	88%
(46)	China	9.6	2d	Rotarix	V11-20	16.5	75	1573	21	1575	72%	55%	83%
(47)	Latin Am. (n=3)	8.4	2d	Rotarix	V11-20	7.5	34	454	27	1392	74%	58%	84%
(48)	Latin Am. (n=6)	8.6	2d	Rotarix	V11-20	7.9	19	2099	7	4211	82%	56%	92%
(49)	Latin Am. (n=10)	8.0	2d	Rotarix	V11-20	8.8	58	7081	10	7205	83%	67%	91%
(49)	Latin Am. (n=10)	8.0	2d	Rotarix	V11-20	20.5	161	7081	32	7205	80%	71%	87%
(50)	China	8.5	3d	RotaTeq	V11-20	9.8	52	1946	11	1930	79%	59%	89%
(51)	Latin Am. (n=5)	9.7	3d	RotaTeq	Hosp/ED	19.0	10	2237	1	2252	90%	22%	99%
(52)	USA (Navajo)	>6	3d	RotaTeq	C11-24	8.8	37	403	4	392	89%	69%	96%
(12)	Viet nam	9.7	3d	RotaTeq	V11-20	8.0	7	442	2	446	72%	-36%	94%
(12)	Viet nam	9.7	3d	RotaTeq	V11-20	12.3	15	442	5	446	67%	10%	88%
Low mortality													
(53)	Europe (n=6)	11.5	2d	Rotarix	V11-20	5.3	60	1302	5	2572	96%	90%	98%
(53)	Europe (n=6)	11.5	2d	Rotarix	V11-20	17.3	127	1302	24	2572	90%	85%	94%
(54)	Finland	8.3	2d	Rotarix	V11-20	5.3	5	123	1	245	90%	15%	99%
(54)	Finland	8.3	2d	Rotarix	V11-20	17.3	10	123	3	245	85%	46%	96%
(55)	Japan	7.7	2d	Rotarix	V11-20	20.6	12	250	2	498	92%	63%	98%
(56)	SE Asia (n=3)	12.0	2d	Rotarix	V11-20	7.4	15	5256	0	5263	97%	46%	100%
(56)	SE Asia (n=3)	12.0	2d	Rotarix	V11-20	31.7	64	5256	2	5263	97%	87%	99%
(56)	SE Asia (n=3)	12.0	2d	Rotarix	V11-20	19.5	51	5256	2	5263	96%	84%	99%
(57)	USA	13.0	2d	Rotarix	All RVGE	7.0	18	107	2	108	89%	54%	97%
(58)	Europe (n=5)	10.0	3d	RotaTeq	C17-24	13.3	43	1188	0	1120	99%	80%	100%
(58)	Europe (n=5)**	10.0	3d	RotaTeq	C17-24	19.0	61	1155	1	1088	98%	87%	100%
(51)	USA	9.7	3d	RotaTeq	Hosp/ED	19.0	58	12179	3	12284	95%	84%	98%
(59)	Finland/USA	10.0	3d	RotaTeq	C17-24	4.4	6	661	0	651	92%	-38%	100%
(55)	Japan	7.6	3d	RotaTeq	C17-24	6.7	10	381	0	380	95%	19%	100%
(60)	USA	>8	3d	RotaTeq	C17-24	5.5	8	183	0	187	94%	1%	100%

* Data only extracted for the South African cohort that was followed for two successive seasons.
** N values were adjusted to be the same for both follow-up periods in Bayesian meta-regression.
*** There were surveillance issues in the first year of trial in Mali that have been postulated to contribute to the low efficacy in the first period, but we did not adjust for this.
[$] Only shows data from the infant schedule arm of the trial. See Figure 3 for a comparison with the neonatal schedule arm.

Table 2. Median instantaneous vaccine efficacy (iVE) and 95% credible intervals by duration of follow-up and setting after two or three doses of oral rotavirus vaccination (infant schedules only)

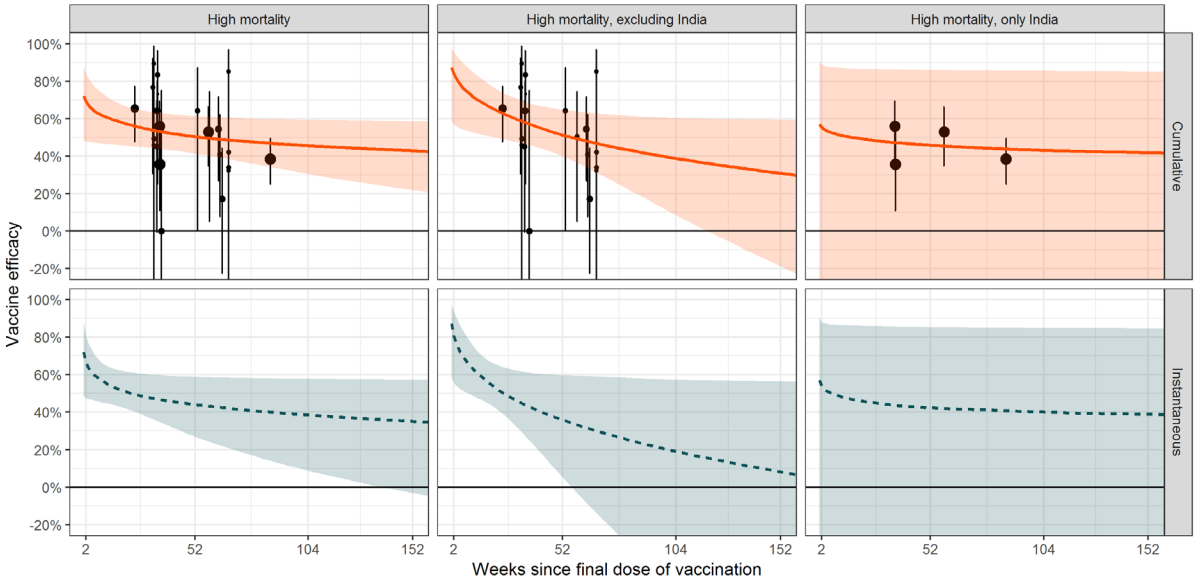
	Low mortality		Medium mortality		High mortality		High mortality (no India)		India	
	iVE	95%CI	iVE	95%CI	iVE	95%CI	iVE	95%CI	iVE	95%CI
2w	98%	93-100%	82%	74-92%	66%	48-81%	81%	56-94%	54%	-78-88%
1m	98%	93-100%	81%	74-90%	62%	47-75%	74%	53-88%	52%	-89-88%
2m	97%	93-99%	80%	73-87%	57%	45-67%	66%	50-79%	49%	-105-87%
3m	96%	92-99%	79%	73-86%	54%	44-64%	61%	48-72%	48%	-108-86%
6m	95%	91-98%	78%	71-84%	49%	40-61%	49%	38-64%	45%	-115-86%
9m	95%	89-98%	77%	69-84%	46%	33-60%	42%	22-61%	43%	-124-86%
12m	94%	87-98%	77%	67-84%	44%	27-59%	36%	5-60%	42%	-128-85%
18m	94%	83-97%	77%	63-84%	41%	17-58%	27%	-26-59%	41%	-135-85%
24m	93%	79-97%	76%	59-83%	38%	9-58%	19%	-54-57%	40%	-139-85%
36m	92%	69-97%	76%	53-83%	35%	-4-57%	7%	-107-56%	39%	-149-85%
48m	91%	58-97%	75%	48-83%	32%	-14-57%	-2%	-154-56%	38%	-154-85%
60m	91%	48-97%	75%	44-83%	30%	-23-57%	-10%	-200-55%	37%	-163-85%

Figure 1. Median and 95% credible intervals of cumulative and instantaneous vaccine efficacy by duration of follow-up and setting after two or three doses of oral rotavirus vaccination (infant schedules only)



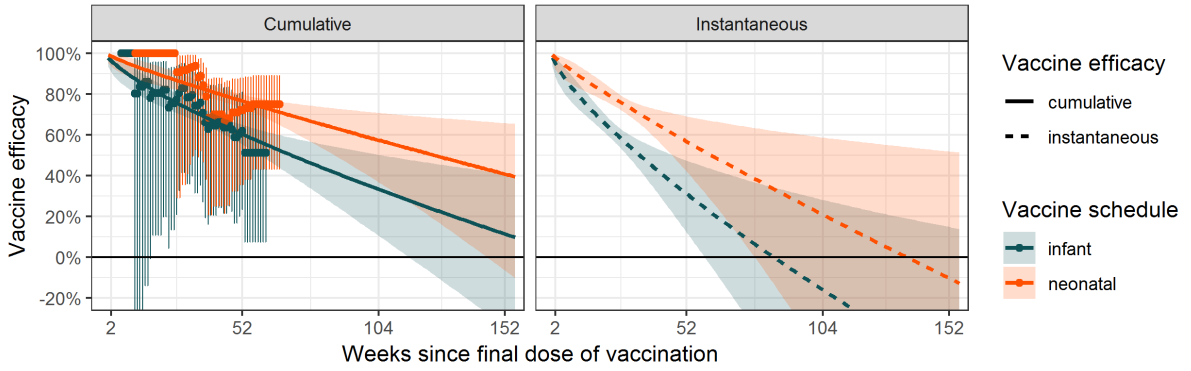
Note: A simple power function was used to represent vaccine waning over time (Appendix A). See Appendix C for equivalent plots based on other potential waning functions.

Figure 2. Median and 95% credible intervals of cumulative and instantaneous vaccine efficacy by duration of follow-up after two or three doses of oral rotavirus vaccination (infant schedules only) in high mortality settings: *sensitivity analysis showing results with and without the Indian data points, and for India alone*



Note: A simple power function was used to represent vaccine waning over time (Appendix A). See Appendix C for equivalent plots based on other potential waning functions.

Figure 3. Median and 95% credible intervals of cumulative and instantaneous vaccine efficacy by duration of follow-up and type of schedule (neonatal versus infant) following three doses of RV3-BB in Indonesia



Note: A simple power function was used to represent vaccine waning over time (Appendix A). See Appendix D for equivalent plots based on other potential waning functions. Data points shown on the left panel represent observed vaccine efficacies derived from cumulative Kaplan-Meier hazard ratios, and error bars with their corresponding 95% confidence intervals. Solid lines (VE) and dashed lines (iVE) represent medians. Shaded areas represent 95% credible intervals.

List of references (Chapter 7)

1. Collaborators GBD. Estimates of global, regional, and national morbidity, mortality, and aetiologies of diarrhoeal diseases: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Infect Dis. 2017.

2. Lanata CF, Fischer-Walker CL, Olascoaga AC, Torres CX, Aryee MJ, Black RE, et al. Global causes of diarrheal disease mortality in children <5 years of age: a systematic review. PLoS One. 2013;8(9):e72788.

3. Tate JE, Burton AH, Boschi-Pinto C, Parashar UD, World Health Organization-Coordinated Global Rotavirus Surveillance N. Global, Regional, and National Estimates of Rotavirus Mortality in Children <5 Years of Age, 2000-2013. Clin Infect Dis. 2016;62 Suppl 2:S96-S105.

4. Rheingans RD, Antil L, Dreibelbis R, Podewils LJ, Bresee JS, Parashar UD. Economic costs of rotavirus gastroenteritis and cost-effectiveness of vaccination in developing countries. J Infect Dis. 2009;200 Suppl 1:S16-27.

5. Thomas SL, Walker JL, Fenty J, Atkins KE, Elliot AJ, Hughes HE, et al. Impact of the national rotavirus vaccination programme on acute gastroenteritis in England and associated costs averted. Vaccine. 2017;35(4):680-6.

6. Council R. Country introductions of rotavirus vaccines. Available at: http://rotacouncil.org/vaccine-introduction/global-introduction-status/ [accessed 31st August 2018].

7. Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, Abate H, Breuer T, Clemens SC, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med. 2006;354(1):11-22.

8. Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med. 2006;354(1):23-33.

9. Colgate ER, Haque R, Dickson DM, Carmolli MP, Mychaleckyj JC, Nayak U, et al. Delayed Dosing of Oral Rotavirus Vaccine Demonstrates Decreased Risk of Rotavirus Gastroenteritis Associated With Serum Zinc: A Randomized Controlled Trial. Clin Infect Dis. 2016;63(5):634-41.

10. Cunliffe NA, Witte D, Ngwira BM, Todd S, Bostock NJ, Turner AM, et al. Efficacy of human rotavirus vaccine against severe gastroenteritis in Malawian children in the first two years of life: a randomized, double-blind, placebo controlled trial. Vaccine. 2012;30 Suppl 1:A36-43.

11. Madhi SA, Kirsten M, Louw C, Bos P, Aspinall S, Bouckenooghe A, et al. Efficacy and immunogenicity of two or three dose rotavirus-vaccine regimen in South African children over two consecutive rotavirus-seasons: a randomized, double-blind, placebo-controlled trial. Vaccine. 2012;30 Suppl 1:A44-51.

12. Zaman K, Dang DA, Victor JC, Shin S, Yunus M, Dallas MJ, et al. Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in

developing countries in Asia: a randomised, double-blind, placebo-controlled trial. Lancet. 2010;376(9741):615-23.

13. Kulkarni PS, Desai S, Tewari T, Kawade A, Goyal N, Garg BS, et al. A randomized Phase III clinical trial to assess the efficacy of a bovine-human reassortant pentavalent rotavirus vaccine in Indian infants. Vaccine. 2017;35(45):6228-37.

14. Isanaka S, Guindo O, Langendorf C, Matar Seck A, Plikaytis BD, Sayinzoga-Makombe N, et al. Efficacy of a Low-Cost, Heat-Stable Oral Rotavirus Vaccine in Niger. N Engl J Med. 2017;376(12):1121-30.

15. Bines JE, At Thobari J, Satria CD, Handley A, Watts E, Cowley D, et al. Human Neonatal Rotavirus Vaccine (RV3-BB) to Target Rotavirus from Birth. N Engl J Med. 2018;378(8):719-30.

16. Bhandari N, Rongsen-Chandola T, Bavdekar A, John J, Antony K, Taneja S, et al. Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian infants: a randomised, double-blind, placebo-controlled trial. Lancet. 2014;383(9935):2136-43.

17. Haidara FC, Tapia MD, Sow SO, Doumbia M, Coulibaly F, Diallo F, et al. Evaluation of a Booster Dose of Pentavalent Rotavirus Vaccine Coadministered With Measles, Yellow Fever, and Meningitis A Vaccines in 9-Month-Old Malian Infants. J Infect Dis. 2018;218(4):606-13.

18. Soares-Weiser K, Maclehose H, Bergman H, Ben-Aharon I, Nagpal S, Goldberg E, et al. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Cochrane Database Syst Rev. 2012;11:CD008521.

19. Lamberti LM, Ashraf S, Walker CL, Black RE. A Systematic Review of the Effect of Rotavirus Vaccination on Diarrhea Outcomes Among Children Younger Than 5 Years. Pediatr Infect Dis J. 2016;35(9):992-8.

20. Ruuska T, Vesikari T. Rotavirus disease in Finnish children: use of numerical scores for clinical severity of diarrhoeal episodes. Scand J Infect Dis. 1990;22(3):259-67.

21. Clark HF, Borian FE, Bell LM, Modesto K, Gouvea V, Plotkin SA. Protective effect of WC3 vaccine against rotavirus diarrhea in infants during a predominantly serotype 1 rotavirus season. J Infect Dis. 1988;158(3):570-87.

22. Altman DG. Confidence intervals for the number needed to treat. BMJ. 1998;317(7168):1309-12.

23. Daly LE. Confidence limits made easy: interval estimation using a substitution method. Am J Epidemiol. 1998;147(8):783-90.

24. Deeks J.J. and Higgins J.P.T. Statistical algorithms in Review Manager 5.1. Available at: https://training.cochrane.org/handbook/statistical-methods-revman5 [Accessed 1st Sept 2018].

25. (2013) R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.

26. Feikin DR, Laserson KF, Ojwando J, Nyambane G, Ssempijja V, Audi A, et al. Efficacy of pentavalent rotavirus vaccine in a high HIV prevalence population in Kenya. Vaccine. 2012;30 Suppl 1:A52-60.

27. Vesikari T, Prymula R, Schuster V, Tejedor JC, Cohen R, Bouckenooghe A, et al. Efficacy and immunogenicity of live-attenuated human rotavirus vaccine in breast-fed and formula-fed European infants. Pediatr Infect Dis J. 2012;31(5):509-13.

28. Vesikari T, Karvonen A, Ferrante SA, Ciarlet M. Efficacy of the pentavalent rotavirus vaccine, RotaTeq(R), in Finnish infants up to 3 years of age: the Finnish Extension Study. Eur J Pediatr. 2010;169(11):1379-86.

29. Vesikari T, Karvonen A, Ferrante SA, Kuter BJ, Ciarlet M. Sustained efficacy of the pentavalent rotavirus vaccine, RV5, up to 3.1 years following the last dose of vaccine. Pediatr Infect Dis J. 2010;29(10):957-63.

30. Armah GE, Kapikian AZ, Vesikari T, Cunliffe N, Jacobson RM, Burlington DB, et al. Efficacy, immunogenicity, and safety of two doses of a tetravalent rotavirus vaccine RRV-TV in Ghana with the first dose administered during the neonatal period. J Infect Dis. 2013;208(3):423-31.

31. Patel M, Glass RI, Jiang B, Santosham M, Lopman B, Parashar U. A systematic review of anti-rotavirus serum IgA antibody titer as a potential correlate of rotavirus vaccine efficacy. J Infect Dis. 2013;208(2):284-94.

32. Chan J, Nirwati H, Triasih R, Bogdanovic-Sakran N, Soenarto Y, Hakimi M, et al. Maternal antibodies to rotavirus: could they interfere with live rotavirus vaccines in developing countries? Vaccine. 2011;29(6):1242-7.

33. Lopman BA, Pitzer VE. Waxing Understanding of Waning Immunity. J Infect Dis. 2018;217(6):851-3.

34. Sindhu KN, Cunliffe N, Peak M, Turner M, Darby A, Grassly N, et al. Impact of maternal antibodies and infant gut microbiota on the immunogenicity of rotavirus vaccines in African, Indian and European infants: protocol for a prospective cohort study. BMJ Open. 2017;7(3):e016577.

35. Velazquez FR, Matson DO, Calva JJ, Guerrero L, Morrow AL, Carter-Campbell S, et al. Rotavirus infection in infants as protection against subsequent infections. N Engl J Med. 1996;335(14):1022-8.

36. Gladstone BP, Ramani S, Mukhopadhya I, Muliyil J, Sarkar R, Rehman AM, et al. Protective effect of natural rotavirus infection in an Indian birth cohort. N Engl J Med. 2011;365(4):337-46.

37. Rogawski ET, Platts-Mills JA, Colgate ER, Haque R, Zaman K, Petri WA, et al. Quantifying the Impact of Natural Immunity on Rotavirus Vaccine Efficacy Estimates: A Clinical Trial in Dhaka, Bangladesh (PROVIDE) and a Simulation Study. J Infect Dis. 2018;217(6):861-8.

38. Burnett E, Lopman BA, Parashar UD. Potential for a booster dose of rotavirus vaccine to further reduce diarrhea mortality. Vaccine. 2017;35(51):7198-203.

39. Kirkwood CD, Ma LF, Carey ME, Steele AD. The rotavirus vaccine development pipeline. Vaccine. 2017.

40. Immergluck LC, Parker TC, Jain S, Laghaie E, Spandorfer P, Jerris RC, et al. Sustained Effectiveness of Monovalent and Pentavalent Rotavirus Vaccines in Children. J Pediatr. 2016;172:116-20 e1.

41. Aslan A, Kurugol Z, Cetin H, Karakaslilar S, Koturoglu G. Comparison of Vesikari and Clark scales regarding the definition of severe rotavirus gastroenteritis in children. Infect Dis (Lond). 2015;47(5):332-7.

42. Givon-Lavi N, Greenberg D, Dagan R. Comparison between two severity scoring scales commonly used in the evaluation of rotavirus gastroenteritis in children. Vaccine. 2008;26(46):5798-801.

43. Jonesteller CL, Burnett E, Yen C, Tate JE, Parashar UD. Effectiveness of Rotavirus Vaccination: A systematic review of the first decade of global post-licensure data, 2006-2016. Clin Infect Dis. 2017.

44. Patel MM, Clark AD, Sanderson CF, Tate J, Parashar UD. Removing the age restrictions for rotavirus vaccination: a benefit-risk modeling analysis. PLoS Med. 2012;9(10):e1001330.

45. Armah GE, Sow SO, Breiman RF, Dallas MJ, Tapia MD, Feikin DR, et al. Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in sub-Saharan Africa: a randomised, double-blind, placebo-controlled trial. Lancet. 2010;376(9741):606-14.

46. Li RC, Huang T, Li Y, Luo D, Tao J, Fu B, et al. Human rotavirus vaccine (RIX4414) efficacy in the first two years of life: a randomized, placebo-controlled trial in China. Hum Vaccin Immunother. 2014;10(1):11-8.

47. Salinas B, Perez Schael I, Linhares AC, Ruiz Palacios GM, Guerrero ML, Yarzabal JP, et al. Evaluation of safety, immunogenicity and efficacy of an attenuated rotavirus vaccine, RIX4414: A randomized, placebo-controlled trial in Latin American infants. Pediatr Infect Dis J. 2005;24(9):807-16.

48. Tregnaghi MW, Abate HJ, Valencia A, Lopez P, Da Silveira TR, Rivera L, et al. Human rotavirus vaccine is highly efficacious when coadministered with routine expanded program of immunization vaccines including oral poliovirus vaccine in Latin America. Pediatr Infect Dis J. 2011;30(6):e103-8.

49. Linhares AC, Velazquez FR, Perez-Schael I, Saez-Llorens X, Abate H, Espinoza F, et al. Efficacy and safety of an oral live attenuated human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in Latin American infants: a randomised, double-blind, placebo-controlled phase III study. Lancet. 2008;371(9619):1181-9.

50. Mo Z, Mo Y, Li M, Tao J, Yang X, Kong J, et al. Efficacy and safety of a pentavalent live human-bovine reassortant rotavirus vaccine (RV5) in healthy Chinese infants: A randomized, double-blind, placebo-controlled trial. Vaccine. 2017;35(43):5897-904.

51. Vesikari T, Itzler R, Matson DO, Santosham M, Christie CD, Coia M, et al. Efficacy of a pentavalent rotavirus vaccine in reducing rotavirus-associated health care utilization across three regions (11 countries). Int J Infect Dis. 2007;11 Suppl 2:S29-35.

52. Grant LR, Watt JP, Weatherholtz RC, Moulton LH, Reid R, Santosham M, et al. Efficacy of a pentavalent human-bovine reassortant rotavirus vaccine against rotavirus gastroenteritis among American Indian children. Pediatr Infect Dis J. 2012;31(2):184-8.

53. Vesikari T, Karvonen A, Prymula R, Schuster V, Tejedor JC, Cohen R, et al. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. Lancet. 2007;370(9601):1757-63.

54. Vesikari T, Karvonen A, Puustinen L, Zeng SQ, Szakal ED, Delem A, et al. Efficacy of RIX4414 live attenuated human rotavirus vaccine in Finnish infants. Pediatr Infect Dis J. 2004;23(10):937-43.

55. Iwata S, Nakata S, Ukae S, Koizumi Y, Morita Y, Kuroki H, et al. Efficacy and safety of pentavalent rotavirus vaccine in Japan: a randomized, double-blind, placebo-controlled, multicenter trial. Hum Vaccin Immunother. 2013;9(8):1626-33.

56. Phua KB, Lim FS, Lau YL, Nelson EA, Huang LM, Quak SH, et al. Rotavirus vaccine RIX4414 efficacy sustained during the third year of life: a randomized clinical trial in an Asian population. Vaccine. 2012;30(30):4552-7.

57. Bernstein DI, Sack DA, Rothstein E, Reisinger K, Smith VE, O'Sullivan D, et al. Efficacy of live, attenuated, human rotavirus vaccine 89-12 in infants: a randomised placebo-controlled trial. Lancet. 1999;354(9175):287-90.

58. Vesikari T, Karvonen A, Prymula R, Schuster V, Tejedor JC, Thollot F, et al. Immunogenicity and safety of the human rotavirus vaccine Rotarix co-administered with routine infant vaccines following the vaccination schedules in Europe. Vaccine. 2010;28(32):5272-9.

59. Block SL, Vesikari T, Goveia MG, Rivers SB, Adeyi BA, Dallas MJ, et al. Efficacy, immunogenicity, and safety of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine at the end of shelf life. Pediatrics. 2007;119(1):11-8.

60. Clark HF, Bernstein DI, Dennehy PH, Offit P, Pichichero M, Treanor J, et al. Safety, efficacy, and immunogenicity of a live, quadrivalent human-bovine reassortant rotavirus vaccine in healthy infants. J Pediatr. 2004;144(2):184-90.

Chapter 8 - Estimation of the incidence, age distribution and case fatality of intussusception in children aged < 5 years

8.1 Contribution of paper to the aim and objectives of the thesis

This paper provides a comprehensive update of the evidence on intussusception incidence rates, age distributions and CFRs in LMICs. This greatly expands the quality and depth of evidence that was used in the previous benefit-risk analysis (Appendix 1). For example, multiple new studies have been published since the time of the last analysis. We also sought more granular data on age distributions than was published in the original articles and broadened the scope to include incidence rates and age distributions up to age 5.0 years. We found high rates of intussusception in the Western Pacific region and very high CFRs in Africa.

8.2 Independent academic contribution

I was the LSHTM principal investigator and first author of the paper. I wrote the R code, ran the statistical analysis, presented the work to the WHO IVIR-AC committee and wrote the first draft of the paper. The systematic review and data gathering were done by others. I resolved conflicts between the two systematic reviewers using Distiller software.

8.3 Ethical approval

This study was approved by the ethical committee (Ref 15595) of the London School of Hygiene and Tropical Medicine (LSHTM).

Global review of the incidence, age distribution and case fatality of intussusception hospital admissions among children aged < 5 years, before the introduction of rotavirus vaccination

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Abstract

Objective To estimate the incidence, age distribution and case fatality of intussusception hospital admissions among children aged < 5 years, before the introduction of rotavirus vaccination

Methods We included all studies published between January 2002 and January 2018. We fitted parametric age distributions to estimate the median age, interquartile age range, and cumulative proportion of intussusception cases estimated to have occurred by standard ages between birth and age 5.0 years. We estimated incidence rates and case fatality ratios (CFRs) for children aged <5 years for each country and each WHO region.

Findings We identified 128 articles containing 227 country datasets (61 age distributions, 71 incidence rates and 95 CFRs). The median age of intussusception ranged from 29 weeks in Africa (83% of cases in the first year of life) to 70 weeks in the Western Pacific region (35% of cases in the first year of life). The median (range) annual incidence of intussusception hospital admissions per 100,000 aged <1 years ranged from 34 (13-56) in Africa to 90 (9-380) in the Western Pacific region. We found extreme differences between the CFRs in Africa (one in ten hospital admissions) and the rest of the world (less than one in every 100-2000 hospital admissions).

Conclusion Intussusception epidemiology varies by country and region. Understanding and recognising these differences will be important when assessing the potential number of intussusception cases associated with rotavirus vaccines.

Introduction

Intussusception is the main cause of bowel obstruction in children aged <5 years. It occurs when a segment of the intestine telescopes or folds back on itself (1). This blocks the passage of food and liquid through the intestine and restricts the supply of blood to the affected area. Some cases of intussusception will spontaneously resolve without treatment, but delayed diagnosis can lead to perforation and infection in the lining of the abdominal cavity (peritonitis). Peritonitis can cause severe abdominal pain, fever, shock and death (2). In high income countries most children are diagnosed quickly with ultrasound or radiograph and the bowel will return to normal after injecting a liquid or gas into the rectum (enema). In more severe cases surgery is usually very successful. However, in parts of Africa and elsewhere, many children will die before reaching healthcare. For those that do reach healthcare, surgery is often the primary method of diagnosis and treatment, leading to death in ~10% of cases (3).

The cause of intussusception is usually unclear, but infections that cause swelling in the bowel wall may be associated (4). In some countries that have introduced oral rotavirus vaccines, a small but elevated risk of intussusception has been reported in the first few weeks after administration of the first and second dose. To limit the scale of potential vaccine-related intussusception cases the vaccine manufacturers have recommended administration of the first dose before 15 weeks of age (and the final dose before 32 weeks of age) when the background rate of intussusception is relatively low (5).

Published intussusception incidence rates, age distributions and case fatality ratios (CFRs) have been reviewed and published by the World Health Organization (WHO) (1960-2002) (2) and Jiang *et al* (2002-2012) (3) but there are a number of reasons why this evidence should now be updated. First, many new studies have been published since 2012. Second, age distributions and incidence rates were previously restricted to children aged <1 year despite many cases being observed between the ages of 1.0 and 5.0 years in some settings (6-8). Third, case-fatality ratios (CFRs) were estimated for a variety of age groups rather than a standard (e.g. <5 years) making it difficult to compare countries and estimate ratios in countries with no data. Fourth, published intussusception age distributions are rarely published by week of age. Obtaining data from authors/investigators at this level of age granularity will improve precision when estimating the potential number of excess intussusception cases after rotavirus vaccine introduction. Other inputs needed for this calculation are already available in weekly age units, such as vaccine coverage/timeliness (9) and the relative risk of intussusception after each dose of rotavirus vaccine (10).

In this paper we provide an updated global review of the incidence, age distribution and case fatality of intussusception hospital admissions among children aged < 5 years of age, before

the introduction of rotavirus vaccination. This will provide an important pre-vaccination baseline to compare with evidence from the post-vaccination era. It will also provide inputs that are critical for assessing the number of excess intussusception cases that could be associated with different rotavirus vaccination schedules in different settings.

Methods

Search strategy

We sought information from published research articles on intussusception incidence rates, age distributions and CFRs in children aged <5 years, before the introduction of rotavirus vaccination. We included all studies published between January 2002 and June 2012 that were identified in a previous review by Jiang *et al* (3). We then added all relevant studies published between June 2012 and January 2018, identified from a new global systematic literature review. This review used search terms that were consistent with the review by Jiang *et al* i.e. "intussusception" or "intestinal invagination". It was conducted in accordance with PRISMA guidelines. We searched PubMed, EMBASE, MEDLINE and Cochrane Library. We restricted the search to articles published in English, French, Spanish and Polish. To increase the relevance of our analysis we excluded all studies published before January 2002. We therefore excluded all studies from an earlier review by WHO (1960-2002) (2). All titles and abstracts identified by the systematic review were screened for inclusion by two reviewers (MHA and LS) using Distiller software. Any disagreements were resolved by a third reviewer (AC). Articles were excluded if: a) it was not possible to extract data for the years prior to rotavirus vaccine introduction; b) the data period ended prior to the year 2000; c) cases were not coded as ICD9-560, ICD10-K56.1, Brighton Collaboration Level 1 (BCL1) or defined clinically as intussusception; d) there were fewer than 35 cases (for age distribution fitting); e) more recent data was published elsewhere for the same population/location (for incidence rates); f) they described animal studies; g) they described individual case reports; h) they focused on a specific subgroup of cases e.g. follow-up evaluations of chronic or recurrent intussusception; i) they were conducted in special populations e.g. HIV positive; or, j) the study had a high risk of bias. All remaining studies were assigned very low, low or medium risk of bias (see Appendix Table 1). If information from multiple countries was published as a single data point it was included if all countries were from the same WHO region and it was clear that none of the country-level data were reported elsewhere.

Data extraction

We compiled a database containing information on intussusception incidence rates, age distributions and CFRs in children aged <5 years. For all studies, we extracted the country, subnational location, study design, case definition, period of data collection and age range. To obtain more granular age distributions we emailed an invitation letter to all authors that were listed in the Jiang *et al* review (2002-2012)(3) and all authors identified in the new systematic review (2012-2018). We invited each author to share a spreadsheet table with counts of intussusception hospital admissions by week of age up to 5.0 years. If the authors did not respond then we extracted the age distributions published in the research article. We also extracted the published incidence rate and the number of intussusception cases and deaths.

A country dataset was defined as any dataset with hospitalised patients before the introduction of rotavirus vaccine, taken from a single study in a single country, and reporting on a single outcome e.g. age distribution, incidence rate, CFR. If a study included multiple years and multiple sites then all pre-vaccination years and subnational sites were aggregated and included in the same country dataset. The main outcome/presentation was hospital admissions, but we also included emergency room visits if admissions were not reported in the same study.

Age distribution of intussusception hospital admissions < 5 years

Age distributions were fitted to all studies that had at least three age bands below the age of 1.0 year to ensure there was enough information to inform the shape of the age distribution. Age distributions that did not capture the entire age range <5 years (e.g. <1 year, <2 years) were adjusted to ensure that each country dataset had a realistic right-hand tail prior to fitting. To do this we calculated the median cumulative proportion of intussusception cases that were reported to have occurred by ages 1, 2, 3, 4 and 5 years in each WHO region, using a subset of country datasets that had a full set of counts in each single year of age up to 5.0 years. The median proportions in each WHO region were then used to estimate the expected number of intussusception cases in each missing single year of age <5 years.

We fitted a range of parametric age distributions <5 years (Gamma, Weibull, Lognormal, Log Logistic, Burr) to each country dataset using Non-linear Least Squares (NLS) and Maximum Likelihood Estimation (MLE). Each distribution was compared using the Root Mean Squared Error (RMSE), Mean Absolute Error (MAE), goodness of fit statistics (Kolmogorov-Smirnov, Cramer-von Mises, Anderson-Darling) and goodness of fit criteria (Akaike's Information Criterion, Bayesian Information Criterion).

We estimated the median age, interquartile age range, and cumulative proportion of intussusception cases estimated to have occurred by standard ages between birth and age 5.0 years. All analyses were conducted using R v.3.4.1 using the R packages *MASS*, *nloptr*, *fitdistrplus*, *actuar* and *mutil*.

Results were stratified by the following WHO regions: the Americas (AMR); Africa (AFR); Eastern Mediterranean (EMR); Europe (EUR); Southeast Asia (SEA); and, Western Pacific (WPR)(11).

Incidence of intussusception hospital admissions <5 years

For country datasets that did not capture the entire age range <5 years (e.g. <1yr, <2yrs) we calculated an adjusted incidence rate per 100,000 per year <5 years. First, we estimated the expected number of cases in each missing single year of age <5 years using the median cumulative proportion of intussusception cases by ages 1, 2, 3, 4 and 5 years in each WHO region. These median proportions were based on the entire set of fitted parametric age distributions <5 years, so included more studies than those used to adjust the right-hand tails of age distributions prior to fitting (see above). Second, we inflated the denominator based on the ratio between the size of the population in the reported age group and the under-five age group. Ratios were determined using UNPOP population data for ages 0, 1, 2, 3, 4 years in the period 2010-2015 (12). Results were stratified by WHO region.

In-hospital intussusception case fatality ratios <5 years

We used three alternative approaches to estimate CFRs for each country dataset and each WHO region. First, we calculated age unadjusted CFRs by dividing reported deaths by reported cases in each country and WHO region. Second, we calculated age unadjusted CFRs and 95% confidence intervals for each country and WHO region using meta-analysis. For meta-analysis we used the *metaprop_one* and *metareg* commands in Stata version 15.1 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC). With *metaprop_one* we chose the logit option, so that binomial distributions were used to model within-study variability. Logistic models with random intercepts were fitted, and the variability of the random intercepts indicated heterogeneity. We also ran a separate meta-analysis with results pooled by national under-five mortality quintile. Quintiles were based on the 2010-2015 under-five mortality rates published by the UNPOP (2017 Revision)(12). Third, we calculated age adjusted CFRs by converting CFRs that did not extend the full 5 year age range (e.g. <1yr, <2yrs) into a CFR aged <5 years. To do this we first calculated the expected number of intussusception cases in the missing age range (e.g. 12-59 months) using the median cumulative proportion of cases expected to occur by each age in each WHO region.

These estimates were based on the full set of fitted parametric age distributions <5 years in each WHO region. To estimate CFRs in the missing age range, the ratio of difference between the CFR in the known and missing age range was assumed to be the same as the ratio of difference between the probability of dying from any cause in the known and missing age ranges during a single year of life. These probabilities were derived from country-specific life tables for the period 2010-2015 (12).

Results

Search results

After exclusions, we identified 128 articles (Figure 1). We included 62 articles from the Jiang *et al* review (2002-2012) and 66 articles from the new search (2012-2018). There were 61 country datasets with age distributions, 71 with incidence rates and 95 with CFRs (Appendix Table 1). We obtained additional age granularity from authors in around half (28/61) of the country datasets with age distributions. We included post-vaccination age distribution and CFR data for one study in Africa (13) because it included high quality prospective data for several African countries and found no elevated risk of intussusception. We also included data from China and Vietnam despite uncertainties about the level of vaccine use in the private market. We included data from four studies that were published after the end date of the systematic review (13-16).

Age distribution of intussusception hospital admissions < 5 years

Prior to fitting, we used a subset of 31 datasets with complete counts in each single year of life between birth and age 5.0 years (Appendix Table 2) to estimate realistic right-hand tails in the datasets with incomplete age distributions <5 years. Using MLE, in most of the 61 country datasets the *Burr* distribution had the most favourable goodness of fit statistics and goodness of fit criteria compared to the *Weibull, Lognormal, Gamma* and *Log Logistic* distributions. However, the fits based on NLS had a lower overall RMSE and a much better visual fit to the data than MLE, particularly around the peak of the age distribution (Figure 2). The *Burr* distribution had more favourable RMSE and MAE statistics than the *Log Logistic* distribution in over 80% of the country datasets, and a better visual fit to distributions with long tails. Our preference was to use a standard approach to fitting, summarising, and extrapolating curves to countries without data so we fitted the *Burr* distribution to all 61 datasets (17) (Figure 3, Appendix Table 3).

In the African, Eastern Mediterranean and South East Asian regions ≥80% of intussusception hospital admissions were in the first year of life, compared to 63% in the Americas, 54% in Europe and 35% in the Western Pacific region (Appendix Table 4). Median (IQR) ages of intussusception hospital admissions were: 29 (22-43) weeks in Africa; 30 (22-42) weeks in the Eastern Mediterranean; 33 (24-47) weeks in South East Asia; 41 (27-69) weeks in the Americas; 47 (29-89) weeks in Europe; and, 70 (42-126) weeks in the Western Pacific region. The median proportion of cases occurring by 15 weeks of age ranged from 2.4% in the Western Pacific region to 6.8% in the Eastern Mediterranean region (Table 1). There was substantial within-region variation in the European and the Western Pacific regions (Appendix Table 4).

Incidence of intussusception hospital admissions <5 years

The median (range) annual incidence rate of intussusception hospital admissions was 8 (3-14) per 100,000 aged <5 years in Africa, 11 (1-34) in the Americas, 19 (13-23) in the Eastern Mediterranean region, 14 (4-49) in Europe, 19 (4-61) in South East Asia and 52 (5-196) in the Western Pacific region (Figure 4, Table 1). Incidence rates in the Western Pacific region ranged from ~5 in Malaysia, to ~200 in Nha Trang, Vietnam. Incidence rates above 70 per 100,000 per year <5 years were found in Japan, South Korea and Vietnam (Appendix Table 5). Globally, we found no correlation (R^2 = <0.1%) between the adjusted incidence rates <5 years and the under-five mortality rate for the period 2010-15. Median incidence rates among children aged <1 year were above 75 per 100,000 per year in South East Asia and in the Eastern Mediterranean and Western Pacific regions (Table 1, Figure 4).

In-hospital intussusception case fatality ratios <5 years

Pooled CFRs in each WHO region varied according to the method used (Table 1). The CFR (95% CI for each region) based on age unadjusted meta-analysis was 11.5% (7.24- 17.78%) in Africa, 0.41% (0.11 – 1.54%) in the Americas, 0.46% (0.02 – 8.74%) in the Eastern Mediterranean region, 0.20% (0.05 – 0.89%) in Europe, 0.27% (0.03 – 2.48%) in South East Asia, and 0.05% (0.02 – 0.12%) in the Western Pacific region, but there was variation within each region (Table 1, Appendix Table 6). We chose to stratify by WHO region rather than under-five mortality quintile. Both had similar explanatory power in meta-regression ($p<0.005$) but WHO region was consistent with the stratification used for age distributions and incidence rates, and had more favourable between group heterogeneity ($p=0.001$ vs $p=0.003$). The strongest predictor of CFRs was whether a country was based in the region of Africa or not. Stratifying by study age group gave no evidence of heterogeneity ($p = 0.7732$) so CFRs were not adjusted for age in meta-analysis.

Discussion

This analysis provides an important update to the existing global evidence on intussusception incidence rates, age distributions and case fatality ratios prior to rotavirus vaccine introduction. More than half of the research articles (67/129) included in our analysis were published after the previous review by Jiang et al (3). In addition, we have provided incidence rates and CFRs that are both unadjusted and adjusted to a standard age group (<5 years), allowing the totality of evidence to be included and compared across countries. We have also benefited from the generosity of many study investigators, who were able to share more precise breakdown of their age data. We fitted standard parametric curves to all datasets using statistically robust methods that will allow estimates of intussusception cases in each week of age <5 years.

Our analysis found that the annual incidence of intussusception ranges from 34 (African region) to 90 (Western Pacific region) per 100,000 children aged <1 year. The previous review by Jiang *et al* estimated a global incidence of 74 in the same age range (3). Several Western Pacific countries reported very high incidence rates. The reason for this is unclear. In one study from this region we were able to analyse only the non-recurrent cases, and the median age was still high (67 weeks) (16). Globally, recurrent cases represented <15% of total intussusception hospital admissions in each of the 32 studies where this proportion was reported. In other studies the proportion was not reported or unclear. There were very few incidence rate data points from the African region (2 data points) and Eastern Mediterranean region (3 data points). Relatively low incidence rates from these regions may simply reflect the lack of access to hospitals. For all datasets we accepted the definition of intussusception provided by the authors. However, different definitions and coding systems could have led to important differences in results. One study in Bangladesh found a very large range of possible incidence rates (0-97 per 100,000 per year, <2 years) depending on whether the study was retrospective or prospective, and whether cases were probable or confirmed (18). Around one-third (25/71) of the country datasets with incidence rates were based on studies with a prospective design, and most (63/71) used specific ICD codes or BCL case definitions. We excluded incidence rates if a more recent data point was reported in the same population/location. In England, estimates of the annual incidence of intussusception hospital admissions <1 year were 66 for the period 1993-1995 (19), 30 for the period 2002-2012 [unpublished from (10)] and 24 for the period 2008-2009 (20). In California, the rate declined from in 51 in 1985-1997 to 37 in 2000-2005 (21).

Countries with higher incidence rates tended to have a higher median age. This effect was largely driven by countries in the Western Pacific region where high incidence rates and high

median ages were commonly reported. Our analysis of age distributions found median ages ranging from 29 weeks in Africa (83% of cases in the first year of life) to 70 weeks in the Western Pacific region (35% of cases in the first year of life). There was substantial within-region variation in Europe and the Western Pacific region. The country datasets in Switzerland and Germany had a much higher median age of intussusception that the median for the European region. In a small number of studies with very high median ages there was some evidence of second peak shortly after the first (6, 22-25). The observed decreases in incidence <1 year in England and the USA partly reflect a shift in intussusception cases to older age groups over time. National Inpatient Survey (NIS) data representing 20% of hospitals in the USA has shown that the proportion of under-five intussusception admissions aged <1 year has declined from 62% in 1994 to 50% in 2004 and continues to decline in the post-vaccine era [unpublished from (26)].

We found extreme differences between the CFRs in Africa (one in ten hospital admissions) and the rest of the world (less than one in every 100-2000 hospital admissions). This gross level of inequality is mainly due to the very high proportion of cases diagnosed and treated with high-risk surgery in Africa (27, 28). Strategies are urgently needed to reduce the time between onset of symptoms and presentation at hospital. This should dramatically reduce the risk of complications and other contraindications that prohibit the use of lower-risk treatment options, such as enemas. Investment is also needed to ensure hospitals have the appropriate imaging equipment (ultrasound, radiograph) and staff required to implement lower-risk treatment (18). We did not formally evaluate the proportion of cases receiving different types of diagnostics and treatment in different settings. This would be a worthwhile follow-up analysis and would inform estimates of the costs of intussusception treatment in different settings.

Our analysis excludes children without access to hospital. Some access to healthcare indicators are reported in household surveys, but these are not available for all countries and do not represent care seeking for emergency conditions that may require surgery (29). This adjustment will be influential in Africa, leading to much higher CFRs than reported in our analysis. Most children with intussusception will die if left untreated, but a proportion will spontaneously resolve without treatment e.g. 25% of hospital admissions in Italy (30), 21% in Turkey (31), 19% in South Africa (32), 10% in Thailand (33) and 2% in Hong Kong (34). Without early intervention, the proportion may be even higher. This suggests that CFRs applied to children without access to hospital should probably not exceed ~90% in most settings.

In the context of rotavirus vaccines, a recent study in Africa encouragingly found no intussusception risk associated with a live oral rotavirus vaccine (13), but an elevated risk has been found with the same vaccine, and other oral rotavirus vaccines, in other parts of the world (35). Our analysis provides inputs that are critical to assess the number of excess intussusception cases that could be associated with different rotavirus vaccination schedules in different settings. It is important to evaluate this at the national level given the substantial country-level variation observed in age distributions, incidence rates and CFRs, as well as vaccine schedules, coverage and timeliness (5, 9). Avoiding the peak age of intussusception is important for the design of rotavirus vaccination schedules because the absolute risk is relative to the background incidence. Our analysis encouragingly found that less than 5% of hospital admissions occurred before age 15 weeks (median of all 71 datasets) when the first dose is typically administered. If the first dose of rotavirus vaccination could be administered at birth (36) this would avoid nearly all of the background incidence. Large scale post-licensure studies are needed to assess whether this strategy can substantially lower the risk of intussusception, without reducing the benefits of rotavirus vaccination. We excluded case counts recorded in the first week of life. Several datasets reported a suspiciously high number in this age group which may be related to errors in the recording of the date of birth/admission or errors in the diagnosis. For example, necrotising enterocolitis and other neonatal congenital problems may be misdiagnosed as intussusception (37).

Conclusion

The incidence, age distribution and case fatality of intussusception hospital admissions varies by region. Understanding and recognising these differences will be important when assessing the number of intussusception cases that could be associated with different rotavirus vaccination schedules in different settings.

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Ethics

This study was approved by the ethical committee (Ref 15595) of the London School of Hygiene and Tropical Medicine (LSHTM).

Competing interests: none declared.

Disclaimer: The finding and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Table 1. Incidence rates, age distributions and CFRs among intussusception hospital admissions aged <5 years in different WHO regions before the introduction of rotavirus vaccines

	Africa	Americas	Eastern Med.	Europe	South East Asia	Western Pacific
Median (IQR) incidence per 100,000 per year						
<1 year	34 (24-45)	36 (27-48)	78 (64-86)	41 (26-68)	77 (24-176)	90 (50-165)
<5 years	8 (6-11)	11 (8-14)	19 (16-21)	14 (9-25)	19 (6-42)	52 (25-92)
Median (IQR) age of admission						
Age in weeks (IQR)	29 (22-43)	41 (27-69)	30 (22-42)	47 (29-89)	33 (24-47)	70 (42-126)
Median parameters of the Burr distribution						
Shape 1 (γ)	4.80	3.62	4.08	2.81	4.17	2.65
Shape 2 (α)	0.44	0.39	0.65	0.44	0.55	0.51
Scale (θ)	22.20	26.15	25.46	29.33	26.39	46.83
Median cumulative % of admissions by age*						
6w	0.1%	0.2%	0.2%	0.5%	0.1%	0.2%
10w	0.9%	1.2%	1.4%	2.0%	1.0%	0.8%
14w	4.4%	3.8%	5.3%	5.0%	3.7%	2.0%
15w	6.0%	4.8%	6.8%	6.0%	4.9%	2.4%
1m	0.0%	0.1%	0.0%	0.2%	0.0%	0.1%
2m	0.5%	0.7%	0.8%	1.4%	0.5%	0.6%
3m	3.2%	3.0%	4.0%	4.1%	2.8%	1.7%
4m	11.0%	7.7%	11.5%	8.6%	8.5%	3.5%
5m	24.3%	14.8%	23.7%	14.4%	18.3%	6.1%
6m	39.4%	23.5%	37.9%	21.0%	30.7%	9.3%
7m	52.5%	32.3%	51.4%	27.7%	43.3%	13.1%
8m	62.7%	40.5%	62.4%	34.2%	54.4%	17.4%
9m	70.2%	47.7%	70.8%	40.1%	63.3%	21.8%
10m	75.9%	53.9%	77.1%	45.5%	70.2%	26.3%
11m	80.1%	59.0%	81.8%	50.2%	75.6%	30.8%
12m	83.4%	63.4%	85.4%	54.4%	79.8%	35.1%
18m	92.9%	78.9%	94.8%	70.8%	91.9%	55.6%
24m	96.1%	85.9%	97.6%	79.2%	95.8%	68.1%
36m	98.3%	92.0%	99.2%	87.3%	98.4%	80.9%
48m	99.1%	94.7%	99.6%	91.0%	99.2%	87.0%
60m	99.4%	96.1%	99.8%	93.2%	99.5%	90.3%
Case fatality ratio						
Pooled number of deaths	407	117	3	18	8	6
Pooled number of cases	3,739	47,616	368	10,365	2,467	11,606
CFR (age unadjusted)	10.89%	0.25%	0.82%	0.17%	0.32%	0.05%
CFR (adjusted to age <5 years)	10.08%	0.17%	0.81%	0.17%	0.32%	0.03%
CFR (age unadjusted) meta-analysis	11.50%	0.41%	0.46%	0.20%	0.27%	0.05%
CFR (age unadjusted) meta-analysis, 95% CI	(7.24% - 17.78%)	(0.11% - 1.54%)	(0.02% - 8.74%)	(0.05% - 0.89%)	(0.03% - 2.48%)	(0.02% - 0.12%)

*The best fitting parameters for each WHO region were calculated by re-fitting Burr distributions to the pooled proportion of intussusception admissions in each week of age <5yrs. Cumulative proportions below 100% by age 60 months indicate that some cases are estimated to occur after this age. The Burr distribution (Burr type XII) has shape 1 (γ), shape 2 (α) and scale (θ), all of which must be positive values (note: the Burr distribution becomes the Log Logistic distribution when the shape 2 parameter equals 1.0). The cumulative distribution function (cdf) of the Burr distribution is:

$$f(x) = 1 - \left[1 + \left(\frac{x}{\theta}\right)^{\gamma}\right]^{-\alpha}$$

Figure 1. Flow diagram to show search for country datasets

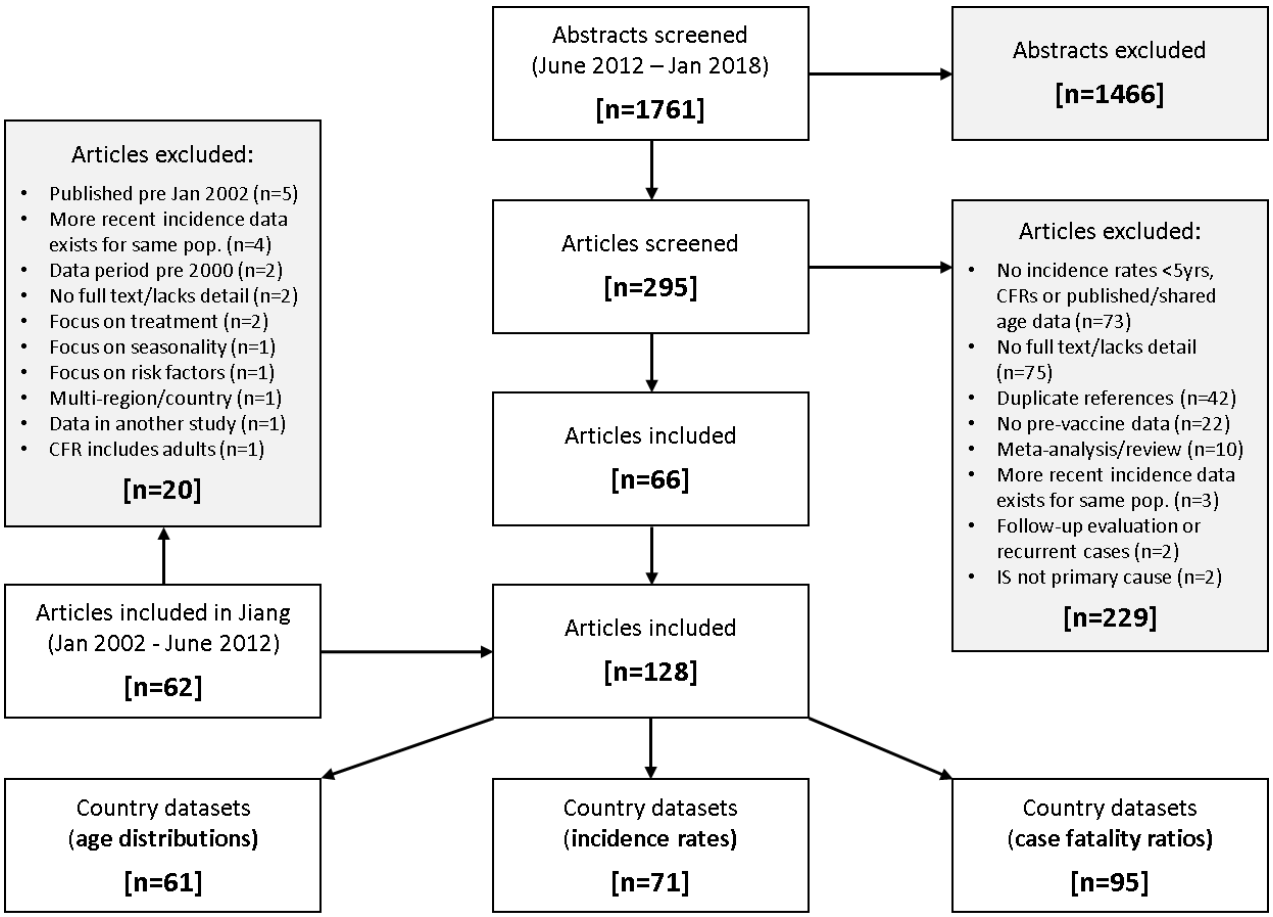
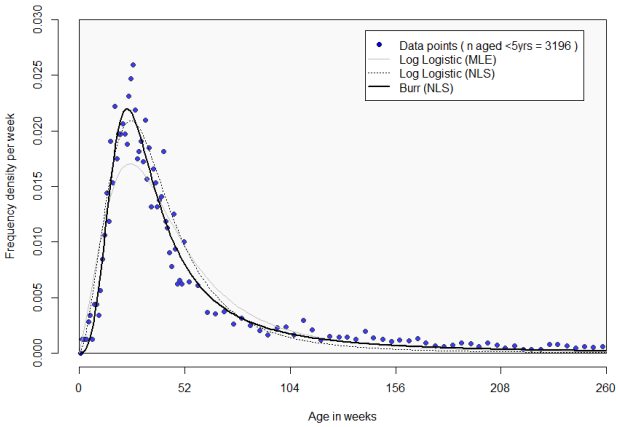
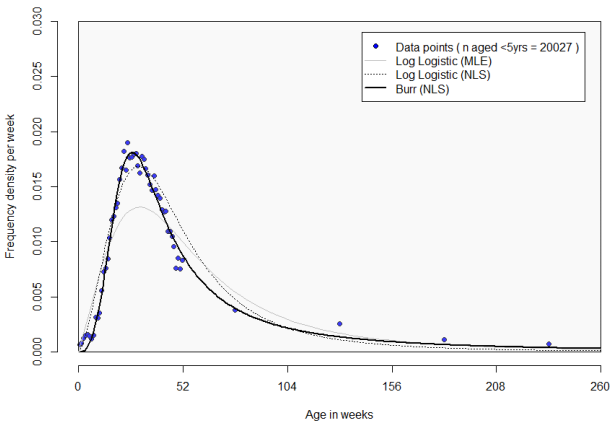


Figure 2. Alternative distributions fitted to age distributions for intussusception hospital admissions among children aged <5 years for selected country datasets

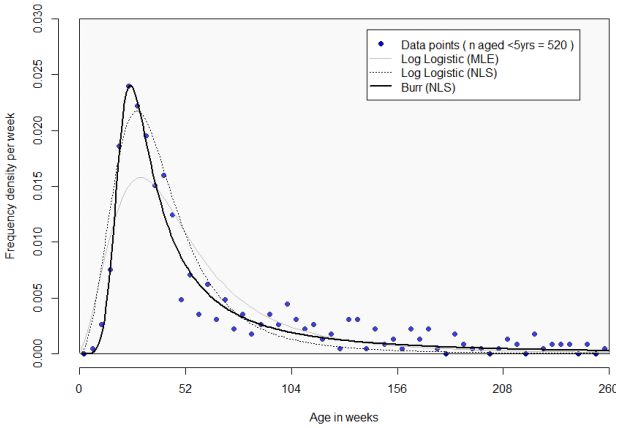
England (2002-2012)



USA (1994-2004)



Hong Kong (1997-2011)



Taiwan (1998-2013)

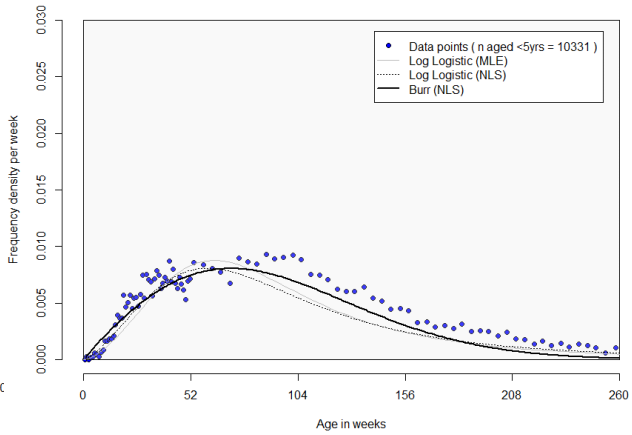
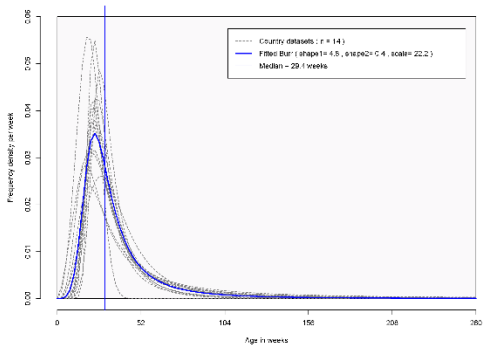
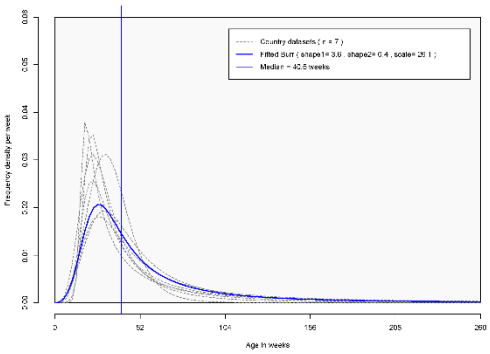


Figure 3. Intussusception hospital admissions among children aged <5 years by WHO region

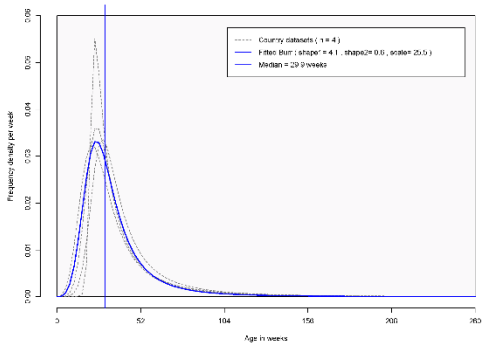
Africa



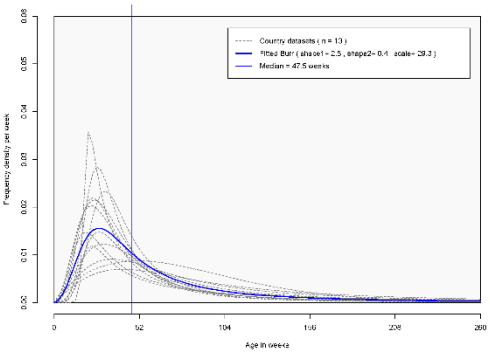
Americas



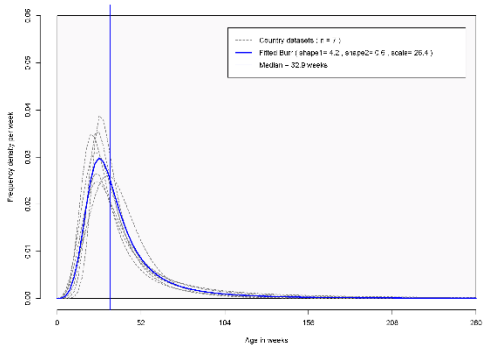
Eastern Mediterranean



Europe



South East Asia



Western Pacific

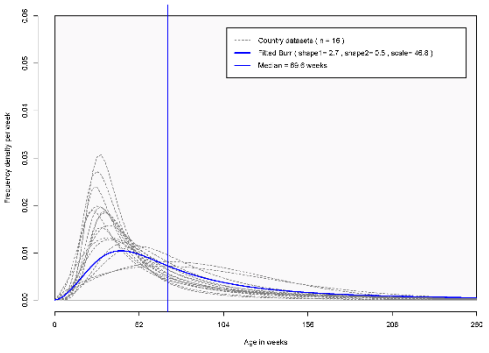
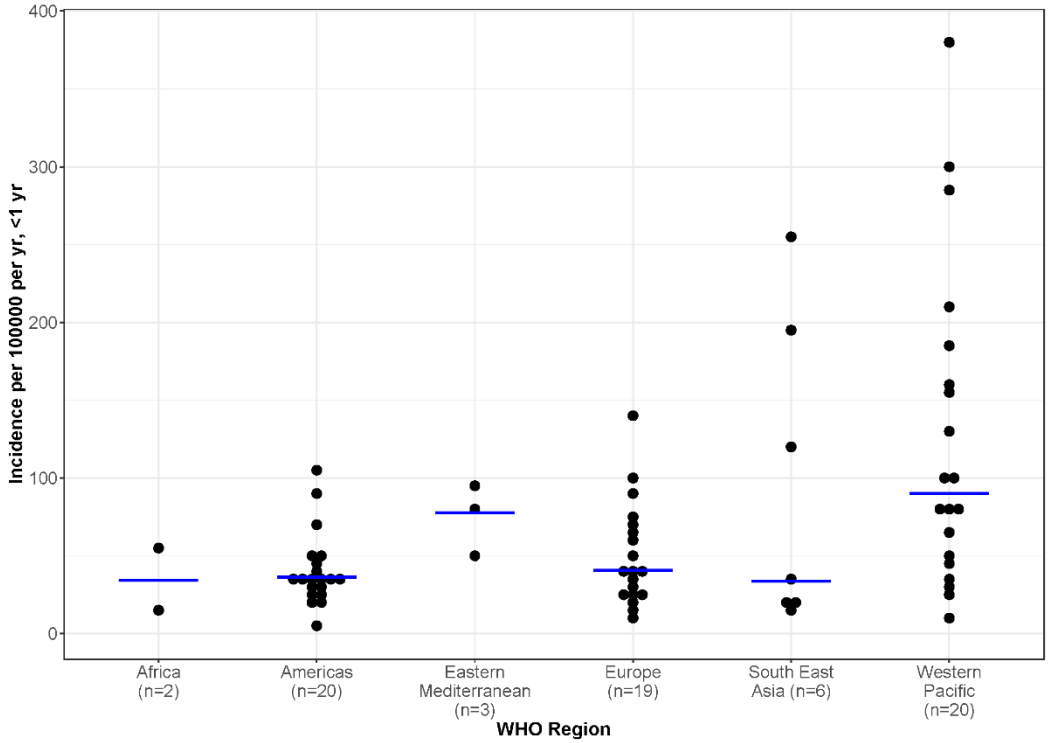
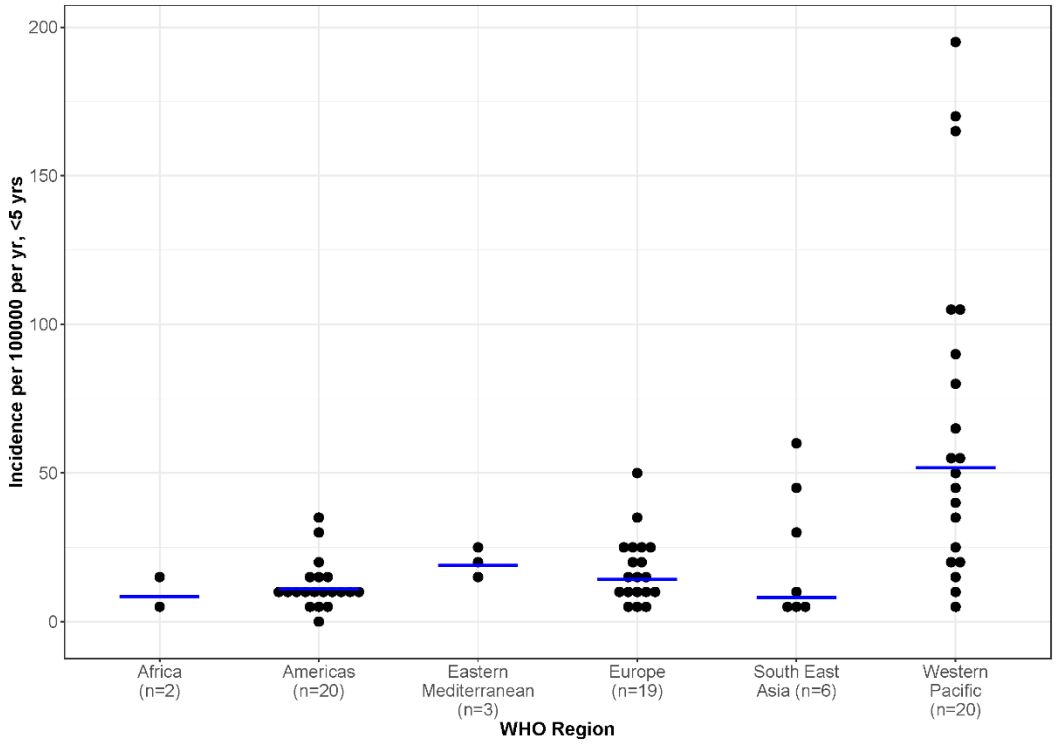


Figure 4. Incidence of intussusception hospital admissions among children aged <1 year and <5 years, by country and WHO region

Aged <1 year



Aged <5 years



Appendix to:

Global review of the incidence, age distribution and case fatality of intussusception hospital admissions among children aged < 5 years, before the introduction of rotavirus vaccination.

Clark A, Hasso-Agopsowicz M, Kraus M, Stockdale L, Sanderson CFB, Parashar U, Tate J.

Appendix Table 1. Characteristics of country datasets included in the analysis

Region	Country	Location	From	To	Prosp. study design?	Specific ICD code or BCL?	Included in Jiang *et al* 2012?	Author shared granular age data?	Single year age counts <5yrs?	Fitted age distro. <5yrs?	Age-specific incidence rate?	CFR?	Risk of bias*	First Author	Year	Ref
TOTAL					42	100	63	33	31	61	71	95				
AFR					11	8	10	9	5	14	2	27				
AMR					12	27	10	6	3	7	20	13				
EMR					1	3	4	2	3	4	3	4				
EUR					8	25	17	6	5	13	19	17				
SEA					6	14	8	1	6	7	7	16				
WPR					4	23	14	9	9	16	20	18				
AFR	Africa	10 countries	1993	2003			Yes			Yes		Yes	Medium	Steele	2012	(28)
AFR	Ethiopia	Addis Ababa	2011	2014						Yes		Yes	Low	Gadisa	2016	(38)
AFR	Ethiopia	6 hospitals	2013	2016	Yes	Yes		Yes		Yes		Yes	Medium	Tate	2018	(13)
AFR	Ghana	Kumasi	2004	2007	Yes		Yes					Yes	Low	Abantanga	2008	(39)
AFR	Ghana	Accra	2008	2009			Yes		Yes	Yes			Low	Enweronu-Laryea	2012	(40)
AFR	Ghana	2 hospitals	2012	2016	Yes	Yes		Yes		Yes		Yes	Medium	Tate	2018	(13)
AFR	Kenya	Eldoret	2000	2003			Yes					Yes	Medium	Kuremu	2004	(41)
AFR	Kenya	National	2002	2013		Yes		Yes	Yes	Yes		Yes	Low	Omore	2016	(42)
AFR	Kenya	Bomet	2009	2013								Yes	Low	Ooko	2016	(43)
AFR	Kenya	5 hospitals	2014	2016	Yes	Yes		Yes	Yes	Yes		Yes	Medium	Tate	2018	(13)
AFR	Malawi	4 hospitals	2013	2016	Yes	Yes		Yes				Yes	Medium	Tate	2018	(13)
AFR	Nigeria	Lagos	1995	2001	Yes		Yes		Yes	Yes		Yes	Medium	Bode	2008	(44)
AFR	Nigeria	Enugu	2008	2009			Yes					Yes	Low	Ekenze	2010	(45)
AFR	Nigeria	Enugu	1998	2007			Yes					Yes	Low	Ekenze	2011	(46)
AFR	Nigeria	Enugu	2009	2013								Yes	Low	Ekenze	2015	(47)
AFR	Nigeria	Ibadan	2002	2011						Yes		Yes	Low	Ogundoyin	2016	(48)
AFR	Nigeria	Ile-Ife	1993	2011						Yes		Yes	Low	Talabi	2013	(49)
AFR	Rwanda	Kigali	2009	2012								Yes	Low	Ngendahayo	2014	(50)

AFR	South Africa	Johannesburg	2007	2010	Yes			Yes				Yes	Low	Carapinha	2016	(32)
AFR	South Africa	9 hospitals	1998	2003			Yes				Yes	Yes	Low	Moore	2010	(51)
AFR	South Africa	Bloemfontein	2003	2011								Yes	Low	Venter	2013	(52)
AFR	South Africa	Not reported	1996	2001			Yes					Yes	Low	Wiersma	2004	(53)
AFR	Tanzania	Dar es Salaam	2000	2004			Yes					Yes	Low	Carneiro	2004	(54)
AFR	Tanzania	Mwanza	2010	2012	Yes				Yes			Yes	Low	Chalya	2014	(55)
AFR	Tanzania	7 hospitals	2013	2016	Yes	Yes		Yes		Yes		Yes	Medium	Tate	2018	(13)
AFR	Zambia	9 hospitals	2007	2011						Yes	Yes	Yes	Low	Mpabalwani	2014	(56)
AFR	Zambia	4 hospitals	2013	2016	Yes	Yes		Yes		Yes		Yes	Medium	Tate	2018	(13)
AFR	Zimbabwe	Harare	2014	2016	Yes	Yes		Yes		Yes		Yes	Medium	Tate	2018	(13)
AMR	Argentina	Mendoza	2003	2005	Yes	Yes					Yes		V. Low	Sáez-Llorens	2013	(57)
AMR	Brazil	Not reported	2003	2005	Yes	Yes					Yes		V. Low	Sáez-Llorens	2013	(57)
AMR	Brazil	National	2001	2006		Yes		Yes	Yes	Yes			Medium	Teles	2015	(58)
AMR	Canada	Toronto	2002	2006								Yes	Low	Bailey	2007	(59)
AMR	Canada	Ontario	2010	2010							Yes		Low	Ducharme	2013	(60)
AMR	Chile	Santiago	2000	2001		Yes	Yes			Yes	Yes	Yes	V. Low	O'Ryan	2003	(61)
AMR	Chile	Not reported	2003	2005	Yes	Yes					Yes		V. Low	Sáez-Llorens	2013	(57)
AMR	Colombia	Cali	2003	2005	Yes	Yes					Yes		V. Low	Sáez-Llorens	2013	(57)
AMR	Costa Rica	San Jose	2003	2005	Yes	Yes					Yes		V. Low	Sáez-Llorens	2013	(57)
AMR	Dominican Rep.	Santo Domingo	2003	2005	Yes	Yes					Yes		V. Low	Sáez-Llorens	2013	(57)
AMR	Honduras	Tegucigalpa	2003	2005	Yes	Yes					Yes		V. Low	Sáez-Llorens	2013	(57)
AMR	Latin America	11 countries	2003	2005	Yes	Yes				Yes		Yes	V. Low	Sáez-Llorens	2013	(57)
AMR	Mexico	Mexico City	2003	2005	Yes	Yes					Yes		V. Low	Sáez-Llorens	2013	(57)
AMR	Nicaragua	Managua	2003	2005	Yes	Yes					Yes		V. Low	Sáez-Llorens	2013	(57)
AMR	Panama	National	1998	2002		Yes	Yes				Yes	Yes	Medium	Sáez-Llorens	2004	(62)
AMR	Panama	Panama City	2003	2005	Yes	Yes					Yes		V. Low	Sáez-Llorens	2013	(57)
AMR	Peru	Lima City	2003	2005	Yes	Yes					Yes		V. Low	Sáez-Llorens	2013	(57)
AMR	Trinidad & Tobago	Champ Fleurs	2000	2007			Yes					Yes	Medium	Tota-Maharaj	2010	(63)
AMR	USA	41 states	1988	2005		Yes		Yes	Yes	Yes			Low	Aboagye	2014	(64)
AMR	USA	Kansas	2001	2004		Yes	Yes					Yes	Low	Burjonrappa	2007	(65)
AMR	USA	California	2000	2005		Yes		Yes		Yes	Yes		Low	Contopoulos-I.	2015	(21)
AMR	USA	Cinc./Nash./Roch.	2001	2006		Yes	Yes				Yes	Yes	Low	Cortese	2009	(66)
AMR	USA	National	1998	2006		Yes						Yes	V. Low	Desai	2012	(67)
AMR	USA	National	2001	2005		Yes	Yes				Yes		Low	Eng	2012	(68)
AMR	USA	Texas	1996	2005								Yes	Low	Munden	2007	(69)
AMR	USA	California	1996	2007		Yes	Yes					Yes	V. Low	Shekherdimian	2011	(70)
AMR	USA	16 States/National	1993	2004		Yes	Yes	Yes	Yes	Yes		Yes	Low	Tate	2008	(26)
AMR	USA	26 States	2000	2005		Yes		Yes			Yes		Low	Tate	2016	(71)
AMR	USA	26 States	2000	2005		Yes	Yes	Yes				Yes	Medium	Yen	2012	(72)
AMR	USA	National	2006	2006		Yes					Yes		Medium	Zickafoose	2012	(73)

AMR	Venezuela	Carabobo	1998	2001		Yes	Yes			Yes	Yes	Yes	Low	Perez-Schael	2003	(74)
EMR	Egypt	Zagazig	2014	2016				Yes	Yes	Yes			Medium	Ahmed	2015	(75)
EMR	Israel (Arab)	North	1992	2009		Yes					Yes		V. Low	Muhsen	2014	(76)
EMR	Israel (Bedouin)	South	1990	2004		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Greenberg	2008	(77)
EMR	Pakistan	Karachi	2012	2015		Yes				Yes		Yes	Low	Yousafzai	2017	(78)
EMR	Saudi Arabia	Abha	1993	2000			Yes					Yes	Low	Al-Malki	2005	(79)
EMR	Saudi Arabia	Riyadh	1984	2000			Yes					Yes	Low	Crankson	2003	(80)
EMR	Tunisia	Monastir	1995	2003	Yes		Yes		Yes	Yes	Yes		Medium	Chouikha	2009	(81)
EUR	Austria	Graz	1999	2006			Yes					Yes	V. Low	Saxena	2007	(82)
EUR	Denmark	National	1980	2001		Yes	Yes			Yes	Yes		Medium	Fischer	2004	(83)
EUR	England	National	2002	2012		Yes		Yes	Yes	Yes			V. Low	Stowe	2016	(35)
EUR	Finland	National	2001	2006			Yes				Yes		Low	Lappalainen	2012	(84)
EUR	Finland	National	1999	2005		Yes					Yes		Low	Leino	2016	(85)
EUR	Finland	National	2000	2005				Yes		Yes			**	Vesikari (unpub)	2018	
EUR	France	Toulouse	2002	2011		Yes				Yes			V. Low	Serayssol	2014	(24)
EUR	Germany	National	2006	2007		Yes	Yes				Yes		V. Low	Jenke	2011	(86)
EUR	Germany	Bavaria	2005	2006		Yes	Yes	Yes	Yes	Yes	Yes		**	Kohl	2010	(87)
EUR	Germany	NRW and Bavaria	2006	2007		Yes	Yes				Yes		Low	Weiss	2011	(88)
EUR	Iceland	National	1986	2010		Yes		Yes	Yes	Yes	Yes		**	Pétursdóttir	2013	(89)
EUR	Israel	Holon	1990	2002			Yes					Yes	**	Eshed	2003	(90)
EUR	Israel (Jewish)	South	1990	2004		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Greenberg	2008	(77)
EUR	Israel (Jewish)	North	1992	2009		Yes					Yes		V. Low	Muhsen	2014	(76)
EUR	Italy	Sicily	2003	2012		Yes				Yes			Low	Costantino	2015	(30)
EUR	Italy	National	2009	2014		Yes				Yes	Yes	Yes	V. Low	Restivo	2017	(91)
EUR	Italy	National	2002	2012		Yes				Yes		Yes	Low	Trotta	2016	(92)
EUR	Netherlands	National	2008	2012		Yes					Yes		V. Low	Gadroen	2017	(93)
EUR	Rep. of Ireland	Waterford	1990	2000			Yes					Yes	Low	Hillal	2002	(94)
EUR	Rep. of Ireland	National	2008	2009	Yes	Yes					Yes		V. Low	Samad	2013	(20)
EUR	Rep. of Ireland	Not reported	2007	2010			Yes					Yes	Low	Tareen	2011	(95)
EUR	Romania	Iasi	2009	2013		Yes						Yes	Low	Tarca	2015	(96)
EUR	Russia	Vladivostok	1994	2005			Yes					Yes	Low	Shapkina	2006	(97)
EUR	Serbia	Belgrade	1995	2012	Yes							Yes	Low	Vujovic	2014	(98)
EUR	Spain	Malaga	NR	NR			Yes					Yes	Medium	Rubi	2002	(99)
EUR	Switzerland	National	2003	2006	Yes	Yes	Yes		Yes	Yes	Yes		V. Low	Buettcher	2007	(100)
EUR	Turkey	Ankara	2002	2014		Yes						Yes	Low	Guney	2016	(31)
EUR	Turkey	Sanliurfa	2010	2012								Yes	Low	Ocal	2014	(101)
EUR	Turkey	Ankara	1991	2007			Yes					Yes	Low	Sonmez	2012	(102)
EUR	Turkey	Ankara	1993	2003			Yes					Yes	Low	Yalcin	2009	(103)
EUR	UK	England	2002	2012		Yes					Yes		Medium	Clark	2014	(10)
EUR	UK	England	2008	2009	Yes	Yes				Yes	Yes		V. Low	Samad	2013	(20)

EUR	UK	N. Ireland	2008	2009	Yes	Yes					Yes		V. Low	Samad	2013	(20)
EUR	UK	Scotland	2008	2009	Yes	Yes					Yes		V. Low	Samad	2013	(20)
EUR	UK	Wales	2008	2009	Yes	Yes					Yes		V. Low	Samad	2013	(20)
EUR	UK/Rep. of Ireland	National	2008	2009	Yes	Yes	Yes					Yes	Low	Samad	2012	(104)
EUR	Uzbekistan	Bukhara	2004	2008		Yes	Yes	Yes		Yes	Yes	Yes	Low	Latipov	2011	(22)
SEA	Bangladesh	Matlab	2004	2006	Yes	Yes	Yes				Yes		Low	Zaman	2009	(18)
SEA	Bangladesh	National	2012	2016	Yes	Yes				Yes			Low	Satter	2017	(105)
SEA	India	Delhi	2000	2003	Yes		Yes				Yes		V. Low	Bahl	2009	(106)
SEA	India	Vellore	2001	2004		Yes	Yes					Yes	Low	Bhowmick	2009	(107)
SEA	India	Chandigargh	2009	2015	Yes	Yes			Yes		Yes	Yes	Low	Gupta	2017	(108)
SEA	India	Vellore	2010	2013								Yes	Low	Jehangir	2014	(109)
SEA	India	Delhi, Pune, Vellore	2010	2013	Yes	Yes					Yes	Yes	Low	John	2014	(110)
SEA	India	28 hospitals	2013	2015		Yes					Yes		Medium	Mathew	2016	(111)
SEA	India	Chennai	2012	2013		Yes			Yes	Yes	Yes	Yes	Low	Mehendale	2016	(112)
SEA	India	Chennai	NR	NR			Yes					Yes	Low	Ramachandran	2008	(113)
SEA	India	Vellore	1991	2000		Yes	Yes			Yes		Yes	Low	Raman	2003	(114)
SEA	India	Manipal, Lucknow	2007	2012		Yes			Yes			Yes	Low	Singh	2014	(115)
SEA	India	Chennai	2013	2016		Yes			Yes	Yes		Yes	Low	Srinivasan	2017	(116)
SEA	India	Vellore	2010	2017		Yes		Yes	Yes	Yes		Yes	Low	Srinivasan	2017	(116)
SEA	Nepal	Kathmandu	2011	2014		Yes				Yes		Yes	V. Low	Rayamajhi	2017	(117)
SEA	Nepal	Dharan	2004	2009								Yes	Low	Shakya	2011	(118)
SEA	Nepal	Katmandu	2008	2009	Yes							Yes	Low	Thapa	2012	(119)
SEA	Thailand	Bangkok	1992	2009			Yes					Yes	Medium	Kruatrachue	2011	(120)
SEA	Thailand	5 hospitals	2001	2006		Yes	Yes		Yes	Yes	Yes	Yes	Medium	Khumjui	2009	(121)
SEA	Thailand	Bangkok	2000	2005		Yes	Yes					Yes	Medium	Pruksananonda	2007	(33)
WPR	Australia	Brisbane	1994	2004			Yes					Yes	**	Blanch	2007	(122)
WPR	Australia	National	1994	2000		Yes						Yes	Low	Justice	2005	(123)
WPR	Australia	Melbourne	1995	2001		Yes	Yes	Yes	Yes	Yes			**	Justice	2006	(124)
WPR	Australia	Melbourne	2001	2006		Yes	Yes	Yes			Yes	Yes	V. Low	Lloyd-Johnsen	2012	(125)
WPR	Australia	National	2000	2006		Yes					Yes		Low	Palupi-Baroto	2015	(126)
WPR	China	Suzhou	2007	2013		Yes					Yes	Yes	**	Cui	2016	(127)
WPR	China	Jinan	2011	2015		Yes					Yes		**	Cui	2018	(14)
WPR	China	Chenzhou, Kaifeng	2009	2013		Yes		Yes		Yes	Yes	Yes	Low	Liu	2018	(15)
WPR	China	Shenyang	2004	2009			Yes					Yes	**	Zhang	2011	(128)
WPR	Hong Kong	National	1997	2011		Yes	Yes	Yes	Yes	Yes	Yes		Low	Hong Kong ISG	2007	(34)
WPR	Hong Kong	Pokfulam	1997	2014				Yes	Yes	Yes			Low	Wong	2015	(129)
WPR	Japan	Akita	1978	2002			Yes		Yes	Yes	Yes		Low	Nakagomi	2006	(130)
WPR	Japan	Akita	2001	2010		Yes		Yes		Yes	Yes		Medium	Noguchi	2012	(131)
WPR	Japan	National	2007	2008		Yes	Yes	Yes	Yes	Yes	Yes	Yes	V. Low	Takeuchi	2012	(8)
WPR	Malaysia	3 hospitals	2000	2003		Yes	Yes		Yes	Yes	Yes	Yes	Low	Giak	2008	(132)

WPR	New Zealand	National	1998	2003		Yes	Yes			Yes	Yes	Yes	Low	Chen	2005	(133)
WPR	New Zealand	Auckland	1998	2007		Yes	Yes					Yes	V. Low	Kodikara	2010	(134)
WPR	Singapore	7 Hospitals	2002	2010	Yes	Yes				Yes	Yes	Yes	Low	Phua	2013	(23)
WPR	Singapore	National	1997	2004	Yes	Yes	Yes				Yes	Yes	Medium	Tan	2009	(135)
WPR	Singapore	1 hospital	2009	2013		Yes						Yes	Low	Yap Shiyi	2017	(136)
WPR	South Korea	Joenbuk	2000	2002		Yes	Yes		Yes	Yes	Yes	Yes	Low	Jo	2009	(137)
WPR	Taiwan	National	1998	2007		Yes	Yes	Yes	Yes	Yes	Yes		Low	Chen	2010	(6)
WPR	Taiwan	National	2000	2007		Yes					Yes		Low	Hsiao	2013	(138)
WPR	Taiwan	Taipei	1995	2010								Yes	Medium	Hsu	2012	(139)
WPR	Taiwan	National	2001	2005		Yes				Yes	Yes	Yes	Low	Yen	2017	(140)
WPR	Vietnam	Hanoi	2002	2004	Yes		Yes			Yes	Yes	Yes	V. Low	Bines	2006	(141)
WPR	Vietnam	Hai Phong, Hue	2013	2016	Yes	Yes		Yes		Yes			Low	Trang	2018	(16)
WPR	Vietnam	Ho Chi Min City	2009	2011		Yes					Yes	Yes	V. Low	Van Trang	2014	(142)
WPR	Vietnam	Nha Trang	2009	2011		Yes			Yes	Yes	Yes		V. Low	Tran	2013	(25)

*Risk of bias (very low, low, medium) was assigned to each included study after assessing: a) selection bias - are participants representative of the general population?; b) baseline confounding - are characteristics of the participants reported?; c) outcome measurement - is the definition of intussusception the same for all participants?; d) blinding at outcome assessment - are data abstractors blinded to the hypothesis?; and, e) description of missing information - are drop-outs, withdrawals, missing data, or controls described?). Studies with valuable data but no full text were assigned ** to indicate that they may have a high risk of bias.

Appendix Table 2. Studies reporting the % of intussusception hospital admissions <5 years by single year of age, before rotavirus vaccine introduction

WHO region	Country	Location	U5MR quintile	Period		n	Cumulative % of admissions by age				
				From	To		1y	2y	3y	4y	5y
AFR	Ghana	Accra	Very high	2008	2009	77	86%	96%	99%	100%	100%
AFR	Kenya	National	High	2002	2013	280	69%	84%	92%	97%	100%
AFR	Kenya	5 hospitals	High	2014	2016	175	78%	93%	96%	98%	100%
AFR	Nigeria	Lagos	Very high	1995	2001	169	90%	96%	98%	99%	100%
AFR	Tanzania	Mwanza	Very high	2010	2012	55	76%	87%	93%	99%	100%
AFR	**Median**						**78%**	**93%**	**96%**	**99%**	**100%**
AMR	Brazil	National	Medium	2001	2006	943	80%	90%	95%	98%	100%
AMR	USA	41 states	Low	1988	2005	1171	62%	83%	95%	100%	100%
AMR	USA	16 states/National	Low	1994	2004	24035	57%	77%	90%	96%	100%
AMR	**Median**						**62%**	**83%**	**95%**	**98%**	**100%**
EMR	Egypt	Zagazig	Medium	2014	2016	132	94%	97%	97%	98%	100%
EUR	Israel (Bedouin)	South	Medium	1990	2004	87	77%	95%	97%	98%	100%
EMR	Tunisia	Monastir	Medium	1995	2003	533	77%	90%	97%	98%	100%
EMR	**Median**						**77%**	**95%**	**97%**	**98%**	**100%**
EUR	England	National	Very low	2002	2012	3196	67%	84%	92%	97%	100%
EUR	Germany	Bavaria	Very low	2005	2011	752	27%	56%	75%	90%	100%
EUR	Iceland	National	Very low	1986	2010	64	70%	91%	95%	100%	100%
EUR	Israel (Jewish)	South	Very low	1990	2004	275	66%	87%	95%	98%	100%
EUR	Switzerland	National	Very low	2003	2006	246	34%	61%	84%	93%	100%
EUR	**Median**						**66%**	**84%**	**92%**	**97%**	**100%**
SEA	India	Vellore	High	2010	2017	219	75%	92%	95%	98%	100%
SEA	India	Chennai	High	2012	2013	201	66%	85%	93%	96%	100%
SEA	India	Chennai	High	2013	2016	284	67%	82%	93%	97%	100%
SEA	India	Chandigarh	High	2009	2015	277	72%	83%	92%	97%	100%
SEA	India	Manipal + Luck.	High	2007	2012	187	56%	79%	91%	97%	100%
SEA	Thailand	5 hospitals	Low	2001	2006	77	84%	94%	96%	100%	100%
SEA	**Median**						**70%**	**84%**	**93%**	**97%**	**100%**
WPR	Australia	Melbourne	Very low	1995	2001	190	78%	93%	97%	99%	100%
WPR	Hong Kong	Pokfulam	Very low	1997	2014	163	53%	73%	86%	94%	100%
WPR	Hong Kong	National	Very low	1997	2011	520	62%	82%	92%	96%	100%
WPR	Japan	National	Very low	2006	2007	1065	25%	55%	78%	91%	100%
WPR	Japan	Akita	Very low	1978	2002	91	45%	70%	91%	98%	100%
WPR	Malaysia	3 hospitals	Low	2000	2003	62	74%	90%	95%	98%	100%
WPR	South Korea	Joenbuk	Very low	2000	2002	408	53%	83%	93%	97%	100%
WPR	Taiwan	National	Very low	1998	2013	10331	24%	58%	83%	94%	100%
WPR	Vietnam	Nha Trang	Medium	2009	2011	192	31%	75%	90%	94%	100%
WPR	**Median**						**53%**	**75%**	**91%**	**96%**	**100%**

Appendix Table 3. Burr age distribution parameters fitted to each country and WHO region

WHO region	Country	Location	U5MR quintile	n age grps	n	Parameters				
						Shape1	Shape2	Scale	RMSE	MAE
AFR	Africa	10 countries	Very high	16	938	0.3	6.3	19.9	1%	1%
AFR	Ethiopia	6 hospitals	Very high	56	207	0.9	3.3	32.3	1%	1%
AFR	Ethiopia	Addis Ababa	Very high	6	121	0.2	4.1	17.8	5%	4%
AFR	Ghana	Accra	Very high	10	77	0.4	7.8	24.7	1%	1%
AFR	Ghana	2 hospitals	Very high	56	485	0.3	6.3	22.4	2%	1%
AFR	Kenya	National	High	60	279	0.3	4.0	16.3	5%	4%
AFR	Kenya	5 hospitals	High	71	175	0.3	6.7	20.2	2%	2%
AFR	Nigeria	Lagos	Very high	27	169	3588.5	3.1	294.1	6%	4%
AFR	Nigeria	Ibadan	Very high	5	53	0.3	8.5	21.1	7%	4%
AFR	Nigeria	Ile-Ife	Very high	7	77	1.9	2.5	34.9	4%	3%
AFR	Tanzania	7 hospitals	Very high	56	257	0.3	7.2	20.1	3%	2%
AFR	Zambia	4 hospitals	Very high	56	78	0.5	5.9	23.4	4%	3%
AFR	Zambia	9 hospitals	Very high	10	121	0.1	14.0	19.4	6%	4%
AFR	Zimbabwe	Harare	Very high	56	115	0.3	5.2	20.5	2%	1%
AFR	Pooled					**0.4**	**4.8**	**22.2**	**1%**	**1%**
AMR	Brazil	National	Medium	19	943	0.5	3.9	23.4	3%	3%
AMR	Chile	Santiago	Low	27	104	0.2	4.9	19.9	3%	2%
AMR	Latin America	11 countries	Medium	27	576	0.2	7.3	19.6	4%	3%
AMR	USA	41 states	Low	99	1171	2.0	3.5	43.0	2%	1%
AMR	USA	16 states /National	Low	56	20027	0.3	3.6	25.2	3%	2%
AMR	USA	California	Low	56	1907	0.5	3.3	31.8	3%	2%
AMR	Venezuela	Carabobo	Medium	16	95	0.1	12.0	16.1	5%	4%
AMR	Pooled			**27**	**23300**	**0.4**	**3.6**	**26.1**	**1%**	**0%**
EMR	Israel (Bedouins)	South	Medium	16	83	0.4	6.1	26.0	2%	1%
EMR	Egypt	Zagazig	Medium	60	132	0.1	17.1	21.2	5%	3%
EMR	Pakistan	Karachi	Very high	27	156	0.4	5.3	23.2	2%	1%
EMR	Tunisia	Monastir	Medium	27	514	0.6	3.7	22.7	3%	2%
EMR	Pooled			**27**	**880**	**0.6**	**4.1**	**25.5**	**1%**	**1%**
EUR	Denmark	National	Very low	7	872	0.7	2.8	29.4	3%	2%
EUR	England	National	Very low	100	3196	0.4	3.5	22.9	2%	1%
EUR	England	England	Very low	16	287	0.5	2.8	25.2	2%	2%
EUR	Finland	National	Very low	27	280	0.4	4.9	24.4	4%	3%
EUR	France	Toulouse	Very low	14	276	8.4	1.7	295.8	2%	2%
EUR	Germany	Bavaria	Very low	16	750	0.6	2.0	61.5	4%	3%
EUR	Iceland	National	Very low	60	64	0.1	14.8	18.7	2%	2%
EUR	Italy	National	Very low	16	3088	0.5	2.2	47.2	3%	2%
EUR	Italy	National	Very low	9	5222	0.4	2.5	33.9	2%	2%
EUR	Italy	Sicily	Very low	16	340	0.2	3.9	24.0	3%	2%
EUR	Israel (Jewish)	South	Very low	16	273	0.4	4.6	29.3	1%	1%
EUR	Switzerland	National	Very low	16	246	0.1	5.7	18.4	7%	5%
EUR	Uzbekistan	Bukhara	High	13	80	0.2	3.3	16.9	10%	5%
EUR	Pooled			**27**	**13539**	**0.4**	**2.8**	**29.3**	**1%**	**1%**
SEAR	Bangladesh	National	High	19	182	0.3	7.5	24.4	4%	3%
SEAR	India	Chennai	High	7	207	1.6	3.2	43.4	5%	4%
SEAR	India	Chennai	High	7	201	0.8	3.5	27.4	6%	5%
SEAR	India	Vellore	High	8	137	0.5	3.6	25.2	4%	3%
SEAR	India	Vellore	High	16	217	0.3	6.2	22.6	2%	2%
SEAR	Nepal	Kathmandu	High	27	101	0.3	5.0	21.7	3%	2%
SEAR	Thailand	5 hospitals	Low	60	77	0.5	4.2	21.2	2%	2%
SEA	Pooled			**27**	**1112**	**0.6**	**4.2**	**26.4**	**0%**	**0%**
WPR	Australia	Melbourne	Very low	16	190	0.5	4.9	26.7	1%	1%
WPR	China	Chenz./, Kaif.	Medium	104	2283	0.2	4.9	24.6	3%	2%
WPR	Hong Kong	Pokfulam	Very low	15	163	0.2	4.4	20.1	4%	3%
WPR	Hong Kong	National	Very low	60	520	0.2	5.8	21.6	2%	1%
WPR	Japan	National	Very low	100	1063	15.9	1.8	524.3	3%	2%
WPR	Japan	Akita	Very low	6	91	0.4	2.9	35.3	6%	5%

WPR	Japan	Akita	Very low	16	232	0.3	4.5	28.1	3%	2%
WPR	South Korea	Joenbuk	Very low	6	408	1.0	2.2	51.4	6%	4%
WPR	Malaysia	3 hospitals	Low	7	62	0.4	4.2	25.4	3%	2%
WPR	New Zealand	National	Very low	38	305	0.5	3.1	28.6	2%	2%
WPR	Singapore	7 Hospitals	Very low	27	223	0.1	5.6	23.7	5%	3%
WPR	Taiwan	National	Very low	100	10331	5180.6	1.9	8709.8	3%	2%
WPR	Taiwan	National	Very low	9	360	0.4	3.3	33.9	4%	3%
WPR	Vietnam	Nha Trang	Medium	60	192	0.8	2.9	61.0	2%	2%
WPR	Vietnam	Hai Phong, Hue	Medium	108	2916	0.4	3.4	43.6	2%	2%
WPR	Vietnam	Hanoi	Medium	68	779	0.2	5.3	26.6	3%	2%
WPR	Pooled					**0.5**	**2.7**	**46.8**	**3%**	**2%**

* The best fitting parameters for each WHO region were calculated by re-fitting Burr distributions to the pooled proportion of intussusception admissions in each week of age <5yrs. The Burr distribution (Burr type XII) has shape 1 (α), shape 2 (γ) and scale (θ), all of which must be positive values. The cumulative distribution function (cdf) is:

$$f(x) = 1 - \left[1 + \left(\frac{x}{\theta}\right)^{\gamma}\right]^{-\alpha}$$

Appendix Table 4. Median (IQR) age and cumulative proportion of intussusception hospital admissions, by age and WHO region

WHO region	Country	Location	U5MR quintile	n age grps	n	IQR (weeks)			Cumulative % of intussusception hospital admissions by age												
						25th	50th	75th	6w	2m	10w	14w	15w	4m	6m	9m	12m	18m	24m	36m	48m	60m
AFR	Africa	10 countries	Very high	16	938	22	30	46	0%	0%	0%	3%	4%	9%	38%	67%	79%	89%	93%	97%	98%	99%
AFR	Ethiopia	6 hospitals	Very high	56	207	24	34	48	0%	1%	2%	6%	7%	11%	30%	61%	79%	93%	97%	99%	100%	100%
AFR	Ethiopia	Addis Ababa	Very high	6	121	22	36	73	0%	1%	2%	7%	9%	14%	34%	54%	65%	77%	82%	88%	91%	93%
AFR	Ghana	Accra	Very high	10	77	25	30	39	0%	0%	0%	0%	1%	2%	30%	75%	89%	97%	99%	100%	100%	100%
AFR	Ghana	2 hospitals	Very high	56	485	24	31	45	0%	0%	0%	2%	2%	5%	33%	67%	81%	92%	95%	98%	99%	99%
AFR	Kenya	National	High	60	279	19	30	57	1%	2%	4%	11%	14%	21%	43%	62%	73%	82%	87%	92%	94%	95%
AFR	Kenya	5 hospitals	High	71	175	23	30	45	0%	0%	0%	2%	3%	7%	38%	68%	80%	90%	94%	97%	98%	99%
AFR	Nigeria	Lagos	Very high	27	169	15	19	24	2%	5%	8%	22%	27%	39%	83%	100%	100%	100%	100%	100%	100%	100%
AFR	Nigeria	Ibadan	Very high	5	53	22	27	35	0%	0%	0%	1%	2%	5%	46%	81%	91%	97%	99%	100%	100%	100%
AFR	Nigeria	Ile-Ife	Very high	7	77	17	25	36	2%	5%	8%	16%	19%	26%	52%	80%	92%	98%	100%	100%	100%	100%
AFR	Tanzania	7 hospitals	Very high	56	257	22	29	42	0%	0%	0%	2%	3%	8%	41%	72%	84%	92%	96%	98%	99%	99%
AFR	Zambia	4 hospitals	Very high	56	78	23	29	38	0%	0%	0%	2%	3%	7%	39%	76%	89%	96%	98%	99%	100%	100%
AFR	Zambia	9 hospitals	Very high	10	121	24	33	56	0%	0%	0%	0%	0%	2%	32%	60%	72%	84%	89%	93%	96%	97%
AFR	Zimbabwe	Harare	Very high	56	115	22	31	50	0%	0%	1%	4%	5%	10%	36%	63%	76%	87%	92%	96%	97%	98%
AFR	Pooled					**22**	**29**	**43**	**0%**	**0%**	**1%**	**4%**	**6%**	**11%**	**39%**	**70%**	**83%**	**93%**	**96%**	**98%**	**99%**	**99%**
AMR	Brazil	National	Medium	19	943	21	30	44	0%	1%	2%	7%	8%	14%	39%	68%	82%	92%	96%	98%	99%	99%
AMR	Chile	Santiago	Low	27	104	24	36	68	0%	0%	1%	4%	5%	9%	30%	54%	66%	79%	85%	90%	93%	95%
AMR	Latin America	11 countries	Medium	27	576	23	32	52	0%	0%	0%	2%	3%	6%	34%	62%	75%	86%	91%	95%	96%	97%
AMR	USA	41 states	Low	99	1171	25	33	43	0%	1%	1%	4%	5%	8%	28%	66%	89%	99%	100%	100%	100%	100%
AMR	USA	16 states/Nat.	Low	56	20027	28	45	86	0%	1%	1%	3%	4%	7%	21%	42%	57%	72%	80%	87%	91%	93%
AMR	USA	California	Low	56	1907	29	43	68	0%	1%	1%	3%	4%	7%	20%	44%	62%	80%	88%	94%	96%	98%
AMR	Venezuela	Carabobo	Medium	16	95	22	33	67	0%	0%	0%	1%	3%	9%	37%	58%	68%	78%	84%	89%	92%	93%
AMR	Pooled			**27**	**23300**	**27**	**41**	**69**	**0%**	**1%**	**1%**	**4%**	**5%**	**8%**	**23%**	**48%**	**63%**	**79%**	**86%**	**92%**	**95%**	**96%**
EMR	Israel (Bedouins)	South	Medium	16	83	27	35	49	0%	0%	0%	1%	1%	3%	22%	60%	78%	91%	95%	98%	99%	99%
EMR	Egypt	Zagazig	Medium	60	132	25	31	44	0%	0%	0%	0%	0%	0%	32%	68%	81%	91%	95%	98%	99%	99%
EMR	Pakistan	Karachi	Very high	27	156	23	31	43	0%	0%	0%	3%	4%	8%	35%	69%	83%	93%	96%	99%	99%	100%
EMR	Tunisia	Monastir	Medium	27	514	20	28	41	0%	2%	3%	9%	11%	17%	44%	72%	84%	93%	97%	99%	99%	100%
EMR	Pooled			**27**	**880**	**22**	**30**	**42**	**0%**	**1%**	**1%**	**5%**	**7%**	**12%**	**38%**	**71%**	**85%**	**95%**	**98%**	**99%**	**100%**	**100%**
EUR	Denmark	National	Very low	7	872	23	35	57	1%	2%	3%	8%	10%	14%	31%	56%	71%	86%	92%	96%	98%	99%
EUR	England	National	Very low	100	3196	24	37	66	0%	1%	2%	6%	7%	11%	29%	52%	66%	80%	86%	92%	94%	96%

EUR	England	England	Very low	16	287	23	37	65	1%	3%	4%	9%	10%	14%	32%	53%	67%	81%	87%	93%	95%	97%
EUR	Finland	National	Very low	27	280	26	35	54	0%	0%	0%	2%	3%	6%	26%	57%	73%	87%	92%	96%	98%	98%
EUR	France	Toulouse	Very low	14	276	43	72	110	1%	2%	2%	4%	5%	6%	11%	22%	33%	55%	72%	91%	97%	99%
EUR	Germany	Bavaria	Very low	16	750	49	94	196	1%	1%	2%	3%	3%	4%	9%	18%	27%	43%	54%	68%	76%	81%
EUR	Iceland	National	Very low	60	64	25	37	73	0%	0%	0%	0%	0%	2%	29%	53%	65%	77%	82%	88%	91%	93%
EUR	Italy	National	Very low	16	3088	40	74	150	1%	1%	2%	4%	4%	6%	12%	24%	35%	52%	64%	76%	83%	86%
EUR	Italy	National	Very low	9	5222	33	58	116	1%	1%	2%	4%	5%	7%	17%	32%	45%	62%	72%	82%	87%	90%
EUR	Italy	Sicily	Very low	16	340	32	57	140	0%	0%	1%	2%	3%	5%	16%	34%	46%	60%	68%	77%	82%	85%
EUR	Israel (Jewish)	South	Very low	16	273	30	42	64	0%	0%	0%	1%	2%	3%	16%	45%	65%	82%	89%	95%	97%	98%
EUR	Switzerland	National	Very low	16	246	38	109	651	0%	0%	0%	1%	2%	4%	13%	25%	33%	43%	49%	56%	61%	64%
EUR	Uzbekistan	Bukhara	High	13	80	27	60	214	1%	2%	3%	7%	8%	11%	24%	37%	46%	57%	63%	70%	75%	78%
EUR	Pooled			**27**	**13539**	**29**	**47**	**89**	**0%**	**1%**	**2%**	**5%**	**6%**	**9%**	**21%**	**40%**	**54%**	**71%**	**79%**	**87%**	**91%**	**93%**
SEAR	Bangladesh	National	High	19	182	26	33	46	0%	0%	0%	0%	1%	2%	24%	64%	80%	92%	96%	98%	99%	99%
SEAR	India	Chennai	High	7	207	26	36	48	0%	1%	1%	4%	5%	8%	25%	58%	80%	96%	99%	100%	100%	100%
SEAR	India	Chennai	High	7	201	21	30	42	0%	1%	2%	7%	9%	14%	40%	71%	86%	95%	98%	99%	100%	100%
SEAR	India	Vellore	High	8	137	24	34	54	0%	1%	2%	6%	7%	11%	31%	58%	73%	86%	92%	96%	98%	98%
SEAR	India	Vellore	High	16	217	24	32	47	0%	0%	0%	2%	2%	5%	31%	65%	79%	90%	94%	97%	99%	99%
SEAR	Nepal	Kathmandu	High	27	101	25	36	62	0%	0%	1%	3%	4%	7%	28%	55%	69%	82%	87%	93%	95%	96%
SEAR	Thailand	5 hospitals	Low	60	77	20	28	41	0%	1%	2%	8%	10%	16%	45%	73%	85%	93%	96%	98%	99%	99%
SEA	Pooled			**27**	**1112**	**24**	**33**	**47**	**0%**	**1%**	**1%**	**4%**	**5%**	**8%**	**31%**	**63%**	**80%**	**92%**	**96%**	**98%**	**99%**	**99%**
WPR	Australia	Melbourne	Very low	16	190	26	35	49	0%	0%	0%	2%	3%	5%	25%	60%	78%	91%	95%	98%	99%	99%
WPR	China	Chenz./Kaif.	Medium	104	2283	30	47	91	0%	0%	0%	1%	2%	3%	17%	40%	55%	71%	78%	86%	90%	92%
WPR	Hong Kong	Pokfulam	Very low	15	163	27	47	109	0%	0%	1%	3%	4%	7%	23%	42%	54%	67%	74%	81%	85%	88%
WPR	Hong Kong	National	Very low	60	520	27	41	79	0%	0%	0%	1%	2%	5%	23%	47%	61%	75%	81%	88%	91%	93%
WPR	Japan	National	Very low	100	1063	53	89	134	1%	1%	2%	3%	3%	4%	8%	15%	24%	43%	60%	83%	94%	98%
WPR	Japan	Akita	Very low	6	91	36	59	111	0%	1%	1%	3%	3%	5%	13%	29%	44%	63%	73%	83%	88%	91%
WPR	Japan	Akita	Very low	16	232	32	49	88	0%	0%	0%	1%	2%	3%	14%	37%	54%	71%	80%	88%	91%	93%
WPR	South Korea	Joenbuk	Very low	6	408	32	52	86	1%	2%	3%	5%	6%	8%	18%	35%	50%	71%	82%	92%	95%	97%
WPR	Malaysia	3 hospitals	Low	7	62	25	35	53	0%	0%	1%	3%	5%	8%	28%	58%	75%	88%	93%	97%	98%	99%
WPR	New Zealand	National	Very low	38	305	26	40	66	0%	1%	2%	6%	7%	10%	26%	49%	65%	81%	88%	94%	96%	97%
WPR	Singapore	7 Hospitals	Very low	27	223	35	63	169	0%	0%	0%	1%	1%	2%	12%	30%	43%	57%	65%	74%	78%	82%
WPR	Taiwan	National	Very low	100	10331	55	86	123	0%	1%	1%	2%	2%	3%	7%	14%	23%	44%	63%	89%	98%	100%
WPR	Taiwan	National	Very low	9	360	33	51	87	0%	0%	1%	2%	3%	4%	14%	34%	51%	71%	80%	89%	93%	95%
WPR	Vietnam	Nha Trang	Medium	60	192	47	70	107	0%	0%	0%	1%	1%	2%	6%	17%	31%	57%	74%	88%	94%	96%
WPR	Vietnam	Hai Phong, Hue	Medium	108	2916	43	67	115	0%	0%	0%	1%	1%	2%	6%	20%	35%	58%	71%	84%	89%	92%
WPR	Vietnam	Hanoi	Medium	68	779	33	51	98	0%	0%	0%	1%	1%	2%	12%	35%	51%	68%	76%	85%	89%	91%
WPR	Pooled					**42**	**70**	**126**	**0%**	**1%**	**1%**	**2%**	**2%**	**3%**	**9%**	**22%**	**35%**	**56%**	**68%**	**81%**	**87%**	**90%**

Appendix Table 5. Studies reporting the incidence of intussusception hospital admissions among children aged <1 year and <5 years, before rotavirus vaccine introduction

WHO region	Country	Location	U5MR quintile	Period From	To	n*	Age group	Rate per 100,0000 per year	Rate adjusted (<1yr)	Rate adjusted (<5yrs)
AFR	South Africa	9 hospitals	High	1998	2003	384	<2yrs	32.0	55.6	13.5
AFR	Zambia	9 hospitals	Very high	2009	2011	105	<2yrs	7.5	12.9	3.3
AFR	**Median**								**34.2**	**8.4**
AMR	Canada	Ontario	Very low	2010	2010	117	<2yrs	18.0	28.2	8.1
AMR	Chile	Santiago	Low	2000	2001	95	<2yrs	33.5	52.0	15.2
AMR	Panama	National	Medium	1998	2002	111	<3yrs	11.0	23.4	7.2
AMR	Argentina	Mendoza	Medium	2003	2005	43	<1yr	105.3	105.3	33.7
AMR	Brazil	Not reported	Medium	2003	2005	19	<1yr	3.8	3.8	1.2
AMR	Chile	Not reported	Low	2003	2005	57	<1yr	47.0	47.0	14.3
AMR	Colombia	Cali	Medium	2003	2005	37	<1yr	37.4	37.4	11.7
AMR	Costa Rica	San Jose	Low	2003	2005	27	<1yr	18.9	18.9	5.7
AMR	Dominican Rep.	Santo Domingo	Medium	2003	2005	36	<1yr	37.8	37.8	11.9
AMR	Honduras	Tegucigalpa	High	2003	2005	40	<1yr	30.4	30.4	9.5
AMR	Mexico	Mexico City	Medium	2003	2005	112	<1yr	87.8	87.8	28.3
AMR	Nicaragua	Managua	Medium	2003	2005	10	<1yr	19.6	19.6	6.0
AMR	Panama	Panama City	Medium	2003	2005	112	<1yr	69.4	69.4	22.3
AMR	Peru	Lima City	High	2003	2005	10	<1yr	25.1	25.1	8.1
AMR	USA	National	Low	2001	2005	22	<1yr	33.0	33.0	9.9
AMR	USA	National	Low	2006	2006	1548	<1yr	36.5	36.5	10.9
AMR	USA	California	Low	2000	2005	1187	<1yr	37.0	37.0	11.1
AMR	USA	Cinc./Nash./Roch.	Low	2001	2006	156	<1yr	49.3	49.3	14.7
AMR	USA	26 States	Low	2000	2005	15231	<1yr	35.9	35.9	10.7
AMR	Venezuela	Carabobo	Medium	1998	2001	67	<1yr	35.0	35.0	11.0
AMR	**Median**								**36.2**	**11.0**
EMR	Tunisia	Monastir	Medium	1984	2003	533	<5yrs	13.0	51.1	13.0
EMR	Israel (Arab)	North	Medium	1992	2009	76	<5yrs	23.2	95.2	23.2
EMR	Israel (Bedouin)	South	Medium	1990	2004	75	<5yrs	18.9	77.5	18.9
EMR	**Median**								**77.5**	**18.9**
EUR	Denmark	National	Very low	1980	2001	1814	<5yrs	27.2	90.9	27.2
EUR	Finland	National	Very low	2001	2006	53	<1yr	20.0	20.0	7.0
EUR	Finland	National	Very low	1999	2005	52	<1yr	12.1	12.1	4.2
EUR	Germany	National	Very low	2006	2007	1200	<2yrs	51.5	75.6	26.2
EUR	Germany	NRW and Bavaria	Very low	2006	2007	169	<1yr	61.7	61.7	23.0
EUR	Germany	Bavaria	Very low	2005	2006	518	<1yr	72.0	72.0	26.8
EUR	Iceland	National	Very low	1986	2010	42	<1yr	40.0	40.0	13.6
EUR	Ireland	National	Very low	2008	2009	21	<1yr	24.8	24.8	8.6
EUR	Israel (Jewish)	South	Very low	1990	2004	241	<5yrs	49.3	137.9	49.3
EUR	Israel (Jewish)	North	Very low	1992	2009	114	<5yrs	36.1	101.0	36.1
EUR	Italy	National	Very low	2009	2014	3088	<5yrs	20.2	64.2	20.2
EUR	Netherlands	National	Very low	2008	2012	15	<3yrs	21.3	42.4	14.6
EUR	Switzerland	National	Very low	2003	2006	294	<3yrs	26.0	51.8	18.0
EUR	UK	England	Very low	2002	2012	2692	<2yrs	18.0	27.0	8.8
EUR	UK	England	Very low	2008	2009	190	<1yr	24.2	24.2	8.5
EUR	UK	N. Ireland	Very low	2008	2009	12	<1yr	40.6	40.6	14.3
EUR	UK	Scotland	Very low	2008	2009	20	<1yr	28.7	28.7	10.1
EUR	UK	Wales	Very low	2008	2009	7	<1yr	16.9	16.9	5.9
EUR	Uzbekistan	Bukhara	High	2004	2008	67	<2yrs	23.0	34.3	11.5
EUR	**Median**								**40.6**	**14.3**
SEA	Bangladesh	Matlab	High	2004	2006	3	<2yrs	9.4	15.6	3.9
SEA	India	Delhi	High	2000	2003	5	<1yr	17.7	17.7	4.3
SEA	India	Chandigargh	High	2009	2015	277	<5yrs	5.0	20.7	5.0
SEA	India	Delhi/Pune/Vellore	High	2010	2013	3	<2yrs	71.0	120.1	28.9
SEA	India	28 hospitals	High	2013	2015	98	<5yrs	46.8	194.1	46.8

SEA	India	Chennai	High	2012	2013	201	<5yrs	61.0	253.0	61.0
SEA	Thailand	5 hospitals	Low	2001	2006	112	<5yrs	8.1	33.6	8.1
SEA	**Median**								**33.6**	**8.1**
WPR	Australia	Melbourne	Very low	2001	2006	135	<2yrs	19.9	23.0	11.4
WPR	Australia	National	Very low	2000	2006	1650	<2yrs	45.1	52.1	25.9
WPR	China	Suzhou	Medium	2007	2013	594	<2yrs	57.3	65.3	33.8
WPR	China	Jinan	Medium	2011	2015	93	<2yrs	86.3	98.3	50.9
WPR	China	Suzhou	Medium	2007	2013	1715	<2yrs	112.9	128.7	66.6
WPR	Hong Kong	National	Very low	1997	2003	531	<5yrs	38.4	82.4	38.4
WPR	Taiwan	National	Very low	1998	2007	8217	<5yrs	45.5	78.6	45.5
WPR	Taiwan	National	Very low	2000	2007	5721	<5yrs	56.6	97.7	56.6
WPR	Taiwan	26 States	Very low	2001	2005	189	<1yr	82.2	82.2	52.7
WPR	Japan	National	Very low	2007	2008	2427	<1yr	185.0	185.0	103.2
WPR	Japan	North	Very low	1978	2002	91	<5yrs	77.8	154.5	77.8
WPR	Japan	Akita	Very low	2001	2010	122	<1yr	158.0	158.0	88.1
WPR	Malaysia	3 hospitals	Low	2000	2003	62	<5yrs	4.8	9.0	4.8
WPR	New Zealand	National	Very low	1998	2003	277	<3yrs	30.0	45.0	21.7
WPR	South Korea	Jeonbuk	Very low	2000	2002	408	<5yrs	106.4	208.6	106.4
WPR	Singapore	National	Very low	1997	2004	217	<2yrs	32.4	36.9	18.8
WPR	Singapore	7 Hospitals	Very low	2002	2010	167	<2yrs	26.1	29.8	15.2
WPR	Vietnam	Hanoi	Medium	2002	2004	533	<1yr	302.0	302.0	172.4
WPR	Vietnam	Ho Chi Min City	Medium	2009	2011	869	<1yr	287.0	287.0	163.9
WPR	Vietnam	Nha Trang	Medium	2009	2011	187	<5yrs	196.1	380.2	196.1
WPR	**Median**								**90.1**	**51.8**

* some numerators were derived from incidence and denominator data

Appendix Table 6. Case fatality ratios for intussusception hospital admissions among children aged <5 years

WHO region	Country	Location	U5MR quintile	Age group	CFR (age unadjusted), meta-analysis					% CFR adjusted to <5 years
					Deaths	Cases	% CFR	L95	U95	
AFR	Africa	10 countries	Very high	<1yr	108	863	12.51%	10.38%	14.91%	10.77%
AFR	Ethiopia	Addis Ababa	Very high	<5yrs+	6	130	4.62%	1.71%	9.78%	4.62%
AFR	Ethiopia	6 hospitals	Very high	<1yr	19	155	12.26%	7.54%	18.48%	10.53%
AFR	Ghana	Kumasi	Very high	<5yrs+	1	44	2.27%	0.06%	12.02%	2.27%
AFR	Ghana	2 hospitals	Very high	<1yr	9	360	2.50%	1.15%	4.69%	2.15%
AFR	Kenya	Eldoret	High	<5yrs+	5	36	13.89%	4.67%	29.50%	13.89%
AFR	Kenya	National	High	<5yrs	18	280	6.43%	3.85%	9.97%	6.43%
AFR	Kenya	Bomet	High	<5yrs+	3	30	10.00%	2.11%	26.53%	10.00%
AFR	Kenya	5 hospitals	High	<1yr	20	126	15.87%	9.97%	23.44%	13.58%
AFR	Malawi	4 hospitals	Very high	<1yr	4	26	15.38%	4.36%	34.87%	13.09%
AFR	Nigeria	Lagos	Very high	<5yrs+	21	174	12.07%	7.63%	17.86%	12.07%
AFR	Nigeria	Enugu	Very high	<5yrs+	7	87	8.05%	3.30%	15.88%	8.05%
AFR	Nigeria	Enugu	Very high	<2yrs	0	20	0.00%	0.00%	16.84%	0.00%
AFR	Nigeria	Ile-Ife	Very high	<5yrs+	12	78	15.38%	8.21%	25.33%	15.38%
AFR	Nigeria	Enugu	Very high	<5yrs+	2	58	3.45%	0.42%	11.91%	3.45%
AFR	Nigeria	Ibadan	Very high	<5yrs+	3	55	5.45%	1.14%	15.12%	5.45%
AFR	Rwanda	Kigali	Very high	<5yrs+	17	60	28.33%	17.45%	41.44%	28.33%
AFR	South Africa	Not reported	High	<5yrs+	10	106	9.43%	4.62%	16.67%	9.43%
AFR	South Africa	9 hospitals	High	<5yrs+	9	423	2.13%	0.98%	4.00%	2.13%
AFR	South Africa	Bloemfontein	High	<5yrs+	0	35	0.00%	0.00%	10.00%	0.00%
AFR	South Africa	Johannesburg	High	<3yrs	9	99	9.09%	4.24%	16.56%	9.01%
AFR	Tanzania	Dar es Salaam	Very high	<5yrs+	7	28	25.00%	10.69%	44.87%	25.00%
AFR	Tanzania	Mwanza	Very high	<5yrs+	8	56	14.29%	6.38%	26.22%	14.29%
AFR	Tanzania	7 hospitals	Very high	<1yr	57	182	31.32%	24.66%	38.60%	26.85%
AFR	Zambia	9 hospitals	Very high	<2yrs	31	92	33.70%	24.17%	44.30%	32.83%
AFR	Zambia	4 hospitals	Very high	<1yr	13	54	24.07%	13.49%	37.64%	20.69%
AFR	Zimbabwe	Harare	Very high	<1yr	8	82	9.76%	4.31%	18.32%	8.37%
	Africa				**407**	**3739**	**11.50%**	**7.24%**	**17.78%**	**10.08%**
AMR	Canada	Toronto	Very low	<5yrs+	0	41	0.00%	0.00%	8.60%	0.00%
AMR	Chile	Santiago	Low	<2yrs	0	86	0.00%	0.00%	4.20%	0.00%
AMR	Latin America	11 countries	Medium	<2yrs	13	476	2.73%	1.46%	4.62%	2.48%
AMR	Panama	National	Medium	<3yrs	1	111	0.90%	0.02%	4.92%	0.87%
AMR	Trinidad & Tobago	Champ Fleurs	High	<3yrs	0	65	0.00%	0.00%	5.52%	0.00%
AMR	USA	Texas	Low	<5yrs+	1	35	2.86%	0.07%	14.92%	2.86%
AMR	USA	Kansas	Low	<5yrs+	0	26	0.00%	0.00%	13.23%	0.00%
AMR	USA	16 States/National	Low	<1yr	14	3,463	0.40%	0.22%	0.68%	0.27%
AMR	USA	Cinc./Nash./Roch.	Low	<1yr	2	156	1.28%	0.16%	4.55%	0.86%
AMR	USA	California	Low	<5yrs+	0	188	0.00%	0.00%	1.94%	0.00%
AMR	USA	26 States	Low	<1yr	6	6,502	0.09%	0.03%	0.20%	0.06%
AMR	USA	National	Low	<1yr	80	36,400	0.22%	0.17%	0.27%	0.15%
AMR	Venezuela	Carabobo	Medium	<1yr	0	67	0.00%	0.00%	5.36%	0.00%
	Americas				**117**	**47616**	**0.41%**	**0.11%**	**1.54%**	**0.17%**
EMR	Israel	Holon	Very low	<5yrs	0	148	0.00%	0.00%	2.46%	0.00%
EMR	Pakistan	Karachi	Very high	<2yrs	3	149	2.01%	0.42%	5.77%	1.97%
EMR	Saudi Arabia	Riyadh	Medium	<3yrs	0	37	0.00%	0.00%	9.49%	0.00%
EMR	Saudi Arabia	Abha	Medium	<5yrs+	0	34	0.00%	0.00%	10.28%	0.00%
	Eastern Mediterranean				**3**	**368**	**0.46%**	**0.02%**	**8.74%**	**0.81%**
EUR	Austria	Graz	Very low	<5yrs+	0	111	0.00%	0.00%	3.27%	0.00%
EUR	Israel (Bedouin)	South	Very low	<5yrs	0	75	0.00%	0.00%	4.80%	0.00%
EUR	Israel (Jewish)	South	Very low	<5yrs	0	241	0.00%	0.00%	1.52%	0.00%
EUR	Italy	National	Very low	<5yrs	6	5,222	0.11%	0.04%	0.25%	0.11%
EUR	Italy	National	Very low	<5yrs	2	3,088	0.06%	0.01%	0.23%	0.06%
EUR	Rep. of Ireland	Waterford	Very low	<2yrs	0	24	0.00%	0.00%	14.25%	0.00%

EUR	Rep. of Ireland	Not reported	Very low	<5yrs+	0	256	0.00%	0.00%	1.43%	0.00%
EUR	Romania	Iasi	Low	<5yrs+	3	45	6.67%	1.40%	18.27%	6.67%
EUR	Russia	Vladivostok	Low	<5yrs+	0	280	0.00%	0.00%	1.31%	0.00%
EUR	Serbia	Belgrade	Low	<5yrs+	0	107	0.00%	0.00%	3.39%	0.00%
EUR	Spain	Malaga	Very low	<5yrs+	1	151	0.66%	0.02%	3.63%	0.66%
EUR	Turkey	Ankara	Medium	<5yrs+	0	179	0.00%	0.00%	2.04%	0.00%
EUR	Turkey	Ankara	Medium	<5yrs+	1	105	0.95%	0.02%	5.19%	0.95%
EUR	Turkey	Sanliurfa	Medium	<5yrs+	0	72	0.00%	0.00%	4.99%	0.00%
EUR	Turkey	Ankara	Medium	<5yrs+	0	81	0.00%	0.00%	4.45%	0.00%
EUR	UK/Rep. of Ireland	National	Very low	<1yr	1	261	0.38%	0.01%	2.12%	0.23%
EUR	Uzbekistan	Bukhara	High	<2yrs	4	67	5.97%	1.65%	14.59%	5.14%
	Europe				**18**	**10,365**	**0.20%**	**0.05%**	**0.89%**	**0.17%**
SEA	India	Vellore	High	<5yrs	1	137	0.73%	0.02%	4.00%	0.73%
SEA	India	Chennai	High	<5yrs+	0	179	0.00%	0.00%	2.04%	0.00%
SEA	India	Vellore	High	<5yrs	0	31	0.00%	0.00%	11.22%	0.00%
SEA	India	Delhi, Pune, Vellore	High	<2yrs	0	3	0.00%	0.00%	70.76%	0.00%
SEA	India	Vellore	High	<2yrs	0	59	0.00%	0.00%	6.06%	0.00%
SEA	India	Manipal, Lucknow	High	<5yrs	0	187	0.00%	0.00%	1.95%	0.00%
SEA	India	Chennai	High	<5yrs	0	201	0.00%	0.00%	1.82%	0.00%
SEA	India	Chennai	High	<5yrs	3	207	1.45%	0.30%	4.18%	1.45%
SEA	India	Vellore	High	<5yrs	0	77	0.00%	0.00%	4.68%	0.00%
SEA	India	Chandigargh	High	<5yrs	0	277	0.00%	0.00%	1.32%	0.00%
SEA	Nepal	Dharan	High	<5yrs+	3	47	6.38%	1.34%	17.54%	6.38%
SEA	Nepal	Kathmandu	High	<5yrs+	0	34	0.00%	0.00%	10.28%	0.00%
SEA	Nepal	Kathmandu	High	<2yrs	1	85	1.18%	0.03%	6.38%	1.14%
SEA	Thailand	Bangkok	Low	<5yrs+	0	94	0.00%	0.00%	3.85%	0.00%
SEA	Thailand	5 hospitals	Low	<5yrs	0	112	0.00%	0.00%	3.24%	0.00%
SEA	Thailand	Bangkok	Low	<5yrs+	0	737	0.00%	0.00%	0.50%	0.00%
	South East Asia				**8**	**2467**	**0.27%**	**0.03%**	**2.48%**	**0.32%**
WPR	Australia	National	Very low	<1yr	1	1,794	0.06%	0.00%	0.31%	0.02%
WPR	Australia	Brisbane	Very low	<5yrs+	0	141	0.00%	0.00%	2.58%	0.00%
WPR	Australia	Melbourne	Very low	<2yrs	0	135	0.00%	0.00%	2.70%	0.00%
WPR	China	Shenyang	Medium	<5yrs+	0	56	0.00%	0.00%	6.38%	0.00%
WPR	China	Suzhou	Medium	<2yrs	0	594	0.00%	0.00%	0.62%	0.00%
WPR	China	Chenzhou, Kaifeng	Medium	<2yrs	0	1,714	0.00%	0.00%	0.21%	0.00%
WPR	Japan	National	Very low	<5yrs+	2	2,427	0.08%	0.01%	0.30%	0.08%
WPR	Malaysia	3 hospitals	Low	<5yrs	0	62	0.00%	0.00%	5.78%	0.00%
WPR	New Zealand	National	Very low	<3yrs	0	277	0.00%	0.00%	1.32%	0.00%
WPR	New Zealand	Auckland	Very low	<5yrs+	0	189	0.00%	0.00%	1.93%	0.00%
WPR	Singapore	National	Very low	<2yrs	0	217	0.00%	0.00%	1.69%	0.00%
WPR	Singapore	7 hospitals	Very low	<2yrs	1	167	0.60%	0.02%	3.29%	0.47%
WPR	Singapore	1 hospital	Very low	<5yrs+	0	391	0.00%	0.00%	0.94%	0.00%
WPR	South Korea	Joenbuk	Very low	<5yrs	1	408	0.25%	0.01%	1.36%	0.25%
WPR	Taiwan	Taipei	Very low	<5yrs+	0	686	0.00%	0.00%	0.54%	0.00%
WPR	Taiwan	National	Very low	<1yr	1	946	0.11%	0.00%	0.59%	0.05%
WPR	Vietnam	Hanoi	Medium	<2yrs	0	533	0.00%	0.00%	0.69%	0.00%
WPR	Vietnam	Ho Chi Min City	Medium	<1yr	0	869	0.00%	0.00%	0.42%	0.00%
	Western Pacific				**6**	**11606**	**0.05%**	**0.02%**	**0.12%**	**0.03%**

List of references (Chapter 8)

1. Bines JE, Liem NT, Justice F, Son TN, Carlin JB, de Campo M, et al. Validation of clinical case definition of acute intussusception in infants in Viet Nam and Australia. Bull World Health Organ. 2006;84(7):569-75.

2. WHO. Acute intussusception in infants and children. Incidence, clinical presentation and management: a global perspective. Geneva: World Health Organization. Document WHO/V & B/02.19. 1–98. 2002.

3. Jiang J, Jiang B, Parashar U, Nguyen T, Bines J, Patel MM. Childhood intussusception: a literature review. PLoS One. 2013;8(7):e68482.

4. GOSH. Intussusception. The Department of General Surgery in collaboration with the Child and Family Information Group. Available at: https://www.gosh.nhs.uk/conditions-and-treatments/conditions-we-treat/intussusception [Accessed 30th April 2018].

5. Patel MM, Clark AD, Sanderson CF, Tate J, Parashar UD. Removing the age restrictions for rotavirus vaccination: a benefit-risk modeling analysis. PLoS Med. 2012;9(10):e1001330.

6. Chen SC, Wang JD, Hsu HY, Leong MM, Tok TS, Chin YY. Epidemiology of childhood intussusception and determinants of recurrence and operation: analysis of national health insurance data between 1998 and 2007 in Taiwan. Pediatr Neonatol. 2010;51(5):285-91.

7. Savoie KB, Thomas F, Nouer SS, Langham MR, Jr., Huang EY. Age at presentation and management of pediatric intussusception: A Pediatric Health Information System database study. Surgery. 2017;161(4):995-1003.

8. Takeuchi M, Osamura T, Yasunaga H, Horiguchi H, Hashimoto H, Matsuda S. Intussusception among Japanese children: an epidemiologic study using an administrative database. BMC Pediatr. 2012;12:36.

9. Clark A, Sanderson C. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. Lancet. 2009;373(9674):1543-9.

10. Clark A, Jit M, Andrews N, Atchison C, Edmunds WJ, Sanderson C. Evaluating the potential risks and benefits of infant rotavirus vaccination in England. Vaccine. 2014;32(29):3604-10.

11. WHO. WHO regional offices. Available at: http://www.who.int/about/regions/en/ [Accessed 1st May 2018].

12. UNPOP. 2010-2015 under-five mortality rates. File INT/3-1: Total population (both sexes combined) by single age, region, subregion and country, annually for 1950-2100 (thousands). File MORT/17-1: Abridged life table, for both sexes combined, by region, subregion and country, 1950-2100. United Nations, Department of Economic and Social Affairs, Population Division (2017). World Population Prospects: The 2017 Revision, DVD Edition. Available at:

https://esa.un.org/unpd/wpp/Download/Standard/Mortality/ [accessed 17th July 2018].

13. Tate JE, Mwenda JM, Armah G, Jani B, Omore R, Ademe A, et al. Evaluation of Intussusception after Monovalent Rotavirus Vaccination in Africa. N Engl J Med. 2018;378(16):1521-8.

14. Cui LL, Geng XY, Zhang J, Zhang J. [Epidemiological characteristics and risk factors of primary intussusception in children among two years old and below, Ji'nan city]. Zhonghua Yu Fang Yi Xue Za Zhi. 2018;52(7):727-33.

15. Liu N, Yen C, Huang T, Cui P, Tate JE, Jiang B, et al. Incidence and epidemiology of intussusception among children under 2years of age in Chenzhou and Kaifeng, China, 2009-2013. Vaccine. 2018.

16. Trang NV, Burnett E, Ly LH, Anh NP, Hung PH, Linh HM, et al. Recurrent intussusception among infants less than 2 years of age in Vietnam. Vaccine. 2018.

17. Goulet V. Actuar Package v 2.3-1. The Burr Distribution. Available at: https://www.rdocumentation.org/packages/actuar/versions/2.3-1/topics/Burr [Accessed 24th July 2018].

18. Zaman K, Breiman RF, Yunus M, Arifeen SE, Mahmud A, Chowdhury HR, et al. Intussusception surveillance in a rural demographic surveillance area in bangladesh. J Infect Dis. 2009;200 Suppl 1:S271-6.

19. Gay N, Ramsay M, Waight P. Rotavirus vaccination and intussusception. Lancet. 1999;354(9182):956.

20. Samad L, Cortina-Borja M, Bashir HE, Sutcliffe AG, Marven S, Cameron JC, et al. Intussusception incidence among infants in the UK and Republic of Ireland: a pre-rotavirus vaccine prospective surveillance study. Vaccine. 2013;31(38):4098-102.

21. Contopoulos-Ioannidis DG, Halpern MS, Maldonado Y. Trends in Hospitalizations for Intussusception in California in Relationship to the Introduction of New Rotavirus Vaccines, 1985-2010. Pediatr Infect Dis J. 2015;34(7):712-7.

22. Latipov R, Khudoyorov R, Flem E. Childhood intussusception in Uzbekistan: analysis of retrospective surveillance data. BMC Pediatr. 2011;11:22.

23. Phua KB, Lee BW, Quak SH, Jacobsen A, Teo H, Vadivelu-Pechai K, et al. Incidence of intussusception in Singaporean children aged less than 2 years: a hospital-based prospective study. BMC Pediatr. 2013;13:161.

24. Serayssol C, Abbo O, Mouttalib S, Claudet I, Labarre D, Galinier P, et al. [Seasonal pattern of intussusceptions in infants and children: is fall/winter predominance still worth consideration? A 10-year retrospective epidemiological study]. Arch Pediatr. 2014;21(5):476-82.

25. Tran LA, Yoshida LM, Nakagomi T, Gauchan P, Ariyoshi K, Anh DD, et al. A High Incidence of Intussusception Revealed by a Retrospective Hospital-Based Study in Nha Trang, Vietnam between 2009 and 2011. Trop Med Health. 2013;41(3):121-7.

26. Tate JE, Simonsen L, Viboud C, Steiner C, Patel MM, Curns AT, et al. Trends in intussusception hospitalizations among US infants, 1993-2004: implications for monitoring the safety of the new rotavirus vaccination program. Pediatrics. 2008;121(5):e1125-32.

27. Mpabalwani EM, Mwenda JM, Tate JE, Parashar UD. Review of Naturally Occurring Intussusception in Young Children in the WHO African Region prior to the Era of Rotavirus Vaccine Utilization in the Expanded Programme of Immunization. J Trop Pediatr. 2017;63(3):221-8.

28. Steele AD, Patel M, Cunliffe NA, Bresee JS, Borgstein E, Parashar UD. Workshop on intussusception in African countries--meeting report. Vaccine. 2012;30 Suppl 1:A185-9.

29. Ozgediz D, Jamison D, Cherian M, McQueen K. The burden of surgical conditions and access to surgical care in low- and middle-income countries. Bull World Health Organ. 2008;86(8):646-7.

30. Costantino C, Restivo V, Cuccia M, Furnari R, Amodio E, Vitale F. Analysis of hospitalizations due to intussusception in Sicily in the pre-rotavirus vaccination era (2003-2012). Ital J Pediatr. 2015;41:52.

31. Guney LH, Fakioglu E, Acer T, Otgun I, Arslan EE, Sagnak Akilli M, et al. Is every intussusception treatment an emergency intervention or surgery? Ulus Travma Acil Cerrahi Derg. 2016;22(2):139-44.

32. Carapinha C, Truter M, Bentley A, Welthagen A, Loveland J. Factors determining clinical outcomes in intussusception in the developing world: Experience from Johannesburg, South Africa. S Afr Med J. 2016;106(2):177-80.

33. Pruksananonda P, Athirakul K, Worawattanakul M, Varavithya W, Pisithpun A, Kitayaporn D, et al. Intussusception in a private tertiary-care hospital, Bangkok, Thailand: a case series. Southeast Asian J Trop Med Public Health. 2007;38(2):339-42.

34. Hong Kong Intussusception Study G. Intussusception trends in Hong Kong children. Hong Kong Med J. 2007;13(4):279-83.

35. Stowe J, Andrews N, Ladhani S, Miller E. The risk of intussusception following monovalent rotavirus vaccination in England: A self-controlled case-series evaluation Ref. No: JVAC-D-16-01124. Vaccine. 2016;34(50):6115.

36. Bines JE, At Thobari J, Satria CD, Handley A, Watts E, Cowley D, et al. Human Neonatal Rotavirus Vaccine (RV3-BB) to Target Rotavirus from Birth. N Engl J Med. 2018;378(8):719-30.

37. Bothara VP, Pandey A, Rawat J. Neonatal intussusception: a review. Available at: https://www.researchgate.net/publication/322299773_Neonatal_Intussusception_A_Review/fulltext/5a520ed1a6fdcc7690025c32/322299773_Neonatal_Intussusception_A_Review.pdf?origin=publication_detail [accessed 30th July 2018]. J Neonatal Surg 2018;7(5).

38. Gadisa A, Tadesse A, Hailemariam B. Patterns and Seasonal Variation of Intussusception in Children: A Retrospective Analysis of Cases Operated in a Tertiary Hospital in Ethiopia. Ethiop Med J. 2016;54(1):9-15.

39. Abantanga FA, Amoah M, Adeyinka AO, Nimako B, Yankey KP. Pneumatic reduction of intussusception in children at the Komfo Anokye Hospital, Kumasi, Ghana. East Afr Med J. 2008;85(11):550-5.

40. Enweronu-Laryea CC, Sagoe KW, Glover-Addy H, Asmah RH, Mingle JA, Armah GE. Prevalence of severe acute rotavirus gastroenteritis and intussusceptions in Ghanaian children under 5 years of age. J Infect Dev Ctries. 2012;6(2):148-55.

41. Kuremu RT. Childhood intussusception at the Moi teaching and Referral Hospital Eldoret: management challenges in a rural setting. East Afr Med J. 2004;81(9):443-6.

42. Omore R, Osawa F, Musia J, Rha B, Ismail A, Kiulia NM, et al. Intussusception Cases Among Children Admitted to Referral Hospitals in Kenya, 2002-2013: Implications for Monitoring Postlicensure Safety of Rotavirus Vaccines in Africa. J Pediatric Infect Dis Soc. 2016;5(4):465-9.

43. Ooko PB, Wambua P, Oloo M, Odera A, Topazian HM, White R. The Spectrum of Paediatric Intestinal Obstruction in Kenya. Pan Afr Med J. 2016;24:43.

44. Bode CO. Presentation and management outcome of childhood intussusception in Lagos: a prospective study. Afr J Paediatr Surg. 2008;5(1):24-8.

45. Ekenze SO, Mgbor SO, Okwesili OR. Routine surgical intervention for childhood intussusception in a developing country. Ann Afr Med. 2010;9(1):27-30.

46. Ekenze SO, Mgbor SO. Childhood intussusception: the implications of delayed presentation. Afr J Paediatr Surg. 2011;8(1):15-8.

47. Ekenze SO, Chukwubuike KE, Ezomike UO, Okere PC, Onuh AC. Pediatric Intussusception and Interventional Radiology in a Developing Country: Experienceand Challenges of Ultrasound Saline Reduction Complementary to Primary Surgery. Available at: http://www.internationalsurgery.org/doi/pdf/10.9738/INTSURG-D-14-00190.1?code=icsu-site [accessed 29th July 2018]. International Surgery. 2015;100:1301–7.

48. Ogundoyin OO, Olulana DI, Lawal TA. Childhood intussusception: Impact of delay in presentation in a developing country. Afr J Paediatr Surg. 2016;13(4):166-9.

49. Talabi AO, Sowande OA, Etonyeaku CA, Adejuyigbe O. Childhood intussusception in Ile-ife: what has changed? Afr J Paediatr Surg. 2013;10(3):239-42.

50. Ngendahayo E, Bonane A, Ntakiyiruta G, Munyanshongore A, Muganga N, Bikoroti J, et al. Preparing for safety monitoring after rotavirus vaccine implementation: a retrospective review of intussusception cases among children at a large teaching hospital in Rwanda, 2009-2012. Pediatr Infect Dis J. 2014;33 Suppl 1:S99-S103.

51. Moore SW, Kirsten M, Muller EW, Numanoglu A, Chitnis M, Le Grange E, et al. Retrospective surveillance of intussusception in South Africa, 1998-2003. J Infect Dis. 2010;202 Suppl:S156-61.

52. Venter JA, le Grange SM, Otto SF, Joubert G. An audit of paediatric intussusception radiological reduction at the Bloemfontein Academic Hospital Complex, Free State, South Africa. Available at: http://www.sajch.org.za/index.php/SAJCH/article/view/531/400 [accessed 29th July 2018]. South African Journal of Child Health 2013;7(2).

53. Wiersma R, Hadley GP. Minimizing surgery in complicated intussusceptions in the Third World. Pediatr Surg Int. 2004;20(3):215-7.

54. Carneiro PM, Kisusi DM. Intussusception in children seen at Muhimbili National Hospital, Dar es Salaam. East Afr Med J. 2004;81(9):439-42.

55. Chalya PL, Kayange NM, Chandika AB. Childhood intussusceptions at a tertiary care hospital in northwestern Tanzania: a diagnostic and therapeutic challenge in resource-limited setting. Ital J Pediatr. 2014;40(1):28.

56. Mpabalwani EM, Chitambala P, Chibumbya JN, Matapo B, Mutambo H, Mwenda JM, et al. Intussusception incidence rates in 9 Zambian hospitals, 2007-2011: prerotavirus vaccine introduction. Pediatr Infect Dis J. 2014;33 Suppl 1:S94-8.

57. Saez-Llorens X, Velazquez FR, Lopez P, Espinoza F, Linhares AC, Abate H, et al. A multi-country study of intussusception in children under 2 years of age in Latin America: analysis of prospective surveillance data. BMC Gastroenterol. 2013;13:95.

58. Teles E, Moscovici L, Monteiro RA, Alves D, Laprega MR, Bellissimo-Rodrigues F. The effectiveness of a rotavirus vaccine in preventing hospitalizations and deaths presumably due to acute infectious diarrhea in Brazilian children: a quasi-experimental study. Rev Soc Bras Med Trop. 2015;48(2):129-35.

59. Bailey KA, Wales PW, Gerstle JT. Laparoscopic versus open reduction of intussusception in children: a single-institution comparative experience. J Pediatr Surg. 2007;42(5):845-8.

60. Ducharme R, Benchimol EI, Deeks SL, Hawken S, Fergusson DA, Wilson K. Validation of diagnostic codes for intussusception and quantification of childhood intussusception incidence in Ontario, Canada: a population-based study. J Pediatr. 2013;163(4):1073-9 e3.

61. O'Ryan M, Lucero Y, Pena A, Valenzuela MT. Two year review of intestinal intussusception in six large public hospitals of Santiago, Chile. Pediatr Infect Dis J. 2003;22(8):717-21.

62. Saez-Llorens X, Guevara JN. Intussusception and rotavirus vaccines: what is the background risk? Pediatr Infect Dis J. 2004;23(4):363-5.

63. Tota-Maharaj R, Rampersad B, Indalsingh R. Barium enema reduction of intussusception in a developing country. West Indian Med J. 2010;59(5):535-9.

64. Aboagye J, Goldstein SD, Salazar JH, Papandria D, Okoye MT, Al-Omar K, et al. Age at presentation of common pediatric surgical conditions: Reexamining dogma. J Pediatr Surg. 2014;49(6):995-9.

65. Burjonrappa SC. Laparoscopic reduction of intussusception: an evolving therapeutic option. JSLS. 2007;11(2):235-7.

66. Cortese MM, Staat MA, Weinberg GA, Edwards K, Rice MA, Szilagyi PG, et al. Underestimates of intussusception rates among US infants based on inpatient discharge data: implications for monitoring the safety of rotavirus vaccines. J Infect Dis. 2009;200 Suppl 1:S264-70.

67. Desai R, Curns AT, Patel MM, Parashar UD. Trends in intussusception-associated deaths among US infants from 1979-2007. J Pediatr. 2012;160(3):456-60.

68. Eng PM, Mast TC, Loughlin J, Clifford CR, Wong J, Seeger JD. Incidence of intussusception among infants in a large commercially insured population in the United States. Pediatr Infect Dis J. 2012;31(3):287-91.

69. Munden MM, Bruzzi JF, Coley BD, Munden RF. Sonography of pediatric small-bowel intussusception: differentiating surgical from nonsurgical cases. AJR Am J Roentgenol. 2007;188(1):275-9.

70. Shekherdimian S, Lee SL. Management of pediatric intussusception in general hospitals: diagnosis, treatment, and differences based on age. World J Pediatr. 2011;7(1):70-3.

71. Tate JE, Yen C, Steiner CA, Cortese MM, Parashar UD. Intussusception Rates Before and After the Introduction of Rotavirus Vaccine. Pediatrics. 2016;138(3).

72. Yen C, Tate JE, Steiner CA, Cortese MM, Patel MM, Parashar UD. Trends in intussusception hospitalizations among US infants before and after implementation of the rotavirus vaccination program, 2000-2009. J Infect Dis. 2012;206(1):41-8.

73. Zickafoose JS, Benneyworth BD, Riebschleger MP, Espinosa CM, Davis MM. Hospitalizations for intussusception before and after the reintroduction of rotavirus vaccine in the United States. Arch Pediatr Adolesc Med. 2012;166(4):350-5.

74. Perez-Schael I, Escalona M, Salinas B, Materan M, Perez ME, Gonzalez G. Intussusception-associated hospitalization among Venezuelan infants during 1998 through 2001: anticipating rotavirus vaccines. Pediatr Infect Dis J. 2003;22(3):234-9.

75. Ahmed HM, Ahmed O, Ahmed RK. Adding a custom made pressure release valve during air enema for intussusception: A new technique. Afr J Paediatr Surg. 2015;12(4):232-5.

76. Muhsen K, Kassem E, Efraim S, Goren S, Cohen D, Ephros M. Incidence and risk factors for intussusception among children in northern Israel from 1992 to 2009: a retrospective study. BMC Pediatr. 2014;14:218.

77. Greenberg D, Givon-Lavi N, Newman N, Wheeler J, Cohen Z, Dagan R. Intussusception in children in Southern Israel: disparity between 2 populations. Pediatr Infect Dis J. 2008;27(3):236-40.

78. Yousafzai MT, Thobani R, Qazi SH, Saddal N, Yen C, Aliabadi N, et al. Intussusception among children less than 2years of age: Findings from pre-vaccine introduction surveillance in Pakistan. Vaccine. 2017.

79. Al-Malki TA. Pediatric intussusception in a Saudi Arabian tertiary hospital. West Afr J Med. 2005;24(4):309-10.

80. Crankson SJ, Al-Rabeeah AA, Fischer JD, Al-Jadaan SA, Namshan MA. Idiopathic intussusception in infancy and childhood. Saudi Med J. 2003;24 Suppl:S18-20.

81. Chouikha A, Fodha I, Maazoun K, Ben Brahim M, Hidouri S, Nouri A, et al. Rotavirus infection and intussusception in Tunisian children: implications for use of attenuated rotavirus vaccines. J Pediatr Surg. 2009;44(11):2133-8.

82. Saxena AK, Seebacher U, Bernhardt C, Hollwarth ME. Small bowel intussusceptions: issues and controversies related to pneumatic reduction and surgical approach. Acta Paediatr. 2007;96(11):1651-4.

83. Fischer TK, Bihrmann K, Perch M, Koch A, Wohlfahrt J, Kare M, et al. Intussusception in early childhood: a cohort study of 1.7 million children. Pediatrics. 2004;114(3):782-5.

84. Lappalainen S, Ylitalo S, Arola A, Halkosalo A, Rasanen S, Vesikari T. Simultaneous presence of human herpesvirus 6 and adenovirus infections in intestinal intussusception of young children. Acta Paediatr. 2012;101(6):663-70.

85. Leino T, Ollgren J, Stromberg N, Elonsalo U. Evaluation of the Intussusception Risk after Pentavalent Rotavirus Vaccination in Finnish Infants. PLoS One. 2016;11(3):e0144812.

86. Jenke AC, Klaassen-Mielke R, Zilbauer M, Heininger U, Trampisch H, Wirth S. Intussusception: incidence and treatment-insights from the nationwide German surveillance. J Pediatr Gastroenterol Nutr. 2011;52(4):446-51.

87. Kohl LJ, Streng A, Grote V, Koletzko S, Liese JG. Intussusception-associated hospitalisations in southern Germany. Eur J Pediatr. 2010;169(12):1487-93.

88. Weiss S, Streng A, Kries R, Liese J, Wirth S, Jenke AC. Incidence of intussusception in early infancy: a capture-recapture estimate for Germany. Klin Padiatr. 2011;223(7):419-23.

89. Petursdottir K, Rosmundsson P, Hannesson PH, Moller PH. [Intussusception in children in Iceland]. Laeknabladid. 2013;99(2):77-81.

90. Eshed I, Witzling M, Gorenstein A, Serour F. [Reduction of intussusception by air enema in children--experience over a 13-year period]. Harefuah. 2003;142(10):659-61, 720, 19.

91. Restivo V, Costantino C, Tramuto F, Vitale F. Hospitalization rates for intussusception in children aged 0-59 months from 2009 to 2014 in Italy. Hum Vaccin Immunother. 2017;13(2):445-9.

92. Trotta F, Da Cas R, Bella A, Santuccio C, Salmaso S. Intussusception hospitalizations incidence in the pediatric population in Italy: a nationwide cross-sectional study. Ital J Pediatr. 2016;42(1):89.

93. Gadroen K, Kemmeren JM, Bruijning-Verhagen PC, Straus SM, Weibel D, de Melker HE, et al. Baseline incidence of intussusception in early childhood before rotavirus vaccine introduction, the Netherlands, January 2008 to December 2012. Euro Surveill. 2017;22(25).

94. Hilal A, MacMahon P, Cosgrove JF. Outcome of acute intussusception in a regional paediatric centre. Ir Med J. 2002;95(2):58-9.

95. Tareen F, Ryan S, Avanzini S, Pena V, Mc Laughlin D, Puri P. Does the length of the history influence the outcome of pneumatic reduction of intussusception in children? Pediatr Surg Int. 2011;27(6):587-9.

96. Tarca E, Savu B, Criscov I, Toma CM, Aprodu SG. Intussusception in infants--storm from a clear sky. Rev Med Chir Soc Med Nat Iasi. 2015;119(1):141-6.

97. Shapkina AN, Shapkin VV, Nelubov IV, Pryanishena LT. Intussusception in children: 11-year experience in Vladivostok. Pediatr Surg Int. 2006;22(11):901-4.

98. Vujovic D, Lukac M, Sretenovic A, Krstajic T, Ljubic V, Antunovic SS. Indications for repeated enema reduction of intussusception in children. Srp Arh Celok Lek. 2014;142(5-6):320-4.

99. Rubi I, Vera R, Rubi SC, Torres EE, Luna A, Arcos J, et al. Air reduction of intussusception. Eur J Pediatr Surg. 2002;12(6):387-90.

100. Buettcher M, Baer G, Bonhoeffer J, Schaad UB, Heininger U. Three-year surveillance of intussusception in children in Switzerland. Pediatrics. 2007;120(3):473-80.

101. Ocal S, Cevik M, Boleken ME, Karakas E. A comparison of manual versus hydrostatic reduction in children with intussusception: single-center experience. Afr J Paediatr Surg. 2014;11(2):184-8.

102. Sonmez K, Turkyilmaz Z, Demirogullari B, Karabulut R, Kale N, Basaklar AC. Intussusception in children: experience with 105 patients in a department of paediatric surgery, Turkey. S Afr J Surg. 2012;50(2):37-9.

103. Yalcin S, Ciftci AO, Karaagaoglu E, Tanyel FC, Senocak ME. Presenting clinical features and outcome in intussusception. Indian J Pediatr. 2009;76(4):401-5.

104. Samad L, Marven S, El Bashir H, Sutcliffe AG, Cameron JC, Lynn R, et al. Prospective surveillance study of the management of intussusception in UK and Irish infants. Br J Surg. 2012;99(3):411-5.

105. Satter SM, Aliabadi N, Yen C, Gastanaduy PA, Ahmed M, Mamun A, et al. Epidemiology of childhood intussusception in Bangladesh: Findings from an active national hospital based surveillance system, 2012-2016. Vaccine. 2017.

106. Bahl R, Saxena M, Bhandari N, Taneja S, Mathur M, Parashar UD, et al. Population-based incidence of intussusception and a case-control study to examine the association of intussusception with natural rotavirus infection among indian children. J Infect Dis. 2009;200 Suppl 1:S277-81.

107. Bhowmick K, Kang G, Bose A, Chacko J, Boudville I, Datta SK, et al. Retrospective surveillance for intussusception in children aged less than five years in a South Indian tertiary-care hospital. J Health Popul Nutr. 2009;27(5):660-5.

108. Gupta M, Kanojia R, Singha R, Tripathy JP, Mahajan K, Saxena A, et al. Intussusception Rate Aamong Uunder-Five-Children Before Introduction of Rotavirus Vaccine in North India. J Trop Pediatr. 2017.

109. Jehangir S, John J, Rajkumar S, Mani B, Srinivasan R, Kang G. Intussusception in southern India: comparison of retrospective analysis and active surveillance. Vaccine. 2014;32 Suppl 1:A99-103.

110. John J, Kawade A, Rongsen-Chandola T, Bavdekar A, Bhandari N, Taneja S, et al. Active surveillance for intussusception in a phase III efficacy trial of an oral monovalent rotavirus vaccine in India. Vaccine. 2014;32 Suppl 1:A104-9.

111. Mathew MA, Venugopal S, Arora R, Kang G. Leveraging the National Rotavirus Surveillance Network for Monitoring Intussusception. Indian Pediatr. 2016;53(7):635-8.

112. Mehendale S, Kumar CP, Venkatasubramanian S, Prasanna T. Intussusception in Children Aged Less than Five years. Indian J Pediatr. 2016;83(10):1087-92.

113. Ramachandran P, Gupta A, Vincent P, Sridharan S. Air enema for intussusception: is predicting the outcome important? Pediatr Surg Int. 2008;24(3):311-3.

114. Raman T, Mukhopadhyaya A, Eapen CE, Aruldas V, Bose A, Sen S, et al. Intussusception in southern Indian children: lack of association with diarrheal disease and oral polio vaccine immunization. Indian J Gastroenterol. 2003;22(3):82-4.

115. Singh JV, Kamath V, Shetty R, Kumar V, Prasad R, Saluja T, et al. Retrospective surveillance for intussusception in children aged less than five years at two tertiary care centers in India. Vaccine. 2014;32 Suppl 1:A95-8.

116. Srinivasan R, Girish Kumar CP, Naaraayan SA, Jehangir S, Thangaraj JWV, Venkatasubramanian S, et al. Intussusception hospitalizations before rotavirus vaccine introduction: Retrospective data from two referral hospitals in Tamil Nadu, India. Vaccine. 2017.

117. Rayamajhi A, Thapa A, Kumar M, Yen C, Tate JE, Parashar UD, et al. Preparing for rotavirus vaccine introduction - A retrospective assessment of the epidemiology of intussusception in children below 2years of age in Nepal. Vaccine. 2017.

118. Shakya VC, Agrawal CS, Sinha AK, Bhatta NK, Khania S, Adhikary S. Childhood Intussusception: A Prospective Institutional Study at BPKIHS. Available at: https://www.nepjol.info/index.php/JNPS/article/view/3862/3519 [accessed 28th July 2018]. J Nepal Paediatr Soc. 2011;31(1).

119. Thapa B, Chaudhary RP, Pun MS, Ral GK. Clinical Analysis, Management and Outcome of Intussusception in Children. Journal of Nepal Paediatric Society. 2012;32(1).

120. Kruatrachue A, Wongtapradit L, Nithipanya N, Ratanaprakarn W. Result of air enema reduction in 737 cases of intussusception. J Med Assoc Thai. 2011;94 Suppl 3:S22-6.

121. Khumjui C, Doung-ngern P, Sermgew T, Smitsuwan P, Jiraphongsa C. Incidence of intussusception among children 0-5 years of age in Thailand, 2001-2006. Vaccine. 2009;27 Suppl 5:F116-9.

122. Blanch AJ, Perel SB, Acworth JP. Paediatric intussusception: epidemiology and outcome. Emerg Med Australas. 2007;19(1):45-50.

123. Justice F, Carlin J, Bines J. Changing epidemiology of intussusception in Australia. J Paediatr Child Health. 2005;41(9-10):475-8.

124. Justice FA, Auldist AW, Bines JE. Intussusception: trends in clinical presentation and management. J Gastroenterol Hepatol. 2006;21(5):842-6.

125. Lloyd-Johnsen C, Justice F, Donath S, Bines JE. Retrospective hospital based surveillance of intussusception in children in a sentinel paediatric hospital: benefits and pitfalls for use in post-marketing surveillance of rotavirus vaccines. Vaccine. 2012;30 Suppl 1:A190-5.

126. Palupi-Baroto R, Lee KJ, Carlin JB, Bines JE. Intussusception in Australia: epidemiology prior to the introduction of rotavirus vaccine. Aust N Z J Public Health. 2015;39(1):11-4.

127. Cui P, Liu N, Li J, Huang T, Ge H, Wu Q, et al. [Epidemiology of intussusception related hospitalizations in children aged <2 years in Suzhou, 2007-2013]. Zhonghua Liu Xing Bing Xue Za Zhi. 2016;37(3):410-4.

128. Zhang Y, Bai YZ, Li SX, Liu SJ, Ren WD, Zheng LQ. Sonographic findings predictive of the need for surgical management in pediatric patients with small bowel intussusceptions. Langenbecks Arch Surg. 2011;396(7):1035-40.

129. Wong CW, Chan IH, Chung PH, Lan LC, Lam WW, Wong KK, et al. Childhood intussusception: 17-year experience at a tertiary referral centre in Hong Kong. Hong Kong Med J. 2015;21(6):518-23.

130. Nakagomi T, Takahashi Y, Arisawa K, Nakagomi O. A high incidence of intussusception in Japan as studied in a sentinel hospital over a 25-year period (1978-2002). Epidemiol Infect. 2006;134(1):57-61.

131. Noguchi A, Nakagomi T, Kimura S, Takahashi Y, Matsuno K, Koizumi H, et al. Incidence of intussusception as studied from a hospital-based retrospective survey over a 10-year period (2001-2010) in Akita Prefecture, Japan. Jpn J Infect Dis. 2012;65(4):301-5.

132. Giak CL, Singh HS, Nallusamy R, Leong TY, Ng TL, Bock HL. Epidemiology of intussusception in Malaysia: a three-year review. Southeast Asian J Trop Med Public Health. 2008;39(5):848-55.

133. Chen YE, Beasley S, Grimwood K, New Zealand Rotavirus Study G. Intussusception and rotavirus associated hospitalisation in New Zealand. Arch Dis Child. 2005;90(10):1077-81.

134. Kodikara H, Lynch A, Morreau P, Vogel S. Ten-year review of intussusception at Starship Hospital: 1998-2007. N Z Med J. 2010;123(1324):32-40.

135. Tan N, Teoh YL, Phua KB, Quak SH, Lee BW, Teo HJ, et al. An update of paediatric intussusception incidence in Singapore: 1997-2007, 11 years of intussusception surveillance. Ann Acad Med Singapore. 2009;38(8):690-2.

136. Yap Shiyi E, Ganapathy S. Intussusception in Children Presenting to the Emergency Department: An Asian Perspective. Pediatr Emerg Care. 2017;33(6):409-13.

137. Jo DS, Nyambat B, Kim JS, Jang YT, Ng TL, Bock HL, et al. Population-based incidence and burden of childhood intussusception in Jeonbuk Province, South Korea. Int J Infect Dis. 2009;13(6):e383-8.

138. Hsiao CC, Tsao LY, Lai CH. Nationwide population-based epidemiologic study of childhood and adulthood intussusception in Taiwan. Pediatr Neonatol. 2013;54(3):188-93.

139. Hsu WL, Lee HC, Yeung CY, Chan WT, Jiang CB, Sheu JC, et al. Recurrent Intussusception: when Should Surgical Intervention be performed? Pediatr Neonatol. 2012;53(5):300-3.

140. Yen C, Shih SM, Tate JE, Wu FT, Huang YC, Parashar UD, et al. Intussusception-related Hospitalizations Among Infants Before and After Private Market Licensure of Rotavirus Vaccines in Taiwan, 2001-2013. Pediatr Infect Dis J. 2017;36(10):e252-e7.

141. Bines JE, Liem NT, Justice FA, Son TN, Kirkwood CD, de Campo M, et al. Risk factors for intussusception in infants in Vietnam and Australia: adenovirus implicated, but not rotavirus. J Pediatr. 2006;149(4):452-60.

142. Van Trang N, Le Nguyen NT, Dao HT, Ho VL, Tran DT, Loewen J, et al. Incidence and Epidemiology of Intussusception among Infants in Ho Chi Minh City, Vietnam. J Pediatr. 2014;164(2):366-71.

9.0 Chapter 9 - Mortality benefits and intussusception risks of rotavirus vaccination

9.1 Contribution of paper to the aim and objectives of the thesis

This paper brings together the various methods and sources of evidence described in chapters 4-8. It outlines the modelling approach, algorithms and assumptions used to estimate benefits and risks. The aim of the paper is fully aligned with the aim of the thesis, to estimate the potential mortality benefits (averted RVGE deaths <5 years of age) and risks (excess intussusception deaths <5 years of age) of alternative rotavirus vaccination schedules in LMICs.

9.2 Independent academic contribution

I was the LSHTM principal investigator for this work. I developed the model, synthesised the evidence, ran the benefit-risk analysis, constructed the tables and figures and wrote the first draft of the paper. I also presented the work to the WHO IVIR-AC committee.

New meta-analyses were done to estimate the risk of intussusception and the relative effectiveness of 1 dose compared to 2/3 doses. I gathered and synthesised the evidence for these, but the actual meta analyses were done by Colin Sanderson and Cochrane Response. Figure 1 (the global map) was prepared by Matt Hasso-Agopsowicz. My contribution to the development of the other modelling inputs (RVGE deaths, RVGE age distributions, coverage and timeliness, rotavirus efficacy and waning, intussusception incidence, age distributions and CFRs) has been described in previous chapters.

9.3 Ethical approval

I did not seek ethical approval for this analysis because it uses data that is in the public domain and uses methods and data inputs that are covered by the LSHTM ethical approvals described in chapters 5, 7 and 8.

Potential mortality benefits and intussusception risks of alternative rotavirus vaccination schedules in 135 low- and middle-income countries

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Abstract

Background: Infant rotavirus vaccines have led to substantial reductions in gastroenteritis hospital admissions and costs, but some studies have reported an elevated risk of intussusception, a rare bowel disorder, in vaccinated infants.

Methods: We estimated the mortality reduction benefits and intussusception risks of two schedules currently recommended by WHO, and explored the potential of 16 alternative schedules, assuming introduction of rotavirus vaccines in 135 low- and middle-income countries (LMICs). We calculated numbers of rotavirus gastroenteritis (RVGE) deaths and intussusception deaths in each week of age for all infants born in the year 2015 between birth and age 5.0 years, for each schedule with and without age restrictions. We calculated benefit-risk ratios (number of RVGE deaths prevented per excess intussusception death) and other indicators.

Findings: We estimate that an age-unrestricted schedule co-administered with Diphtheria-Tetanus-Pertussis (DTP) vaccination could prevent ~65,000 RVGE deaths (38% reduction) and lead to 146 excess intussusception deaths (1.0% increase) compared to no vaccination; a benefit-risk ratio of 446:1 (2.5th and 97.5th percentiles, 194:1 - 1383:1). Infants that received their first dose before 15 weeks and their last dose before 32 weeks had a benefit-risk ratio of 623:1 (2.5th and 97.5th percentiles, 275:1 - 2046:1) compared to 186:1 (84:1 – 522:1) among infants vaccinated after these ages. If each country were to implement the age-unrestricted schedule with the greatest predicted impact on RVGE deaths (including birth and/or booster doses) around 72,000 RVGE deaths could be prevented (42% reduction) and 107 excess intussusception deaths caused (0.7% increase) compared to no vaccination (benefit-risk ratio 666:1).

Interpretation: Rotavirus vaccines have a favourable benefit-risk profile in LMICs. Schedules involving birth and booster doses could further increase benefits and reduce risks, but more research is needed to assess their feasibility, safety and impact.

Introduction

Infant rotavirus vaccines have led to substantial reductions in gastroenteritis hospital admissions compared to pre-introduction baselines (1), but some studies have reported an elevated risk of intussusception, a rare bowel disorder, in vaccinated infants (2, 3). In 2012 we estimated the potential mortality benefits and intussusception risks of introducing rotavirus vaccines into the national immunization programmes of 158 countries (4). That analysis provided reassurance about the highly positive benefit-risk profile of rotavirus vaccines. It also informed a World Health Organization (WHO) recommendation to remove age restrictions for vaccination given that the benefits of preventing additional rotavirus mortality from later vaccination greatly exceeded the intussusception risks (5). Since our 2012 analysis, estimates of the number of rotavirus gastroenteritis (RVGE) deaths in children <5 years of age (without vaccination) have decreased from ~450,000 in 2008 to ~200,000 in 2015 (6). The evidence for several other modelling parameters has also been significantly strengthened, including: a) a meta-regression to estimate the instantaneous efficacy of live oral rotavirus vaccines by duration of follow-up (7); b) a systematic review of the age distribution of RVGE hospital admissions in children <5 years of age (8); c) a systematic review of intussusception incidence rates, age distributions and case fatality ratios (CFRs) in children <5 years of age (9); and, d) a systematic review and meta-analysis of the relative risk of intussusception shortly after administration of rotavirus vaccination (10), including the first published risk estimates from a high mortality setting (11). Hence, we are in a position to generate updated and much more robust benefit-risk estimates.

The scale of potential mortality benefits and intussusception risks is linked to the choice of vaccination schedule. For programmatic and economic reasons rotavirus vaccines are currently co-administered with Diphtheria-Tetanus-Pertussis (DTP)-containing vaccines in the first six months of life. All countries currently give two doses with DTP1 and DTP2, or three doses with DTP1, DTP2, and DTP3 as per current WHO recommendations. Rotavirus programmes using these schedules have demonstrated high and durable efficacy in high-income countries but more modest efficacy in low- and middle-income countries (LMICs) (4). This has stimulated interest in the potential value of alternative schedules to help improve impact. This could include a birth dose given at the same time as Bacillus Calmette-Guérin (BCG)(12) and/or a booster dose given with the first dose of measles-containing vaccine (MCV1, referred to hereafter as Meas1) (13). A birth dose has the potential to prevent disease that occurs very early in life, and has been shown to be efficacious (12). A booster dose has the potential to mitigate the effects of waning rotavirus vaccine protection and has been shown to be non-interfering and immune-boosting in trials (7). The optimal number and timing of

doses (concurrent with different combinations of BCG, DTP1, DTP2, DTP3 and Meas1) will depend on several criteria, including the balance of benefits to risks.

The aim of this analysis is to provide national decision makers in LMICs with evidence on the potential mortality benefits and risks of the two current rotavirus vaccination schedules, and to explore whether alternative schedules could have some advantages.

Methods

We included all LMICs, defined as countries with a GNI per capita below $12,236 in the 2018 fiscal year (14). To calculate potential benefits and risks we used UNIVAC (universal vaccine decision support model), an Excel-based static cohort model with a finely disaggregated age structure (weeks of age <5 years) (15). In each of the 135 countries, we predicted the experience of all infants born in the year 2015 from birth to age 5.0 years. For each vaccination schedule, we calculated numbers of doses administered, fully vaccinated infants (FVI), RVGE deaths, intussusception cases and intussusception deaths in children <5 years of age. Estimated benefits (RVGE deaths averted) and risks (excess intussusception cases and deaths) were calculated by comparing each schedule scenario to a scenario with no rotavirus vaccination. We further estimated the incremental benefits and risks of moving from age-restricted schedules to age-unrestricted schedules. The primary outcome was the benefit-risk ratio (number of RVGE deaths prevented per excess intussusception death). We also estimated the percent reduction in RVGE deaths, percent increase in intussusception deaths, number of FVI per excess intussusception case, and number of RVGE deaths prevented per dose administered.

Vaccination schedule scenarios

There are several licensed rotavirus vaccines available today, but insufficient comparative evidence from the same populations to demonstrate conclusive superiority of one brand over another in terms of vaccine efficacy/effectiveness/impact (4, 16, 17) or intussusception risks (3, 18). We therefore ran a product-neutral analysis assuming that the vaccine products were equivalent. To limit the number of vaccine schedule scenarios to a practical list, we assumed that no schedules would require more than three doses, and that the first dose would always be co-administered with either BCG or DTP1. We ran scenarios for 18 schedules in 135 countries (Table 1). For the first 11 schedule options (all primary dose schedules) we ran scenarios with and without strict adherence to age restrictions (first dose <15 weeks; last dose < 32 weeks).

Potential benefits of rotavirus vaccination

For each country we predicted the number of person-years lived between birth and age 5.0 years in the 2015 birth cohort (19) and multiplied this by the RVGE mortality rate among children <5 years of age to estimate the number of RVGE deaths expected to occur between birth and age 5.0 years. Three sources of country-specific rotavirus mortality rates for children <5 years of age were recently updated (WHO/CDC (20), IHME/GBD (21) and MCEE (21)) so we used them to calculate means and 95% confidence intervals for each country in the year 2015, treating the three separate estimates as distinct samples from a population. For countries that had introduced rotavirus vaccines prior to 2016, we used WHO/UNICEF coverage estimates to identify the year of introduction, and used the RVGE mortality rate for the year before vaccine introduction (22). RVGE deaths <5 years were assigned to each week of age by applying Log Logistic age distributions estimated in a recent global systematic review of 92 hospital datasets (8). If no dataset was available for a given country, then we used the Log Logistic age distribution for the relevant under-five mortality stratum, defined by the median scale and shape parameters in each stratum. The median age were 38 weeks (inter-quartile range IQR: 25-58), 43 weeks (IQR: 28-68), 46 weeks (IQR: 29-72) and 65 weeks (IQR: 40-107) in countries with very high, high, medium and low/very low child mortality, respectively.

For a given *week* of age, the number of RVGE deaths was estimated by the following equation:

$$R_w * (1 - (C_{3w} * E_{3w} + (C_{2w} - C_{3w}) * E_{2w} + (C_{1w} - C_{2w}) * E_{1w}))$$

Where:

R_w	=	Number of RVGE deaths in week of age (without vaccination)
E_{1w}	=	1-dose vaccine efficacy in week of age, adjusted for vaccine waning
E_{2w}	=	2-dose vaccine efficacy in week of age, adjusted for vaccine waning
E_{3w}	=	3-dose vaccine efficacy in week of age, adjusted for vaccine waning
C_{1w}	=	Coverage of dose one in week of age, adjusted for age restriction scenario
C_{2w}	=	Coverage of dose two in week of age, adjusted for age restriction scenario
C_{3w}	=	Coverage of dose three in week of age, adjusted for age restriction scenario

For BCG, DTP1, DTP2, DTP3 and Meas1 we estimated the proportion of final (age 3.0 years) coverage achieved in each week of age using Log Logistic curves fitted to age- and country-specific coverage rates derived from survival analysis of 73 nationally representative household surveys (R v 3.4.0, packages *MASS* and *fitdistrplus*) (23). Methods used for the survival analyses have been described elsewhere (23). Compared to lognormal, gamma and weibull distributions, the Log Logistic distribution had the most favourable goodness of fit (based on the Akaike Information Criterion - AIC). For countries without a recent household survey we identified the target ages for BCG, DTP1, DTP2, DTP3 and Meas1 in each country

(24) and used timeliness curves defined by the median of the Log Logistic scale and shape parameters for all other countries with the same schedule. For countries with unique schedules and no timeliness data, we used the average parametric curve for the closest matching schedule and added a shift parameter to capture the difference in the target ages. All age-specific coverage estimates were scaled to national WHO/UNICEF coverage estimates for the year 2015 (22).

We assumed that vaccine protection would start two weeks after administration of each dose. We assumed the same vaccine efficacy for two and three doses, but applied waning in the interval between doses. We estimated the efficacy of rotavirus vaccination in each week of follow-up based on a Bayesian meta-regression analysis, and gamma function fitted to 50 observation points from 31 randomised controlled trials (RCTs)(7). We assumed that efficacy against severe RVGE was a reasonable proxy for efficacy against RVGE deaths. Different efficacy/waning assumptions were used for countries in different child mortality strata. We further assumed the same rate of waning protection following one, two or three doses. The relative efficacy of 1 dose compared to 2 or 3 doses was estimated to be 0.63 (95% CI 0.51 – 0.79) based on a random effects meta-analysis of published estimates of vaccine effectiveness against RVGE hospital admissions from 10 case control studies in LMICs (Appendix Table 1) (17).

Potential risks of rotavirus vaccination

Previously described methods (25) were used to estimate excess intussusception cases in the two periods of risk (1-7 days and 8-21 days) following both the first and second dose. In each country, the number of excess (vaccine-related) intussusception cases was calculated as follows:

$PY \times (C_w - C_{w-1})$	number of new doses given in week of age
$\times$	
$[I_w \times (RR_{1-7} - 1)$	incidence of vaccine-related intussusception cases, 1-7 day period
$+$	
$I_{w+1} \times (RR_{8-21} - 1)$	incidence of vaccine-related intussusception cases, 8-14 day period
$+$	
$I_{w+2} \times (RR_{8-21} - 1)]$	incidence of vaccine-related intussusception cases, 15-21 day period

Where:

PY	=	Mid-year population for single year of age
C_w	=	Cumulative coverage estimate for the week of age
C_{w-1}	=	Cumulative coverage estimate for the week preceding the current week of age
I_w	=	Age-specific incidence of intussusception week 1 after dose (1-7 days)
I_{w+1}	=	Age-specific incidence of intussusception week 2 after dose (8-14 days)
I_{w+2}	=	Age-specific incidence of intussusception in week 3 after dose (15-21 days)
RR_{1-7}	=	Relative risk of intussusception versus background rate 1-7 days after dose
RR_{8-21}	=	Relative risk of intussusception versus background rate 8-21 days after dose.

Estimates of the background incidence of intussusception were based on the incidence of intussusception hospital admissions from 71 pre-vaccination country datasets identified in a recent systematic literature review (9). The median incidence of hospital admissions within its WHO region was used for each country without data. Intussusception incidence rates among children <5 years of age were based on children who were admitted to hospital (I_H).

We assumed that all countries with very low and low mortality would have 100% access to treatment. For all other countries we divided I_H by the average 2010-2015 DTP1 coverage estimates (range from 53% in Somalia to 99% in China)(22), assumed to be a proxy for access to intussusception treatment, in order to calculate overall/community incidence rates. The adjusted national annual incidence rates were 9 (range 4-17) per 100,000 children <5 year of age in Africa, 11 (1-35) in the Americas, 19 (13-36) in the Eastern Mediterranean region, 14 (4-36) in Europe, 19 (4-33) in South East Asia and 54 (5-185) in the Western Pacific region. We estimated the number of intussusception cases in each week of age <5 years based on parametric (Burr) age distributions fitted to 61 country datasets identified in the recent systematic review (9). The median ages ranged from 29 weeks in Africa (83% of cases in the first year of life) to 70 weeks in the Western Pacific region (35% of cases in the first year of life). For countries without a fitted age distribution, we used the distribution fitted to the pooled age distributions of counts for each WHO region.

Intussusception mortality rates per 100,000 children <5 years of age per year were calculated as:

$$I_M = (I_H * CFR_H) + (((I_H / DTP1) - I_H) * 90\%)$$

Where:

I_M	=	Mortality rate for intussusception hospital admissions <5 years of age
I_H	=	Incidence rate for intussusception hospital admissions <5 years of age
CFR_H	=	In-hospital intussusception case fatality ratio (CFR) <5 years of age
DTP1	=	DTP1 coverage (proxy for access to intussusception treatment)

In-hospital CFRs (CFR_H) were based on the pooled estimate for each WHO region, based on a meta-analysis of 95 data points identified in a global systematic review.(9) Pooled estimates ranged from 0.05% 95% CI 0.02 - 0.12%) in the Western Pacific region to 11.5% (7.2 - 17.8%) in Africa. We assumed a 90% CFR for children without access to hospital based on the proportion (10%) of children in a Bangkok case series who improved spontaneously without treatment (26).

We estimated the relative risk of intussusception (compared to the background incidence rate) in the 1-7 day period and 8-21 day period after the first and second dose. We only evaluated risk estimates based on the self-controlled case series (SCCS) method because this is based on large numbers of post-licensure vaccine recipients, and is less prone to the biases associated with other approaches (such as lack of statistical power to detect rare events, known and unknown differences between case and control groups). Post-licensure SCCS data points were taken from a recently updated global systematic literature review of the relative risk of intussusception (10). We derived risk estimates for the 1-7 and 8-21 day post-vaccination periods if they were not explicitly reported, using the same approach used in a previous global meta-analysis (2). We excluded a Finnish study because it was not possible to derive estimates for the periods of interest (27). All available global risk estimates were pooled using a random effects meta-analysis (Table 2). In the 1-7 day period the pooled relative risk was 4.2 (95% CI 2.3 - 7.9) after dose 1 and 1.5 (1.0 - 2.1) after dose 2. The corresponding values for the 8-21 day period were 1.8 (1.4 – 2.3) and 1.3 (1.0 – 1.6). There is a tendency towards little or no excess risk as the under-five mortality rate increases (Appendix Figure 1) but this is based on very few studies from LMICs so we conservatively used the global pooled estimate. We assumed the relative risks were only dose-dependent and did not change with age of vaccine administration. For age-restricted neonatal schedules, we assumed the first dose had to be administered before 15 weeks but allowed all subsequent doses, including doses given with DTP1, to be given up to 32 weeks of age.

Uncertainty and scenario analysis

We ran probabilistic simulations to calculate 95% uncertainty intervals around the benefit-risk ratios and the number of FVI per excess intussusception case, for age-restricted and age-unrestricted schedules co-administered with DTP. Parameters and their distributions are described in Appendix Table 2. In addition, we ran three alternative 'what-if' scenarios:

i) a scenario with less rapid waning efficacy, based on a power function that has been described in detail elsewhere (7);
ii) a scenario with double the mean duration of protection for all primary doses administered as part of a neonatal dose schedule, consistent with the results of the RV3-BB trial in Indonesia (Appendix Figure 2)(7, 12); and,
iii) a scenario with pessimistic assumptions about access to intussusception treatment, based on the proportion of children who are within two hours of a public hospital (28). We used country-specific values for 46 African countries, and assumed the population-weighted proportion (71%) for all other high/very high mortality countries.

Results

We evaluated benefits and risks for 31 low income, 51 lower-middle income and 53 upper-middle income countries. We estimated ~170,000 RVGE deaths <5 years of age in the year 2015, of which 17-41% could be prevented by vaccination, depending on the schedule used. We estimated ~14,500 background intussusception deaths <5 years of age in the year 2015 for all 135 LMICs combined, of which no more than ~150 deaths (~1%) were attributed to rotavirus vaccination for any schedule evaluated (Table 3).

Benefits and risks of currently recommended WHO schedules

For age-unrestricted schedules co-administered with DTP, the predicted reduction in RVGE deaths was 17%, 29% and 32% for one, two and three dose schedules, respectively. The number of doses required to prevent each death was ~3400, ~4000 and ~5200, respectively (Table 3). A three-dose age-unrestricted schedule co-administered with DTP could prevent ~65,000 RVGE deaths (38% reduction) and lead to 146 excess intussusception deaths (1.0% increase), compared to no vaccination; a benefit-risk ratio of 446:1 (2.5^{th} and 97.5^{th} percentiles, 194:1 - 1383:1). Infants that received their first dose before 15 weeks and their last dose before 32 weeks had a benefit-risk ratio of 623:1 (2.5^{th} and 97.5^{th} percentiles, 275:1 - 2046:1) compared to 186:1 (84:1 – 522:1) among infants vaccinated after these ages. Compared to an age-restricted schedule, the age-unrestricted schedule is estimated to prevent an additional ~11,000 RVGE deaths and cause an additional 59 intussusception deaths (Table 3). Among children vaccinated outside of the age windows, the benefit-risk ratio was greater than 100:1 in 87% (117/135) of LMICs, but in eight countries (Argentina, Equatorial Guinea, Mauritius, Moldova, Samoa, Syria, Tonga, Vietnam) the ratio was below 50:1 (Appendix Table 3). For infants vaccinated inside the age windows, we estimate one excess intussusception case per 95,000 FVI (2.5^{th} and 97.5^{th} percentiles 39,000 – 304,000) compared to 31,000 (2.5^{th} and 97.5^{th} percentiles 13,000 – 87,000) among children vaccinated outside the age windows (Appendix Table 3).

Benefits and risks of schedules not currently recommended by WHO

For all age-unrestricted schedules we found that giving the first dose with BCG rather than DTP1 reduced the estimated number of excess intussusception deaths by more than 50% (Table 3). If each country were to implement the age-unrestricted schedule with the greatest predicted impact on RVGE deaths (including birth and/or booster doses) around 72,000 RVGE deaths could be prevented (42% reduction) and 107 excess intussusception deaths caused (0.7% increase) compared to no vaccination (benefit-risk ratio 666:1). Thus, compared to current age-unrestricted schedules co-administered with DTP, more deaths could be

prevented (72,000 vs 65,000) and fewer intussusception deaths caused (107 vs 146). Compared to age-restricted schedules co-administered with DTP, far more deaths could be prevented (72,000 vs 54,000 deaths prevented) and intussusception deaths would be slightly higher (107 vs 87). Excess intussusception deaths are only slightly higher (0.74% vs 0.60% increase) because the schedules with the highest impact typically involve co-administering the first dose with BCG when the background risk of intussusception is lower.

However, the schedule with the highest predicted reduction in RVGE deaths varied considerably by country (Figure 1, Appendix Table 4, Appendix Figure 3). In 28 countries a neonatal schedule (with BCG+DTP1+DTP3) predicted the highest impact, but in most other countries combinations involving a booster dose (either with or without a birth dose) were likely to be best.

Using a power waning function (less rapid waning) improved the estimated impact and benefit-risk ratios (Appendix Tables 5 and 6). If doses given as part of a neonatal schedule were assumed to have double the mean duration of protection, then schedules with a birth dose had the highest predicted impact in most countries (Appendix Tables 7 and 8). A scenario with pessimistic access to care assumptions had less favourable benefit-risk ratios (202:1 versus 446:1 for a three-dose age-unrestricted schedule co-administered with DTP) but there were no more than ~350 excess intussusception deaths each year across all countries modelled for any schedule evaluated (Appendix Tables 9 and 10).

Discussion

Our previous analysis was based on the 2010 birth cohort in 158 countries defined by WHO as in strata B, C, D or E. This classification, based on rates of all-cause child mortality in the year 1999, is now almost twenty years old (29). This time we used the 2018 World Bank classification of LMICs. We excluded high income countries (HICs) because the overwhelming majority of RVGE and intussusception deaths are in LMICs. Other factors such as healthcare treatment costs and cost-effectiveness become more influential in HICs, and these were beyond the scope of our analysis. Compared to the previous analysis(4) we estimated far fewer RVGE deaths averted in the 2015 birth cohort for an equivalent age-unrestricted 3-dose schedule (DTP1+DTP2+DTP3). This is because of lower official estimates of the number of RVGE deaths without vaccination, mainly due to improved access to supportive care following acute gastroenteritis in LMICs, but also due to improved methods of RVGE mortality estimation (6). Our estimates of excess intussusception deaths were also much lower because the median age of intussusception from recent estimates was higher (9),

resulting in fewer background intussusception cases around the time of DTP1 vaccination. Our new benefit-risk ratio for an age-unrestricted schedule co-administered with DTP (446:1), is more favourable than our previous estimate (371:1), with the benefits of rotavirus vaccine introduction still greatly exceeding the risk.

In our previous analysis we found that removing age restrictions from a standard infant schedule co-administered with DTP could prevent an additional ~47,000 RVGE deaths and cause an additional ~300 intussusception deaths each year (4). In our new analysis the equivalent estimates for a standard 3-dose DTP schedule are much lower (~11,000 RVGE deaths prevented and 59 excess intussusception deaths) but the incremental benefit-risk ratio is more favourable (186:1 versus 154:1). Our new analysis therefore still supports the WHO recommendation to remove age restrictions in countries where the benefit would greatly exceed the risk (5).

We conservatively used a global pooled estimate of the relative risk of intussusception, but this may greatly over-estimate the risk in many LMICs. Only one study (a multi-country study in Africa (11)) has evaluated post-licensure risk of intussusception in a high mortality setting, and this found no elevated risk of intussusception. Had we applied a gradient of risk consistent with under-five mortality, we would have predicted zero excess risk in many LMICs, including large countries such as India, Nigeria and Pakistan. More post-licensure estimates are needed to confirm the finding of no risk in high mortality settings. However, even with pessimistic risk assumptions, there was less than one excess intussusception case per 60,000 FVI for a standard schedule co-administered with DTP. This is far more favourable than the rate associated with RotaShield® (more than one case per 10,000 FVI), an early rotavirus vaccine that was withdrawn from the market following evidence of its link with intussusception (30).

To our knowledge this is the first estimate of the number of background intussusception deaths in LMICs (~14,500). The Global Burden of Disease Project (GBD 2017) estimated 22,395 deaths globally due to paralytic ileus and intestinal obstruction, and 31,460 deaths for all digestive disorders combined, for children <5 years of age in the year 2015 (31). We used DTP1 coverage as a proxy for access to intussusception treatment because it may better represent care-seeking for very severe conditions than household survey indicators based on milder symptoms. A more pessimistic scenario, based on the proportion of children with timely (two-hour) access to public hospitals was influential (led to less favourable benefit-risk ratios), but this is probably too pessimistic as many intussusception cases in Africa are known to present to hospital more than two days after the onset of symptoms (32). In medium mortality countries, access to care adjustments led to large increases in the background

intussusception mortality rate relative to the (often very low) pre-vaccination RVGE mortality rate. Had we assumed 100% access to treatment in medium mortality countries (as per the low and very low mortality stratum), then the benefit-risk ratios would have been far more favourable. Better estimates of intussusception treatment utilisation are needed.

Our analysis highlights the potential value of a birth dose in future rotavirus vaccination programmes. A birth dose has the potential to avoid the peak background age of intussusception as well as preventing rotavirus deaths that occur very early in life. We assumed that the risks of intussusception were relative to the baseline incidence, rather than assuming an absolute risk difference. This assumption favoured neonatal schedules. However, our base case analysis also assumed that doses administered as part of a neonatal schedule would have equivalent efficacy/waning assumptions to those administered as part of an infant schedule, but evidence suggests they may have more durable protection. Indeed, with this assumption, schedules with a birth doses had the highest predicted impact in most countries. In some countries neonatal schedules did not predict the highest impact because infant schedules achieved higher impact during the peak age of RVGE disease (e.g. Bangladesh) or because no BCG visit currently exists (e.g. Lebanon, Suriname). However, an important feature of many of the countries where neonatal schedules were not preferred (including large countries such as India and DR Congo) is that BCG coverage was lower than DTP1 coverage in the year 2015. In these countries our calculations of vaccine impact did not allow for opportunities to catch-up on missed doses at later visits. This is probably not realistic. More evidence is needed on the post-licensure safety of birth doses, and on the efficacy and feasibility of administering the globally licensed rotavirus vaccines at birth. The RV3-BB vaccine demonstrated high initial efficacy following a neonatal schedule, but it is unclear if the currently licensed vaccines would have similar efficacy if administered as a neonatal schedule.

Our analysis also highlights the potential benefit of booster doses to mitigate the waning protection of rotavirus vaccines (33). We assumed that a 3rd dose co-administered with Meas1 would have the same efficacy (and waning) as the 2nd dose co-administered with DTP. This assumption is consistent with a Rotarix® immunogenicity study in Bangladesh, where seropositivity (IgA titres $\geq$ 20 U/mL) increased from 53% to 70% after a 3rd dose was administered concurrently with the first dose of measles vaccine (13). A study in Mali also found an increase in IgA titres and no negative impact on the immune response of other vaccines administered at the same visit e.g. measles, yellow fever (34). However, more evidence is needed on the clinical efficacy and safety of booster doses, particularly since most cases of vaccine-related intussusception with RotaShield® were associated with doses administered as part of a catch-up campaign among older infants (35). However, these were

associated with the first and second dose, and post-licensure studies have reported no significant relative risk with the third dose of RotaTeq administered at ~6 months (13).

We used a transparent static cohort model to estimate the potential direct effects of vaccination by week of age. Inclusion of herd effects could make the benefit-risk ratios more favourable in some settings, but it would be challenging to obtain robust estimates of the scale and duration of these effects in each of the 135 LMICs. Transmission dynamic models calibrated to data from Niger (36) and India (37) have predicted a minimal contribution of indirect effects, and while short-term herd effects have been observed in El Salvador (38), Ghana (1), Moldova (1) and Rwanda (39), no substantial herd effects were observed in Malawi,(40), South Africa (41), Tanzania (1) or Zambia (42). Transmission dynamic models could be used to help anticipate the longer-term effects of different schedules on the age-specific incidence and severity of natural infections. This would ideally require data on social mixing and transmission patterns in very granular age groups <5 years of age. In the interim, our analysis provides a useful starting point for thinking about the schedules that might have advantages in different countries. Beyond this, with the aggregated impact on RVGE deaths <5 years of age not exceeding 50% for any schedule or scenario evaluated, more efficacious rotavirus vaccines would be needed to achieve more substantial improvements in impact in LMICs.

Conclusion

Rotavirus vaccination has a favourable benefit-risk profile in LMICs despite pessimistic assumptions about the potential scale of intussusception risks. Schedules involving birth and booster doses could further increase benefits and reduce risks, but more research is needed to assess their feasibility, safety and impact.

Contributors

AC developed the model, constructed the tables and figures and wrote the first draft. All authors have read, contributed to, and approved the final version of the manuscript.

Declaration of interests

All authors declare no conflicts of interest.

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Table 1. List of rotavirus schedules evaluated

#	Rotavirus doses co-administered with:	Birth dose schedule?	Booster dose schedule?	Age-restricted scenario?	Age-unrestricted scenario?
1	BCG	Yes		Yes	Yes
2	DTP1			Yes	Yes
3	BCG + DTP1	Yes		Yes	Yes
4	BCG + DTP2	Yes		Yes	Yes
5	BCG + DTP3	Yes		Yes	Yes
6	DTP1 + DTP2^			Yes	Yes
7	DTP1 + DTP3			Yes	Yes
8	BCG + DTP1 + DTP2[$]	Yes		Yes	Yes
9	BCG + DTP1 + DTP3	Yes		Yes	Yes
10	BCG + DTP2 + DTP3	Yes		Yes	Yes
11	DTP1 + DTP2 + DTP3^			Yes	Yes
12	BCG + Meas1	Yes	Yes		Yes
13	DTP1 + Meas1		Yes		Yes
14	BCG + DTP1 + Meas1	Yes	Yes		Yes
15	BCG + DTP2 + Meas1	Yes	Yes		Yes
16	BCG + DTP3 + Meas1	Yes	Yes		Yes
17	DTP1 + DTP2 + Meas1*		Yes		Yes
18	DTP1 + DTP3 + Meas1		Yes		Yes

^ schedules recommended by WHO. The three-dose schedule has been evaluated in efficacy trials for Rotarix, RotaTeq, ROTAVAC, ROTASIIL and RV3-BB. The two-dose schedule has been evaluated in Rotarix efficacy studies (7).

[$] schedule evaluated in RV3-BB efficacy study in Indonesia (12).

*schedule evaluated in Rotarix immunogenicity studies in Bangladesh (13) and Mali (34).

Table 2. Pooled random effects meta-analysis of the relative risk of intussusception in the 1-7 day period and 8-21 day period after administration of rotavirus vaccine doses 1 and 2

Country	2010-2015 under five mortality rate per 1000 live births	Vaccine	Period post dose 1						Period post dose 2					
			1-7 days			8-21 days			1-7 days			8-21 days		
			Mid	L95	U95	Mid	L95	U95	Mid	L95	U95	Mid	L95	U95
Singapore(43)	3	Rotarix	8·4	2·4	29·0	1·5	0·9	2·5	3·1	0·4	12·4	1·5	0·2	11·7
Australia(18)	5	Rotarix	6·8	2·4	19·0	3·5	1·3	8·9	2·8	1·1	7·3	2·1	1·0	4·6
Australia(18)	5	RotaTeq	9·9	3·7	26·4	6·3	2·8	14·4	2·8	1·2	6·8	1·8	0·8	3·9
England(2)	5	Rotarix	13·8	6·4	28·3	1·6	0·3	3·8	2·2	0·5	5·0	2·8	1·4	5·3
USA1(44)	7	Rotarix	1·6	0·3	5·8	-	-	-	0·7	-0·1	3·0	-	-	-
USA2(3)	7	Rotarix	-	-	-	-	-	-	3·5	0·5	25·1	1·2	0·4	3·4
Multinational(45)	7	RotaTeq	3·5	1·8	6·6	0·9	0·5	1·6	1·6	0·9	3·1	1·1	0·6	1·8
USA2(3)	7	RotaTeq	9·1	2·2	38·6	1·8	0·8	4·1	1·8	0·4	7·2	0·9	0·5	1·8
Brazil(46)	18	Rotarix	1·1	0·3	3·3	0·5	0·2	1·3	2·6	1·3	5·2	1·1	0·7	1·9
Mexico1(46)	23	Rotarix	5·3	3·0	9·3	1·0	0·5	1·9	1·8	0·9	3·8	2·2	1·4	3·5
Mexico2(47)	23	Rotarix	6·5	4·2	10·1	1·1	0·9	1·4	1·3	0·8	2·1	1·0	0·8	1·2
South Africa(48)	47	Rotarix	1·0	0·7	1·6	2·8	0·7	10·6	2·1	1·2	3·6	0·9	0·6	1·6
7 African countries(40)	67	Rotarix	0·3	0·0	1·0	1·0	0·3	2·3	0·8	0·2	1·7	0·7	0·4	1·2
Pooled (random effects) with I-squared = 83%			**4·2**	**2·3**	**7·9**	**1·8**	**1·4**	**2·3**	**1·5**	**1·0**	**2·1**	**1·3**	**1·0**	**1·6**

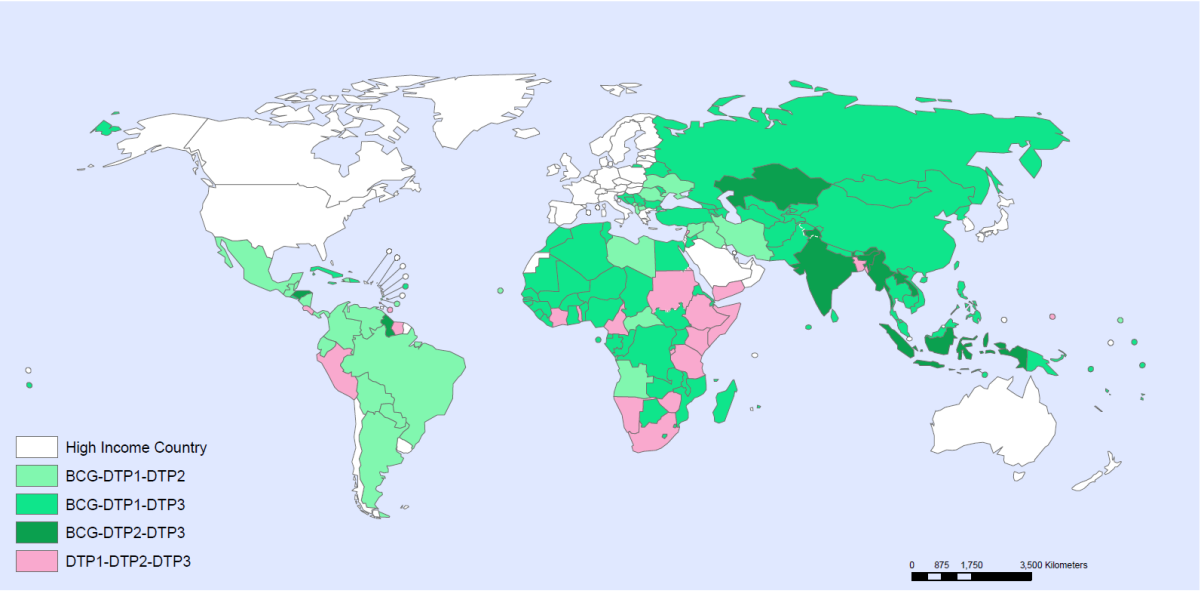
Table 3. Potential benefits and risks of alternative rotavirus vaccination schedule options if used in all 135 low- and middle-income countries

Schedule	Doses		RVGE deaths <5 years			Intussusception deaths <5 years			Summary indicators				
Vaccines in the existing schedule that rotavirus would be co-administered with	Total doses (millions)	Fully vaccinated children (FVC) (millions)	Number	Averted	*Incremental* number averted vs age-restricted	Number	Excess vs no vaccine	*Incremental* excess number vs age-restricted	% reduction in RVGE deaths	Doses per RVGE death averted	Number of FVC per excess IS case	RVGE deaths averted per excess IS death	*Incremental* RVGE deaths averted per excess IS death vs age-restricted
NO VACCINE	**0**	**0**	**169,450**	-	-	**14,478**	-	-	-	-	-	-	-
Age-restricted (primary)													
BCG	109	104	140,066	29,384	-	14,498	21	-	17.3%	3,712	838,053	1,420	-
DTP1	87	82	141,323	28,126	-	14,531	54	-	16.6%	3,085	177,189	524	-
BCG+DTP1	217	102	118,208	51,241	-	14,515	38	-	30.2%	4,236	299,990	1,357	-
BCG+DTP2	213	99	115,630	53,820	-	14,536	58	-	31.8%	3,969	172,357	924	-
BCG+DTP3	192	79	118,111	51,338	-	14,540	62	-	30.3%	3,740	136,944	829	-
DTP1+DTP2^	173	82	120,829	48,621	-	14,564	87	-	28.7%	3,567	106,531	561	-
DTP1+DTP3	164	73	121,110	48,340	-	14,572	94	-	28.5%	3,397	85,499	512	-
BCG+DTP1+DTP2	321	99	111,746	57,704	-	14,515	38	-	34.1%	5,571	290,268	1,529	-
BCG+DTP1+DTP3	300	79	109,115	60,335	-	14,515	38	-	35.6%	4,970	230,160	1,598	-
BCG+DTP2+DTP3	296	79	110,324	59,125	-	14,536	58	-	34.9%	5,014	136,687	1,015	-
DTP1+DTP2+DTP3^	250	73	115,469	53,981	-	14,564	87	-	31.9%	4,646	95,149	623	-
Age-unrestricted (primary)													
BCG	114	108	138,147	31,303	1,919	14,512	34	14	18.5%	3,652	501,786	910	140
DTP1	117	111	134,966	34,484	6,357	14,584	106	53	20.4%	3,397	89,616	324	121
BCG+DTP1	227	107	115,233	54,217	2,975	14,527	49	11	32.0%	4,190	255,004	1,109	267
BCG+DTP2	225	105	112,435	57,015	3,195	14,551	73	15	33.6%	3,952	152,843	780	216
BCG+DTP3	223	101	112,616	56,833	5,495	14,559	81	19	33.5%	3,924	130,653	699	284
DTP1+DTP2^	230	107	111,331	58,119	9,498	14,624	146	59	34.3%	3,966	63,209	398	160
DTP1+DTP3	226	102	111,080	58,370	10,030	14,632	154	59	34.4%	3,887	56,731	380	169
BCG+DTP1+DTP2	338	105	108,232	61,218	3,514	14,526	48	10	36.1%	5,523	255,667	1,269	335
BCG+DTP1+DTP3	335	101	104,188	65,262	4,927	14,526	49	11	38.5%	5,145	241,584	1,338	447
BCG+DTP2+DTP3	334	101	105,787	63,662	4,537	14,551	73	15	37.6%	5,246	146,921	872	308
DTP1+DTP2+DTP3^	339	102	104,501	64,949	10,968	14,623	146	59	38.3%	5,238	60,045	446	186
Age-unrestricted (booster)													
BCG+Meas1	222	73	119,210	50,240	-	14,537	60	-	29.6%	4,426	128,271	842	-
DTP1+Meas1	225	73	116,653	52,797	-	14,609	131	-	31.2%	4,276	45,914	403	-
BCG+DTP1+Meas1	335	73	102,302	67,148	-	14,527	49	-	39.6%	4,987	173,813	1,376	-
BCG+DTP2+Meas1	332	73	100,947	68,503	-	14,551	73	-	40.4%	4,857	105,773	938	-
BCG+DTP3+Meas1	329	72	103,072	66,378	-	14,559	81	-	39.2%	4,964	93,984	818	-
DTP1+DTP2+Meas1	338	72	99,777	69,673	-	14,623	146	-	41.1%	4,861	42,810	478	-
DTP1+DTP3+Meas1	333	72	101,489	67,961	-	14,631	154	-	40.1%	4,916	40,444	442	-

^ shaded rows reflect the current WHO recommended schedule options

Figure 1. Schedules with the highest predicted impact on RVGE deaths <5 years of age

Age-restricted schedules

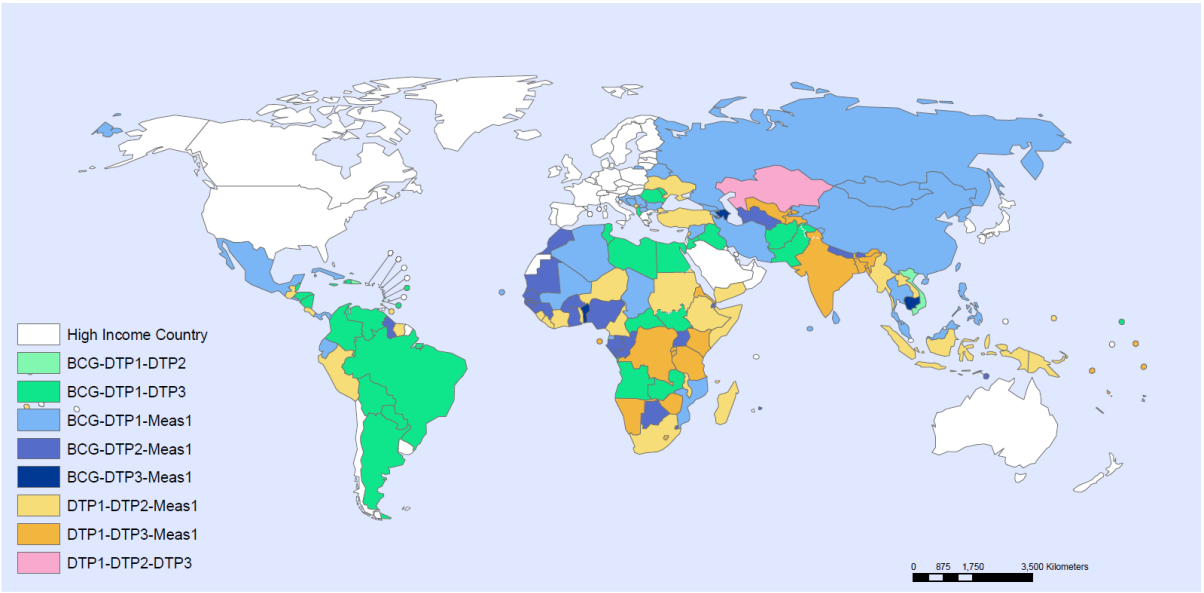


The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: <type data source>
Map Production: <type unit name>
World Health Organization

World Health Organization

Age-unrestricted schedules



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

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World Health Organization

World Health Organization

Appendix to:

Potential mortality benefits and intussusception risks of alternative rotavirus vaccination schedule options in 135 low- and middle-income countries.

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Appendix Table 1. Relative effectiveness of 1 dose of rotavirus vaccination (compared to 2/3 doses) against rotavirus-positive hospital admissions in LMICs

Country	Vaccine	RR of 1 dose (1 - VE)			RR of 2/3 doses (1 - VE)			Relative VE of 1 dose compared to 2/3 doses		
		Mid	L95	U95	Mid	L95	U95	Mid	L95	U95
Bolivia(49)	Rotarix	0.64	0.41	1.00	0.31	0.21	0.46	0.48	0.27	0.88
Bolivia(50)	Rotarix	0.74	0.42	0.75	0.41	0.27	0.63	0.55	0.33	0.93
Botswana(51)	Rotarix	0.46	0.19	1.07	0.47	0.24	0.92	1.02	0.34	3.05
Brazil(52)	Rotarix	0.40	0.25	0.63	0.28	0.15	0.56	0.70	0.31	1.57
El Salvador(53)	Rotarix	0.49	0.33	0.74	0.24	0.16	0.36	0.49	0.28	0.87
Mexico(46)	Rotarix	0.16	0.01	1.55	0.06	0.00	0.84	0.38	0.01	14.18
Moldova(54)	Rotarix	0.40	0.15	0.96	0.21	0.12	0.38	0.53	0.18	1.55
Nicaragua(55)	RotaTeq	0.45	0.25	0.83	0.51	0.32	0.81	1.13	0.53	2.42
South Africa(56)	Rotarix	0.60	0.43	0.84	0.43	0.32	0.60	0.72	0.45	1.13
Zambia(57)	Rotarix	0.38	0.04	3.61	0.44	0.14	0.66	1.16	0.11	12.52
Pooled (random effects)		**0.57**	**0.49**	**0.66**	**0.35**	**0.28**	**0.43**	**0.63**	**0.51**	**0.79**

10 case control studies with partial VE estimates from LMICs were identified from a recent review by Jonesteller et al(17). We used (1 – VE) to calculate the risk ratios (with 95% confidence intervals) in each study for 1 dose and for 2/3 doses. We carried out a meta-analysis of the difference in each study between ln(RR[1 dose]) and ln(RR[2/3 doses]) to provide a paired analysis estimate of the mean ratio of RR[2/3 doses] to RR[1 dose]. This ratio was used to estimate the relative effectiveness of 1 dose compared to 2/3 doses. We used the Stata command metan (58).

Appendix Table 2. Parameters and distributions used for probabilistic simulations*

Parameter	Base case (95% CI)	Probability distribution	Source
Population projections for the 2015 birth cohort			
Population by single age/year between birth and 5.0 years	Country-specific	Beta-PERT (mid = UNPOP medium variant, range = UNPOP low/high variant)	(19)
Disease burden estimates			
RVGE mortality rate <5 years	Country-specific	Beta-PERT (mid = Log transformed mean of 3 sources of country estimates, range = 95% CI)	(6)
Intussusception incidence rate <5 years	Country-specific	Beta-PERT (mid = median for country/WHO region, range = 95% CI for country or IQR for region)	(9)
Intussusception mortality rate <5 years	Country-specific	Beta-PERT (mid = median for country/WHO region, range = 95% CI for country or IQR for region)	(9)
Age distribution of RVGE deaths			
Log Logistic scale parameter[$]	Country-specific	Beta-PERT (mid = best fit for country/U5MR stratum, range = 95% CI for country/U5MR stratum)	(8)
Age distribution of background intussusception cases			
Burr distribution scale parameter[$]	Country-specific	Beta-PERT (mid = best fit for country/WHO region, range = 95% CI for country/WHO region)	(9)
Vaccine coverage			
Doses with BCG, DTP1, DTP2, DTP3 or Meas1	Country-specific	Beta-PERT (mid = WUENIC 2015, range = WUENIC 2015 +/-10%)	(22)
Vaccine timeliness			
Log Logistic scale parameter[$]	Country-specific	Beta-PERT (mid = best fit for country or schedule stratum, range = median age +/-10%)	(23)
Initial efficacy against RVGE mortality (2wks after dose administered)[$]			
Low mortality	99.6% (99.4-99.7)	Beta (alpha = 4918.07, beta = 19.83, [A] = 0%, [B] = 100%)	(7)
Medium mortality	91.4% (89.8-92.7)	Beta (alpha = 1394.26, beta = 131.74, [A] = 0%, [B] = 100%)	(7)
High mortality (excluding India)	88.0% (85.8-90.2)	Beta (alpha = 723.19, beta = 98.31, [A] = 0%, [B] = 100%)	(7)
India	70.0% (63.8-75.5)	Beta (alpha = 163.63, beta = 69.98, [A] = 0%, [B] = 100%)	(7)
Mean duration of vaccine efficacy in months [$]			
Low mortality	176.8 (114.7-268.0)	Gamma (alpha = 21.82, beta = 8.41)	(7)
Medium mortality	121.9 (81.3-182.4)	Gamma (alpha = 24.01, beta = 5.28)	(7)
High mortality (excluding India)	8.3 (6.4-11.2)	Gamma (alpha = 50.75, beta = 0.17)	(7)
India	17.9 (8.8-38.2)	Gamma (alpha = 7.56, beta = 2.76)	(7)
Relative efficacy of 1 dose versus 2/3 doses			
Low- and middle-income countries (LMICs)	0.63 (0.51-0.79)	Beta (alpha = 27.05, beta = 15.68, [A] = 0, [B] = 1)	Ap. Table 1
Relative risk of vaccine-related intussusception vs background rate			
Dose 1, 1-7 days	4.2 (2.3-7.9)	Lognormal (m = ln(4.2), sd = 0.32)	Table 2
Dose 1, 8-21 days	1.8 (1.4-2.3)	Lognormal (m = ln(1.8), sd = 0.13)	Table 2
Dose 2, 1-7 days	1.5 (1.0-2.1)	Lognormal (m = ln(1.0), sd = 0.18)	Table 2
Dose 2, 8-21 days	1.3 (1.0-1.6)	Lognormal (m = ln(1.0), sd = 0.11)	Table 2

*We calculated 95% uncertainty intervals for age-restricted and age-unrestricted schedules co-administered with DTP1+DTP2+DTP3. Intervals represent the 2.5th and 97.5th percentiles of 1000 Monte-Carlo simulations. We compared estimates of the benefit-risk ratio after 100, 200, 300 runs etc., and found stability (no change in the whole number of the ratio) after ~200 runs for central estimates (mean, median) and after ~500 runs for 2.5th and 97.5th percentiles. The deterministic estimate of the benefit-risk ratio was consistent with the median, and generally lower than the mean, of the 1000 benefit-risk ratios, so this value was reported as the central estimate for consistency with the estimates for other schedules.

[$] Other associated parameters of the distribution were fixed during PSA simulations. For example, a three-parameter gamma distribution was used to estimate VE over time. Two parameters (VE after 2 weeks, mean duration) were varied in PSA. The third parameter (alpha) was fixed for low (0.93), medium (0.4), high (excluding India) (0.69) mortality strata, and for India alone (0.27).

Appendix Table 3. Potential benefit-risk ratios and FVI per excess intussusception case, with 95% uncertainty intervals, for infants inside and outside the age restriction windows (first dose before 15 weeks, last dose before 32 weeks) for a 3-dose schedule co-administered with DTP: *base case scenario*

Country	Infants within age window				Infants outside age window			
	RVGE deaths averted per excess IS death	95% uncertainty range	Number of FVI per excess IS case	95% uncertainty range	RVGE deaths averted per excess IS death	95% uncertainty range	Number of FVI per excess IS case	95% uncertainty range
ALL 135 LMICs	**623**	**(275 - 2046)**	**95149**	**(37524 - 303736)**	**186**	**(84 - 522)**	**30668**	**(12731 - 86510)**
Afghanistan	411	(179 - 1455)	69278	(31336 - 214952)	121	(54 - 385)	19045	(8449 - 56147)
Albania	270	(120 - 913)	94108	(36315 - 266821)	170	(76 - 552)	158425	(64011 - 434406)
Algeria	90	(41 - 343)	111033	(49412 - 340660)	56	(26 - 201)	60937	(26920 - 172093)
Angola	1685	(788 - 6092)	76429	(33560 - 243185)	868	(414 - 2538)	106060	(46206 - 276441)
Argentina	37	(18 - 126)	38535	(19154 - 138610)	19	(9 - 62)	53846	(26676 - 174077)
Armenia	200	(82 - 540)	113381	(45956 - 321407)	128	(52 - 332)	70414	(28667 - 192802)
Azerbaijan	301	(138 - 999)	120225	(49048 - 342466)	236	(109 - 738)	73868	(29731 - 202290)
Bangladesh	22196	(1631 - 36233)	1843580	(182359 - 4271518)	3182	(242 - 4112)	142179	(15429 - 270882)
Belarus	380	(73 - 1105)	109371	(44634 - 304926)	274	(53 - 790)	77125	(31231 - 212185)
Belize	583	(251 - 1797)	112631	(49678 - 340786)	313	(132 - 865)	186648	(80759 - 515292)
Benin	2147	(939 - 6818)	200038	(89005 - 667134)	671	(286 - 1805)	54586	(23764 - 148053)
Bhutan	790	(255 - 2106)	122081	(43714 - 383907)	264	(91 - 626)	37557	(13396 - 110382)
Bolivia	3701	(1691 - 12110)	121881	(53245 - 367069)	2204	(984 - 6480)	170308	(74008 - 474883)
Bosnia & Herzegovina	557	(119 - 1517)	98292	(39507 - 277219)	345	(73 - 903)	85736	(34761 - 233105)
Botswana	430	(201 - 1452)	143042	(63327 - 455741)	211	(102 - 624)	65479	(29384 - 179586)
Brazil	13263	(817 - 24065)	648210	(57564 - 1344826)	7550	(505 - 12614)	994756	(97286 - 1824685)
Bulgaria	2048	(333 - 6821)	125607	(51326 - 357540)	1226	(200 - 4054)	77626	(31271 - 212426)
Burkina Faso	1653	(718 - 4960)	158401	(70584 - 504850)	644	(275 - 1770)	41226	(19223 - 127426)
Burundi	3898	(1575 - 12211)	243976	(110041 - 829851)	901	(359 - 2310)	32646	(13896 - 87269)
Cabo Verde	262	(116 - 842)	101362	(44635 - 325512)	124	(54 - 343)	132690	(57727 - 359363)
Cambodia	411	(197 - 1343)	101456	(39817 - 312274)	209	(101 - 628)	73191	(28494 - 194326)
Cameroon	2633	(1105 - 8345)	213480	(95403 - 711472)	589	(244 - 1548)	34994	(15008 - 97250)
Central African Republic	1058	(489 - 3687)	81975	(36598 - 272585)	268	(122 - 707)	36475	(15911 - 93831)
Chad	1065	(478 - 3533)	103662	(45963 - 347917)	321	(138 - 849)	36070	(15619 - 96947)
China	304	(141 - 968)	49000	(19557 - 152605)	136	(63 - 403)	21266	(8569 - 62499)
Colombia	410	(182 - 1290)	106895	(48379 - 337088)	213	(93 - 596)	234396	(105355 - 665122)
Comoros	821	(374 - 2828)	179653	(80423 - 611314)	278	(125 - 772)	95218	(42386 - 257175)
Congo	600	(266 - 1855)	150101	(66532 - 474222)	236	(104 - 651)	42078	(17795 - 119851)
Costa Rica	2471	(339 - 7137)	281490	(88553 - 710704)	1334	(190 - 3665)	1102220	(371777 - 2538855)
Côte d'Ivoire	1521	(683 - 5142)	167106	(75316 - 556894)	446	(196 - 1175)	45432	(19621 - 123787)

Croatia	421	(60 - 1560)	91120	(35316 - 258732)	262	(38 - 958)	156645	(63114 - 429596)
Cuba	742	(165 - 2353)	124623	(54443 - 375326)	388	(87 - 1190)	174139	(75673 - 485566)
DR Congo	1480	(646 - 4634)	180188	(80062 - 592845)	424	(183 - 1163)	49447	(21549 - 136295)
Djibouti	476	(204 - 1539)	75976	(34714 - 239843)	167	(74 - 451)	28577	(12620 - 81975)
Dominican Republic	790	(349 - 2583)	198656	(90852 - 623943)	308	(148 - 959)	106250	(50429 - 330820)
Ecuador	283	(130 - 946)	106609	(46573 - 321150)	147	(69 - 445)	151055	(65762 - 417980)
Egypt	1066	(299 - 4632)	128465	(56375 - 750167)	476	(141 - 1191)	314393	(127753 - 995792)
El Salvador	809	(354 - 2508)	138467	(60115 - 427179)	710	(301 - 1812)	1914512	(782943 - 4678763)
Equatorial Guinea	146	(61 - 645)	72509	(32287 - 233995)	40	(16 - 153)	26228	(11364 - 67915)
Eritrea	916	(375 - 2823)	203432	(91154 - 676166)	379	(155 - 986)	67323	(29423 - 183797)
Ethiopia	481	(147 - 1840)	188970	(56238 - 771983)	190	(87 - 569)	56028	(24490 - 169180)
Fiji	3228	(1323 - 9376)	102958	(40420 - 314011)	1191	(496 - 3416)	41252	(16803 - 119244)
Gabon	316	(134 - 946)	168847	(74897 - 557631)	106	(44 - 276)	47827	(20994 - 131097)
Gambia	868	(414 - 3210)	146602	(65221 - 463356)	464	(225 - 1451)	60092	(26478 - 167681)
Georgia	2157	(380 - 6795)	124361	(50855 - 353957)	1297	(230 - 3968)	77244	(31132 - 211172)
Ghana	2492	(938 - 9798)	439313	(177255 - 1824114)	317	(129 - 881)	39932	(17060 - 109465)
Grenada	2906	(777 - 8533)	119629	(52983 - 397597)	1236	(323 - 3319)	304846	(135937 - 842511)
Guatemala	1013	(457 - 3159)	70052	(31095 - 215146)	653	(289 - 1688)	175381	(77086 - 463741)
Guinea	682	(305 - 2225)	150971	(66715 - 499238)	199	(88 - 526)	30799	(13302 - 85286)
Guinea-Bissau	1849	(754 - 5834)	161113	(72279 - 534972)	670	(269 - 1757)	70833	(31081 - 194224)
Guyana	3084	(1119 - 8196)	121486	(52834 - 370504)	2459	(926 - 6141)	328001	(141509 - 907193)
Haiti	934	(423 - 3329)	125304	(55873 - 394856)	327	(148 - 1037)	54175	(23489 - 146989)
Honduras	4085	(1301 - 10455)	146272	(58257 - 431939)	11550	(3463 - 25360)	2816042	(1095229 - 6971471)
India	450	(183 - 1750)	100993	(35540 - 418222)	99	(42 - 290)	20293	(7486 - 65840)
Indonesia	554	(166 - 1577)	70022	(25076 - 215774)	288	(85 - 745)	33942	(11973 - 96496)
Iran	486	(96 - 1027)	46995	(21170 - 149263)	248	(49 - 493)	64280	(28556 - 184291)
Iraq	106	(48 - 337)	32172	(14481 - 101982)	51	(23 - 141)	48673	(21560 - 133002)
Jamaica	380	(157 - 1130)	134556	(59096 - 424987)	150	(61 - 399)	259660	(111268 - 713162)
Jordan	178	(57 - 375)	50447	(22696 - 151098)	97	(31 - 198)	29948	(13451 - 87663)
Kazakhstan	718	(323 - 2449)	88478	(36022 - 249131)	412	(184 - 1360)	86640	(34385 - 236525)
Kenya	2295	(878 - 8887)	478074	(200141 - 1920814)	230	(86 - 628)	18576	(7876 - 51226)
Kiribati	1068	(516 - 3541)	93376	(36667 - 285289)	466	(220 - 1430)	38709	(15758 - 111132)
Kyrgyzstan	1049	(436 - 2923)	114236	(45692 - 326019)	596	(245 - 1570)	137417	(55560 - 377402)
Lao PDR	783	(354 - 2493)	72207	(28583 - 224813)	376	(169 - 1090)	29061	(11821 - 82175)
Lebanon	592	(42 - 2808)	46316	(20827 - 146748)	298	(22 - 1359)	64199	(28404 - 182125)
Lesotho	3237	(1282 - 10690)	266629	(119270 - 928600)	982	(378 - 2431)	172521	(76515 - 450386)
Liberia	1216	(571 - 4277)	120845	(54011 - 398085)	361	(169 - 979)	62273	(27329 - 162042)
Libya	89	(29 - 206)	46610	(21000 - 148078)	51	(16 - 105)	63756	(28320 - 182793)
Madagascar	662	(302 - 2273)	158162	(69792 - 522113)	221	(99 - 600)	39855	(17333 - 109573)
Malawi	2561	(1016 - 8260)	223241	(100307 - 755193)	591	(238 - 1528)	76934	(33210 - 195039)
Malaysia	22079	(867 - 34825)	299706	(17434 - 516761)	9536	(391 - 14246)	277942	(16594 - 429684)
Maldives	1041	(76 - 4918)	63296	(21645 - 201690)	484	(36 - 2223)	78635	(28037 - 230275)
Mali	1322	(606 - 4629)	160116	(70563 - 530571)	381	(175 - 1052)	36272	(15742 - 99144)
Marshall Islands	9620	(2817 - 20050)	53589	(21135 - 166846)	6284	(2031 - 13346)	82740	(33416 - 237787)
Mauritania	1558	(701 - 5014)	202232	(89080 - 655078)	419	(184 - 1122)	28247	(12086 - 80490)
Mauritius	123	(50 - 382)	211235	(94227 - 698206)	41	(17 - 109)	68585	(29971 - 187892)

Mexico	332	(165 - 1161)	42802	(21771 - 155442)	143	(70 - 443)	54904	(27829 - 168628)
Micronesia (FSO)	373	(137 - 2159)	43050	(16961 - 134275)	232	(82 - 1317)	73400	(29563 - 204942)
Mongolia	649	(179 - 7434)	92249	(36095 - 276319)	360	(99 - 4122)	53179	(21220 - 155824)
Montenegro	468	(67 - 1721)	84394	(34078 - 240985)	296	(44 - 1066)	139155	(55624 - 371715)
Morocco	1971	(347 - 4325)	66031	(29767 - 202655)	905	(160 - 1860)	31681	(14415 - 91085)
Mozambique	891	(404 - 2869)	134706	(59800 - 432457)	357	(159 - 931)	53240	(23361 - 147143)
Myanmar	350	(156 - 1139)	54067	(18527 - 173053)	225	(98 - 634)	69331	(24781 - 203256)
Namibia	979	(392 - 2989)	274918	(122988 - 943295)	175	(68 - 430)	29433	(12589 - 78633)
Nepal	384	(143 - 1286)	135395	(44315 - 490216)	91	(36 - 245)	20007	(7203 - 66350)
Nicaragua	7651	(2828 - 22384)	222947	(74128 - 561500)	3988	(1462 - 10576)	313280	(108196 - 718355)
Niger	2125	(948 - 6733)	142212	(63388 - 468087)	600	(256 - 1536)	53437	(23158 - 138465)
Nigeria	353	(158 - 1098)	50262	(21331 - 150790)	229	(110 - 642)	26726	(11900 - 72103)
North Korea	785	(253 - 2205)	117880	(42288 - 371171)	222	(75 - 592)	36648	(13075 - 107786)
Pakistan	402	(152 - 1653)	93659	(38171 - 343516)	95	(39 - 309)	16544	(7557 - 47027)
Panama	1543	(393 - 3478)	137592	(39179 - 333371)	742	(197 - 1473)	220955	(65776 - 471632)
Papua New Guinea	309	(145 - 1058)	86938	(34075 - 272505)	113	(54 - 343)	46492	(18851 - 128044)
Paraguay	570	(248 - 1943)	111965	(49548 - 341924)	362	(162 - 1094)	161866	(70528 - 445532)
Peru	817	(313 - 2541)	135162	(51510 - 375925)	859	(332 - 2307)	778563	(291983 - 1848699)
Philippines	286	(134 - 914)	77495	(30457 - 237973)	120	(54 - 348)	35407	(14378 - 99595)
Republic of Moldova	66	(26 - 178)	108933	(41590 - 309108)	38	(15 - 100)	103094	(40327 - 286185)
Romania	2638	(584 - 7128)	261092	(51420 - 360021)	1817	(399 - 4713)	195109	(67003 - 604695)
Russian Federation	1275	(191 - 4531)	106907	(43613 - 299562)	925	(138 - 3311)	80053	(32414 - 220265)
Rwanda	2060	(861 - 6523)	313717	(138421 - 1076955)	346	(134 - 890)	8675	(3661 - 24914)
Saint Lucia	373	(129 - 1038)	123127	(53789 - 370823)	195	(69 - 507)	172050	(74765 - 479740)
Saint Vincent & the Gr.	682	(243 - 1926)	121603	(53296 - 366970)	356	(130 - 930)	170873	(74309 - 475293)
Samoa	63	(27 - 270)	68017	(26713 - 208255)	21	(9 - 84)	33347	(13568 - 91267)
Sao Tome and Principe	1207	(466 - 3723)	294973	(131072 - 1040610)	397	(155 - 957)	212403	(93874 - 545434)
Senegal	968	(400 - 3045)	192965	(86464 - 641994)	294	(123 - 780)	48560	(20947 - 136029)
Serbia	816	(116 - 3024)	111477	(45193 - 315418)	537	(78 - 1966)	99420	(40408 - 272879)
Sierra Leone	3814	(1624 - 12178)	190494	(85289 - 649500)	1135	(470 - 2933)	88118	(38614 - 235963)
Solomon Islands	1300	(588 - 3947)	100579	(39551 - 307241)	568	(250 - 1636)	40670	(16570 - 117358)
Somalia	247	(111 - 861)	38547	(17684 - 122104)	78	(35 - 227)	16224	(7110 - 43872)
South Africa	332	(174 - 1264)	95671	(47882 - 348315)	79	(43 - 255)	33608	(16712 - 100917)
South Sudan	407	(189 - 1391)	114429	(50893 - 378537)	120	(55 - 317)	42436	(18625 - 110658)
Sri Lanka	992	(111 - 3250)	63296	(21645 - 201690)	476	(53 - 1569)	78635	(28037 - 230275)
Sudan	4074	(1376 - 9851)	89762	(41361 - 287683)	1383	(452 - 2863)	34278	(15208 - 99642)
Suriname	239	(109 - 819)	166186	(72637 - 527044)	122	(57 - 370)	121352	(52548 - 354948)
Swaziland	2902	(1153 - 9610)	352377	(157052 - 1237222)	1832	(713 - 4701)	898648	(396133 - 2350494)
Syrian Arab Republic	28	(7 - 277)	21738	(9944 - 68900)	12	(3 - 98)	38733	(17389 - 103221)
Tajikistan	2170	(909 - 6006)	134110	(54621 - 379584)	1392	(575 - 3652)	71588	(29224 - 197100)
Tanzania	2108	(885 - 8215)	364837	(157561 - 1463874)	371	(158 - 1020)	58450	(25469 - 165802)
TFYR Macedonia	1443	(217 - 5072)	109639	(44765 - 310778)	1021	(154 - 3567)	69753	(28806 - 193383)
Thailand	3362	(128 - 9271)	86525	(15162 - 220580)	1980	(82 - 5509)	136178	(28077 - 299240)
Timor-Leste	564	(200 - 1623)	103394	(36699 - 321230)	167	(63 - 428)	19694	(7106 - 58109)
Togo	1801	(735 - 5830)	221421	(99300 - 750442)	489	(197 - 1249)	92119	(40821 - 242671)
Tonga	64	(31 - 207)	79352	(31174 - 243151)	23	(11 - 70)	34799	(14148 - 98761)

Tunisia	209	(46 - 391)	58969	(22527 - 171260)	131	(30 - 223)	178871	(72374 - 446615)
Turkey	165	(62 - 448)	92004	(35548 - 260879)	104	(39 - 271)	155690	(62839 - 426872)
Turkmenistan	2356	(1025 - 7492)	126654	(51617 - 360500)	1571	(703 - 4821)	77401	(31138 - 212159)
Tuvalu	746	(335 - 2443)	99528	(39296 - 304214)	332	(158 - 1064)	40999	(16715 - 117936)
Uganda	655	(275 - 2090)	144169	(64222 - 473373)	275	(114 - 710)	78925	(35129 - 209039)
Ukraine	1643	(434 - 4149)	53044	(21776 - 150003)	981	(252 - 2289)	20713	(8368 - 54174)
Uzbekistan	1130	(329 - 6888)	100492	(27402 - 367343)	1029	(361 - 4663)	79425	(29759 - 227981)
Vanuatu	129	(60 - 444)	65762	(25851 - 202144)	54	(25 - 173)	30616	(12425 - 85763)
Venezuela	398	(175 - 1317)	75899	(32783 - 271323)	132	(59 - 353)	76110	(33051 - 203200)
Viet Nam	164	(44 - 1189)	55998	(24864 - 170950)	39	(12 - 319)	17784	(8072 - 54157)
Yemen	360	(155 - 1096)	70644	(32031 - 223960)	117	(50 - 304)	18676	(8402 - 52246)
Zambia	4094	(843 - 13271)	644523	(142978 - 2193397)	712	(184 - 1614)	141845	(38334 - 319803)
Zimbabwe	2903	(910 - 11748)	301904	(102474 - 1226337)	717	(284 - 2063)	142848	(62348 - 405825)

Appendix Table 4. Potential benefits and risks of a standard age-restricted three-dose infant schedule (co-administered with DTP1+DTP2+DTP3) compared to age-restricted and age-unrestricted schedules with the highest predicted impact in each country: *base case scenario*

Country	NO VACCINE		Age-restricted standard schedule (DTP1+DTP2+DTP3)			Age-restricted schedule with the highest predicted impact on RVGE deaths<5 years				Age-unrestricted schedule with the highest predicted impact on RVGE deaths<5 years			
	RVGE deaths <5 years	IS deaths <5 years	% impact on RVGE deaths	% increase in IS deaths	RVGE deaths averted per excess IS death	Schedule with highest predicted impact	% impact on RVGE deaths	% increase in IS deaths	RVGE deaths averted per excess IS death	Schedule with highest predicted impact	% impact on RVGE deaths	% increase in IS deaths	RVGE deaths averted per excess IS death
ALL 135 LMICs	**169,450**	**14,478**	**32%**	**0.6%**	**623**		**36%**	**0.4%**	**1,107**		**42%**	**0.7%**	**666**
Afghanistan	2,420	296	21%	0.4%	411	BCG-DTP1-DTP3	32%	0.3%	777	BCG-DTP1-DTP3	37%	0.5%	562
Albania	1	0	59%	1.0%	270	BCG-DTP1-DTP2	74%	0.4%	811	BCG-DTP1-DTP3	77%	0.4%	785
Algeria	206	48	16%	0.7%	90	BCG-DTP1-DTP3	47%	0.5%	367	BCG-DTP1-Meas1	52%	0.5%	409
Angola	6,921	125	31%	1.0%	1,685	BCG-DTP1-DTP2	39%	0.3%	7,254	BCG-DTP1-DTP3	42%	0.3%	6,770
Argentina	36	65	56%	0.8%	37	BCG-DTP1-DTP2	72%	0.3%	141	BCG-DTP1-DTP3	74%	0.3%	130
Armenia	2	1	38%	0.6%	200	BCG-DTP1-DTP3	68%	0.3%	733	BCG-DTP1-Meas1	74%	0.3%	774
Azerbaijan	74	7	24%	0.9%	301	BCG-DTP1-DTP3	30%	0.4%	768	BCG-DTP3-Meas1	42%	0.6%	799
Bangladesh	1,623	11	40%	0.3%	22,196	DTP1-DTP2-DTP3	40%	0.3%	22,196	DTP1-DTP3-Meas1	56%	0.6%	12,174
Belarus	1	0	32%	0.5%	380	BCG-DTP1-DTP3	86%	0.5%	1,053	BCG-DTP1-Meas1	90%	0.5%	1,038
Belize	1	0	59%	0.9%	583	BCG-DTP1-DTP2	71%	0.3%	1,906	BCG-DTP1-DTP3	76%	0.4%	1,628
Benin	1,582	39	41%	0.8%	2,147	BCG-DTP1-DTP3	47%	0.2%	9,367	BCG-DTP3-Meas1	51%	0.5%	4,006
Bhutan	6	0	40%	0.7%	790	BCG-DTP1-DTP3	45%	0.2%	2,848	BCG-DTP2-Meas1	52%	0.4%	1,650
Bolivia	253	3	41%	0.9%	3,701	BCG-DTP1-DTP2	50%	0.3%	13,876	BCG-DTP1-DTP3	54%	0.3%	13,551
Bosnia & Herzegovina	0	0	52%	0.6%	557	BCG-DTP1-DTP3	84%	0.3%	2,044	BCG-DTP1-Meas1	86%	0.3%	2,071
Botswana	43	3	37%	1.3%	430	BCG-DTP1-DTP3	45%	0.4%	1,764	BCG-DTP2-Meas1	52%	0.7%	1,142
Brazil	1,032	3	58%	1.5%	13,263	BCG-DTP1-DTP2	74%	0.5%	51,357	BCG-DTP1-DTP3	77%	0.5%	48,288
Bulgaria	2	0	67%	0.8%	2,048	BCG-DTP1-DTP3	85%	0.3%	5,876	BCG-DTP1-Meas1	88%	0.4%	5,654
Burkina Faso	2,279	48	42%	1.2%	1,653	BCG-DTP1-DTP3	49%	0.3%	7,339	BCG-DTP2-Meas1	53%	0.6%	4,224
Burundi	1,606	21	47%	0.9%	3,898	DTP1-DTP2-DTP3	47%	0.9%	3,898	DTP1-DTP3-Meas1	53%	1.2%	3,436
Cabo Verde	4	1	58%	1.3%	262	BCG-DTP1-DTP2	71%	0.3%	1,214	BCG-DTP1-Meas1	74%	0.4%	1,151
Cambodia	212	64	38%	0.3%	411	BCG-DTP1-DTP3	39%	0.1%	1,354	BCG-DTP3-Meas1	47%	0.2%	897
Cameroon	2,967	60	44%	0.8%	2,633	DTP1-DTP2-DTP3	44%	0.8%	2,633	DTP1-DTP2-Meas1	50%	1.1%	2,172
Central African Republic	928	42	30%	0.6%	1,058	BCG-DTP1-DTP2	38%	0.2%	3,445	BCG-DTP1-DTP3	40%	0.3%	2,840
Chad	4,309	182	16%	0.4%	1,065	BCG-DTP1-DTP3	25%	0.3%	1,807	BCG-DTP1-Meas1	31%	0.7%	1,107
China	1,384	414	26%	0.3%	304	BCG-DTP1-DTP3	73%	0.2%	978	BCG-DTP1-Meas1	77%	0.3%	908
Colombia	152	26	61%	0.9%	410	BCG-DTP1-DTP2	69%	0.2%	2,279	BCG-DTP1-DTP3	71%	0.2%	2,328
Comoros	39	2	43%	0.9%	821	BCG-DTP1-DTP3	46%	0.2%	4,132	DTP1-DTP2-Meas1	51%	1.2%	736
Congo	252	14	35%	1.0%	600	BCG-DTP1-DTP3	43%	0.3%	2,510	BCG-DTP2-Meas1	46%	0.5%	1,535

Costa Rica	2	0	81%	0.9%	2,471	DTP1-DTP2-DTP3	81%	0.9%	2,471	DTP1-DTP2-Meas1	85%	1.0%	2,453
Côte d'Ivoire	2,477	75	42%	0.9%	1,521	DTP1-DTP2-DTP3	42%	0.9%	1,521	DTP1-DTP2-Meas1	51%	1.4%	1,167
Croatia	0	0	70%	0.8%	421	BCG-DTP1-DTP3	88%	0.3%	1,257	BCG-DTP1-Meas1	91%	0.4%	1,215
Cuba	3	0	71%	0.9%	742	BCG-DTP1-DTP3	89%	0.3%	2,843	BCG-DTP1-Meas1	92%	0.3%	2,644
DR Congo	12,377	435	38%	0.7%	1,480	BCG-DTP1-DTP3	40%	0.2%	5,820	DTP1-DTP3-Meas1	46%	1.2%	1,077
Djibouti	26	2	39%	0.9%	476	BCG-DTP1-DTP3	45%	0.3%	1,667	BCG-DTP2-Meas1	48%	0.5%	1,020
Dominican Republic	74	9	17%	0.2%	790	BCG-DTP1-DTP3	60%	0.2%	2,784	BCG-DTP1-DTP2	70%	0.2%	2,756
Ecuador	95	23	48%	0.7%	283	BCG-DTP1-DTP2	64%	0.2%	1,103	BCG-DTP1-Meas1	66%	0.3%	1,017
Egypt	1,095	98	70%	0.7%	1,066	BCG-DTP1-DTP3	77%	0.0%	123,972	BCG-DTP1-DTP3	77%	0.0%	51,557
El Salvador	50	5	69%	0.9%	809	BCG-DTP1-DTP3	75%	0.2%	5,273	BCG-DTP1-Meas1	76%	0.2%	5,327
Equatorial Guinea	42	13	11%	0.3%	146	BCG-DTP1-DTP3	18%	0.1%	602	BCG-DTP1-Meas1	19%	0.1%	530
Eritrea	269	9	28%	0.9%	916	BCG-DTP1-DTP3	31%	0.3%	3,559	DTP1-DTP3-Meas1	40%	1.4%	873
Ethiopia	5,130	407	22%	0.6%	481	DTP1-DTP2-DTP3	22%	0.6%	481	DTP1-DTP2-Meas1	38%	1.3%	367
Fiji	7	0	65%	0.3%	3,228	BCG-DTP1-DTP3	74%	0.1%	8,234	BCG-DTP1-Meas1	77%	0.2%	7,607
Gabon	57	7	33%	0.8%	316	BCG-DTP1-DTP3	41%	0.3%	1,153	BCG-DTP2-Meas1	45%	0.5%	691
Gambia	130	4	33%	1.3%	868	BCG-DTP1-DTP3	41%	0.4%	3,213	BCG-DTP2-Meas1	50%	0.7%	2,338
Georgia	2	0	70%	0.8%	2,157	BCG-DTP1-DTP3	86%	0.4%	6,049	BCG-DTP1-Meas1	90%	0.4%	5,954
Ghana	1,436	56	44%	0.5%	2,492	BCG-DTP1-DTP3	47%	0.1%	16,353	BCG-DTP2-Meas1	51%	0.3%	4,352
Grenada	0	0	73%	0.7%	2,906	DTP1-DTP2-DTP3	73%	0.7%	2,906	DTP1-DTP2-Meas1	85%	1.0%	2,536
Guatemala	349	13	33%	0.9%	1,013	BCG-DTP1-DTP2	38%	0.3%	3,959	DTP1-DTP2-Meas1	44%	1.3%	946
Guinea	1,097	71	24%	0.5%	682	BCG-DTP1-DTP3	33%	0.2%	2,330	BCG-DTP2-Meas1	35%	0.4%	1,433
Guinea-Bissau	197	4	37%	1.0%	1,849	BCG-DTP1-DTP3	42%	0.3%	5,777	BCG-DTP2-Meas1	48%	0.8%	2,989
Guyana	11	0	42%	1.0%	3,084	BCG-DTP2-DTP3	46%	0.4%	7,557	BCG-DTP2-Meas1	51%	0.5%	7,994
Haiti	375	24	25%	0.4%	934	BCG-DTP1-DTP2	33%	0.3%	1,875	BCG-DTP1-DTP3	39%	0.5%	1,173
Honduras	103	1	48%	1.0%	4,085	BCG-DTP2-DTP3	48%	0.4%	9,799	BCG-DTP1-DTP3	51%	0.2%	22,485
India	25,839	4,025	31%	0.4%	450	BCG-DTP2-DTP3	34%	0.3%	716	DTP1-DTP3-Meas1	40%	0.9%	292
Indonesia	3,000	157	27%	0.9%	554	BCG-DTP2-DTP3	28%	0.6%	920	DTP1-DTP2-Meas1	40%	1.4%	532
Iran	213	20	59%	1.3%	486	BCG-DTP1-DTP2	74%	0.4%	2,021	BCG-DTP1-Meas1	77%	0.5%	1,861
Iraq	669	189	29%	1.0%	106	BCG-DTP1-DTP2	42%	0.3%	474	BCG-DTP1-DTP3	43%	0.4%	431
Jamaica	3	1	64%	0.7%	380	BCG-DTP1-DTP3	74%	0.2%	1,336	BCG-DTP1-DTP3	77%	0.3%	1,212
Jordan	25	5	26%	0.7%	178	BCG-DTP1-DTP3	75%	0.6%	649	BCG-DTP1-DTP3	77%	0.6%	614
Kazakhstan	46	5	55%	0.8%	718	BCG-DTP2-DTP3	73%	0.3%	2,167	DTP1-DTP2-DTP3	76%	1.3%	599
Kenya	1,986	90	43%	0.4%	2,295	DTP1-DTP2-DTP3	43%	0.4%	2,295	DTP1-DTP3-Meas1	50%	0.7%	1,519
Kiribati	4	0	32%	0.2%	1,068	BCG-DTP1-DTP3	36%	0.1%	2,745	DTP1-DTP3-Meas1	41%	0.4%	922
Kyrgyzstan	45	3	64%	0.9%	1,049	BCG-DTP1-DTP3	75%	0.3%	4,372	BCG-DTP1-Meas1	76%	0.3%	4,454
Lao PDR	431	54	23%	0.2%	783	BCG-DTP2-DTP3	27%	0.2%	1,169	DTP1-DTP2-Meas1	43%	0.5%	625
Lebanon	5	0	60%	1.2%	592	DTP1-DTP2-DTP3	60%	1.2%	592	DTP1-DTP2-Meas1	75%	1.8%	504
Lesotho	187	3	48%	0.8%	3,237	BCG-DTP1-DTP3	48%	0.2%	17,371	DTP1-DTP3-Meas1	54%	1.1%	2,874
Liberia	443	16	32%	0.7%	1,216	BCG-DTP1-DTP3	34%	0.2%	4,749	DTP1-DTP2-Meas1	38%	1.0%	1,062
Libya	8	3	40%	1.3%	89	BCG-DTP1-DTP2	50%	0.4%	358	BCG-DTP1-DTP3	54%	0.5%	344
Madagascar	1,696	109	26%	0.6%	662	BCG-DTP1-DTP3	31%	0.3%	1,735	DTP1-DTP2-Meas1	40%	1.4%	429
Malawi	1,556	35	49%	0.9%	2,561	BCG-DTP1-DTP3	50%	0.2%	13,172	DTP1-DTP2-Meas1	52%	0.9%	2,520
Malaysia	17	0	71%	0.9%	22,079	BCG-DTP1-DTP3	89%	0.3%	87,740	BCG-DTP1-Meas1	92%	0.3%	78,643
Maldives	0	0	71%	1.0%	1,041	BCG-DTP1-DTP3	89%	0.3%	4,486	BCG-DTP1-Meas1	92%	0.4%	4,034
Mali	2,438	83	28%	0.6%	1,322	BCG-DTP1-DTP3	38%	0.4%	2,758	BCG-DTP1-Meas1	44%	0.7%	1,871

Marshall Islands	1	0	36%	0.4%	9,620	BCG-DTP1-DTP2	45%	0.2%	27,569	BCG-DTP1-DTP3	49%	0.2%	27,358
Mauritania	400	12	31%	0.7%	1,558	BCG-DTP1-DTP3	40%	0.3%	4,229	BCG-DTP2-Meas1	43%	0.5%	2,649
Mauritius	1	1	59%	0.9%	123	BCG-DTP1-DTP3	65%	0.5%	258	BCG-DTP2-Meas1	72%	0.8%	167
Mexico	626	142	58%	0.8%	332	BCG-DTP1-DTP2	75%	0.2%	1,465	BCG-DTP1-Meas1	76%	0.2%	1,481
Micronesia (FSO)	1	0	36%	0.4%	373	DTP1-DTP2-DTP3	36%	0.4%	373	DTP1-DTP2-Meas1	45%	0.5%	340
Mongolia	9	3	77%	0.4%	649	BCG-DTP1-DTP3	79%	0.1%	2,723	BCG-DTP1-Meas1	81%	0.1%	2,768
Montenegro	0	0	67%	0.8%	468	BCG-DTP1-DTP2	79%	0.3%	1,455	DTP1-DTP2-Meas1	84%	1.2%	423
Morocco	604	9	38%	1.3%	1,971	BCG-DTP1-DTP3	48%	0.7%	4,514	BCG-DTP2-Meas1	52%	1.0%	3,324
Mozambique	2,160	84	32%	0.9%	891	BCG-DTP1-DTP3	45%	0.4%	3,140	BCG-DTP1-Meas1	49%	0.4%	2,877
Myanmar	818	82	34%	1.0%	350	BCG-DTP2-DTP3	41%	0.5%	765	DTP1-DTP2-Meas1	48%	1.5%	329
Namibia	108	6	42%	0.7%	979	DTP1-DTP2-DTP3	42%	0.7%	979	DTP1-DTP3-Meas1	49%	1.0%	858
Nepal	258	42	39%	0.6%	384	BCG-DTP1-DTP3	42%	0.2%	1,472	BCG-DTP2-Meas1	46%	0.5%	584
Nicaragua	53	0	59%	0.9%	7,651	BCG-DTP1-DTP2	74%	0.3%	29,781	BCG-DTP1-DTP3	77%	0.3%	28,282
Niger	4,557	94	36%	0.8%	2,125	BCG-DTP1-DTP3	37%	0.2%	9,672	DTP1-DTP2-Meas1	43%	1.1%	1,832
Nigeria	35,129	2,103	23%	1.1%	353	BCG-DTP1-DTP3	27%	0.8%	556	BCG-DTP2-Meas1	32%	1.0%	512
North Korea	151	17	64%	0.7%	785	BCG-DTP1-DTP3	73%	0.2%	2,864	BCG-DTP1-Meas1	76%	0.3%	2,468
Pakistan	7,694	971	29%	0.6%	402	BCG-DTP1-DTP3	38%	0.3%	1,100	BCG-DTP1-DTP3	41%	0.5%	678
Panama	25	1	57%	0.9%	1,543	BCG-DTP1-DTP2	74%	0.3%	5,961	BCG-DTP1-Meas1	76%	0.3%	5,514
Papua New Guinea	191	89	34%	0.2%	309	BCG-DTP1-DTP3	36%	0.1%	733	DTP1-DTP2-Meas1	41%	0.3%	298
Paraguay	41	3	38%	0.9%	570	BCG-DTP1-DTP2	46%	0.3%	2,093	BCG-DTP1-DTP3	51%	0.3%	2,072
Peru	144	8	43%	1.0%	817	DTP1-DTP2-DTP3	43%	1.0%	817	DTP1-DTP2-Meas1	49%	1.1%	837
Philippines	1,893	811	28%	0.2%	286	BCG-DTP1-DTP3	33%	0.1%	707	BCG-DTP1-Meas1	38%	0.1%	719
Republic of Moldova	1	1	50%	0.7%	66	BCG-DTP1-DTP3	72%	0.3%	267	BCG-DTP1-DTP3	73%	0.3%	270
Romania	8	0	68%	0.8%	2,638	BCG-DTP1-DTP2	88%	0.4%	7,883	BCG-DTP1-DTP3	90%	0.4%	7,576
Russian Federation	54	3	31%	0.5%	1,275	BCG-DTP1-DTP3	86%	0.5%	3,699	BCG-DTP1-Meas1	89%	0.5%	3,619
Rwanda	700	19	40%	0.7%	2,060	BCG-DTP1-DTP3	41%	0.1%	12,405	DTP1-DTP3-Meas1	49%	1.0%	1,828
Saint Lucia	0	0	59%	0.9%	373	BCG-DTP1-DTP3	67%	0.6%	678	BCG-DTP1-DTP3	76%	0.7%	584
Saint Vincent & the Gr.	0	0	59%	0.9%	682	BCG-DTP1-DTP2	74%	0.3%	2,633	BCG-DTP1-DTP3	77%	0.3%	2,448
Samoa	0	1	57%	0.3%	63	BCG-DTP1-DTP3	62%	0.1%	173	DTP1-DTP2-Meas1	64%	0.4%	55
Sao Tome and Principe	7	0	44%	0.8%	1,207	BCG-DTP1-DTP3	44%	0.1%	9,033	DTP1-DTP3-Meas1	52%	1.0%	1,105
Senegal	876	34	36%	1.0%	968	BCG-DTP1-DTP3	42%	0.3%	3,380	BCG-DTP2-Meas1	45%	0.7%	1,761
Serbia	1	0	72%	0.9%	816	BCG-DTP1-DTP3	90%	0.3%	3,379	BCG-DTP1-Meas1	91%	0.3%	3,434
Sierra Leone	1,263	15	39%	0.8%	3,814	BCG-DTP1-DTP3	42%	0.2%	16,719	DTP1-DTP2-Meas1	47%	1.2%	3,195
Solomon Islands	9	1	40%	0.3%	1,300	BCG-DTP1-DTP3	44%	0.1%	3,333	DTP1-DTP3-Meas1	50%	0.5%	1,110
Somalia	2,432	415	22%	0.5%	247	DTP1-DTP2-DTP3	22%	0.5%	247	DTP1-DTP2-Meas1	27%	0.7%	220
South Africa	1,734	267	41%	0.8%	332	DTP1-DTP2-DTP3	41%	0.8%	332	DTP1-DTP2-Meas1	46%	1.1%	261
South Sudan	937	102	16%	0.4%	407	BCG-DTP1-DTP3	19%	0.1%	1,586	BCG-DTP1-DTP3	20%	0.1%	1,371
Sri Lanka	11	1	73%	1.0%	992	BCG-DTP1-DTP3	90%	0.3%	4,194	BCG-DTP1-Meas1	93%	0.3%	3,784
Sudan	2,726	30	40%	0.9%	4,074	DTP1-DTP2-DTP3	40%	0.9%	4,074	DTP1-DTP2-Meas1	50%	1.3%	3,381
Suriname	1	0	35%	0.4%	239	DTP1-DTP2-DTP3	35%	0.4%	239	DTP1-DTP2-Meas1	63%	1.1%	173
Swaziland	77	2	47%	0.6%	2,902	BCG-DTP1-DTP3	49%	0.1%	21,638	BCG-DTP2-Meas1	52%	0.3%	7,077
Syrian Arab Republic	80	136	36%	0.8%	28	BCG-DTP1-DTP2	48%	0.3%	114	BCG-DTP1-Meas1	50%	0.3%	103
Tajikistan	236	5	34%	0.7%	2,170	BCG-DTP1-DTP3	47%	0.4%	5,872	DTP1-DTP3-Meas1	53%	1.2%	2,014
Tanzania	2,880	109	49%	0.6%	2,108	DTP1-DTP2-DTP3	49%	0.6%	2,108	DTP1-DTP3-Meas1	57%	1.0%	1,494
TFYR Macedonia	1	0	37%	0.6%	1,443	BCG-DTP1-DTP2	83%	0.4%	4,348	BCG-DTP1-Meas1	87%	0.4%	4,273

Thailand	65	1	71%	1.7%	3,362	BCG-DTP1-DTP3	89%	0.5%	13,381	BCG-DTP1-Meas1	92%	0.6%	12,559
Timor-Leste	90	9	30%	0.5%	564	BCG-DTP1-DTP3	35%	0.3%	1,408	BCG-DTP2-Meas1	42%	0.6%	783
Togo	609	17	43%	0.9%	1,801	DTP1-DTP2-DTP3	43%	0.9%	1,801	DTP1-DTP2-Meas1	48%	0.9%	1,803
Tonga	0	1	56%	0.3%	64	BCG-DTP1-DTP3	60%	0.1%	172	DTP1-DTP2-Meas1	65%	0.4%	55
Tunisia	15	3	70%	2.0%	209	BCG-DTP1-DTP3	77%	0.4%	1,111	BCG-DTP1-DTP3	78%	0.4%	1,127
Turkey	53	21	58%	0.9%	165	BCG-DTP1-DTP3	65%	0.5%	300	DTP1-DTP2-Meas1	73%	1.2%	150
Turkmenistan	89	2	37%	0.9%	2,356	BCG-DTP1-DTP3	46%	0.4%	6,472	BCG-DTP2-Meas1	51%	0.5%	5,541
Tuvalu	0	0	37%	0.3%	746	BCG-DTP1-DTP3	42%	0.1%	1,887	DTP1-DTP3-Meas1	49%	0.5%	656
Uganda	2,478	150	35%	0.9%	655	BCG-DTP1-DTP3	39%	0.3%	2,005	BCG-DTP2-Meas1	47%	0.7%	1,194
Ukraine	13	1	20%	0.2%	1,643	BCG-DTP1-DTP2	35%	0.1%	5,762	DTP1-DTP2-Meas1	46%	0.8%	1,245
Uzbekistan	181	4	33%	1.3%	1,130	BCG-DTP1-DTP3	41%	0.6%	3,204	DTP1-DTP3-Meas1	49%	1.7%	1,296
Vanuatu	5	5	30%	0.2%	129	BCG-DTP1-DTP3	32%	0.1%	332	DTP1-DTP3-Meas1	35%	0.3%	108
Venezuela	273	36	58%	1.1%	398	BCG-DTP1-DTP2	75%	0.3%	1,811	BCG-DTP1-DTP3	77%	0.4%	1,585
Viet Nam	365	854	29%	0.1%	164	BCG-DTP1-DTP3	64%	0.1%	276	BCG-DTP1-DTP2	73%	0.1%	221
Yemen	1,434	170	29%	0.7%	360	DTP1-DTP2-DTP3	29%	0.7%	360	DTP1-DTP2-Meas1	39%	1.2%	267
Zambia	1,235	21	45%	0.6%	4,094	BCG-DTP1-DTP3	49%	0.2%	15,196	BCG-DTP1-DTP3	53%	0.3%	10,472
Zimbabwe	1,295	29	44%	0.7%	2,903	DTP1-DTP2-DTP3	44%	0.7%	2,903	DTP1-DTP3-Meas1	50%	0.9%	2,554

Appendix Table 5. Potential benefits and risks of alternative rotavirus vaccination schedule options if used in all 135 low- and middle-income countries: *scenario with the waning function changed from a gamma function (more rapid waning) to a power function (more conservative waning)*

Schedule	Doses		RVGE deaths <5 years			Intussusception deaths <5 years			Summary indicators				
Vaccines in the existing schedule that rotavirus would be co-administered with	Total doses (millions)	Fully vaccinated children (FVC) (millions)	Number	Averted	*Incremental* number averted vs age-restricted	Number	Excess vs no vaccine	*Incremental* excess number vs age-restricted	% reduction in RVGE deaths	Doses per RVGE death averted	Number of FVC per excess IS case	RVGE deaths averted per excess IS death	*Incremental* RVGE deaths averted per excess IS death vs age-restricted
NO VACCINE	**0**	**0**	**169,450**	-	-	**14,478**	-	-	-	-	-	-	-
Age-restricted (primary)													
BCG	109	104	135,263	34,187	-	14,498	21	-	20.2%	3,191	838,053	1,652	-
DTP1	87	82	137,736	31,713	-	14,531	54	-	18.7%	2,736	177,189	590	-
BCG+DTP1	217	102	112,240	57,210	-	14,515	38	-	33.8%	3,793	299,990	1,515	-
BCG+DTP2	213	99	111,119	58,331	-	14,536	58	-	34.4%	3,662	172,357	1,001	-
BCG+DTP3	192	79	114,338	55,112	-	14,540	62	-	32.5%	3,484	136,944	889	-
DTP1+DTP2^	173	82	116,659	52,791	-	14,564	87	-	31.2%	3,285	106,531	609	-
DTP1+DTP3	164	73	118,007	51,443	-	14,572	94	-	30.4%	3,191	85,499	545	-
BCG+DTP1+DTP2	321	99	107,522	61,928	-	14,515	38	-	36.5%	5,191	290,268	1,641	-
BCG+DTP1+DTP3	300	79	105,686	63,764	-	14,515	38	-	37.6%	4,702	230,160	1,689	-
BCG+DTP2+DTP3	296	79	107,248	62,202	-	14,536	58	-	36.7%	4,765	136,687	1,068	-
DTP1+DTP2+DTP3^	250	73	112,738	56,712	-	14,564	87	-	33.5%	4,422	95,149	654	-
Age-unrestricted (primary)													
BCG	114	108	133,212	36,238	2,051	14,512	34	14	21.4%	3,154	501,786	1,054	150
DTP1	117	111	130,918	38,532	6,819	14,584	106	53	22.7%	3,039	89,616	362	129
BCG+DTP1	227	107	109,103	60,347	3,137	14,527	49	11	35.6%	3,764	255,004	1,234	281
BCG+DTP2	225	105	107,846	61,604	3,273	14,551	73	15	36.4%	3,657	152,843	843	221
BCG+DTP3	223	101	109,052	60,397	5,285	14,559	81	19	35.6%	3,692	130,653	743	273
DTP1+DTP2^	230	107	106,827	62,623	9,832	14,624	146	59	37.0%	3,680	63,209	429	166
DTP1+DTP3	226	102	107,822	61,628	10,184	14,632	154	59	36.4%	3,681	56,731	401	171
BCG+DTP1+DTP2	338	105	103,968	65,482	3,554	14,526	48	10	38.6%	5,163	255,667	1,358	339
BCG+DTP1+DTP3	335	101	101,179	68,271	4,507	14,526	49	11	40.3%	4,918	241,584	1,400	409
BCG+DTP2+DTP3	334	101	103,026	66,424	4,222	14,551	73	15	39.2%	5,027	146,921	910	286
DTP1+DTP2+DTP3^	339	102	101,863	67,587	10,875	14,623	146	59	39.9%	5,033	60,045	464	184
Age-unrestricted (booster)													
BCG+Meas1	222	73	116,456	52,994	-	14,537	60	-	31.3%	4,196	128,271	888	-
DTP1+Meas1	225	73	114,590	54,860	-	14,609	131	-	32.4%	4,115	45,914	418	-
BCG+DTP1+Meas1	335	73	100,043	69,407	-	14,527	49	-	41.0%	4,824	173,813	1,422	-
BCG+DTP2+Meas1	332	73	99,833	69,617	-	14,551	73	-	41.1%	4,779	105,773	953	-
BCG+DTP3+Meas1	329	72	102,406	67,044	-	14,559	81	-	39.6%	4,915	93,984	826	-
DTP1+DTP2+Meas1	338	72	98,761	70,689	-	14,623	146	-	41.7%	4,791	42,810	485	-
DTP1+DTP3+Meas1	333	72	101,139	68,310	-	14,631	154	-	40.3%	4,891	40,444	445	-

^ shaded rows reflect the current WHO recommended schedule options

Appendix Table 6. Potential benefits and risks of a standard age-restricted three-dose infant schedule (co-administered with DTP1+DTP2+DTP3) compared to age-restricted and age-unrestricted schedules with the highest predicted impact in each country: *scenario with the waning function changed from a gamma function (more rapid waning) to a power function (more conservative waning)*

Country	NO VACCINE		Age-restricted standard schedule (DTP1+DTP2+DTP3)			Age-restricted schedule with the highest predicted impact on RVGE deaths<5 years				Age-unrestricted schedule with the highest predicted impact on RVGE deaths<5 years			
	RVGE deaths <5 years	IS deaths <5 years	% impact on RVGE deaths	% increase in IS deaths	RVGE deaths averted per excess IS death	Schedule with highest predicted impact	% impact on RVGE deaths	% increase in IS deaths	RVGE deaths averted per excess IS death	Schedule with highest predicted impact	% impact on RVGE deaths	% increase in IS deaths	RVGE deaths averted per excess IS death
ALL 135 LMICs	**169,450**	**14,478**	**33%**	**0.6%**	**654**		**38%**	**0.3%**	**1,374**		**43%**	**0.7%**	**726**
Afghanistan	2,420	296	21%	0.4%	425	BCG-DTP1-DTP3	33%	0.3%	807	BCG-DTP1-DTP3	38%	0.5%	573
Albania	1	0	59%	1.0%	269	BCG-DTP1-DTP2	75%	0.4%	818	BCG-DTP1-DTP3	77%	0.4%	776
Algeria	206	48	16%	0.7%	95	BCG-DTP1-DTP3	49%	0.5%	386	BCG-DTP1-Meas1	54%	0.5%	419
Angola	6,921	125	32%	1.0%	1,723	BCG-DTP1-DTP2	41%	0.3%	7,517	BCG-DTP1-DTP3	43%	0.3%	6,932
Argentina	36	65	56%	0.8%	37	BCG-DTP1-DTP2	73%	0.3%	142	BCG-DTP1-DTP3	74%	0.3%	129
Armenia	2	1	41%	0.6%	217	BCG-DTP1-DTP3	75%	0.3%	804	BCG-DTP1-Meas1	76%	0.3%	796
Azerbaijan	74	7	29%	0.9%	352	BCG-DTP1-DTP3	35%	0.4%	902	BCG-DTP3-Meas1	45%	0.6%	858
Bangladesh	1,623	11	44%	0.3%	24,273	DTP1-DTP2-DTP3	44%	0.3%	24,273	DTP1-DTP3-Meas1	56%	0.6%	12,338
Belarus	1	0	33%	0.5%	391	BCG-DTP1-DTP2	89%	0.5%	1,081	BCG-DTP1-Meas1	91%	0.5%	1,047
Belize	1	0	59%	0.9%	581	BCG-DTP1-DTP2	72%	0.3%	1,921	BCG-DTP1-DTP3	75%	0.4%	1,612
Benin	1,582	39	42%	0.8%	2,220	BCG-DTP1-DTP3	49%	0.2%	9,766	BCG-DTP2-Meas1	52%	0.4%	5,004
Bhutan	6	0	42%	0.7%	839	BCG-DTP1-DTP3	48%	0.2%	3,029	BCG-DTP2-Meas1	53%	0.4%	1,692
Bolivia	253	3	42%	0.9%	3,777	BCG-DTP1-DTP2	52%	0.3%	14,355	BCG-DTP1-DTP3	55%	0.3%	13,769
Bosnia & Herzegovina	0	0	53%	0.6%	571	BCG-DTP1-DTP3	87%	0.3%	2,101	BCG-DTP1-Meas1	87%	0.3%	2,095
Botswana	43	3	39%	1.3%	452	BCG-DTP1-DTP3	48%	0.4%	1,866	BCG-DTP2-Meas1	53%	0.7%	1,165
Brazil	1,032	3	58%	1.5%	13,217	BCG-DTP1-DTP2	75%	0.5%	51,774	BCG-DTP1-DTP3	76%	0.5%	47,776
Bulgaria	2	0	69%	0.8%	2,103	BCG-DTP1-DTP3	88%	0.3%	6,034	BCG-DTP1-Meas1	89%	0.4%	5,712
Burkina Faso	2,279	48	43%	1.2%	1,714	BCG-DTP1-DTP3	51%	0.3%	7,602	BCG-DTP2-Meas1	54%	0.6%	4,280
Burundi	1,606	21	49%	0.9%	4,064	DTP1-DTP2-DTP3	49%	0.9%	4,064	DTP1-DTP3-Meas1	54%	1.2%	3,452
Cabo Verde	4	1	58%	1.3%	262	BCG-DTP1-DTP2	71%	0.3%	1,224	BCG-DTP1-Meas1	73%	0.4%	1,134
Cambodia	212	64	41%	0.3%	451	BCG-DTP1-DTP3	43%	0.1%	1,490	BCG-DTP3-Meas1	49%	0.2%	929
Cameroon	2,967	60	45%	0.8%	2,672	DTP1-DTP2-DTP3	45%	0.8%	2,672	DTP1-DTP2-Meas1	50%	1.1%	2,180
Central African Republic	928	42	30%	0.6%	1,061	BCG-DTP1-DTP2	39%	0.2%	3,508	BCG-DTP1-DTP3	41%	0.3%	2,874
Chad	4,309	182	17%	0.4%	1,104	BCG-DTP1-DTP3	26%	0.3%	1,891	BCG-DTP1-Meas1	32%	0.7%	1,134
China	1,384	414	27%	0.3%	311	BCG-DTP1-DTP2	74%	0.2%	998	BCG-DTP1-Meas1	76%	0.3%	901
Colombia	152	26	60%	0.9%	409	BCG-DTP1-DTP2	70%	0.2%	2,301	BCG-DTP1-DTP3	70%	0.2%	2,308
Comoros	39	2	44%	0.9%	853	BCG-DTP1-DTP3	49%	0.2%	4,321	BCG-DTP2-Meas1	52%	0.5%	1,983

Congo	252	14	36%	1.0%	622	BCG-DTP1-DTP3	44%	0.3%	2,596	BCG-DTP2-Meas1	47%	0.5%	1,553
Costa Rica	2	0	83%	0.9%	2,530	DTP1-DTP2-DTP3	83%	0.9%	2,530	DTP1-DTP2-Meas1	86%	1.0%	2,471
Côte d'Ivoire	2,477	75	43%	0.9%	1,567	DTP1-DTP2-DTP3	43%	0.9%	1,567	DTP1-DTP2-Meas1	52%	1.4%	1,184
Croatia	0	0	72%	0.8%	432	BCG-DTP1-DTP3	90%	0.3%	1,290	BCG-DTP1-Meas1	92%	0.4%	1,228
Cuba	3	0	72%	0.9%	760	BCG-DTP1-DTP3	91%	0.3%	2,918	BCG-DTP1-Meas1	93%	0.3%	2,671
DR Congo	12,377	435	39%	0.7%	1,504	BCG-DTP1-DTP3	40%	0.2%	5,931	DTP1-DTP2-Meas1	46%	1.1%	1,153
Djibouti	26	2	40%	0.9%	495	BCG-DTP1-DTP3	47%	0.3%	1,739	BCG-DTP2-Meas1	49%	0.5%	1,041
Dominican Republic	74	9	17%	0.2%	795	BCG-DTP1-DTP3	62%	0.2%	2,872	BCG-DTP1-DTP2	72%	0.2%	2,828
Ecuador	95	23	47%	0.7%	282	BCG-DTP1-DTP2	65%	0.2%	1,114	BCG-DTP1-DTP3	66%	0.3%	1,009
Egypt	1,095	98	67%	0.7%	1,016	BCG-DTP1-DTP3	74%	0.0%	119,259	BCG-DTP1-DTP3	74%	0.0%	49,430
El Salvador	50	5	69%	0.9%	803	BCG-DTP1-DTP3	75%	0.2%	5,294	BCG-DTP1-DTP3	76%	0.2%	5,303
Equatorial Guinea	42	13	12%	0.3%	152	BCG-DTP1-DTP3	19%	0.1%	648	BCG-DTP1-Meas1	21%	0.1%	558
Eritrea	269	9	32%	0.9%	1,064	BCG-DTP1-DTP3	36%	0.3%	4,146	DTP1-DTP3-Meas1	43%	1.4%	941
Ethiopia	5,130	407	24%	0.6%	525	DTP1-DTP2-DTP3	24%	0.6%	525	DTP1-DTP2-Meas1	39%	1.3%	382
Fiji	7	0	66%	0.3%	3,263	BCG-DTP1-DTP3	75%	0.1%	8,335	BCG-DTP1-Meas1	77%	0.2%	7,573
Gabon	57	7	36%	0.8%	337	BCG-DTP1-DTP3	44%	0.3%	1,239	BCG-DTP2-Meas1	47%	0.5%	722
Gambia	130	4	35%	1.3%	941	BCG-DTP1-DTP3	44%	0.4%	3,498	BCG-DTP2-Meas1	52%	0.7%	2,413
Georgia	2	0	72%	0.8%	2,217	BCG-DTP1-DTP3	88%	0.4%	6,221	BCG-DTP1-Meas1	91%	0.4%	6,019
Ghana	1,436	56	47%	0.5%	2,614	BCG-DTP1-DTP3	49%	0.1%	17,171	BCG-DTP2-Meas1	52%	0.3%	4,446
Grenada	0	0	75%	0.7%	2,977	DTP1-DTP2-DTP3	75%	0.7%	2,977	DTP1-DTP2-Meas1	85%	1.0%	2,557
Guatemala	349	13	36%	0.9%	1,076	BCG-DTP1-DTP2	40%	0.3%	4,231	DTP1-DTP2-Meas1	45%	1.3%	983
Guinea	1,097	71	25%	0.5%	709	BCG-DTP1-DTP3	34%	0.2%	2,441	BCG-DTP1-Meas1	36%	0.3%	2,090
Guinea-Bissau	197	4	39%	1.0%	1,930	BCG-DTP1-DTP3	44%	0.3%	6,070	BCG-DTP2-Meas1	49%	0.8%	3,047
Guyana	11	0	44%	1.0%	3,203	BCG-DTP1-DTP3	49%	0.2%	14,830	BCG-DTP2-Meas1	52%	0.5%	8,195
Haiti	375	24	26%	0.4%	969	BCG-DTP1-DTP2	34%	0.3%	1,965	BCG-DTP1-DTP3	40%	0.5%	1,212
Honduras	103	1	50%	1.0%	4,239	BCG-DTP2-DTP3	50%	0.4%	10,202	BCG-DTP1-DTP3	53%	0.2%	23,301
India	25,839	4,025	35%	0.4%	507	BCG-DTP1-DTP3	38%	0.1%	2,511	DTP1-DTP2-Meas1	41%	0.8%	345
Indonesia	3,000	157	31%	0.9%	624	BCG-DTP2-DTP3	32%	0.6%	1,036	DTP1-DTP2-Meas1	42%	1.4%	572
Iran	213	20	59%	1.3%	486	BCG-DTP1-DTP2	75%	0.4%	2,046	BCG-DTP1-DTP3	76%	0.5%	1,845
Iraq	669	189	30%	1.0%	107	BCG-DTP1-DTP2	43%	0.3%	483	BCG-DTP1-DTP3	44%	0.4%	437
Jamaica	3	1	64%	0.7%	379	BCG-DTP1-DTP3	75%	0.2%	1,354	BCG-DTP1-DTP3	76%	0.3%	1,203
Jordan	25	5	25%	0.7%	171	BCG-DTP1-DTP2	72%	0.6%	624	BCG-DTP1-DTP3	73%	0.6%	583
Kazakhstan	46	5	56%	0.8%	728	BCG-DTP2-DTP3	75%	0.3%	2,200	DTP1-DTP2-DTP3	75%	1.3%	594
Kenya	1,986	90	46%	0.4%	2,442	DTP1-DTP2-DTP3	46%	0.4%	2,442	DTP1-DTP3-Meas1	51%	0.7%	1,551
Kiribati	4	0	34%	0.2%	1,134	BCG-DTP1-DTP3	38%	0.1%	2,924	DTP1-DTP3-Meas1	42%	0.4%	940
Kyrgyzstan	45	3	64%	0.9%	1,050	BCG-DTP1-DTP3	75%	0.3%	4,406	BCG-DTP1-DTP3	76%	0.3%	4,417
Lao PDR	431	54	25%	0.2%	880	BCG-DTP2-DTP3	30%	0.2%	1,312	DTP1-DTP2-Meas1	45%	0.5%	652
Lebanon	5	0	61%	1.2%	607	DTP1-DTP2-DTP3	61%	1.2%	607	DTP1-DTP2-Meas1	76%	1.8%	511
Lesotho	187	3	50%	0.8%	3,383	BCG-DTP1-DTP3	50%	0.2%	18,196	DTP1-DTP3-Meas1	54%	1.1%	2,893
Liberia	443	16	33%	0.7%	1,264	BCG-DTP1-DTP3	36%	0.2%	5,009	BCG-DTP1-Meas1	39%	0.2%	4,780
Libya	8	3	41%	1.3%	91	BCG-DTP1-DTP2	51%	0.4%	371	BCG-DTP1-DTP3	55%	0.5%	350
Madagascar	1,696	109	27%	0.6%	684	BCG-DTP1-DTP3	32%	0.3%	1,795	DTP1-DTP2-Meas1	40%	1.4%	433
Malawi	1,556	35	50%	0.9%	2,596	BCG-DTP1-DTP3	50%	0.2%	13,367	DTP1-DTP2-Meas1	52%	0.9%	2,526
Malaysia	17	0	73%	0.9%	22,634	BCG-DTP1-DTP3	91%	0.3%	90,077	BCG-DTP1-Meas1	93%	0.3%	79,951
Maldives	0	0	72%	1.0%	1,067	BCG-DTP1-DTP3	91%	0.3%	4,604	BCG-DTP1-Meas1	93%	0.4%	4,088

Mali	2,438	83	29%	0.6%	1,375	BCG-DTP1-DTP3	40%	0.4%	2,885	BCG-DTP1-Meas1	46%	0.7%	1,926
Marshall Islands	1	0	38%	0.4%	10,014	BCG-DTP1-DTP2	48%	0.2%	29,186	BCG-DTP1-DTP3	51%	0.2%	28,403
Mauritania	400	12	33%	0.7%	1,618	BCG-DTP1-DTP3	42%	0.3%	4,404	BCG-DTP1-Meas1	45%	0.4%	3,483
Mauritius	1	1	65%	0.9%	137	BCG-DTP1-DTP3	73%	0.5%	287	BCG-DTP1-Meas1	76%	0.6%	243
Mexico	626	142	59%	0.8%	334	BCG-DTP1-DTP2	76%	0.2%	1,485	BCG-DTP1-DTP3	76%	0.2%	1,471
Micronesia (FSO)	1	0	38%	0.4%	389	DTP1-DTP2-DTP3	38%	0.4%	389	DTP1-DTP2-Meas1	47%	0.5%	350
Mongolia	9	3	75%	0.4%	635	BCG-DTP1-DTP3	78%	0.1%	2,668	BCG-DTP1-Meas1	78%	0.1%	2,673
Montenegro	0	0	68%	0.8%	480	BCG-DTP1-DTP2	81%	0.3%	1,494	DTP1-DTP2-Meas1	85%	1.2%	428
Morocco	604	9	39%	1.3%	2,030	BCG-DTP1-DTP3	49%	0.7%	4,657	BCG-DTP1-Meas1	53%	0.8%	4,337
Mozambique	2,160	84	33%	0.9%	920	BCG-DTP1-DTP3	47%	0.4%	3,270	BCG-DTP1-Meas1	51%	0.4%	2,951
Myanmar	818	82	37%	1.0%	374	BCG-DTP2-DTP3	43%	0.5%	819	DTP1-DTP2-Meas1	50%	1.5%	338
Namibia	108	6	46%	0.7%	1,054	DTP1-DTP2-DTP3	46%	0.7%	1,054	DTP1-DTP3-Meas1	51%	1.0%	883
Nepal	258	42	41%	0.6%	402	BCG-DTP1-DTP3	44%	0.2%	1,532	BCG-DTP2-Meas1	48%	0.5%	599
Nicaragua	53	0	59%	0.9%	7,624	BCG-DTP1-DTP2	74%	0.3%	30,022	BCG-DTP1-DTP3	76%	0.3%	27,973
Niger	4,557	94	38%	0.8%	2,206	BCG-DTP1-DTP3	39%	0.2%	10,147	DTP1-DTP2-Meas1	44%	1.1%	1,861
Nigeria	35,129	2,103	24%	1.1%	369	BCG-DTP1-DTP3	28%	0.8%	587	BCG-DTP1-Meas1	33%	1.0%	547
North Korea	151	17	64%	0.7%	794	BCG-DTP1-DTP3	74%	0.2%	2,900	BCG-DTP1-Meas1	75%	0.3%	2,437
Pakistan	7,694	971	30%	0.6%	417	BCG-DTP1-DTP3	39%	0.3%	1,140	BCG-DTP1-DTP3	42%	0.5%	699
Panama	25	1	57%	0.9%	1,541	BCG-DTP1-DTP2	75%	0.3%	6,021	BCG-DTP1-Meas1	76%	0.3%	5,471
Papua New Guinea	191	89	37%	0.2%	329	BCG-DTP1-DTP3	39%	0.1%	787	BCG-DTP1-Meas1	42%	0.1%	800
Paraguay	41	3	40%	0.9%	593	BCG-DTP1-DTP2	48%	0.3%	2,213	BCG-DTP1-DTP3	52%	0.3%	2,144
Peru	144	8	45%	1.0%	852	BCG-DTP1-DTP2	45%	0.2%	4,373	DTP1-DTP2-Meas1	50%	1.1%	858
Philippines	1,893	811	29%	0.2%	303	BCG-DTP1-DTP3	36%	0.1%	759	BCG-DTP1-Meas1	40%	0.1%	750
Republic of Moldova	1	1	50%	0.7%	65	BCG-DTP1-DTP3	72%	0.3%	269	BCG-DTP1-DTP3	73%	0.3%	268
Romania	8	0	70%	0.8%	2,716	BCG-DTP1-DTP2	90%	0.4%	8,099	BCG-DTP1-DTP3	92%	0.4%	7,669
Russian Federation	54	3	32%	0.5%	1,301	BCG-DTP1-DTP3	88%	0.5%	3,772	BCG-DTP1-Meas1	89%	0.5%	3,640
Rwanda	700	19	44%	0.7%	2,261	BCG-DTP1-DTP3	45%	0.1%	13,597	BCG-DTP3-Meas1	51%	0.6%	3,193
Saint Lucia	0	0	59%	0.9%	371	BCG-DTP1-DTP3	67%	0.6%	684	BCG-DTP1-DTP3	75%	0.7%	579
Saint Vincent & the Gr.	0	0	59%	0.9%	680	BCG-DTP1-DTP2	75%	0.3%	2,654	BCG-DTP1-DTP3	77%	0.3%	2,421
Samoa	0	1	58%	0.3%	64	BCG-DTP1-DTP3	63%	0.1%	177	BCG-DTP1-Meas1	64%	0.1%	174
Sao Tome and Principe	7	0	47%	0.8%	1,291	BCG-DTP1-DTP3	47%	0.1%	9,669	DTP1-DTP3-Meas1	53%	1.0%	1,126
Senegal	876	34	38%	1.0%	1,022	BCG-DTP1-DTP3	44%	0.3%	3,558	BCG-DTP1-Meas1	47%	0.5%	2,728
Serbia	1	0	74%	0.9%	837	BCG-DTP1-DTP3	92%	0.3%	3,467	BCG-DTP1-Meas1	92%	0.3%	3,478
Sierra Leone	1,263	15	41%	0.8%	3,984	BCG-DTP1-DTP3	44%	0.2%	17,580	DTP1-DTP2-Meas1	48%	1.2%	3,273
Solomon Islands	9	1	42%	0.3%	1,380	BCG-DTP1-DTP3	47%	0.1%	3,547	DTP1-DTP3-Meas1	51%	0.5%	1,134
Somalia	2,432	415	23%	0.5%	257	DTP1-DTP2-DTP3	23%	0.5%	257	DTP1-DTP2-Meas1	27%	0.7%	223
South Africa	1,734	267	41%	0.8%	331	DTP1-DTP2-DTP3	41%	0.8%	331	DTP1-DTP2-Meas1	45%	1.1%	258
South Sudan	937	102	17%	0.4%	422	BCG-DTP1-DTP3	20%	0.1%	1,667	BCG-DTP1-DTP3	21%	0.1%	1,432
Sri Lanka	11	1	74%	1.0%	1,012	BCG-DTP1-DTP3	92%	0.3%	4,292	BCG-DTP1-Meas1	94%	0.3%	3,819
Sudan	2,726	30	42%	0.9%	4,253	DTP1-DTP2-DTP3	42%	0.9%	4,253	DTP1-DTP2-Meas1	51%	1.3%	3,448
Suriname	1	0	35%	0.4%	238	DTP1-DTP2-DTP3	35%	0.4%	238	DTP1-DTP2-Meas1	61%	1.1%	168
Swaziland	77	2	49%	0.6%	3,022	BCG-DTP1-DTP3	51%	0.1%	22,551	BCG-DTP2-Meas1	53%	0.3%	7,219
Syrian Arab Republic	80	136	36%	0.8%	28	BCG-DTP1-DTP2	49%	0.3%	115	BCG-DTP1-Meas1	50%	0.3%	103
Tajikistan	236	5	36%	0.7%	2,289	BCG-DTP1-DTP3	49%	0.4%	6,182	BCG-DTP2-Meas1	53%	0.5%	5,249
Tanzania	2,880	109	51%	0.6%	2,183	DTP1-DTP2-DTP3	51%	0.6%	2,183	DTP1-DTP3-Meas1	57%	1.0%	1,491

TFYR Macedonia	1	0	38%	0.6%	1,478	BCG-DTP1-DTP2	86%	0.4%	4,462	BCG-DTP1-Meas1	88%	0.4%	4,318
Thailand	65	1	72%	1.7%	3,444	BCG-DTP1-DTP3	91%	0.5%	13,734	BCG-DTP1-Meas1	93%	0.6%	12,726
Timor-Leste	90	9	32%	0.5%	599	BCG-DTP1-DTP3	37%	0.3%	1,498	BCG-DTP2-Meas1	43%	0.6%	805
Togo	609	17	45%	0.9%	1,869	DTP1-DTP2-DTP3	45%	0.9%	1,869	DTP1-DTP2-Meas1	49%	0.9%	1,834
Tonga	0	1	57%	0.3%	64	BCG-DTP1-DTP3	61%	0.1%	174	DTP1-DTP2-Meas1	63%	0.4%	54
Tunisia	15	3	69%	2.0%	204	BCG-DTP1-DTP3	76%	0.4%	1,095	BCG-DTP1-DTP3	76%	0.4%	1,097
Turkey	53	21	58%	0.9%	165	BCG-DTP1-DTP3	65%	0.5%	302	BCG-DTP1-DTP3	73%	0.6%	281
Turkmenistan	89	2	39%	0.9%	2,478	BCG-DTP1-DTP3	48%	0.4%	6,837	BCG-DTP2-Meas1	52%	0.5%	5,699
Tuvalu	0	0	40%	0.3%	801	BCG-DTP1-DTP3	46%	0.1%	2,033	BCG-DTP2-Meas1	50%	0.2%	1,532
Uganda	2,478	150	37%	0.9%	697	BCG-DTP1-DTP3	42%	0.3%	2,158	BCG-DTP2-Meas1	48%	0.7%	1,226
Ukraine	13	1	21%	0.2%	1,735	BCG-DTP1-DTP2	37%	0.1%	6,105	DTP1-DTP2-Meas1	48%	0.8%	1,251
Uzbekistan	181	4	36%	1.3%	1,221	BCG-DTP1-DTP3	45%	0.6%	3,477	BCG-DTP2-Meas1	51%	0.6%	3,481
Vanuatu	5	5	32%	0.2%	137	BCG-DTP1-DTP3	35%	0.1%	355	DTP1-DTP2-Meas1	36%	0.3%	120
Venezuela	273	36	57%	1.1%	393	BCG-DTP1-DTP2	75%	0.3%	1,804	BCG-DTP1-DTP3	76%	0.4%	1,557
Viet Nam	365	854	30%	0.1%	167	BCG-DTP1-DTP3	65%	0.1%	280	BCG-DTP1-DTP2	75%	0.1%	226
Yemen	1,434	170	30%	0.7%	373	DTP1-DTP2-DTP3	30%	0.7%	373	DTP1-DTP2-Meas1	40%	1.2%	271
Zambia	1,235	21	45%	0.6%	4,118	BCG-DTP1-DTP3	50%	0.2%	15,338	BCG-DTP1-DTP3	54%	0.3%	10,532
Zimbabwe	1,295	29	46%	0.7%	3,049	DTP1-DTP2-DTP3	46%	0.7%	3,049	DTP1-DTP2-Meas1	50%	0.7%	3,190

Appendix Table 7. Potential benefits and risks of alternative rotavirus vaccination schedule options if used in all 135 low- and middle-income countries:
scenario assuming all doses given as part of a neonatal schedule have double the mean duration of protection as doses given as part of a non-neonatal schedule

Schedule	Doses		RVGE deaths <5 years			Intussusception deaths <5 years			Summary indicators				
Vaccines in the existing schedule that rotavirus would be co-administered with	Total doses (millions)	Fully vaccinated children (FVC) (millions)	Number	Averted	*Incremental* number averted vs age-restricted	Number	Excess vs no vaccine	*Incremental* excess number vs age-restricted	% reduction in RVGE deaths	Doses per RVGE death averted	Number of FVC per excess IS case	RVGE deaths averted per excess IS death	*Incremental* RVGE deaths averted per excess IS death vs age-restricted
NO VACCINE	**0**	**0**	**169,450**	-	-	**14,478**	-	-	-	-	-	-	-
Age-restricted (primary)													
BCG	109	104	129,991	39,459	-	14,498	21	-	23.3%	2,764	838,053	1,907	-
DTP1	87	82	141,323	28,126	-	14,531	54	-	16.6%	3,085	177,189	524	-
BCG+DTP1	217	102	103,769	65,680	-	14,515	38	-	38.8%	3,304	299,990	1,740	-
BCG+DTP2	213	99	102,779	66,671	-	14,536	58	-	39.3%	3,203	172,357	1,144	-
BCG+DTP3	192	79	106,485	62,965	-	14,540	62	-	37.2%	3,049	136,944	1,016	-
DTP1+DTP2^	173	82	120,829	48,621	-	14,564	87	-	28.7%	3,567	106,531	561	-
DTP1+DTP3	164	73	121,110	48,340	-	14,572	94	-	28.5%	3,397	85,499	512	-
BCG+DTP1+DTP2	321	99	98,947	70,502	-	14,515	38	-	41.6%	4,559	290,268	1,868	-
BCG+DTP1+DTP3	300	79	96,912	72,538	-	14,515	38	-	42.8%	4,133	230,160	1,922	-
BCG+DTP2+DTP3	296	79	98,884	70,566	-	14,536	58	-	41.6%	4,200	136,687	1,211	-
DTP1+DTP2+DTP3^	250	73	115,469	53,981	-	14,564	87	-	31.9%	4,646	95,149	623	-
Age-unrestricted (primary)													
BCG	114	108	127,594	41,855	2,396	14,512	34	14	24.7%	2,730	501,786	1,217	175
DTP1	117	111	134,966	34,484	6,357	14,584	106	53	20.4%	3,397	89,616	324	121
BCG+DTP1	227	107	100,130	69,320	3,639	14,527	49	11	40.9%	3,277	255,004	1,417	326
BCG+DTP2	225	105	99,012	70,438	3,767	14,551	73	15	41.6%	3,198	152,843	964	254
BCG+DTP3	223	101	100,427	69,023	6,058	14,559	81	19	40.7%	3,230	130,653	849	313
DTP1+DTP2^	230	107	111,331	58,119	9,498	14,624	146	59	34.3%	3,966	63,209	398	160
DTP1+DTP3	226	102	111,080	58,370	10,030	14,632	154	59	34.4%	3,887	56,731	380	169
BCG+DTP1+DTP2	338	105	94,895	74,555	4,053	14,526	48	10	44.0%	4,534	255,667	1,546	387
BCG+DTP1+DTP3	335	101	91,758	77,692	5,154	14,526	49	11	45.8%	4,321	241,584	1,593	468
BCG+DTP2+DTP3	334	101	94,111	75,339	4,773	14,551	73	15	44.5%	4,432	146,921	1,032	324
DTP1+DTP2+DTP3^	339	102	104,501	64,949	10,968	14,623	146	59	38.3%	5,238	60,045	446	186
Age-unrestricted (booster)													
BCG+Meas1	222	73	108,445	61,005	-	14,537	60	-	36.0%	3,644	128,271	1,023	-
DTP1+Meas1	225	73	116,653	52,797	-	14,609	131	-	31.2%	4,276	45,914	403	-
BCG+DTP1+Meas1	335	73	89,759	79,691	-	14,527	49	-	47.0%	4,201	173,813	1,633	-
BCG+DTP2+Meas1	332	73	89,975	79,475	-	14,551	73	-	46.9%	4,186	105,773	1,088	-
BCG+DTP3+Meas1	329	72	93,080	76,369	-	14,559	81	-	45.1%	4,314	93,984	941	-
DTP1+DTP2+Meas1	338	72	99,777	69,673	-	14,623	146	-	41.1%	4,861	42,810	478	-
DTP1+DTP3+Meas1	333	72	101,489	67,961	-	14,631	154	-	40.1%	4,916	40,444	442	-

^ shaded rows reflect the current WHO recommended schedule options

Appendix Table 8. Potential benefits and risks of a standard age-restricted three-dose infant schedule (co-administered with DTP1+DTP2+DTP3) compared to age-restricted and age-unrestricted schedules with the highest predicted impact in each country: *scenario assuming all doses given as part of a neonatal schedule have double the mean duration of protection as doses given as part of a non-neonatal schedule*

Country	NO VACCINE		Age-restricted standard schedule (DTP1+DTP2+DTP3)			Age-restricted schedule with the highest predicted impact on RVGE deaths<5 years				Age-unrestricted schedule with the highest predicted impact on RVGE deaths<5 years			
	RVGE deaths <5 years	IS deaths <5 years	% impact on RVGE deaths	% increase in IS deaths	RVGE deaths averted per excess IS death	Schedule with highest predicted impact	% impact on RVGE deaths	% increase in IS deaths	RVGE deaths averted per excess IS death	Schedule with highest predicted impact	% impact on RVGE deaths	% increase in IS deaths	RVGE deaths averted per excess IS death
ALL 135 LMICs	**169,450**	**14,478**	**32%**	**0.6%**	**623**		**43%**	**0.3%**	**1,526**		**48%**	**0.5%**	**1,147**
Afghanistan	2,420	296	21%	0.4%	411	BCG-DTP1-DTP3	39%	0.3%	942	BCG-DTP1-DTP3	44%	0.5%	662
Albania	1	0	59%	1.0%	270	BCG-DTP1-DTP2	78%	0.4%	852	BCG-DTP1-DTP3	81%	0.4%	819
Algeria	206	48	16%	0.7%	90	BCG-DTP1-DTP3	58%	0.5%	453	BCG-DTP1-Meas1	62%	0.5%	488
Angola	6,921	125	31%	1.0%	1,685	BCG-DTP1-DTP2	47%	0.3%	8,739	BCG-DTP1-DTP3	50%	0.3%	8,036
Argentina	36	65	56%	0.8%	37	BCG-DTP1-DTP2	76%	0.3%	148	BCG-DTP1-DTP3	78%	0.3%	136
Armenia	2	1	38%	0.6%	200	BCG-DTP1-DTP3	74%	0.3%	792	BCG-DTP1-Meas1	79%	0.3%	819
Azerbaijan	74	7	24%	0.9%	301	BCG-DTP1-DTP3	43%	0.4%	1,099	BCG-DTP2-Meas1	53%	0.6%	1,060
Bangladesh	1,623	11	40%	0.3%	22,196	BCG-DTP1-DTP3	51%	0.0%	209,062	BCG-DTP3-Meas1	65%	0.7%	13,028
Belarus	1	0	32%	0.5%	380	BCG-DTP1-DTP3	89%	0.5%	1,091	BCG-DTP1-Meas1	92%	0.5%	1,063
Belize	1	0	59%	0.9%	583	BCG-DTP1-DTP2	75%	0.3%	2,001	BCG-DTP1-DTP3	79%	0.4%	1,699
Benin	1,582	39	41%	0.8%	2,147	BCG-DTP1-DTP3	58%	0.2%	11,494	BCG-DTP2-Meas1	60%	0.4%	5,828
Bhutan	6	0	40%	0.7%	790	BCG-DTP1-DTP3	56%	0.2%	3,573	BCG-DTP2-Meas1	62%	0.4%	1,968
Bolivia	253	3	41%	0.9%	3,701	BCG-DTP1-DTP2	60%	0.3%	16,662	BCG-DTP1-DTP3	64%	0.3%	15,884
Bosnia & Herzegovina	0	0	52%	0.6%	557	BCG-DTP1-DTP3	87%	0.3%	2,121	BCG-DTP1-Meas1	89%	0.3%	2,126
Botswana	43	3	37%	1.3%	430	BCG-DTP1-DTP3	56%	0.4%	2,194	BCG-DTP1-Meas1	61%	0.4%	2,080
Brazil	1,032	3	58%	1.5%	13,263	BCG-DTP1-DTP2	78%	0.5%	53,930	BCG-DTP1-DTP3	80%	0.5%	50,391
Bulgaria	2	0	67%	0.8%	2,048	BCG-DTP1-DTP3	89%	0.3%	6,090	BCG-DTP1-Meas1	91%	0.4%	5,801
Burkina Faso	2,279	48	42%	1.2%	1,653	BCG-DTP1-DTP3	59%	0.3%	8,840	BCG-DTP1-Meas1	62%	0.4%	8,155
Burundi	1,606	21	47%	0.9%	3,898	BCG-DTP1-DTP3	56%	0.2%	23,832	BCG-DTP2-Meas1	60%	0.5%	9,875
Cabo Verde	4	1	58%	1.3%	262	BCG-DTP1-DTP2	74%	0.3%	1,275	BCG-DTP1-Meas1	77%	0.4%	1,200
Cambodia	212	64	38%	0.3%	411	BCG-DTP1-DTP3	51%	0.1%	1,788	BCG-DTP3-Meas1	57%	0.2%	1,086
Cameroon	2,967	60	44%	0.8%	2,633	BCG-DTP1-DTP3	45%	0.1%	16,442	DTP1-DTP2-Meas1	50%	1.1%	2,172
Central African Republic	928	42	30%	0.6%	1,058	BCG-DTP1-DTP2	45%	0.2%	4,057	BCG-DTP1-DTP3	47%	0.3%	3,320
Chad	4,309	182	16%	0.4%	1,065	BCG-DTP1-DTP3	31%	0.3%	2,216	BCG-DTP1-Meas1	37%	0.7%	1,318
China	1,384	414	26%	0.3%	304	BCG-DTP1-DTP3	77%	0.2%	1,031	BCG-DTP1-Meas1	80%	0.3%	948
Colombia	152	26	61%	0.9%	410	BCG-DTP1-DTP2	73%	0.2%	2,395	BCG-DTP1-DTP3	74%	0.2%	2,431
Comoros	39	2	43%	0.9%	821	BCG-DTP1-DTP3	57%	0.2%	5,060	BCG-DTP2-Meas1	60%	0.5%	2,296

Congo	252	14	35%	1.0%	600	BCG-DTP1-DTP3	52%	0.3%	3,017	BCG-DTP1-Meas1	54%	0.3%	2,768
Costa Rica	2	0	81%	0.9%	2,471	DTP1-DTP2-DTP3	81%	0.9%	2,471	DTP1-DTP2-Meas1	85%	1.0%	2,453
Côte d'Ivoire	2,477	75	42%	0.9%	1,521	BCG-DTP1-DTP3	47%	0.2%	8,941	DTP1-DTP2-Meas1	51%	1.4%	1,167
Croatia	0	0	70%	0.8%	421	BCG-DTP1-DTP3	91%	0.3%	1,303	BCG-DTP1-Meas1	94%	0.4%	1,247
Cuba	3	0	71%	0.9%	742	BCG-DTP1-DTP3	92%	0.3%	2,946	BCG-DTP1-Meas1	95%	0.3%	2,712
DR Congo	12,377	435	38%	0.7%	1,480	BCG-DTP1-DTP3	47%	0.2%	6,865	BCG-DTP2-Meas1	49%	0.5%	3,119
Djibouti	26	2	39%	0.9%	476	BCG-DTP1-DTP3	55%	0.3%	2,032	BCG-DTP1-Meas1	57%	0.4%	1,822
Dominican Republic	74	9	17%	0.2%	790	BCG-DTP1-DTP3	64%	0.2%	2,947	BCG-DTP1-DTP2	74%	0.2%	2,912
Ecuador	95	23	48%	0.7%	283	BCG-DTP1-DTP2	67%	0.2%	1,159	BCG-DTP1-Meas1	69%	0.3%	1,063
Egypt	1,095	98	70%	0.7%	1,066	BCG-DTP1-DTP3	80%	0.0%	128,169	BCG-DTP1-DTP3	80%	0.0%	53,241
El Salvador	50	5	69%	0.9%	809	BCG-DTP1-DTP3	79%	0.2%	5,530	BCG-DTP1-Meas1	79%	0.2%	5,572
Equatorial Guinea	42	13	11%	0.3%	146	BCG-DTP1-DTP3	23%	0.1%	772	BCG-DTP1-Meas1	24%	0.1%	660
Eritrea	269	9	28%	0.9%	916	BCG-DTP1-DTP3	44%	0.3%	5,039	BCG-DTP2-Meas1	51%	0.5%	2,873
Ethiopia	5,130	407	22%	0.6%	481	BCG-DTP1-DTP3	27%	0.2%	1,572	BCG-DTP2-Meas1	41%	0.9%	582
Fiji	7	0	65%	0.3%	3,228	BCG-DTP1-DTP3	78%	0.1%	8,659	BCG-DTP1-Meas1	81%	0.2%	7,959
Gabon	57	7	33%	0.8%	316	BCG-DTP1-DTP3	52%	0.3%	1,469	BCG-DTP2-Meas1	56%	0.5%	847
Gambia	130	4	33%	1.3%	868	BCG-DTP1-DTP3	53%	0.4%	4,169	BCG-DTP2-Meas1	60%	0.7%	2,814
Georgia	2	0	70%	0.8%	2,157	BCG-DTP1-DTP3	89%	0.4%	6,277	BCG-DTP1-Meas1	92%	0.4%	6,111
Ghana	1,436	56	44%	0.5%	2,492	BCG-DTP1-DTP3	57%	0.1%	20,099	BCG-DTP2-Meas1	61%	0.3%	5,161
Grenada	0	0	73%	0.7%	2,906	DTP1-DTP2-DTP3	73%	0.7%	2,906	DTP1-DTP2-Meas1	85%	1.0%	2,536
Guatemala	349	13	33%	0.9%	1,013	BCG-DTP1-DTP2	47%	0.3%	4,970	BCG-DTP2-Meas1	51%	0.5%	2,738
Guinea	1,097	71	24%	0.5%	682	BCG-DTP1-DTP3	40%	0.2%	2,861	BCG-DTP1-Meas1	42%	0.3%	2,452
Guinea-Bissau	197	4	37%	1.0%	1,849	BCG-DTP1-DTP3	51%	0.3%	7,108	BCG-DTP1-Meas1	57%	0.5%	5,733
Guyana	11	0	42%	1.0%	3,084	BCG-DTP1-DTP3	57%	0.2%	17,459	BCG-DTP2-Meas1	61%	0.5%	9,545
Haiti	375	24	25%	0.4%	934	BCG-DTP1-DTP2	40%	0.3%	2,299	BCG-DTP1-DTP3	47%	0.5%	1,410
Honduras	103	1	48%	1.0%	4,085	BCG-DTP1-DTP3	59%	0.2%	26,225	BCG-DTP1-DTP3	61%	0.2%	27,180
India	25,839	4,025	31%	0.4%	450	BCG-DTP2-DTP3	39%	0.3%	821	BCG-DTP2-Meas1	44%	0.3%	807
Indonesia	3,000	157	27%	0.9%	554	BCG-DTP2-DTP3	38%	0.6%	1,245	BCG-DTP2-Meas1	45%	0.7%	1,305
Iran	213	20	59%	1.3%	486	BCG-DTP1-DTP2	78%	0.4%	2,125	BCG-DTP1-Meas1	81%	0.5%	1,944
Iraq	669	189	29%	1.0%	106	BCG-DTP1-DTP2	49%	0.3%	555	BCG-DTP1-DTP3	51%	0.4%	503
Jamaica	3	1	64%	0.7%	380	BCG-DTP1-DTP3	78%	0.2%	1,406	BCG-DTP1-DTP3	80%	0.3%	1,266
Jordan	25	5	26%	0.7%	178	BCG-DTP1-DTP3	77%	0.6%	671	BCG-DTP1-DTP3	79%	0.6%	632
Kazakhstan	46	5	55%	0.8%	718	BCG-DTP2-DTP3	77%	0.3%	2,281	BCG-DTP2-DTP3	79%	0.3%	2,319
Kenya	1,986	90	43%	0.4%	2,295	BCG-DTP1-DTP3	50%	0.0%	28,825	BCG-DTP3-Meas1	56%	0.5%	2,251
Kiribati	4	0	32%	0.2%	1,068	BCG-DTP1-DTP3	45%	0.1%	3,451	BCG-DTP2-Meas1	49%	0.2%	2,533
Kyrgyzstan	45	3	64%	0.9%	1,049	BCG-DTP1-DTP3	79%	0.3%	4,591	BCG-DTP1-Meas1	80%	0.3%	4,653
Lao PDR	431	54	23%	0.2%	783	BCG-DTP2-DTP3	36%	0.2%	1,581	BCG-DTP2-Meas1	48%	0.3%	1,367
Lebanon	5	0	60%	1.2%	592	DTP1-DTP2-DTP3	60%	1.2%	592	DTP1-DTP2-Meas1	75%	1.8%	504
Lesotho	187	3	48%	0.8%	3,237	BCG-DTP1-DTP3	59%	0.2%	21,349	BCG-DTP2-Meas1	63%	0.5%	7,448
Liberia	443	16	32%	0.7%	1,216	BCG-DTP1-DTP3	42%	0.2%	5,895	BCG-DTP1-Meas1	46%	0.2%	5,607
Libya	8	3	40%	1.3%	89	BCG-DTP1-DTP2	60%	0.4%	430	BCG-DTP1-DTP3	63%	0.5%	404
Madagascar	1,696	109	26%	0.6%	662	BCG-DTP1-DTP3	38%	0.3%	2,092	BCG-DTP2-Meas1	43%	0.7%	985
Malawi	1,556	35	49%	0.9%	2,561	BCG-DTP1-DTP3	58%	0.2%	15,381	BCG-DTP2-Meas1	60%	0.5%	5,704
Malaysia	17	0	71%	0.9%	22,079	BCG-DTP1-DTP3	92%	0.3%	90,927	BCG-DTP1-Meas1	94%	0.3%	80,968
Maldives	0	0	71%	1.0%	1,041	BCG-DTP1-DTP3	92%	0.3%	4,648	BCG-DTP1-Meas1	94%	0.4%	4,145

Mali	2,438	83	28%	0.6%	1,322	BCG-DTP1-DTP3	47%	0.4%	3,377	BCG-DTP1-Meas1	53%	0.7%	2,246
Marshall Islands	1	0	36%	0.4%	9,620	BCG-DTP1-DTP2	56%	0.2%	34,296	BCG-DTP1-DTP3	60%	0.2%	33,154
Mauritania	400	12	31%	0.7%	1,558	BCG-DTP1-DTP3	49%	0.3%	5,140	BCG-DTP1-Meas1	52%	0.4%	4,074
Mauritius	1	1	59%	0.9%	123	BCG-DTP1-DTP3	71%	0.5%	280	BCG-DTP1-Meas1	77%	0.6%	247
Mexico	626	142	58%	0.8%	332	BCG-DTP1-DTP2	79%	0.2%	1,541	BCG-DTP1-Meas1	80%	0.2%	1,548
Micronesia (FSO)	1	0	36%	0.4%	373	BCG-DTP1-DTP2	44%	0.1%	1,487	BCG-DTP2-Meas1	47%	0.2%	974
Mongolia	9	3	77%	0.4%	649	BCG-DTP1-DTP3	82%	0.1%	2,833	BCG-DTP1-Meas1	83%	0.1%	2,867
Montenegro	0	0	67%	0.8%	468	BCG-DTP1-DTP2	82%	0.3%	1,508	DTP1-DTP2-Meas1	84%	1.2%	423
Morocco	604	9	38%	1.3%	1,971	BCG-DTP1-DTP3	57%	0.7%	5,379	BCG-DTP1-Meas1	61%	0.8%	5,018
Mozambique	2,160	84	32%	0.9%	891	BCG-DTP1-DTP3	55%	0.4%	3,819	BCG-DTP1-Meas1	59%	0.4%	3,436
Myanmar	818	82	34%	1.0%	350	BCG-DTP2-DTP3	51%	0.5%	971	BCG-DTP2-Meas1	58%	0.6%	990
Namibia	108	6	42%	0.7%	979	BCG-DTP1-DTP3	53%	0.1%	9,628	BCG-DTP2-Meas1	58%	0.3%	3,219
Nepal	258	42	39%	0.6%	384	BCG-DTP1-DTP3	51%	0.2%	1,772	BCG-DTP1-Meas1	55%	0.2%	1,670
Nicaragua	53	0	59%	0.9%	7,651	BCG-DTP1-DTP2	77%	0.3%	31,272	BCG-DTP1-DTP3	80%	0.3%	29,510
Niger	4,557	94	36%	0.8%	2,125	BCG-DTP1-DTP3	45%	0.2%	11,902	BCG-DTP2-Meas1	49%	0.4%	5,390
Nigeria	35,129	2,103	23%	1.1%	353	BCG-DTP1-DTP3	33%	0.8%	692	BCG-DTP1-Meas1	38%	1.0%	643
North Korea	151	17	64%	0.7%	785	BCG-DTP1-DTP3	77%	0.2%	3,013	BCG-DTP1-Meas1	79%	0.3%	2,575
Pakistan	7,694	971	29%	0.6%	402	BCG-DTP1-DTP3	45%	0.3%	1,321	BCG-DTP1-Meas1	49%	0.5%	813
Panama	25	1	57%	0.9%	1,543	BCG-DTP1-DTP2	78%	0.3%	6,264	BCG-DTP1-Meas1	80%	0.3%	5,763
Papua New Guinea	191	89	34%	0.2%	309	BCG-DTP1-DTP3	46%	0.1%	933	BCG-DTP1-Meas1	50%	0.1%	939
Paraguay	41	3	38%	0.9%	570	BCG-DTP1-DTP2	57%	0.3%	2,599	BCG-DTP1-DTP3	61%	0.3%	2,498
Peru	144	8	43%	1.0%	817	BCG-DTP1-DTP2	53%	0.2%	5,140	BCG-DTP2-Meas1	57%	0.4%	2,543
Philippines	1,893	811	28%	0.2%	286	BCG-DTP1-DTP3	42%	0.1%	900	BCG-DTP1-Meas1	47%	0.1%	880
Republic of Moldova	1	1	50%	0.7%	66	BCG-DTP1-DTP3	75%	0.3%	281	BCG-DTP1-DTP3	76%	0.3%	282
Romania	8	0	68%	0.8%	2,638	BCG-DTP1-DTP2	91%	0.4%	8,173	BCG-DTP1-DTP3	93%	0.4%	7,781
Russian Federation	54	3	31%	0.5%	1,275	BCG-DTP1-DTP3	89%	0.5%	3,815	BCG-DTP1-Meas1	91%	0.5%	3,701
Rwanda	700	19	40%	0.7%	2,060	BCG-DTP1-DTP3	54%	0.1%	16,237	BCG-DTP3-Meas1	60%	0.6%	3,753
Saint Lucia	0	0	59%	0.9%	373	BCG-DTP1-DTP3	70%	0.6%	712	BCG-DTP1-DTP3	79%	0.7%	610
Saint Vincent & the Gr.	0	0	59%	0.9%	682	BCG-DTP1-DTP2	78%	0.3%	2,765	BCG-DTP1-DTP3	81%	0.3%	2,554
Samoa	0	1	57%	0.3%	63	BCG-DTP1-DTP3	65%	0.1%	183	BCG-DTP1-Meas1	67%	0.1%	182
Sao Tome and Principe	7	0	44%	0.8%	1,207	BCG-DTP1-DTP3	56%	0.1%	11,437	BCG-DTP2-Meas1	61%	0.4%	3,543
Senegal	876	34	36%	1.0%	968	BCG-DTP1-DTP3	51%	0.3%	4,143	BCG-DTP1-Meas1	55%	0.5%	3,189
Serbia	1	0	72%	0.9%	816	BCG-DTP1-DTP3	93%	0.3%	3,500	BCG-DTP1-Meas1	94%	0.3%	3,529
Sierra Leone	1,263	15	39%	0.8%	3,814	BCG-DTP1-DTP3	52%	0.2%	20,584	BCG-DTP2-Meas1	55%	0.5%	9,068
Solomon Islands	9	1	40%	0.3%	1,300	BCG-DTP1-DTP3	55%	0.1%	4,184	BCG-DTP2-Meas1	59%	0.2%	3,080
Somalia	2,432	415	22%	0.5%	247	BCG-DTP1-DTP3	22%	0.1%	1,679	DTP1-DTP2-Meas1	27%	0.7%	220
South Africa	1,734	267	41%	0.8%	332	BCG-DTP1-DTP3	45%	0.1%	2,324	BCG-DTP1-DTP3	46%	0.1%	2,237
South Sudan	937	102	16%	0.4%	407	BCG-DTP1-DTP3	24%	0.1%	1,957	BCG-DTP1-DTP3	25%	0.1%	1,676
Sri Lanka	11	1	73%	1.0%	992	BCG-DTP1-DTP3	93%	0.3%	4,342	BCG-DTP1-Meas1	95%	0.3%	3,880
Sudan	2,726	30	40%	0.9%	4,074	BCG-DTP1-DTP3	42%	0.2%	19,098	BCG-DTP2-Meas1	53%	0.8%	5,675
Suriname	1	0	35%	0.4%	239	DTP1-DTP2-DTP3	35%	0.4%	239	DTP1-DTP2-Meas1	63%	1.1%	173
Swaziland	77	2	47%	0.6%	2,902	BCG-DTP1-DTP3	60%	0.1%	26,297	BCG-DTP2-Meas1	62%	0.3%	8,374
Syrian Arab Republic	80	136	36%	0.8%	28	BCG-DTP1-DTP2	51%	0.3%	120	BCG-DTP1-Meas1	52%	0.3%	108
Tajikistan	236	5	34%	0.7%	2,170	BCG-DTP1-DTP3	58%	0.4%	7,282	BCG-DTP2-Meas1	62%	0.5%	6,127
Tanzania	2,880	109	49%	0.6%	2,108	BCG-DTP1-DTP3	58%	0.1%	19,058	BCG-DTP2-Meas1	65%	0.6%	3,091

TFYR Macedonia	1	0	37%	0.6%	1,443	BCG-DTP1-DTP2	86%	0.4%	4,504	BCG-DTP1-Meas1	89%	0.4%	4,383
Thailand	65	1	71%	1.7%	3,362	BCG-DTP1-DTP3	92%	0.5%	13,865	BCG-DTP1-Meas1	94%	0.6%	12,903
Timor-Leste	90	9	30%	0.5%	564	BCG-DTP1-DTP3	44%	0.3%	1,766	BCG-DTP2-Meas1	50%	0.6%	936
Togo	609	17	43%	0.9%	1,801	BCG-DTP1-DTP3	52%	0.2%	11,313	BCG-DTP2-Meas1	55%	0.5%	4,292
Tonga	0	1	56%	0.3%	64	BCG-DTP1-DTP3	63%	0.1%	181	BCG-DTP1-Meas1	65%	0.1%	181
Tunisia	15	3	70%	2.0%	209	BCG-DTP1-DTP3	80%	0.4%	1,158	BCG-DTP1-DTP3	81%	0.4%	1,170
Turkey	53	21	58%	0.9%	165	BCG-DTP1-DTP3	68%	0.5%	315	BCG-DTP1-Meas1	77%	0.6%	296
Turkmenistan	89	2	37%	0.9%	2,356	BCG-DTP1-DTP3	57%	0.4%	8,033	BCG-DTP2-Meas1	61%	0.5%	6,649
Tuvalu	0	0	37%	0.3%	746	BCG-DTP1-DTP3	54%	0.1%	2,407	BCG-DTP2-Meas1	59%	0.2%	1,800
Uganda	2,478	150	35%	0.9%	655	BCG-DTP1-DTP3	50%	0.3%	2,569	BCG-DTP2-Meas1	56%	0.7%	1,429
Ukraine	13	1	20%	0.2%	1,643	BCG-DTP1-DTP2	37%	0.1%	6,094	DTP1-DTP2-Meas1	46%	0.8%	1,245
Uzbekistan	181	4	33%	1.3%	1,130	BCG-DTP1-DTP3	53%	0.6%	4,129	BCG-DTP2-Meas1	59%	0.6%	4,085
Vanuatu	5	5	30%	0.2%	129	BCG-DTP1-DTP3	41%	0.1%	420	BCG-DTP2-Meas1	43%	0.1%	299
Venezuela	273	36	58%	1.1%	398	BCG-DTP1-DTP2	79%	0.3%	1,894	BCG-DTP1-DTP3	80%	0.4%	1,650
Viet Nam	365	854	29%	0.1%	164	BCG-DTP1-DTP3	67%	0.1%	291	BCG-DTP1-DTP2	77%	0.1%	233
Yemen	1,434	170	29%	0.7%	360	DTP1-DTP2-DTP3	29%	0.7%	360	DTP1-DTP2-Meas1	39%	1.2%	267
Zambia	1,235	21	45%	0.6%	4,094	BCG-DTP1-DTP3	57%	0.2%	17,572	BCG-DTP1-DTP3	61%	0.3%	12,039
Zimbabwe	1,295	29	44%	0.7%	2,903	BCG-DTP1-DTP3	54%	0.1%	26,723	BCG-DTP2-Meas1	58%	0.3%	7,732

Appendix Table 9. Potential benefits and risks of alternative rotavirus vaccination schedule options if used in all 135 low- and middle-income countries:
scenario assuming access to healthcare in high/very high mortality settings is equivalent to the proportion of children with 2-hour access to public hospitals

Schedule	Doses		RVGE deaths <5 years			Intussusception deaths <5 years			Summary indicators				
Vaccines in the existing schedule that rotavirus would be co-administered with	Total doses (millions)	Fully vaccinated children (FVC) (millions)	Number	Averted	*Incremental* number averted vs age-restricted	Number	Excess vs no vaccine	*Incremental* excess number vs age-restricted	% reduction in RVGE deaths	Doses per RVGE death averted	Number of FVC per excess IS case	RVGE deaths averted per excess IS death	*Incremental* RVGE deaths averted per excess IS death vs age-restricted
NO VACCINE	**0**	**0**	**169,450**	**-**	**-**	**33,513**	**-**	**-**	**-**	**-**	**-**	-	-
Age-restricted (primary)													
BCG	109	104	140,066	29,384	-	33,544	31	-	17.3%	3,714	766,452	945	-
DTP1	87	82	141,323	28,126	-	33,623	111	-	16.6%	3,091	155,907	254	-
BCG+DTP1	217	102	118,208	51,241	-	33,575	63	-	30.2%	4,238	277,449	817	-
BCG+DTP2	213	99	115,630	53,820	-	33,634	121	-	31.8%	3,974	153,682	444	-
BCG+DTP3	192	79	118,111	51,338	-	33,650	137	-	30.3%	3,745	119,493	374	-
DTP1+DTP2^	173	82	120,829	48,621	-	33,704	191	-	28.7%	3,575	92,582	254	-
DTP1+DTP3	164	73	121,110	48,340	-	33,730	217	-	28.5%	3,405	73,785	223	-
BCG+DTP1+DTP2	321	99	111,746	57,704	-	33,575	63	-	34.1%	5,573	268,455	920	-
BCG+DTP1+DTP3	300	79	109,115	60,335	-	33,575	63	-	35.6%	4,972	212,866	962	-
BCG+DTP2+DTP3	296	79	110,324	59,125	-	33,634	121	-	34.9%	5,019	121,877	488	-
DTP1+DTP2+DTP3^	250	73	115,469	53,981	-	33,704	191	-	31.9%	4,655	82,690	282	-
Age-unrestricted (primary)													
BCG	114	108	138,147	31,303	1,919	33,574	62	31	18.5%	3,655	440,158	508	63
DTP1	117	111	134,966	34,484	6,357	33,737	224	113	20.4%	3,408	81,055	154	56
BCG+DTP1	227	107	115,233	54,217	2,975	33,592	80	17	32.0%	4,193	235,715	680	174
BCG+DTP2	225	105	112,435	57,015	3,195	33,665	153	31	33.6%	3,958	135,448	374	102
BCG+DTP3	223	101	112,616	56,833	5,495	33,694	181	44	33.5%	3,931	114,206	313	125
DTP1+DTP2^	230	107	111,331	58,119	9,498	33,834	322	131	34.3%	3,978	56,669	181	73
DTP1+DTP3	226	102	111,080	58,370	10,030	33,858	346	128	34.4%	3,900	50,705	169	78
BCG+DTP1+DTP2	338	105	108,232	61,218	3,514	33,591	78	16	36.1%	5,526	236,453	782	226
BCG+DTP1+DTP3	335	101	104,188	65,262	4,927	33,592	79	17	38.5%	5,147	223,327	821	294
BCG+DTP2+DTP3	334	101	105,787	63,662	4,537	33,665	152	31	37.6%	5,252	130,219	418	146
DTP1+DTP2+DTP3^	339	102	104,501	64,949	10,968	33,834	322	131	38.3%	5,252	53,828	202	84
Age-unrestricted (booster)													
BCG+Meas1	222	73	119,210	50,240	-	33,639	126	-	29.6%	4,432	113,455	398	-
DTP1+Meas1	225	73	116,653	52,797	-	33,800	288	-	31.2%	4,289	41,353	183	-
BCG+DTP1+Meas1	335	73	102,302	67,148	-	33,592	80	-	39.6%	4,989	160,619	843	-
BCG+DTP2+Meas1	332	73	100,947	68,503	-	33,665	152	-	40.4%	4,863	93,720	449	-
BCG+DTP3+Meas1	329	72	103,072	66,378	-	33,694	181	-	39.2%	4,972	82,126	366	-
DTP1+DTP2+Meas1	338	72	99,777	69,673	-	33,834	322	-	41.1%	4,873	38,377	217	-
DTP1+DTP3+Meas1	333	72	101,489	67,961	-	33,858	345	-	40.1%	4,930	36,145	197	-

^ shaded rows reflect the current WHO recommended schedule options

Appendix Table 10. Potential benefits and risks of a standard age-restricted three-dose infant schedule (co-administered with DTP1+DTP2+DTP3) compared to age-restricted and age-unrestricted schedules with the highest predicted impact in each country: *scenario assuming access to healthcare in high/very high mortality settings is equivalent to the proportion of children with 2-hour access to public hospitals*

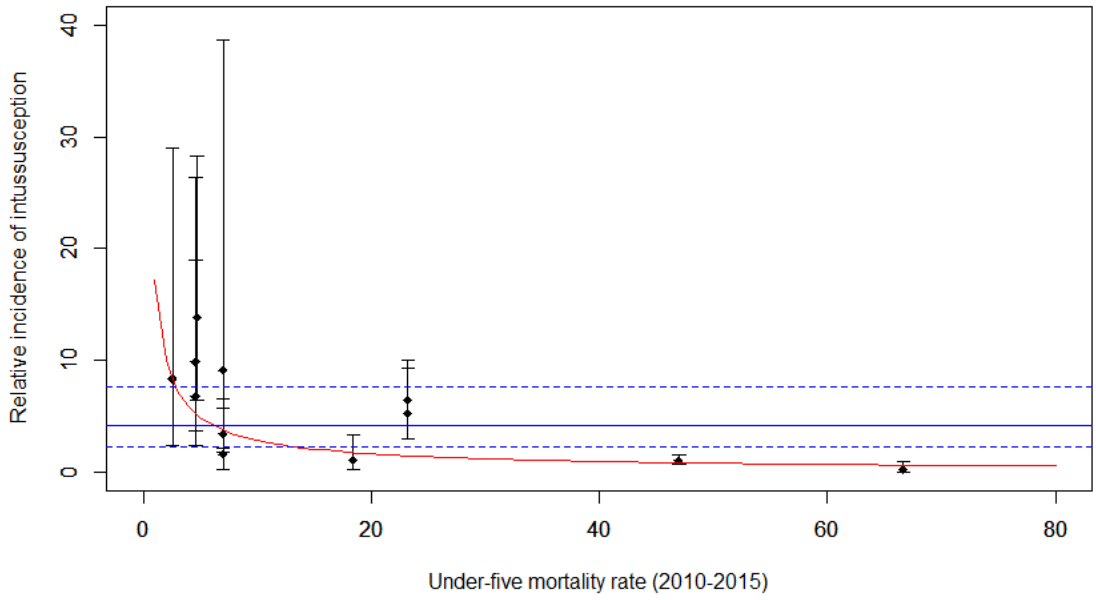
Country	NO VACCINE		Age-restricted standard schedule (DTP1+DTP2+DTP3)			Age-restricted schedule with the highest predicted impact on RVGE deaths<5 years				Age-unrestricted schedule with the highest predicted impact on RVGE deaths<5 years			
	RVGE deaths <5 years	IS deaths <5 years	% impact on RVGE deaths	% increase in IS deaths	RVGE deaths averted per excess IS death	Schedule with highest predicted impact	% impact on RVGE deaths	% increase in IS deaths	RVGE deaths averted per excess IS death	Schedule with highest predicted impact	% impact on RVGE deaths	% increase in IS deaths	RVGE deaths averted per excess IS death
ALL 135 LMICs	**169,450**	**33,513**	**32%**	**0.6%**	**282**		**36%**	**0.3%**	**524**		**42%**	**0.8%**	**263**
Afghanistan	2,420	369	21%	0.4%	329	BCG-DTP1-DTP3	32%	0.3%	623	BCG-DTP1-DTP3	37%	0.5%	450
Albania	1	0	59%	1.0%	270	BCG-DTP1-DTP2	74%	0.4%	811	BCG-DTP1-DTP3	77%	0.4%	785
Algeria	206	188	16%	0.7%	23	BCG-DTP1-DTP3	47%	0.5%	94	BCG-DTP1-Meas1	52%	0.5%	105
Angola	6,921	291	31%	1.0%	726	BCG-DTP1-DTP2	39%	0.3%	3,125	BCG-DTP1-DTP3	42%	0.3%	2,917
Argentina	36	65	56%	0.8%	37	BCG-DTP1-DTP2	72%	0.3%	141	BCG-DTP1-DTP3	74%	0.3%	130
Armenia	2	1	38%	0.6%	200	BCG-DTP1-DTP3	68%	0.3%	733	BCG-DTP1-Meas1	74%	0.3%	774
Azerbaijan	74	47	24%	0.9%	43	BCG-DTP1-DTP3	30%	0.4%	111	BCG-DTP3-Meas1	42%	0.6%	115
Bangladesh	1,623	221	40%	0.3%	1,151	DTP1-DTP2-DTP3	40%	0.3%	1,151	DTP1-DTP3-Meas1	56%	0.6%	631
Belarus	1	0	32%	0.5%	380	BCG-DTP1-DTP3	86%	0.5%	1,053	BCG-DTP1-Meas1	90%	0.5%	1,038
Belize	1	0	59%	0.9%	583	BCG-DTP1-DTP2	71%	0.3%	1,906	BCG-DTP1-DTP3	76%	0.4%	1,628
Benin	1,582	59	41%	0.8%	1,406	BCG-DTP1-DTP3	47%	0.2%	6,132	BCG-DTP3-Meas1	51%	0.5%	2,622
Bhutan	6	5	40%	0.7%	65	BCG-DTP1-DTP3	45%	0.2%	235	BCG-DTP2-Meas1	52%	0.4%	136
Bolivia	253	49	41%	0.9%	242	BCG-DTP1-DTP2	50%	0.3%	909	BCG-DTP1-DTP3	54%	0.3%	888
Bosnia & Herzegovina	0	0	52%	0.6%	557	BCG-DTP1-DTP3	84%	0.3%	2,044	BCG-DTP1-Meas1	86%	0.3%	2,071
Botswana	43	8	37%	1.3%	148	BCG-DTP1-DTP3	45%	0.4%	606	BCG-DTP2-Meas1	52%	0.7%	392
Brazil	1,032	3	58%	1.5%	13,263	BCG-DTP1-DTP2	74%	0.5%	51,357	BCG-DTP1-DTP3	77%	0.5%	48,288
Bulgaria	2	0	67%	0.8%	2,048	BCG-DTP1-DTP3	85%	0.3%	5,876	BCG-DTP1-Meas1	88%	0.4%	5,654
Burkina Faso	2,279	251	42%	1.2%	317	BCG-DTP1-DTP3	49%	0.3%	1,407	BCG-DTP2-Meas1	53%	0.6%	810
Burundi	1,606	25	47%	0.9%	3,251	DTP1-DTP2-DTP3	47%	0.9%	3,251	DTP1-DTP3-Meas1	53%	1.2%	2,865
Cabo Verde	4	1	58%	1.3%	262	BCG-DTP1-DTP2	71%	0.3%	1,214	BCG-DTP1-Meas1	74%	0.4%	1,151
Cambodia	212	336	38%	0.3%	79	BCG-DTP1-DTP3	39%	0.1%	259	BCG-DTP3-Meas1	47%	0.2%	171
Cameroon	2,967	99	44%	0.8%	1,598	DTP1-DTP2-DTP3	44%	0.8%	1,598	DTP1-DTP2-Meas1	50%	1.1%	1,318
Central African Republic	928	67	30%	0.6%	663	BCG-DTP1-DTP2	38%	0.2%	2,160	BCG-DTP1-DTP3	40%	0.3%	1,780
Chad	4,309	260	16%	0.4%	746	BCG-DTP1-DTP3	25%	0.3%	1,266	BCG-DTP1-Meas1	31%	0.7%	775
China	1,384	414	26%	0.3%	304	BCG-DTP1-DTP3	73%	0.2%	978	BCG-DTP1-Meas1	77%	0.3%	908

Colombia	152	26	61%	0.9%	410	BCG-DTP1-DTP2	69%	0.2%	2,279	BCG-DTP1-DTP3	71%	0.2%	2,328
Comoros	39	1	43%	0.9%	1,241	BCG-DTP1-DTP3	46%	0.2%	6,246	DTP1-DTP2-Meas1	51%	1.2%	1,113
Congo	252	32	35%	1.0%	266	BCG-DTP1-DTP3	43%	0.3%	1,113	BCG-DTP2-Meas1	46%	0.5%	681
Costa Rica	2	0	81%	0.9%	2,471	DTP1-DTP2-DTP3	81%	0.9%	2,471	DTP1-DTP2-Meas1	85%	1.0%	2,453
Côte d'Ivoire	2,477	195	42%	0.9%	586	DTP1-DTP2-DTP3	42%	0.9%	586	DTP1-DTP2-Meas1	51%	1.4%	450
Croatia	0	0	70%	0.8%	421	BCG-DTP1-DTP3	88%	0.3%	1,257	BCG-DTP1-Meas1	91%	0.4%	1,215
Cuba	3	0	71%	0.9%	742	BCG-DTP1-DTP3	89%	0.3%	2,843	BCG-DTP1-Meas1	92%	0.3%	2,644
DR Congo	12,377	1,112	38%	0.7%	579	BCG-DTP1-DTP3	40%	0.2%	2,277	DTP1-DTP3-Meas1	46%	1.2%	421
Djibouti	26	4	39%	0.9%	304	BCG-DTP1-DTP3	45%	0.3%	1,064	BCG-DTP2-Meas1	48%	0.5%	651
Dominican Republic	74	9	17%	0.2%	790	BCG-DTP1-DTP3	60%	0.2%	2,784	BCG-DTP1-DTP2	70%	0.2%	2,756
Ecuador	95	23	48%	0.7%	283	BCG-DTP1-DTP2	64%	0.2%	1,103	BCG-DTP1-Meas1	66%	0.3%	1,017
Egypt	1,095	98	70%	0.7%	1,066	BCG-DTP1-DTP3	77%	0.0%	123,972	BCG-DTP1-DTP3	77%	0.0%	51,557
El Salvador	50	5	69%	0.9%	809	BCG-DTP1-DTP3	75%	0.2%	5,273	BCG-DTP1-Meas1	76%	0.2%	5,327
Equatorial Guinea	42	6	11%	0.3%	294	BCG-DTP1-DTP3	18%	0.1%	1,213	BCG-DTP1-Meas1	19%	0.1%	1,067
Eritrea	269	83	28%	0.9%	97	BCG-DTP1-DTP3	31%	0.3%	378	DTP1-DTP3-Meas1	40%	1.4%	93
Ethiopia	5,130	1,280	22%	0.6%	153	DTP1-DTP2-DTP3	22%	0.6%	153	DTP1-DTP2-Meas1	38%	1.3%	117
Fiji	7	0	65%	0.3%	3,228	BCG-DTP1-DTP3	74%	0.1%	8,234	BCG-DTP1-Meas1	77%	0.2%	7,607
Gabon	57	7	33%	0.8%	348	BCG-DTP1-DTP3	41%	0.3%	1,268	BCG-DTP2-Meas1	45%	0.5%	760
Gambia	130	15	33%	1.3%	231	BCG-DTP1-DTP3	41%	0.4%	854	BCG-DTP2-Meas1	50%	0.7%	622
Georgia	2	0	70%	0.8%	2,157	BCG-DTP1-DTP3	86%	0.4%	6,049	BCG-DTP1-Meas1	90%	0.4%	5,954
Ghana	1,436	90	44%	0.5%	1,562	BCG-DTP1-DTP3	47%	0.1%	10,248	BCG-DTP2-Meas1	51%	0.3%	2,727
Grenada	0	0	73%	0.7%	2,906	DTP1-DTP2-DTP3	73%	0.7%	2,906	DTP1-DTP2-Meas1	85%	1.0%	2,536
Guatemala	349	83	33%	0.9%	157	BCG-DTP1-DTP2	38%	0.3%	612	DTP1-DTP2-Meas1	44%	1.3%	146
Guinea	1,097	111	24%	0.5%	438	BCG-DTP1-DTP3	33%	0.2%	1,498	BCG-DTP2-Meas1	35%	0.4%	921
Guinea-Bissau	197	17	37%	1.0%	448	BCG-DTP1-DTP3	42%	0.3%	1,400	BCG-DTP2-Meas1	48%	0.8%	724
Guyana	11	3	42%	1.0%	155	BCG-DTP2-DTP3	46%	0.4%	381	BCG-DTP2-Meas1	51%	0.5%	403
Haiti	375	50	25%	0.4%	441	BCG-DTP1-DTP2	33%	0.3%	885	BCG-DTP1-DTP3	39%	0.5%	554
Honduras	103	34	48%	1.0%	145	BCG-DTP2-DTP3	48%	0.4%	348	BCG-DTP1-DTP3	51%	0.2%	798
India	25,839	12,827	31%	0.4%	141	BCG-DTP2-DTP3	34%	0.3%	225	DTP1-DTP3-Meas1	40%	0.9%	92
Indonesia	3,000	1,696	27%	0.9%	51	BCG-DTP2-DTP3	28%	0.6%	85	DTP1-DTP2-Meas1	40%	1.4%	49
Iran	213	20	59%	1.3%	486	BCG-DTP1-DTP2	74%	0.4%	2,021	BCG-DTP1-Meas1	77%	0.5%	1,861
Iraq	669	411	29%	1.0%	49	BCG-DTP1-DTP2	42%	0.3%	218	BCG-DTP1-DTP3	43%	0.4%	198
Jamaica	3	1	64%	0.7%	380	BCG-DTP1-DTP3	74%	0.2%	1,336	BCG-DTP1-DTP3	77%	0.3%	1,212
Jordan	25	5	26%	0.7%	178	BCG-DTP1-DTP3	75%	0.6%	649	BCG-DTP1-DTP3	77%	0.6%	614
Kazakhstan	46	5	55%	0.8%	718	BCG-DTP2-DTP3	73%	0.3%	2,167	DTP1-DTP2-DTP3	76%	1.3%	599
Kenya	1,986	110	43%	0.4%	1,880	DTP1-DTP2-DTP3	43%	0.4%	1,880	DTP1-DTP3-Meas1	50%	0.7%	1,245
Kiribati	4	3	32%	0.2%	180	BCG-DTP1-DTP3	36%	0.1%	463	DTP1-DTP3-Meas1	41%	0.4%	155
Kyrgyzstan	45	3	64%	0.9%	1,049	BCG-DTP1-DTP3	75%	0.3%	4,372	BCG-DTP1-Meas1	76%	0.3%	4,454
Lao PDR	431	146	23%	0.2%	292	BCG-DTP2-DTP3	27%	0.2%	436	DTP1-DTP2-Meas1	43%	0.5%	233
Lebanon	5	0	60%	1.2%	592	DTP1-DTP2-DTP3	60%	1.2%	592	DTP1-DTP2-Meas1	75%	1.8%	504
Lesotho	187	19	48%	0.8%	553	BCG-DTP1-DTP3	48%	0.2%	2,969	DTP1-DTP3-Meas1	54%	1.1%	491
Liberia	443	42	32%	0.7%	473	BCG-DTP1-DTP3	34%	0.2%	1,848	DTP1-DTP2-Meas1	38%	1.0%	413
Libya	8	44	40%	1.3%	5	BCG-DTP1-DTP2	50%	0.4%	22	BCG-DTP1-DTP3	54%	0.5%	21
Madagascar	1,696	371	26%	0.6%	195	BCG-DTP1-DTP3	31%	0.3%	510	DTP1-DTP2-Meas1	40%	1.4%	126
Malawi	1,556	46	49%	0.9%	1,927	BCG-DTP1-DTP3	50%	0.2%	9,908	DTP1-DTP2-Meas1	52%	0.9%	1,895

Malaysia	17	0	71%	0.9%	22,079	BCG-DTP1-DTP3	89%	0.3%	87,740	BCG-DTP1-Meas1	92%	0.3%	78,643
Maldives	0	0	71%	1.0%	1,041	BCG-DTP1-DTP3	89%	0.3%	4,486	BCG-DTP1-Meas1	92%	0.4%	4,034
Mali	2,438	179	28%	0.6%	611	BCG-DTP1-DTP3	38%	0.4%	1,274	BCG-DTP1-Meas1	44%	0.7%	864
Marshall Islands	1	0	36%	0.4%	9,620	BCG-DTP1-DTP2	45%	0.2%	27,569	BCG-DTP1-DTP3	49%	0.2%	27,358
Mauritania	400	87	31%	0.7%	214	BCG-DTP1-DTP3	40%	0.3%	582	BCG-DTP2-Meas1	43%	0.5%	364
Mauritius	1	1	59%	0.9%	123	BCG-DTP1-DTP3	65%	0.5%	258	BCG-DTP2-Meas1	72%	0.8%	167
Mexico	626	142	58%	0.8%	332	BCG-DTP1-DTP2	75%	0.2%	1,465	BCG-DTP1-Meas1	76%	0.2%	1,481
Micronesia (FSO)	1	2	36%	0.4%	42	DTP1-DTP2-DTP3	36%	0.4%	42	DTP1-DTP2-Meas1	45%	0.5%	39
Mongolia	9	3	77%	0.4%	649	BCG-DTP1-DTP3	79%	0.1%	2,723	BCG-DTP1-Meas1	81%	0.1%	2,768
Montenegro	0	0	67%	0.8%	468	BCG-DTP1-DTP2	79%	0.3%	1,455	DTP1-DTP2-Meas1	84%	1.2%	423
Morocco	604	246	38%	1.3%	72	BCG-DTP1-DTP3	48%	0.7%	166	BCG-DTP2-Meas1	52%	1.0%	122
Mozambique	2,160	430	32%	0.9%	174	BCG-DTP1-DTP3	45%	0.4%	613	BCG-DTP1-Meas1	49%	0.4%	562
Myanmar	818	311	34%	1.0%	93	BCG-DTP2-DTP3	41%	0.5%	203	DTP1-DTP2-Meas1	48%	1.5%	87
Namibia	108	11	42%	0.7%	544	DTP1-DTP2-DTP3	42%	0.7%	544	DTP1-DTP3-Meas1	49%	1.0%	477
Nepal	258	188	39%	0.6%	86	BCG-DTP1-DTP3	42%	0.2%	330	BCG-DTP2-Meas1	46%	0.5%	131
Nicaragua	53	0	59%	0.9%	7,651	BCG-DTP1-DTP2	74%	0.3%	29,781	BCG-DTP1-DTP3	77%	0.3%	28,282
Niger	4,557	485	36%	0.8%	414	BCG-DTP1-DTP3	37%	0.2%	1,884	DTP1-DTP2-Meas1	43%	1.1%	357
Nigeria	35,129	518	23%	1.1%	1,434	BCG-DTP1-DTP3	27%	0.8%	2,259	BCG-DTP2-Meas1	32%	1.0%	2,081
North Korea	151	17	64%	0.7%	785	BCG-DTP1-DTP3	73%	0.2%	2,864	BCG-DTP1-Meas1	76%	0.3%	2,468
Pakistan	7,694	1,765	29%	0.6%	221	BCG-DTP1-DTP3	38%	0.3%	605	BCG-DTP1-DTP3	41%	0.5%	373
Panama	25	1	57%	0.9%	1,543	BCG-DTP1-DTP2	74%	0.3%	5,961	BCG-DTP1-Meas1	76%	0.3%	5,514
Papua New Guinea	191	199	34%	0.2%	138	BCG-DTP1-DTP3	36%	0.1%	327	DTP1-DTP2-Meas1	41%	0.3%	133
Paraguay	41	27	38%	0.9%	67	BCG-DTP1-DTP2	46%	0.3%	245	BCG-DTP1-DTP3	51%	0.3%	243
Peru	144	91	43%	1.0%	70	DTP1-DTP2-DTP3	43%	1.0%	70	DTP1-DTP2-Meas1	49%	1.1%	72
Philippines	1,893	2,213	28%	0.2%	105	BCG-DTP1-DTP3	33%	0.1%	259	BCG-DTP1-Meas1	38%	0.1%	264
Republic of Moldova	1	1	50%	0.7%	66	BCG-DTP1-DTP3	72%	0.3%	267	BCG-DTP1-DTP3	73%	0.3%	270
Romania	8	0	68%	0.8%	2,638	BCG-DTP1-DTP2	88%	0.4%	7,883	BCG-DTP1-DTP3	90%	0.4%	7,576
Russian Federation	54	3	31%	0.5%	1,275	BCG-DTP1-DTP3	86%	0.5%	3,699	BCG-DTP1-Meas1	89%	0.5%	3,619
Rwanda	700	34	40%	0.7%	1,152	BCG-DTP1-DTP3	41%	0.1%	6,936	DTP1-DTP3-Meas1	49%	1.0%	1,022
Saint Lucia	0	0	59%	0.9%	373	BCG-DTP1-DTP3	67%	0.6%	678	BCG-DTP1-DTP3	76%	0.7%	584
Saint Vincent & the Gr.	0	0	59%	0.9%	682	BCG-DTP1-DTP2	74%	0.3%	2,633	BCG-DTP1-DTP3	77%	0.3%	2,448
Samoa	0	1	57%	0.3%	63	BCG-DTP1-DTP3	62%	0.1%	173	DTP1-DTP2-Meas1	64%	0.4%	55
Sao Tome and Principe	7	0	44%	0.8%	1,134	BCG-DTP1-DTP3	44%	0.1%	8,486	DTP1-DTP3-Meas1	52%	1.0%	1,038
Senegal	876	154	36%	1.0%	211	BCG-DTP1-DTP3	42%	0.3%	738	BCG-DTP2-Meas1	45%	0.7%	384
Serbia	1	0	72%	0.9%	816	BCG-DTP1-DTP3	90%	0.3%	3,379	BCG-DTP1-Meas1	91%	0.3%	3,434
Sierra Leone	1,263	68	39%	0.8%	868	BCG-DTP1-DTP3	42%	0.2%	3,803	DTP1-DTP2-Meas1	47%	1.2%	727
Solomon Islands	9	16	40%	0.3%	73	BCG-DTP1-DTP3	44%	0.1%	188	DTP1-DTP3-Meas1	50%	0.5%	63
Somalia	2,432	362	22%	0.5%	283	DTP1-DTP2-DTP3	22%	0.5%	283	DTP1-DTP2-Meas1	27%	0.7%	252
South Africa	1,734	127	41%	0.8%	698	DTP1-DTP2-DTP3	41%	0.8%	698	DTP1-DTP2-Meas1	46%	1.1%	549
South Sudan	937	522	16%	0.4%	80	BCG-DTP1-DTP3	19%	0.1%	312	BCG-DTP1-DTP3	20%	0.1%	269
Sri Lanka	11	1	73%	1.0%	992	BCG-DTP1-DTP3	90%	0.3%	4,194	BCG-DTP1-Meas1	93%	0.3%	3,784
Sudan	2,726	1,200	40%	0.9%	103	DTP1-DTP2-DTP3	40%	0.9%	103	DTP1-DTP2-Meas1	50%	1.3%	86
Suriname	1	0	35%	0.4%	239	DTP1-DTP2-DTP3	35%	0.4%	239	DTP1-DTP2-Meas1	63%	1.1%	173
Swaziland	77	7	47%	0.6%	824	BCG-DTP1-DTP3	49%	0.1%	6,148	BCG-DTP2-Meas1	52%	0.3%	2,011
Syrian Arab Republic	80	136	36%	0.8%	28	BCG-DTP1-DTP2	48%	0.3%	114	BCG-DTP1-Meas1	50%	0.3%	103

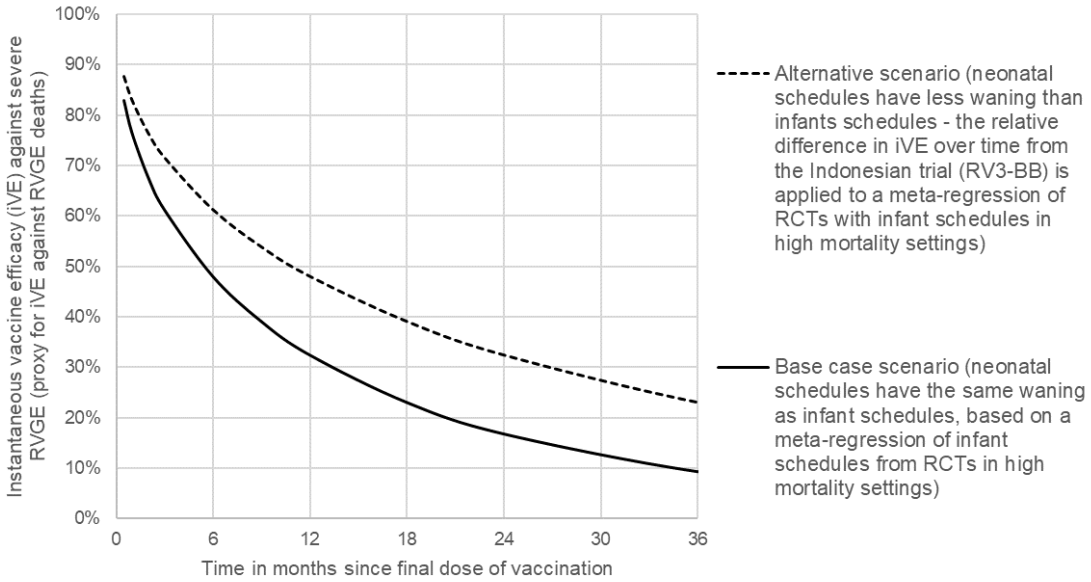
Tajikistan	236	63	34%	0.7%	175	BCG-DTP1-DTP3	47%	0.4%	474	DTP1-DTP3-Meas1	53%	1.2%	163
Tanzania	2,880	343	49%	0.6%	670	DTP1-DTP2-DTP3	49%	0.6%	670	DTP1-DTP3-Meas1	57%	1.0%	475
TFYR Macedonia	1	0	37%	0.6%	1,443	BCG-DTP1-DTP2	83%	0.4%	4,348	BCG-DTP1-Meas1	87%	0.4%	4,273
Thailand	65	1	71%	1.7%	3,362	BCG-DTP1-DTP3	89%	0.5%	13,381	BCG-DTP1-Meas1	92%	0.6%	12,559
Timor-Leste	90	14	30%	0.5%	342	BCG-DTP1-DTP3	35%	0.3%	855	BCG-DTP2-Meas1	42%	0.6%	475
Togo	609	27	43%	0.9%	1,150	DTP1-DTP2-DTP3	43%	0.9%	1,150	DTP1-DTP2-Meas1	48%	0.9%	1,151
Tonga	0	1	56%	0.3%	64	BCG-DTP1-DTP3	60%	0.1%	172	DTP1-DTP2-Meas1	65%	0.4%	55
Tunisia	15	3	70%	2.0%	209	BCG-DTP1-DTP3	77%	0.4%	1,111	BCG-DTP1-DTP3	78%	0.4%	1,127
Turkey	53	21	58%	0.9%	165	BCG-DTP1-DTP3	65%	0.5%	300	DTP1-DTP2-Meas1	73%	1.2%	150
Turkmenistan	89	38	37%	0.9%	94	BCG-DTP1-DTP3	46%	0.4%	259	BCG-DTP2-Meas1	51%	0.5%	222
Tuvalu	0	0	37%	0.3%	746	BCG-DTP1-DTP3	42%	0.1%	1,887	DTP1-DTP3-Meas1	49%	0.5%	656
Uganda	2,478	203	35%	0.9%	484	BCG-DTP1-DTP3	39%	0.3%	1,483	BCG-DTP2-Meas1	47%	0.7%	883
Ukraine	13	1	20%	0.2%	1,643	BCG-DTP1-DTP2	35%	0.1%	5,762	DTP1-DTP2-Meas1	46%	0.8%	1,245
Uzbekistan	181	135	33%	1.3%	34	BCG-DTP1-DTP3	41%	0.6%	96	DTP1-DTP3-Meas1	49%	1.7%	39
Vanuatu	5	7	30%	0.2%	103	BCG-DTP1-DTP3	32%	0.1%	265	DTP1-DTP3-Meas1	35%	0.3%	86
Venezuela	273	36	58%	1.1%	398	BCG-DTP1-DTP2	75%	0.3%	1,811	BCG-DTP1-DTP3	77%	0.4%	1,585
Viet Nam	365	854	29%	0.1%	164	BCG-DTP1-DTP3	64%	0.1%	276	BCG-DTP1-DTP2	73%	0.1%	221
Yemen	1,434	289	29%	0.7%	212	DTP1-DTP2-DTP3	29%	0.7%	212	DTP1-DTP2-Meas1	39%	1.2%	157
Zambia	1,235	68	45%	0.6%	1,265	BCG-DTP1-DTP3	49%	0.2%	4,695	BCG-DTP1-DTP3	53%	0.3%	3,236
Zimbabwe	1,295	75	44%	0.7%	1,122	DTP1-DTP2-DTP3	44%	0.7%	1,122	DTP1-DTP3-Meas1	50%	0.9%	987

Appendix Figure 1. Relative risk of intussusception reported in studies using the SCCS methodology, 1-7 days after administration of the first dose of Rotarix or RotaTeq



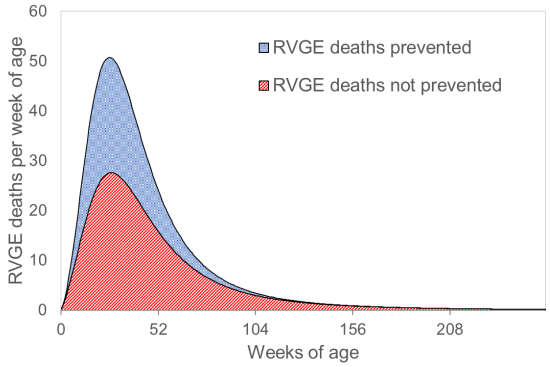
Black point represent each study observation and their respective 95% confidence intervals. Blue lines represent the pooled estimate (and 95% confidence intervals) calculated in a global random effects meta-analysis. The red line represents the maximum likelihood fit for the relationship between under-five mortality and relative risk, and suggests no risk in countries with an under-five mortality rate of 40 or more per 1000 live births. This would exclude any risk in ~65 high mortality countries.

Appendix Figure 2. Estimated instantaneous vaccine efficacy (iVE) of live oral rotavirus vaccines in high mortality settings by duration of follow-up: alternative scenarios of waning after 2/3 doses for neonatal and infant schedules

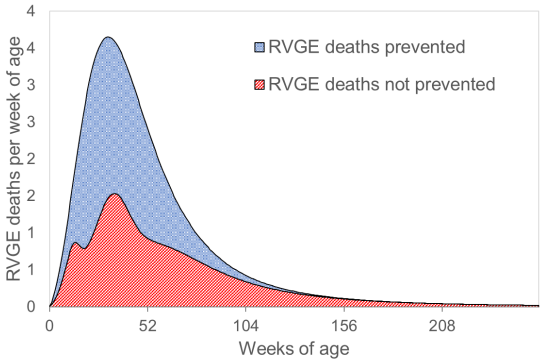


Appendix Figure 3. Graphical examples of age-unrestricted rotavirus vaccination schedules predicted to have the highest impact on RVGE deaths aged <5 years, compared to no vaccination

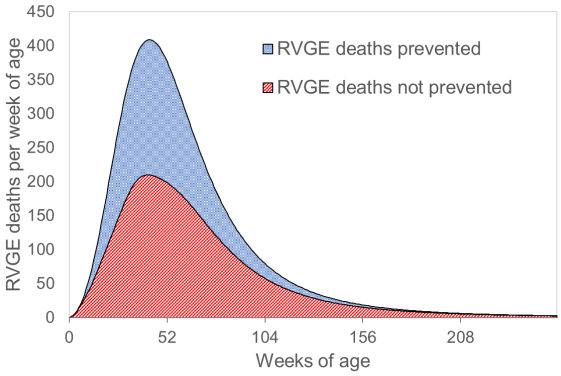
Afghanistan, RV with BCG+DTP1+DTP3



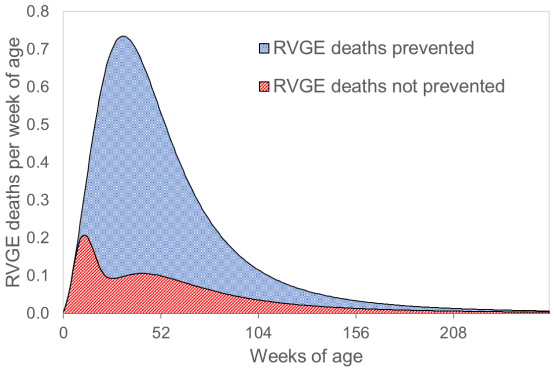
Algeria, RV with BCG+DTP1+Meas1



India, RV with DTP1+DTP3+Meas1



Kazakhstan, RV with DTP1+DTP2+DTP3



List of references (Chapter 9)

1. Burnett E, Jonesteller CL, Tate JE, Yen C, Parashar UD. Global Impact of Rotavirus Vaccination on Childhood Hospitalizations and Mortality From Diarrhea. J Infect Dis. 2017;215(11):1666-72.

2. Stowe J, Andrews N, Ladhani S, Miller E. The risk of intussusception following monovalent rotavirus vaccination in England: A self-controlled case-series evaluation. Vaccine. 2016;34(32):3684-9.

3. Yih WK, Lieu TA, Kulldorff M, Martin D, McMahill-Walraven CN, Platt R, et al. Intussusception risk after rotavirus vaccination in U.S. infants. N Engl J Med. 2014;370(6):503-12.

4. Patel MM, Clark AD, Sanderson CF, Tate J, Parashar UD. Removing the age restrictions for rotavirus vaccination: a benefit-risk modeling analysis. PLoS Med. 2012;9(10):e1001330.

5. WHO. WHO position paper – January 2013. Rotavirus. Weekly Epidemiological Review (WER) Available at: http://wwwwhoint/wer/2013/wer8805/en/ [Accessed 7 Feb 2018]. 2013;88(5):49–64.

6. Clark A, Black R, Tate J, Roose A, Kotloff K, Lam D, et al. Estimating global, regional and national rotavirus deaths in children aged <5 years: Current approaches, new analyses and proposed improvements. PLoS One. 2017;12(9):e0183392.

7. Clark A, Van Zandvoort K, Flasche S, Sanderson C, Bines J, Tate J, et al. Estimating instantaneous efficacy of live oral rotavirus vaccines by duration of follow-up (forthcoming).

8. Hasso-Agopsowicz M. LC, Lopman B., Sanderson C., Cohen A., Global Rotavirus Surveillance Network, Tate J., Riveros X., Henao-Restrepo AM., Clark, A. Age distribution of rotavirus disease in children aged <5 years before the introduction of rotavirus vaccination (forthcoming).

9. Clark A. KM, Hasso-Agopsowicz M., Stockdale L., Parashar U., Tate J. Global review of the incidence, age distribution and case fatality of intussusception hospital admissions among children aged < 5 years, before the introduction of rotavirus vaccination (forthcoming).

10. Response. C. Unpublished update to: Soares-Weiser K et al. Rotavirus vaccine schedules: a systematic review of safety and efficacy from RCTs and observational studies of childhood schedules using RV1 and RV5 vaccines . Report to WHO/Initiative for Vaccine Research, 2012. Available from http://www.who.int/immunization/sage/meetings/2012/april/Soares_K_et_ al_SAGE_April_rotavirus.pdf [accessed January 2013].

11. Tate JE, Mwenda JM, Armah G, Jani B, Omore R, Ademe A, et al. Evaluation of Intussusception after Monovalent Rotavirus Vaccination in Africa. N Engl J Med. 2018;378(16):1521-8.

12. Bines JE, At Thobari J, Satria CD, Handley A, Watts E, Cowley D, et al. Human Neonatal Rotavirus Vaccine (RV3-BB) to Target Rotavirus from Birth. N Engl J Med. 2018;378(8):719-30.

13. Zaman K, Fleming JA, Victor JC, Yunus M, Bari TI, Azim T, et al. Noninterference of Rotavirus Vaccine With Measles-Rubella Vaccine at 9 Months of Age and Improvements in Antirotavirus Immunity: A Randomized Trial. J Infect Dis. 2016;213(11):1686-93.

14. Bank W. World Bank list of economies (June 2017). Available at: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups [Accessed 7th February 2018].

15. UNIVAC (Universal vaccine decision support model). Available at: www.provac-toolkit.com [Accessed 7th Feb 2018].

16. Immergluck LC, Parker TC, Jain S, Laghaie E, Spandorfer P, Jerris RC, et al. Sustained Effectiveness of Monovalent and Pentavalent Rotavirus Vaccines in Children. J Pediatr. 2016;172:116-20 e1.

17. Jonesteller CL, Burnett E, Yen C, Tate JE, Parashar UD. Effectiveness of Rotavirus Vaccination: A Systematic Review of the First Decade of Global Postlicensure Data, 2006-2016. Clin Infect Dis. 2017;65(5):840-50.

18. Carlin JB, Macartney KK, Lee KJ, Quinn HE, Buttery J, Lopert R, et al. Intussusception risk and disease prevention associated with rotavirus vaccines in Australia's National Immunization Program. Clin Infect Dis. 2013;57(10):1427-34.

19. UNWPP. The 2017 Revision of the United Nations World Population Prospects. Available at: https://esa.un.org/unpd/wpp/. [Accessed 7th February 2018].

20. Tate J. World Health Organization / Centers for Disease Control. Estimates of rotavirus deaths aged <5 years in the year 2015. Unpublished. 2018.

21. Troeger C, Khalil IA, Rao PC, Cao S, Blacker BF, Ahmed T, et al. Rotavirus Vaccination and the Global Burden of Rotavirus Diarrhea Among Children Younger Than 5 Years. JAMA Pediatr. 2018.

22. WHO/UNICEF. WHO/UNICEF Estimates of National Immunization Coverage (WUENIC). Version 15th July 2017. Available at: http://www.who.int/immunization/monitoring_surveillance/routine/coverage/en/index4.html [Accessed 7th Feb 2018]

23. Clark A, Sanderson C. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. Lancet. 2009;373(9674):1543-9.

24. WHO. Immunization schedule data (July 2017 version). Available at: www.who.int/immunization/monitoring_surveillance/data/schedule_data.xls [Accessed 12th December 2017].

25. Clark A, Jit M, Andrews N, Atchison C, Edmunds WJ, Sanderson C. Evaluating the potential risks and benefits of infant rotavirus vaccination in England. Vaccine. 2014;32(29):3604-10.

26. Pruksananonda P, Athirakul K, Worawattanakul M, Varavithya W, Pisithpun A, Kitayaporn D, et al. Intussusception in a private tertiary-care hospital, Bangkok, Thailand: a case series. Southeast Asian J Trop Med Public Health. 2007;38(2):339-42.

27. Leino T, Ollgren J, Stromberg N, Elonsalo U. Evaluation of the Intussusception Risk after Pentavalent Rotavirus Vaccination in Finnish Infants. PLoS One. 2016;11(3):e0144812.

28. Ouma PO, Maina J, Thuranira PN, Macharia PM, Alegana VA, English M, et al. Access to emergency hospital care provided by the public sector in sub-Saharan Africa in 2015: a geocoded inventory and spatial analysis. Lancet Glob Health. 2018;6(3):e342-e50.

29. WHO. List of Member States by WHO Region and Mortality Stratum. Cost effectiveness and strategic planning (WHO-CHOICE). http://www.who.int/choice/demography/mortality_strata/en/ [Accessed March 2018]

30. Murphy TV, Gargiullo PM, Massoudi MS, Nelson DB, Jumaan AO, Okoro CA, et al. Intussusception among infants given an oral rotavirus vaccine. N Engl J Med. 2001;344(8):564-72.

31. 2017 G. Digestive disorders aged <5 years in the year 2015. Global Burden of Disease (GBD) Project 2017. Available at: http://ghdx.healthdata.org/gbd-results-tool [Accessed 14th Feb 2018].

32. Mpabalwani EM, Mwenda JM, Tate JE, Parashar UD. Review of Naturally Occurring Intussusception in Young Children in the WHO African Region prior to the Era of Rotavirus Vaccine Utilization in the Expanded Programme of Immunization. J Trop Pediatr. 2017;63(3):221-8.

33. Burnett E, Lopman BA, Parashar UD. Potential for a booster dose of rotavirus vaccine to further reduce diarrhea mortality. Vaccine. 2017;35(51):7198-203.

34. Haidara FC, Tapia MD, Sow SO, Doumbia M, Coulibaly F, Diallo F, et al. Evaluation of a Booster Dose of Pentavalent Rotavirus Vaccine Coadministered With Measles, Yellow Fever, and Meningitis A Vaccines in 9-Month-Old Malian Infants. J Infect Dis. 2018;218(4):606-13.

35. Simonsen L, Viboud C, Elixhauser A, Taylor RJ, Kapikian AZ. More on RotaShield and intussusception: the role of age at the time of vaccination. J Infect Dis. 2005;192 Suppl 1:S36-43.

36. Park J, Goldstein J, Haran M, Ferrari M. An ensemble approach to predicting the impact of vaccination on rotavirus disease in Niger. Vaccine. 2017;35(43):5835-41.

37. Rose J, Homa L, Meropol SB, Debanne SM, Bielefeld R, Hoyen C, et al. Health impact and cost-effectiveness of a domestically-produced rotavirus vaccine in India: A model based analysis. PLoS One. 2017;12(11):e0187446.

38. Yen C, Armero Guardado JA, Alberto P, Rodriguez Araujo DS, Mena C, Cuellar E, et al. Decline in rotavirus hospitalizations and health care visits for childhood diarrhea following rotavirus vaccination in El Salvador. Pediatr Infect Dis J. 2011;30(1 Suppl):S6-S10.

39. Ngabo F, Tate JE, Gatera M, Rugambwa C, Donnen P, Lepage P, et al. Effect of pentavalent rotavirus vaccine introduction on hospital admissions for diarrhoea and rotavirus in children in Rwanda: a time-series analysis. Lancet Glob Health. 2016;4(2):e129-36.

40. Bennett A, Pollock L, Jere KC, Pitzer VE, Parashar U, Tate JE, et al. Direct and possible indirect effects of vaccination on rotavirus hospitalisations among children in Malawi four years after programmatic introduction. Vaccine. 2018.

41. Groome MJ, Zell ER, Solomon F, Nzenze S, Parashar UD, Izu A, et al. Temporal Association of Rotavirus Vaccine Introduction and Reduction in All-Cause Childhood Diarrheal Hospitalizations in South Africa. Clin Infect Dis. 2016;62 Suppl 2:S188-95.

42. Mpabalwani EM, Simwaka CJ, Mwenda JM, Mubanga CP, Monze M, Matapo B, et al. Impact of Rotavirus Vaccination on Diarrheal Hospitalizations in Children Aged <5 Years in Lusaka, Zambia. Clin Infect Dis. 2016;62 Suppl 2:S183-7.

43. Yung CF, Chan SP, Soh S, Tan A, Thoon KC. Intussusception and Monovalent Rotavirus Vaccination in Singapore: Self-Controlled Case Series and Risk-Benefit Study. J Pediatr. 2015;167(1):163-8 e1.

44. Haber P, Parashar UD, Haber M, DeStefano F. Intussusception after monovalent rotavirus vaccine-United States, Vaccine Adverse Event Reporting System (VAERS), 2008-2014. Vaccine. 2015;33(38):4873-7.

45. Escolano S, Hill C, Tubert-Bitter P. Intussusception risk after RotaTeq vaccination: evaluation from worldwide spontaneous reporting data using a self-controlled case series approach. Vaccine. 2015;33(8):1017-20.

46. Patel MM, Lopez-Collada VR, Bulhoes MM, De Oliveira LH, Bautista Marquez A, Flannery B, et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. N Engl J Med. 2011;364(24):2283-92.

47. Velazquez FR, Colindres RE, Grajales C, Hernandez MT, Mercadillo MG, Torres FJ, et al. Postmarketing surveillance of intussusception following mass introduction of the attenuated human rotavirus vaccine in Mexico. Pediatr Infect Dis J. 2012;31(7):736-44.

48. Groome Mea. Rotavirus vaccine intussusception risk in South Africa using the self controlled case series method.

49. Patel MM, Patzi M, Pastor D, Nina A, Roca Y, Alvarez L, et al. Effectiveness of monovalent rotavirus vaccine in Bolivia: case-control study. BMJ. 2013;346:f3726.

50. Pringle KD, Patzi M, Tate JE, Iniguez Rojas V, Patel M, Inchauste Jordan L, et al. Sustained Effectiveness of Rotavirus Vaccine Against Very Severe Rotavirus Disease Through the Second Year of Life, Bolivia 2013-2014. Clin Infect Dis. 2016;62 Suppl 2:S115-20.

51. Gastanaduy PA, Steenhoff AP, Mokomane M, Esona MD, Bowen MD, Jibril H, et al. Effectiveness of Monovalent Rotavirus Vaccine After Programmatic Implementation in Botswana: A Multisite Prospective Case-Control Study. Clin Infect Dis. 2016;62 Suppl 2:S161-7.

52. Ichihara MY, Rodrigues LC, Teles Santos CA, Teixeira Mda G, De Jesus SR, Alvim De Matos SM, et al. Effectiveness of rotavirus vaccine against hospitalized rotavirus diarrhea: A case-control study. Vaccine. 2014;32(23):2740-7.

53. de Palma O, Cruz L, Ramos H, de Baires A, Villatoro N, Pastor D, et al. Effectiveness of rotavirus vaccination against childhood diarrhoea in El Salvador: case-control study. BMJ. 2010;340:c2825.

54. Gheorghita S, Birca L, Donos A, Wasley A, Birca I, Cojocaru R, et al. Impact of Rotavirus Vaccine Introduction and Vaccine Effectiveness in the Republic of Moldova. Clin Infect Dis. 2016;62 Suppl 2:S140-6.

55. Patel M, Pedreira C, De Oliveira LH, Tate J, Orozco M, Mercado J, et al. Association between pentavalent rotavirus vaccine and severe rotavirus diarrhea among children in Nicaragua. JAMA. 2009;301(21):2243-51.

56. Groome MJ, Page N, Cortese MM, Moyes J, Zar HJ, Kapongo CN, et al. Effectiveness of monovalent human rotavirus vaccine against admission to hospital for acute rotavirus diarrhoea in South African children: a case-control study. Lancet Infect Dis. 2014;14(11):1096-104.

57. Beres LK, Tate JE, Njobvu L, Chibwe B, Rudd C, Guffey MB, et al. A Preliminary Assessment of Rotavirus Vaccine Effectiveness in Zambia. Clin Infect Dis. 2016;62 Suppl 2:S175-82.

58. StataCorp. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC. 2017.

10.0 Chapter 10: Reflections on thesis research

In this chapter the overall results of the thesis and its implications for informing national and global decision-making are considered. This is more comprehensive than the discussion section of the benefit-risk paper (Chapter 9) but there is considerable overlap, and some of the content appears in both.

10.1 Estimation of rotavirus vaccine mortality benefits

This research has involved the review and development of new methods for estimating RVGE deaths and granular RVGE age distributions in children <5 years of age, in the absence of vaccination. It has also involved new methods for estimating the potential timeliness, efficacy and waning of rotavirus vaccination in different settings. Taken as a whole, this substantially updates and strengthens the evidence necessary for estimating the mortality reduction benefits of rotavirus vaccination in different LMICs.

For this analysis a transparent static cohort model was used to estimate the potential direct effects of rotavirus vaccination by week of age. Herd effects were excluded, and this could have led to under-estimates of vaccine impact in some settings. Including herd effects would make benefit-risk ratios more favourable, but it would have been very challenging to obtain robust estimates of the scale and duration of these effects in each of the 135 LMICs. Two important birth cohort studies from India (1) and Mexico (2) have provided estimates of the level of protection acquired from successive natural rotavirus infections, and these data could have been extrapolated to a wider number of countries. However, this may not have been appropriate, and there are other important uncertainties e.g. about the level and duration of vaccine protection against asymptomatic natural infections. Transmission dynamic models calibrated to data from Niger (3) and India (4) have suggested a very small contribution from indirect effects, and while short-term herd effects have been observed in post-introduction studies in El Salvador (5), Ghana (6), Moldova (6) and Rwanda (7), no substantial herd effects were observed in Malawi,(8), South Africa (9), Tanzania (6) or Zambia (10). The incremental value of including herd immunity effects in benefit-risk analysis is also limited given the highly positive benefit-risk ratios without including them. In the context of schedules, transmission dynamic models could have been used to explore the potential effects of different schedules on the age-specific incidence and severity of natural infections. This could provide some

validation (or raise important questions) about the schedules predicted to have the highest impact in different countries. However, this would ideally require data on social mixing and transmission patterns in very granular age groups <5 years of age. In the interim, our analysis provides a useful starting point for thinking about the schedules that might have advantages in different countries.

Not all children have the same risk of dying before their fifth birthday. For several reasons (nationality, wealth, education, nutrition etc.) some children are more vulnerable than others. The gross disparity in child mortality between rich and poor nations is well documented but there are very large differences within countries, which are masked by aggregated national mortality rates (11). In principle, if all children have equal access to timely and effective health care, then it follows that the most vulnerable groups will see the biggest improvements in health, and disparities in child mortality will reduce. In reality not all children have the same access to effective health care. Indeed, children at greatest risk of disease mortality are in many contexts the least likely to have access to preventative or curative health care. If the two are highly correlated (high risk and low access), the most vulnerable children will not be reached, and disparities will increase – the so called *inverse equity hypothesis* (12) or *inverse care law* (13): the most vulnerable in society benefit the least. Improvements in coverage may ultimately start to reach the most vulnerable groups leading to overall improvements in equity, but the evidence suggests this is not yet happening in many of the world's poorest countries (14). Most modelled estimates of health benefit, including the results of this analysis, assume that all children benefit equally from an intervention. Failure to account for differences in individual risk and individual protection could lead to inflated estimates of effective coverage, and thus health benefit, in the most vulnerable groups. Rheingans *et al* were the first to evaluate formally the inverse equity effect for a vaccine, using the example of rotavirus vaccination in 25 high mortality countries. For eight of the countries, the bias can be quantified by comparing estimates of deaths prevented based on disparities in risk/coverage with estimates based on nationally reported risk/coverage alone. In Bangladesh, DR Congo, Ethiopia, Kenya, Niger and Uganda the bias was less than 5%, but in India it was 8% and in Nigeria it was 20% (15). The major weakness of this analysis was that it was restricted to a single indicator of heterogeneity (wealth quintile), so the study is unlikely to represent the true extent of the bias. In reality, there is likely to be a wide range of correlated predictors of mortality and a similar set of predictors for coverage and timeliness of vaccination. Wealth may be just one part of the story; other factors, including nutrition, maternal education, access, rurality etc.,

are also likely to be important (16). An adjustment for inverse equity would have led to lower estimates of RVGE deaths prevented in this study, but equally could have led to lower estimates of intussusception deaths caused. This could be the case if the background incidence and case fatality risk of intussusception were much higher in children excluded from the vaccination programme, which seems likely. Vaccinated infants would then have a lower background incidence rate and case fatality risk than the average estimated for the entire cohort, leading to fewer vaccine-related intussusception deaths. Conversely, vaccine-related risks may be lower in infants with lower socioeconomic status. There is some support for this hypothesis given the relatively lower relative risks shown in high mortality settings compared to low mortality settings (Chapter 9, Appendix Figure 1).

A more general concern about estimates of rotavirus vaccine impact on mortality, is whether the rotavirus attributable fraction among GE hospital admissions is a reasonable proxy for rotavirus-attributable fraction among GE deaths. Our analysis of the various RVGE estimates methods suggests that acute water diarrhoea (with which rotavirus is primarily associated) may represent a lower proportion of GE deaths than GE admissions. Evidence is emerging on the impact of rotavirus vaccines on hospital admissions (17), but more research is needed to assess the impact of rotavirus vaccines on GE deaths in high mortality settings.

10.2 Estimation of rotavirus vaccine-related intussusception risks

This research has collected new data and developed new methods for estimating the incidence, age distribution, case fatality and vaccine-related relative risks of intussusception among children <5 years of age, in LMICs. This substantially updates the evidence necessary for estimating vaccine-related intussusception risks in different LMICs. In particular, our analysis highlights the inequity of outcomes for children in Africa, compared to children in the rest of the world. In Africa, more investment is needed to increase access to hospitals and equip those hospitals with the appropriate imaging technology and trained staff. This should be coupled with strategies to raise community awareness about the need for urgent treatment when children experience symptoms of intussusception. This would help to shift the primary form of diagnoses away from high-risk surgery towards lower-risk enema treatment.

This analysis may provide the first estimate of the background number of intussusception deaths in LMICs (~14,500). This estimate is highly uncertain because

it relies on fairly crude assumptions about access to healthcare and CFRs among children without access to hospitals. The Global Burden of Disease Project (GBD 2017) estimated 22,395 deaths globally due to paralytic ileus and intestinal obstruction, and 31,460 deaths for all digestive disorders combined, for children <5 years of age in the year 2015 (18). DTP1 coverage was used as a proxy for access to intussusception treatment because it may better represent care-seeking for very severe conditions than household survey indicators based on milder symptoms. A more pessimistic scenario, based on the proportion of children with timely (two-hour) access to public hospitals was influential (led to less favourable benefit-risk ratios), but this is probably too pessimistic as many intussusception cases in Africa are known to present to hospital more than two days after the onset of symptoms (19). In medium mortality countries, changes to access to care parameters led to large increases in the background intussusception mortality rate relative to the (often very low) pre-vaccination RVGE mortality rate. Had 100% access to treatment been assumed in medium mortality countries (as per the low and very low mortality stratum), then the benefit-risk ratios would have been far more favourable. Better estimates of intussusception treatment utilisation rates are needed.

A global pooled estimate of the relative risk of intussusception was used, but this may greatly over-estimate the risk in many LMICs. Only one study (a multi-country study in Africa (20)) has evaluated post-licensure risk of intussusception in a high mortality setting, and this found no elevated risk of intussusception. Had a gradient of risk been applied, consistent with under-five mortality, zero excess cases would have been predicted in many LMICs, including large countries such as India, Nigeria and Pakistan. More post-licensure estimates are needed to confirm the finding of no risk in high mortality settings. However, even with pessimistic risk assumptions, there was less than one excess intussusception case per 60,000 FVI for a standard schedule co-administered with DTP. This is far more favourable than the rate associated with RotaShield® (more than one case per 10,000 FVI), an early rotavirus vaccine that was withdrawn from the market following evidence of its link with intussusception (21).

Another important consideration in settings where an elevated risk has been documented, is whether rotavirus vaccination may simply be triggering intussusception events that would otherwise occur in the same children anyway at a later date (22).

10.3 Estimation of the benefit-risk ratio for rotavirus vaccines

My colleagues and I previously evaluated the 2010 birth cohort in 158 countries defined by WHO as in strata B, C, D or E. This classification, based on rates of all-cause child mortality in the year 1999, is now almost twenty years old.(23) This time we used the 2018 World Bank classification of LMICs. Compared to the previous analysis (24) far fewer RVGE deaths were averted for an equivalent age-unrestricted 3-dose schedule (DTP1+DTP2+DTP3). This is because of lower official estimates of the number of RVGE deaths without vaccination, mainly due to improved access to supportive care such as oral rehydration following acute gastroenteritis in LMICs, but also due to improved methods of RVGE mortality estimation (25). Estimates of excess intussusception deaths were also much lower because the median age of intussusception from recent estimates was higher (26), resulting in fewer background intussusception cases around the time of DTP1 vaccination. The new benefit-risk ratio for an age-unrestricted schedule co-administered with DTP (446:1), is more favourable than the previous estimate (371:1), with the benefits of rotavirus vaccine introduction still greatly exceeding the risk.

Other benefit-risk analyses in LMICs have reported ratios of 395:1 in Latin America (27) and 260:1 in Brazil and Mexico (28). Several benefit-risk analyses have also been published for high income countries. In England, my colleagues and I previously estimated that Rotarix® would cause 88 fewer RVGE deaths for every additional intussusception death (benefit-risk ratio 88:1)(29). The benefit-risk ratio for deaths was estimated to be 273:1 in France (30), 77:1 in the USA (31) and 366:1 in Japan (32). HICs were excluded from the analysis reported here because deaths from rotavirus and intussusception are extremely rare in these settings, so other factors become more influential. These include the costs to Governments of providing treatment in clinics and hospitals, and the costs to families of seeking healthcare and taking time off work (29). These factors, as well as other economic considerations (e.g. cost-effectiveness, budget impact), were beyond the scope of this thesis. In addition, some of the essential data required to evaluate HICs, such as vaccine timeliness, are not routinely available in the public domain.

In our previous analysis we found that removing age restrictions from a standard infant schedule co-administered with DTP could prevent an additional ~47,000 RVGE deaths and cause an additional ~300 intussusception deaths each year (24). In the new analysis the equivalent estimates for a standard 3-dose DTP schedule are

much lower (~11,000 RVGE deaths prevented and 59 excess intussusception deaths) but the incremental benefit-risk ratio is more favourable (186:1 versus 154:1). This analysis therefore still supports the WHO recommendation to remove age restrictions in countries where the benefit would greatly exceed the risk (33).

10.4 Alternative schedules for rotavirus vaccination

This analysis highlights the potential value of a birth dose in future rotavirus vaccination programmes. A birth dose has the potential to avoid the peak background age of intussusception as well as preventing rotavirus deaths that occur very early in life. The risks of intussusception were assumed to be relative to the baseline incidence, rather than assuming an absolute risk difference. This assumption favoured neonatal schedules. However, the base case analysis also assumed that doses administered as part of a neonatal schedule would have equivalent efficacy/waning assumptions to those administered as part of an infant schedule, but evidence suggests they may have more durable protection. Indeed, with this assumption, schedules with a birth doses had the highest predicted impact in most countries. In some countries neonatal schedules did not predict the highest impact because infant schedules achieved higher impact during the peak age of RVGE disease (e.g. Bangladesh) or because no BCG visit currently exists (e.g. Lebanon, Suriname). However, an important feature of many of the countries where neonatal schedules were not preferred (including large countries such as India and DR Congo) is that BCG coverage was lower than DTP1 coverage in the year 2015. In these countries calculations of vaccine impact did not allow for opportunities to catch-up on missed doses at later visits. This is probably not realistic. More evidence is needed on the post-licensure safety of birth doses, and on the efficacy and feasibility of administering the globally licensed rotavirus vaccines at birth. The RV3-BB vaccine demonstrated high initial efficacy following a neonatal schedule, but it is unclear if the currently licensed vaccines would have similar efficacy if administered as a neonatal schedule.

This analysis also highlights the potential benefit of booster doses to mitigate the waning protection of rotavirus vaccines (34). A 3rd dose co-administered with Meas1 was assumed to have the same efficacy (and waning) as a 2nd dose co-administered with DTP. This assumption is consistent with a Rotarix® immunogenicity study in Bangladesh, where seropositivity (IgA titres ≥ 20 U/mL) increased from 53% to 70% after a 3rd dose was administered concurrently with the first dose of measles vaccine (35). A study in Mali also found an increase in IgA titres and no negative impact on

the immune response of other vaccines administered at the same visit e.g. measles and yellow fever (36). However, more evidence is needed on the clinical efficacy and safety of booster doses, particularly since most cases of vaccine-related intussusception with RotaShield® were associated with doses administered as part of a catch-up campaign among older infants (37). However, these were associated with the first and second dose, and post-licensure studies have reported no significant relative risk with the third dose of RotaTeq administered at ~6 months (35).

Equivalent efficacy and waning was assumed following two or three doses co-administered with DTP because post-licensure studies have found no material difference in schedules that use two or three doses (17, 38). Schedules that incorporated a third dose co-administered with DTP had a small incremental advantage over schedules with only two primary doses because the third dose provided some mitigation for short-term waning. In South Africa and Malawi a 2-dose Rotarix schedule co-administered with DTP2 and DTP3 was directly compared to a 3-dose Rotarix schedule co-administered with DTP1, DTP2 and DTP3. In both settings the delayed 2-dose schedule had similar initial efficacy but less durable protection than the 3-dose schedule (39). Schedule options without a first dose administered with BCG or DTP1 were excluded as they do not provide direct vaccine protection to infants in the first 2 months of life.

Schedule options that would involve introducing a new immunisation visit were not evaluated as this would be costly and may negatively impact overall coverage of the immunisation programme. In addition, options that would involve changes to the recommended target ages for BCG, DTP and MCV were excluded, as this would have implications for other diseases not considered in this analysis.

10.5 Potential areas of further research

One potentially convenient way to explore the influence of indirect and/or inverse equity effects on predictions of rotavirus vaccine mortality benefit would be to use an individual-based simulation model. Models of this kind, also known as agent-based models or micro-simulation models, track the life histories of individuals in the population, and then aggregate the results. Simulating individuals is advantageous if the risk of an event, such as rotavirus mortality or vaccination, is likely to depend on multiple variables or risk factors, such as age, wealth, nutrition, education etc. These attributes can be assigned to individuals relatively easily and new attributes can be

added as required without the need to restructure the entire model. In principle this type of model is also well-suited to incorporating transmission and the influence of immunity acquired from repeated natural wild type infections, and waning can conveniently be captured for each individual irrespective of when they receive the vaccine. It would be difficult to calibrate such a model to data from 135 countries, so one or two countries with good data could be selected and evaluated in greater depth. An individual-based model was developed by Rose *et al* to evaluate the impact of ROTAVAC® in India (4), and Clark and Sanderson have previously developed an individual based model to assess the impact of rotavirus and other vaccines in Bangladesh and Peru (40).

Another important avenue for further research would be to assess the potential economic implications of alternative schedule options in LMICs. In this analysis the dose efficiency of each option was calculated (number of doses administered per RVGE death prevented). For age-unrestricted schedules co-administered with DTP, the predicted reduction in RVGE deaths was 17%, 29% and 32% for one, two and three dose schedules, respectively, but the number of doses required to prevent each death was ~3400, ~4000 and ~5200, respectively (Chapter 9, Table 3). An incremental cost-effectiveness analysis could more clearly elucidate the incremental value-for-money of the 18 different schedule options compared to one another and compared to standard willingness to pay benchmarks. This analysis should also try to estimate the potential costs involved in changing a schedule such as training staff, changes to staff time, cold chain cost implications, community awareness campaigns, printing new vaccination cards etc. This may be revealing because a small incremental increase in predicted benefit may not be a wise use of Government funds. This analysis could be extended to consider the cost implications (price per dose, wastage, cold chain costs etc.) of the vaccine brands that are available globally (i.e. currently Rotarix, RotaTeq and ROTAVAC) and potentially other brands in the pipeline.

10.6 Implications of research for individual, national and global decision-making

One important dimension of this analysis is how individual families and caregivers perceive potential benefits and risks of vaccination, and how their priorities may differ from those who are responsible for the public health of the population (41). The potential negative consequences of adverse events on the coverage of other vaccines adds another layer of complexity. In England, concerns about the safety of whole-cell pertussis and MMR (measles mumps and rubella) vaccines have led to substantial

short-term declines in coverage (65). However, countries with a clearly documented small level of intussusception risks continue to have high coverage of rotavirus vaccination, suggesting that the current low levels of risk are currently acceptable to both individuals and health policy makers.

At national level, our analysis provides information that can be used to make more informed assessments. The next step should be to update country-specific policy briefs (example shown in Appendix 10) that were previously commissioned by WHO and published online (www.vaccine-schedules.com). The target audience for these policy briefs is National Immunization Advisory Groups of Experts (NITAGs) or their equivalents in LMICs. In addition, the UNIVAC decision support model used in this analysis is a user-friendly decision support model designed to be used at country-level (www.provac-toolkit.com). This could be used to build within-country consensus about data values and explore scenarios appropriate for the national context (42). We find that our results depend quite strongly on the country and the type of schedule used, so a national focus will be important. The optimal schedule for each country will also depend on several other locally relevant criteria including costs, cost-effectiveness and other programmatic considerations. In the absence of better evidence from clinical trials or conflicting predictions from transmission models, one approach would be to implement favourable schedules in specific geographical locations with good surveillance and assess whether they offer material advantages in impact and/or safety compared to existing schedules.

At the global level, the results of this thesis support the current WHO recommendations favouring the use of rotavirus vaccines globally, and the removal of age restrictions in countries where the benefits greatly exceed the risk. The policy briefs and decision-support tools described above should help countries to make more informed decisions based on their local data and context. The Global Advisory Committee on Vaccines Safety (GACVS) and Strategic Advisory Group of Experts (SAGE) are the principal advisory groups to WHO on issues around the safety and acceptability of rotavirus vaccines. Currently the committee members have to make value judgements informed by the best available evidence on benefits and risks, as well as other criteria. However, one way to improve the consistency of recommendations around the benefits and risks of different vaccines, would be to develop a rule/threshold for the minimum number of deaths that would need to be prevented per death caused, in order for the vaccine in question to be recommended. This would then serve as a transparent threshold for future recommendation made by

GACVS and SAGE about any vaccine. For example, similar benefit-risk deliberations may be needed for Dengue vaccines, and a threshold would ensure consistency between vaccines. In 2012, the WHO recommended the removal of the manufacturer's age restriction on the basis of a benefit-risk ratio of 150:1, suggesting a ratio of this order is considered to be acceptable (24). The lowest published estimate of the benefit-risk ratio for deaths is 77:1, as reported in the USA (31). In our analysis, some countries had a benefit-risk ratio below 50:1 but many were medium mortality countries where assumptions about access to treatment (and intussusception CFRs) were very influential. A threshold could stimulate more engagement from policy makers about the need to re-assess benefit-risk using their own locally-relevant data and decision criteria. This would ideally include an assessment of the potential merits of alternative schedules that could further increase impact and reduce risks.

10.7 Final reflections and conclusion

In this analysis, rotavirus vaccination has a favourable benefit-risk profile in most LMICs despite pessimistic assumptions about the potential scale of intussusception risks. This analysis also supports the current WHO recommendation to remove age restrictions in countries where the benefits of late vaccination greatly exceed the risks. Further, it provides a useful starting point for thinking about the schedules that might have advantages in different countries. Schedules involving birth and booster doses could further increase benefits and reduce risks, but more research is needed to assess their feasibility, safety and impact. Beyond this, with the aggregated impact on RVGE deaths <5 years of age not exceeding 50% for any schedule or scenario evaluated, more efficacious rotavirus vaccines would be needed to achieve more substantial improvements in impact in LMICs.

List of references (Chapter 10)

1. Gladstone BP, Ramani S, Mukhopadhya I, Muliyil J, Sarkar R, Rehman AM, et al. Protective effect of natural rotavirus infection in an Indian birth cohort. N Engl J Med. 2011;365(4):337-46.

2. Velazquez FR, Matson DO, Calva JJ, Guerrero L, Morrow AL, Carter-Campbell S, et al. Rotavirus infections in infants as protection against subsequent infections. N Engl J Med. 1996;335(14):1022-8.

3. Park J, Goldstein J, Haran M, Ferrari M. An ensemble approach to predicting the impact of vaccination on rotavirus disease in Niger. Vaccine. 2017;35(43):5835-41.

4. Rose J, Homa L, Meropol SB, Debanne SM, Bielefeld R, Hoyen C, et al. Health impact and cost-effectiveness of a domestically-produced rotavirus vaccine in India: A model based analysis. PLoS One. 2017;12(11):e0187446.

5. Yen C, Armero Guardado JA, Alberto P, Rodriguez Araujo DS, Mena C, Cuellar E, et al. Decline in rotavirus hospitalizations and health care visits for childhood diarrhea following rotavirus vaccination in El Salvador. Pediatr Infect Dis J. 2011;30(1 Suppl):S6-S10.

6. Burnett E, Jonesteller CL, Tate JE, Yen C, Parashar UD. Global Impact of Rotavirus Vaccination on Childhood Hospitalizations and Mortality From Diarrhea. J Infect Dis. 2017;215(11):1666-72.

7. Ngabo F, Tate JE, Gatera M, Rugambwa C, Donnen P, Lepage P, et al. Effect of pentavalent rotavirus vaccine introduction on hospital admissions for diarrhoea and rotavirus in children in Rwanda: a time-series analysis. Lancet Glob Health. 2016;4(2):e129-36.

8. Bennett A, Pollock L, Jere KC, Pitzer VE, Parashar U, Tate JE, et al. Direct and possible indirect effects of vaccination on rotavirus hospitalisations among children in Malawi four years after programmatic introduction. Vaccine. 2018.

9. Groome MJ, Zell ER, Solomon F, Nzenze S, Parashar UD, Izu A, et al. Temporal Association of Rotavirus Vaccine Introduction and Reduction in All-Cause Childhood Diarrheal Hospitalizations in South Africa. Clin Infect Dis. 2016;62 Suppl 2:S188-95.

10. Mpabalwani EM, Simwaka CJ, Mwenda JM, Mubanga CP, Monze M, Matapo B, et al. Impact of Rotavirus Vaccination on Diarrheal Hospitalizations in Children Aged <5 Years in Lusaka, Zambia. Clin Infect Dis. 2016;62 Suppl 2:S183-7.

11. Save the Children. Lives on the Line. An Agenda for Ending Preventable Child Deaths. Available at: https://www.savethechildren.net/raceforsurvival/images/livesontheline.pdf [accessed 1st September 2018]. 2013.

12. Victora CG, Vaughan JP, Barros FC, Silva AC, Tomasi E. Explaining trends in inequities: evidence from Brazilian child health studies. Lancet. 2000;356(9235):1093-8.

13. Hart JT. The inverse care law. Lancet. 1971;1(7696):405-12.

14. Delamonica E, Minujin A, Gulaid J. Monitoring equity in immunization coverage. Bull World Health Organ. 2005;83(5):384-91.

15. Rheingans R, Atherly D, Anderson J. Distributional impact of rotavirus vaccination in 25 GAVI countries: estimating disparities in benefits and cost-effectiveness. Vaccine. 2012;30 Suppl 1:A15-23.

16. Bosch-Capblanch X, Banerjee K, Burton A. Unvaccinated children in years of increasing coverage: how many and who are they? Evidence from 96 low- and middle-income countries. Trop Med Int Health. 2012;17(6):697-710.

17. Jonesteller CL, Burnett E, Yen C, Tate JE, Parashar UD. Effectiveness of Rotavirus Vaccination: A Systematic Review of the First Decade of Global Postlicensure Data, 2006-2016. Clin Infect Dis. 2017;65(5):840-50.

18. GBD. Digestive disorders aged <5 years in the year 2015. Global Burden of Disease (GBD) Project 2017. Available at: http://ghdx.healthdata.org/gbd-results-tool [Accessed 14th Feb 2018].

19. Mpabalwani EM, Mwenda JM, Tate JE, Parashar UD. Review of Naturally Occurring Intussusception in Young Children in the WHO African Region prior to the Era of Rotavirus Vaccine Utilization in the Expanded Programme of Immunization. J Trop Pediatr. 2017;63(3):221-8.

20. Tate JE, Mwenda JM, Armah G, Jani B, Omore R, Ademe A, et al. Evaluation of Intussusception after Monovalent Rotavirus Vaccination in Africa. N Engl J Med. 2018;378(16):1521-8.

21. Murphy TV, Gargiullo PM, Massoudi MS, Nelson DB, Jumaan AO, Okoro CA, et al. Intussusception among infants given an oral rotavirus vaccine. N Engl J Med. 2001;344(8):564-72.

22. Konno T, Suzuki H, Kutsuzawa T, Imai A, Katsushima N, Sakamoto M, et al. Human rotavirus infection in infants and young children with intussusception. J Med Virol. 1978;2(3):265-69.

23. WHO. List of Member States by WHO Region and Mortality Stratum. Cost effectiveness and strategic planning (WHO-CHOICE). http://www.who.int/choice/demography/mortality_strata/en/ [Accessed March 2018]

24. Patel MM, Clark AD, Sanderson CF, Tate J, Parashar UD. Removing the age restrictions for rotavirus vaccination: a benefit-risk modeling analysis. PLoS Med. 2012;9(10):e1001330.

25. Clark A, Black R, Tate J, Roose A, Kotloff K, Lam D, et al. Estimating global, regional and national rotavirus deaths in children aged <5 years: Current approaches, new analyses and proposed improvements. PLoS One. 2017;12(9):e0183392.

26. Clark A. KM, Hasso-Agopsowicz M., Stockdale L., Parashar U., Tate J. Global review of the incidence, age distribution and case fatality of intussusception hospital admissions among children aged < 5 years, before the introduction of rotavirus vaccination (forthcoming).

27. Desai R, Parashar UD, Lopman B, de Oliveira LH, Clark AD, Sanderson CF, et al. Potential intussusception risk versus health benefits from rotavirus vaccination in Latin America. Clin Infect Dis. 2012;54(10):1397-405.

28. Patel MM, Lopez-Collada VR, Bulhoes MM, De Oliveira LH, Bautista Marquez A, Flannery B, et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. N Engl J Med. 2011;364(24):2283-92.

29. Clark A. JM, Andrews N., Atchison C., Edmunds J., Sanderson C., . Evaluating the potential risks and benefits of infant rotavirus vaccination in England. Vaccine. 2014.

30. Lamrani A, Tubert-Bitter P, Hill C, Escolano S. A benefit-risk analysis of rotavirus vaccination, France, 2015. Euro Surveill. 2017;22(50).

31. Desai R, Cortese MM, Meltzer MI, Shankar M, Tate JE, Yen C, et al. Potential intussusception risk versus benefits of rotavirus vaccination in the United States. Pediatr Infect Dis J. 2013;32(1):1-7.

32. Ledent E, Lieftucht A, Buyse H, Sugiyama K, McKenna M, Holl K. Post-Marketing Benefit-Risk Assessment of Rotavirus Vaccination in Japan: A Simulation and Modelling Analysis. Drug Saf. 2016;39(3):219-30.

33. WHO. WHO position paper – January 2013. Rotavirus. Weekly Epidemiological Review (WER) Available at: http://wwwwhoint/wer/2013/wer8805/en/ [Accessed 7 Feb 2018]. 2013;88(5):49–64.

34. Burnett E, Lopman BA, Parashar UD. Potential for a booster dose of rotavirus vaccine to further reduce diarrhea mortality. Vaccine. 2017;35(51):7198-203.

35. Zaman K, Fleming JA, Victor JC, Yunus M, Bari TI, Azim T, et al. Noninterference of Rotavirus Vaccine With Measles-Rubella Vaccine at 9 Months of Age and Improvements in Antirotavirus Immunity: A Randomized Trial. J Infect Dis. 2016;213(11):1686-93.

36. Haidara FC, Tapia MD, Sow SO, Doumbia M, Coulibaly F, Diallo F, et al. Evaluation of a Booster Dose of Pentavalent Rotavirus Vaccine Coadministered With Measles, Yellow Fever, and Meningitis A Vaccines in 9-Month-Old Malian Infants. J Infect Dis. 2018;218(4):606-13.

37. Simonsen L, Viboud C, Elixhauser A, Taylor RJ, Kapikian AZ. More on RotaShield and intussusception: the role of age at the time of vaccination. J Infect Dis. 2005;192 Suppl 1:S36-43.

38. Immergluck LC, Parker TC, Jain S, Laghaie E, Spandorfer P, Jerris RC, et al. Sustained Effectiveness of Monovalent and Pentavalent Rotavirus Vaccines in Children. J Pediatr. 2016;172:116-20 e1.

39. Madhi SA, Cunliffe NA, Steele D, Witte D, Kirsten M, Louw C, et al. Effect of human rotavirus vaccine on severe diarrhea in African infants. Malawi Med J. 2016;28(3):108-14.

40. Clark A., Sanderson C. Child Vaccination Microsimulation Model (CVMM) used to estimate the cost-effectiveness of rotavirus, haemophilus influenzae type b (Hib) and

hepatitis B vaccination in Bangladesh and Peru. Report submitted to the UK Department for International Development (DFID). 2005.

41. Fine PE, Clarkson JA. Individual versus public priorities in the determination of optimal vaccination policies. Am J Epidemiol. 1986;124(6):1012-20.

42. UNIVAC (Universal vaccine decision support model). Available at: www.provac-toolkit.com [Accessed 7th Feb 2018].

Appendices

Appendix 1

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Removing the Age Restrictions for Rotavirus Vaccination: A Benefit-Risk Modeling Analysis

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Abstract

Background: To minimize potential risk of intussusception, the World Health Organization (WHO) recommended in 2009 that rotavirus immunization should be initiated by age 15 weeks and completed before 32 weeks. These restrictions could adversely impact vaccination coverage and thereby its health impact, particularly in developing countries where delays in vaccination often occur.

Methods and Findings: We conducted a modeling study to estimate the number of rotavirus deaths prevented and the number of intussusception deaths caused by vaccination when administered on the restricted schedule versus an unrestricted schedule whereby rotavirus vaccine would be administered with DTP vaccine up to age 3 years. Countries were grouped on the basis of child mortality rates, using WHO data. Inputs were estimates of WHO rotavirus mortality by week of age from a recent study, intussusception mortality based on a literature review, predicted vaccination rates by week of age from USAID Demographic and Health Surveys, the United Nations Children's Fund (UNICEF) Multiple Indicator Cluster Surveys (MICS), and WHO-UNICEF 2010 country-specific coverage estimates, and published estimates of vaccine efficacy and vaccine-associated intussusception risk. On the basis of the error estimates and distributions for model inputs, we conducted 2,000 simulations to obtain median estimates of deaths averted and caused as well as the uncertainty ranges, defined as the 5th–95th percentile, to provide an indication of the uncertainty in the estimates. We estimated that in low and low-middle income countries a restricted schedule would prevent 155,800 rotavirus deaths (5th–95th centiles, 83,300–217,700) while causing potentially 253 intussusception deaths (76–689). In contrast, vaccination without age restrictions would prevent 203,000 rotavirus deaths (102,000–281,500) while potentially causing 547 intussusception deaths (237–1,160). Thus, removing the age restrictions would avert an additional 47,200 rotavirus deaths (18,700–63,700) and cause an additional 294 (161–471) intussusception deaths, for an incremental benefit-risk ratio of 154 deaths averted for every death caused by vaccine. These extra deaths prevented under an unrestricted schedule reflect vaccination of an additional 21%–25% children, beyond the 63%–73% of the children who would be vaccinated under the restricted schedule. Importantly, these estimates err on the side of safety in that they assume high vaccine-associated risk of intussusception and do not account for potential herd immunity or non-fatal outcomes.

Conclusions: Our analysis suggests that in low- and middle-income countries the additional lives saved by removing age restrictions for rotavirus vaccination would far outnumber the potential excess vaccine-associated intussusception deaths.

Please see later in the article for the Editors' Summary.

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Abbreviations: DHS, Demographic and Health Survey; DTP, diphtheria-tetanus-pertussis; MICS, Multiple Indicator Cluster Survey; RR, relative risk; UNICEF, United Nations Children's Fund; WHO, World Health Organization.

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Introduction

Rotavirus infection is the leading cause of fatal diarrhea among children younger than 5 y, accounting for 453,000 deaths in the year 2008 based on recently published World Health Organization (WHO) estimates [1]. To curb this large toll of severe rotavirus disease, in 2006, the WHO recommended two rotavirus vaccines—Rotarix (GSK Biologicals) and RotaTeq (Merck & Co.)—for use in Europe and the Americas, and in 2009, they expanded this recommendation to all children worldwide [2]. These recommendations reflected the growing availability of evidence of the good efficacy profile of rotavirus vaccines—first from clinical trials in high- and middle-income countries in the Americas and Europe in 2006 and then also from low-income settings in Africa and Asia in 2009 [3–6].

Because a previous rotavirus vaccine (RotaShield) was found to be associated with intussusception, a rare form of bowel obstruction [7], the pivotal pre-licensure trials in the Americas and Europe for both currently available rotavirus vaccines were conducted in over 60,000 infants each to exclude this risk; these trials did not show an increase in risk of vaccine-associated intussusception similar to that found with Rotashield [3,4]. However, recent data on the postlicensure safety of rotavirus vaccines generated from these countries has suggested a possible low level risk of intussusception (~one to two excess cases per 100,000 vaccinated infants) in some countries but not in others [8,9]. On the basis of considerations that this low level risk is greatly exceeded by the observed health benefits of vaccination, national and international policy and regulatory bodies have continued to support recommendations for use of rotavirus vaccine [8,9].

In 2009, WHO recommended that rotavirus vaccines should not be initiated for infants aged 15 wk or older, with all doses being completed by 32 wk [2]. These age restrictions were driven by concerns about intussusception risk. Natural intussusception rarely occurs before 3 mo of age and the incidence increases 10-fold between 3 and 6 mo of age [10]. Therefore, a constant vaccine-associated relative risk (RR) of intussusception, particularly with the first vaccine dose that has been primarily associated with risk, would translate to more excess cases if infants were vaccinated late, beyond 3 mo of age. Similar findings were observed in the United States after use of RotaShield, prompting a debate about whether restriction of RotaShield to infants younger than 3 mo of age would have averted withdrawal of the vaccine [10–12]. A consequence of these strict age restrictions in countries with vaccination delays is that those arriving late for immunization would potentially not have access to the benefits of rotavirus vaccination [13,14].

To facilitate decision making, we previously undertook a scenario analysis assessing the benefits and risks of a rotavirus vaccination strategy with and without an age restriction [15]. Since this analysis, new evidence has been published on several key parameters for the scenario analysis, including data on efficacy of rotavirus vaccines in Africa and Asia [5,6], the effect of rotavirus vaccines on diarrhea deaths [16,17], postlicensure data on risk of intussusception with current rotavirus vaccines [8,9,18], the release of updated estimates of rotavirus mortality by WHO [1] and age distribution of rotavirus disease by week of age [19], and updated data on timeliness of vaccination coverage in low- and middle-income countries [20]. The availability of these new data and the imminent introduction of rotavirus vaccines in many developing countries in Africa during the next 2 y prompted us to revise our previous analysis to provide policy makers with the most up-to-date evidence to inform decisions of best approaches to global implementation of rotavirus vaccines.

Methods

We focused this analysis exclusively on the benefits of rotavirus mortality reduction and potential risk of fatal intussusception in children <5 y of age in 158 low- and middle-income countries with a birth cohort of 123.6 million where 99.9% of the global rotavirus mortality occurs. To explore the effect of age restriction in different parts of the world, we grouped these countries on the basis of child mortality rates, according to WHO mortality strata [21], and assigned to one of four groups: group B and C (countries with low child mortality), group D-Americas (countries in the Americas with high child mortality), group D-Asia (countries in Asia with high child mortality), and group D & E-Africa (countries in Africa with high child mortality). Because group A countries with very low child mortality (i.e., high-income) represent <0.1% of the global rotavirus deaths, they were excluded from this analysis.

Vaccination Strategies and Coverage Estimates

For both immunization strategies, restricted and unrestricted, we assumed that rotavirus vaccine would be given at the same time as the diphtheria-tetanus-pertussis (DTP) vaccine and that vaccine coverage in the individual countries would be equal to the proportion of infants receiving each of the three DTP doses by week of age (i.e., proportion vaccinated, ρ_v) during the first 3 y of life. Under the restricted schedule, if infants received their first DTP dose by ≤14 wk of age, we assumed they would receive all doses up to 32 wk of age, but if they first appeared after 14 wk, they would remain unvaccinated. On the unrestricted schedule, vaccine would be administered according to the age-specific coverage rates for each of the DTP dose up to 3 y of age.

Our DTP coverage estimates are based on vaccination data from household USAID Demographic and Health Surveys (DHSs) [22] and the United Nations Children's Fund (UNICEF) Multiple Indicator Cluster Surveys (MICS) [23] that were administered in 48 countries between 1996 and 2009. To estimate coverage for countries without DHS or MICS data, overall WHO-UNICEF 2010 country-specific coverage estimates were converted into age-specific coverage rates using regression coefficients to predict lognormal curves of timeliness. These were derived from the available DHS/MICS survey data and extrapolated to countries without a survey within a WHO region and mortality stratum. Timeliness was determined by WHO sub-region and adjusted for trends between the DHS/MICS survey year and 2010 using the WHO-UNICEF 2010 best estimates for DTP coverage data, drop-out rate between DTP1 and DTP3, the target age recommended in the country schedule, and the gross domestic product per capita [24]. This process was done separately for DTP1 and DTP3. DTP2 timeliness assumed the average of the regression coefficients used for DTP1 and DTP3.

Our analysis does not allow catch-up immunization and assumes no improvement in timeliness with the introduction of rotavirus vaccine.

Assessment of Benefits—Base Scenario

Estimated numbers of country-specific rotavirus deaths (λ_{rv}) were obtained from WHO, using the 95% CIs to define the triangular distributions around the point estimate (Table 1) [1]. On the basis of a WHO-sponsored review of published and unpublished studies on age distribution of diarrhea mortality and

Table 1. Estimates of rotavirus mortality and intussusception incidence by WHO mortality group.

Mortality, Incidence, and Fatality	WHO Mortality Group Estimate (Lower Bound, Upper Bound)							
	B & C		D: Americas		D: Asia		D & E: Africa	
Rotavirus mortality	26,700	(24,000–29,000)	5,300	(4,600–5,900)	188,300	(160,000–217,000)	232,500	(198,000–268,000)
Intussusception incidence (range)	53.3	(17.7–88.2)	53.3	(17.7–88.2)	53.3	(17.7–88.2)	53.3	(17.7–88.2)
Intussusception case fatality	5%	(4–6)	10%	(8–12)	25%	(20–30)	25%	(20–30)

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rotavirus-associated hospitalizations by week of age, we predicted 1-wk gamma age distributions for the first year of life and 4-wk age categories thereafter for countries in different WHO regions [19].

Rotavirus vaccine efficacy (ε_{rv}) against fatal rotavirus disease was estimated from clinical trials or vaccine effectiveness studies in each WHO region (Tables 1–2) [3,5,6,25–29]. Because efficacy against rotavirus mortality could not be directly measured in the trials, we applied efficacy estimates against the most severe rotavirus disease outcome reported in the study [3,5,6,25–29]. This approach was reasonable given that three nationwide studies from Latin America have documented reductions in diarrhea deaths after vaccine introduction that has approximated reductions based on the efficacy of these vaccines against severe rotavirus disease [16,17,30]. Because both rotavirus vaccines have performed similarly in clinical trials, we assumed the same overall efficacy for the two-dose Rotarix and the three-dose RotaTeq vaccine. The efficacy parameters were age-stratified (<1 y and >1 y of age) because studies have documented lower efficacy among children older than 1 y of age [5,25,27]. Efficacy of partial vaccination (first dose) was also available from one country in the B & C region [27], and one country in the D-Americas region [25], but not for D-Asia and D & E-Africa. We therefore reduced the point estimates for full vaccine efficacy for Asia and Africa by the same proportion as the relative difference in efficacy between the full and partial series in D: Americas region. We used 95% CIs from the respective studies to define the beta distribution around the vaccine efficacy point estimates.

The number of rotavirus deaths prevented was obtained from $\lambda_{rv}\varepsilon_{rv}\rho_v$, where λ_{rv} is the number of rotavirus deaths by week of age, ε_{rv} is the vaccine efficacy, and ρ_v is the proportion vaccinated by week of age.

Assessment of Risk—Base Scenario

Risk of intussusception has been documented after postlicensure use of Rotarix and RotaTeq in four different studies [8,9,31,32]. Each of these studies identified an approximate 4- to 6-fold increase in risk relative to background during the first week after dose 1 (Table 3), a magnitude of risk that would not have been detected in the clinical trials. No effect modification of risk with age at vaccination was reported in these studies, but the first dose of vaccine was largely administered before 15 wk. In two

Table 2. Estimates of efficacy for partial and full series of rotavirus vaccine against the most severe reported outcome of rotavirus gastroenteritis, by WHO mortality group.

WHO Mortality Group	Reference	Location	Outcome	Vaccine Efficacy[a]			
				<1 y of Age		1 y of Age	
				Percent	(95% CI)	Percent	(95% CI)
Full series efficacy during first year of life							
B & C[b]	[26]	Latin America	≥19	97	84–100	97	84–100
D: Americas[b]	[25]	Nicaragua	≥15	77	39–92	77	39–92
D: Asia/D & E Africa	[5,6,29]	Bangladesh, Vietnam, Ghana, Kenya, Mali	≥15	67	37–84	34	−16 to 63
D & E Africa[c]	[28][b]	South Africa & Malawi	≥11	61	44–73	—	—
Partial series efficacy							
B & C	[27]	El Salvador	Hospitalizations	51	26–67	51	26–67
D: Americas	[25]	Nicaragua	Hospitalizations	55	22–74	55	22–74
D: Asia/D & E Africa[d]	—	—	—	48	30–68	24	0–51

[a]Because vaccine efficacy against rotavirus deaths was not available, the model input was efficacy against the most severe reported form of rotavirus gastroenteritis in the clinical trial (≥11 denotes "severe" diarrhea and ≥15 denotes "very severe" diarrhea on 20 point Vesikari clinical scoring system).

[b]No decline in efficacy by age was reported by age for the very severe outcome, thus the efficacy estimate for children <2 were applied to both age groups <1 and 1 y of age.

[c]This trial measured efficacy during the first year of life. No estimates of efficacy were available against very severe disease that would serve as a better proxy for death (i.e., Vesikari ≥15) at these sites in Malawi and South Africa. Consistent with all other rotavirus efficacy trials where positive correlation exists between efficacy and severity score, it was assumed that efficacy in South Africa and Malawi would be higher against Vesikari score ≥15 than Vesikari ≥11. For the model, estimates of efficacy against "very severe" rotavirus diarrhea were from sites in Africa and Asia where these data were available [5,6,29].

[d]Because no partial vaccine efficacy estimates were available for Africa and Asia, we assumed that a proportional difference in efficacy between full and partial vaccination that was observed in high mortality country of Nicaragua [25].

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Table 3. Pooled estimates of risk after doses 1 and 2 of rotavirus vaccine.

Country	Reference	Rotavirus Vaccine	RR	Lower 95% Limit	Upper 95% Limit
Dose 1					
Australia	[8]	Pentavalent	3.9	1.5	9.9
Australia	[8]	Monovalent	4.1	1.3	13.5
Mexico	[9]	Monovalent	5.3	3	9.3
Mexico	[31]	Monovalent	6.5	4.2	10.1
Global reporting	[32]	Monovalent	5.0	1.7	14.3
Pooled estimate[a]			**5.5**	**4.1**	**7.5**
Dose 2					
Mexico	[9]	Monovalent	1.8	0.9	3.8
Mexico	[31]	Monovalent	1.3	0.8	2.1
Brazil	[9]	Monovalent	2.6	1.3	5.2
Pooled estimate[a]			**1.7**	**1.2**	**2.4**

[a]We used the weighted average of the logarithm of the RR, $\sum$log(RRi)ωi/$\sum\omega$i, where weight (ωi) for each study is the inverse of the variance computed from the reported 95% CIs [33]. The variance of the weighted average log RR is the inverse of the sum of each weight ($1/\sum\omega$i) and was used to compute the 95% CIs for the pooled risk estimate.

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additional countries, no risk of intussusception was identified after the first vaccine dose [9,18]. Risk of intussusception was not identified after the first dose in Brazil (RR = 1.1; 95% CI = 0.3–3.3) or the United States (RR = 1.2; 95% CI = 0.03–6.8). However in view of the wide CIs, particularly in the United States, a risk of small magnitude similar to that detected in the other four studies cannot be excluded [9,18]. In Brazil, a statistically significant 2-fold risk was also identified in the first week after dose 2.

We obtained dose-specific pooled estimates of RR from each of the regions where some increase in RR of intussusception was identified (Table 3). To err on the side of risk, we excluded the US safety data from the pooled analysis because no risk was identified. For pooled estimates of vaccine-associated intussusception risk, we used the weighted average of the logarithm of the RR, $\sum log(RR_i)\omega_i/\sum\omega_i$, where weight ($\omega_i$) for each study [8,9,31,32] is the inverse of the variance computed from the reported 95% CIs [33]. The variance of the weighted average log RR is the inverse of the sum of the each weight ($1/\sum\omega_i$) and was used to compute the 95% CIs for the pooled risk estimate. For the uncertainty analyses, we used the 95% CIs to define the gamma distribution around the RR estimates.

The average annual incidence of natural intussusception by week of age (λ_{is}) was estimated from published studies. Because natural intussusception is a very rare disease, we restricted our review to studies reporting either national incidence of intussusception or incidence of intussusception from a minimum of five hospitals with known catchment population, stratified by age [34–51]. While intussusception incidence in this review ranged from 18–88 per 100,000 infants, the age distribution of intussusception was similar between the different studies. Thus, to obtain intussusception incidence by week of age (λ_{is}), we applied the global intussusception incidence among infants and fit a gamma curve to intussusception surveillance data from the United States [45], the only country where intussusception incidence was available by week of age. For uncertainty analysis, parameters of the gamma curve for λ_{is} were sampled from a normal distribution, assuming standard deviation is equal to 5% of the mid-parameter values.

Death caused by intussusception is uncommon in industrialized countries, occurring in <1% of the cases [52]. In a recently conducted national study from 16 hospitals in Mexico and 43 hospitals in Brazil (WHO group B & C), case fatality for intussusception was 1% and 5%, respectively [9]. One large study from nine countries across Africa indicated an average case fatality of about 12% [53]. No reliable estimates of case fatality were available for countries in D-Americas and D-Asia. Thus, we conservatively estimated the case fatality (δ_{is}) to be 5% for B & C countries, 10% for D-Americas, 25% for D-Asia, and 25% for D & E-Africa. We sampled from a beta distribution, assuming standard deviation is equal to 5% of the mid parameter values to specify the upper and lower limits of δ_{is} in uncertainty analyses.

The number of intussusception deaths associated with vaccination, during the first week after dose 1 and 2, was obtained from $B\rho_v[(\lambda_{is}RR_i) - \lambda_{is}]\delta_{is}$, where B is the number of births, ρ_v is the proportion vaccinated by week of age, λ_{is} is the intussusception incidence by week of age, RR_i is the RR during the week after each dose, and δ_{is} the proportion of intussusception events that lead to death.

Sensitivity Analysis

We conducted a one-way sensitivity analysis to determine the impact on the benefit-risk ratios when assuming four conservative scenarios that would favor risk and one that would favor vaccine: (1) We assumed a relative increase of 20% in incidence and case fatality of intussusception. (2) We explored the impact of effect modification of risk by age at vaccination, by doubling estimates of RR of intussusception when dose 1 of rotavirus vaccine was administered to infants older than 14 wk of age. (3) We assumed a scenario of low vaccine efficacy by inputting the lower confidence limit for each of the efficacy estimates. (4) We explored the effect of a "pessimistic" situation combining all of the preceding three scenarios. (5) We also assessed the effect of an "optimistic" scenario of high vaccine efficacy related to factors such as possible indirect benefits or higher efficacy among children vaccinated at older ages with lesser interference of vaccine take from circulating transplacental antibodies.

Uncertainty Analysis

The above analyses yielded estimates of rotavirus deaths averted and intussusception deaths caused under age-restricted and -unrestricted

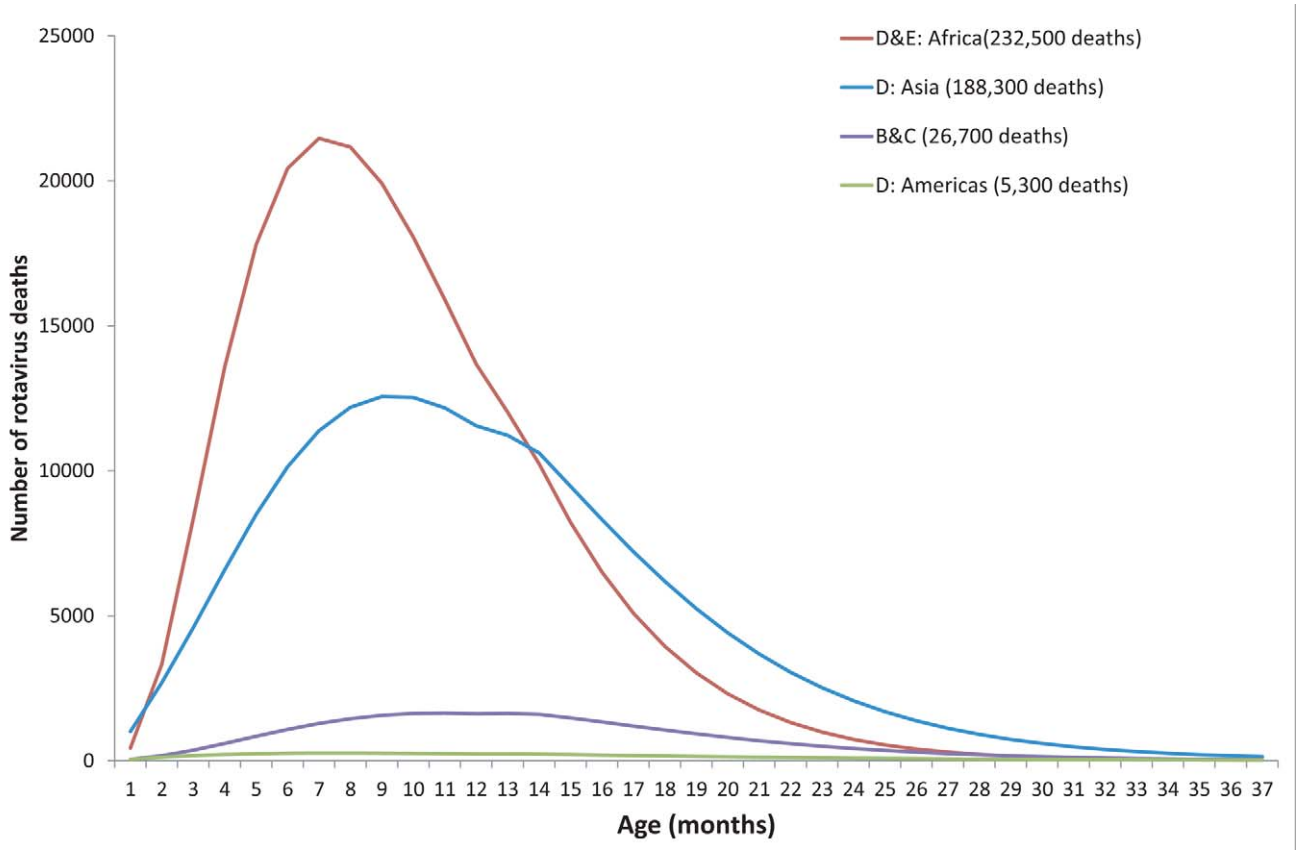

Figure 1. Age distribution of rotavirus deaths among children under 5 y, by WHO mortality group.
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vaccination strategies. We conducted a probabilistic uncertainty analysis to assess the potential impact of simultaneous variation of each of the model inputs (λ_{rv}, ε_{rv}, ρ_v, λ_{is}, RR) on the precision of the benefit-risk estimates. We shifted the lognormal timeliness curves and gamma rotavirus and intussusception age curves by simultaneously sampling new shape, shift, and scale parameters for each run, with each parameter being sampled from a normal distribution with standard deviation equal to 5% of the original parameter value. On the basis of the error estimates and error distributions described for each of the model inputs, we conducted 2,000 simulations to obtain the median estimates of deaths averted and caused as well as the uncertainty ranges, defined as the 5th–95th percentile, to provide an indication of the uncertainty in the estimates. All analyses were done with Microsoft EXCEL (Microsoft Corp, 2007).

Results

Approximately 453,000 rotavirus-associated deaths are estimated among children younger than 5 y annually without a rotavirus vaccination program (Figure 1). We project that a rotavirus vaccination program under the current age-restricted schedule would prevent almost 33% or 155,800 of these deaths (5th–95th centiles, 83,300–217,700) if delivered at the same ages at which the DTP vaccine is currently being delivered in these countries (Table 4). Without the age restrictions, a program would prevent 45% or 203,000 deaths of all rotavirus deaths (102,000–281,500), which would represent 47,200 more deaths prevented (18,700–63,700) than with an age-restricted schedule. These additional deaths prevented under an unrestricted vaccination schedule reflect an additional 18%, 21%, 25%, and 22% of the children receiving DTP1 in the WHO B & C, D-Americas, D-Asia, and D-Africa countries, respectively, compared to the age-restricted schedule in these countries (Figure 2).

From the perspective of risk, a rotavirus vaccination program limiting vaccination to children <15 wk of age would cause about 253 intussusception deaths (76–689) (Table 4). In contrast, a program without age restrictions would cause nearly 547 intussusception deaths (237–1,160). Thus, a vaccination policy without any age restrictions for use of rotavirus vaccines in low- and middle-income WHO countries would avert an additional 47,200 rotavirus-associated deaths and cause an additional 294 intussusception-associated deaths, compared to the current age-restricted strategy (Table 5). The median incremental benefit-risk ratio in all mortality strata was nearly 154 deaths averted for every death caused, ranging from 55–318 deaths averted for every death caused across the different mortality strata (Figures 3 and 4).

Under the scenarios of effect modification of risk with age at vaccination and increased incidence and case fatality of intussusception, an unrestricted schedule would cause 603 (174–946) and 423 (232–678) excess deaths, respectively, while averting about 47,200 rotavirus deaths (18,700–63,700) (Table 5). A scenario where efficacy approximated the lower confidence limit in the clinical trials would avert an additional 20,400 rotavirus deaths (8,500–34,300) under an unrestricted schedule. With pessimistic assumptions of high intussusception incidence and case fatality, high risk, and low efficacy, a vaccination program without age restrictions would cause 868 intussusception deaths (506–1,362) while preventing 20,400 rotavirus deaths (8,500–34,300), for a

Table 4. Rotavirus deaths averted versus excess intussusception deaths caused under age-restricted and age-unrestricted rotavirus vaccination strategies, by WHO mortality group and age.

Vaccination Strategy	Rotavirus Deaths Averted (95% CI)[a]			Intussusception Deaths Caused[a] (95% CI)			Benefit to Risk Ratio
	Age Restriction[b]	No Age Restriction	Excess	Age Restriction[b]	No Age Restriction	Excess	
B & C countries							
Median	18,200	22,700	4,500	35	53	18	247
5th percentile	15,500	19,700	4,200	10	19	9	138
95th percentile	20,500	25,200	4,700	94	127	33	519
D: Americas							
Median	2,600	3,300	700	3	5	2	343
5th percentile	1,400	1,800	400	1	2	1	152
95th percentile	3,200	4,000	800	9	12	3	674
D: Asia							
Median	55,400	76,800	21,400	118	275	157	133
5th percentile	25,200	32,200	7,000	36	120	84	43
95th percentile	83,400	115,300	31,900	317	576	259	286
D: Africa							
Median	79,600	100,200	20,600	96	212	116	167
5th percentile	40,300	46,900	6,600	28	96	68	50
95th percentile	111,100	138,300	27,200	265	441	176	328
All strata							
Median	155,800	203,000	47,200	253	547	294	154
5th percentile	83,300	102,000	18,700	76	237	161	55
95th percentile	217,700	281,500	63,700	689	1,160	471	318

[a]Estimates of rotavirus deaths averted and intussusception deaths caused are based on efficacy, risk, and case-fatality parameters in Tables 1–3. Vaccination coverage is based on DTP vaccination rates from household DHSs and UNICEF MICSs.
[b]Age restriction denotes dose 1 administration by 15 wk and the full series by 32 wk of age.
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benefit-risk ratio of 24. In contrast, the benefit-risk ratio would approximate 220 (116–407) under an optimistic scenario of high vaccine efficacy.

Discussion

Our analysis demonstrates that if first dose of rotavirus vaccine is restricted to children 14 wk of age or younger, rotavirus vaccines would prevent about 155,800 of the 453,000 rotavirus deaths occurring in children <5 y of age annually worldwide while resulting in 253 intussusception deaths. While most of the gap in preventable rotavirus deaths is due to the moderate efficacy of the vaccines in high mortality settings, the current age restrictions on rotavirus vaccination also contribute by potentially excluding nearly 21%–25% of the world's children, those with the highest risk of rotavirus mortality, from receiving these vaccines. Lifting the age restriction for the first dose of rotavirus vaccination would save an additional 47,200 lives yearly and would result in an additional 294 intussusception deaths, for an incremental benefit of saving 154 lives for each excess intussusception death caused.

In the past 5 y, with the introduction of rotavirus vaccines in nearly 30 countries worldwide, substantial experience has been gained with regard to the safety and effectiveness of these vaccines in the real-world setting, including against deaths [8,9,16–18,25,27,54,55]. Moreover, clinical trials for these vaccines have documented their efficacy in target populations of Asia and Africa, where majority of the rotavirus deaths occur. Given these encouraging data, the ability of the vaccines to reach children with the highest mortality will be a major determinant of their life-saving impact.

Our base estimates are conservative, erring on the side of overestimating vaccine risk for four reasons. First, over 45 publications have documented remarkable declines in severe diarrhea and rotavirus disease, including deaths, since their introduction in national immunization programs worldwide [55]. Many of these studies from different locations have demonstrated significant declines in unvaccinated members of the community, indicating indirect benefits of vaccination that we did not account for in our analysis [56–59]. Second, because of interference from circulating transplacental antibodies during the first several months of life, immune response to vaccine and thus efficacy is likely to be higher when children are vaccinated at older ages. For example, anti-rotavirus IgA geometric mean titers for Vietnamese infants vaccinated against rotavirus at 9 and 13 wk were lower (77 U/ml) compared to infants vaccinated at 9 and 17 wk of life (176 U/ml) [60]. Third, we assumed that some risk of intussusception exists following each of the first two doses of rotavirus vaccine in all countries worldwide; however, risk of intussusception has varied by setting, and robust studies in two large countries have not identified risk after dose 1 [9,18]. Fourth, even in our base scenario, we assumed high rates of intussusception case fatality in all WHO regions, about 2-fold higher than those reported in the literature.

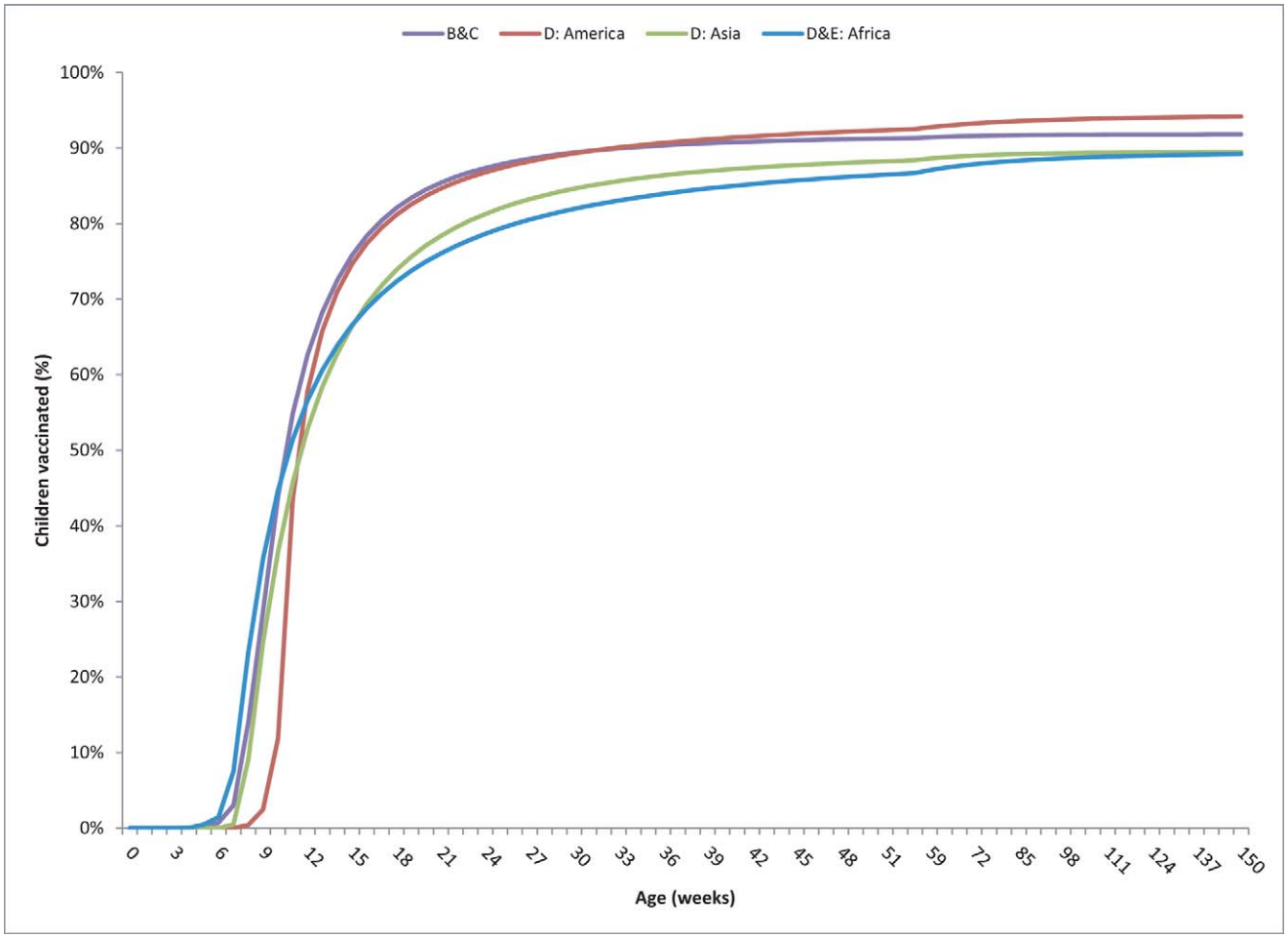

Figure 2. Vaccine coverage for dose 1 of DTP by week of age and WHO mortality group based on the DHSs and UNICEF MICs.
doi:10.1371/journal.pmed.1001330.g002

On the other hand, the benefit-risk ratios might be inflated due to several factors. First, our base scenario assumes that the risk of intussusception relative to background does not increase with age. After the withdrawal of RotaShield, a debate persisted with regard to whether the RR of intussusception might have been higher for infants vaccinated beyond 14 wk of age [11,12]. While limited data from an evaluation in Mexico does not suggest effect modification of risk by age for current vaccines [9], we incorporated a scenario of increased risk with age at vaccination that indicated that vaccination would avert 75 rotavirus deaths for each excess intussusception death. Second, our model might have overestimated vaccine coverage among children at the highest risk of dying from rotavirus as these might be the hardest to reach, thus inflating the mortality benefits of vaccination relative to the risks in our model. However, data from Mexico and Brazil, where substantial reductions in diarrhea deaths have occurred in all regions of both countries after the introduction of vaccine [16,17], provides some reassurance that vaccine is reaching those at the highest risk of dying.

While the numerical benefits of relaxing the age restriction on rotavirus vaccination exceed the risks, other factors are relevant for policy considerations. First, the age restrictions for rotavirus vaccines potentially offer an incentive to improve timeliness of vaccination, which would potentially have far reaching benefits beyond just prevention of rotavirus disease. However, reasons for delays in vaccination in developing countries are complex and it is not known if a policy of restricting the first dose of rotavirus vaccines alone would be a sufficient motivational factor for parents and countries to improve timeliness of vaccination. Indeed, some delays may be due to unavoidable factors, such as contraindications. Second, while the unrestricted vaccination scenario allows for vaccination at any age during the first 3 y of life, few children arrive for vaccination beyond 1 y of life. It is important to note that delays in vaccination particularly beyond 1 y of life will reduce benefits substantially because of increasing probability of acquiring natural immunity from wild-type rotavirus infection. Third, a death caused by an intervention may be perceived worse than a death caused by a failure to intervene [61–63]. However, some evidence suggests that individuals may regret disease resulting from withholding vaccine as much as side effects from vaccination [63]. Furthermore, after the RotaShield experience, ethicists argued equal culpability for deaths caused by withholding the vaccine as for deaths resulting from the vaccine [64]. Finally, our analysis did not address high income countries where mortality from both rotavirus disease and from intussusception is uncommon, and thus the benefit-risk considerations will differ. Furthermore, vaccination is more timely in these settings (e.g., in the United States, 93% of the DTP1 is given by 15 wk of age [65]), and thus decisions will likely have to be made at a country level based on evaluation of local data.

In summary, using emerging, real-world data on rotavirus and intussusception mortality and rotavirus vaccine efficacy, safety,

Table 5. Additional lives saved versus deaths caused by loosening the age restrictions for rotavirus vaccines in WHO high and very high mortality group.

Scenario	Median (5th Percentile, 95th Percentile)					
	Lives Saved		Deaths Caused		Benefit/Risk Ratio	
Base[a]	47,200	(18,700–63,700)	294	(161–471)	154	(55–318)
Base+higher intussusception rate and case fatality[b]	47,200	(18,700–63,700)	423	(232–678)	107	(38–221)
Base+increase RR with age at dose 1[c]	47,200	(18,700–63,700)	603	(174–946)	75	(27–143)
Base with low vaccine efficacy	20,400	(8,500–4,300)	294	(161–471)	71	(24–159)
Pessimistic[d]	14,400	(7,400–28,300)	703	(459–1,042)	24	(9–51)
Optimistic (Base+high vaccine efficacy)[e]	65,800	(39,900–77,000)	294	(161–471)	220	(116–407)

[a]Assumes point estimates for vaccine efficacy and intussusception risk and case-fatality estimates presented in Tables 1–3.
[b]Assumes 20% relative increase in incidence and case fatality of intussusception compared to base scenario.
[c]Assumes a doubling of RR of vaccine associated risk of intussusception among children receiving dose 1 beyond 15 wk of age.
[d]Pessimistic scenario assumes base scenario with: (1) 20% increase in background incidence and case fatality of intussusception compared to base scenario; (2) doubling of relative among children vaccinated with dose 1 beyond 15 wk of age; and (3) lower 95% confidence limit for vaccine efficacy.
[e]Optimistic scenario assumes the upper confidence limit for vaccine efficacy in each setting.
doi:10.1371/journal.pmed.1001330.t005

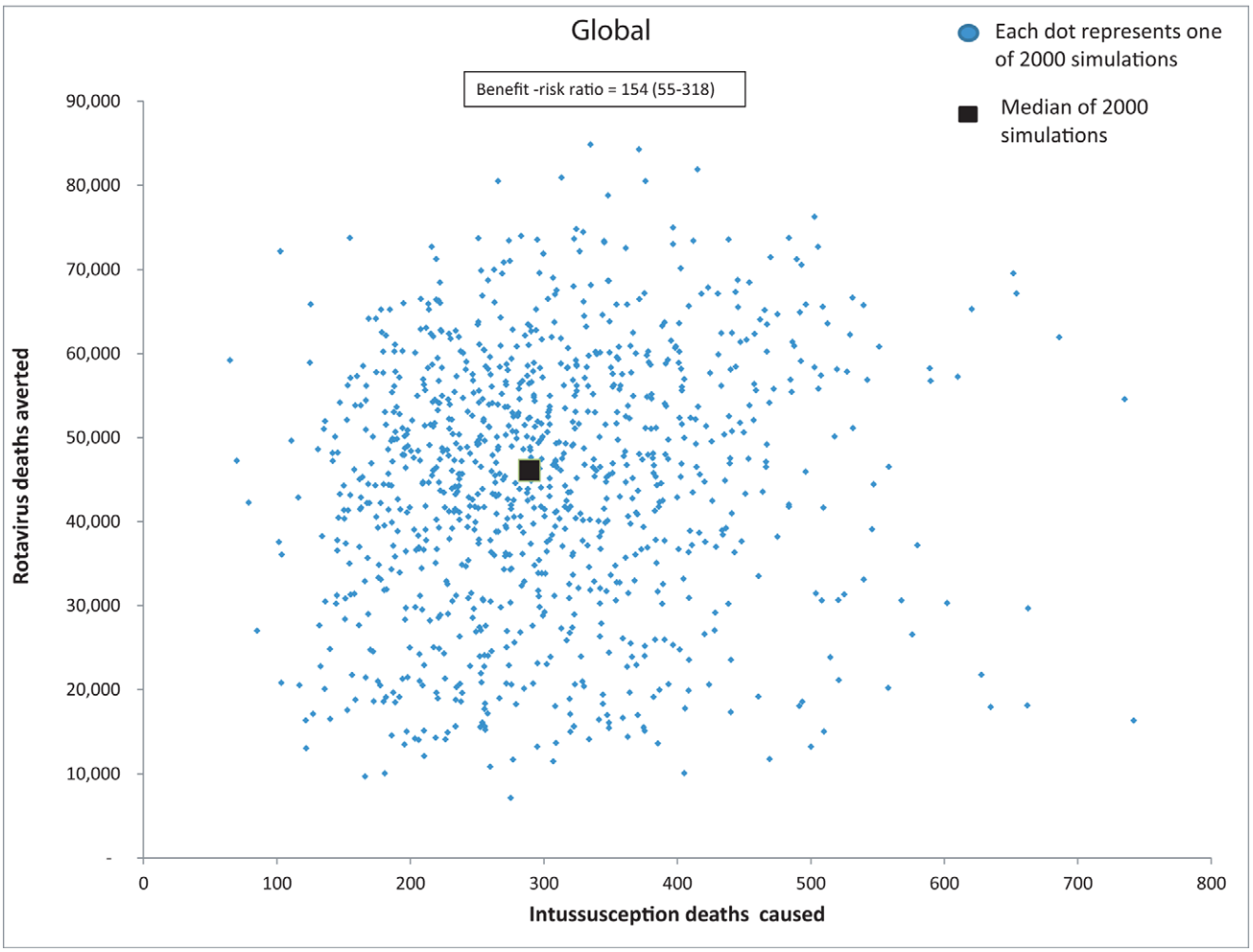

Figure 3. Global analysis of the relationship between esimated number of rotavirus gastroenteritis deaths avoided versus intussusception deaths caused by removal of the age restrictions for rotavirus vaccination. These estimates are from 2,000 simulations with each blue dot representing a potential estimate of rotavirus deaths prevented (y-axis) versus intussusception deaths caused (x-axis) from removal of the age restrictions given the uncertainty on the parameters in the model: rotavirus mortality, vaccine efficacy, vaccine coverage, intussusception incidence, intussusception risk from vaccine, and intussusception fatality. The black square represents the median estimate.
doi:10.1371/journal.pmed.1001330.g003

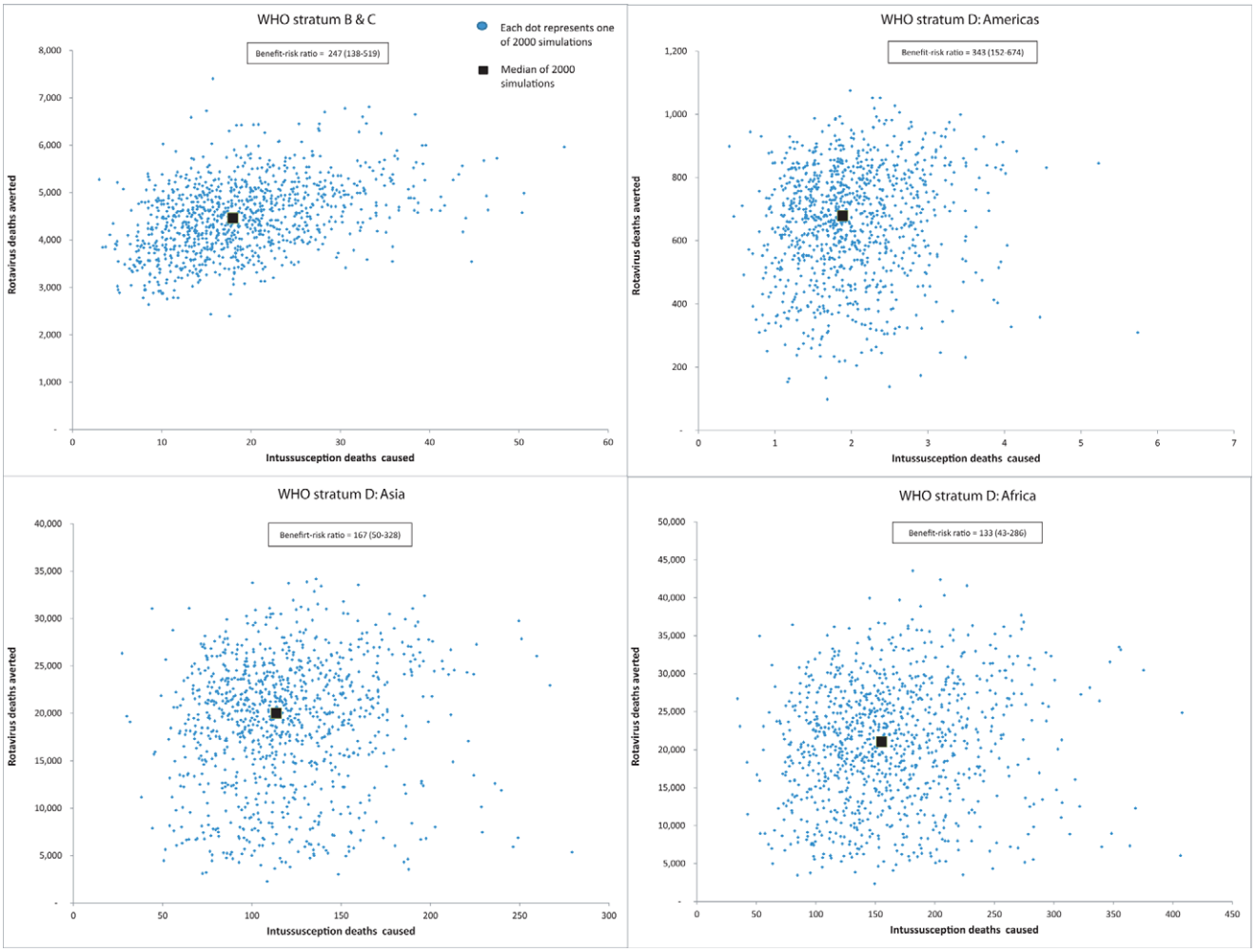

Figure 4. WHO region specific analysis of relationship between esimated number of rotavirus gastroenteritis deaths avoided versus intussusception deaths caused by removal of the age restrictions for rotavirus vaccination. These estimates are from 2,000 simulations with each blue dot representing a potential estimate of rotavirus deaths prevented (y-axis) versus intussusception deaths caused (x-axis) from removal of the age restrictions given the uncertainty on the parameters in the model: rotavirus mortality, vaccine efficacy, vaccine coverage, intussusception incidence, intussusception risk from vaccine, and intussusception fatality. The black square represents the median estimate. Because group A countries with very low child mortality (i.e., high-income) represent <0.1% of the global rotavirus deaths, they were excluded from this analysis.
doi:10.1371/journal.pmed.1001330.g004

and coverage, we estimate that removing the age restrictions on rotavirus vaccination would avert 47,200 additional rotavirus deaths in low- and middle-income countries. In April 2012, WHO's Strategic Advisory Group of Experts reviewed the evidence presented in this paper and recognized that the 15-wk and 32-wk age restrictions for rotavirus vaccines are preventing vaccination of many vulnerable children [66]. SAGE encourages timely vaccination, but no longer universally recommends the age restrictions, supporting their removal in seetings where mortality benefits outweigh the risk so that many thousands more deaths would be averted and immunization programs are able to immunize children who are currently excluded from the benefits of rotavirus vaccines. Age restriction policies will ultimately be decided at country level, but this analysis has shown a clear case for a change in policy that will be particularly instrumental for saving lives in settings where mortality from rotavirus is high and delays in timing of vaccination are common.

Author Contributions

Conceived and designed the experiments: MP UP AC CS. Analyzed the data: MP CS AC. Contributed reagents/materials/analysis tools: MP AC CS JT UP. Wrote the first draft of the manuscript: MP. Contributed to the writing of the manuscript: MP AC CS JT UP. ICMJE criteria for authorship read and met: MP AC CS JT UP. Agree with manuscript results and conclusions: MP AC CS JT UP.

References

1. Tate JE, Burton AH, Boschi-Pinto C, Steele AD, Duque J, et al. (2011) 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect Dis 12: 136–141.
2. WHO (2009) Rotavirus vaccines: an update. Wkly Epidemiol Rec 84: 533–540.
3. Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, Abate H, Breuer T, et al. (2006) Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med 354: 11–22.
4. Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, et al. (2006) Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med 354: 23–33.

5. Armah GE, Sow SO, Breiman RF, Dallas MJ, Tapia MD, et al. (2010) Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in sub-Saharan Africa: a randomised, double-blind, placebo-controlled trial. Lancet 376: 606–614.
6. Zaman K, Dang DA, Victor JC, Shin S, Yunus M, et al. (2010) Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in Asia: a randomised, double-blind, placebo-controlled trial. Lancet 376: 615–623.
7. Murphy TV, Gargiullo PM, Massoudi MS, Nelson DB, Jumaan AO, et al. (2001) Intussusception among infants given an oral rotavirus vaccine. N Engl J Med 344: 564–572.
8. Buttery JP, Danchin MH, Lee KJ, Carlin JB, McIntyre PB, et al. (2011) Intussusception following rotavirus vaccine administration: post-marketing surveillance in the National Immunization Program in Australia. Vaccine 29: 3061–3066.
9. Patel MM, Lopez-Collada VR, Bulhoes MM, De Oliveira LH, Bautista Marquez A, et al. (2011) Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. N Engl J Med 364: 2283–2292.
10. Patel MM, Haber P, Baggs J, Zuber P, Bines JE, et al. (2009) Intussusception and rotavirus vaccination: a review of the available evidence. Expert Rev Vaccines 8: 1555–1564.
11. Gargiullo PM, Murphy TV, Davis RL (2006) Is there a safe age for vaccinating infants with tetravalent rhesus-human reassortant rotavirus vaccine? J Infect Dis 194: 1793–1794; author reply 1794–1795.
12. Rothman KJ, Young-Xu Y, Arellano F (2006) Age dependence of the relation between reassortant rotavirus vaccine (RotaShield) and intussusception. J Infect Dis 193: 898; author reply 898–899.
13. World Health Organization (WHO). Global and national estimates of deaths under age five attributable to rotavirus infection: 2004 (as of 31 March 2006). Available: http://www.who.int/immunization_monitoring/burden/rotavirus_estimates/en/. Accessed 16 June 2008.
14. Clark A, Sanderson C (2009) Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. Lancet 373: 1543–1549.
15. Patel MM, Clark AD, Glass RI, Greenberg H, Tate J, et al. (2009) Broadening the age restriction for initiating rotavirus vaccination in regions with high rotavirus mortality: benefits of mortality reduction versus risk of fatal intussusception. Vaccine 27: 2916–2922.
16. do Carmo GM, Yen C, Cortes J, Siqueira AA, de Oliveira WK, et al. (2011) Decline in diarrhea mortality and admissions after routine childhood rotavirus immunization in Brazil: a time-series analysis. PLoS Med 8: e1001024. doi:10.1371/journal.pmed.1001024
17. Richardson V, Hernandez-Pichardo J, Quintanar-Solares M, Esparza-Aguilar M, Johnson B, et al. (2010) Effect of rotavirus vaccination on death from childhood diarrhea in Mexico. N Engl J Med 362: 299–305.
18. Shui IM, Baggs J, Patel M, Parashar U, Rett M, et al. (2012) Risk of intussusception following administration of a pentavalent rotavirus vaccine in US infants. JAMA 307: 598–604.
19. Sanderson C, Clark A, Taylor D, Bolanos B, Fine P (2012) Global review of rotavirus morbidity and mortality data by age and region. Paper for the Initiative for Vaccine Research, World Health Organization, Geneva. Available:http://www.who.int/immunization/sage/meetings/2012/april/Sanderson_et_al_SAGE_April_rotavirus.pdf. Accessed 12 April 2012.
20. Akmatov MK, Mikolajczyk RT (2011) Timeliness of childhood vaccinations in 31 low and middle-income countries. J Epidemiol Community Health 66: e14.
21. WHO (2003) List of Member States by.WHO region and mortality stratum. Available: http://www.who.int/whr/2003/en/member_states_182-184_en.pdf. Accessed 12 March 2012.
22. DHS (ENDES) (2000) Programa DHS/Macro International Inc. Available: http://www.measuredhs.com. Accessed 16 January 2012.
23. UNICEF (2004) Multiple indicator cluster survey (MICS). Available: http://www.unicef.org/statistics/index_24302.html. Accessed 31 January 2012.
24. WHO-UNICEF (2012) WHO-UNICEF estimates of DTP1 coverage. Available: http://apps.who.int/immunization_monitoring/en/globalsummary/timeseries/tswucoveragedtp1.htm. Accessed 31 January 2012].
25. Patel M, Pedreira C, De Oliveira LH, Tate J, Orozco M, et al. (2009) Association between pentavalent rotavirus vaccine and severe rotavirus diarrhea among children in Nicaragua. JAMA 301: 2243–2251.
26. Linhares AC, Velazquez FR, Perez-Schael I, Saez-Llorens X, Abate H, et al. (2008) Efficacy and safety of an oral live attenuated human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in Latin American infants: a randomised, double-blind, placebo-controlled phase III study. Lancet 371: 1181–1189.
27. de Palma O, Cruz L, Ramos H, de Baires A, Villatoro N, et al. (2010) Effectiveness of rotavirus vaccination against childhood diarrhoea in El Salvador: case-control study. BMJ 340: c2825.
28. Madhi SA, Cunliffe NA, Steele D, Witte D, Kirsten M, et al. (2010) Effect of human rotavirus vaccine on severe diarrhea in African infants. N Engl J Med 362: 289–298.
29. Breiman RF, Zaman K, Armah G, Sow SO, Dang DA, et al. (2012) Ad hoc analyses of health outcomes from the 5 sites participating in the africa and asia clinical efficacy trials of oral pentavalent rotavirus vaccine. Vaccine 30 Suppl 1: A24–A29.
30. Lanzieri TM, Linhares AC, Costa I, Kolhe DA, Cunha MH, et al. (2011) Impact of rotavirus vaccination on childhood deaths from diarrhea in Brazil. Int J Infect Dis 15: e206–210.
31. Velazquez FR, Colindres RE, Grajales C, Hernandez MT, Mercadillo MG, et al. (2012) Postmarketing surveillance of intussusception following mass introduction of the attenuated human rotavirus vaccine in Mexico. Pediatr Infect Dis J 31: 736–744.
32. Escolano S, Farrington CP, Hill C, Tubert-Bitter P (2011) Intussusception after rotavirus vaccination–spontaneous reports. N Engl J Med 365: 2139.
33. Woolf B (1955) On estimating the relation between blood group and disease. Ann Hum Genet 19: 251–253.
34. Abate H, Linhares AC, Venegas G, Vergara RF, Lopez P, et al. A multi-center study of intussusception in Latin America: first year results [abstract]. Presented at: ICP; 15–20 August 2004; Cancun, Mexico.
35. Buettcher M, Baer G, Bonhoeffer J, Schaad UB, Heininger U (2007) Three-year surveillance of intussusception in children in Switzerland. Pediatrics 120: 473–480.
36. Chen YE, Beasley S, Grimwood K (2005) Intussusception and rotavirus associated hospitalisation in New Zealand. Arch Dis Child 90: 1077–1081.
37. Fischer TK, Bihrmann K, Perch M, Koch A, Wohlfahrt J, et al. (2004) Intussusception in early childhood: a cohort study of 1.7 million children. Pediatrics 114: 782–785.
38. Gay N, Ramsay M, Waight P (1999) Rotavirus vaccination and intussusception. Lancet 354: 956.
39. Ho WL, Yang TW, Chi WC, Chang HJ, Huang LM, et al. (2005) Intussusception in Taiwanese children: analysis of incidence, length of hospitalization and hospital costs in different age groups. J Formos Med Assoc 104: 398–401.
40. Justice F, Carlin J, Bines J (2005) Changing epidemiology of intussusception in Australia. J Paediatr Child Health 41: 475–478.
41. Nelson EA, Tam JS, Glass RI, Parashar UD, Fok TF (2002) Incidence of rotavirus diarrhea and intussusception in Hong Kong using standardized hospital discharge data. Pediatr Infect Dis J 21: 701–703.
42. O'Ryan M, Lucero Y, Pena A, Valenzuela MT (2003) Two year review of intestinal intussusception in six large public hospitals of Santiago, Chile. Pediatr Infect Dis J 22: 717–721.
43. Perez-Schael I, Escalona M, Salinas B, Materan M, Perez ME, et al. (2003) Intussusception-associated hospitalization among Venezuelan infants during 1998 through 2001: anticipating rotavirus vaccines. Pediatr Infect Dis J 22: 234–239.
44. Saez-Llorens X, Guevara JN (2004) Intussusception and rotavirus vaccines: what is the background risk? Pediatr Infect Dis J 23: 363–365.
45. Tate JE, Simonsen L, Viboud C, Steiner C, Patel MM, et al. (2008) Trends in intussusception hospitalizations among US infants, 1993–2004: implications for monitoring the safety of the new rotavirus vaccination program. Pediatrics 121: e1125–1132.
46. Moore SW, Kirsten M, Muller EW, Numanoglu A, Chitnis M, et al. (2010) Retrospective surveillance of intussusception in South Africa, 1998–2003. J Infect Dis 202 Suppl: S156–161.
47. Latipov R, Khudoyorov R, Flem E (2011) Childhood intussusception in Uzbekistan: analysis of retrospective surveillance data. BMC Pediatr 11: 22.
48. Kohl LJ, Streng A, Grote V, Koletzko S, Liese JG (2010) Intussusception-associated hospitalisations in southern Germany. Eur J Pediatr 169: 1487–1493.
49. Chen SC, Wang JD, Hsu HY, Leong MM, Tok TS, et al. (2010) Epidemiology of childhood intussusception and determinants of recurrence and operation: analysis of national health insurance data between 1998 and 2007 in Taiwan. Pediatr Neonatol 51: 285–291.
50. Bissantz N, Jenke AC, Trampisch M, Klaassen-Mielke R, Bissantz K, et al. (2011) Hospital-based, prospective, multicentre surveillance to determine the incidence of intussusception in children aged below 15 years in Germany. BMC Gastroenterol 11: 26.
51. Bahl R, Saxena M, Bhandari N, Taneja S, Mathur M, et al. (2009) Population-based incidence of intussusception and a case-control study to examine the association of intussusception with natural rotavirus infection among indian children. J Infect Dis 200 Suppl 1: S277–281.
52. Bines JE, Patel M, Parashar U (2009) Assessment of postlicensure safety of rotavirus vaccines, with emphasis on intussusception. J Infect Dis 200 Suppl 1: S282–290.
53. Steele AD, Patel M, Cunliffe N, Bresee J, Parashar U (2012) Retrospective review of intussusception in 9 African countries. Vaccine 30: Suppl 1: A185–A189.
54. Patel MM, Steele D, Gentsch JR, Wecker J, Glass RI, et al. (2011) Real-world impact of rotavirus vaccination. Pediatr Infect Dis J 30: S1–S5.
55. Patel MM, Glass R, Desai R, Tate JE, Parashar UD (2012) Fulfilling the promise of rotavirus vaccines: how far have we come since licensure? Lancet Infect Dis 12: 561–570.
56. Yen C, Armero Guardado JA, Alberto P, Rodriguez Araujo DS, Mena C, et al. (2011) Decline in rotavirus hospitalizations and health care visits for childhood diarrhea following rotavirus vaccination in El Salvador. Pediatr Infect Dis J 30: S6–S10.
57. Field EJ, Vally H, Grimwood K, Lambert SB (2010) Pentavalent rotavirus vaccine and prevention of gastroenteritis hospitalizations in australia. Pediatrics 126: e506–512.

58. Cortes JE, de Oliveira LH, Patel MM, Parashar U, Cortese M (2011) Reduction of diarrhea-associated hospitalizations among children aged <5 years in Panama following the introduction of rotavirus vaccine. Pediatr Infect Dis J 30: S16–S20.
59. Braeckman T, Van Herck K, Raes M, Vergison A, Sabbe M, et al. (2011) Rotavirus vaccines in Belgium: policy and impact. Pediatr Infect Dis J 30: S21–S24.
60. Anh DD, Carlos CC, Thiem DV, Hutagalung Y, Gatchalian S, et al. (2011) Immunogenicity, reactogenicity and safety of the human rotavirus vaccine RIX4414 (Rotarix) oral suspension (liquid formulation) when co-administered with expanded program on immunization (EPI) vaccines in Vietnam and the Philippines in 2006–2007. Vaccine 29: 2029–2036.
61. Ball LK, Evans G, Bostrom A (1998) Risky business: challenges in vaccine risk communication. Pediatrics 101: 453–458.
62. Bauch CT, Earn DJ (2004) Vaccination and the theory of games. Proc Natl Acad Sci U S A 101: 13391–13394.
63. Connolly T, Reb J (2003) Omission bias in vaccination decisions: Where's the "omission"? Where's the "bias"? Organ Behav Hum Dec 91: 186–202.
64. Weijer C (2000) The future of research into rotavirus vaccine. BMJ 321: 525–526.
65. Available: http://www.cdc.gov/nchs/nis.htm. Accessed 3 January 2012.
66. WHO (2012) Meeting of the strategic advisory group of experts on immunization, April 2012–conclusions and recommendations. Wkly Epidemiol Rec 87: 212–213.

Editors' Summary

Background. Rotavirus causes severe diarrhea and vomiting. It is responsible for a large number of hospitalizations among young children in developed countries (an estimated 60,000 hospitalizations per year in the US in 2005, for example). In poor countries, rotavirus is a major cause of death in children under five. In 1998, the first rotavirus vaccine, called RotaShield, was approved in the US by the Food and Drug Administration. Shortly after the vaccine became widely used, doctors noticed a small increase in a problem called intussusception among the vaccinated infants. Intussusception is a rare type of bowel obstruction that occurs when the bowel telescopes in on itself. Prompt treatment of intussusception normally leads to full recovery, but some children with the condition need surgery, and when the disease is left untreated it can be fatal. Because intussusception is a serious condition and because very few children die from rotavirus infection in the United States, the US authorities stopped recommending vaccination with RotaShield in 1999. The manufacturer withdrew the vaccine from the market shortly thereafter.

Since then, two new vaccines (named Rotarix and RotaTeq) have been developed. Before they were approved in the US and elsewhere, they were extensively tested for any adverse side effects, especially intussusception. No increase in the risk for intussusception was found in these studies, and both are now approved and recommended for vaccination of infants around the world.

Why Was This Study Done? Since 2006, hundreds of thousands of infants have been vaccinated with Rotarix or RotaTeq, with safety being closely monitored. Some countries have reported a small increase in intussusception (one to four additional cases per 100,000 vaccinated infants, compared with one per 2,000 of cases that occur in unvaccinated children). This increase is much lower than the one seen previously with RotaShield. In response to these findings, authorities in the US and other developed countries as well as the World Health Organization declared that the benefits of the vaccine outweigh the risks of the small number of additional intussusception cases in both developed and poor countries. However, because older infants have a higher risk of naturally occurring intussusception, they decided that the course of vaccination (three oral doses for Rotarix and two for RotaTeq) should be initiated before 15 weeks of age and completed before the age of 32 weeks. This is usually not a problem in countries with easy access to health facilities. However, in many poor countries where delays in infant vaccination are common, giving the vaccine only to very young children means that many others who could benefit from its protection will be excluded. In this study, the researchers examined the risks and benefits of rotavirus vaccination in poor countries where most of the rotavirus deaths occur. Specifically, they looked at the benefits and risks if the age restrictions were removed, with a particular emphasis on allowing infants to initiate rotavirus immunization even if they arrive after 15 weeks of age.

What Did the Researchers Do and Find? The researchers used the most recent estimates for how well the vaccines protect children in Africa and Asia from becoming infected with rotavirus, how many deaths from rotavirus infection can be avoided by vaccination, how many additional cases of intussusception will likely occur in vaccinated children, and what proportion of children would be excluded from rotavirus vaccination because they are too old when they come to a health facility for their infant vaccination. They then estimated the number of rotavirus deaths prevented and the number of intussusception deaths caused by vaccination in two scenarios. The first one (the restricted scenario) corresponds to previous guidelines from WHO and others, in which rotavirus vaccination needs to be initiated before 15 weeks and the full series completed before 32 weeks. The second one (called the unrestricted scenario) allows rotavirus vaccination of children alongside current routinely administered vaccines up to three years of age, recognizing that most children receive their vaccination by 1 year of life.

The researchers estimated that removing the age restriction would prevent an additional 154 rotavirus deaths for each intussusception death caused by the vaccine. Under the unrestricted scenario, roughly a third more children would get vaccinated, which would prevent an additional approximately 47,000 death from rotavirus while causing approximately 300 additional intussusception deaths.

They also calculated some best- and worst-case scenarios. The worst-case scenario assumed a much higher risk of intussusception for children receiving their first dose after 15 weeks of life than what has been seen anywhere, and also that an additional 20% of children with intussusception would die from it than what was already assumed in their routine scenario (again, a higher number than seen in reality). In addition, it assumes a lower protection from rotavirus death for the vaccine than has been observed in children vaccinated so far. In this pessimistic case, the number of rotavirus deaths prevented was 24 for each intussusception death caused by the vaccine.

What Do These Findings Mean? If one accepts that deaths caused by a vaccine are not fundamentally different from deaths caused by a failure to vaccinate, then these results show that the benefits of lifting the age restriction for rotavirus vaccine clearly outweigh the risks, at least when only examining mortality outcomes. The calculations are valid only for low-income countries in Africa and Asia where both vaccination delays and deaths from rotavirus are common. The risk-benefit ratio will be different elsewhere. There are also additional risks and benefits that are not included in the study's estimates. For example, early vaccination might be seen as less of an urgent priority when this vaccine can be had at a later date, leaving very young children more vulnerable. On the other hand, when many children in the community are vaccinated, even the unvaccinated children are less likely to get infected (what is known as "herd immunity"), something that has not been taken into account in the benefits here. The results of this study (and its limitations) were reviewed in April 2012 by WHO's Strategic Advisory Group of Experts. The group then recommended that, while early vaccination is still strongly encouraged, the age restriction on rotavirus vaccination should be removed in countries where delays in vaccination and rotavirus mortality are common so that more vulnerable children can be vaccinated and deaths from rotavirus averted.

Additional Information. Please access these Web sites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.1001330.

- The World Health Organization provides information on rotavirus

- Wikipedia has information on rotavirus vaccine and intussusception (note that Wikipedia is a free online encyclopedia that anyone can edit; available in several languages)
- The US Centers for Disease Control and Prevention rotavirus vaccination page includes a link to frequently asked questions
- PATH Rotavirus Vaccine Access and Delivery has timely, useful updates on status of rotavirus vaccines globally

Appendix 2

Refers to:

Chapter 2, WHO position paper, January 2013

World Health Organization

Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

1ST FEBRUARY 2013, 88th YEAR / 1er FÉVRIER 2013, 88e ANNÉE
No. 5, **2013**, **88**, 49–64
http://www.who.int/wer

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Rotavirus vaccines

WHO position paper – January 2013

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and combinations of vaccines against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale immunization programmes; they summarize essential background information on diseases and vaccines, and conclude with the current WHO position on the use of vaccines worldwide.

The papers have been reviewed by external experts and WHO staff, and are reviewed and endorsed by the WHO Strategic Advisory Group of Experts on Immunization (SAGE).[1] The position papers are intended for use mainly by national public health officials and managers of immunization programmes. They may also be of interest to international funding agencies, vaccine manufacturers, the medical community, the scientific media, and the public. A description of the processes followed for the development of vaccine position papers is available at http://www.who.int/immunization/position_papers/position_paper_process.pdf

This position paper replaces the corresponding WHO position paper of 2007 and its update of 2009; it summarizes recent developments in the field, in particular the potential of rotavirus vaccines to further reduce mortality by employing more flexible immunization schedules. All WHO recommendations appear at the end of this paper and reflect those offered by SAGE. Rotavirus vaccines were last discussed by SAGE at its meeting in April 2012; evidence presented at the meeting

[1] See http://www.who.int/immunization/sage/en

Vaccins antirotavirus

Note de synthèse de l'OMS

Conformément à son mandat qui consiste à orienter les États Membres sur les questions de santé publique, l'OMS diffuse une série de notes de synthèse régulièrement mises à jour sur les vaccins et associations de vaccins qui intéressent la santé publique internationale. Ces notes, qui concernent avant tout l'utilisation des vaccins dans les programmes de vaccination à grande échelle, résument les informations de base essentielles sur les maladies et les vaccins dont il est question et indiquent la position actuelle de l'OMS sur l'utilisation des vaccins dans le contexte mondial.

Elles ont été soumises à l'examen d'un certain nombre d'experts externes et de membres du personnel de l'OMS et font l'objet d'un examen et d'une approbation par le groupe consultatif stratégique d'experts de l'OMS (SAGE) sur la vaccination.[1] Les notes de synthèse sont principalement destinées aux responsables nationaux de la santé publique et des programmes de vaccination. Elles peuvent toutefois aussi intéresser les organismes internationaux de financement, les fabricants de vaccins, le corps médical dans son ensemble, les médias scientifiques et le grand public. Le processus suivi pour l'élaboration des notes de synthèse sur les vaccins est décrit sur: http://www.who.int/immunization/position_papers/position_paper_process.pdf

La présente note actualisée, qui remplace le document correspondant publié en 2007 et la mise à jour de 2009, récapitule l'évolution récente sur le terrain, en particulier le potentiel qu'on les vaccins antirotavirus pour réduire davantage la mortalité en permettant des calendriers de vaccination plus flexibles. Toutes les recommandations de l'OMS sont données à la fin du document et reprennent celles proposées par le SAGE. Le sujet des vaccins antirotavirus a été discuté pour la dernière fois par le SAGE lors de sa réunion

[1] Voir http://www.who.int/immunization/sage/fr

can be accessed at http://www.who.int/immunization/sage/previous/en/index.html.

Background

Epidemiology

Rotaviruses infect nearly every child by the age of 3–5 years and are globally the leading cause of severe, dehydrating diarrhoea in children aged <5 years. In low income countries the median age at the primary rotavirus infection ranges from 6 to 9 months (80% occur among infants <1 year old) whereas in high income countries, the first episode may occasionally be delayed until the age of 2–5 years, though the majority still occur in infancy (65% occur among infants <1 year old).[2]

In most low income countries in Asia and Africa, rotavirus epidemiology is characterized by one or more periods of relatively intense rotavirus circulation against a background of year-round transmission, whereas in high income countries with temperate climates a distinct winter seasonality is typically observed. This difference, as well as differences in health care availability and childhood co-morbidity, drive the marked inequality in rotavirus disease burden between low and high income countries.[3]

WHO estimates that in 2008, approximately 453 000 (420 000–494 000) rotavirus gastroenteritis (RVGE)-associated child deaths occurred worldwide (updated WHO estimates on global mortality due to RVGE are soon to be published). These fatalities accounted for about 5% of all child deaths and a cause-specific mortality rate of 86 deaths per 100 000 population aged <5 years. About 90% of all rotavirus-associated fatalities occur in low income countries in Africa and Asia and are related to poor health care. National cause-specific mortality rates ranged from 474/100 000 (Afghanistan) to < 1/100 000 (63 countries); in 4 countries (Afghanistan, Burundi, Chad and Somalia) mortality rates of >300/100 000 were recorded.[4]

Each year during the pre-vaccination era 1986–2000, >2 million children worldwide were hospitalized for rotavirus infections.[5] In a recent report of sentinel hospital-based rotavirus surveillance from 35 nations representing each of the 6 WHO Regions and different economic levels, an average of 40% (range 34%–45%) of hospitalizations for diarrhoea among children aged <5 years were attributable to rotavirus infection.[6]

en avril 2012. Le site http://www.who.int/immunization/sage/previous/en/index.html permet d'accéder aux données factuelles présentées lors de cette réunion.

Informations générales

Épidémiologie

À l'âge de 3 à 5 ans, pratiquement tous les enfants ont été infectés par les rotavirus qui, partout dans le monde, sont la première cause de diarrhée sévère avec déshydratation chez les enfants de <5 ans. Dans les pays à faible revenu, l'âge médian de l'infection primaire à rotavirus s'établit entre 6 et 9 mois (80% des cas surviennent chez les nourrissons de moins d'un an) alors que, dans les pays à revenu élevé, le premier épisode n'arrive parfois pas avant l'âge de 2 à 5 ans, bien qu'en majorité, les nourrissons restent les plus atteints (65% des cas se produisent chez les nourrissons de <1 an).[2]

Dans la plupart des pays à faible revenu d'Asie et d'Afrique, l'épidémiologie du rotavirus se caractérise par une ou plusieurs périodes de circulation relativement intense, par rapport à une transmission de fond toute l'année alors que, dans les pays à revenu élevé des régions à climat tempéré, on observe classiquement une saisonnalité hivernale marquée. Cette différence et celles existant au niveau de la disponibilité des soins et des morbidités concomitantes dans l'enfance, induisent une forte inégalité de la charge de morbidité imputable aux rotavirus entre les pays à revenu faible et élevé.[3]

L'OMS estime qu'en 2008, il y a eu environ 453 000 (420 000-494 000) décès d'enfants liés à des gastroentérites à rotavirus (GERV) dans le monde (des estimations actualisées de l'OMS sur la mortalité mondiale due aux GERV vont être publiées prochainement). Ces morts ont représenté environ 5% des décès d'enfants, avec un taux de mortalité spécifique de 86 décès pour 100 000 enfants de <5 ans. Près de 90% des décès dus aux rotavirus surviennent dans les pays à faible revenu en Afrique et en Asie et ils sont liés à la mauvaise qualité des soins de santé. Les taux de mortalité spécifiques nationaux sont allés de 474/100 000 (Afghanistan) à <1/100 000 (63 pays); dans 4 pays (Afghanistan, Burundi, Somalie et Tchad) on a enregistré des taux de mortalité >300/100 000.[4]

Chaque année, de 1986 à 2000, avant l'existence de la vaccination, >2 millions d'enfants dans le monde ont été hospitalisés pour des rotaviroses.[5] Dans un rapport récent de la surveillance des rotavirus par des hôpitaux sentinelles de 35 pays représentant chacune des 6 régions de l'OMS et des niveaux économiques différents, en moyenne 40% (entre 34% et 45%) des hospitalisations pour diarrhée chez des enfants de <5 ans étaient dues à des rotaviroses.[6]

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[2] Sanderson C et al. *Global review of rotavirus morbidity and mortality data by age and WHO region.* Report to WHO/IVB, 2011 (www.who.int/entity/immunization/sage/meetings/2012/april/presentations_background_docs/en/ - 45k).

[3] *Detailed review paper on rotavirus vaccines* (presented to the WHO Strategic Advisory Group of Experts (SAGE) on Immunization in April 2009). Geneva, World Health Organization, 2009. Available from (http://www.who.int/immunization/sage/3_Detailed_Review_Paper_on_Rota_Vaccines_17_3_2009.pdf).

[4] WHO estimate for January 2012: http://www.who.int/immunization_monitoring/burden/rotavirus_estimates/en/index.html

[5] Parashar DU et al. Global illness and deaths caused by rotavirus disease in children. *Emerging Infectious Diseases*, 2003, 9:565–572.

[6] See No. 47, 2008, pp. 421–425.

[2] Sanderson C et al. *Global review of rotavirus morbidity and mortality data by age and WHO region.* Report to WHO/IVB, 2011 (www.who.int/entity/immunization/sage/meetings/2012/april/presentations_background_docs/en/ - 45k).

[3] *Detailed review paper on rotavirus vaccines* (présenté à la Réunion OMS du Groupe stratégique consultatif d'experts sur la vaccination en avril 2012). Genève, Organisation mondiale de la Santé, 2009. Disponible sur (http://www.who.int/immunization/sage/3_Detailed_Review_Paper_on_Rota_Vaccines_17_3_2009.pdf). [Document disponible en anglais uniquement.]

[4] WHO estimate for January 2012: http://www.who.int/immunization_monitoring/burden/rotavirus_estimates/en/index.html

[5] Parashar DU et al. Global illness and deaths caused by rotavirus disease in children. *Emerging Infectious Diseases*, 2003, 9:565–572.

[6] Voir N° 47, 2008, pp. 421-425.

The universal occurrence of rotavirus infections even in settings with high standards of hygiene testifies to the high transmissibility of this virus.

Pathogen, disease and laboratory diagnosis

The pathogen

Rotaviruses are classified as a genus in the family of *Reoviridae*. The triple-layered viral particle encompasses a viral genome consisting of 11 segments of double-stranded RNA that encode 6 structural viral proteins (VPs) and 5 or 6 non-structural proteins (NSPs). Reassortment of the 11 gene segments may take place in coinfected host cells during the viral replication cycle. Formation of reassortants is in part responsible for the wide variety of rotavirus strains found in nature; even reassortants of animal-human strains have been identified. The outermost viral layer contains the viral proteins VP7 and VP4, which elicit the production of neutralizing antibodies in the host and hence are considered important for protective immunity. In human rotaviruses, at least 12 different VP7 antigens (G-types) and 15 different VP4 antigen (P-types) have been identified. As the combination of G- and P-types can vary independently, a binomial typing system is used to identify strains. Currently, 5 G-P combinations (G1P[8], G2P[4], G3P[8], G4P[8]) and G9P[8]) account for approximately 90% of all human rotavirus infections in many parts of the world; type G1P[8] is the most prevalent combination. However, data from countries in Asia and Africa show greater strain diversity with several rotavirus types circulating simultaneously. The prevalent types may vary from one season to the next, even within the same geographical area. The type of rotavirus does not usually correlate with the severity of the disease. There are currently no known laboratory markers for rotavirus virulence.[7, 8]

During the first episode of rotavirus infection, rotaviruses are shed for several days in very high concentrations (>10^{12} particles/gram) in the stools and vomitus of infected individuals. Transmission occurs primarily by the faecal-oral route directly from person to person, or indirectly via contaminated fomites.

Disease

Rotavirus infections affect primarily the mature enterocytes on the tips of the small intestinal villi. Destruction of these cells reduces the absorptive capacity of the villi, resulting in diarrhoea.

The clinical spectrum of rotavirus disease is wide, ranging from transient loose stools to severe diarrhoea and vomiting causing dehydration, electrolyte disturbances, shock and death. In typical cases, following an incubation period of 1–3 days, the onset of disease is abrupt, with fever and vomiting followed by explosive watery

Le fait que les infections à rotavirus sévissent dans le monde entier, même dans les milieux aux normes d'hygiène élevées, atteste de la forte transmissibilité de ce virus.

Agent pathogène, maladie et diagnostic en laboratoire

Agent pathogène

Les rotavirus sont classés en tant que genre dans la famille des réoviridés. La particule virale est dotée d'une capside protéique à triple couche et a un génome qui est constitué d'un ARN double-brin composé de 11 segments et qui code pour 6 protéines structurales (VP) et 5 ou 6 protéines non structurales (NSP). Un réassortiment des 11 segments génétiques peut s'opérer dans des cellules hôtes subissant une co-infection pendant le cycle de réplication du virus. L'apparition de virus réassortis est en partie responsable de la grande variété des souches rencontrées dans la nature et on en a même observées qui résultaient du réassortiment entre des souches humaines et animales. La couche virale la plus externe contient les protéines virales VP7 et VP4, qui déclenchent la production d'anticorps neutralisants chez l'hôte et qui sont donc considérés comme jouant un rôle important dans l' immunité protectrice. Chez les rotavirus de l'homme, on a identifié au moins 12 antigènes VP7 (sérotypes G) et 15 antigènes VP4 (sérotypes P) différents. Les sérotypes G et P pouvant se combiner indépendamment, on a eu recours à un système de typage binomial pour identifier les souches. Actuellement, dans de vastes régions du monde, 5 combinaisons (G1P[8], G2P[4], G3P[8], G4P[8] et G9P[8]) sont à l'origine d'environ 90% de la totalité des rotaviroses humaines, le type G1P[8] ayant la plus forte prévalence. En revanche, des données provenant d'Asie et d'Afrique révèlent une plus grande diversité des types de rotavirus en circulation simultanée. Les sérotypes prévalents peuvent varier d'une saison à l'autre, y compris au sein d'une même zone géographique. Il n'y a pas habituellement de corrélation entre le sérotype et la gravité de la maladie. Il n'y a pas actuellement de marqueurs connus permettant de déterminer en laboratoire la virulence d'un rotavirus.[7, 8]

Au cours du premier épisode de rotavirose, les virus sont excrétés pendant plusieurs jours à de très fortes concentrations (>10^{12} particules/gramme) dans les selles et les vomissures des sujets infectés. La transmission se fait principalement par voie féco-orale directe entre 2 personnes, ou indirectement par des matières contaminées.

Maladie

Les rotaviroses touchent principalement les entérocytes matures au sommet des villosités intestinales. La destruction de ces cellules réduit la capacité d'absorption des villosités, ce qui provoque la diarrhée.

Le spectre clinique des rotaviroses est très large, allant d'un ramollissement transitoire des selles à une diarrhée sévère et des vomissements, entraînant une déshydratation, des troubles électrolytiques, un état de choc et la mort. Dans les cas typiques, après une incubation de 1 à 3 jours, la maladie se manifeste brutalement, avec de la fièvre, des vomissements, suivis d'une

[7] Hu L et al. Rotavirus non-structural proteins: structure and function. *Current Opinion in Virology*, 2012, 2:380–388.

[8] *Manual of rotavirus detection and characterization methods* (WHO/IVB/08.17). Geneva, World Health Organization, 2009. Available from http://www.who.int/nuvi/rotavirus/WHO_IVB_08.17_eng.pdf, accessed January 2013.

[7] Hu L et al. Rotavirus non-structural proteins: structure and function. *Current Opinion in Virology*, 2012, 2:380–388.

[8] *Manual of rotavirus detection and characterization methods* (WHO/IVB/08.17). Genève, Organisation mondiale de la Santé, 2009. Disponible sur http://www.who.int/vaccines-documents/DocsPDF02/www635.pdf, consulté en juin 2011. [Document disponible en anglais uniquement.]

diarrhoea. Without adequate fluid replacement, dehydration may ensue. Detailed clinical scoring systems have been developed to facilitate comparison of disease severity, particularly in vaccine trials. Gastrointestinal symptoms normally disappear within 3–7 days, but may last for up to 2–3 weeks. Although in most cases, recovery is complete, fatalities due to RVGE may occur, mainly in children ≤1 year of age.[2, 9, 10]

No specific therapy is currently available against rotaviruses. As with other childhood diarrhoeas, the cornerstones of treatment are fluid replacement to prevent dehydration, and zinc treatment which decreases the severity and duration of diarrhoea. Solutions of low-osmolarity oral rehydration salts (ORS) are more effective in replacing fluids than previous ORS formulations. Additional treatment measures during the diarrhoeal episode include continued feeding, including breastfeeding, and if ORS are not available, use of appropriate fluids available in the home.[11]

Laboratory diagnosis

An etiological diagnosis of rotavirus gastroenteritis requires laboratory confirmation. A range of diagnostic tests are commercially available: enzyme immunoassays for detection of rotavirus antigen directly in stool specimens are widely used, as are also the less sensitive, but rapid and simple-to-use test strips and latex agglutination assays. Reverse transcription polymerase chain reaction (RT-PCR), which is highly sensitive in detecting small concentrations of rotavirus in stool specimens, is also used for strain identification and further differentiation.[8]

Protective immunity

Protection against rotavirus infection is mediated by both humoral and cellular components of the immune system. Following the first infection, the serological response is directed mainly against the specific viral serotype (i.e. a homotypic response), whereas a broader, heterotypic antibody response is elicited following ≥1 subsequent rotavirus infections.[12]

A study that monitored 200 Mexican infants from birth to 2 years of age by weekly home visits and stool collections, detected on the basis of the fecal excretion of virus or a serologic response a total of 316 rotavirus infections, of which 52% were first and 48% repeated infections. Children with 1, 2, or 3 previous infections had progressively lower risk of subsequent rotavirus infection (adjusted relative risk, 0.62, 0.40, and 0.34, respectively) or of diarrhoea (adjusted relative risk, 0.23,

diarrhée explosive et aqueuse. Si l'on ne remplace pas suffisamment les liquides perdus, il peut s'ensuivre une déshydratation. Des systèmes d'évaluation clinique précis ont été mis au point pour permettre une comparaison plus facile de la gravité, notamment dans le cadre des essais de vaccins. Les symptômes gastro-intestinaux disparaissent normalement au bout de 3 à 7 jours, mais peuvent perdurer pendant 2 à 3 semaines. Bien que, dans la plupart des cas, la récupération soit totale, les GERV peuvent entraîner la mort, principalement pour les nourrissons jusqu'à l'âge d'un an.[2, 9, 10]

Il n'existe actuellement aucun traitement spécifique. Comme pour d'autres diarrhées de l'enfance, la thérapie se fonde sur le remplacement des liquides pour éviter la déshydratation et l'administration de zinc, qui diminue la gravité et la durée de la diarrhée. Les solutions de sels de réhydratation orale (SRO) à osmolarité réduite sont plus efficaces pour remplacer les liquides perdus que les anciennes présentations. Les mesures thérapeutiques complémentaires au cours de l'épisode diarrhéique comprennent la poursuite de l'alimentation, y compris l'allaitement au sein et, s'il n'y a pas de SRO, l'utilisation des liquides adaptés disponibles à domicile.[11]

Examens diagnostiques au laboratoire

Le diagnostic étiologique d'une gastroentérite à rotavirus nécessite la confirmation d'un laboratoire. Il existe sur le marché toute une gamme d'essais: les tests immunoenzymatiques pour la détection directe des antigènes de rotavirus dans les échantillons de selles sont largement utilisés, de même que des bandelettes réactives et des test d'agglutination sur latex, rapides mais moins sensibles. On a aussi recours à la RT-PCR (transcription inverse couplée à l'amplification génique), très sensible pour détecter de faibles concentrations de rotavirus dans les échantillons de selles, identifier et différentier les souches.[8]

Immunité protectrice

La protection contre les rotaviroses fait appel à la fois à la médiation humorale et cellulaire du système immunitaire. La primo-infection entraîne une réponse sérologique dirigée principalement contre le sérotype viral présent (c'est-à-dire une réponse homotypique), tandis qu'une ou plusieurs infections à rotavirus ultérieures induisent une réponse en anticorps plus large et hétérotypique.[12]

Une étude surveillant 200 nourrissons mexicains de la naissance à l'âge de 2 ans au moyen de visites hebdomadaires au domicile et de prélèvements de selles a détecté, sur la base de l'excrétion fécale du virus ou d'une réponse sérologique, un total de 316 rotaviroses, dont 52% étaient des primo-infections et 48% des réinfections. Les enfants ayant déjà eu 1, 2 ou 3 infections avaient progressivement un risque plus faible de contracter de nouveau une rotavirose (risque relatif ajusté, 0,62, 0,40 et 0,34 respectivement) ou une diarrhée (risque relatif ajusté,

[9] Gladstone BP et al. Protective effect of natural rotavirus infection in an Indian birth cohort. *New England Journal of Medicine*, 2011, 365:337–346.

[10] Velazquez FR, Matson DO, Calva JJ et al. Rotavirus infection in infants as protection against subsequent infections. *New England Journal of Medicine*, 1996, 335:1022–1028.

[11] *Oral rehydration salts. Production of the new ORS* (WHO/FCH/CAH/06.1). Geneva, WHO/UNICEF, 2006. Available from http://whqlibdoc.who.int/hq/2006/WHO_FCH_CAH_06.1.pdf, accessed January 2013.

[12] Angel J et al. Rotavirus immune responses and correlates of protection. *Current Opinion in Virology*, 2012, 419-425.

[9] Gladstone BP et al. Protective effect of natural rotavirus infection in an Indian birth cohort. *New England Journal of Medicine*, 2011, 365:337–346.

[10] Velazquez FR, Matson DO, Calva JJ et al. Rotavirus infection in infants as protection against subsequent infections. *New England Journal of Medicine*, 1996, 335:1022–1028.

[11] *Oral rehydration salts. Production of the new ORS* (WHO/FCH/CAH/06.1). Genève, OMS/UNICEF, 2006. Disponible sur http://whqlibdoc.who.int/hq/2006/WHO_FCH_CAH_06.1.pdf, consulté en janvier 2013.

[12] Angel J et al. Rotavirus immune responses and correlates of protection. *Current Opinion in Virology*, 2012, 419-425.

0.17, and 0.08) than children who had no previous infections. Subsequent infections were significantly less severe than first infections (p=0.02) and second infections were more likely to be caused by another G type (p=0.05).[10] However, one study from India reported that the risk of severe disease continued after several re-infections.[9]

In immunocompromised patients, natural rotavirus infection is not regularly associated with severe diarrhoea or systemic disease, although shedding of the virus may be prolonged. However, individuals with congenital immunodeficiency, bone marrow transplantation or solid organ transplantation sometimes experience severe, prolonged and even fatal RVGE.[13] In South Africa, the estimated incidence of acute RVGE was 2.3 fold (95% confidence interval: 1.8–2.9) higher in HIV-infected than in non-infected individuals.[14] A study in Malawi found no differences in rotavirus disease severity for hospitalized children with and without HIV infection, but of 29 HIV-infected and 45 HIV-uninfected children who completed at least 3 weeks of follow-up, 6 (21%) HIV-infected children shed rotavirus, compared with 2 (4%) HIV-uninfected children (relative risk 4.7 [95% CI: 1.0–21.5], p=0.05). Shedding was not associated with diarrhoea.[15]

The immune correlates of protection against rotavirus infection are incompletely defined, but the immune responses to the VP4 and VP7 proteins are generally believed to be important. Serum anti-rotavirus IgA antibody responses have been used as a measure of immunogenicity of all the live attenuated rotavirus vaccines evaluated.[16]

Rotavirus vaccines

Currently available vaccines are live, oral, attenuated rotavirus strains of human and/or animal origin that replicate in the human intestine. Two oral rotavirus vaccines are marketed internationally: the monovalent (RV1) Rotarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium) and the pentavalent (RV5) RotaTeq® (Merck & Co. Inc., West Point, PA, USA). In this document the 2 vaccines are referred to as RV1 and RV5, respectively. Lanzhou lamb rotavirus vaccine,manufactured by the Lanzhou Institute of Biomedical Products in China, and Rotavin-M1, manufactured by Polyvac in Viet Nam, are not available internationally and hence not further discussed here.

WHO guidelines to assure the quality, safety and efficacy of live attenuated rotavirus vaccines are available.[15]

0,23, 0,17 et 0,08) par rapport aux enfants sans antécédents d'infection. Les rotaviroses ultérieures ont été nettement moins graves que les primo-infections (p=0,02) et les deuxièmes infections ont eu une plus grande probabilité d'être causée par un autre sérotype G (p=0,05).[10] Néanmoins, une étude en Inde a signalé que le risque de maladie grave persistait après plusieurs réinfections.[9]

Chez les sujets immunodéprimés, les rotaviroses naturelles ne s'associent pas systématiquement à des diarrhées sévères ou à une maladie systémique, bien que l'excrétion du virus puisse se prolonger. En revanche, chez les sujets atteints d'immunodéficience congénitale ou ayant eu une transplantation de moelle osseuse ou d'un organe solide, il arrive d'observer des gastroentérites à rotavirus sévères, prolongées et parfois mortelles.[13] En Afrique du Sud, l'estimation de l'incidence de la gastroentérite aiguë à rotavirus a été 2,3 fois supérieure (intervalle de confiance (IC) à 95%: 1,8-2,9) chez les sujets infectés par le VIH par rapport aux personnes séronégatives.[14] Une étude au Malawi n'a pas révélé de différence dans la gravité de la rotavirose chez les enfants hospitalisés avec ou sans VIH mais, sur les 29 enfants séropositifs et les 45 séronégatifs ayant achevé au moins 3 semaines de suivi, 6 enfants infectés par le VIH (21%) excrétaient des rotavirus, contre 2 (4%) enfants séronégatifs (risque relatif 4,7 [IC à 95%: 1,0-21,5], p=0,05). L'excrétion n'a pas été associée à une diarrhée.[15]

Les indicateurs de la protection immunitaire contre les rotaviroses ne sont pas complètement définis, mais on pense en général que les réponses immunitaires aux protéines VP4 et VP7 jouent un rôle important. Les réponses des anticorps sériques IgA spécifiques ont été utilisées pour mesurer l'immunogénicité de tous les vaccins antirotavirus vivants atténués qui ont été évalués.[16]

Vaccins antirotavirus

Les vaccins actuellement disponibles contiennent des souches vivantes, atténuées, d'origine humaine et/ou animale, administrées par voie orale et se répliquant dans l'intestin grêle. Deux vaccins oraux sont commercialisés au niveau international: le Rotarix®, monovalent (RV1) (GlaxoSmithKline Biologicals, Rixensart, Belgique) et le RotaTeq®, pentavalent (RV5) (Merck & Co. Inc., West Point, PA, États-Unis d'Amérique). Dans le présent article, nous nous réfèrerons à ces 2 vaccins en les appelant respectivement RV1 et RV5. Le vaccin de Lanzhou, préparé à partir d'une souche de rotavirus d'agneau par le Lanzhou Institute of Biomedical Products en Chine et le Rotavin-M1, fabriqué par Polyvac au Viet Nam, ne sont pas disponibles sur le marché international et ne seront donc pas discutés davantage ici.

Il existe des lignes directrices de l'OMS pour garantir la qualité, l'innocuité et l'efficacité des vaccins antirotavirus vivants atténués.[15]

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[13] Clark HF et al. Rotavirus vaccines. In: Plotkin S, Orenstein W, Offit P, eds. *Vaccines*, 6th ed. Elsevier Saunders, 2013:669-687.

[14] Groome MJ et al. Five-year cohort study on the burden of hospitalisation for acute diarrhoeal disease in African HIV-infected and HIV-uninfected children: potential benefits of rotavirus vaccine. *Vaccine*, 2012, 30 Suppl 1:A173-178.

[15] Cunliffe NA et al. Effect of concomitant HIV infection on presentation and outcome of rotavirus gastroenteritis in Malawian children. *Lancet*, 2001, 358(9281):550–555.

[16] *Guidelines to assure the quality, safety and efficacy of live attenuated rotavirus vaccine* Annex 3). Geneva, World Health Organization, 2007, WHO Technical report series 941. Available from http://www.who.int/entity/biologicals/publications/trs/areas/vaccines/rotavirus/Annex%203%20rotavirus%20vaccines.pdf, accessed January 2013.

[13] Clark HF et al. Rotavirus vaccines. In: Plotkin S, Orenstein W, Offit P, eds. *Vaccines*, 6th ed. Elsevier Saunders, 2013:669-687.

[14] Groome MJ et al. Five-year cohort study on the burden of hospitalisation for acute diarrhoeal disease in African HIV-infected and HIV-uninfected children: potential benefits of rotavirus vaccine. *Vaccine*, 2012, 30 Suppl 1:A173-178.

[15] Cunliffe NA et al. Effect of concomitant HIV infection on presentation and outcome of rotavirus gastroenteritis in Malawian children. *Lancet*, 2001, 358(9281):550-555.

[16] *Guidelines to assure the quality, safety and efficacy of live attenuated rotavirus vaccine* Annex 3). Genève, Organisation mondiale de la Santé, 2007. Série de rapports techniques de l'OMS No 941. Disponible sur http://www.who.int/entity/biologicals/publications/trs/areas/vaccines/rotavirus/Annex%203%20rotavirus%20vaccines.pdf, consulté en janvier 2013. [Document disponible en anglais uniquement.]

The monovalent human rotavirus vaccine (lyophilized and liquid)

RV1 is a live, oral vaccine originating from a G1P[8] strain that was isolated from a case of infantile gastroenteritis. This strain has undergone multiple passages in tissue culture and the resulting attenuated vaccine strain, RIX4414, is propagated in Vero cells. First prepared as a lyophilized vaccine, a ready-to-use liquid formulation containing the same RIX4414 strain has subsequently been developed for 2 presentations: oral applicator and squeezable tube. The vaccine should be kept at 2–8 °C, protected from light, and should not be frozen. The vaccine shelf-life is 3 years. Each dose contains a suspension of at least $10^{6.0}$ – the median cell culture infective dose (CCID50) – of live, attenuated human G1P[8] rotavirus particles . The volume is 1ml for the lyophilized formulation and 1.5ml for the liquid formulation. The vaccine should be used immediately after reconstitution (for the lyophilized formulation) or after opening (for the liquid presentation). If not used immediately, reconstituted RV1 can be stored either refrigerated (2–8 °C) or at ambient temperature <25 °C but should be given within 24 hours. All presentations have a vaccine vial monitor (VVM 14).

The 2 vaccine doses are administered at an interval of at least 4 weeks. According to the manufacturer, the first dose should be administered to infants ≥6 weeks of age and the second dose prior to 24 weeks of age.[17, 18] For WHO recommended schedules see WHO recommendations below.

The pentavalent human-bovine reassortant rotavirus vaccine

RV5 is an oral vaccine that contains 5 reassortant rotaviruses developed from human and bovine (WC3) parent rotavirus strains. Four WC3-based reassortants express one of the VP7 proteins G1, G2, G3 or G4 from the human strains and the VP4 protein P7[5] from the bovine strain, whereas the fifth reassortant virus expresses the VP4 protein P1A[8] from a human strain and the G6 protein from the bovine parent strain. The reassortants are subsequently propagated in Vero cells using standard cell-culture techniques.

Each dose (2 ml) of the vaccine contains a minimum titre of approximately 2.0 – 2.8 x 10^6 infectious units per reassortant, and not greater than 116 x 10^6 infectious units per aggregate dose. The 5 reassortant strains are suspended in a solution of buffer and stabilizer that should be stored at 2–8 °C. RV5 should not be frozen. Following removal from refrigeration, the vaccine should be used as soon as possible. The vaccine tubes do not have VVMs.

The manufacturer's recommended schedule prescribes 3 oral doses at ages 2, 4 and 6 months. The first dose should be administered between ages 6–12 weeks and subsequent doses at intervals of 4–10 weeks. The man-

Le vaccin antirotavirus humain monovalent (lyophilisé et liquide)

Le RV1 est un vaccin oral vivant préparé avec une souche G1P[8] isolée à partir d'un cas de gastro-entérite infantile. Cette souche a subi de nombreux passages en culture tissulaire et la souche vaccinale atténuée qui en a résulté, RIX4414, est propagée sur cellules Vero. Tout d'abord préparé sous forme lyophilisée, une présentation liquide, prête à l'emploi, de la même souche RIX4414 a été ensuite élaborée sous 2 conditionnements: applicateur pour administration orale et tube souple. Il doit être conservé à 2-8 °C, protégé de la lumière et ne pas être congelé. Il a une durée de conservation de 3 ans. Chaque dose contient une dose médiane d'au moins $10^{6.0}$ unités infectieuses en culture cellulaire (DI50 en CC) de rotavirus vivant, atténué, humain G1P[8]. Le volume est de 1 ml sous forme lyophilisée et de 1,5 ml sous forme liquide. Le vaccin doit être utilisé immédiatement après reconstitution (pour la forme lyophilisée) ou après ouverture (pour la forme liquide). En cas d'utilisation différée, le RV1 reconstitué peut être conservé réfrigéré (2-8°C) ou à température ambiante jusqu'à 25°C mais pas >24 heures. Toutes les ampoules ont une pastille de contrôle (PVC 14).

Les 2 doses vaccinales sont administrées à un intervalle d'au moins 4 semaines. Selon le fabricant, la première doit être administrée à des nourrissons âgés d'au moins 6 semaines et la seconde avant l'âge de 24 semaines.[17, 18] Pour connaître le calendrier préconisé par l'OMS, voir ci-après les «Recommandations de l'OMS».

Le vaccin antirotavirus pentavalent réassorti bovin-humain

Le RV5 est un vaccin oral contenant 5 souches de rotavirus (WC3) réassorties obtenues à partir de souches mères d'origine humaine et bovine. Quatre souches réassorties expriment une des protéines VP7 G1, G2, G3 ou G4 provenant des souches humaines et la protéine VP4 P7[5] issue de la souche bovine, tandis que le cinquième virus réassorti exprime la protéine VP4 P1A[8] venant d'une souche humaine et la protéine G6 de la souche mère bovine. Les souches réassorties sont ensuite propagées sur cellules Vero par des techniques de cultures cellulaires classiques.

Chaque dose vaccinale (2 ml) contient un titre minimal d'environ 2,0 - 2,8 x 10^6 unités infectieuses par souches réassorties et pas plus de 116 x 10^6 unités infectieuses par dose combinée. Les 5 souches réassorties sont mises en suspension dans une solution tampon stabilisée qui doit être conservée à 2-8°C. Le RV5 ne doit pas être congelé. Après avoir été retiré du froid, le vaccin doit être utilisé aussi vite que possible. Les tubes n'ont pas de PCV.

Le calendrier recommandé par le fabricant consiste à administrer 3 doses orales aux âges de 2, 4 et 6 mois. La première dose sera administrée entre 6 et 12 semaines et les suivantes à des intervalles de 4 à 10 semaines. Le fabricant recommande d'ache-

[17] See http://www.who.int/entity/immunization_standards/vaccine_quality/Rotarix_liquid_tube_product_insert_text_2009.pdf

[18] See http://www.who.int/entity/immunization_standards/vaccine_quality/Rotarix_liquid_oral_applicator_product_insert_text_2009.pdf

[17] Voir http://www.who.int/entity/immunization_standards/vaccine_quality/Rotarix_liquid_tube_product_insert_text_2009.pdf

[18] Voir http://www.who.int/entity/immunization_standards/vaccine_quality/Rotarix_liquid_oral_applicator_product_insert_text_2009.pdf

ufacturer recommends that all 3 doses should be administered by age 32 weeks.[19] For WHO recommended schedules see WHO recommendations below.

Efficacy and effectiveness of the rotavirus vaccine

A recent Cochrane review[20] shows that RV1 and RV5 are most efficacious against severe RVGE in subregions with very low or low child and adult mortality (WHO mortality strata A and B as defined below),[21] although the vaccines are also efficacious in subregions with high child mortality and high or very high adult mortality (WHO strata D and E).[20] Based on 11 RCTs of RV1 and 6 RCTs of RV5, this Cochrane review showed protection against severe RVGE after 1 and/or 2 years of follow up, ranging from approximately 80%–90% with modest waning over the period of observation in stratum A as compared to approximately 40%–60% efficacy over 2 years of follow up in stratum E.

However, since the incidence of severe rotavirus disease is significantly higher in high child mortality settings, the numbers of severe disease cases and deaths averted by vaccines in these settings are likely to be higher than in low mortality settings, despite the lower vaccine efficacy.[3, 22]

A descriptive review of observational studies mostly from high income and middle income countries, and a systematic review of observational and impact studies from industrialized countries have reported a substantial reduction in disease burden within a few years of vaccine implementation and also some evidence of herd protection in unvaccinated older children and adults. Data also suggest that rotavirus vaccination has delayed the onset and decreased the magnitude of the yearly seasons in several high income countries.[23, 24]

Observational studies in Mexico and Brazil after the introduction of RV1 reported a reduction in diarrhoea-related deaths in infants and young children.[25, 26] In

ver la série de prises vaccinales au plus tard à l'âge de 32 semaines.[19] Pour connaître le calendrier préconisé par l'OMS, voir ci-après «Recommandations de l'OMS».

Efficacité et performance du vaccin antirotavirus

Selon une étude récente de Cochrane,[20] le RV1 et le RV5 sont les plus efficaces contre les gastroentérites sévères à rotavirus dans les sous-régions ayant une mortalité faible ou très faible des enfants et des adultes (voir ci-dessous la définition par l'OMS des strates de mortalité A et B),[21] bien que les vaccins soient efficaces également dans les sous régions ayant une forte mortalité des enfants et une mortalité forte ou très forte des adultes (strates D et E de l'OMS).[20] Sur la base de 11 essais contrôlés randomisés (ECR) pour le RV1 et 6 pour le RV5, cette étude a mis à jour une protection contre les gastroentérites sévères à rotavirus après 1 et/ou 2 ans de suivi, allant d'environ 80%-90%, avec une faible diminution sur la période d'observation dans la strate A, à une efficacité d'environ 40%-60% sur 2 ans de suivi dans la strate E.

Toutefois, comme l'incidence des rotaviroses sévères est nettement plus élevée dans les milieux où il y a une forte mortalité des enfants, le nombre des cas graves et des décès évités par la vaccination dans ce cadre est probablement plus élevé qu'en situation de faible mortalité, malgré une efficacité plus faible du vaccin.[3, 22]

Un examen descriptif des études d'observation, provenant pour la plupart de pays à revenu élevé ou intermédiaire, et un examen systématique des études d'observation et d'impact dans les pays industrialisés ont indiqué une baisse substantielle de la charge de morbidité dans les quelques années suivant la mise en œuvre du vaccin et aussi quelques signes d'une immunité de groupe bénéficiant aux enfants plus âgés et aux adultes non vaccinés. Les données laissent à penser par ailleurs que la vaccination antirotavirus a retardé le démarrage et réduit l'ampleur des épidémies saisonnières dans plusieurs pays à haut revenu.[23, 24]

Des études d'observation au Mexique et au Brésil après l'introduction du RV1 ont indiqué une baisse du nombre des décès dus aux diarrhées chez les nourrissons et les jeunes enfants.[25, 26] Au

[19] See http://www.who.int/entity/immunization_standards/vaccine_quality/RotaTeq_Product_Insert.pdf and http://www.merck.com/product/usa/pi_circulars/r/rotateq/rotateq_pi.pdf

[20] Soares-Weiser K et al. Vaccines for preventing rotavirus diarrhoea: vaccines in use. *Cochrane Database Systematic Review*, 2012, 11:CD008521.

[21] To aid in cause of death and burden of disease analyses, WHO subregions are stratified (A through E) based on levels of child and adult mortality: Stratum A, very low child and very low adult mortality; Stratum B, low child and low adult mortality; Stratum C, low child and high adult mortality; Stratum D, high child and high adult mortality; Stratum E, high child and very high adult mortality. The 9 low- and middle-income subregions included in the model are: African Region: D and E; Region of the Americas: B and D; South-East Asia Region: B and D, Eastern Mediterranean Region: B and D, and Western Pacific Region: B. Please consult the *List of Member States by WHO region and mortality stratum* available at www.who.int/entity/whr/2003/en/member_states_182-184_en.pdf, accessed January 2013.

[22] Grading of scientific evidence – Tables 1–4: Does RV1and RV5 induce protection against rotavirus morbidity and mortality in young children both in low and high mortality settings? Available from http://www.who.int/immunization/position_papers/rotavirus_grad_rv1_rv5_protection

[23] Patel MM et al. Removing the Age Restrictions for Rotavirus Vaccination: A Benefit-Risk Modeling Analysis. *PLoS Medicine*, 2012, 9: e1001330.

[24] Giaquinto C et al. Summary of effectiveness and impact of rotavirus vaccination with the oral pentavalent rotavirus vaccine: a systematic review of the experience in industrialized countries. *Human Vaccines*, 2011, 7:734–748.

[25] Richardson V et al. Effect of rotavirus vaccination on death from childhood diarrhoea in Mexico. *New England Journal of Medicine*, 2010, 362:299–305.

[26] do Carmo GM et al. Decline in diarrhoea mortality and admissions after routine childhood rotavirus immunization in Brazil: a time-series analysis. *PLoS Medicine*, 2011,8:e1001024

[19] Voir http://www.who.int/entity/immunization_standards/vaccine_quality/RotaTeq_Product_Insert.pdf et http://www.merck.com/product/usa/pi_circulars/r/rotateq/rotateq_pi.pdf

[20] Soares-Weiser K et al. Vaccines for preventing rotavirus diarrhoea: vaccines in use. *Cochrane Database Systemic Review*, 2012, 11:CD008521.

[21] Pour aider à analyser les causes de mortalité et la charge de morbidité, les sous-régions de l'OMS ont été réparties en strates (A à E) selon les niveaux de mortalité des enfants et des adultes: strate A, très faible mortalité des enfants et des adultes; strate B, faible mortalité des enfants et des adultes; strate C, faible mortalité des enfants et forte mortalité des adultes; strate D, forte mortalité des enfants et des adultes; strate E, très forte mortalité des enfants et des adultes. Les 9 sous-régions à revenu faible ou intermédiaire intégrées dans le modèle sont les suivantes: Région africaine: D et E; Région des Amériques: B et D; Région de l'Asie du Sud-Est: B et D, Région de la Méditerranée orientale: B et D, et Région du Pacifique occidental: B. Veuillez-vous référer à la Liste des États Membres par Région OMS et strate de mortalité sur: www.who.int/entity/whr/2003/en/member_states_182-184_en.pdf, consulté en janvier 2013.

[22] Cotation des preuves scientifiques – Tableaux 1-4: Le RV1 et le RV5 induisent-ils une protection contre la morbidité et la mortalité imputables aux rotavirus chez le jeune enfant dans les situations de faible et de forte mortalité? Disponible sur http://www.who.int/immunization/position_papers/rotavirus_grad_rv1_rv5_protection

[23] Patel MM et al. Removing the Age Restrictions for Rotavirus Vaccination: A Benefit-Risk Modeling Analysis. *PLoS Medicine*, 2012, 9: e1001330.

[24] Giaquinto C et al. Summary of effectiveness and impact of rotavirus vaccination with the oral pentavalent rotavirus vaccine: a systematic review of the experience in industrialized countries. *Human Vaccines*, 2011, 7:734–748.

[25] Richardson V et al. Effect of rotavirus vaccination on death from childhood diarrhoea in Mexico. *New England Journal of Medicine*, 2010, 362:299–305.

[26] do Carmo GM et al. Decline in diarrhoea mortality and admissions after routine childhood rotavirus immunization in Brazil: a time-series analysis. *PLoS Medicine*, 2011,8:e1001024

Mexico, the estimated decline in the rate of diarrhoea-related deaths was greatest among infants <11 months of age (a relative reduction of 41% (95% CI: 36%–47%). There was also a relative reduction among children aged 12 23 months (29%, 95% CI: 17%–39%) but no significant reduction was observed in children 24–59 months of age (7%, 95% CI: 14%–26%).[25] In Brazil, a study reported that compared to expected rates based on pre-vaccine era trends, rates for diarrhoea-related mortality were 22% (95% CI: 6%–44%) lower than expected. The largest reductions in deaths (22%–28%) were among children younger than 2 years, who had the highest rates of vaccination. In contrast, lower reductions in deaths (4%, 95% CI: 30%–29%) were noted among children 2–4 years of age, who were not age-eligible for vaccination during the study period.[26]

No randomized control trials (RCTs) have been conducted to specifically assess differences in all-cause mortality between different vaccine schedules or among studies in different WHO mortality strata.[20] Data from case-control studies show that RV1 and RV5 are more efficacious when the full course is given, but some protection may also be achieved following an incomplete vaccination series. For example, RV5 exhibits substantial effectiveness against RVGE before completion of the full 3 dose regimen.[20, 27]

The interchangeability of RV1 and RV5 has not been studied.

RV1 and RV5 have similar efficacy against severe RVGE in countries where a high diversity of strains co-circulate, suggesting an important role for heterotypic protective immunity. However, indirect evidence suggests that homotypic immunity also plays a role in protection against subsequent RV infection. Characterization of RV strains present in the environment post-vaccination is needed to exclude population-based selection of 'escape' strains due to long-term pressure exerted by homotypic immunity.[11]

Duration of protection

Published RCTs are not adequately powered to conclude definitively whether or not efficacy wanes for either RV1 or RV5. With RV5, one RCT that enrolled subjects from 11 countries, reported an efficacy against severe disease estimated at 98% (95% CI: 88%–100%) during the first rotavirus season and 88% (95% CI: 49%–99%) during the second season.[28] An extension of this trial demonstrated a sustained reduction in the number of hospitalizations for rotavirus disease also 3 years after vaccination.[29] Reports from RCTs were consistent with little

Mexique, la diminution estimative du taux de mortalité imputable aux diarrhées a été la plus grande chez les nourrissons âgés de <11 mois (baisse relative de 41% (IC à 95%: 36%-47%). Il y a eu aussi une baisse relative chez les enfants âgés de 12 à 23 mois (29%, IC à 95%: 17%-39%), mais aucune diminution significative n'a été observée chez les enfants de 24 à 59 mois (7%, IC à 95%: 14%-26%).[25] Au Brésil, une étude a indiqué qu'en comparaison avec les taux escomptés sur la base des tendances avant l'ère de la vaccination, les taux de mortalité imputable à la diarrhée étaient inférieurs de 22% (IC à 95%: 6%-44%) à ce qu'on aurait pu attendre. Les plus fortes diminutions de la mortalité (22%-28%) ont été observées chez les enfants de <2 ans, qui avaient aussi les taux de vaccination les plus élevés. À l'inverse, des baisses plus faibles de la mortalité (4%, IC à 95%: 30%-29%) ont été enregistrées chez les enfants de 2 à 4 ans, qui avaient dépassé l'âge de la vaccination au cours de la période de l'étude.[26]

Aucun ECR n'a été fait pour évaluer spécifiquement la mortalité toutes causes confondues entre les différents calendriers de vaccination ou entre les études faites dans les diverses strates de mortalité de l'OMS.[20] Les données des études cas-témoins établissent que le RV1 et le RV5 sont plus efficaces quand le calendrier complet est administré, mais qu'on peut arriver à obtenir un certain degré de protection après des séries incomplètes de vaccination. Par exemple, le RV5 montre une nette efficacité contre la gastroentérite à rotavirus avant d'avoir terminé la série complète de 3 doses.[20, 27]

L'interchangeabilité du RV1 et du RV5 n'a pas été étudiée.

Le RV1 et le RV5 ont une efficacité similaire contre la GERV sévère dans les pays où il y a une circulation concomitante d'une grande diversité de souches, ce qui évoque un rôle important pour l'immunité protectrice hétérotypique. En revanche, des preuves indirectes tendent à indiquer que l'immunité homotypique pourrait également jouer un rôle dans la protection contre des rotaviroses ultérieures. La caractérisation des souches présentes dans l'environnement après la vaccination est nécessaire pour exclure la sélection de souches «d'échappement» dans les populations à cause d'une pression durable de l'immunité homotypique.[11]

Durée de la protection

Les ECR publiés n'ont pas une puissance suffisante pour conclure définitivement à une diminution dans le temps de l'efficacité du RV1 ou du RV5. Pour le RV5, un ECR ayant recruté des sujets dans 11 pays ont indiqué une efficacité contre la rotavirose sévère estimée à 98% (IC à 95%: 88%-100%) pendant la première saison et 88% (IC à 95%: 49%-99%) pendant la seconde.[28] Une extension de cet essai a mis en évidence une diminution durable du nombre des hospitalisations pour rotavirose également 3 ans après la vaccination.[29] Les rapports des ECR ont concordé avec une légère diminution de l'efficacité du

[27] Wang FT et al. Effectiveness of an Incomplete RotaTeq® (RV5) Vaccination Regimen in Preventing Rotavirus Gastroenteritis in the United States. *The Pediatric Infectious Disease Journal*, 2012, [Epub ahead of print].

[28] Vesikari T et al. Safety and efficacy of pentavalent human-bovine (WC3) reassortant rotavirus vaccine in preventing rotavirus gastroenteritis and reducing associated health care resource utilization. *The New England Journal of Medicine*, 2006, 354:23–33.

[29] Vesikari T et al. Efficacy of the pentavalent rotavirus vaccine, RotaTeq®, in Finnish infants up to 3 years of age: the Finnish Extension Study. *European Journal of Pediatrics*, 2010, 169: 1379–1386.

[27] Wang FT et al. Effectiveness of an Incomplete RotaTeq® (RV5) Vaccination Regimen in Preventing Rotavirus Gastroenteritis in the United States. *The Pediatric Infectious Disease Journal*, 2012, [Epub ahead of print].

[28] Vesikari T et al. Safety and efficacy of pentavalent human-bovine (WC3) reassortant rotavirus vaccine in preventing rotavirus gastroenteritis and reducing associated health care resource utilization. *The New England Journal of Medicine*, 2006, 354:23–33.

[29] Vesikari T et al. Efficacy of the pentavalent rotavirus vaccine, RotaTeq®, in Finnish infants up to 3 years of age: the Finnish Extension Study. *European Journal of Pediatrics*, 2010, 169: 1379–1386.

decrease in the efficacy of RV1 against severe rotavirus disease during the second season of follow-up, from 83% (95% CI: 67%–92%) to 79% (95% CI: 66%–87%) in Latin America[30] and from 96% (95% CI: 90%–99%) to 86% (95% CI: 76%–92%) in Europe.[31] A RCT of RV1 conducted in 3 high income settings in Asia reported sustained efficacy against severe RVGE of 100% (95% CI: 67.5%–100%) during the third year of life.[32]

In contrast, a study of RV5 conducted in 3 countries in sub-Saharan Africa reported an estimated efficacy of 39.3% (95% CI: 19.1%–54.7%) against severe RVGE over the full follow-up period with an estimated 64.2% (95% CI: 40.2%–79.4%) during the first year after vaccination and 19.6% (95% CI: 15.7%–44.4%) in the second year after vaccination.[33] For RV1 in South Africa, results from the extended follow-up of a RCT are inconclusive given the lack of power in the extension study.[34]

There is currently insufficient evidence to make a general recommendation on the need for a third dose of RV1 in the primary series. A RCT directly assessing vaccine efficacy against severe RVGE in South Africa and Malawi did not show statistically significant differences between 2 doses and 3 doses of RV1; 58.7%, (95% CI: 35.7%–74%) and 63.7%, (95% CI: 42.4%–77.8%), respectively.[35] However, in South African children, the efficacy of 2 or 3 doses of RV1 against severe RVGE over 2 consecutive rotavirus seasons was 32% ($p = 0.487$) and 85% ($p = 0.006$), respectively, as compared to the placebo group.[34] Similarly, although significant reduction of RVGE of any severity was observed in the 2-dose group (49%; $p = 0.007$), the reduction was lower than that in the 3-dose group (68%; $p < 0.001$). Further adequately powered studies would be helpful to explore whether additional doses have a favourable risk/benefit ratio in high mortality settings and whether partial vaccination is also efficacious against severe rotavirus diarrhoea.[36]

Vaccine safety and precautions

In a recent review of efficacy and safety of the current rotavirus vaccines that included 41 trials with 186 263 participants, no differences were observed

RV1 contre la rotavirose sévère lors de la deuxième saison de suivi: de 83% (IC à 95%: 67%-92%) à 79% (IC à 95%: 66%-87%) en Amérique latine[30] et de 96% (IC à 95%: 90%-99%) à 86% (IC à 95%: 76%-92%) en Europe.[31] Un ECR du RV1, mené dans 3 milieux à haut revenu en Asie, a indiqué une efficacité durable contre la GERV sévère de 100% (IC à 95%: 67,5%-100%) pendant la troisième année de vie.[32]

Inversement, une étude menée sur le RV5 dans 3 pays africains a indiqué une efficacité estimative de 39,3% (IC à 95%: 19,1%-54,7%) contre la GERV sévère pendant toute la période de suivi, avec une estimation à 64,2% (IC à 95%: 40,2%-79,4%) pendant la première année après la vaccination et 19,6% (IC à 95%: 15,7%-44,4%) pendant la seconde année.[33] Pour le RV1 en Afrique du Sud, les résultats du suivi étendu d'un ECR ne sont pas concluants en raison du manque de puissance de l'étude d'extension.[34]

On n'a pas pour l'instant de données suffisantes pour faire une recommandation générale sur la nécessité d'ajouter une troisième dose à la série du RV1. Un ECR évaluant directement l'efficacité de la vaccination contre la GERV sévère en Afrique du Sud et au Malawi n'a pas révélé de différences statistiques significatives entre 2 et 3 doses de RV1; 58,7%, (IC à 95%: 35,7%-74%) et 63,7%, (IC à 95%: 42,4%-77,8%), respectivement.[35] En revanche, chez des enfants d'Afrique du Sud, l'efficacité de 2 ou 3 doses de RV1 contre la GERV sévère sur 2 saisons consécutives a été de 32% ($p = 0,487$) et 85% ($p = 0,006$), respectivement, par rapport au groupe placebo.[34] De même, bien qu'on ait observé une baisse significative des GERV, toutes gravités confondues, dans le groupe à 2 doses (49%; $p = 0.007$), la diminution a été plus faible dans le groupe à 3 doses (68%; $p < 0.001$). D'autres études ayant la puissance requise seraient utiles pour examiner si des doses supplémentaires ont un rapport risque–avantage favorable dans les situations de forte mortalité et si la vaccination partielle est également efficace contre les diarrhées sévères à rotavirus.[36]

Innocuité du vaccin et précautions

Lors d'un examen récent de l'efficacité et de l'innocuité des vaccins antirotavirus couvrant 41 essais avec 186 263 participants, aucune différence n'a été observée entre les groupes

[30] Linhares AC et al. Efficacy and safety of an oral live attenuated human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in Latin American infants: a randomised, double-blind, placebo-controlled phase III study. *Lancet*, 2008, 371:1181–1189.

[31] Vesikari T et al. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. *Lancet*. 2007, 24, 370:1757–1763.

[32] Phua KB et al. Rotavirus vaccine RIX4414 efficacy sustained during the third year of life: a randomized clinical trial in an Asian population. *Vaccine*, 2012, 30:4552–4557.

[33] Armah GE et al. Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in sub-Saharan Africa: a randomised, double-blind, placebo-controlled trial. *Lancet*, 2010, 376:606–614.

[34] Madhi SA et al. Efficacy and immunogenicity of 2 or 3 dose rotavirus-vaccine regimen in South African children over two consecutive rotavirus-seasons: a randomized, double-blind, placebo-controlled trial. *Vaccine*, 2012, 30 Suppl 1:A44-51.

[35] Madhi SA et al. Effect of human rotavirus vaccine on severe diarrhoea in African infants. *New England Journal of Medicine*, 2010, 362:289-298.

[36] Grading of scientific evidence – Tables 5–6: Is giving a third dose of RV1 superior to the currently recommended 2-dose schedule? (Table 5); Is partial vaccination also efficacious against severe rotavirus diarrhoea? (Table 6). Available from http://www.who.int/immunization/position_papers/rotavirus_grad_rv1_3rd_dose

[30] Linhares AC et al. Efficacy and safety of an oral live attenuated human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in Latin American infants: a randomised, double-blind, placebo-controlled phase III study. *Lancet*, 2008, 371:1181–1189.

[31] Vesikari T et al. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. *Lancet*. 2007, 24, 370:1757–1763.

[32] Phua KB et al. Rotavirus vaccine RIX4414 efficacy sustained during the third year of life: a randomized clinical trial in an Asian population. *Vaccine*, 2012, 30:4552–4557.

[33] Armah GE et al. Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in sub-Saharan Africa: a randomised, double-blind, placebo-controlled trial. Lancet, 2010, 376:606–614.

[34] Madhi SA et al. Efficacy and immunogenicity of 2 or 3 dose rotavirus-vaccine regimen in South African children over two consecutive rotavirus-seasons: a randomized, double-blind, placebo-controlled trial. *Vaccine*, 2012, 30 Suppl 1:A44-51.

[35] Madhi SA et al. Effect of human rotavirus vaccine on severe diarrhoea in African infants. *New England Journal of Medicine*, 2010, 362:289-298.

[36] Cotation des preuves scientifiques – Tableaux 5-6: L'administration d'une troisième dose de RV1 est-elle supérieure au calendrier de 2 doses actuellement recommandé? (Tableau 5); La vaccination partielle est-elle également efficace contre la diarrhée sévère à rotavirus? (Tableau 6). Disponible sur http://www.who.int/immunization/position_papers/rotavirus_grad_rv1_3rd_dose

between the vaccine groups and the placebo groups in terms of events that required discontinuation of the vaccination schedule.[19]

A RCT that enrolled a total of 100 HIV-positive infants aged 6–10 weeks in South Africa found that 3 doses of RV1 were tolerated well and elicited a satisfactory immune response without aggravating the immunologic or HIV condition.[37] Similarly, a RCT in Kenya showed no significant differences in serious or non-serious adverse events between the 88 HIV-exposed RV5 recipients versus the 89 HIV-exposed placebo recipients who were vaccinated at approximately 6, 10, and 14 weeks of age.[38]

Simultaneous administration of RV1 or RV5 with other vaccines of the infant immunization programme, including combined diphtheria, tetanus toxoid and acellular pertussis vaccine (DTaP), inactivated poliovirus vaccine (IPV), *H. influenzae* type b conjugate (Hib), hepatitis B vaccine, and pneumococcal conjugate vaccine have been shown not to interfere significantly with the protective immune responses or safety profile of the respective vaccines.[39, 40] Although OPV may have an inhibitory effect on the immune response to the first dose of both rotavirus vaccines, this interference does not persist after administration of subsequent doses of rotavirus vaccines.[41]

Breastfeeding and prematurity (<37 weeks' gestation) do not seem to significantly impair the response to the rotavirus vaccines.[20, 42]

Contraindications for using rotavirus vaccines are severe hypersensitivity to any of their components and severe immunodeficiency including severe combined immunodeficiency (SCID). Vaccination should be postponed in case of ongoing acute gastroenteritis or fever with moderate to severe illness. These vaccines are not routinely recommended for infants with a history of intussusception or intestinal malformations possibly predisposing for intussusception.

In 2010, contamination of RV1 with full length DNA from porcine circovirus was reported and subsequently, low levels of DNA fragments of this virus were also detected in bulk lots of RV5.[43] Porcine circovirus is not known to infect or cause disease in humans. GACVS has concluded that given the extensive clinical data supporting the safety of both RV1and RV5 and the benefits of

Un ECR ayant recruté au total 100 nourrissons séropositifs pour le VIH et âgés de 6 à 10 semaines en Afrique du Sud a révélé que 3 doses de RV1 étaient bien tolérées et induisaient une réponse immunitaire satisfaisante sans aggraver l'état immunologique ou pathologique lié au VIH.[37] De même, un ECR au Kenya n'a pas mis en évidence de différences significatives au niveau des effets indésirables graves ou bénins entre 88 sujets ayant reçu le RV5 et exposés au VIH et 89 sujets d'un groupe placebo, également exposés au VIH, vaccinés aux âges d'environ 6, 10 et 14 semaines.[38]

Lors de l'administration simultanée du RV1 ou du RV5 et d'autres vaccins du programme de vaccination infantile, parmi lesquels celui associant l'anatoxine diphtérique, l'anatoxine tétanique et le vaccin anticoquelucheux acellulaire (DTCa), le vaccin antipoliomyélitique inactivé (VPI), le vaccin conjugué contre *H. influenzae* type b (Hib), le vaccin anti-hépatite B et le vaccin antipneumococcique conjugué, on n'a pas observé d'interférence significative avec les réponses immunitaires de protection ou les profils d'innocuité des autres vaccins.[39, 40] Bien que le VPO puisse avoir un effet inhibiteur sur la réponse immunitaire à la première dose des 2 vaccins antirotavirus, cette interférence ne persiste pas après l'administration des doses suivantes des vaccins antirotavirus.[41]

L'allaitement au sein et la prématurité (<37 semaines de gestation) ne semblent pas nuire sensiblement à la réponse aux vaccins antirotavirus.[20, 42]

Les contre-indications à l'utilisation des vaccins antirotavirus sont une forte hypersensibilité à l'un de leurs constituants ou une immunodéficience sévère, dont le déficit immunitaire combiné sévère (SCID). La vaccination doit être différée en cas de gastroentérite aiguë en cours ou de fièvre accompagnant une affection modérée à grave. D'ordinaire, ces vaccins ne sont pas recommandés aux nourrissons avec des antécédents d'invagination ou de malformations intestinales les prédisposant à ce type de problème.

En 2010, on a signalé la contamination d'un RV1 avec la séquence complète d'ADN d'un circovirus porcin et, ensuite, de faibles teneurs en fragments d'ADN de ce virus ont aussi été décelés dans des lots de RV5 en vrac.[43] Le circovirus porcin n'est pas connu pour infecter l'homme ou être pathogène pour lui. Le Comité consultatif mondial de la Sécurité vaccinale a conclu que, compte tenu de la multitude des données cliniques

[37] Steele AD et al. Safety, reactogenicity, and immunogenicity of human rotavirus vaccine RIX4414 in human immunodeficiency virus-positive infants in South Africa. *Pediatric Infectious Disease Journal*, 2011, 30:125–130.

[38] Laserson KF et al. Safety of the pentavalent rotavirus vaccine (PRV), RotaTeq(®), in Kenya, including among HIV-infected and HIV-exposed infants. *Vaccine*, 2012, 30 Suppl 1:A61–70.

[39] See http://us.gsk.com/products/assets/us_rotarix.pdf

[40] See http://www.merck.com/product/usa/pi_circulars/r/rotateq/rotateq_pi.pdf

[41] Soares-Weiser K et al. *Rotavirus vaccine schedules: a systematic review of safety and efficacy from RCTs and observational studies of childhood schedules using RV1 and RV5 vaccines*. Report to WHO/Initiative for Vaccine Research, 2012. Available from http://www.who.int/immunization/sage/meetings/2012/april/Soares_K_et_al_SAGE_April_rotavirus.pdf, accessed January 2013.

[42] Goveia MG et al. Efficacy of pentavalent human-bovine (WC3) reassortant rotavirus vaccine based on breastfeeding frequency. *The Pediatric Infectious Disease Journal*, 2008, 27:656–658.

[43] McClenahan SD et al. Molecular and infectivity studies of porcine circovirus in vaccines. *Vaccine*, 2011,29:4745–4753.

[37] Steele AD et al. Safety, reactogenicity, and immunogenicity of human rotavirus vaccine RIX4414 in human immunodeficiency virus-positive infants in South Africa. *Pediatric Infectious Disease Journal*, 2011, 30:125–130.

[38] Laserson KF et al. Safety of the pentavalent rotavirus vaccine (PRV), RotaTeq(®), in Kenya, including among HIV-infected and HIV-exposed infants. *Vaccine*, 2012, 30 Suppl 1:A61–70.

[39] Voir http://us.gsk.com/products/assets/us_rotarix.pdf

[40] Voir http://www.merck.com/product/usa/pi_circulars/r/rotateq/rotateq_pi.pdf

[41] Soares-Weiser K et al. *Rotavirus vaccine schedules: a systematic review of safety and efficacy from RCTs and observational studies of childhood schedules using RV1 and RV5 vaccines*. Rapport fait à l'OMS/ Initiative pour la recherche sur les vaccins, 2012. Disponible sur http://www.who.int/immunization/sage/meetings/2012/april/Soares_K_et_al_SAGE_April_rotavirus.pdf, consulté en janvier 2013. [Document disponible en anglais uniquement.]

[42] Goveia MG et al. Efficacy of pentavalent human-bovine (WC3) reassortant rotavirus vaccine based on breastfeeding frequency. *The Pediatric Infectious Disease Journal*, 2008, 27:656–658.

[43] McClenahan SD et al. Molecular and infectivity studies of porcine circovirus in vaccines. *Vaccine*, 2011,29:4745–4753.

rotavirus vaccination for children, the benefits of vaccination far outweigh any currently known risk associated with use of either rotavirus vaccine.[44]

The risk of intussusception

Post-licensure surveillance showed that the previously marketed rotavirus vaccine, RotaShield® (Wyeth-Lederle), carried an attributable risk of intussusception estimated at 1:10 000 recipients.[45] Intussusception, an intestinal invagination resulting in obstruction, is characterized clinically by intermittent severe abdominal pain, blood in the stools, a palpable lump in the abdomen, and vomiting. This serious and potentially fatal condition was associated primarily with the first of the 3 oral vaccine doses and the highest attributable risk was found in infants >3 months of age. The pathogenic mechanisms involved in intussusception following rotavirus vaccination remain poorly defined.

RCTs conducted so far have lacked power to rule out very small relative risks of association between RV1or RV5 and intussusception in narrow risk windows, for example the 1–7 day period after dose 1.[20, 46] However, no increased risk of intussusception was detected with either RV1or RV5 in 2 RCTs, each of which including approximately 60 000–70 000 infants (30 000–35 000 received rotavirus vaccine) and designed to detect a risk similar to that seen with Rotashield®.[28, 47]

Using self-controlled case-series and case-control methods the potential association between RV1 and intussusception was investigated after routine immunization of infants in Mexico and Brazil.[48] The study included 615 case patients (285 in Mexico and 330 in Brazil) and 2050 controls. An increased risk of intussusception 1–7 days after the first dose of RV1 was identified among infants in Mexico using both the self-controlled case-series method (incidence ratio, 5.3; 95% CI: 3.0–9.3) and the case-control method (odds ratio, 5.8; 95% CI: 2.6–13.0). Among infants in Brazil no significant risk was found after the first dose, but an increased risk by a factor of 1.9 to 2.6 was seen 1–7 days after the second dose. A combined annual excess of 96 cases of intussusception in Mexico (approximately 1 per 51 000 infants) and in Brazil (approximately 1 per 68 000 infants) and of 5 deaths due to intussusception was attributable to RV1.

A prospective, active surveillance study for intussusception in infants following RV1 vaccination was per-

étayant l'innocuité du RV1 comme du RV5, ainsi que des bénéfices de la vaccination antirotavirus pour les enfants, les avantages de celle-ci dépassent de loin les risques actuellement connus en relation avec l'utilisation de l'un ou l'autre de ces 2 vaccins.[44]

Le risque d'invagination intestinale

La pharmacovigilance a mis en évidence que le RotaShield® (Wyeth-Lederle), un vaccin antirotavirus commercialisé auparavant, s'accompagnait d'un risque attribuable d'invagination intestinale estimé à 1/10 000 sujets vaccinés.[45] L'invagination intestinale, ou intussusception, provoquant une obstruction, se caractérise sur le plan clinique par des douleurs abdominales intermittentes sévères, du sang dans les selles, une masse palpable dans l'abdomen et des vomissements. On a associé avant tout cette affection grave et potentiellement mortelle à la première des 3 doses orales de vaccin et l'on a trouvé le risque attribuable le plus élevé chez les nourrissons âgés de >3 mois. Les mécanismes pathogènes impliqués dans l'invagination intestinale postvaccinale restent mal définis.

Les ECR menés jusqu'à présent n'ont pas eu la puissance nécessaire pour exclure de très faibles risques relatifs d'association entre le RV1 ou le RV5 et l'invagination intestinale dans des fenêtres étroites, par exemple sur une période de 1 à 7 jours suivant la première dose.[20, 46] Toutefois, 2 ECR n'ont pas détecté d'augmentation du risque d'invagination intestinale pour le RV1 ou le RV5; chacun d'entre eux a porté sur environ 60 à 70 000 nourrissons (30 000-35 000 ont été vaccinés) et a été conçu pour déceler un risque similaire à celui observé avec le Rotashield®.[28, 47]

À l'aide de la méthode des séries de cas auto-contrôlées et de la méthode cas-témoin, une enquête sur le lien potentiel entre le RV1 et l'invagination intestinale a été faite après la vaccination systématique des nourrissons au Mexique et au Brésil.[48] L'étude a couvert 615 cas (285 au Mexique et 330 au Brésil) et 2050 témoins. Un risque accru d'invagination intestinale de 1 à 7 jours après la première dose de RV1 a été repéré chez les nourrissons au Mexique en appliquant à la fois la méthode des séries de cas auto-contrôlées (ratio d'incidence, 5,3; IC à 95%: 3,0-9,3) et la méthode cas-témoins (rapport des côtes o, 5,8; IC à 95%: 2,6-13,0). Chez les nourrissons au Brésil, aucun risque significatif n'a été mis en évidence après la première dose, mais un risque accru d'un facteur de 1,9 à 2,6 a été observé de 1 à 7 jours après la deuxième dose. Un excédent annuel combiné de 96 cas d'invaginations intestinales au Mexique (environ 1 pour 51 000 nourrissons) et au Brésil (environ 1 pour 68 000 nourrissons) et de 5 décès dus à l'invagination intestinale a été attribué au RV1.

Une étude prospective de surveillance active de l'invagination intestinale chez les nourrissons après la vaccination par le RV1

[44] See No 30, 2010, pp. 285–292.

[45] *Acute intussusception in infants and young children* (WHO/V&B/.02.19). Geneva, World Health Organization, 2002. Available at http://www.who.int/vaccinesdocuments/DocsPDF06/www640.pdf, accessed January 2013.

[46] Buttery JP et al. Intussusception following rotavirus vaccine administration: post-marketing surveillance in the National Immunization Program in Australia. *Vaccine*, 2011, 29:3061–3066.

[47] Ruiz-Palacios GM et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *New England Journal of Medicine*, 2006, 354:11–22.

[48] Patel MM et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. *New England Journal of Medicine*, 2011, 364:2283–2292

[44] Voir N° 30, 2010, pp. 285-292.

[45] *Acute intussusception in infants and young children* (WHO/V&B/.02.19). Genève, Organisation mondiale de la Santé, 2002. Disponible sur http://www.who.int/vaccinesdocuments/DocsPDF06/www640.pdf consulté en janvier 2013. [Document disponible en anglais uniquement.]

[46] Buttery JP et al. Intussusception following rotavirus vaccine administration: post-marketing surveillance in the National Immunization Program in Australia. *Vaccine*, 2011, 29:3061–3066.

[47] Ruiz-Palacios GM et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *New England Journal of Medicine*, 2006, 354:11–22.

[48] Patel MM et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. *New England Journal of Medicine*, 2011, 364:2283–2292

formed in Mexico during the period 2008–2010.[49] The relative incidence of intussusception within 31 days of vaccination was 1.8 (95% CI: 1.2–2.5; p=0.001) post-dose 1 and 1.1 (95% CI: 0.8–1.5; p=0.8) post-dose 2. The relative incidence of intussusception within 7 days of vaccination was 6.5 post-dose 1 (95% CI: 4. 2–10.1; p<0.001) and 1.3 post-dose 2 (95% CI: 0.8–2.1; p=0.3). The attributable risk of intussusception within 7 days of vaccine dose 1 was estimated at 3 to 4 additional cases of intussusception per 100 000 vaccinated infants.

In Australia, an excess of observed compared to expected cases of intussusception was reported for both RV1 and RV5 among children 1–3 months of age. With RV1, the relative risk was 3.5 (95% CI: 0.7–10.1) 1–7 days after the first dose and 1.5 (95% CI: 0.4–3.9) 1–21 days after the first dose. The corresponding figures for RV5 were 5.3 (95% CI: 1.1–15.4) and 3.5 (95% (CI: 1.3–7.6).[46]

Two large cohort studies with active follow-up assessed the risk of intussusception following receipt of RV5 in the USA. In one US study, covering the period 2006–2010, a total of 786 725 RV5 doses, including 309 844 first doses, were administered to infants 4–34 weeks of age. Comparing the incidence of intussusception between rotavirus vaccine recipients and similarly aged recipients of other infant vaccines, no statistically significant increased risk of intussusception with RV5 was observed for either comparison group following any dose in either the 1–7 day or 1–30 day risk window.[50] The other US study, which compared the risk of intussusception between 85 397 RV5 recipients and 62 820 DTaP recipients found 6 and 5 confirmed cases of intussusception, respectively, within 30 days following either dose. The relative risk of intussusception was 0.8 (95% CI: 0.2–3.5).[51]

Thus, in some but not all settings, post-marketing surveillance of both currently available rotavirus vaccines has detected a small increased risk of intussusception (about 1–2/100 000 infants vaccinated) shortly after the first dose. Where present, this risk is 5–10 times lower than that observed with the previously licensed RotaShield®, and the benefits of rotavirus vaccination against severe diarrhoea and death from rotavirus infection far exceeds the risk of intussusception.[52]

Administration of the first and last dose of RV1 and RV5 at different ages inside the recommended age window has not shown any impact on the incidence of serious adverse events including intussusception.[53] No

a été faite au Mexique sur la période 2008-2010.[49] L'incidence relative de l'invagination intestinale dans les 31 jours suivant la vaccination a été de 1,8 (IC à 95%: 1,2-2,5; p=0,001) après la dose 1 et de 1,1 (IC à 95%: 0,8-1,5; p=0,8) après la dose 2. L'incidence relative dans les 7 jours suivant la vaccination a été de 6,5 (IC à 95%: 4,2-10,1; p<0,001) après la dose 1 et de 1,3 après la dose 2 (IC à 95%: 0,8-2,1; p=0,3). Le risque attribuable d'invagination intestinale dans les 7 jours suivant la dose 1 a été estimé à 3 à 4 cas supplémentaires pour 100 000 enfants vaccinés.

En Australie, on a signalé pour le RV1 comme pour le RV5 un excédent des cas d'invagination intestinale observés par rapport au nombre attendu chez les enfants âgés de 1 à 3 mois. Avec le RV1, le risque relatif a été de 3,5 (IC à 95%: 0,7-10,1) de 1 à 7 jours après la première dose et de 1,5 (IC à 95%: 0,4-3,9) de 1 à 21 jours après la première dose. Pour le RV5, les chiffres correspondants ont été de 5,3 (IC à 95%: 1,1-15,4) et de 3,5 (IC à 95%: 1,3-7,6).[46]

Deux grandes études de cohorte avec suivi actif ont évalué le risque d'invagination intestinale après administration du RV5 aux États-Unis d'Amérique. Dans l'une d'entre elles, couvrant la période 2006-2010, au total 786 725 doses de RV5, dont 309 844 premières doses, ont été administrées à des nourrissons âgés de 4 à 34 semaines. En comparant l'incidence de l'invagination intestinale entre les sujets vaccinés contre le rotavirus et ceux du même âge vaccinés contre d'autres maladies infantiles, aucune augmentation statistiquement significative du risque n'a été observée pour le RV5 dans les 2 groupes de la comparaison, que ce soit sur la période du risque de 1 à 7 jours ou de 1 à 30 jours après la vaccination.[50] L'autre étude américaine, qui a comparé le risque d'invagination intestinale entre 85 397 sujets vaccinés par le RV5 et 62 820 vaccinés par le DTCa, a mis en évidence 6 et 5 cas confirmés respectivement, dans les 30 jours suivant l'administration, quelle que soit la dose. Le risque relatif d'invagination intestinale a été de 0,8 (IC à 95%: 0,2-3,5).[51]

Dans certaines situations donc, mais pas toutes, la surveillance post-commercialisation des 2 vaccins antirotavirus actuellement disponibles a décelé une légère augmentation du risque d'invagination intestinale (environ 1-2/100 000 nourrissons vaccinés) peu après la première dose. Lorsqu'il existe, ce risque est inférieur de 5 à 10 fois à celui observé avec le RotaShield®, vaccin précédemment homologué, et les bénéfices de la vaccination antirotavirus contre les diarrhées sévères et la mort par rotavirose dépassent de loin le risque d'invagination intestinale.[52]

L'administration de la première et de la dernière doses de RV1 et de RV5 à différents âges à l'intérieur de la période recommandée n'a pas eu d'impact avéré sur l'incidence des événements indésirables graves, dont l'invagination intestinale.[53] On

[49] Velázquez FR et al. Postmarketing Surveillance of Intussusception Following Mass Introduction of the monovalent human Rotavirus Vaccine in Mexico_(UGG)_(EPI PLAN). *The Pediatric Infectious Disease Journal*, 2012, 31:736–744.

[50] Shui IM et al. Risk of intussusception following administration of a pentavalent rotavirus vaccine in US infants. *JAMA: the Journal of the American Medical Association*, 2012, 307:598–604.

[51] Loughlin J et al. Postmarketing evaluation of the short-term safety of the pentavalent rotavirus vaccine. *The Pediatric Infectious Disease Journal*, 2012,31:292–296.

[52] See No 6, 2012, pp. 53–60.

[53] Grade table 7: Is it safe to administer the first dose of vaccine at different ages? Available from http://www.who.int/immunization/position_papers/rotavirus_grad_safe_first_dose_ages

[49] Velázquez FR et al. Postmarketing Surveillance of Intussusception Following Mass Introduction of the monovalent human Rotavirus Vaccine in Mexico_(UGG)_(EPI PLAN). *The Pediatric Infectious Disease Journal*, 2012, 31:736–744.

[50] Shui IM et al. Risk of intussusception following administration of a pentavalent rotavirus vaccine in US infants. *JAMA: the Journal of the American Medical Association*, 2012, 307:598–604.

[51] Loughlin J et al. Postmarketing evaluation of the short-term safety of the pentavalent rotavirus vaccine. *The Pediatric Infectious Disease Journal*, 2012,31:292–296.

[52] Voir N° 6, 2012, pp. 53-60.

[53] Tableau 7 de cotation: L'administration de la première dose de vaccin à différents âges est-elle sûre? Disponible sur http://www.who.int/immunization/position_papers/rotavirus_grad_safe_first_dose_ages

data are available on the possible risk of such events outside the recommended age window. There is limited information on the background rates of intussusception in settings of high mortality due to RVGE and no data on the risk of intussusception following rotavirus vaccination in such settings.

Optimizing immunization schedules

Ideally, vaccination schedules should be designed to provide benefits to those at highest risk of severe disease and death. Based on pooled data from studies of 38 populations, at least 3 of which are from each WHO Region, 1%, 3%, 6%, 8%, 10%, 22% and 32% of all RVGE events had occurred by age 6, 9, 13, 15 and 17, 26 and 32 weeks, respectively, although with substantial heterogeneity between populations. Mortality was limited to RVGE events before 32 weeks of age.[2] Although in many parts of the world there are relatively few admissions for RVGE before the scheduled first dose of the rotavirus vaccine (at the age 6–12 weeks), RVGE in very young children is more common in low income settings. Children in the poorest, typically rural, households with the highest risk of mortality seem to have the earliest exposure to rotavirus and the lowest level of vaccine protection.[2]

To maximize its impact, the rotavirus vaccine has to be given before RVGE occurs and before a sizeable proportion of the target population acquires natural infection. The impact of rotavirus vaccination depends on effectiveness, timeliness and coverage. In developing countries where natural infection occurs early, completion of the immunization schedule early in infancy is desirable, though programmatically challenging.[54]

Previously, WHO recommended that rotavirus immunization be initiated by 15 weeks of age when background intussusception rates are reportedly low. However, this policy could exclude a substantial number of children from vaccination, especially in low income countries where delays in vaccination are common.

A model was used to predict the number of deaths prevented by rotavirus vaccination and the number of intussusception deaths caused by rotavirus vaccination when administered on the previously recommended, restricted schedule (initiate by 15 weeks and complete by 32 weeks) versus a schedule allowing vaccination up to 3 years of age. Countries were grouped by WHO child mortality strata and the inputs were stratum-specific estimates of rotavirus mortality, intussusception mortality, and predicted vaccination rates by week of age, and vaccine efficacy and vaccine-associated intussusception risk.[23]

The model estimated that a restricted schedule would prevent 155 800 rotavirus deaths (5th–95th centiles,

ne dispose pas de données sur le risque éventuel de ces manifestations en dehors de la tranche d'âge recommandée. Les informations sont limitées sur la fréquence spontanée de l'invagination intestinale dans les situation de forte mortalité par GERV et l'on n'a pas de donnée sur le risque de cette affection après la vaccination antirotavirus dans ces milieux.

Optimisation des calendriers de vaccination

Dans l'idéal, les calendriers de vaccination doivent être conçus pour bénéficier à ceux qui sont le plus exposés au risque de maladie grave et de mort. Sur la base des données regroupées d'études dans 38 populations, dont au moins 3 dans chaque région de l'OMS, 1%, 3%, 6%, 8%, 10%, 22% et 32% de tous les cas de GERV avaient eu lieu aux âges de 6, 9, 13, 15 et 17, 26 et 32 semaines respectivement, malgré une hétérogénéité substantielle des populations. La mortalité s'est limitée aux cas de GERV avant l'âge de 32 semaines.[2] Bien que, dans de nombreuses régions du monde, il y ait relativement peu d'hospitalisations pour GERV avant la première dose de vaccin antirotavirus au calendrier (à l'âge de 6 à 12 semaines), cette maladie est plus commune chez les très jeunes enfants dans les milieux à faible revenu. Les enfants dans les ménages les plus pauvres, ruraux en général, avec le risque de mortalité le plus élevé, semblent avoir l'exposition la plus précoce au rotavirus et le plus faible niveau de protection vaccinale.[2]

Pour avoir le maximum d'effet, le vaccin antirotavirus doit être administré avant la survenue d'une gastroentérite à rotavirus et avant qu'une proportion assez grande de la population n'ait contracté l'infection naturelle. L'impact de la vaccination dépend de son efficacité, du respect du calendrier et de la couverture. Dans les pays en développement où l'infection naturelle survient à un âge précoce, il est souhaitable d'achever rapidement le calendrier de vaccination en bas âge, bien que cela puisse présenter des difficultés pour les programmes.[54]

Auparavant, l'OMS recommandait de commencer la vaccination antirotavirus avant l'âge de 15 semaines au plus tard, lorsque la fréquence spontanée des invaginations intestinales est faible, selon les informations disponibles. Cette politique pourrait cependant exclure un grand nombre d'enfants, notamment dans les pays à faible revenu où les retards de vaccination sont courants.

Un modèle a été utilisé pour prédire le nombre de décès évités par la vaccination antirotavirus et le nombre de décès par invagination intestinales dus à cette vaccination lorsqu'elle est administrée en suivant le calendrier restreint recommandé précédemment (début jusqu'à l'âge de 15 semaines et fin à 32 semaines) par rapport à un calendrier autorisant la vaccination jusqu'à l'âge de 3 ans. Les pays ont été regroupés selon les strates de mortalité de l'OMS pour les enfants et l'on a entré des estimations spécifiques des strates portant sur la mortalité due au rotavirus, la mortalité par invagination intestinale, les taux prévisibles de vaccination selon l'âge en semaines, l'efficacité du vaccin et le risque d'invagination intestinale associé à la vaccination.[23]

Selon les estimations du modèle, un calendrier restreint éviterait 155 800 décès dus au rotavirus (5e-95e centile, 83 300-217 700)

[54] Cherian T et al. Rotavirus vaccines in developing countries: the potential impact, implementation challenges, and remaining questions. *Vaccine*, 2012: 30 Suppl 1:A3–6.

[54] Cherian T et al. Rotavirus vaccines in developing countries: the potential impact, implementation challenges, and remaining questions. *Vaccine*, 2012: 30 Suppl 1:A3–6.

83 300–217 700) while causing 253 intussusception deaths (76–689). Vaccination without age restrictions would prevent 203 000 rotavirus deaths (102 000–281 500) while causing 547 intussusception deaths (237–1160). Thus, the model predicted that removing the age restrictions would avert an additional 47 200 rotavirus deaths (18 700–63 000) and cause an additional 294 (161–471) intussusception deaths for an incremental benefit-risk ratio of 154 deaths averted for every death caused by the vaccine. These additional deaths prevented under an unrestricted versus restricted schedule reflect additional 21%–28% children who would potentially be eligible for rotavirus vaccination. Thus, in low and middle income countries, the additional lives saved by removing age restrictions for rotavirus vaccination would by far outnumber the excess vaccine-associated intussusception deaths.[22]

Cost effectiveness of vaccination against rotavirus infection

Estimates of the annual cost per disability-adjusted life year (DALY) averted and of the proportion (%) of rotavirus deaths averted through introduction of rotavirus vaccines vary between US$ 8 and US$ 87, and 32% and 44%, for Afghanistan and Bangladesh, respectively. For India, the country with the highest number of recorded deaths due to RVGE, the corresponding figures were US$ 57 and 34%, whereas for the Democratic Republic of Congo, Ethiopia, and Nigeria these figures varied between US$ 19–27 and 28–31%. The estimates are based on the expected introduction of rotavirus vaccination into the respective national immunization programmes within the next few years (2012–2018) and on forecasts of the vaccination coverage that can then be expected for a first dose administered before the age of 15 weeks and a second dose by age 32 weeks.

Recent cost-effectiveness modeling in Kenya predicted that cumulated over the first 5 years of life, the estimated prevented costs totaled US$ 1 782 761 (direct and indirect costs) with an associated 48 585 DALYs saved. Irrespective of the vaccine used, vaccination against rotavirus disease was found to be cost effective.[55]

A generic approach to the development of cost-effectiveness models for rotavirus vaccines in national immunization programmes has been proposed.[56]

WHO recommendations

Rotavirus vaccines should be included in all national immunization programmes and considered a priority, particularly in countries with high RVGE-associated fatality rates, such as in south and south-eastern Asia and sub-Saharan Africa.

The use of rotavirus vaccines should be part of a comprehensive strategy to control diarrhoeal diseases with

tout en causant 253 décès par invagination intestinale (76-689). La vaccination sans restriction d'âge permettrait d'éviter 203 000 décès dus au rotavirus (102 000-281 500) mais entraînerait 547 décès par invagination intestinale (237-1160). Le modèle prédit donc que la levée des restrictions d'âge permettrait d'éviter 47 200 décès supplémentaires dus au rotavirus (18 700-63 000) et provoquerait 294 décès supplémentaires par invagination intestinale (161-471) pour un ratio bénéfice-risque supplémentaire de 154 décès évité pour chaque mort due au vaccin. On retrouve dans ces décès supplémentaires évités avec un calendrier sans restriction par rapport à un calendrier restreint, les 21% à 28% d'enfants supplémentaires qui, potentiellement, rempliraient les conditions pour être vaccinés contre le rotavirus. Donc, dans les pays à revenu faible ou intermédiaire, les vies supplémentaires sauvées en levant les restrictions d'âge pour la vaccination antirotavirus dépasseraient de loin l'excédent de mortalité par invagination intestinale due au vaccin.[22]

Coût-efficacité de la vaccination contre les rotaviroses

Les estimations du coût annuel par année de vie ajustée sur l'incapacité (DALY) évitée et de la proportion (%) de décès par rotavirose évité par l'introduction des vaccins antirotavirus varient entre US$ 8 et US$ 87, et entre 32% et 44%, pour l'Afghanistan et le Bangladesh respectivement. Pour l'Inde, le pays enregistrant le plus grand nombre de décès par gastroentérite à rotavirus, les chiffres correspondants étaient de US$57 et 34%, alors qu'en Éthiopie, au Nigéria et en République démocratique du Congo, ils s'établissent dans des fourchettes de US$19-27 et 28-31%. Les estimations se fondent sur l'introduction escomptée de la vaccination antirotavirus dans les programmes nationaux de vaccination concernés au cours des prochaines années (2012-2018) et sur les prévisions de la couverture vaccinale à laquelle on peut s'attendre pour une première dose administrée avant l'âge de 15 semaines et une seconde dose jusqu'à l'âge de 32 semaines.

Une modélisation récente du rapport coût-efficacité au Kenya a prédit en chiffres cumulés sur les 5 premières années de la vie des coûts évités d'un total de US$ 1 782 761 (coûts directs et indirects) et 48 585 DALY associées. Quel que soit le vaccin utilisé, la vaccination antirotavirus s'est avérée d'un bon rapport coût-efficacité.[55]

Une approche générale pour l'élaboration de modèles de coût-efficacité pour les vaccins antirotavirus dans les programmes de vaccination a été proposée.[56]

Recommandations de l'OMS

Les vaccins antirotavirus devraient être intégrés dans tous les programmes nationaux de vaccination et considérés comme prioritaires, en particulier dans les pays ayant des taux de mortalité par GERV élevés, comme en Asie du Sud et du Sud-Est, ainsi qu'en Afrique subsaharienne.

L'utilisation des vaccins antirotavirus devrait faire partie d'une stratégie globale de lutte contre les affections diarrhéiques, avec

[55] van Hoek AJ et al. (2012) A cost effectiveness and capacity analysis for the introduction of universal rotavirus vaccination in Kenya: Comparison between Rotarix and RotaTeq Vaccines. *PLoS ONE*, 2012, 7: e47511.

[56] Postma MJ et al. Comparative review of 3 cost-effectiveness models for rotavirus vaccines in national immunization programs; a generic approach applied to various regions in the world. *BMC Medicine*, 2011, 9:84.

[55] van Hoek AJ et al. (2012) A cost effectiveness and capacity analysis for the introduction of universal rotavirus vaccination in Kenya: Comparison between Rotarix and RotaTeq Vaccines. *PLoS ONE*, 2012, 7: e47511.

[56] Postma MJ et al. Comparative review of 3 cost-effectiveness models for rotavirus vaccines in national immunization programs; a generic approach applied to various regions in the world. *BMC Medicine*, 2011, 9:84.

the scaling up of both prevention (promotion of early and exclusive breastfeeding, handwashing, improved water supply and sanitation) and treatment packages. WHO/UNICEF recommend that all children receive solutions of low-osmolarity ORS to prevent and treat dehydration due to diarrhoea. Breast milk is also an excellent rehydration fluid and should be given to children still breastfeeding along with ORS. In addition to fluid replacement, children with diarrhoea should continue to be fed during the episode. Food intake supports fluid absorption from the gut into the bloodstream to prevent dehydration and helps maintain nutritional status and ability to fight infection. Children should also simultaneously receive zinc treatment which reduces the duration and severity of diarrhoea episodes, stool volume and the need for advanced medical care.[57, 58] Plans for introduction of rotavirus vaccines should consider the epidemiology of the disease by age, the coverage and actual age at vaccination and an evaluation of the estimated public health impact and potential risks. In addition, cost-effectiveness assessment, issues of affordability of the vaccine, financial and operational impact on the immunization delivery system, and careful examination of current immunization practices should be taken into account.

Introduction of rotavirus vaccine should be accompanied by measures to ensure high vaccination coverage and timely administration of each dose.

Following a review of new evidence on age- specific burden of rotavirus disease and deaths, timeliness of vaccination, and the safety and effectiveness of different immunization schedules, WHO continues to recommend that the first dose of rotavirus vaccine be administered as soon as possible after 6 weeks of age, along with diphtheria-tetanus-pertussis (DTP) vaccination, to ensure induction of protection prior to natural rotavirus infection.

Although early immunization is still favoured, the manufacturers' conventional age restrictions on the first and last dose of rotavirus vaccines may have prevented vaccination of many vulnerable children in settings where the DTP doses are given late (i.e. after 15 weeks for DTP1 or after 32 weeks for DTP 2 or DTP3). By allowing infants to receive rotavirus vaccine together with DTP regardless of the time of vaccination, immunization programmes will be able to reach children who were previously excluded from the benefits of rotavirus vaccines. Because of the typical age distribution of RVGE, rotavirus vaccination of children >24 months of age is not recommended.

RV1 should be administered orally in a 2-dose schedule at the time of DTP1 and DTP2 with an interval of at

le renforcement des mesures de prévention (promotion de l'allaitement précoce et exclusif au sein, lavage des mains, amélioration de l'approvisionnement en eau et de l'assainissement) et de traitement. L'OMS et l'UNICEF recommandent d'administrer à tous les enfants des solutions de SRO à osmolarité réduite pour prévenir et traiter la déshydratation due à la diarrhée. Le lait maternel est aussi un excellent liquide de réhydratation et doit être donné avec les SRO aux enfants qui sont encore allaités. Outre le remplacement des liquides, les enfants doivent continuer à s'alimenter pendant l'épisode diarrhéique. L'ingestion d'aliments contribue à l'absorption des liquides dans l'intestin et à leur passage dans la circulation sanguine pour éviter la déshydratation; elle aide au maintien de l'état nutritionnel et à la capacité de combattre les infections. Il faut également donner en même temps à ces enfants un traitement de zinc qui réduit la durée et la gravité des épisodes diarrhéiques, le volume des selles et le besoin de recourir à des soins médicaux de pointe.[57, 58] Les plans pour l'introduction des vaccins antirotavirus doivent envisager l'épidémiologie de la maladie en fonction de l'âge, la couverture et l'âge véritable de la vaccination et évaluer les estimations de l'impact et des risques potentiels pour la santé publique. De plus, il faudrait aussi prendre en compte une évaluation du rapport coût-efficacité, les questions d'accessibilité économique du vaccin, les répercussions financières et opérationnelles sur le système d'administration de la vaccination et un examen soigneux des pratiques en usage.

L'introduction des vaccins antirotavirus devrait s'accompagner de mesures garantissant une forte couverture de la vaccination et l'administration de chaque dose en temps voulu.

Après un examen des nouvelles données factuelles sur la charge des rotaviroses et la mortalité selon l'âge, la ponctualité de la vaccination, ainsi que l'innocuité et l'efficacité des différents calendriers de vaccination, l'OMS continue de recommander l'administration de la première dose du vaccin antirotavirus dès que possible après l'âge de 6 semaines, en même temps que la vaccination contre la diphtérie, le tétanos et la coqueluche (DTC), pour induire la protection avant la survenue d'une rotavirose naturelle.

Bien que la vaccination précoce reste préférée, les limites indiquées typiquement par les fabricants pour l'âge à l'administration de la première et de la dernière dose des vaccins antirotavirus pourraient avoir empêché la vaccination de nombreux enfants vulnérables dans les milieux où les doses de DTC sont administrées tardivement (c'est-à-dire après 15 semaines pour le DTC1 ou après 32 semaines pour le DTC2 ou le DTC3). En permettant une administration concomitante avec le DTC quel que soit l'âge, les programmes de vaccination pourront couvrir des enfants auparavant privés des bénéfices apportés par les vaccins antirotavirus. Compte tenu de la répartition typique de la GERV selon l'âge, la vaccination antirotavirus des enfants âgés de >24 mois n'est pas recommandée.

Le RV1 doit être administré par voie orale en 2 doses au même moment que le DTC1 et le DTC2, avec un intervalle d'au moins

[57] *Diarrhoea: why children are still dying and what can be done.* Geneva, WHO/UNICEF, 2009. Available from http://www.who.int/maternal_child_adolescent/documents/9789241598415/en/index.html, accessed January 2013.

[58] *Pneumonia and diarrhoea: tackling the deadliest diseases for the world's poorest children.* New York, UNICEF, 2012. Available from http://www.unicef.org/media/files/UNICEF_P_D_complete_0604.pdf, accessed January 2013.

[57] *Diarrhoea: why children are still dying and what can be done.* Genève, OMS/UNICEF, 2009. Disponible sur http://www.who.int/maternal_child_adolescent/documents/9789241598415/en/index.html, consulté en janvier 2013. [Document disponible en anglais uniquement.]

[58] *Pneumonia and diarrhoea: tackling the deadliest diseases for the world's poorest children.* New York, UNICEF, 2012. Disponible sur http://www.unicef.org/media/files/UNICEF_P_D_complete_0604.pdf, consulté en janvier 2013. [Document disponible en anglais uniquement.]

least 4 weeks between doses. RV5 should be administered orally in a 3-dose schedule at the time of the DTP1, DTP2, and DTP3 contacts, with an interval of at least 4 weeks between doses. With both vaccines, prematurely born infants should follow the vaccination schedules recommended for their chronological age.

Rotavirus vaccinations can be administered simultaneously with other vaccines in the infant immunization programme.

Apart from a low risk of intussusception (about 1–2 per 100 000 infants vaccinated) the current rotavirus vaccines are considered safe and well tolerated.

Proper planning and training of staff to conduct pharmacovigilance should take place before the vaccine is introduced. Countries should develop a strategy to inform relevant health staff that although the benefits outweigh the risks, a small potential risk of intussusception after rotavirus vaccination remains. Countries should also ensure that caregivers are adequately counseled to recognize danger signs of dehydration or intussusception that should prompt immediate medical consultation.

Given the background rate of natural intussusception and the large number of children included in national immunization programmes, intussusception cases are expected to occur by chance alone following rotavirus vaccination. It is important to establish the baseline incidence of intussusception at sentinel sites and to use epidemiological studies, such as the self-controlled case series method, to assess the safety of rotavirus vaccines.[59]

Severe allergic reaction (e.g. anaphylaxis) after a previous dose, and severe immunodeficiency including severe combined immunodeficiency, are contraindications for rotavirus vaccination. Precautions are necessary if there is a history of intussusception or intestinal malformations, chronic gastrointestinal disease, and severe acute illness. Vaccination should be postponed in case of ongoing acute gastroenteritis or fever with moderate to severe illness.

The epidemiological impact of rotavirus vaccination should be monitored. High-quality surveillance should be conducted in selected countries and defined populations, including high child mortality settings. However, lack of population-based surveillance should not be an impediment to the introduction of rotavirus vaccine. ■

[59] See No 8, 2011, pp. 61–72.

4 semaines entre les doses. Pour le RV5, le calendrier prévoit 3 doses administrées au même moment que le DTC1, le DTC2 et le DTC3, avec un intervalle d'au moins 4 semaines entre les doses. Pour les 2 vaccins, les calendriers de vaccination applicables aux enfants prématurés sont ceux recommandés en fonction de leur âge chronologique.

Les vaccins antirotavirus peuvent être administrés en même temps que les autres vaccins du programme de vaccination infantile.

Mis à part le faible risque d'invagination intestinale (environ 1-2 pour 100 000 nourrissons vaccinés), on considère que les vaccins antirotavirus sont sûrs et bien tolérés.

Avant d'introduire le vaccin, il convient de mettre en place une planification et une formation suffisantes du personnel pour assurer la pharmacovigilance. Les pays devraient élaborer une stratégie pour informer les personnels de santé concernés qu'il subsiste un faible risque d'invagination intestinale après la vaccination antirotavirus, bien que les avantages dépassent ce risque. Ils devraient aussi s'assurer que les personnes s'occupant des enfants reçoivent les conseils nécessaires pour reconnaître les signes de danger de déshydratation ou d'invagination intestinale nécessitant de consulter immédiatement un médecin.

Compte tenu de la fréquence naturelle spontanée des invaginations intestinales et du grand nombre d'enfants couverts par les programmes de vaccination nationaux, il faut s'attendre à ce que des cas d'invagination surviennent fortuitement après la vaccination antirotavirus. Il est important d'établir l'incidence de départ de cette affection dans des sites sentinelles et d'utiliser des études épidémiologiques, comme les séries de cas auto-contrôlées, pour évaluer l'innocuité des vaccins antirotavirus.[59]

Des réactions allergiques sévères (anaphylaxie par exemple) après une dose administrée précédemment et l'immunodéficience sévère, y compris le déficit immunitaire combiné sévère, sont des contre-indications aux vaccins antirotavirus, tandis que les précautions d'emploi comportent les antécédents d'invagination ou de malformations intestinales, une affection gastro-intestinale chronique et une maladie aiguë sévère. La vaccination doit être différée en cas de gastroentérite aiguë en cours ou de fièvre accompagnant une affection modérée à grave.

Il faut surveiller l'impact épidémiologique de la vaccination antirotavirus. Une surveillance de grande qualité sera menée dans certains pays et populations, y compris dans des situations de forte mortalité infantile. Toutefois, l'absence de surveillance basée dans la population ne devrait pas être considérée comme un obstacle à l'introduction de cette vaccination. ■

[59] Voir N° 8, 2011, pp. 61-72.

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Appendix 3

Refers to:

Chapter 4, S1 Table, Information about the data used for new analyses

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S1 Table. Information about the data used for new analyses

New analysis	Where and how data was collected	Ethics statement
Clinical syndromes of U5 diarrhoea hospitalisations	WHO/CDC review of paediatric logbooks (Indonesia) and electronic discharge data (Rwanda and Zambia) from 50 hospitals included in the WHO-coordinated Global Sentinel Site Rotavirus Surveillance Network – GRSN.	All WHO GRSN surveillance data is from public health surveillance records. All data were anonymized prior to access and analysis. Institutional ethical approval was granted by CDC for the review of logbooks and analysis of the GRSN database. More details about GRSN are available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6329a5.htm
	CMC/CDC review of paediatric logbooks from 7 hospitals included in the Indian National Hospital Rotavirus Surveillance Network – NRSN.	All data were available under an existing disease burden project approved by the Institutional Review Board at the Christian Medical College (CMC) in Vellore. All data were anonymized prior to access and analysis.
	All data were collected as part of the previously published Global Enteric Multicenter Study – GEMS (Kotloff K. Lancet 2013). Data were from 27 hospitals from 5 country sites included in GEMS.	GEMS was approved by the ethics committee at the University of Maryland, Baltimore, MD, USA, and at every field site. Written informed consent was obtained from the parent or primary caretaker of each participant before initiation of study activities. All data were anonymized prior to access and analysis. Datasets are available upon request from: http://www.medschool.umaryland.edu/CVD/Projects/Global-Enteric-Multicenter-Study-GEMS/
Clinical syndromes of U5 diarrhoea deaths	Investigation of a representative sample of child deaths identified in a household survey, including deaths in the community or a health facility, using the birth history method with follow-up questions to the mother or caregiver of the deceased child. Verbal autopsy data collected as part of national or multi-district verbal/social autopsy (VASA) studies in Cameroon (18,000 households in 2012), Malawi (24,000 households in 2012), Niger (25,000 households in 2010) and Nigeria (40,680 households in 2014). For more details please see Adewemimo A. et al (PLOS One 2017) http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0178129.	All four VASA studies underwent ethical review and were approved by the Johns Hopkins University Institutional Review Board and the respective national ethical review committee of each study country. All data were anonymized prior to access and analysis. Nigeria data available from: https://doi.org/10.5281/zenodo.569864 Niger data available upon request from the National Institute of Statistics (INS – Niger): http://www.stat-niger.org/nada/index.php/catalog/70#page=accesspolicy&tab=study-desc
Rotavirus-positive proportion in U5 diarrhoea hospitalisations and U5 diarrhoea deaths in GEMS	All data were collected as part of the previously published Global Enteric Multicenter Study – GEMS (Kotloff K. Lancet 2013). Data from 6 of the 7 country sites included in GEMS.	GEMS was approved by the ethics committee at the University of Maryland, Baltimore, MD, USA, and at every field site. Written informed consent was obtained from the parent or primary caretaker of each participant before initiation of study activities. All data were anonymized prior to access and analysis. Datasets are available upon request from: http://www.medschool.umaryland.edu/CVD/Projects/Global-Enteric-Multicenter-Study-GEMS/. The verbal autopsy data from GEMS are not publicly available. These data are collected by the site's Demographic Surveillance System (DSS) and were shared with GEMS. Thus the sharing, but not the procedure, was described in the GEMS

		protocol. All data were anonymized prior to access and analysis.
Rotavirus attributable fraction among rotavirus-positive U5 diarrhoea hospitalisations in GEMS	All data were collected as part of the previously published Global Enteric Multicenter Study – GEMS (Kotloff K. Lancet 2013). Data were from 6 of the 7 country sites included in GEMS.	GEMS was approved by the ethics committee at the University of Maryland, Baltimore, MD, USA, and at every field site. Written informed consent was obtained from the parent or primary caretaker of each participant before initiation of study activities. All data were anonymized prior to access and analysis. Datasets are available upon request from: http://www.medschool.umaryland.edu/CVD/Projects/Global-Enteric-Multicenter-Study-GEMS/

Appendix 4

Refers to:

Chapter 4, S1 Appendix, Further details on the comparison of rotavirus mortality estimates from GBD, CHERG and WHO/CDC

S1 Appendix. Further details on the comparison of rotavirus mortality estimates from GBD, CHERG and WHO/CDC

GBD, CHERG and WHO/CDC used different methods to:

(i) select data points (rotavirus-positive proportions);
(ii) extrapolate data points to individual countries;
(iii) account for rotavirus vaccine coverage;
(iv) convert rotavirus-positive proportions to rotavirus attributable fractions; and,
(v) calculate uncertainty ranges.

The following provides a fuller description of these differences:

Data points (rotavirus-positive proportions)

CHERG identified 242 data points (rotavirus-positive proportions) from 76 countries; GBD identified 1336 data points from 71 countries; and, WHO/CDC identified 774 data points from 90 countries. 110 countries were included by at least one of the three sources, and only 42 were identified by all three. There was considerable variation in the combination of other countries included by each source (see Table below).

S1 Appendix Table. Number of countries with data points (rotavirus-positive proportions <5 years) included by CHERG, GBD and WHO/CDC by WHO region

WHO region	CHERG	GBD	WHO /CDC	All three sources	At least one source
AFRO	15	14	20	8	25
AMRO	10	11	18	8	19
EMRO	11	8	16	5	16
EURO	23	23	18	9	31
SEARO	6	5	7	4	7
WPRO	11	10	11	8	12
GLOBAL	**76**	**71**	**90**	**42**	**110**

Where possible, GBD and WHO/CDC disaggregated studies into sub-national sites and 12-month periods, and entered each as a separate data point.

All three groups excluded any data points that did not represent at least 12 months of data, thus avoiding seasonality issues. However, the groups differed on other inclusion and exclusion criteria. CHERG and WHO/CDC did not include rotavirus proportions derived from outpatients, but GBD included data points for both outpatients and inpatients, and made an explicit adjustment for inpatient status in their regression model. 33 of the 71 countries included by GBD had rotavirus-positive proportions for both inpatients and outpatients, 6 countries had data points for outpatients only (Austria, Denmark, Germany, Iceland, Saudi Arabia, Zambia) and 32 countries had data points for inpatients only. CHERG and GBD included data points from studies published from January 1990 onwards. WHO/CDC only included data points with a mid-year data collection point from July 1998 onwards. GBD and WHO/CDC excluded data points based on fewer than 100 tested diarrhoea samples but CHERG did not set a lower threshold for this. WHO/CDC only included studies that reported data points for the entire <5 year age range whereas both CHERG and GBD included data points reported for narrower age bands (e.g. <2yrs) and made adjustments to account for missing data. GBD did not use GRSN data, but this was the only source of evidence used in 20 of the 32 GRSN countries included by CHERG and 16 of the 61 GRSN countries included by WHO/CDC.

CHERG found 39% rotavirus positivity in 180 single-pathogen inpatient studies compared to 20% rotavirus-positivity in 24 inpatient studies that tested for at least 5 pathogens [1]. This suggests a bias associated with single-pathogen rotavirus studies. Rotavirus studies may be more likely to be conducted in areas with higher rotavirus prevalence, and more likely to exclude acute bloody and persistent diarrhoea cases, leading to inflated estimates of the rotavirus-positive proportion. To allow further investigation of this bias, future estimates should report the number of pathogens tested for each data point used.

The methods used by WHO/CDC and CHERG are relatively straightforward and derived from data points that are in general, publicly available. WHO routinely publishes summary reports of the GRSN data, but it is not currently possible to download this information in an editable spreadsheet format. Greater access to this information would permit its use by all groups in future estimates. The methods used by GBD are more complex and include a small proportion of data points that are not available publicly. In an effort to increase transparency,

GBD will release all of its computer codes in future GBD releases. They do however acknowledge that it would be very difficult for others to replicate their estimates without intimate understanding of their source files and code [2].

Recent Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) have recommended publication of a spreadsheet table with details about the data points used to inform estimates [3]. We recommend a set of minimum variables that should be included in future estimates (see first recommendation in main manuscript). The GATHER checklist also requires detailed documentation of inclusion and exclusion criteria and methods of data analysis, and should help to increase transparency in reporting of methods in future updates.

Extrapolating rotavirus-positive proportions to individual countries

Different methods are used to extrapolate sub-national data points to individual countries. WHO/CDC and GBD use regression models. CHERG calculates a median for each region and then extrapolates this to all countries within each region. Covariates used by WHO/CDC were the calendar year, Millennium Development Goal (MDG) region, national under-five mortality rate and national rotavirus vaccine coverage level. GBD use their *Dismod-MR* regression model, a Bayesian, hierarchical, mixed-effects meta-regression model with fixed effects for sex, inpatient sample status and broad screening method and random effects to account for super-region, region, country, age and calendar year.

All three groups assumed that sub-national data points were representative of the national situation. However, most GRSN sites and most other sites reported in the published literature are located in major urban areas where socioeconomic conditions, environmental risks and access to treatment may be different to the rest of the country. Issues of representativeness can be overcome if regression models include characteristics that are specific to each sub-national data point e.g. proportion of patients from rural areas, under-five mortality rate, private/public hospital, secondary/tertiary hospital etc. However, both GBD and WHO/CDC used national variables to define sub-national data points when constructing their respective regression models. This is a reasonable approach in the absence of detailed sub-national information about each site. However, where possible, groups should extract and test the importance of other potentially influential sub-national characteristics e.g. private/public

hospital, secondary/tertiary hospital, under-five mortality rate, proportion of patients from rural areas etc. If it is not feasible to collect this information from all sites, then a more detailed review of the GRSN dataset could be informative, and would allow comparison of several sub-national sites within the same countries.

WHO/CDC restricted their dataset to data points collected after July 1998 because previous literature reviews had shown an increase in the rotavirus-positive proportion from 22% (for studies published 1986-1999) to 39% (for studies published 2000-2004). This warrants further scrutiny. In particular, whether the trend is still observed after correcting for the improved sensitivity of testing in more recent years (e.g. rectal swabs vs EIA) and the increased number of single-pathogen rotavirus studies conducted in more recent years. These single-pathogen studies were shown by CHERG to give a significantly higher rotavirus-positive proportion than multiple pathogen studies. If such a trend were to exist after correcting for these potential biases, then regression models could explicitly account for the period of data collection. Period effects may be closely linked to the stage of economic development in each country, and thus may already be captured by existing covariates e.g. GDP per capita, under-five mortality rate etc. However, estimates for historical years published by GBD (1990-2013) and WHO/CDC (2000-2013) indicate very little change in the proportion of U5 diarrhoea deaths caused by rotavirus each year. This suggests the effect is either not observed in the datasets, or does exist, and is not appropriately captured in the regression models.

Accounting for rotavirus vaccine coverage

CHERG did not account for vaccine coverage in their 2010 estimates because very few countries had introduced rotavirus vaccines before that year. For the purpose of this comparison exercise, the pre-vaccine rotavirus-positive proportions reported by CHERG for 2010 were applied to pre-vaccine era U5 diarrhoea deaths estimated by CHERG for 2013, and no adjustment was made for the small number of countries that had introduced rotavirus vaccination before 2013. To estimate U5 diarrhoea deaths in the year 2013, GBD included rotavirus vaccine introduction status as a binary covariate in their *CODEm* regression model. However, the rotavirus-attributable fractions used by GBD for years with rotavirus vaccination, were based on data points (rotavirus-positive proportions) extracted from the pre-vaccine era. Vaccine-adjusted estimates of U5 diarrhoea deaths were therefore combined

with rotavirus-attributable fractions that had not been adjusted for rotavirus vaccine use. WHO/CDC included a binary covariate in their regression model used to predict the rotavirus-positive proportion. This covariate was used to differentiate sites that had introduced rotavirus vaccines to a reasonable level of coverage (>60% coverage of children aged <1 year, at least 12 months after vaccine introduction). However, the 2000-2013 CHERG estimates of U5 diarrhoea deaths available at the time of the analysis were not adjusted for rotavirus vaccine use [4]. WHO/CDC therefore combined U5 diarrhoea deaths that had not been adjusted for vaccine use, with rotavirus-positive proportions that had been. In summary, both GBD and WHO/CDC estimates were adjusted for rotavirus vaccine impact at one level of the analysis but not both, and this may have led to over-estimation of rotavirus deaths in a small number of countries that had introduced rotavirus vaccination in 2013. Including a rotavirus vaccine coverage covariate at both levels of the analysis (U5 diarrhoea deaths, rotavirus-positive proportion) would partly overcome this problem. However, if separate regression models or separate sources of estimates are used at each level of the analysis, this may lead to estimates of U5 diarrhoea deaths and U5 rotavirus deaths that are not internally consistent in post-vaccination years. This could be overcome by generating a single estimate of the number of rotavirus deaths prevented by vaccination, and adjusting both the number of U5 diarrhoea deaths and the number of U5 rotavirus deaths by the same consistent number. Joint WHO/UNICEF estimates of coverage have been standardised across countries (accounting for both household surveys and administrative data) and should ideally be used for these adjustments.

Converting rotavirus-positive proportions to rotavirus attributable fractions

WHO/CDC used the rotavirus-positive proportion as a direct proxy for the rotavirus attributable fraction, and did not make further adjustments.

CHERG added together: (a) the median rotavirus-positive proportion, based on all included data points; (b) the median pathogen-positive proportions reported for all other enteric pathogens, based on studies that sought 5-13 pathogens (n=27); and, (c) the median proportion of stool samples with unknown etiology, based on 12 studies that sought at least 8 pathogens. The total summed to greater than 100%, so all medians were rescaled to 100%. Pathogen-positive proportions were therefore converted into something closer to pathogen-

attributable fractions. The rescaling of pathogen-positive proportions is one approach to attributing mixed infections to a single cause, but this does not account for differences in pathogenicity. Re-analysis of diarrhoeal samples from GEMS using a pan-molecular approach with real-time, quantitative PCR [5, 6] suggests that the pathogenicity of different organisms is very different. The low prevalence of rotavirus identified in the stools of healthy controls compared to diarrhoea hospitalisations in GEMS (3% vs 38% - See main manuscript, Table 3) suggests that rotavirus is likely to be an important cause of severe diarrhoea whenever it is detected. A similar pattern (6% vs 27%) was also observed in the Malnutrition and Enteric Disease Study (MAL-ED) where children from 8 sites in South America, Africa and Asia were followed from birth until age 24 months [7]. The proportion of samples with unknown etiology (34%) was also included in the CHERG rescaling process, but this did not account for variability in the performance of the conventional tests used to identify each pathogen. Retesting of stool samples from the GEMS case control study using the Polymerase Chain Reaction (PCR) TaqMan® array card recently found significant variation in test performance [8]. It should be noted that the results of the new PCR analyses were not available at the time the 2010 CHERG estimates were developed.

GBD derived rotavirus-attributable fractions by multiplying rotavirus-positive proportions by 1/(1-OR), where OR is the odds ratio derived from the GEMS case control study, and reflects the odds of having MSD if rotavirus is detected in the stool using the conventional EIA test. ORs were calculated for all enteric pathogens included in GEMS. The average ORs of countries with GEMS sites in African and Asian sub-regions were applied to other countries in that sub-region. The average ORs across all GEMS sites was applied to all other countries. The original GEMS analysis [9] first calculated odds ratios, and then adjusted for the presence of other pathogens using the Bruzzi correction [10]. GBD derived their own ORs from the GEMS dataset; these ORs did not account for socio-demographic characteristics but did account for inter-site variability [11]. In both the primary GEMS analysis and GBD reanalysis the ORs were calculated using MSD cases, which include both outpatients and inpatients. GBD apply attributable fractions for each pathogen to diarrhoea deaths and any remaining deaths not assigned to a cause are considered to be unknown. The number of diarrhoea deaths with an unknown cause was around 40% in GBD 2013 [11].

Uncertainty

WHO/CDC estimates include uncertainty in the proportion of U5 diarrhoea deaths due to rotavirus, but not higher level uncertainty in U5 deaths and U5 diarrhoea deaths. Both CHERG and GBD generate probabilistic uncertainty intervals that account for uncertainty in U5 deaths, the proportion due to diarrhoea, and the proportion due to rotavirus. In addition, GBD includes uncertainty in the GEMS odds ratios applied to rotavirus-positive proportions. CHERG separately presented uncertainty that was due to parameter inputs versus specific methodological choices e.g. they showed deaths with and without the inclusion of single-pathogen studies.

References for S1 Appendix

1. Lanata CF, Fischer-Walker CL, Olascoaga AC, Torres CX, Aryee MJ, Black RE. Global causes of diarrheal disease mortality in children <5 years of age: a systematic review. PLoS One. 2013;8(9):e72788.

2. Theo Vos RB, David E Phillips, Alan D Lopez, Christopher J L Murray. Authors Reply to Correspondence - Causes of child death: comparison of MCEE and GBD 2013 estimates. Li Liu, Robert E Black, Simon Cousens, Colin Mathers, Joy E Lawn, Daniel R Hogan. Published Online May 23, 2015 http://dx.doi.org/10.1016/ S0140-6736(15)60663-8.

3. Stevens GA, Alkema L, Black RE, Boerma JT, Collins GS, Ezzati M, et al. Guidelines for Accurate and Transparent Health Estimates Reporting: the GATHER statement. Lancet. 2016.

4. World Health Organization. Child cause of death estimates 2000-2013. Available at: http://www.who.int/entity/healthinfo/global_burden_disease/childCOD_estimates_2000_2013.xls?ua=1. Accessed 11 January 2017.

5. Liu J, Kabir F, Manneh J, Lertsethtakarn P, Begum S, Gratz J, et al. Development and assessment of molecular diagnostic tests for 15 enteropathogens causing childhood diarrhoea: a multicentre study. Lancet Infect Dis. 2014;14(8):716-24.

6. Platts-Mills JA, Gratz J, Mduma E, Svensen E, Amour C, Liu J, et al. Association between stool enteropathogen quantity and disease in Tanzanian children using TaqMan array cards: a nested case-control study. Am J Trop Med Hyg. 2014;90(1):133-8.

7. Platts-Mills JA, Babji S, Bodhidatta L, Gratz J, Haque R, Havt A, et al. Pathogen-specific burdens of community diarrhoea in developing countries: a multisite birth cohort study (MAL-ED). Lancet Glob Health. 2015;3(9):e564-75.

8. Liu J, Platts-Mills JA, Juma J, Kabir F, Nkeze J, Okoi C, et al. Use of quantitative molecular diagnostic methods to identify causes of diarrhoea in children: a reanalysis of the GEMS case-control study. Lancet. 2016;388(10051):1291-301.

9. Blackwelder WC, Biswas K, Wu Y, Kotloff KL, Farag TH, Nasrin D, et al. Statistical methods in the Global Enteric Multicenter Study (GEMS). Clin Infect Dis. 2012;55 Suppl 4:S246-53.

10. Bruzzi P, Green SB, Byar DP, Brinton LA, Schairer C. Estimating the population attributable risk for multiple risk factors using case-control data. Am J Epidemiol. 1985;122(5):904-14.

11. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(9963):117-71.

Appendix 5

Refers to:

Chapter 6, Supplementary webappendix, Timing of children's vaccinations in 45 low-income and middle-income countries

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Appendix to:

The timing of children's vaccinations in 45 low- and middle-income countries

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Table W1: Survey countries, years and sample sizes

				Sample sizes					
	Year of	WHO	pop aged	age at interview		with full valid dates of birth and vaccination			
Country	survey	region	< 3y (000s)	< 5	< 3	BCG	DPT1	DPT3	MCV
Bangladesh	2004	SEAR	11,076	6,908	4,154	1,801	1,780	1,357	965
Benin	2001	AFR	837	5,349	3,260	1,795	1,676	1,285	966
Bolivia	2003	AMR	730	10,448	6,043	4,024	3,918	2,880	2,351
Brazil	1996	AMR	10,836	5,045	3,072	1,988	1,985	1,563	1,423
Burkina Faso	2003	AFR	1,474	10,645	6,261	2,499	2,400	1,799	1,426
Cambodia	2000	WPR	987	8,834	5,054	649	622	407	364
Cameroon	2004	AFR	1,629	8,125	4,943	1,032	1,002	813	575
Chad	2004	AFR	1,074	5,635	3,340	548	585	309	271
Colombia	2005	AMR	2,715	14,621	8,806	5,875	5,667	4,526	3,563
Comoros	1996	AFR	75	1,145	1,145	645	623	475	384
Congo	2005	AFR	332	4,835	3,099	1,645	1,521	1,194	784
Côte d'Ivoire	1998	AFR	1,695	1,992	1,273	730	698	546	465
Dominican Republic	2002	AMR	657	11,362	7,070	3,166	2,847	1,903	1,986
Egypt	2005	EMR	5,094	13,851	8,453	4,916	4,668	3,953	3,671
Eritrea	2002	AFR	426	6,366	3,626	2,009	2,011	1,691	1,291
Gabon	2000	AFR	95	4,405	2,776	1,335	828	488	586
Ghana	2003	AFR	1,866	3,844	2,324	1,321	1,345	1,136	915
Guatemala	1998	AMR	1,182	4,943	3,012	1,511	1,567	1,176	1,123
Guinea	2005	AFR	911	6,364	3,952	671	602	444	314
Haiti	2000	AMR	752	6,685	4,120	1,703	2,023	1,232	1,218
Honduras	2005	AMR	563	10,800	6,528	5,053	4,967	4,200	3,224
India	2005	SEAR	76,330	51,555	30,666	8,999	9,222	7,508	5,527
Kenya	2003	AFR	3,417	5,949	3,682	1,646	1,617	1,277	880
Kyrgyz Republic	1997	EUR	304	1,127	1,127	771	718	601	439
Lesotho	2004	AFR	169	3,697	2,310	742	705	597	457
Madagascar	2003	AFR	1,825	5,415	3,245	1,370	1,318	1,114	795
Malawi	2004	AFR	1,410	10,914	6,869	3,928	4,137	3,454	2,622
Mali	2001	AFR	1,277	13,097	7,958	2,433	2,153	1,374	1,331
Mauritania	2000	AFR	261	4,764	2,865	730	696	428	366
Morocco	2003	EMR	1,796	6,180	3,669	2,436	2,300	2,037	1,574
Mozambique	2003	AFR	2,106	10,326	6,253	3,738	3,639	2,893	2,401
Namibia	2000	AFR	153	3,989	2,503	1,404	1,384	1,165	867
Nicaragua	2001	AMR	406	6,986	4,227	2,999	2,918	2,517	1,888
Niger	1998	AFR	1,516	4,798	4,798	1,308	1,196	884	686
Nigeria	2003	AFR	14,277	6,029	3,690	599	461	258	230
Peru	2004	AMR	1,714	5,168	3,134	1,144	1,095	952	613
Rwanda	2005	AFR	918	8,649	5,527	1,807	1,767	1,550	1,113
Senegal	2005	AFR	1,097	10,944	6,896	1,187	1,157	899	659
Tanzania	1999	AFR	3,932	3,215	1,980	1,181	1,151	963	733
Togo	1998	AFR	599	4,168	4,168	2,019	1,836	1,227	976
Turkey	1998	EUR	4,067	3,565	2,195	431	579	470	356
Uganda	2000	AFR	3,229	7,113	4,409	1,548	1,494	985	805
Uzbekistan	1996	EUR	1,636	1,324	1,324	1,052	1,019	904	758
Yemen	1997	EMR	2,056	12,451	7,571	1,358	1,385	1,063	839
Zambia	2001	AFR	1,196	6,877	4,329	2,550	2,475	2,000	1,754
Median country	2002		1,277	6,180	3,952	1,548	1,521	1,176	880
IQR	2000		657	4,764	3,012	1,052	1,002	813	586
	2004		2,056	10,326	6,043	2,436	2,300	1,799	1,426

Table W2 gives information on the countries and dates covered by the surveys included in the study, together with information about sample sizes and numbers of children for whom the information needed to calculate age at vaccination was complete and valid. For MCV in Chad there were only 271 children with full data, and for DTP3 in Nigeria only 258, but most of the cells in tables W5 and W6 are based on imputation from at least 1000 vaccinations with valid ages.

Table W2: Variation between surveys in completeness of data

	percentiles [1]	*25th*	*50th*	*75th*
Date of birth	% invalid or incomplete	9.6	20.5	30.6
	% with day of birth missing	9.6	20.5	31.3
	% with month imputed by DHS	0.0	0.2	1.0
	% with year imputed by DHS	0.0	0.0	0.0
If BCG given[2]	% with vaccination card and date	64.1	72.3	78.5
	% of dates invalid or incomplete	0.2	0.9	1.9
	% of dates missing day	0.1	0.3	0.5
	% of dates missing month	0.0	0.3	0.9
	% of dates missing year	0.1	0.9	1.9
If DTP1 given[2]	% with vaccination card and date	55.3	63.5	74.1
	% of dates invalid or incomplete	0.2	0.5	1.2
	% of dates missing day	0.1	0.1	0.2
	% of dates missing month	0.1	0.3	0.8
	% of dates missing year	0.2	0.5	1.2
If DTP3 given[2]	% with vaccination card and date	65.3	79.2	85.1
	% of dates invalid or incomplete	0.1	0.4	0.9
	% of dates missing day	0.0	0.1	0.2
	% of dates missing month	0.0	0.3	0.7
	% of dates missing year	0.1	0.4	0.9
If MCV given[2]	% with vaccination card and date	57.1	68.4	77.2
	% of dates invalid or incomplete	0.0	0.1	0.4
	% of dates missing day	0.1	0.3	0.5
	% of dates missing month	0.2	0.5	0.8
	% of dates missing year	0.2	0.5	0.8

1. Percentiles indicate the variation between countries; eg the 50th percentile is the median of the distribution of country-specific values
2. According to vaccination card with date, card without date or mother's recall

Information on how the completeness of data varied between country surveys is given in Table W3. Dates were counted as invalid if day, month or year were missing, or if the date was self-contradictory (e.g. 30 February) or out of order (e.g. vaccination after mother's interview). Dates of interview were complete and valid in all cases.

The table gives percentiles. For example it can be seen that for the most complete quarter of the surveys, day of the month of birth was missing in 9.5% of the children or fewer, and in the least complete quarter it was missing in 31.4% or more. There were, however, fewer missing days of birth among children who had been vaccinated (25th percentile 4.4%, median 13.2%, 75th percentile 25.5%). Survey data on month and year of birth were almost complete.

If the day of the month of birth was missing this was imputed as follows: if the child had been given BCG on a known date, and the difference between the month of birth and the month of BCG was less than 5, the child's age at BCG was imputed from the distribution of known ages for children given BCG on the same day of the month and with the same difference between month of birth and month of BCG. The exact date of birth was then calculated from the date of BCG and imputed age at BCG. Otherwise a random day in the child's first month of life was used.

Table W3: Distributions of regression coefficients b and p-values for H_o:b = 0 (45 surveys)

		coefficients				p-values			
	percentiles	*25th*	*50th*	*75th*	*95th*	*5th*	*25th*	*50th*	*75th*
DPT1	mean age (days) at vaccination in baseline group	47.8	59.2	67.2	89.1	0.00	0.00	0.00	0.00
	if female	0.99	1.01	1.03	1.06	0.04	0.24	0.36	0.69
	if rural	1.03	1.08	1.14	1.30	0.00	0.00	0.03	0.21
	per year of mother's education (up to 13)	0.98	0.99	0.99	1.00	0.00	0.00	0.03	0.16
	mother's age at birth	0.97	0.98	1.00	1.02	0.00	0.09	0.28	0.67
	per place in the birth oder (up to 8)	1.01	1.02	1.03	1.05	0.00	0.01	0.11	0.42
	if born in hospital, not home	0.85	0.89	0.93	1.02	0.00	0.00	0.01	0.16
	if child's age at interview is 1-1.9	1.08	1.14	1.24	1.48	0.00	0.00	0.00	0.02
	if child's age at interview is 2-2.9	1.11	1.22	1.38	1.90	0.00	0.00	0.00	0.01
DPT3	mean age (days) at vaccination in baseline group	125.6	135.3	166.5	208.1	0.00	0.00	0.00	0.00
	if female	0.99	1.00	1.01	1.04	0.04	0.21	0.43	0.69
	if rural	1.02	1.09	1.12	1.26	0.00	0.00	0.00	0.05
	per year of mother's education (up to 13)	0.98	0.99	0.99	1.00	0.00	0.00	0.00	0.04
	mother's age at birth	0.98	0.99	1.00	1.02	0.00	0.04	0.19	0.45
	per place in the birth oder (up to 8)	1.01	1.02	1.02	1.05	0.00	0.00	0.10	0.35
	if born in hospital, not home	0.90	0.93	0.97	1.04	0.00	0.00	0.01	0.08
	if child's age at interview is 1-1.9	1.10	1.14	1.21	1.36	0.00	0.00	0.00	0.00
	if child's age at interview is 2-2.9	1.15	1.25	1.35	1.71	0.00	0.00	0.00	0.00

Ages at vaccination were imputed for cases in which the evidence for vaccination was mother's recall, or there was no date on the card. Separate regression analyses were carried out for each country to identify characteristics associated with variations in age at each vaccination. Then if a vaccination date was missing, an age at vaccination was sampled from a distribution based on known values of age at vaccination (ie values calculated from complete and valid dates of vaccination and dates of birth) for children in that country with similar characteristics.

The upper part of Table W4 shows how the relationships between log(age at DTP1) and the different predictors (1,2) varied between countries. The lower part of the table does the same for DPT3. It shows the median and quartile values for the 45 country-specific coefficients and p-values. The original coefficients *b* have been transformed to e^b, so the coefficients are multiplicative, the baseline being the mean age at vaccination in the country in question for a firstborn boy aged less than 1 at the time of the interview who lived in an urban area, was born at home to a mother aged 16 or less with no years of education. Thus for DPT3 the figure of 1.12 for the 75th percentile of coefficients for 'if rural' indicates that in the 75% of countries for which the effect of rurality was weakest, the independent effect of living in a rural area was to multiply the age at DTP3 by less than 1.12 – so for 25% of the countries the effect was at least 1.12. The figure of 0.05 for the 75th percentile of p-values for 'if rural' indicates that in the 75% of countries with the lowest p-values for the rurality coefficient, all the p-values were less than 0.05.

The effects of age at interview are mainly attributable to the different lengths of follow-up involved, but may also be partly linked to recall and trend effects. In the imputation, all the factors in the table except for gender were used for all the surveys, but age at interview was measured in quarters of a year and all the variables were treated as categorical. It can be seen that in general the effects of the different predictors were similar for DPT1 and DPT3. However the explanatory power of the models for each country was quite modest, with median adjusted R-squareds of 5% for DPT1 and 12% for DPT3.

Imputation cannot address 'complete' under-reporting in the survey, which occurs when loss or disposal of the card is combined with failure of mothers' recall. If this is primarily because of loss of cards, and this in turn is associated with problems with vaccine delivery, the result of under-reporting is likely to be underestimated delays. On the other hand if for example cards are more likely to be disposed of when vaccination is complete, this will lead to over-estimates.

Table W4: Delays after target in ages at vaccination: 25th, 50th and 75th percentiles, by country

	BCG					DPT1					DPT3					MCV				
	target	percentile delay (weeks)				target	percentile delay (weeks)				target	percentile delay (weeks)				target	percentile delay (weeks)			
	age(w)	25th	50th	75th	IQR	age(w)	25th	50th	75th	IQR	age(w)	25th	50th	75th	IQR	age(w)	25th	50th	75th	IQR
Bangladesh	0	6.4	8.4	11.0	4.6	6	1.1	2.9	5.6	4.4	14	3.4	7.1	12.7	9.3	38	1.9	3.9	7.6	5.7
Benin	0	0.1	0.6	2.0	1.9	6	0.4	1.3	3.6	3.1	14	1.7	4.5	11.7	10.0	39	0.4	2.7	8.3	7.9
Bolivia	0	0.1	1.7	6.0	5.9	9	0.2	1.9	6.4	6.3	26	0.5	4.6	14.6	14.1	52	0.4	4.4	19.2	18.9
Brazil	0	2.3	4.6	7.4	5.1	9	0.2	0.7	3.2	3.0	26	1.0	3.0	9.0	8.0	39	0.6	2.0	6.4	5.9
Burkina	0	1.0	2.9	7.3	6.3	9	0.0	1.9	6.7	6.7	17	1.6	6.6	18.9	17.3	39	0.1	3.1	10.4	10.3
Cambodia	0	2.9	7.0	16.3	13.4	6	1.7	4.4	13.7	12.0	14	4.8	11.2	27.9	23.1	39	0.7	5.3	14.7	14.0
Cameroon	0	0.9	2.7	6.9	6.0	6	0.3	1.6	5.6	5.3	14	2.1	4.7	10.4	8.3	39	-0.1	2.0	6.7	6.9
Chad	0	1.7	6.3	20.1	18.4	6	1.0	8.0	20.3	19.3	14	6.4	17.8	39.5	33.1	39	-3.3	5.1	20.4	23.7
Colombia	0	0.1	0.7	3.6	3.4	9	0.2	1.0	3.7	3.6	26	0.0	2.2	7.5	7.4	52	-23.8	-16.5	1.7	25.4
Comoros	0	0.4	1.9	6.6	6.1	6	0.7	3.4	8.0	7.3	14	5.5	11.8	27.4	21.9	39	0.1	4.1	15.9	15.7
Congo	0	0.3	1.4	4.3	4.0	9	0.0	1.0	3.3	3.3	17	0.5	2.5	6.0	5.6	39	0.3	1.7	5.3	5.0
Cote d'Ivoire	0	0.4	1.4	5.4	5.0	6	0.9	3.0	8.0	7.1	14	3.1	8.2	19.5	16.4	39	0.0	2.7	12.9	12.9
Dominican R	0	0.1	0.7	3.4	3.3	9	0.3	1.2	4.4	4.1	26	-5.7	0.5	5.6	11.3	52	-24.9	-19.2	-9.9	15.0
Egypt	0	1.0	2.0	4.3	3.3	9	-0.1	0.3	1.3	1.4	26	-0.1	0.6	2.0	2.1	39	-0.1	0.6	1.9	2.0
Eritrea	0	0.3	6.6	11.6	11.3	6	0.4	2.0	6.6	6.1	14	1.7	3.8	9.8	8.1	39	-0.3	1.0	5.1	5.4
Gabon	0	0.6	2.0	6.0	5.4	6	0.7	3.0	7.9	7.1	14	3.8	8.1	17.9	14.1	39	0.1	3.0	10.1	10.0
Ghana	0	0.6	3.0	7.1	6.6	6	0.7	2.6	5.6	4.9	14	2.7	6.1	13.5	10.9	39	0.0	2.4	7.3	7.3
Guatemala	0	2.9	6.9	17.3	14.4	9	0.9	4.2	10.3	9.4	17	7.0	15.3	30.5	23.4	39	1.4	5.7	15.3	13.9
Guinea	0	0.1	1.1	3.1	3.0	6	0.6	2.0	5.9	5.3	14	2.9	6.1	12.9	10.0	39	-0.4	1.1	6.0	6.4
Haiti	0	1.0	4.1	10.3	9.3	6	1.0	3.4	9.7	8.7	14	3.9	11.4	25.8	21.9	39	0.7	5.7	23.9	23.1
Honduras	0	0.1	0.4	4.4	4.3	9	0.0	0.4	1.7	1.7	26	0.6	2.2	5.9	5.3	52	0.2	1.2	3.8	3.6
India	0	1.7	5.3	9.7	8.0	6	1.0	2.9	6.3	5.3	14	3.2	6.2	12.8	9.6	39	0.3	2.7	6.9	6.6
Kenya	0	0.7	3.0	6.7	6.0	6	0.3	1.4	4.1	3.9	14	1.1	3.2	7.5	6.4	39	-0.3	1.7	5.6	5.9
Kyrgyz	0	0.4	0.6	0.7	0.3	9	0.2	1.0	3.7	3.6	22	2.0	4.4	9.3	7.3	52	0.4	1.4	4.1	3.7
Lesotho	0	0.1	1.4	4.4	4.3	6	0.6	1.1	2.9	2.3	14	2.1	4.1	9.1	7.0	39	1.0	2.9	7.3	6.3
Madagascar	0	1.3	4.6	8.9	7.6	6	0.6	1.9	5.6	5.0	14	2.2	4.8	11.2	9.0	39	0.1	1.6	5.1	5.0
Malawi	0	2.6	6.9	12.3	9.7	6	1.1	3.1	7.1	6.0	14	3.9	8.5	16.1	12.1	39	1.0	4.4	9.0	8.0
Mali	0	1.3	3.4	13.4	12.1	6	0.6	2.9	13.1	12.6	14	3.1	8.8	26.1	23.0	39	-1.3	3.1	16.1	17.4
Mauritania	0	0.6	3.7	13.1	12.6	6	0.6	3.6	13.7	13.1	14	3.5	9.4	21.9	18.4	39	-1.2	2.4	15.1	16.3
Morocco	0	1.6	2.1	2.7	1.1	6	0.6	1.3	2.4	1.9	14	2.2	3.5	5.8	3.6	39	0.1	1.0	3.1	3.0
Mozambique	0	0.3	1.3	5.3	5.0	6	2.9	4.3	8.3	5.4	14	4.4	8.9	18.4	14.0	39	0.0	2.1	8.4	8.4
Namibia	0	0.1	0.1	1.3	1.1	6	0.1	0.7	1.9	1.7	14	1.1	2.4	6.8	5.7	39	0.1	0.9	3.4	3.3
Nicaragua	0	0.1	0.4	4.3	4.1	9	0.2	0.9	4.3	4.1	26	-6.8	-2.0	7.0	13.9	52	0.4	2.8	10.1	9.7
Niger	0	0.7	4.6	10.6	9.9	6	1.3	3.4	9.1	7.9	14	4.2	8.2	19.1	14.9	39	-4.2	3.3	11.0	15.1
Nigeria	0	0.9	2.7	7.3	6.4	6	0.3	2.4	8.9	8.6	14	1.7	5.1	13.5	11.9	39	-0.3	2.3	8.1	8.4
Peru	0	0.3	1.6	3.1	2.9	9	0.0	0.4	2.0	2.0	17	0.3	1.6	4.6	4.3	52	0.4	1.8	4.7	4.3
Rwanda	0	1.1	2.3	3.9	2.7	6	0.4	1.1	2.6	2.1	14	1.4	2.9	5.4	4.0	39	0.6	2.4	5.0	4.4
Senegal	0	1.1	3.1	6.6	5.4	6	0.6	2.6	5.3	4.7	14	2.5	6.2	11.4	8.9	39	0.1	2.7	8.0	7.9
Tanzania	0	0.3	1.9	5.3	5.0	4	1.0	3.0	6.0	5.0	12	3.4	7.3	14.3	10.9	39	0.3	2.4	6.3	6.0
Togo	0	0.7	2.1	5.9	5.1	6	0.9	2.3	6.9	6.0	14	3.1	7.5	18.7	15.6	39	-0.3	3.3	11.1	11.4
Turkey	8	0.4	1.6	3.6	3.1	8	1.6	3.6	6.9	5.3	16	4.2	7.8	13.7	9.4	39	1.0	2.9	6.9	5.9
Uganda	0	1.4	6.1	13.7	12.3	6	1.1	4.0	12.3	11.1	14	3.5	9.2	21.5	18.0	39	0.0	2.7	9.6	9.6
Uzbekistan	0.4	0.0	0.3	0.5	0.4	9	0.7	3.3	10.0	9.3	17	3.5	11.0	27.5	24.0	39	1.0	5.7	17.6	16.6
Yemen	0	4.7	7.9	14.3	9.6	6	0.7	3.0	7.1	6.4	14	3.2	7.2	13.7	10.4	39	-0.9	1.1	6.6	7.4
Zambia	0	1.6	4.9	10.1	8.6	6	2.9	5.0	9.3	6.4	14	5.4	10.7	20.4	15.0	39	0.1	2.7	8.7	8.6
Median		0.7	2.3	6.6	5.4		0.6	2.4	6.3	5.3		2.7	6.2	13.5	10.9		0.1	2.7	7.6	7.9
Lower quartile		0.3	1.4	4.3	3.4		0.3	1.2	3.7	3.6		1.4	3.5	9.0	8.0		-0.3	1.7	5.3	5.9
Upper quartile		1.3	4.6	10.3	8.6		1.0	3.3	8.3	7.1		3.5	8.5	19.1	15.6		0.4	3.1	11.0	13.9

Negative values indicate vaccination before target date. Both Colombia and the Dominican Republic responded to local outbreaks of measles by bringing forward their vaccination programmes.

List of references for web appendix

1. Domblowski KJ, Lantz PM, Freed GL. The need for surveillance of delay in age-appropriate immunization. Am J Prev Med 2002; 23: 36-42.
2. Akmatov MK, Kretzchmar, Kramer A, Mikolajczyk RT, Timeliness of vaccination and its effect on fraction of vaccinated population. Vaccine 2008; 26:3805-3811

Appendix 6

Refers to:

Chapter 7, Appendix A, Further details about waning functions

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Appendix A – Further details about the alternative waning functions considered

Equations of the alternative waning functions evaluated and Deviance Information Criteria

We used two analyses in our study, a meta-regression to generate pooled estimates of vaccine efficacy, and a Poisson regression in which we investigated waning of an individual trial where we had weekly-follow up data. Different waning functions were compared visually, statistically (comparing the Deviance Information Criteria), and were assessed for biological plausibility. Estimated cumulative vaccine efficacies were converted to instantaneous vaccine efficacies using the method outlined in Appendix B.

1. Pooled analysis – meta-regression

We fitted curves estimating overall cumulative vaccine efficacy to the observed cumulative vaccine efficacies. We performed a Poisson regression using a hierarchical Bayesian model, where study-specific relative risks were centred around an overall latent relative risk (RR) in each respective mortality stratum.

We investigated multiple waning functions. In waning functions that are listed as bounded, the RR is bounded between 0 and 1. As a result, *cumulative* vaccine efficacy in these functions is bounded between 100% and 0%. Note that this does not necessarily bound the *instantaneous* vaccine efficacy, as a *cumulative* vaccine efficacy above 0% can still result from negative *instantaneous* vaccine efficacies in a certain period.

The table below illustrates the functional form of the natural logarithm of the latent time-specific RR as fitted in each respective waning function in the meta-regression. Time specific cumulative vaccine efficacy was then estimated as $1 - e^{\log(RR)}$. Note that the entire waning function is used in computing the RR, and that individual parameters in each waning function are not easily interpretable. Each function has up to 4 different parameters, depending on the complexity of the waning function: σ, t, α, and β. σ was estimated for each study separately as σ_i (centred around an overall latent σ, which prior was assigned mean 0 and standard deviation equal to the square root of the estimated between study variance), whereas α and β were the same across studies. t is the time-component of the function and refers to the months since final dose of vaccination was administered.

The high mortality stratum was modelled three times. Once including all countries, once excluding India, and once for India only. Because the analysis for India only included two studies, the hierarchical construct of the analysis over-inflated uncertainty around our estimates. As a result, we removed the hierarchical component of our model from the analysis with India only, assuming exactly the same distribution for σ in the two studies.

Model	Log relative risk
No waning	$\theta(t) = \sigma$
Linear	$\theta(t) = \sigma + \alpha + \log(t)$
Power	$\theta(t) = \sigma + e^{\alpha}\log(t)$
Power 2	$\theta(t) = \sigma + \alpha\,\log(t)$
Power 3	$\theta(t) = \sigma + \alpha\, t$
Power (bounded)	$\theta(t) = \alpha + e^{\beta}\log(t) - \log(e^{\sigma} + e^{\alpha} t^{e^{\beta}})$
Sigmoid (bounded)	$\theta(t) = \sigma - \log(\mathrm{e}^{\sigma} + \mathrm{e}^{\alpha}\mathrm{e}^{-\mathrm{e}^{\beta} t})$
Gamma (bounded)*	$\theta(t) = \log(\Gamma(\mathrm{t}, e^{\sigma}, e^{\beta}))$

* Γ refers to the cumulative gamma function

2. Head-to-head trial: Analysis of Indonesia trial/Bines

We used the same functions (with the exception of 'No waning', which was purely used for illustrative purposes in the meta-regression) to look at data from a single trial in Indonesia (belonging to the high under 5 mortality stratum). The methodology and results from this trial are published elsewhere[1]. For this study, we obtained weekly follow-up data from three arms: a placebo group, a group vaccinated using a neonatal schedule (0-5 days, 8-10 weeks, 14-16 weeks) and a group vaccinated using an infant schedule (8-10 weeks, 14-16 weeks, 18-20 weeks). We used this data to construct cumulative hazard estimates and used the same fitting approach as in our meta-regression, fitting to these cumulative estimates. The functional form of the natural logarithms of each fitted RR is illustrated in the table below. They differ from those used in the meta-regression only in that we added a parameter ρ which adjusts for potential confounding between the two vaccinated schedules. Coefficient ρ was multiplied by an indicator variable which was set to 1 for the infant schedule and set to 0 for the neonatal schedule. In other words, ρ was included in the equation in estimated vaccine efficacy in the infant schedule but omitted in estimating vaccine efficacy in the neonatal schedule. The parameters in the waning function, σ, α, and β, were estimated separately and independent from one another in each respective schedule.

Model	Log relative rate
Linear	$\theta(t) = \sigma + \alpha + \log(t) + \rho$
Power	$\theta(t) = \sigma + e^{\alpha}\log(t) + \rho$
Power 2	$\theta(t) = \sigma + \alpha \log(t) + \rho$
Power 3	$\theta(t) = \sigma + \alpha\, t + \rho$
Power (bounded)	$\theta(t) = \alpha + e^{\beta} \log(t) - \log(e^{\sigma} + e^{\alpha} t^{e^{\beta}}) + \rho$
Sigmoid (bounded)	$\theta(t) = \sigma - \log(\mathrm{e}^{\sigma} + \mathrm{e}^{\alpha}\mathrm{e}^{-\mathrm{e}^{\beta}t}) + \rho$
Gamma (bounded)[i]	$\theta(t) = \log(\Gamma(\mathrm{t}, e^{\sigma}, e^{\beta})) + \rho$
i. Γ refers to the cumulative gamma function	

Comparison of alternative waning functions

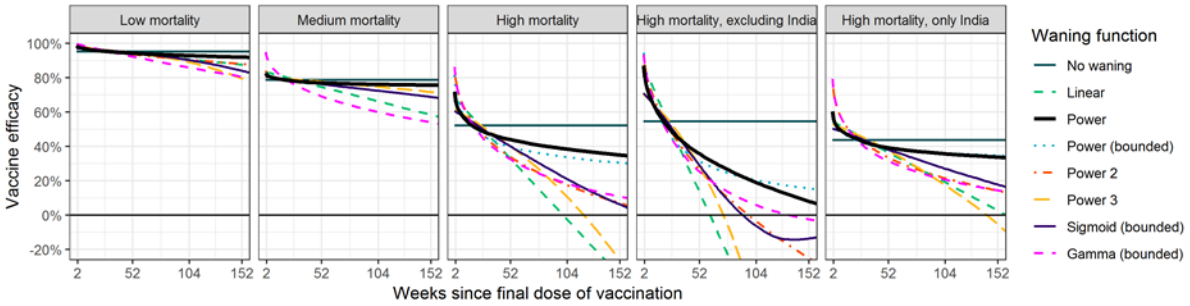
The table below gives the DIC value for each respective function in each respective stratum. DIC values should be compared relative to all values in each column. Although the 'no waning' function had generally good DIC values in the pooled analysis, it performed the worst in the Indonesia analysis. Similarly, waning Rotavirus vaccine efficacy is broadly accepted. Although we included this function for comparability, we determined it to be biologically unlikely.

Deviance Information Criteria (DIC)

Function	Low mortality	Medium mortality	High mortality	High mortality (no India)	India	Indonesia
No waning	154.2	133.5	314.0	250.6	65.6	958.9
Linear	154.9	134.6	315.4	252.9	65.7	911.6
Power	152.6	133.8	315.6	250.5	65.5	914.2
Power 2	152.6	134.8	315.9	250.8	66.1	913.6
Power 3	153.0	135.0	314.9	250.5	66.4	921.5
Power (bounded)	153.2	134.0	315.0	251.2	66	912.6
Sigmoid (bounded)	153.1	134.3	314.9	250.8	65.7	920.7
Gamma (bounded)	152.0	137.3	315.0	249.8	65.8	913.7

Visual comparison

The plots below show, for each function, the median estimated waning of instantaneous vaccine efficacy by mortality strata following 2/3 doses of oral rotavirus vaccination (infant schedules only). The full set of plots for all other functions can be found in Appendix C (pooled analysis) and Appendix D (Indonesia analysis).



The simple power function (Power) was used in the main paper because it had few parameters and goodness of fit (DIC scores) that were consistently favourable across all strata, compared to the other functions considered. The gamma (bounded) would be a reasonable alternative to use in high mortality countries, but had the worst fit in the medium mortality stratum.

References

1. Bines JE, At Thobari J, Satria CD, et al. Human Neonatal Rotavirus Vaccine (RV3-BB) to Target Rotavirus from Birth. *N Engl J Med* 2018;**378**(8):719-730.

Appendix 7

Refers to:

Chapter 7, Appendix B, Approximating instantaneous vaccine efficacy

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Appendix B - Approximating instantaneous vaccine efficacy from cumulative vaccine efficacy

Vaccine efficacy is usually defined as the reduction in the incidence rate in vaccinated compared to unvaccinated people, and estimated as 1 - RR, where RR is the risk or rate ratio. This works fine when the RR is constant over time, i.e. vaccine efficacy does not wane. However, vaccine efficacy that wanes over time may be overestimated if not properly accounted for.

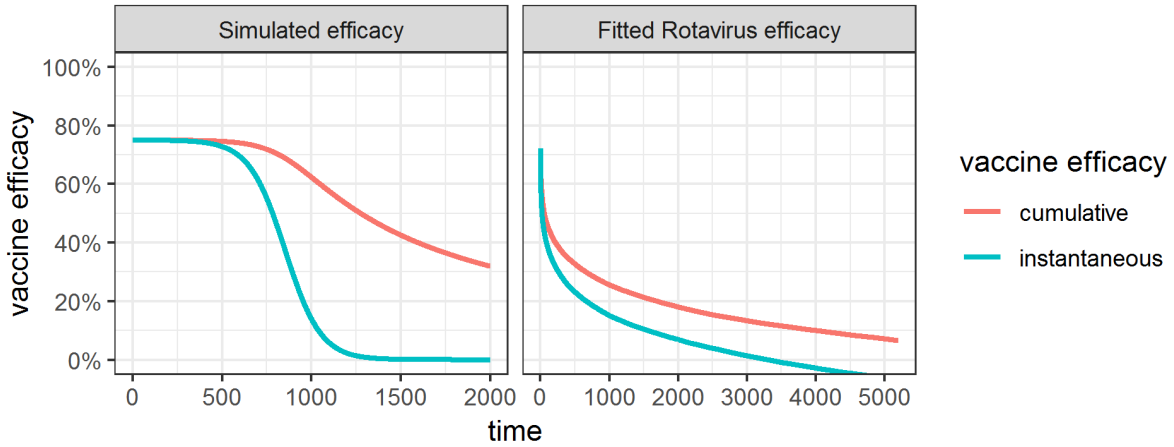
In our study, we have extracted the total number of severe rotavirus-positive gastroenteritis cases occurring at different time-points, in multiple randomized clinical trials (RCT) aiming to assess efficacy of rotavirus vaccines. We then used a hierarchical Bayesian meta-regression model to fit a number of curves through the observed number of cases over time, allowing for waning vaccine efficacy, in order to retrieve a curve that best explains the observed data. This curve gives an estimate of waning (cumulative) vaccine efficacy.

As we will show in the equations below, the value of the cumulative vaccine efficacy at time *t* is influenced by the values of the true *instantaneous* vaccine efficacy prior to time *t*. Because *instantaneous* vaccine efficacies before time *t* may be higher than the *instantaneous* vaccine efficacy at time *t*, the *cumulative* vaccine efficacy at time *t* may overestimate the actual *instantaneous* vaccine efficacy at time *t.*

This is illustrated by figure B1 below, which shows both cumulative and instantaneous vaccine efficacies. The left panel shows the result of simulated data in a hypothetical RCT. The cumulative vaccine efficacy clearly overestimates the (known) simulated instantaneous vaccine efficacy. The right panel shows the vaccine efficacy as modelled with a Power function in the high mortality stratum in our study. The cumulative vaccine efficacy is fitted to the empiric data, whilst the instantaneous vaccine efficacy is derived from the fitted cumulative vaccine efficacy, using the method we will present below.

This document will explain the method that was used in converting cumulative vaccine efficacy to instantaneous vaccine efficacy. We will use a general example. The theoretical underpinning and steps used to do this conversion are described below, along with its assumptions and limitations.

Figure B1. Cumulative and instantaneous vaccine efficacy



The left panel shows the cumulative vaccine efficacy and true instantaneous vaccine efficacy in a simulated hypothetical vaccine efficacy trial. The right panel shows the cumulative vaccine efficacy of Rotavirus vaccines against severe rotavirus-positive gastroenteritis as modelled with a power function in the high mortality stratum in our study along with its corresponding approximated instantaneous vaccine efficacy. It is equivalent to Figure 1 in our main paper.

Background

Smith et al (1) proposed two models of vaccine efficacy considering different models of action of the vaccine, which Halloran, Haber, and Longini (2) later described as the *leaky* and *all-or-nothing* models and extended further to incorporate heterogeneity.

Kanaan and Farrington (3) devised a framework which can be used to assess waning vaccine efficacy over time, and can incorporate all models described by Halloran et al (2): *leaky*, *all-or-nothing*, *leaky-or-nothing*, *all-or-leaky*, and potentially increased heterogeneity using multiple strata of vaccine-action in the vaccinated group. They proposed two models in which vaccine-efficacy might wane: the selection-model, being the with-waning extension of the *all-or-nothing* model, and the deterioration-model, being the with-waning extension of the *leaky* model.

Vaccines can provide protection against actual infection after exposure to a pathogen, against the amount of infectiousness after infection of a pathogen, and against the development or severity of disease after infection with a pathogen. Here, we will assume that vaccine efficacy relates to the protection against development of disease.

Figure B2 illustrates the dynamics that would occur in a hypothetical randomised controlled trial (RCT) under the two methods of vaccine action: *all-or-nothing* and *leaky*. Individuals are randomised (*R*), after which a proportion π will receive the vaccine, and a proportion $1 - \pi$ a placebo. Participants are susceptible at the start of the trial, indicated by the S_u and S_{v*} compartments for the unvaccinated and vaccinated stratum respectively. Unvaccinated individuals will become infected at a rate $\lambda(t)$, and flow to compartment I_u.

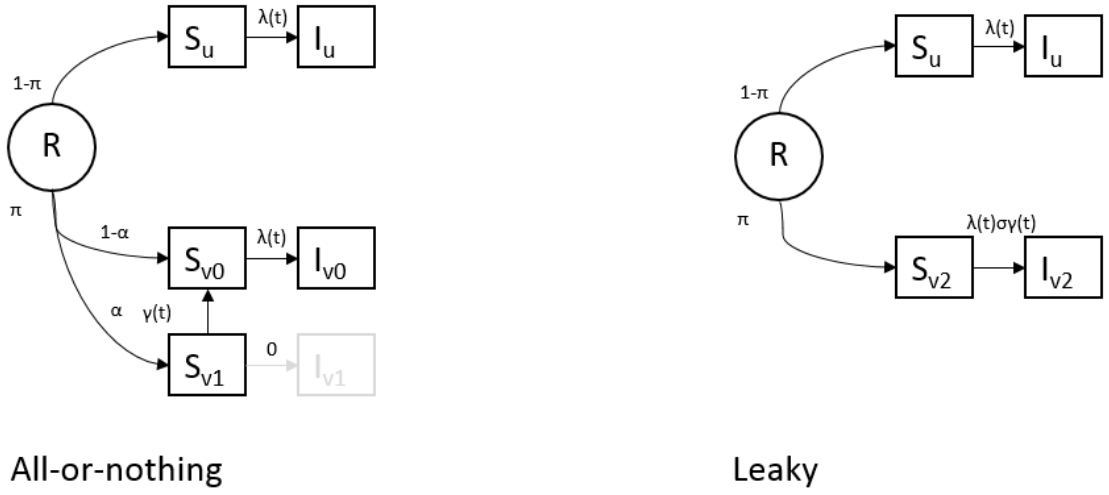
In the *all-or-nothing* model of vaccine action, a proportion α of those vaccinated will be fully protected against the infection (compartment S_{v1}). As long as the vaccine is protective, they will never experience disease. In contrast, the vaccine provides no protection at all for a proportion $1 - \alpha$ of those vaccinated. As a result, these individuals will become infected at the same rate as unvaccinated individuals. Following Kanaan and Farrington (3), in the *all-or-nothing* model, waning of vaccine efficacy may occur as a selection effect. Subsequently, vaccinated individuals will lose protection and flow from the protected compartment S_{v1} to the unprotected compartment S_{v0}. The amount of individuals who lose protection is explained by the waning function, $\gamma(t)$.

In the *leaky* model of vaccine action, the vaccine is assumed to provide some level of protection for all vaccinated individuals. The baseline force of infection is reduced by a proportion σ. Here, waning may occur as a result of a deterioration effect, where the level of protection reduces over time, again denoted by the function $\gamma(t)$ in figure B2.

These models may be extended to incorporate more heterogeneity in vaccine response. For instance, the leaky model may be extended to have multiple substrata (S_{v1}, S_{v2}, S_{v3}, …), in the vaccinated individuals, where participants in different strata have different levels of protection.

The α parameter in the *all-or-nothing* model is the equivalent of the relative risk of disease, whereas the σ parameter in the *leaky* model represents the relative rate. In the absence of waning vaccine efficacy, when $\gamma(t) = 0$, vaccine efficacy is estimated as $1 - \alpha$, or $1 - \sigma$. In contrast, in the presence of waning, vaccine-efficacy at time t is estimated as $1 - \alpha\gamma(t)$ or $1 - \sigma\gamma(t)$.

Figure B2. Compartmental models for a hypothetical randomized controlled trial under different assumptions of the mode of vaccine action



Compartmental models for the *all-or-nothing* mode of vaccine action and the *leaky* mode of vaccine action.

Methods

Estimating vaccine efficacy

Estimation of the relative risk is straightforward:

$$RR = \frac{risk\ in\ vaccinated}{risk\ in\ placebo} = \frac{cases\ in\ vaccinated / total\ vaccinated}{cases\ in\ unvaccinated / total\ unvaccinated} \quad (1)$$

Note that, when calculating risks, the numerator holds the sum of all cases accrued over the study period, whilst the denominator holds all individuals who were at risk of becoming a case at the start of the study period. When the relative risk is constant over time, equation 1 will give a good measure for the relative risk throughout the entire study period. However, if vaccine efficacy wanes, and the relative risk increases over time, the calculation in equation 1 will only give an estimation of the average relative risk throughout the entire time-period, i.e. the cumulative relative risk.

To estimate the relative rate, researchers can use parametric survival analyses such as Poisson or Cox regression. These often make the assumption that hazards are proportional over time, meaning that the relative rate remains constant. This assumption is clearly violated when vaccine efficacy wanes. Nonparametric methods (4), such as Kaplan Meier survival estimates (5), do not make the assumption of proportional hazards, and may be used as an alternative.

The Kaplan Meier Survival estimate can be estimated as

$$S_{KM}(t) = \prod_{x=0}^{t} \left(1 - \frac{Y_x}{N_x}\right)^{dx} \quad (2)$$

Where Y_x is the number of events observed at time *x* and N_x is the risk set size at time *x* (or total number of people at risk at time *x*, accounting for censoring). These survival estimates can be used to estimate the cumulative hazard at any time *t* as follows:

$$H_{KM}(t) = -\log S_{KM}(t) \quad (3)$$

The cumulative hazard in the vaccinated, $H_{KM,v}$, and unvaccinated, $H_{KM,u}$, at time *t*, can then be used to estimate ϑ_t,the cumulative hazard ratio at time t:

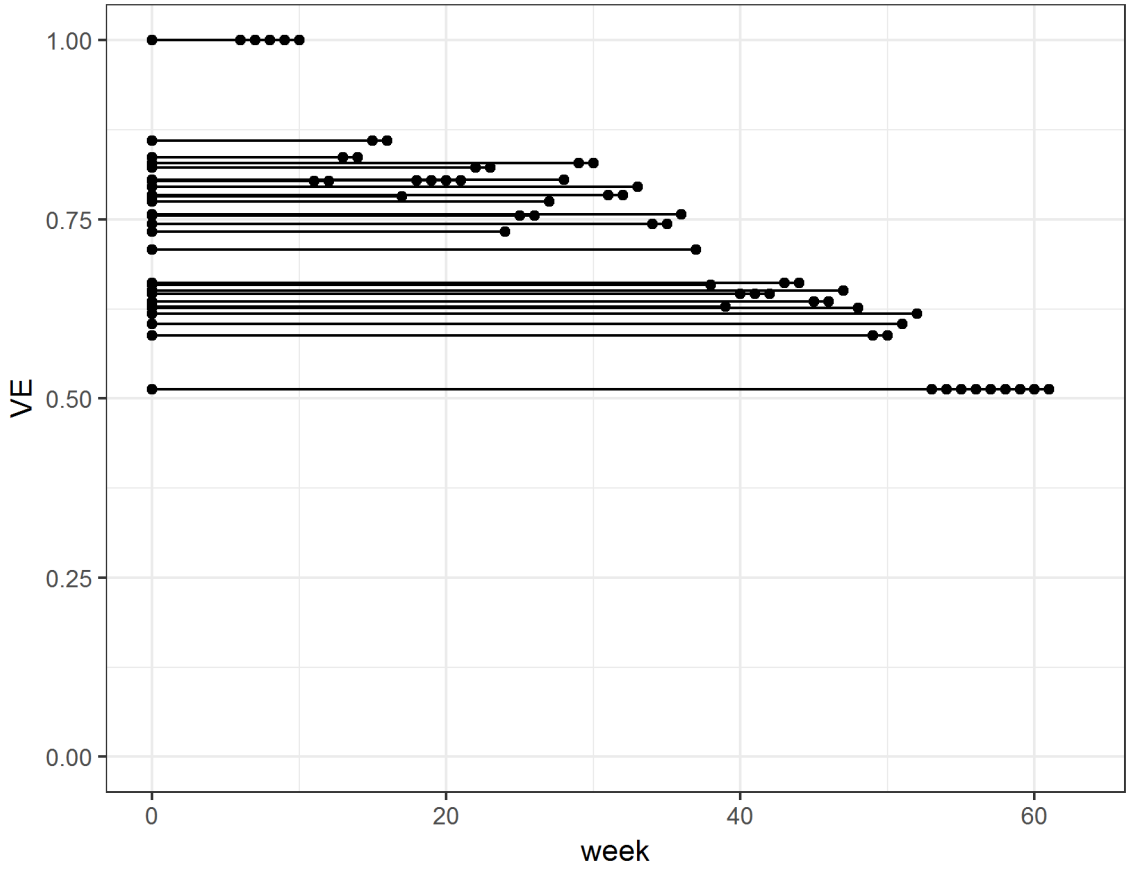
$$\theta(t) = \frac{H_{KM,v}(t)}{H_{KM,u}(t)} \quad (4)$$

Which can be used to estimate cumulative vaccine efficacy at time *t*:

$$VEc(t) = 1 - \theta(t) \quad (5)$$

Following equation 1, the survival estimate at time *t* is a result of the product of all risks in the risk sets up until time *t*. Subsequently, the cumulative vaccine efficacies as calculated in equation 5 will give the vaccine efficacy over the entire period up until time *t*, rather than the vaccine efficacy at time *t*. This is illustrated in figure B3. Again, this is a measure of the cumulative vaccine efficacy.

Figure B3. Cumulative vaccine efficacy derived from the Kaplan-Meier method.



Cumulative vaccine efficacies are derived from the infant schedule in the RV3-BB trial estimating vaccine efficacy against severe rotavirus gastroenteritis (6). Vaccine efficacies reported in a certain week (points on the right) are the average vaccine efficacies over the periods as illustrated by the solid lines.

In practice, researchers will usually be interested in the exact level of protection at time *t*, i.e. the instantaneous vaccine efficacy. We will now present a method to approximate instantaneous vaccine efficacy from cumulative vaccine efficacy, based on the Kaplan-Meier method described above.

Approximating instantaneous vaccine efficacy

For the unvaccinated arm, equation (2) can be rewritten as:

$$S_{KM,u}(t) = \prod_{x=0}^{t}\left(1 - \frac{\lambda_x N_x}{N_x}\right)^{dx} \quad (6)$$

Where λ_x is the force-of-infection at time *x*. N_x cancels out, so:

$$S_{KM,u}(t) = \prod_{x=0}^{t}(1 - \lambda_x)^{dx} \quad (7)$$

As the rate ratio is the reduction (or increase) of the force of infection, in this case as a result of immunisation, we can rewrite equation 5 for vaccinated individuals as follows:

$$S_{KM,v}(t) = \prod_{x=0}^{t}(1 - \lambda_x\sigma_x)^{dx} \quad (8)$$

Where σ_x is the instantaneous rate ratio at time *x*. Putting all these equations together, cumulative vaccine efficacy can be estimated as:

$$VEc(t) = 1 - \theta(t) = 1 - \frac{-\log\prod_{x=0}^{t}(1 - \lambda_x\sigma_x)^{dx}}{-\log\prod_{x=0}^{t}(1 - \lambda_x)^{dx}} \quad (9)$$

Unfortunately, this cannot easily be rewritten to estimate the instantaneous vaccine efficacy, σ_x. However, as λ_x is the force of infection, this rate is usually very small. And as a result, equation 9 can be approximated by:

$$\lim_{\lambda_x \to 0} -\log\prod_{x=0}^{t}(1 - \lambda_x)^{dx} = \int_{x=0}^{t}\lambda_x dx \quad (10)$$

Which is similar to the Nelson-Aalen estimator of the cumulative hazard rate (7,8). This can be used to rewrite equation 3, to estimate the cumulative rate ratio at time *t*:

$$\theta(t) = \frac{\int_{x=0}^{t}\lambda_x\sigma_x dx}{\int_{x=0}^{t}\lambda_x\, dx} \quad (11)$$

Ordinary survival analyses often assume proportional hazards, i.e. rate-ratios remain constant over time, in which case equation 11 would be:

$$\theta(t) = \frac{\int_{x=0}^{t} \lambda_x \sigma dx}{\int_{x=0}^{t} \lambda_x \, dx} = \sigma \quad (12)$$

I.e. the cumulative rate-ratio and instantaneous rate-ratio would be the same. Following equation 12, this is irrespective of any change in the baseline-rate λ_x, assuming that this rate is the same in the vaccinated and unvaccinated groups. Ideally, infections in the vaccinated and unvaccinated arms are always observed and censored after becoming a case. However, individuals may get asymptomatic infections which are not observed in the study, but boost immunity, especially in the unvaccinated. This may alter the baseline rate in the unvaccinated arm of the trial, such that rates in the vaccinated and unvaccinated arm are no longer similar. Eventually, this can lead to an overestimation of the relative rate when natural immunity in the unvaccinated arm increases, as has been shown for rotavirus vaccines (9).

Because we are modelling waning vaccine-efficacy, we obviously assume that the rate-ratio does not remain constant over time. Assuming a time-dependent rate-ratio, equation 11 can be rewritten as:

$$\sigma(t) = \theta(t) + \int_{x=0}^{t} (\theta(t) - \sigma(x)) \frac{\lambda_x}{\lambda_t} dx \quad (13)$$

There are two issues with this equation. First, in order to retrieve instantaneous vaccine efficacy at time *t*, we need all instantaneous vaccine efficacies up until time *t*. Second, the change in the baseline-rate between time *x* and time *t* needs to be accounted for, as the cumulative rate ratio observed at time *t* is affected by the interaction between changes in the baseline-rate, and changes in the instantaneous relative rate.

The first issue can be easily accounted for, as the instantaneous relative rate at the first time-point is the same as the cumulative relative rate at that time-point:

$$\sigma_1 = \theta_1 \quad (14)$$

This rate can subsequently be used to estimate the instantaneous relative rate at the second time-point, and so on.

It is harder to account for changes in the baseline rate over time, as this is often unknown. In infectious disease epidemiology, we know that rates change over time. For instance, seasonal patterns can result from changes in the temperature or from changes in contact rates in a population. However, we can make the bold assumption that this rate remains stable over time. This assumption is often made when parametric survival analyses are used. One could aim to retrieve changes in the baseline rate over time, for instance by building a natural history model, but this is outside the scope of the methodology presented here. Making the assumption of time-independent rates, equation 13 can be rewritten as:

$$\sigma(t) = \theta(t) + \int_{x=0}^{t} (\theta(t) - \sigma(x)) \, dx \quad (15)$$

Which can be used to retrieve the instantaneous rate ratio at time *t*. Eventually, this instantaneous rate ratio can be used to estimate instantaneous vaccine efficacy at time *t*:

$$VEi(t) = 1 - \sigma(t) \quad (16)$$

We will now present results of simulated data to show the success of this method.

Simulations

We simulated data following the compartmental models as illustrated in figure B2. Although our method would generally only work for a leaky vaccine, we will simulate data for both *all-or-nothing* and *leaky* vaccines.

The following differential equations (17-25) can be used to describe transmission in the trial for the all-or-nothing vaccine. Note that, in contrast to mathematical transmission models, the force-of-infection *λ(t)* does not depend on the number of infectious individuals in the trial. We assume that the individuals in the trial are part of a larger population, and that transmission mainly occurs due to the infections outside of this population.

$$\frac{dS_u}{dt} = -\lambda(t) \tag{17}$$

$$\frac{dI_u}{dt} = \lambda(t)S_u \tag{18}$$

$$\frac{dS_{v0}}{dt} = -\lambda(t) + \gamma(t)S_{v1} \tag{19}$$

$$\frac{dS_{v1}}{dt} = -\gamma(t) \tag{20}$$

$$\frac{dI_{v0}}{dt} = \lambda(t)S_{v0} \tag{21}$$

In simulations where the vaccine wanes, we assume that waning follows a sigmoidal shape, which can be described as:

$$\gamma(t) = \frac{1}{1 + 5000e^{-0.01t}} \tag{22}$$

In simulations where the vaccine does not wane, this parameter is always set to 1:

$$\gamma(t) = 1 \tag{23}$$

Similarly, in simulations where the force of infection changes over time, it is assumed to follow a sine-curve:

$$\lambda(t) = 0.004\left(1 + 0.1\sin\frac{t}{80}\right) \tag{24}$$

In simulations where this force of infection is fixed, we assume

$$\lambda(t) = 0.004 \quad (25)$$

Dynamics in the leaky mode of vaccine action can be described through the following differential equations (26-30):

$$\frac{dS_u}{dt} = -\lambda(t) \quad (26)$$

$$\frac{dI_u}{dt} = \lambda(t)S_u \quad (27)$$

$$\frac{dS_{v2}}{dt} = -\lambda(t)\sigma(t) \quad (28)$$

$$\frac{dI_{v2}}{dt} = \lambda(t)\sigma(t)S_{v2} \quad (29)$$

Where *λ(t)* takes on the same values as in equations 24 and 25 for simulations with or without a changing baseline force of infection.

Waning vaccine efficacy is again modelled as a sine-curve, similar to that in equation 22. The instantaneous rate ratio, *σ(t)*, is defined as

$$\sigma(t) = \frac{1-\phi}{1+5000e^{-0.01t}} \quad (30)$$

Where *Φ* is the vaccine efficacy after administration at the start of the trial.

In all simulations, for both methods of vaccine action, the ratio of vaccinated versus placebo is 1:1, i.e. $\pi = 0.5$. The total study population size, *N*, is set to 1000. Initial vaccine efficacy is set to 75%, so $\alpha = 0.75$ in the *all-or-nothing* vaccine, and *Φ* is set to 0.75 in the *leaky* vaccine.

We ran the model for 2000 timesteps. We estimated cumulative vaccine efficacy twice, using risk ratios, as in equation 1, and using cumulative hazard ratios, as in equation 5. In the *all-or-nothing* vaccine, compartments V_0 and V_1 were combined to calculate cumulative measures, as the individual level of protection would normally be unknown in a clinical trial.

Actual instantaneous rate ratios were estimated as:

$$RR(t) = 1\frac{S_{v0}}{S_{v0}+S_{v1}+S_{v2}} + 0\frac{S_{v1}}{S_{v0}+S_{v1}+S_{v2}} + \sigma(t)\frac{S_{v2}}{S_{v0}+S_{v1}+S_{v2}} \quad (31)$$

Which reduces to:

$$RR(t) = \frac{S_{v0}}{S_{v0}+S_{v1}} \quad (32)$$

In the *all-or nothing* vaccine (i.e, instantaneous rate ratios are equivalent to the proportion of vaccinated susceptibles that is unprotected). In the leaky vaccine, the instantaneous rate ratio is simply:

$$RR(t) = \sigma(t) \tag{33}$$

Instantaneous risk ratios were estimated as:

$$RRb(t) = 1\frac{S_{v0} + I_{v0}}{S_{v0} + S_{v1} + S_{v2} + I_{v0} + I_{v1} + I_{v2}} + 0\frac{S_{v1} + I_{v1}}{S_{v0} + S_{v1} + S_{v2} + I_{v0} + I_{v1} + I_{v2}} + \sigma(t)\frac{S_{v2}+I_{v2}}{S_{v0} + S_{v1} + S_{v2} + I_{v0} + I_{v1} + I_{v2}} \tag{34}$$

The main difference with the formula for the instantaneous rate ratio is that infected individuals (I_{v0}, I_{v1}, and I_{v2}) are not censored when the risk ratio is estimated, whilst they are censored when the rate ratio is estimated.

For the *all-or-nothing* vaccine, equation 34 reduces to:

$$RRb(t) = \frac{S_{v0} + I_{v0}}{S_{v0} + S_{v1} + S_{v2} + I_{v0} + I_{v1} + I_{v2}} \tag{35}$$

Which is again equivalent to the proportion of individuals in the vaccinated group that has lost protection, including individuals who have been infected.

For the leaky vaccine, this again reduces to:

$$RRb(t) = \sigma(t) \tag{36}$$

Indicating that the instantaneous risk ratio and instantaneous rate ratio are the same for the leaky vaccine.

Instantaneous rate ratios are approximated in two ways. First, it is assumed that the baseline rates remain constant over time (equation 15), as will most often be the case in practice. However, as this is simulated data, we know exactly how baseline rates change over time. Therefore, we will also estimate instantaneous rate ratios adjusting for changes in the baseline rate (equation 16). We always use cumulative rate ratios in converting to instantaneous measures, regardless of the mode of vaccine action.

We simulate four scenarios: scenario A with a fixed baseline rate and no waning vaccine efficacy; scenario B with a fixed baseline rate and waning vaccine efficacy; scenario C with a changing baseline rate but no waning vaccine efficacy; and scenario D with a changing baseline rate and waning vaccine efficacy.

Results

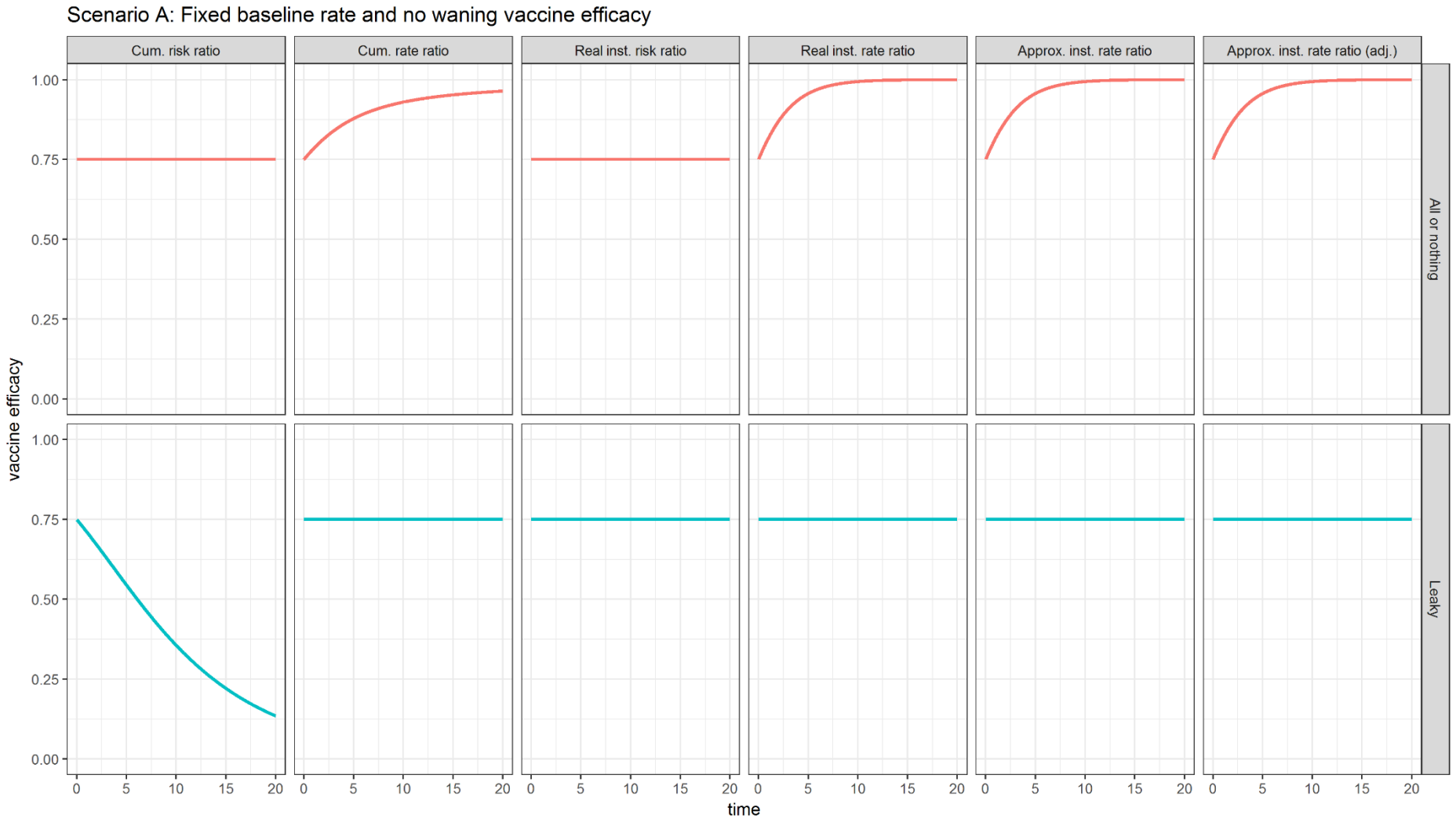


Figure B4. Simulated results for scenario A. Columns show vaccine efficacies derived from, from left to right, the cumulative risk ratio, the cumulative rate ratio, the real instantaneous risk ratio, the real instantaneous rate ratio, and the unadjusted and adjusted approximated instantaneous rate ratio, where the cumulative rate ratio shown in the second column is converted.

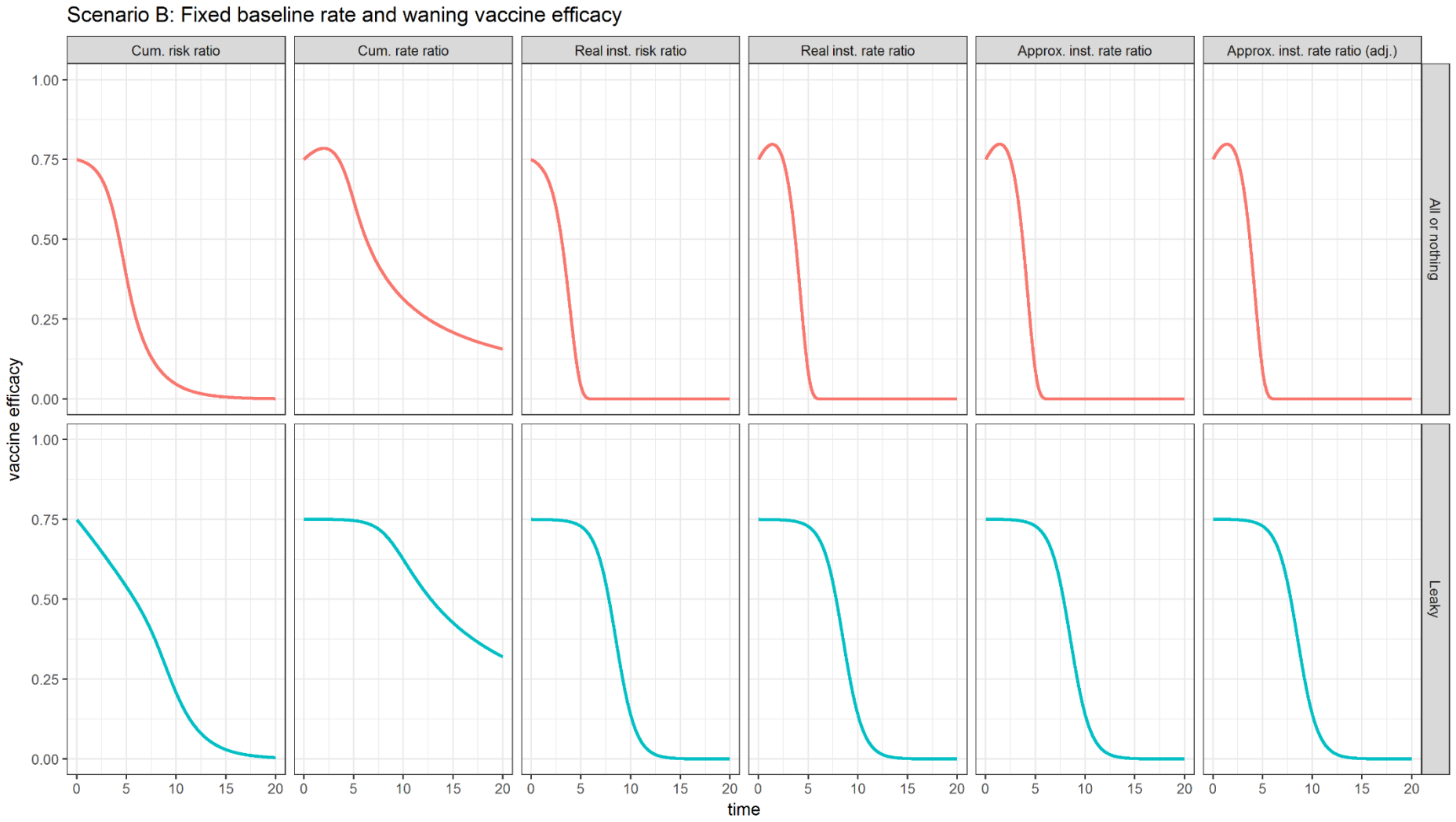


Figure B5. Simulated results for scenario B. Columns show vaccine efficacies derived from, from left to right, the cumulative risk ratio, the cumulative rate ratio, the real instantaneous risk ratio, the real instantaneous rate ratio, and the unadjusted and adjusted approximated instantaneous rate ratio, where the cumulative rate ratio shown in the second column is converted.

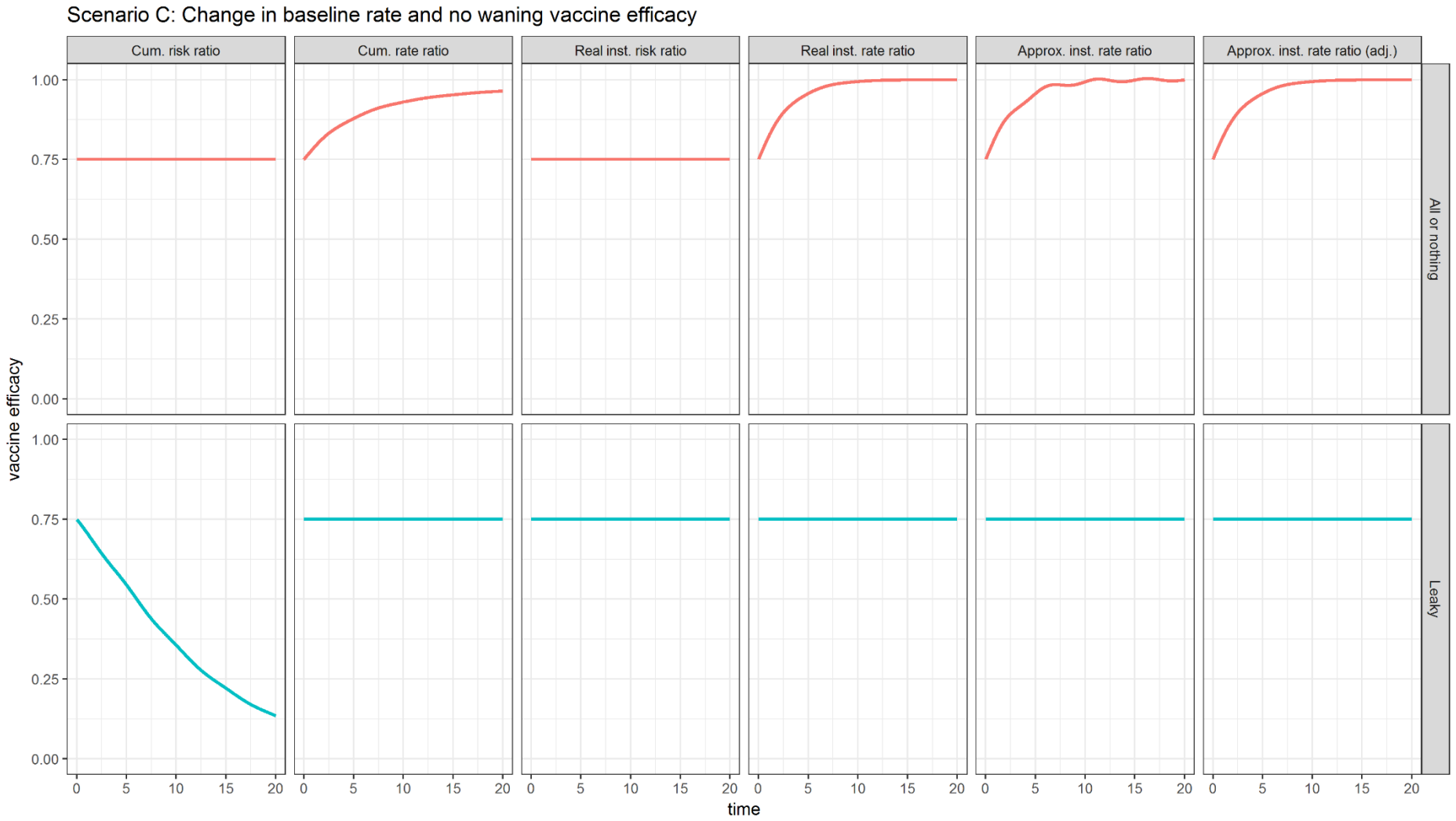


Figure B6. Simulated results for scenario C. Columns show vaccine efficacies derived from, from left to right, the cumulative risk ratio, the cumulative rate ratio, the real instantaneous risk ratio, the real instantaneous rate ratio, and the unadjusted and adjusted approximated instantaneous rate ratio, where the cumulative rate ratio shown in the second column is converted.

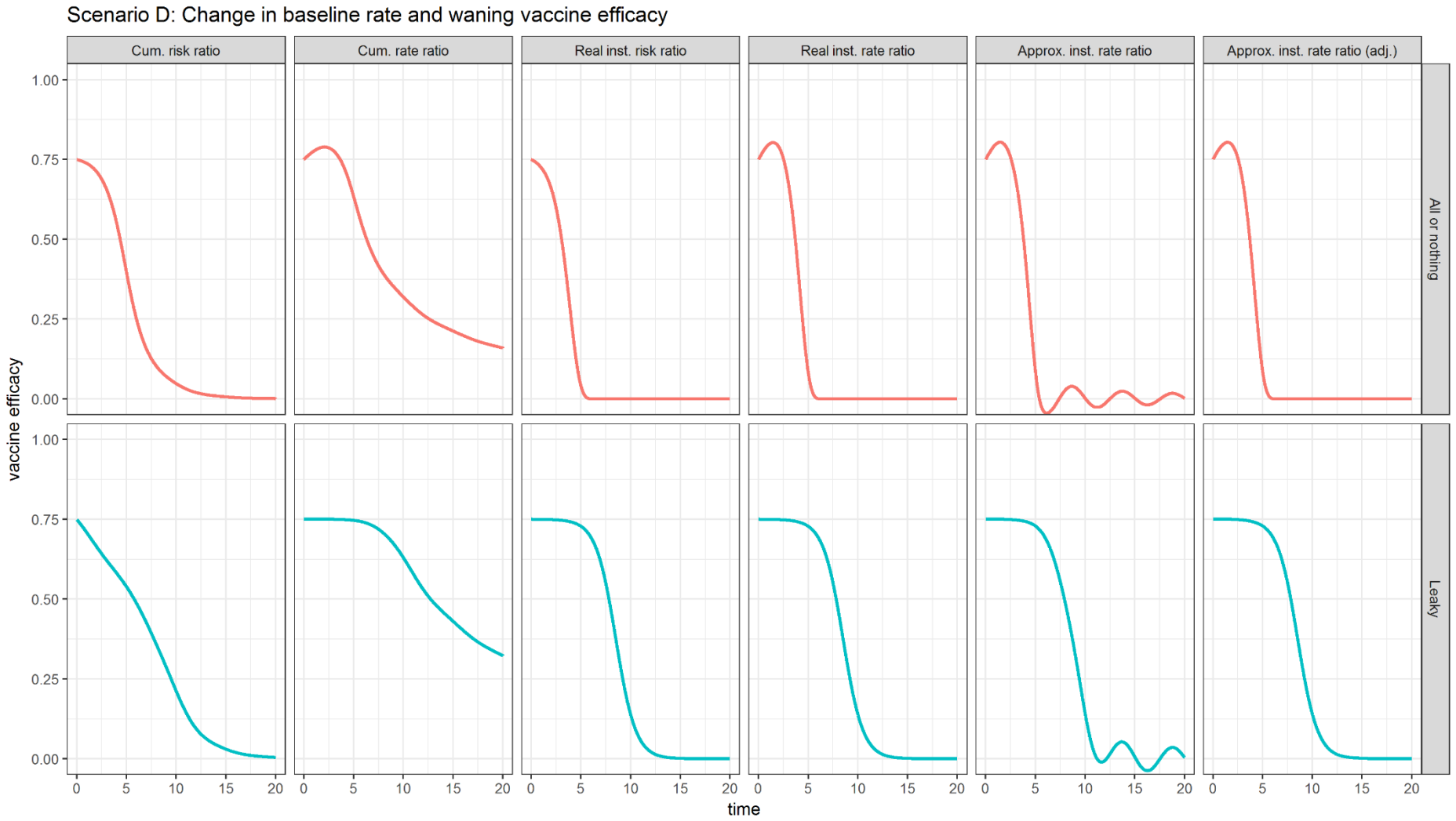


Figure B7. Simulated results for scenario D. Columns show vaccine efficacies derived from, from left to right, the cumulative risk ratio, the cumulative rate ratio, the real instantaneous risk ratio, the real instantaneous rate ratio, and the unadjusted and adjusted approximated instantaneous rate ratio, where the cumulative rate ratio shown in the second column is converted.

The results of the simulations show a number of things. First, the cumulative vaccine efficacies in scenario A clearly illustrate that vaccine efficacy should be estimated using a risk ratio for *all-or-nothing* vaccines and using a rate-ratio for *leaky* vaccines.

When a rate ratio is used to estimate vaccine efficacy of an *all-or-nothing* vaccine, it will appear to wax over time, as shown in the second column of figure B4. This effect occurs because infected individuals are censored when rate ratios are estimated (assuming full ascertainment of infections). As a result, the only susceptible individuals who remain in the cohort after follow-up are those who are fully protected, or whose vaccine efficacy is 100%.

Similarly, if vaccine efficacy is estimated using a risk ratio for a *leaky* vaccine, vaccine efficacy will appear to wane, until it is 0%. Because vaccinated individuals are only partially protected against the infection, they will eventually all become infected, given that the trial goes on for long enough and the force of infection remains the same. As vaccinated individuals become infected, the entire vaccinated stratum (both susceptible and ever infected) will become similar to the unvaccinated stratum, and vaccine efficacy decreases to 0%.

The results from scenario A also make it apparent that, in the *leaky* vaccine, instantaneous vaccine efficacy is the same as cumulative vaccine efficacy.

Scenario B shows that the existence of waning vaccine efficacy already becomes apparent in estimates derived from the cumulative relative risk and the cumulative relative rate. However, as these vaccine efficacies reflect the average vaccine efficacies in the period between the first timepoint and the reported timepoint, vaccine efficacy is overestimated as time progresses. In the *all-or-nothing* vaccine, cumulative vaccine efficacy (derived from the cumulative risk ratio, first column) is clearly an overestimation of the real instantaneous vaccine efficacy (derived from the real instantaneous risk ratio, third column). The same can be observed for the *leaky* vaccine (second column compared to the fourth column).

Scenario B also shows the success of the approximated instantaneous vaccine efficacy. As the baseline rate is fixed, the two approximated instantaneous vaccine efficacies (unadjusted: fifth column, and adjusted: sixth column) will be the same. They both retrieve the real instantaneous vaccine efficacy (fourth column).

Scenario C shows that a change in the baseline rate has no effect on the correct cumulative measures of vaccine efficacy for the respective models, if vaccine efficacy does not wane. However, it becomes evident from scenario D that a change in the baseline rate does have an effect when vaccine efficacy wanes over time. It has a small effect on the cumulative efficacies, although it is nearly unobservable (because cumulative vaccine efficacies represent average vaccine efficacies). However, this effect becomes apparent when cumulative measures are converted to instantaneous measures, without adjustment for this change in baseline rates (fifth column). Although the unadjusted approximated instantaneous values are similar to the real instantaneous values, they differ from the true values. Unadjusted instantaneous efficacies will fluctuate around the true instantaneous efficacies, depending on the magnitude of the change in force of infection. Adjusting for those fluctuations (last column), true instantaneous vaccine efficacy is again successfully retrieved.

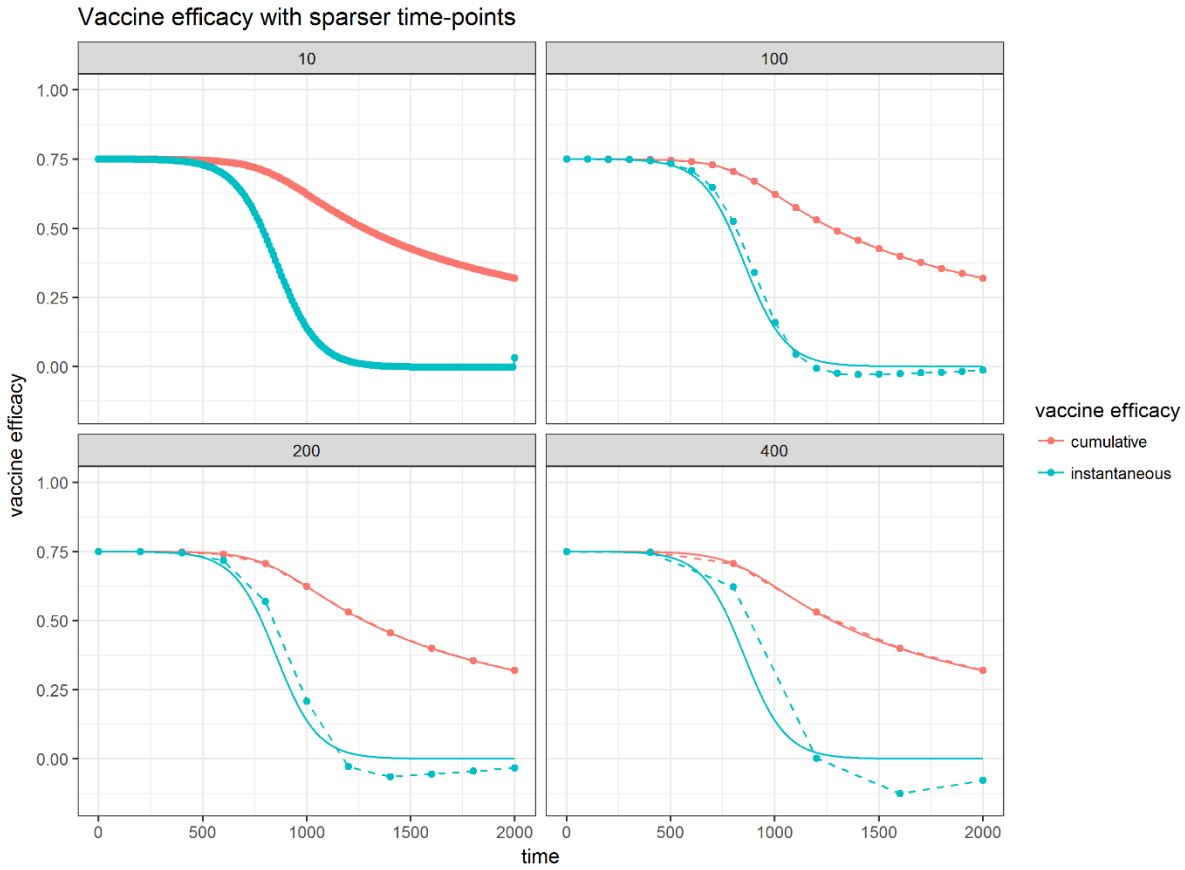
This method is designed to convert cumulative rate ratios to instantaneous rate ratios, and rate ratios should only be used for leaky vaccines. However, note that the approximated instantaneous vaccine efficacies in this particular simulation were surprisingly similar to the real instantaneous vaccine efficacy derived from the real instantaneous risk ratio. In the simulation presented here,

waning of vaccine efficacy was very strong, as eventually all vaccinated individuals lost their protection. If waning would be less extreme, this method would become less reliable *for all-or-nothing* vaccines.

Sparse data

Because this basically method converts a vector of all cumulative vaccine efficacies in a given time-period, it works best when cumulative vaccine efficacy is reported as detailed as possible. Figure B8 shows what may happen to the converted instantaneous vaccine efficacy, when cumulative vaccine efficacy is only available for sparser time-periods. As data on cumulative vaccine efficacy become less detailed (red dots), approximated instantaneous vaccine efficacy becomes less reliable. Researchers may overcome this issue by fitting a curve through cumulative vaccine efficacies in order to get detailed estimates, which can subsequently be converted to instantaneous vaccine efficacy.

Figure B8. Instantaneous vaccine efficacy with sparser time-points.



Cumulative vaccine efficacy is estimated based on the cumulative rate ratio for the leaky model presented in scenario B (no change in baseline rate, but with waning vaccine efficacy). Cumulative vaccine efficacies are plotted in red, whilst instantaneous vaccine efficacies are plotted in blue. Titles of the panels indicate sparsity of the available time-points (10 times smaller, 100 times smaller, 200 times smaller, and 400 times smaller). Solid lines represent vaccine efficacies when data is available for all time-points. Points represent actual data which is used in the approximation.

Limitations

There are several limitations to the method presented here. First, it is only applicable for *leaky* vaccines, and will fail for *all-or-nothing* vaccines. However, one might argue how realistic an *all-or-nothing* vaccine really is. In practice, all vaccines may be leaky, where there is heterogeneity in the level of protection the vaccine offers (i.e. the vaccine may offer full protection for a small proportion of vaccinated individuals, whereas a second proportion is 80% protected, and yet another only 40%). This protection may then gradually wane, as in the *leaky* vaccine presented here, rather than either offer full protection or no protection at all, as in the *all-or-nothing* vaccine presented here.

Second, when the force of infection changes over time, which is common for infectious agents, this change in force of infection will interact with the waning of the vaccine efficacy, and the instantaneous vaccine efficacy should be appropriately adjusted. One may be able to use a dynamic transmission model to retrieve changes in baseline rates over time.

Third, the calculation of instantaneous vaccine efficacy at time *t* is dependent on all instantaneous vaccine efficacies up until time *t*. Therefore, all cumulative vaccine efficacies up until time *t* must be known, ideally at small time-steps. Moreover, estimating all instantaneous vaccine efficacies up until time *t* may be computationally intensive.

Researchers should also bear in mind that this method assumes that all infections are accrued and censored, which will not be the case in many trials for vaccines against infections where asymptomatic infections are common.

However, the method presented here does seem to be effective in converting cumulative vaccine efficacies to instantaneous vaccine efficacies, and may assist researchers with a new way to investigate waning of vaccine efficacy. Ideally, approximated instantaneous vaccine efficacies would be compared to true instantaneous vaccine efficacies, i.e. immunological markers that provide a good correlate or surrogate of protection.

Reference list

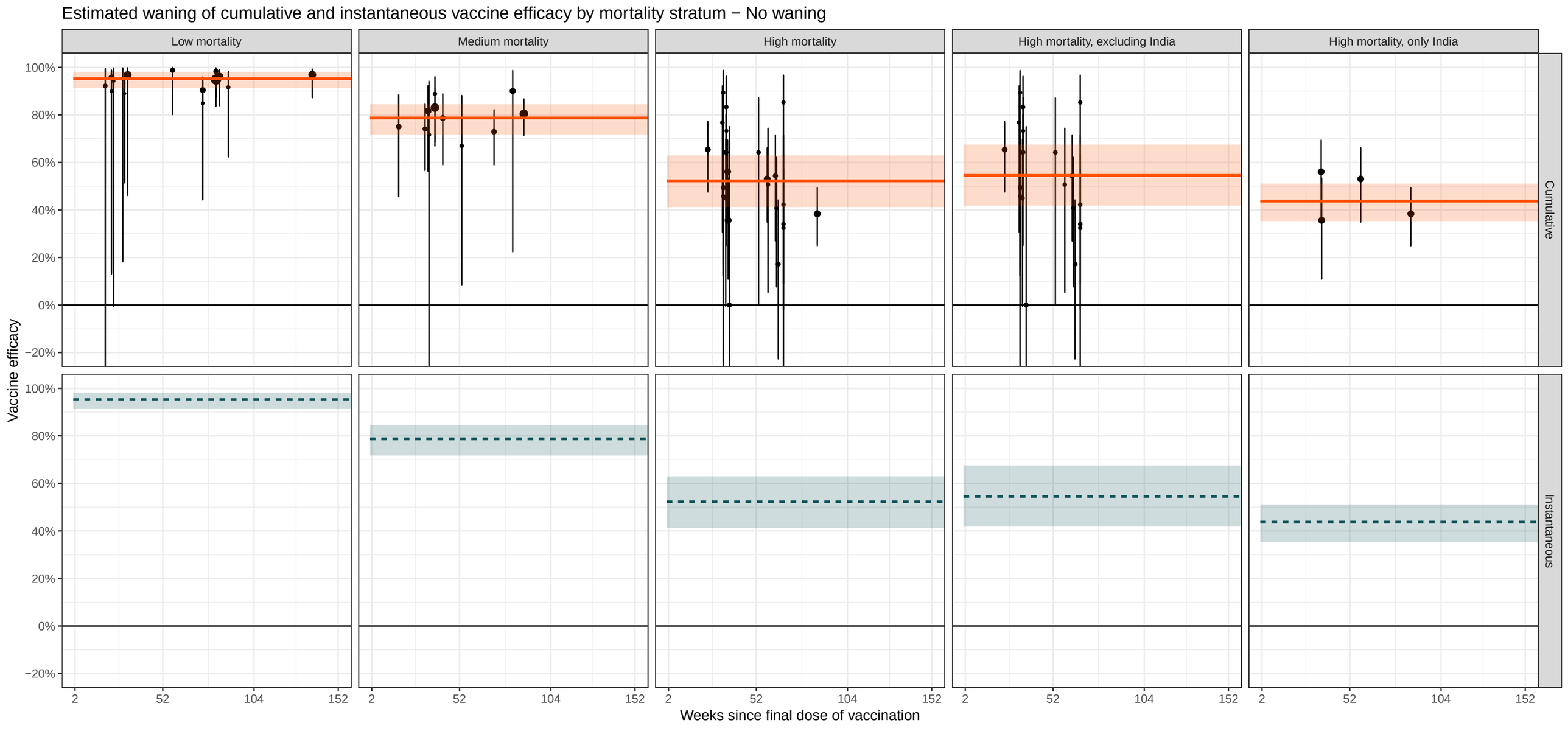
1. Smith, P.G., Rodrigues, L.C. and Fine, P.E.M., 1984. Assessment of the protective efficacy of vaccines against common diseases using case-control and cohort studies. *International journal of epidemiology*, *13*(1), pp.87-93.
2. Halloran, M.E., Haber, M. and Longini Jr, I.M., 1992. Interpretation and estimation of vaccine efficacy under heterogeneity. *American Journal of Epidemiology*, *136*(3), pp.328-343.
3. Kanaan, M.N. and Farrington, C.P., 2002. Estimation of waning vaccine efficacy. *Journal of the American Statistical Association*, *97*(458), pp.389-397.4.
4. Cole, S.R. and Hudgens, M.G., 2010. Survival analysis in infectious disease research: describing events in time. *AIDS (London, England)*, *24*(16), p.2423.
5. Kaplan, E.L. and Meier, P., 1958. Nonparametric estimation from incomplete observations. *Journal of the American statistical association*, *53*(282), pp.457-481.
6. Bines, J.E., At Thobari, J., Satria, C.D., Handley, A., Watts, E., Cowley, D., Nirwati, H., Ackland, J., Standish, J., Justice, F. and Byars, G., 2018. Human neonatal rotavirus vaccine (RV3-BB) to target rotavirus from birth. *New England Journal of Medicine*, *378*(8), pp.719-730.
7. Nelson, W., 1972. Theory and applications of hazard plotting for censored failure data. *Technometrics*, *14*(4), pp.945-966.

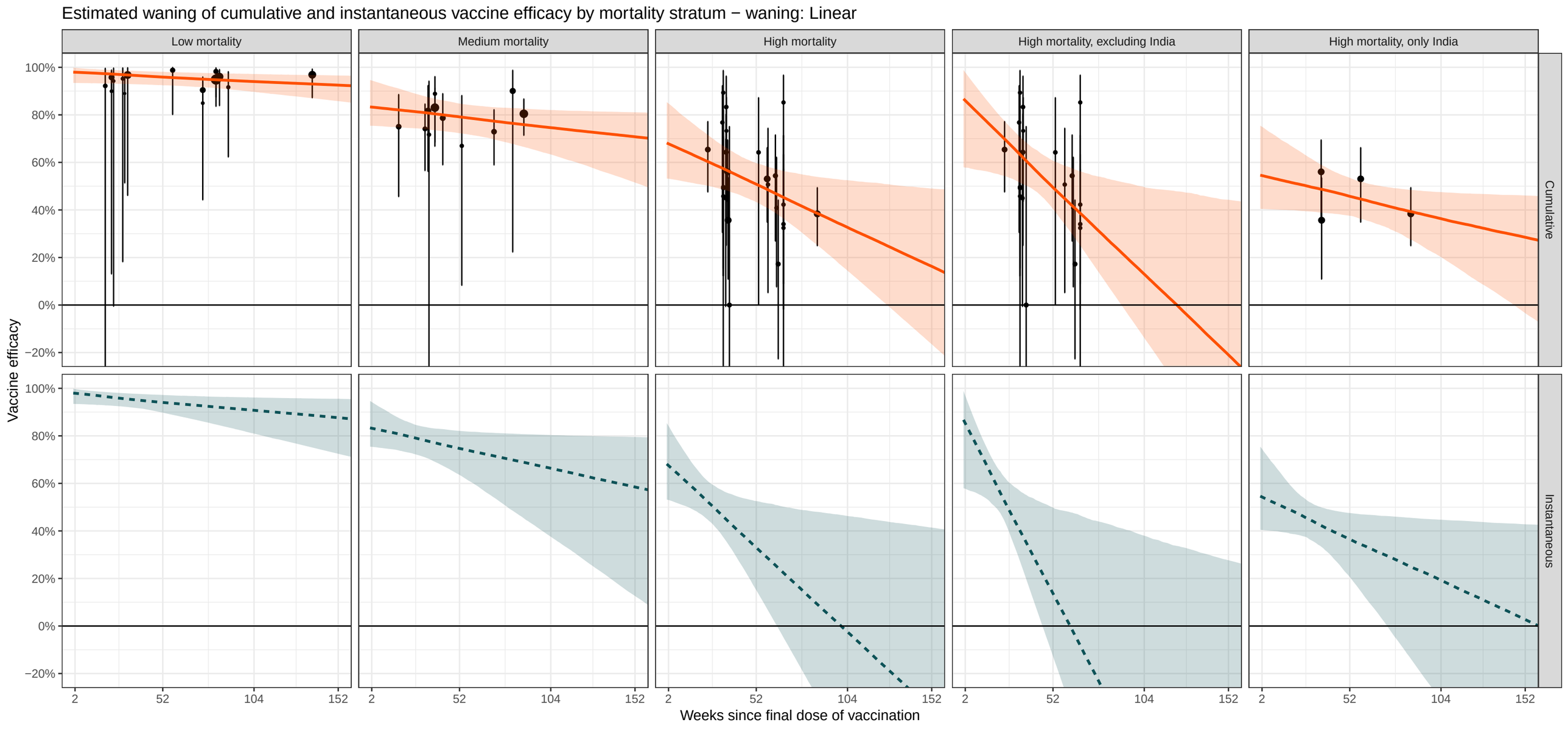
8. Aalen, O., 1978. Nonparametric inference for a family of counting processes. *The Annals of Statistics*, pp.701-726
9. Rogawski, E.T., Platts-Mills, J.A., Colgate, E.R., Haque, R., Zaman, K., Petri, W.A. and Kirkpatrick, B.D., 2018. Quantifying the impact of natural immunity on rotavirus vaccine efficacy estimates: a clinical trial in Dhaka, Bangladesh (PROVIDE) and a simulation study. *The Journal of infectious diseases*, *217*(6), pp.861-868.

Appendix 8

Refers to:

Chapter 7, Appendix C, Waning functions for pooled analysis


Estimated waning of cumulative and instantaneous vaccine efficacy by mortality stratum − No waning
Low mortality
Medium mortality
High mortality
High mortality, excluding India
High mortality, only India
Cumulative
Instantaneous
Vaccine efficacy
100%
80%
60%
40%
20%
0%
−20%
2
52
104
152
Weeks since final dose of vaccination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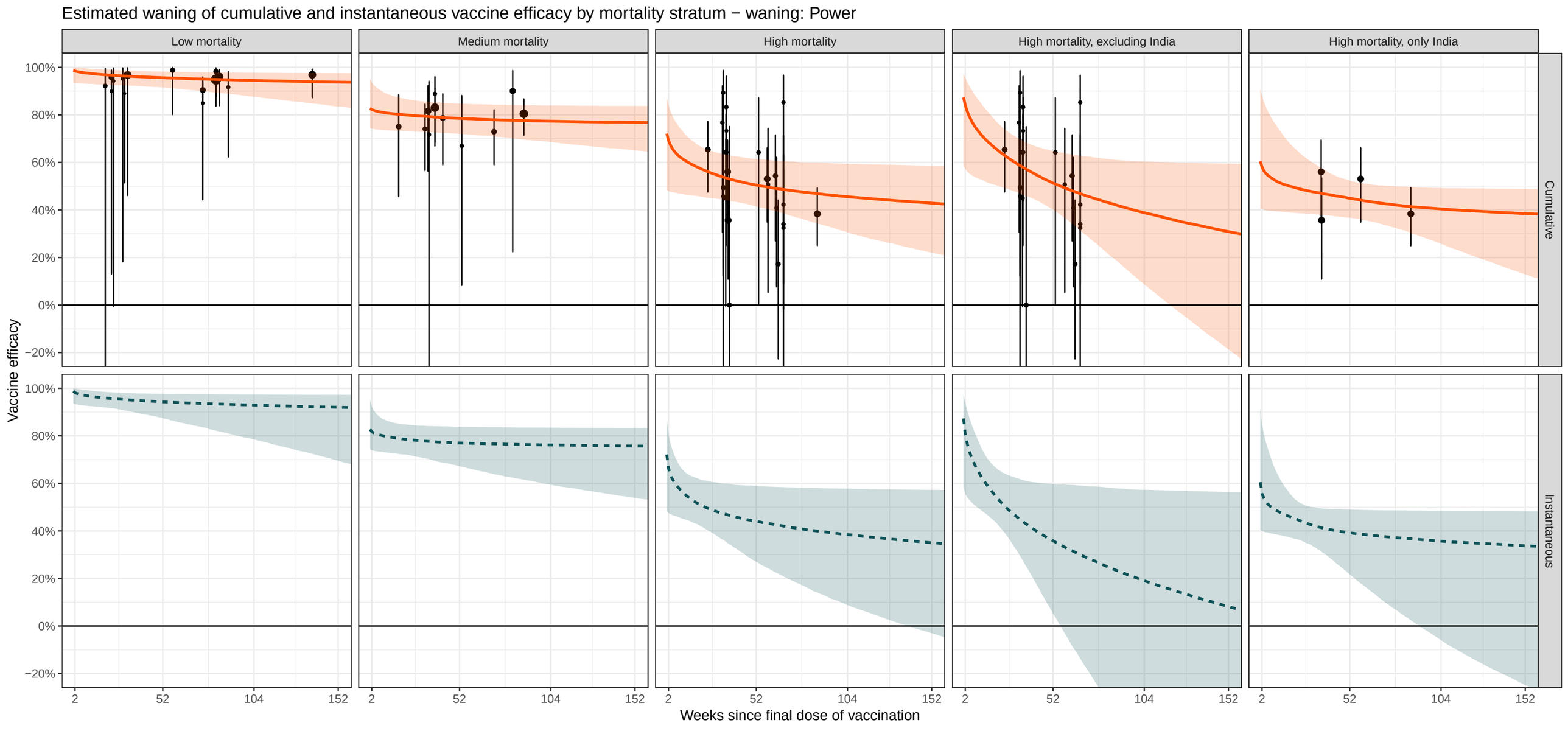
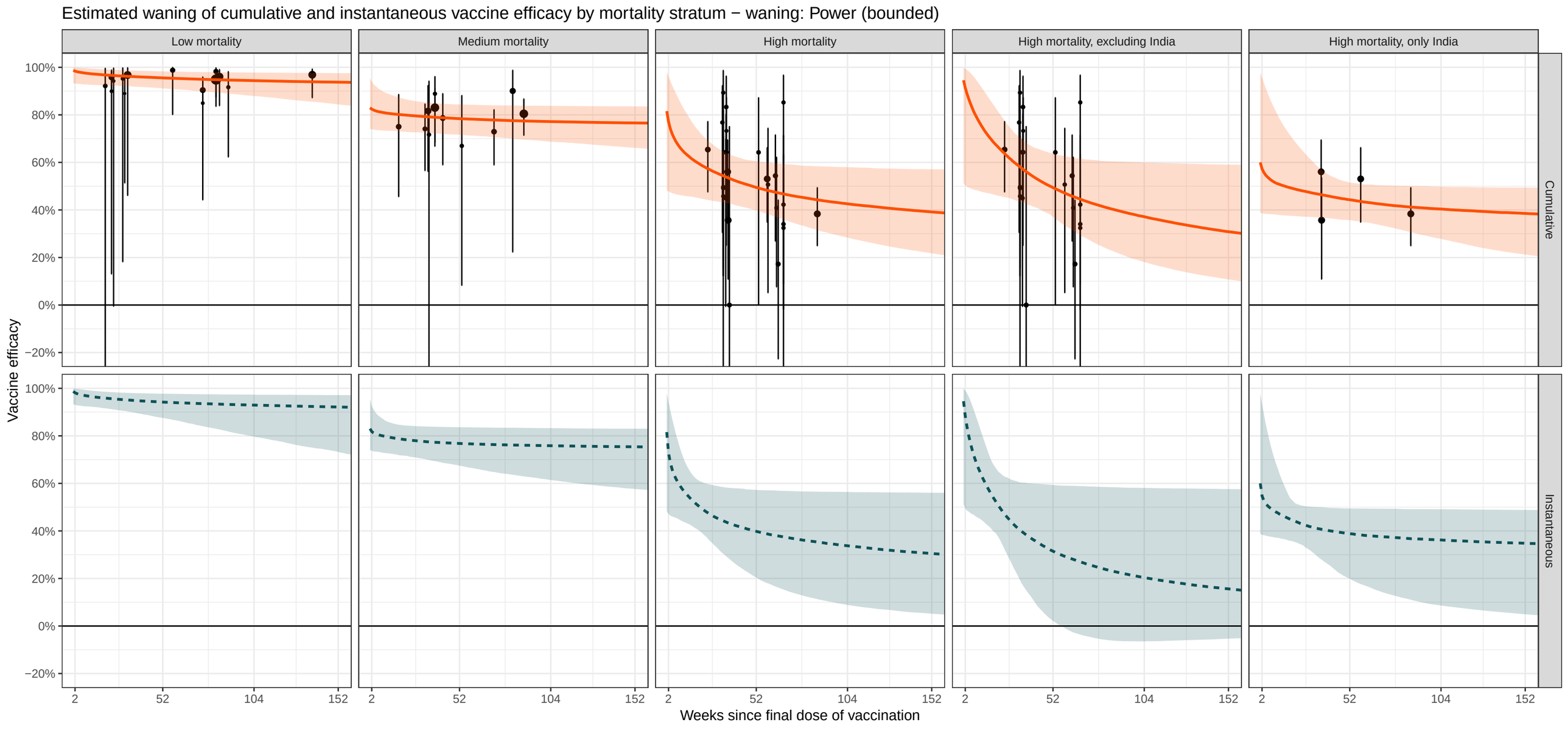
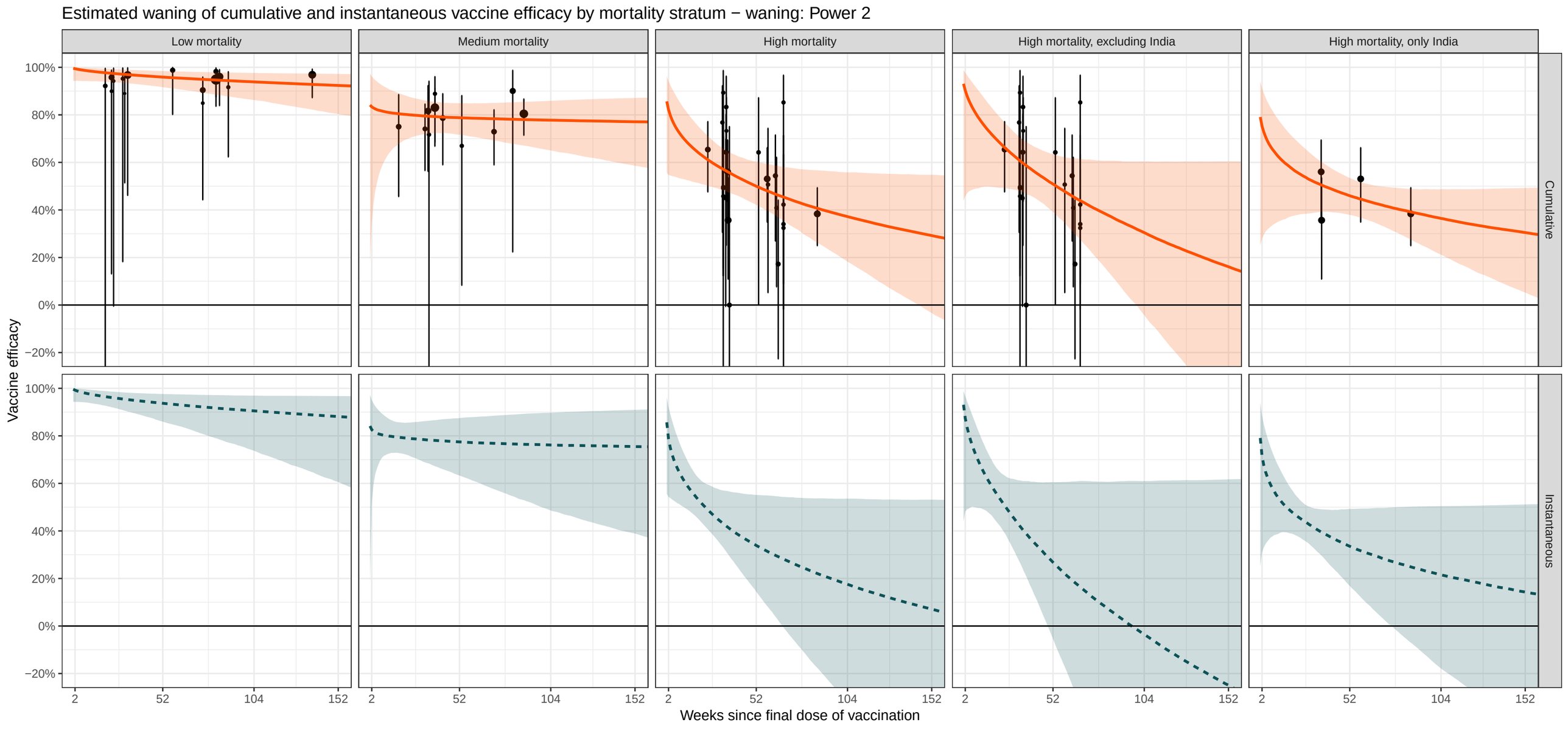
Low mortality
Medium mortality
High mortality
High mortality, excluding India
High mortality, only India
Cumulative
Instantaneous
Vaccine efficacy
100%
80%
60%
40%
20%
0%
−20%
2
52
104
152
Weeks since final dose of vaccination


Estimated waning of cumulative and instantaneous vaccine efficacy by mortality stratum − waning: Power
Low mortality
Medium mortality
High mortality
High mortality, excluding India
High mortality, only India
Cumulative
Instantaneous
Vaccine efficacy
100%
80%
60%
40%
20%
0%
−20%
2
52
104
152
Weeks since final dose of vaccination


Estimated waning of cumulative and instantaneous vaccine efficacy by mortality stratum − waning: Power (bounded)
Low mortality
Medium mortality
High mortality
High mortality, excluding India
High mortality, only India
Cumulative
Instantaneous
Vaccine efficacy
100%
80%
60%
40%
20%
0%
−20%
2
52
104
152
Weeks since final dose of vaccination


Estimated waning of cumulative and instantaneous vaccine efficacy by mortality stratum − waning: Power 2
Low mortality
Medium mortality
High mortality
High mortality, excluding India
High mortality, only India
Cumulative
Instantaneous
Vaccine efficacy
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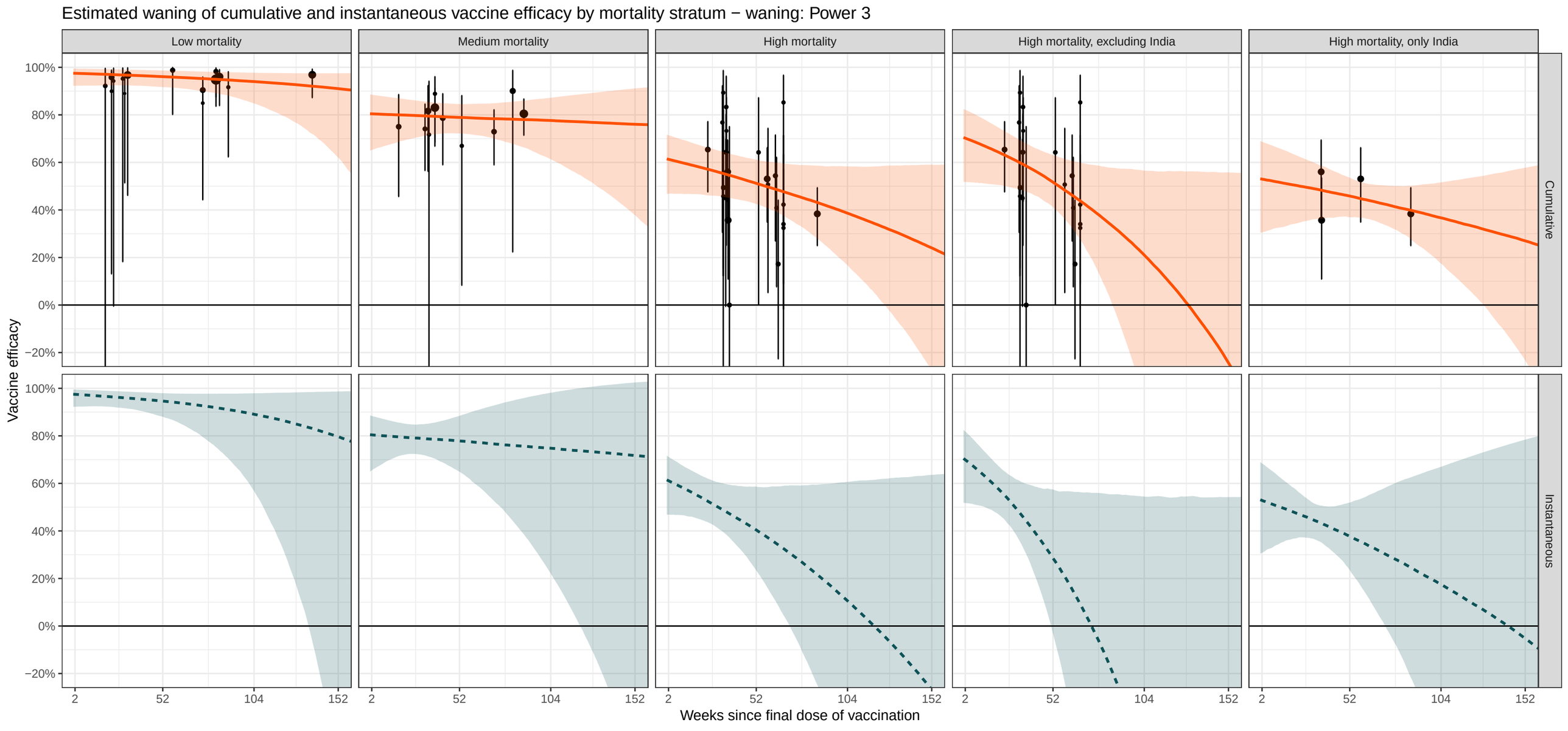
80%
60%
40%
20%
0%
−20%
2
52
104
152
Weeks since final dose of vaccination


Estimated waning of cumulative and instantaneous vaccine efficacy by mortality stratum − waning: Power 3
Low mortality
Medium mortality
High mortality
High mortality, excluding India
High mortality, only India
Cumulative
Instantaneous
Vaccine efficacy
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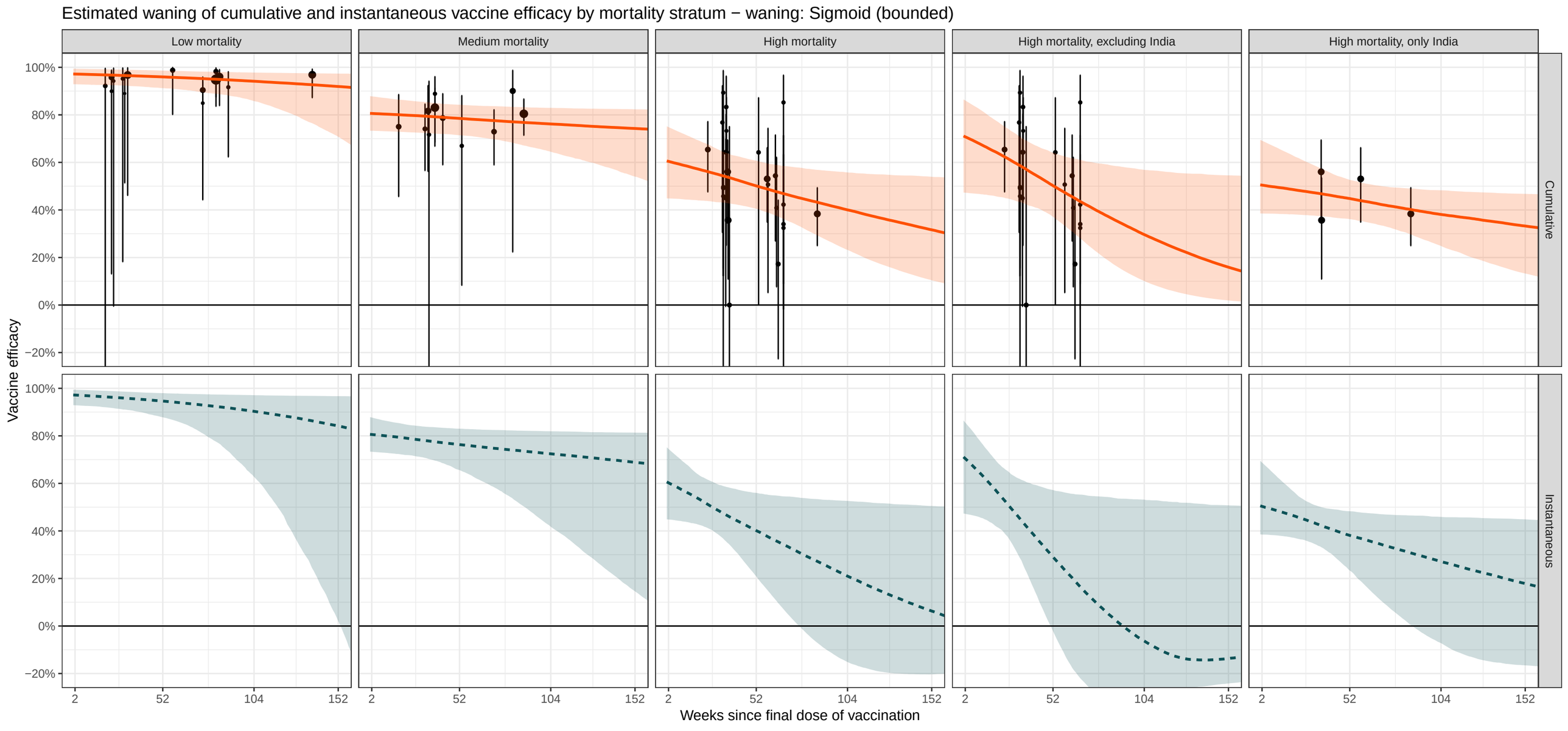
60%
40%
20%
0%
−20%
2
52
104
152
Weeks since final dose of vaccination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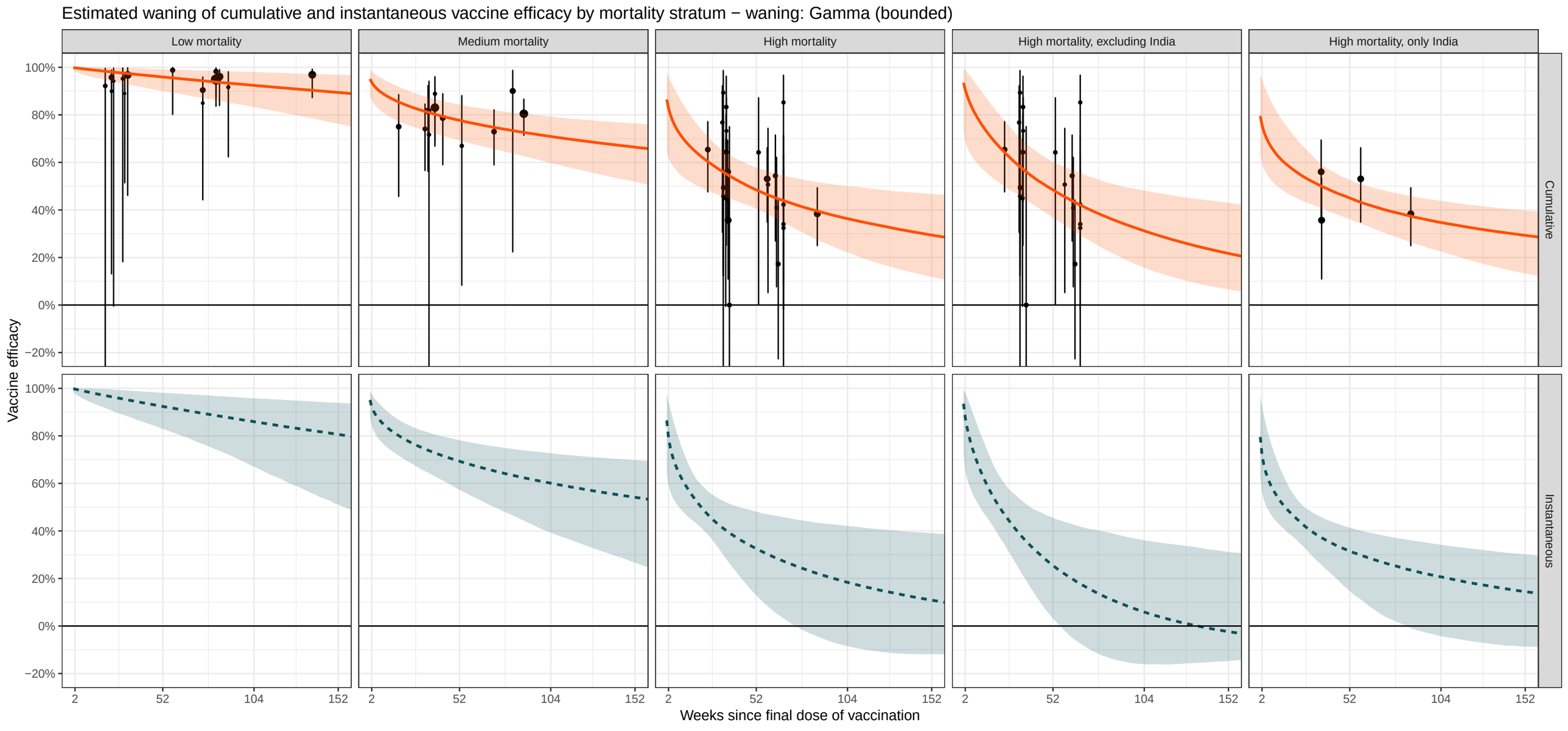
Medium mortality
High mortality
High mortality, excluding India
High mortality, only India
Cumulative
Instantaneous
Vaccine efficacy
100%
80%
60%
40%
20%
0%
−20%
2
52
104
152
Weeks since final dose of vaccination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Low mortality
Medium mortality
High mortality
High mortality, excluding India
High mortality, only India
Cumulative
Instantaneous
Vaccine efficacy
100%
80%
60%
40%
20%
0%
−20%
2
52
104
152
Weeks since final dose of vaccination

Appendix 9

Refers to:

Chapter 7, Appendix D, Waning functions for Indonesia analysis

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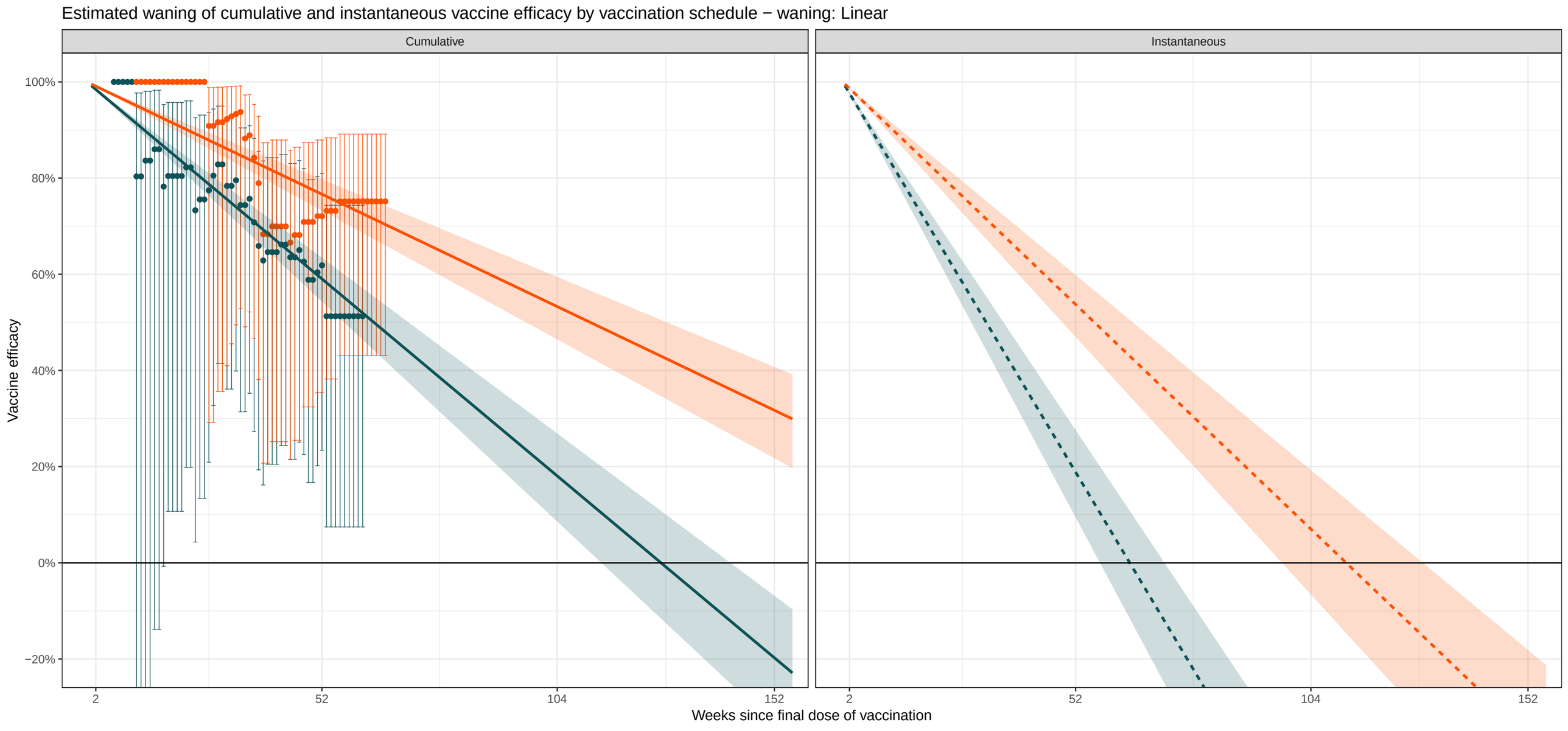
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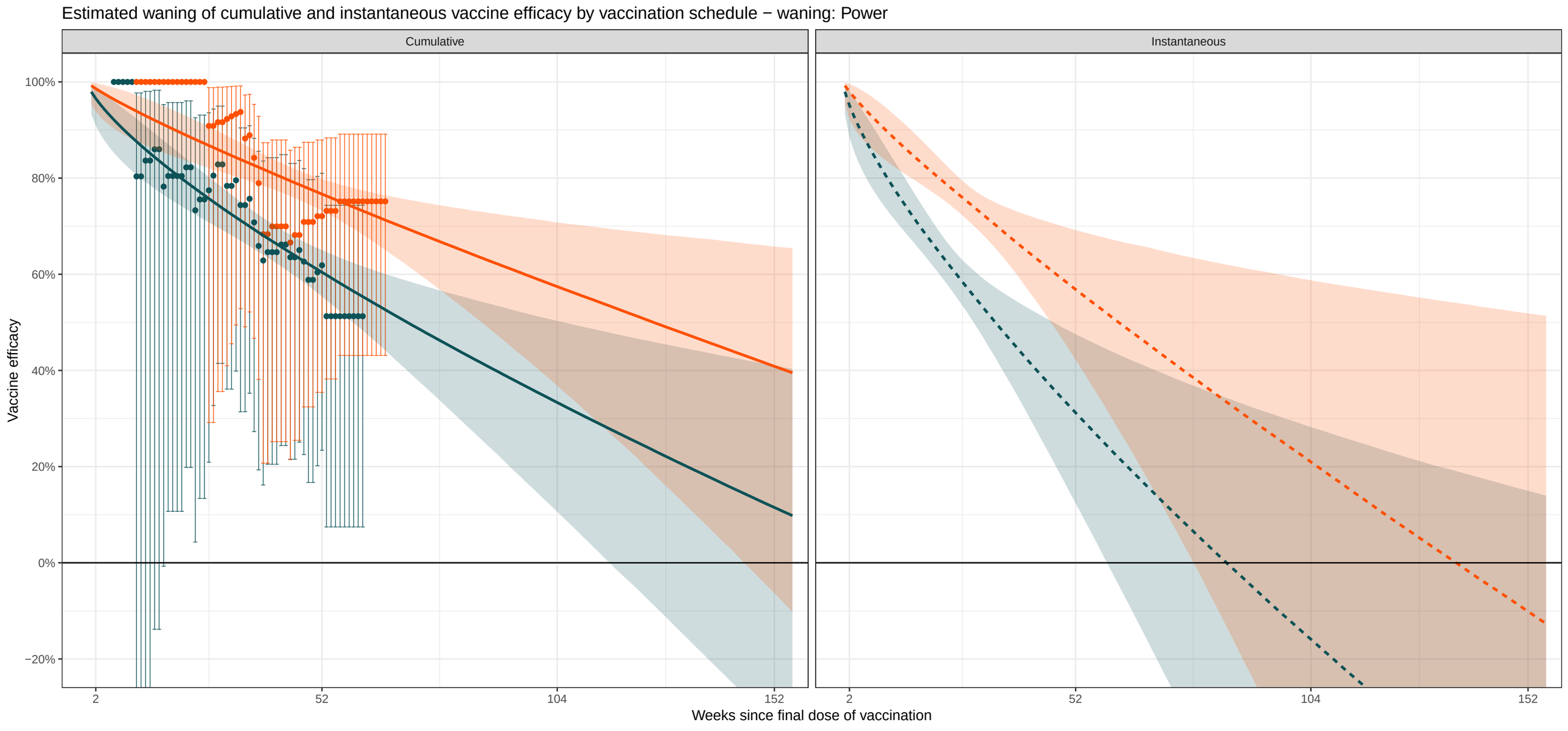
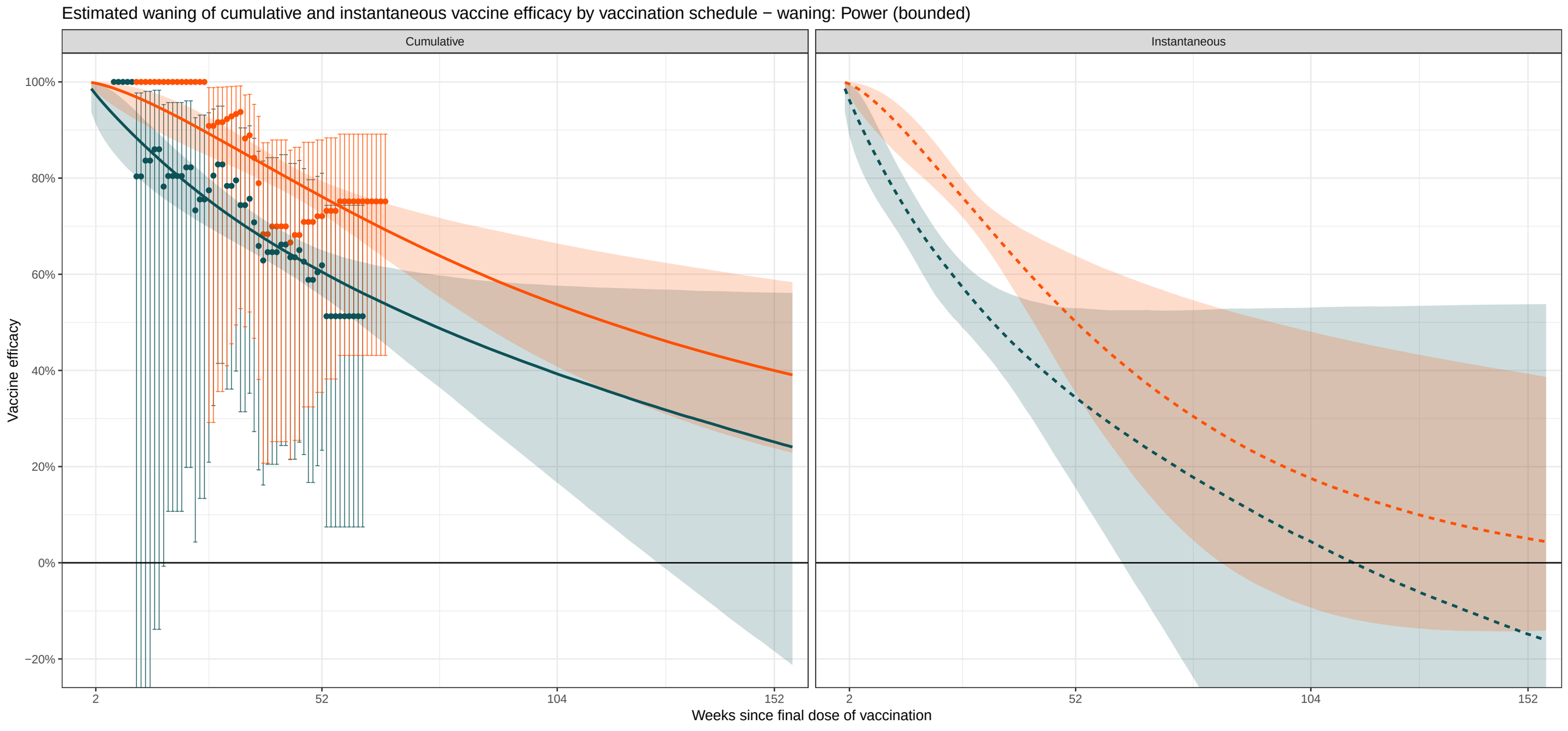
Cumulative
Instantaneous
Vaccine efficacy
100%
80%
60%
40%
20%
0%
−20%
2
52
104
152
Weeks since final dose of vaccination


Estimated waning of cumulative and instantaneous vaccine efficacy by vaccination schedule − waning: Power
Cumulative
Instantaneous
Vaccine efficacy
100%
80%
60%
40%
20%
0%
−20%
2
52
104
152
Weeks since final dose of vaccination


Estimated waning of cumulative and instantaneous vaccine efficacy by vaccination schedule − waning: Power (bounded)
Cumulative
Instantaneous
Vaccine efficacy
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80%
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40%
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2
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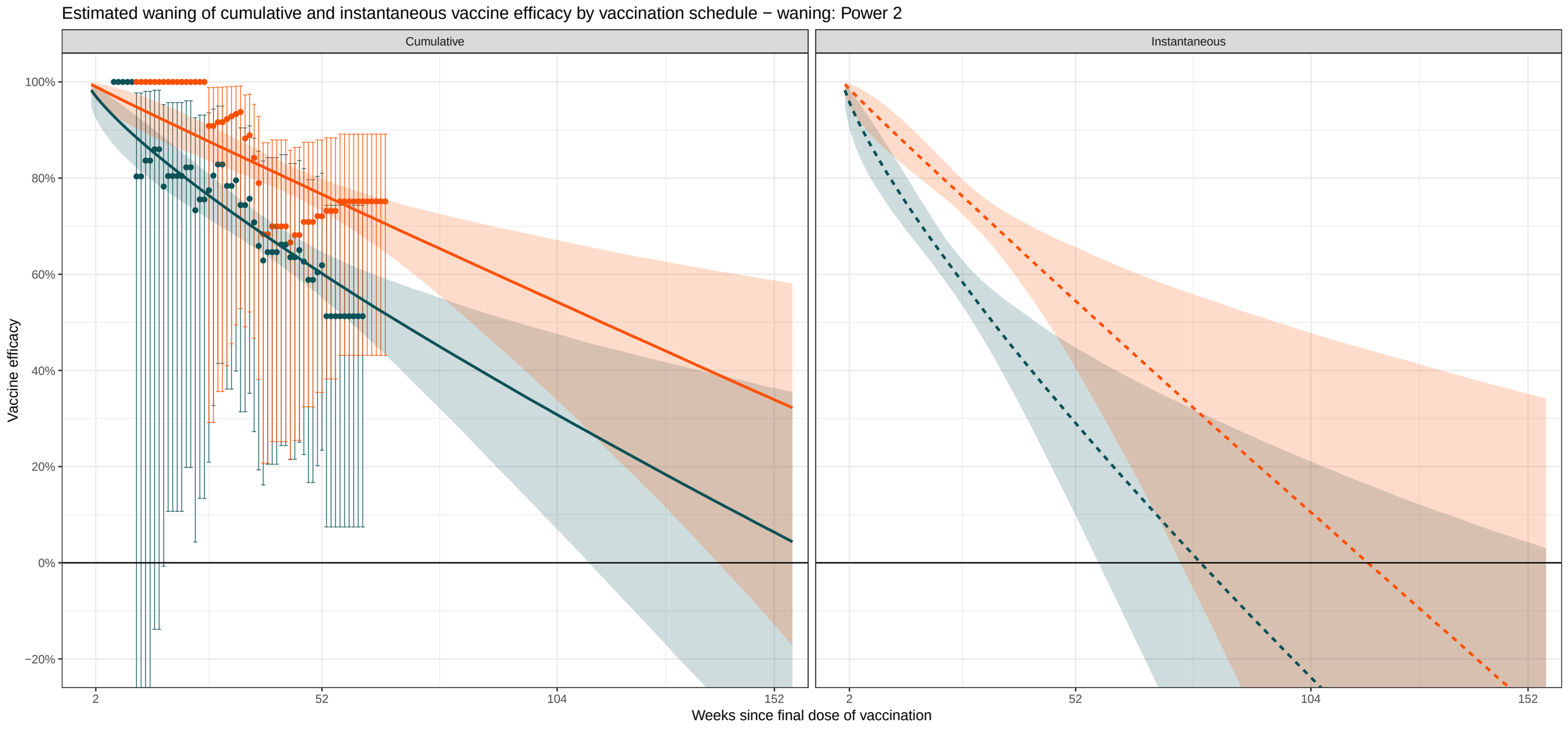
104
152
Weeks since final dose of vaccination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Instantaneous
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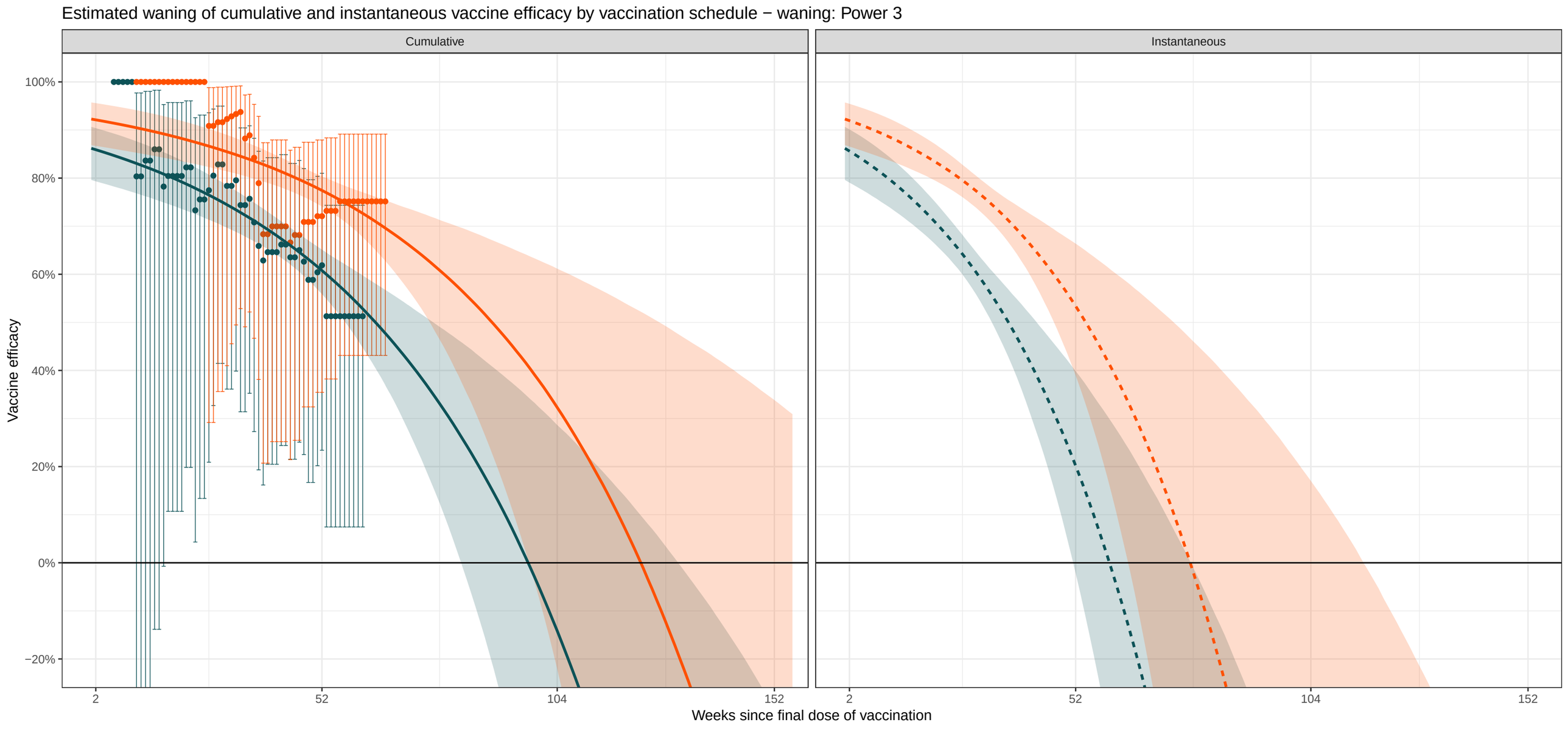
104
152
Weeks since final dose of vaccination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Instantaneous
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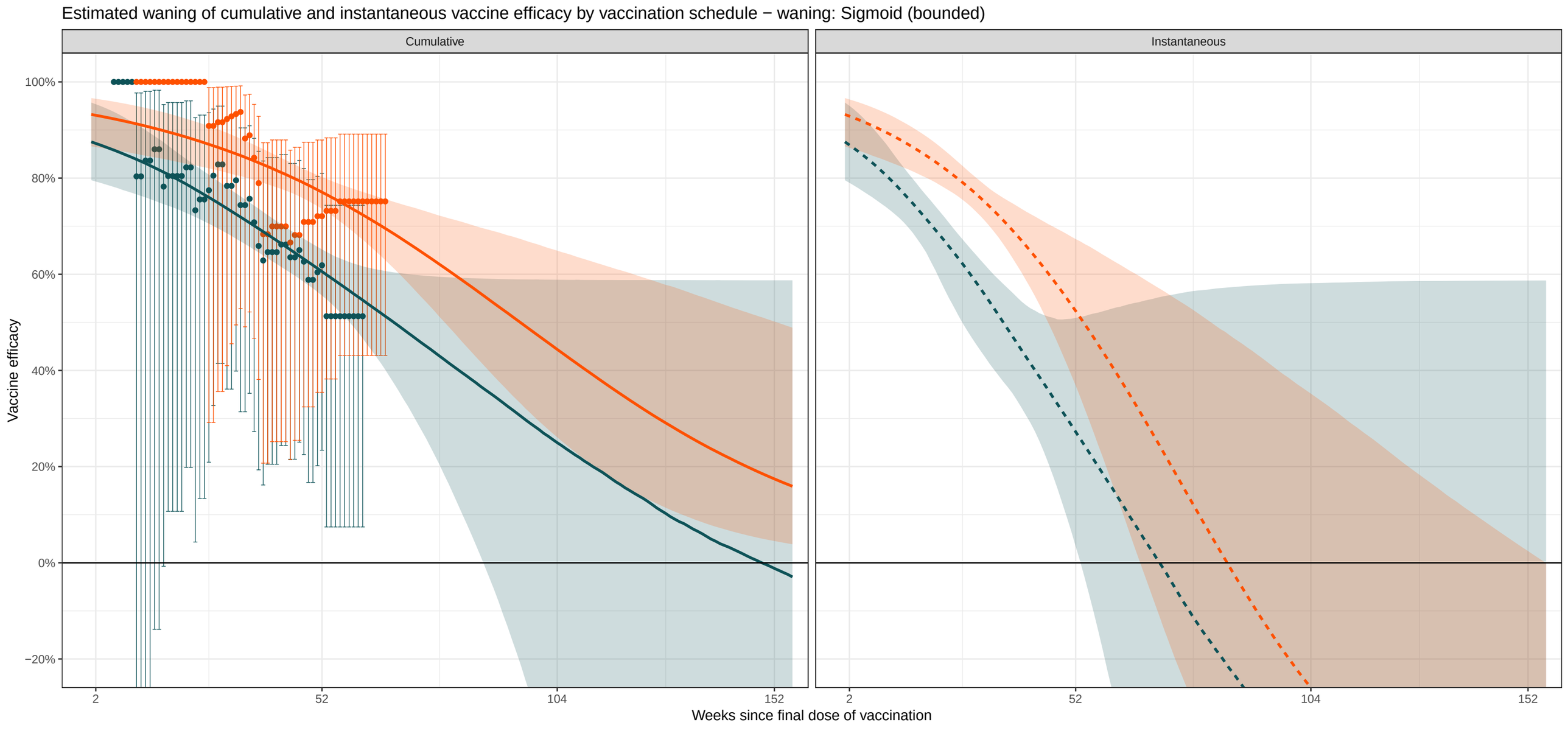
40%
20%
0%
−20%
2
52
104
152
Weeks since final dose of vaccination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Instantaneous
Vaccine efficacy
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80%
60%
40%
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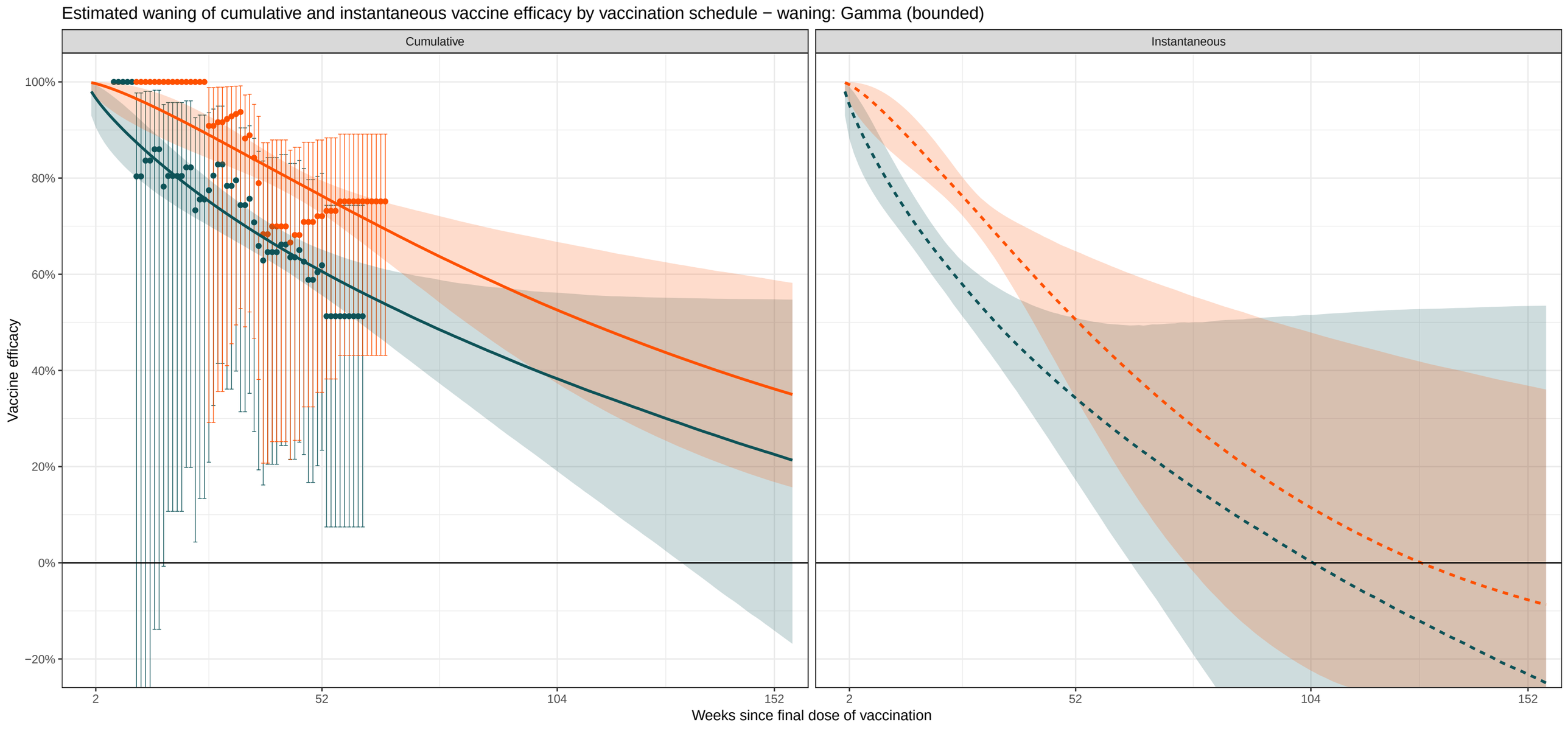
0%
−20%
2
52
104
152
Weeks since final dose of vaccination


Estimated waning of cumulative and instantaneous vaccine efficacy by vaccination schedule − waning: Gamma (bounded)
Cumulative
Instantaneous
Vaccine efficacy
100%
80%
60%
40%
20%
0%
−20%
2
52
104
152
Weeks since final dose of vaccination

Appendix 10

Refers to:

Chapter 10, Example benefit-risk policy brief for Afghanistan

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What are the implications of the new SAGE recommendations for rotavirus vaccines?

Countries which are PLANNING TO INTRODUCE rotavirus vaccine	Countries which have ALREADY INTRODUCED rotavirus vaccine
As part of your vaccine introduction plan and together with your NITAG, ***SELECT*** *the immunization schedule with the greatest potential for preventing rotavirus-related disease and deaths.* This includes review of: - the actual ages at which each dose of DTP/penta vaccine is given; - the peak age of rotavirus gastroenteritis cases and deaths; - the possible risks and benefits of choosing a schedule without age limitation, in terms of potential additional intussusception deaths and additional rotavirus deaths prevented.	Review progress of your introduction plan with your NITAG and ***ASSESS*** *whether or not the removal of age restrictions would prevent additional rotavirus -related disease and deaths.* This includes review of: - the actual ages at which each dose of rotavirus vaccine is given; - the peak age of rotavirus gastroenteritis cases and deaths; - the possible risks and benefits of removing age limitations in the schedule in terms of potential additional intussusception deaths and additional rotavirus deaths prevented .

Plan to expand the benefits of rotavirus vaccines

Do most children receive their pentavalent or rotavirus vaccines doses by the recommended ages?

YES

Deliver rotavirus vaccination at 6 weeks of age or soon after with pentavalent vaccine, even if delayed
AND
monitor regularly to ensure vaccine doses are given on time and high vaccination coverage is achieved

NO

Deliver rotavirus vaccine with pentavalent vaccine, even if delayed

AND
develop a plan to ensure vaccine doses are given on time and high vaccination coverage is achieved

Enhance capacity to further assess

Inform relevant health care staff that although the benefits outweigh the risks, a small potential risk of intussusception after rotavirus vaccination remains and ensure that caregivers are adequately counselled on how to recognize the danger signs that mean a sick baby should be brought to medical attention immediately.

Establish or strengthen post-marketing surveillance .
This should focus on documenting any cases of intussusception.

2012, 87, 201–216 No. 21

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

25 MAY 2012, 87th YEAR / 25 MAI 2012, 87e ANNÉE
No. 21, 2012, 87, 201–216
http://www.who.int/wer

Contents

ROTAVIRUS VACCINE SCHEDULES

The WHO Strategic Advisory Group of Experts on Immunization (SAGE) reviewed new evidence that afforded an opportunity to avert additional deaths from rotavirus disease, including systematic reviews of rotavirus disease burden and effectiveness of different immunization schedules, improved estimates of the benefits in different epidemiological settings, and additional data on the risk of intussusception after rotavirus vaccination. SAGE was informed by separate reviews by both the Global Advisory Committee on Vaccine Safety and the Immunization Practice Advisory Committee.

The risk benefit analysis continues to favour early immunization but the current age restrictions for the first dose (<15 weeks) and last dose (<32 weeks) are preventing vaccination of many vulnerable children.

By removing the age restrictions, programmes will be able to immunize children who are currently excluded from the benefits of rotavirus vaccines and this is likely to include some of the children most vulnerable to severe rotavirus disease. Many thousands more deaths would be averted, but with the possibility of a small additional increase in intussusception cases.

SAGE also noted that in view of the age distribution of rotavirus disease, providing rotavirus vaccine to children older than 24 months of age will be of little benefit.

Considering the above, SAGE continues to recommend that the first dose of rotavirus vaccine be administered along with DTP, as soon as possible after 6 weeks of age as this maximizes protection.

SAGE recognized that countries have different burdens of disease and may or may not have introduced rotavirus vaccines. For this reason, countries should develop their own plans for how the removal of age restrictions on vaccine administration can be introduced in a manner that supports existing programmes.

SAGE encouraged all countries to establish or strengthen post-marketing surveillance which should focus on documenting any intussusception cases.

SAGE also stressed that vaccination is a dynamic field that will always be challenged by new data.

Immunization Vaccines & Biologicals
World Health Organization
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World Health Organization

Immunizing children against rotavirus:

Making the most of every contact

To maximize its impact, rotavirus vaccine has to be given before Rotavirus Gastro-Enteritis (RVGE) occurs.

Protection of children through vaccination before RVGE cases occur depends on both the actual age at which each dose is given and on rotavirus vaccine coverage.

It is critical to administer each dose of vaccine at the recommended age.

Rotavirus vaccine coverage needs to be high, especially among children at higher risk of rotavirus death.

The expected benefits of rotavirus vaccine (in terms of rotavirus deaths averted) outweigh the potential risks (intussusception deaths associated with rotavirus vaccine).

Afghanistan

ABOUT THIS LEAFLET

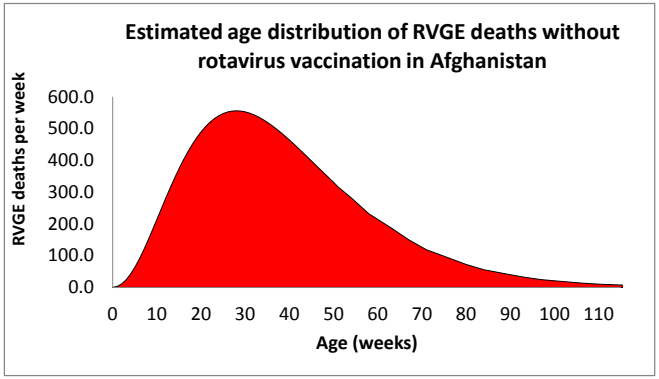
Countries should develop their own plans on how rotavirus vaccine can be introduced in a manner that strengthens existing immunization programmes.
To stimulate and assist this process at national level, this leaflet contains information available at the global level together with estimates generated by various models. However, it is important that the information in this leaflet is enriched by and checked against other locally relevant data, and that NITAG members, decision makers at the national immunization programme and other key stakeholders review and discuss these data together with any other available evidence.

Additional information is available at:

www.vaccine-schedules.com
www.who.int/nuvi/rotavirus/en/index.html

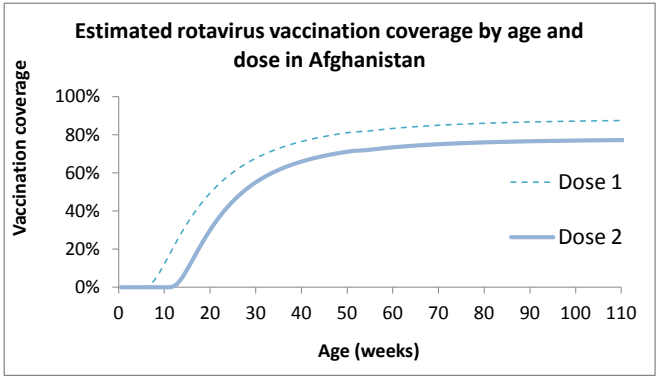
These data do not constitute official WHO estimates.
Estimates are correct as of:

3rd June 2013



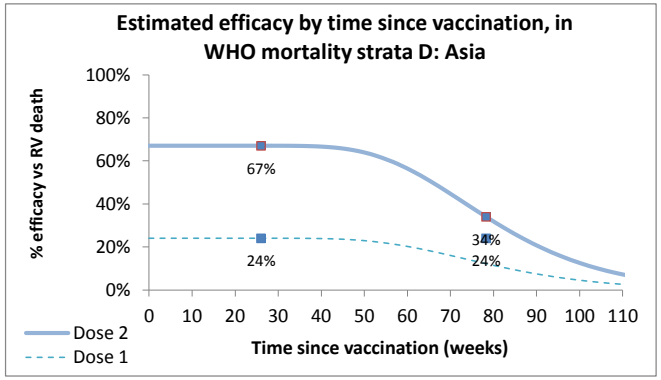
1. To maximize its impact rotavirus vaccine has to be given before RVGE occurs.

Rotavirus vaccine helps to prevent a leading cause of severe diarrhoea in children (c. 40% of hospitalizations in children aged <5 years globally). It is estimated that nearly all children will be exposed to rotavirus before age 5, regardless of where they are born. Children in low-income countries may acquire the infection early during the first year of life. For Afghanistan, this age distribution was based on a global literature review and regression analysis using data from Afghanistan, Egypt, Iran, Iraq, Jordan, Libya, Morocco, Oman, Pakistan, Sudan, Syria, Tunisia, Yemen. Source: Sanderson 2012



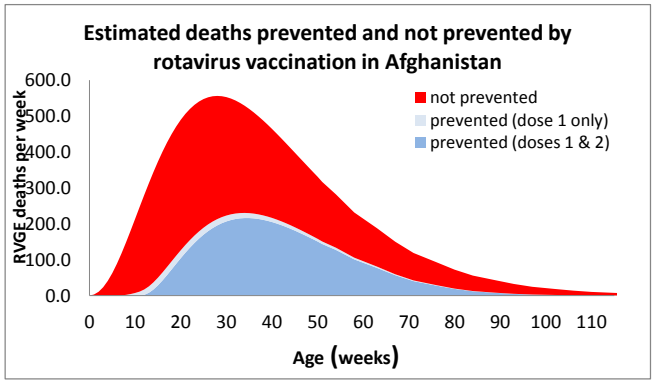
2. It is critical to administer each dose of vaccine at the recommended age and to achieve high coverage

Vaccination should be scheduled as early as possible. This is especially important for rotavirus vaccine as many children will be exposed during the first months of life. Thus it is very important to ensure that each dose is given at the recommended age and not delayed. In Afghanistan, age-specific vaccination coverage was based on household surveys (DHS/MICS) or a regression analysis in countries without a survey. Timeliness of vaccination was scaled to the 2011 estimates of DTP coverage as reported by WHO. Countries with surveys in the relevant WHO sub-region were: Djibouti, Egypt, Iraq. Source: Sanderson 2012



3. It is important to use regionally appropriate estimates of vaccine efficacy

The efficacy of the rotavirus vaccine against severe disease and hospitalisation has been found to be lower in Africa and Asia than in other parts of the world, so it is important to consider whether efficacy assumptions are regionally appropriate. Clinical trials have reported vaccine efficacy during the first and second year of life. This allows the duration of clinical protection to be estimated over time. A sigmoid shape is assumed. In Afghanistan, modelling studies have used 67% efficacy against severe rotavirus disease (as a proxy for rotavirus mortality) based on studies conducted in other countries with a similar mortality profile. Source: Brieman Vaccine (Bang, Viet, Ghn, Ken, Mal, RV5)



4. Maximizing the benefits of rotavirus vaccine requires that each dose is given on at the recommended age and high coverage is achieved

The number of RVGE (rotavirus gastroenteritis) deaths prevented by vaccination is determined by: the age at which cases occur, coverage, timeliness of each dose, and vaccine efficacy (taking time since vaccination into account). If rotavirus vaccine is given at the same visits as doses of DTP/pentavalent vaccine, a model estimates that the numbers of cases represented by the blue shaded area shown above could be prevented by the vaccine. Rotavirus vaccine will prevent many but not all cases and deaths of RVGE, partly because the vaccine is not 100% effective, but partly because some children will get RVGE before they are vaccinated. Provision of the vaccine is also an opportunity to remind caregivers about other things they can do to prevent diarrhoea deaths, such as breast feeding, ORS, zinc etc.

Estimated deaths caused and prevented by rotavirus vaccination

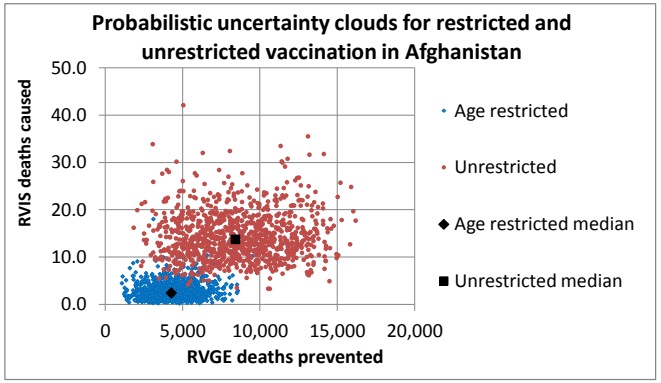
	Potential RVIS deaths caused	*Potential RVGE deaths averted*	*Risk benefit ratio*
Age restricted	2.9	4,348	1519
Age un-restricted	14.4	8,510	591
Difference	11.5	4,162	360

RVIS: vaccine-related intussusception RVGE: rotavirus gastro-enteritis

Relative risk of RVIS vs background risk = 5.5 after 1st dose and 1.7 after 2nd dose

5. The benefits of rotavirus vaccine (rotavirus deaths averted) outweigh the risks (rotavirus vaccine-related intussusception deaths)

In some countries (Australia, Mexico, Brazil) post-licensure data on intussusception (blockage of the bowel) associated with rotavirus vaccine (RVIS) suggest a low-level risk of RVIS of approximately 1-2 cases per 100,000 vaccinees. In other countries such as the US no increased risk has been documented to date, but there are insufficient data to exclude the possibility. All data available on RVIS are from vaccinees who received the 1st dose by 15 weeks of age and the last dose by 32 weeks of age. Thus there is a very limited basis for estimating RVIS risk when the 1st dose is given after 15 weeks of age. Natural intussusception rarely occurs before 3 months of age but the incidence increases ten-fold between 3 and 6 months of age. Health care staff should be aware of the possibility of an increased although very small risk of RVIS, and must be encouraged to strengthen the detection, reporting and investigation of intussusception cases.



6. The benefits of rotavirus vaccination continue to outweigh the risks after accounting for uncertainty in the calculations

Each dot on the chart above represents a different combination of possible model parameter values. The chart shows the result of 1000 possible combinations. The orange dots are for 'unrestricted' vaccination and the blue are for 'restricted' vaccination. SAGE, the principal advisory group to WHO on vaccination, has recommended that age restrictions be removed in settings with high rotavirus mortality to increase the potential number of lives that could be saved by the vaccine. Note very the different scales on the two axes.