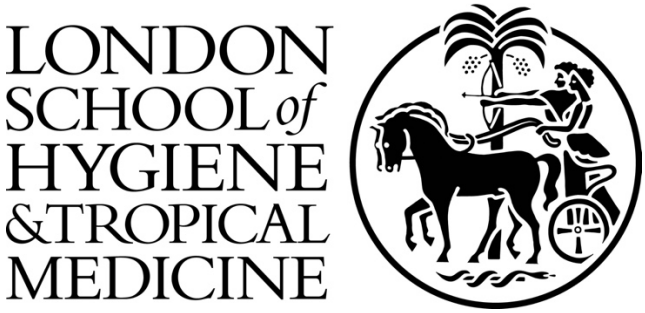

Mathematical and statistical modelling to inform polio and measles vaccination programming

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Declaration

Statement of Own Work

I, Megan Auzenbergs, confirm that the work presented in this thesis is my own. Any information derived from other sources has been indicated in the thesis. I have read and understood the school's definition of plagiarism and cheating given in the Research Degrees Handbook.

Megan Auzenbergs

COVID-19 impact statement

This PhD began in April 2020 at the start of the COVID-19 pandemic. Undoubtedly, the pandemic and switch to remote working affected my PhD, especially during the first formative year of my studies. At the start, I had a different secondary supervisor. Both of my supervisors began contributing towards modelling work for the UK pandemic response, resulting in infrequent supervisory meetings. I switched secondary supervisors and topics during the pandemic, and under the supervision of Dr. Kaja Abbas and Prof Mark Jit, began working on measles modelling projects. Alongside the return to the office, I resumed polio research, the topic initially proposed for this PhD. Additionally, global stakeholder engagement was hindered during the pandemic as many in-person meetings and conferences I had planned to attend or was invited to present at were cancelled or moved to online forums. Despite these obstacles, I was still able to produce high quality research during this difficult time and make a meaningful contribution to the field of vaccine epidemiology.

Abstract

An important criterion for eradication of a disease is the availability of an efficacious vaccine that can be administered to reduce the global worldwide disease incidence to zero. However, deployment strategies for vaccination vary across diseases and geographies and depend on many factors, such as disease burden, political will, vaccine availability and financial resources. Polio and measles are two vaccine preventable diseases that have been targeted for eradication and global elimination, respectively, but have different transmission dynamics, vaccines and mechanisms of vaccine administration. For this PhD, I use statistical and mathematical models to explore aspects of polio and measles vaccination programming, from measuring the efficiency and cost-effectiveness of vaccination strategies, to evaluating vaccine impact and comparing disease surveillance systems. The overall aim of my thesis is to assess the effect of different vaccination strategies for polio and measles using statistical and mathematical models.

First, I explore the costs and benefits of different polio vaccination strategies using a compartmental transmission model. I evaluate outbreak risk and associated costs if a case of wild poliovirus serotype 1 (WPV1) was imported into a low- and middle-income country (LMIC) in sub-Saharan Africa. I model varying frequencies of preventative supplementary immunisation activities (SIAs) in comparison to a baseline comparator strategy consisting of only routine immunisation (RI) and outbreak response. This work concluded that both annual and biennial preventative SIAs are cost-effective when RI coverage is low. At higher levels of RI coverage, annual preventative SIAs are more costly, but result in the greatest probability of no outbreaks in comparison to the baseline strategy with no preventative SIAs.

Next, I use the Dynamic Measles Immunization Calculation Engine (DynaMICE) to estimate the incremental health effects of routine measles vaccination and measles SIAs in 14 high-burden countries: India, Nigeria, Indonesia, Ethiopia, China, Philippines, Uganda, Democratic Republic of the Congo (DRC), Pakistan, Angola, Madagascar, Ukraine, Malawi, and Somalia. I evaluate the effectiveness and efficiency of historical vaccination strategies that were implemented at varying points in time in the high-burden countries. I found that adding routine measles containing vaccine (MCV) dose 2 to MCV dose 1 (MCV1) prevented fewer cases and deaths than adding SIAs to MCV1. However, despite larger incremental effects, adding SIAs to MCV1 showed reduced efficiency because of the wide age range targeted by SIAs.

Finally, I explore the role of vaccination in seeding future vaccine derived poliovirus (VDPV) outbreaks. I estimate the time from emergence to VDPV outbreak detection across all poliovirus serotypes and evaluate factors associated with decreased time to detection. This work emphasises the role of surveillance in VDPV detection and the importance of maintaining surveillance for poliomyelitis even after local elimination is achieved to quickly respond to both emergence of VDPVs and potential importations.

Collectively, the research included in this PhD demonstrates the utility of using statistical and mathematical models to inform global vaccination programming. Whilst measles and polio are ultimately different diseases with independent goals and targets for elimination and eradication, there are parallels in the evaluation of vaccination strategies for both diseases. Understanding the risks and benefits of different vaccination strategies and factors that can improve quality and efficiency are important for global policy and decision-making.

Acknowledgements

I would like to thank my supervisors Dr. Kathleen M O'Reilly and Dr. Kaja Abbas, and Dr. Han Fu, who sits on my advisory board, for their intellectual insight, advice and mentoring throughout my PhD. During my studies, I was also mentored by Prof Mark Jit, Prof Felicity Cutts, Prof Anna Vassall, Dr. Simon Procter, Dr. Yang Liu, Dr. Stéphane Hué, Dr. Sushant Sahastrabuddhe, Clara Maure, Dr. Oliver Brady and Dr. Grace Macklin.

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I value the comradery and friendship with other PhD students and postdocs within the Centre for Mathematical Modelling of Infectious Diseases (CMMID), namely, Tomoka Nakamura, Dr. Alyssa Sbarra and Dr. Emily Nightingale. I thank my family, friends and especially my partner for their unending support and patience while I worked to complete my PhD.

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Acronyms

AFP	Acute Flaccid Paralysis
AIC	Akaike information criteria
aVDPV	ambiguous Vaccine Derived Poliovirus
BCG	Bacillus Calmette-Guérin
BMGF	Bill and Melinda Gates Foundation
bOPV	bivalent Oral Polio Vaccine
BUGS	Bayesian inference using Gibbs sampling
CAR	Central African Republic
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CMA	Cost-minimization analysis
CMMID	Centre for Mathematical Modelling of Infectious Diseases
CUA	Cost-utility analysis
cVDPV	circulating Vaccine Derived Poliovirus
DALYs	Disability-Adjusted Life Year
DHS	Demographic and Health Surveys
DRC	Democratic Republic of the Congo
DTP	Diphtheria-Tetanus-Pertussis vaccine
DynaMICE	Dynamic Measles Immunization Calculation Engine
EPI	Expanded Programme for Immunisation
ES	Environmental Surveillance
EtR	Evidence to Recommendation
GAVI	Global Alliance for Vaccines and Immunization
GMRLN	Global Measles Rubella Laboratory Network
GPEI	Global Polio Eradication Initiative
HiB	Haemophilus influenzae type B
IA2030	Immunization Agenda 2021-2030
IDM	Institute for Disease Modeling
IgM	Immunoglobulin M
IHME	Institute for Health Metrics and Evaluation
IPV	Inactivated Polio Vaccine
IRR	Incidence Rate Ratio
iVDPV	immunodeficiency-associated Vaccine Derived Poliovirus
LMICs	Low-and-Middle-Income Countries
LSHTM	London School of Hygiene & Tropical Medicine
MCMC	Markov chain Monte Carlo
MCV	Measles Containing Vaccine
MCV1	Measles Containing Vaccine dose 1
MCV2	Measles Containing Vaccine dose 2
MMR	Measles-Mumps-Rubella

mOPV2	monovalent Oral Polio Vaccine serotype 2
MWMR	Morbidity and Mortality Weekly Reports
NITAGs	National Immunisation Technical Advisory Groups
NNV	Number of doses Needed to Vaccinate
nOPV2	novel Oral Polio Vaccine serotype 2
ODE	Ordinary Differential Equation
OPV	Oral Polio Vaccine
oSIA	outbreak response Supplementary Immunisation Activity
pSIA	preventative Supplementary Immunisation Activity
QUALYs	Quality-Adjusted Life Years
RI	Routine Immunisation
R_0	Basic reproductive number
SIAs	Supplementary Immunisation Activities
tOPV	trivalent Oral Polio Vaccine
UNICEF	United Nations Children's Fund
VAPP	Vaccine-Associated Paralytic Polio
VDPV	Vaccine Derived Poliovirus
VIMC	Vaccine Impact Modelling Consortium
WHA	World Health Assembly
WHO	World Health Organization
WPV1	Wild Poliovirus Serotype 1
WUENIC	WHO and UNICEF Estimates of National Immunization Coverage

1. Chapter 1: Introduction

1.1 Introduction

1.1.1 Motivation for this thesis

Vaccines have been consistently shown to be the public health intervention which results in the largest reduction in disease burden or mortality for every dollar spent. Since inception of the Expanded Programme for Immunisation (EPI) in 1974, vaccination has averted 154 million deaths, alongside substantial gains in childhood survival in all global regions [1]. In the latest Global Vaccine Action Plan (2020) and Immunization Agenda 2030 (IA2030), several goals were set to improve access to life-saving vaccines, including the interruption of wild poliovirus transmission and elimination of measles [2, 3].

In addition to the tremendous reduction in global polio and measles incidence attributed to vaccination, an improved understanding of the risks and benefits of different vaccination strategies is needed to inform vaccine policy. To make informed decisions about future vaccination programming, is important to understand specific factors that drive successful vaccination strategies and if any approaches can be improved or made more efficient.

In this thesis, I use statistical and mathematical models to evaluate vaccination strategies for both polio and measles. This introductory chapter explores the biology of viruses, temporal trends in global epidemiology, vaccines available, targets for elimination and eradication and vaccination strategies deployed for each disease. I highlight existing evidence gaps in vaccination programming and outline my research objectives to contribute to future decision making.

1.1.2 Overview of the viruses

1.1.2.1 Poliovirus

Poliovirus is an enterovirus belonging to the Picornaviridae family that is the causative agent of poliomyelitis, a paralysing infection that exclusively infects humans. Transmission of the virus occurs from person-to-person via the faecal-oral route, or through food or water contaminated with infected human faeces. There are three different serotypes of poliovirus (1, 2, & 3), each with a slightly different capsid protein and varying viral antigenicity. Wild poliovirus (WPV) type 1 is the most common strain of the virus found in nature, but all serotypes are highly infectious [4]. Poliovirus infection targets the spinal cord, resulting in paralytic disease knows as poliomyelitis or polio. Paralysis

usually occurs in the legs, and while some cases recover from polio, the disease can result in life-long disability or death, especially if the paralysis reaches respiratory muscles and prevents breathing. Infected people who do not have any symptoms of poliomyelitis can still shed virus, which is able to survive in infected faeces for many weeks, allowing for ongoing transmission [5].

1.1.2.2 Measles virus

Measles virus is a highly contagious paramyxovirus that causes measles disease, which is characterised by a systemic rash. Complications from measles can lead to death, especially in younger malnourished or immunosuppressed children. Long-term morbidity is also associated with measles as infected individuals are predisposed to other infections through immunosuppression [6]. Transmission of the virus occurs from person-to-person, specifically, through contact with infected nasal or throat secretions or by breathing air that was breathed by a measles infected person [7]. Measles can affect all age groups, although children are often disproportionately affected in measles endemic settings due to lack of immunity, induced by both vaccination and natural infection [6].

1.1.3 Disease surveillance

1.1.3.1 Polio surveillance

The World Health Organization (WHO) defines a case of acute flaccid paralysis (AFP) as a child <15 years of age presenting with sudden onset of paralysis or muscle weakness, due to any cause [8]. As AFP is also symptom of poliomyelitis, two key performance indicators are used to measure the sensitivity and quality of AFP surveillance: (1) non-polio AFP rate and (2) the proportion of AFP cases with adequate stool specimens. For the non-polio AFP rate, a country's surveillance system is expected to detect at least one case of non-polio AFP in every 100,000 children under 15 years of age. Additionally, at least 80% of AFP cases should have adequate stool specimens, where 'adequate' refers to both the quality of the sample and the timeliness of collection [8].

Another form of poliovirus surveillance is environmental surveillance (ES), which utilises wastewater systems to examine sewage for the presence of poliovirus isolates. Because infected individuals excrete poliovirus for several weeks, even if they are asymptomatic, large amounts of excreted poliovirus can remain in the environment. Even though this type of surveillance does not directly identify infected individuals, it can provide valuable information about the populations that the wastewater system serves [9]. From 2022-2023, of the 28 countries with ongoing poliovirus transmission or considered at high risk of an outbreak, only 20 (71%) met the target rate of AFP

surveillance [10]. Therefore, ES is particularly beneficial in areas where AFP surveillance is lacking or inadequate.

1.1.3.2 Measles surveillance

Measles surveillance is case-based and depends on clinical diagnoses based on symptomatic manifestations of measles virus. Symptoms include fever and generalised maculopapular rash. Although the utility of ES for measles virus detection has been demonstrated in high-income countries [11], ES is rarely done for measles in low-and-middle-income countries (LMICs). Suspected measles cases undergo laboratory confirmation to detect measles-specific immunoglobulin M (IgM) antibodies in serum samples and are reported through the Global Measles Rubella Laboratory Network (GMRLN) [12]. Enzyme immunoassays are used for laboratory confirmation, but research on different rapid-diagnostic tests for measles IgM antibodies is currently being done to assess sensitivity of alternative confirmatory detection methods, especially in low resource settings [12]. Like AFP surveillance for polio, specific key indicators are established to measure the sensitivity of measles surveillance. One such indicator is that at least 2 suspected cases per 100,000 population should be identified and confirmed as neither measles nor rubella [12].

1.1.4 Vaccinology

Vaccines are biological substances that protect against a particular disease or pathogen by stimulating the body's immune response [13]. Different biological mechanisms, administration routes, dose scheduling (see Table 1) and dosing recommendations exist for different vaccines. Following receipt of a vaccine, a person can become protected from a disease if their body has successfully used the vaccine to mount a protective immune response. *Immunity* is usually measured using a laboratory test and determines if a person has antibodies present in the blood, referred to as *seroconversion*. *Active immunity* involves the production of antibodies against a particular disease and occurs following vaccination or by natural infection with a disease [13]. *Passive immunity* is protection from a disease through antibodies produced by another human, for example, when *maternal antibodies* are passed from mother to child, but these antibodies usually decrease over time [13].

Vaccine efficacy varies across different vaccines and is a measure of how effective a vaccine is at protecting an individual against infection and/or disease or protecting an individual from severe disease or hospitalisation. Vaccine efficacy is measured by a vaccinated individual's reduced risk of infection relative to a susceptible, unvaccinated individual [14] and often refers to the estimated protection obtained from phase 3 clinical trials. For example, if a vaccine has an efficacy of 90%, it

means that in controlled trials, people who received the vaccine were 90% less likely to develop the infection and/or disease or become hospitalised compared to those who did not receive the vaccine.

Vaccine effectiveness can be derived from phase clinical 4 trials as well as mass (or more targeted) vaccination campaigns. Vaccine effectiveness can also be measured against infection and/or disease, but an important distinction between vaccine efficacy and effectiveness is that vaccine effectiveness is derived from the general population rather than the specific population enrolled in clinical trials. Vaccine effectiveness can also depend on the reduced rate of viral transmission for an individual in a particular population with a given level of vaccination *coverage*, or the proportion of the population that has received a vaccine [14]. Vaccine effectiveness and vaccine efficacy often differ. For example, the Pfizer-BioNTech (BNT162b2) vaccine had an initial vaccine efficacy of 95% efficacy against symptomatic COVID-19 infection after two doses (based on the Phase 3 clinical trial) [15], but the real-world effectiveness was approximately 88% against symptomatic disease from the Delta variant [16].

It is also important to note that vaccine efficacy can vary not only by antigen, but also on outcome of interest. Sterilising immunity occurs when the immune response completely prevents a pathogen from infecting a host and the individual cannot spread the disease [17]. In other words, the immune system eliminates the pathogen before it can begin to replicate in the body. As a result, a person with sterilising immunity does not get infected and therefore cannot transmit the pathogen to others. Some vaccines, like the measles vaccine, can produce sterilising immunity in most people, which is why measles transmission is rare among vaccinated populations. Immunity against morbidity refers to the ability of the immune system to prevent the severe consequences or illness associated with infection, even if the pathogen still manages to enter and replicate in the body [18]. In this case, a person may get infected, but their immune system controls the infection to the point that they experience mild or no symptoms, and are protected from severe disease, hospitalization, or death. Many COVID-19 vaccines offer strong protection against severe illness, hospitalisation, and death, even though vaccinated individuals can still get infected.

Herd immunity occurs when a sufficient proportion of a population has acquired immunity to a disease or infection either through vaccination or recovering from natural infection. If herd immunity is achieved, transmission of infection from person to person is unlikely at the population level [13]. The proportion of the population that is required to be immune for herd immunity to be achieved is referred to as the *herd immunity threshold*. The herd immunity threshold varies for different diseases. For example, to achieve herd immunity for polio, 80-85% of the population needs to be immunised,

whilst measles requires 90-95% of the population to be immunised because it is a more contagious disease [19-21].

1.1.4.1 Polio vaccines

Two forms of polio vaccine are currently available: a live Sabin oral poliovirus vaccine (OPV) that induces mucosal immunity, prevents infection and therefore halts transmission; and an injectable inactivated poliovirus vaccine (IPV) that contains live attenuated forms of the virus, but only protects from disease (poliomyelitis), and does not induce mucosal immunity to prevent infection or onwards transmission. OPV is therefore integral to polio eradication as it prevents circulating poliovirus transmission and helps move towards the permanent reduction of worldwide infections to zero. Additionally, the OPV can be administered via drops in the mouth and does not require injectable equipment or a cold chain to ensure temperature-controlled storage and transport. bOPV vaccine efficacy against clinical poliomyelitis, obtained from a case-control study comparing immunocompetent (i.e. immune) children to unvaccinated children (i.e. no bOPV doses), was estimated at 82% after one dose, 96% after two doses and 98% after three or more doses of bOPV [22]. For IPV, data on the vaccine efficacy against clinical poliomyelitis is limited. For example, in Senegal, a case-control study during an outbreak of poliomyelitis in 1986–1987 resulted in an estimated efficacy of 36% after a single dose and 89% efficacy for two IPV doses [23], although both estimates had very broad 95% confidence intervals, whilst a study in the USA found efficacy to be 44% and 82% for one and two doses, respectively [24].

Research on the long-term immunogenicity of IPV and OPV estimates that protective antibodies against all three poliovirus serotypes lasts for *at least* 18 years and no statistically significant difference in levels of protection were found between IPV and OPV [25]. This age distinction is important because most poliovirus cases occur in the under-five age group, meaning that the duration of protection for IPV and OPV exceeds the ages at which children are most at risk of poliovirus infection [26].

Prior to 2016, trivalent oral polio vaccine (tOPV) was administered, which contains components of all poliovirus serotypes. After the certified elimination of wild poliovirus type 2 in 2015, serotype 2 was withdrawn from the tOPV and the bivalent vaccine (bOPV) was routinely used instead, which contains antigens against serotypes 1 and 3 only. This event is referred to as '*The Switch*'. *The Switch* was accomplished globally in a two-week period at the end of April 2016 and consequently, 100% of countries had reported cessation by the end of May 2016 [27]. Since then, because the genetically unstable Sabin vaccine perpetuates the spread and existence of poliomyelitis, complete removal of

OPV from use has become an important part of the polio eradication strategy, referred to hereafter as 'bOPV cessation'.

1.1.4.2 Vaccine derived poliovirus

OPV is important for polio eradication, although it also poses a problem due to the genetic instability of viral strains comprising the vaccine [28]. During viral replication in the intestine, the live attenuated virus can undergo mutations, causing it to lose the attenuation and gain transmissibility and neurovirulence similar to WPV [29, 30]. Whilst OPV can be beneficial for stopping poliovirus transmission, vaccine-derived polioviruses (VDPVs) can arise consequently. By definition, a VDPV is a poliovirus strain that originates from OPV but has >1% nucleotide divergence from the vaccine strain (known as the Sabin strain), increasing both the risk of paralysis and transmissibility [28]. Therefore, when vaccine strains are excreted, much like wild type poliovirus would be, VDPVs can be shed. In areas where sanitation infrastructure is insufficient and vaccination coverage is low, VDPVs can circulate (cVDPV) in the community and cause outbreaks.

cVDPVs are of particular concern in areas of low vaccine coverage, as the virus can establish circulation and maintain transmission [31]. OPV vaccination, or lack thereof, is a key risk factor for occurrence of cVDPV outbreaks. Other risk factors include continued OPV use at low rates of coverage, prior elimination of the corresponding WPV serotype, use of monovalent OPV (mOPV), bOPV in SIAs, and insensitive acute flaccid paralysis (AFP) surveillance [28]. Concerningly, cVDPVs carry the same public health risk as WPVs as these revertant strains have recovered the neurovirulence and transmissibility that can lead to poliomyelitis, and outbreaks can potentially re-establish endemicity in regions with low vaccination coverage [28].

Following *The Switch*, a global cohort of children had limited, or no, immunity against serotype 2. Consequently, vaccine derived outbreaks of paralytic poliomyelitis associated with serotype 2 (VDPV2) emerged. To respond to these outbreaks, the only solution at the time was to administer mOPV serotype 2 during reactive outbreak response Supplementary Immunisation Activities (oSIAs), potentially seeding future VDPV2 outbreaks. As the risks of OPV have begun to outweigh the benefits, the continued use of mOPV2 has been deemed unnecessary due to ongoing VDPV2 cases [32]. A novel OPV2 (nOPV2), with greater genetic stability has been developed and licensed for emergency use. In 2022, over 94% of the type 2 vaccine used in outbreak response was nOPV2 and by the end of 2023, over 600 million doses of nOPV2 have been administered via oSIAs in over 28 countries [33].

1.1.4.3 Measles vaccines

There are four measles containing vaccine (MCV) types — measles only as a standalone vaccine, combination measles-rubella vaccine, measles-mumps-rubella (MMR) vaccine and measles-mumps-rubella-varicella vaccine. LMICs with a high burden of measles usually administer standalone measles vaccine or measles-rubella vaccine whilst many high-income countries, such as the UK and USA predominantly administer MMR. All measles vaccine types are live-attenuated vaccines and require both injectable equipment and a cold chain to ensure temperature-controlled storage and transport.

The research included in this thesis primarily features vaccination strategies that use MCV. The efficacy of MCV varies based on whether it is administered as one dose or two doses. For example, one dose of the measles vaccine (MCV1) provides approximately 93% efficacy in preventing measles infection and a second dose (MCV2) increases the efficacy to 97%-99%, providing near-complete protection against measles infection [34]. This second dose is important to catch individuals who did not develop immunity from the first dose. Previously, it was thought that the sterilising immunity induced by measles vaccination provided lifetime protection, with no waning over time [35]. However, recent research has shown the contrary to be true amongst MMR vaccinated individuals in England [36]. For example, Robert et al. (2024) estimated the waning rate in England was slow (95% credible interval: 0.036% to 0.044% per year) but was sufficient to increase measles burden because vaccinated cases caused onwards transmission.

1.1.4.4 Vaccination schedules

Vaccination schedules for both polio and measles vary by country. For polio, high income countries in Europe and North America predominantly administer IPV only. For example, the US Centres for Disease Control and Prevention recommend four doses of IPV given at 2, 4 6-18 months of age and a fourth dose between ages 4 and 6 years. Most non-polio endemic countries at high risk of polio outbreaks (countries in the WHO African, Eastern Mediterranean, South East Asian and Western Pacific regions), recommend four doses of bOPV and at least one dose IPV given in a sequential schedule, with the first IPV dose given alongside the fourth dose of bOPV [37]. However, Table 1 shows how the exact age at which these doses are given can vary between countries.

Since the introduction of measles vaccination in high-income countries in the 1960s and in low-income and middle-income countries in the 1970s and 1980s, recommendations around measles vaccination strategies have been revised. For measles, the WHO recommends MCV dose 1 (MCV1) should be given during the first year of life, ideally at age 9 months or age 12 months and MCV dose 2 (MCV2) is

recommended to be given between age 15 months and 18 months. As of 2023, all countries have implemented at least one dose of MCV [38]. Although, different countries implemented MCV2 at different points in time, and as of 2024, Benin, Central African Republic (CAR), Gabon, and South Sudan have not yet introduced a second dose [38]. Table 1 includes the schedules for measles vaccines in the 14-measles high-burden countries modelled in this PhD.

***Table 1. Age at which polio and measles vaccine doses are given across a range of countries as of December 2023**. IPV = inactivated polio vaccine, OPV = oral polio vaccine, MR = measles-rubella vaccine, MCV = measles containing vaccine, MMR = Measles, mumps rubella vaccine, AFRO = African region, EMRO = Eastern Mediterranean region, SEARO = South East Asia region, WPRO = Western Pacific region, EURO = European region. Data source: https://immunizationdata.who.int (accessed on 6 June 2024).*

Country	WHO Region	Vaccine	Months of age																							Years of age													
			Birth	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Angola	AFRO	IPV						4					9																											
		OPV	Birth			2		4		6																														
		MR											9						15																					
Botswana	AFRO	IPV						4																																
		OPV				2	3	4														18											7						
		MR											9									18																	
Cameroon	AFRO	IPV											9																										
		OPV	Birth		1	2	3																																
		MR											9									18																	
Central African Republic	AFRO	IPV																																					
		OPV	Birth		1	2	3																																
		MCV											9																										
Chad	AFRO	IPV											9																										
		OPV	Birth		1	2	3																																
		MCV											9						15																				
Congo	AFRO	IPV						4																																
		OPV	Birth		1	2	3	4																																
		MR											9						15																				
DRC	AFRO	IPV					3						9																										
		OPV	Birth		1	2	3																																
		MCV											9						15																				
Ethiopia	AFRO	IPV					3						9																										
		OPV	Birth		1	2	3																																
		MCV											9						15																				
Madagascar	AFRO	IPV					3						9																										
		OPV	Birth		1	2	3																																
		MCV											9						15	16	17	18	19	20	21	22	23													
Malawi	AFRO	IPV					3						9																										
		OPV	Birth		1	2	3																																
		MR											9						15																				
Mali	AFRO	IPV					3						9																										
		OPV	Birth		1	2	3																																
		MCV											9			12	13	14	15	16	17	18	19	20	21	22	23													
Mozambique	AFRO	IPV						4					9																										
		OPV	Birth		1	2	3	4																																
		MR											9									18																	
Niger	AFRO	IPV					3						9																										
		OPV	Birth		1	2	3																																
		MCV											9							16																			
Nigeria	AFRO	IPV			1		3						9																										
		OPV	Birth		1	2	3																																
		MCv											9						15																				
South Africa	AFRO	IPV			1	2	3						9									18																	
		OPV	Birth		1																																		
		MCV											9						15																				
South Sudan	AFRO	IPV					3						9																										
		OPV			1	2	3																																
		MCV											9																										
Tanzania	AFRO	IPV					3						9																										
		OPV			1	2	3																																
		MR											9									18																	
Zambia	AFRO	IPV					3						9																										
		OPV			1	2	3																																
		MR											9									18																	
Zimbabwe	AFRO	IPV					3						9																										
		OPV			1	2	3															18																	
		MR											9									18																	
Afghanistan	EMRO	IPV					3						9																										
		OPV	Birth		1	2	3						9																										
		MCV											9									18																	
Pakistan	EMRO	IPV					3						9																										
		OPV	Birth		1	2	3																																
		MR											9						15																				
Somalia	EMRO	IPV					3						9																										
		OPV	Birth		1	2	3																																
		MCV											9						15																				
Sudan	EMRO	IPV			1		3						9																										
		OPV			1	2	3																																
		MCV											9																										
India	SEARO	IPV			1		3						9																										
		OPV	Birth		1	2	3													16	17	18	19	20	21	22	23	1	2											
		MR											9	10	11					16	17	18	19	20	21	22	23												
Indonesia	SEARO	IPV						4					9																										
		OPV			2	3	4	5																																
		MR											9									18												7					
Philippines	WPRO	IPV					3						9																										
		OPV			1	2	3																																
		MMR											9			12	13	14	15																				
China	WPRO	IPV				2	3																																
		OPV						4																						3				4						
		MMR										8										18																	
Ukraine	EURO	IPV				2		4																															
		OPV								6												18											6						14
		MMR														12																							

1.1.4 Vaccination strategies

1.1.4.1 Routine immunisation and the Expanded Programme for Immunisation

Routine immunisation (RI) refers to vaccinations given at recommended routine vaccination schedules and are usually delivered in a medical setting, sometimes alongside other childhood vaccines, as part of the EPI. The Expanded Programme for Immunisation (EPI) is a global initiative established by the WHO in 1974 with the primary goal of ensuring that all children, especially those in LMICs, are immunised against common, vaccine preventable diseases. The EPI initially focused on six vaccine-preventable diseases: tuberculosis, poliomyelitis diphtheria, tetanus, pertussis, and measles, however, now, the programme has expanded to also include: hepatitis B, Haemophilus influenzae type B, pneumococcal disease, rotavirus, human papillomavirus, rubella, yellow fever, Japanese encephalitis, meningococcal meningitis, typhoid, and in some regions, influenza and cholera [39]. The EPI continues to evolve, and new vaccines are considered for inclusion as they become available and based on the disease burden in specific regions. Vaccinations delivered through RI are usually indicated in medical records or denoted on a vaccination card. For polio, RI includes both bOPV and IPV. For measles, both MCV1 and MCV2 can be delivered via RI, if the country has implemented the second dose.

1.1.4.2 Supplementary Immunisation Activities

Supplementary immunisation activities (SIAs) occur in addition to RI and target hard-to-reach populations otherwise missed by RI. Preventative SIAs (pSIAs) boost population immunity and are done to prevent outbreaks, whilst reactive outbreak response SIAs (oSIAs) occur following an outbreak and aim to increase population immunity to stop an ongoing outbreak.

Both preventative and reactive polio SIAs occur with the bOPV and are given via drops in the mouth and usually involve going house-to-house and vaccinating all children in a defined target area under five years of age. SIAs remain controversial because of their expense and shift in resources away from routine services. Especially within the African continent and in Afghanistan and Pakistan, repeated use of SIAs appear to reduce the impact of improving OPV RI coverage within children under five years of age [40]. For polio SIAs, an important distinction is that the target population for both pSIAs and oSIAs include all children (usually under five years of age) in a defined geographical area, regardless of previous vaccination history (i.e. *non-selective* SIAs). Conversely, preventative measles SIAs are usually *selective*, meaning that they consider previous measles vaccination history. Target populations for measles oSIAs depend on the outbreak risk assessment, if there is a high risk of measles spread, then

the oSIA will be *non-selective* in vaccinating susceptible individuals in the affected area, regardless of vaccination history [41].

Like polio SIAs, measles SIAs also aim to vaccinate hard-to-reach children with MCV and usually target children between 9-59 months of age, although the impact of extending the upper age limit for measles SIAs is currently under research, with an upper age limit of 14-years. However, due to the cold chain requirements, the campaigns are usually fixed-post campaigns, meaning they do not go door-to-door, and instead set up a central vaccination hub in a defined geographical area [42]. Examples of these posts include: (1) *permanent* fixed immunization posts, which are often located at permanent health facilities and community health posts. Immunisation services are provided at these health facilities for the days during the SIA. These sites will also serve as depots for storage and distribution of vaccine to temporary fixed sites and mobile teams; (2) *temporary* outreach immunization posts, which may be located at schools, churches, mosques, local administrators' offices, bus depots, roadblocks, market areas, border crossing points, village squares, etc. Villages and settlements with small populations may also be served through these temporary posts. MCV vaccination will be provided at these sites for either the duration of the campaign or partially, depending on the population density; and (3) *mobile* immunisation posts, which move from community to community reaching populations that are living in hard-to-reach areas without access to a fixed site, are too small to justify an all-day fixed post or are unlikely to visit the fixed sites. Villages and settlements with very small populations may also be served through these mobile posts [42].

1.1.4.3 Polio outbreak response

A poliovirus outbreak is defined as detection of WPV or cVDPV with evidence of community transmission. This can be demonstrated several ways: (1) virus detection in a human sample, (2) two separate ES detections from two different ES sites with no overlapping catchment areas, or from the same site >2 months apart, or (3) a newly detected cVDPV that can be genetically linked to another VDPV [43]. All poliovirus detections are notifiable under International Health Regulations and trigger a public health investigation and risk assessment. Within 72 hours of initial detections, all polio outbreaks are graded—grade 1 outbreaks can be managed in-country, grade 2 outbreaks require regional or WHO support, and grade 3 outbreaks are emergencies that require global support and usually involve multiple geographical regions [43]. WHO standard operating procedures for polio state that within 56 days of detection, large-scale outbreak response should occur, usually involving an oSIA [43], that vaccinates children under five years of age, regardless of previous vaccination history.

1.1.4.4 Measles outbreak response

A measles outbreak is defined as five or more epidemiologically linked (geography and time) measles cases with onset of rashes occurring 7-21 days apart, or at least 2 laboratory confirmed measles cases that are genetically linked [44]. The same aforementioned outbreak grading criteria for polio is used for grading measles outbreaks and all outbreaks trigger an investigation and risk assessment. Quantitatively, the magnitude of a measles outbreak can be determined using the test positivity rate of specimens from at least ten or more suspected cases, where the test positivity rate is defined as the proportion of suspected measles cases with specimens collected that are then laboratory confirmed for measles. In outbreaks with low measles circulation or where herd immunity exists, the test positivity rate would be low, whilst during larger measles outbreaks among susceptible populations, the test positivity rate could exceed 75% [44]. If the risk of measles spread is medium or low, an oSIA may be *selective*, meaning a child's vaccination status is checked (based on a vaccination card, registration book or electronic registry) and only susceptible individuals in the affected area receive MCV [44]. If the risk assessment finds a high risk of measles spread, then the oSIA will be *non-selective* in vaccinating susceptible individuals in the affected area, regardless of vaccination history. An oSIA should be completed within 7-10 days of measles outbreak confirmation and an outbreak can officially be declared over if no epidemiologically or virologically linked measles cases occur for 46 days from the date of onset of the last case [44].

1.1.5 Epidemiology over time

1.1.5.1 Polio epidemiology

The global incidence of WPV has dramatically declined since the late 1900s, mostly driven by the vaccination approaches outlined above, shown by the differences between Figure 1A versus Figure 1B. As of June 2024, WPV was only endemic in Afghanistan and Pakistan, although cVDPV outbreaks are more geographically widespread. In 2019, the African Region was certified free from endogenous transmission of WPV, with the last clinical case reported in Nigeria in August 2016 [45, 46]. However, in early late 2021 and early 2022, Malawi and Mozambique reported WPV1 cases, respectively, linked to ongoing circulation in Pakistan [47, 48].

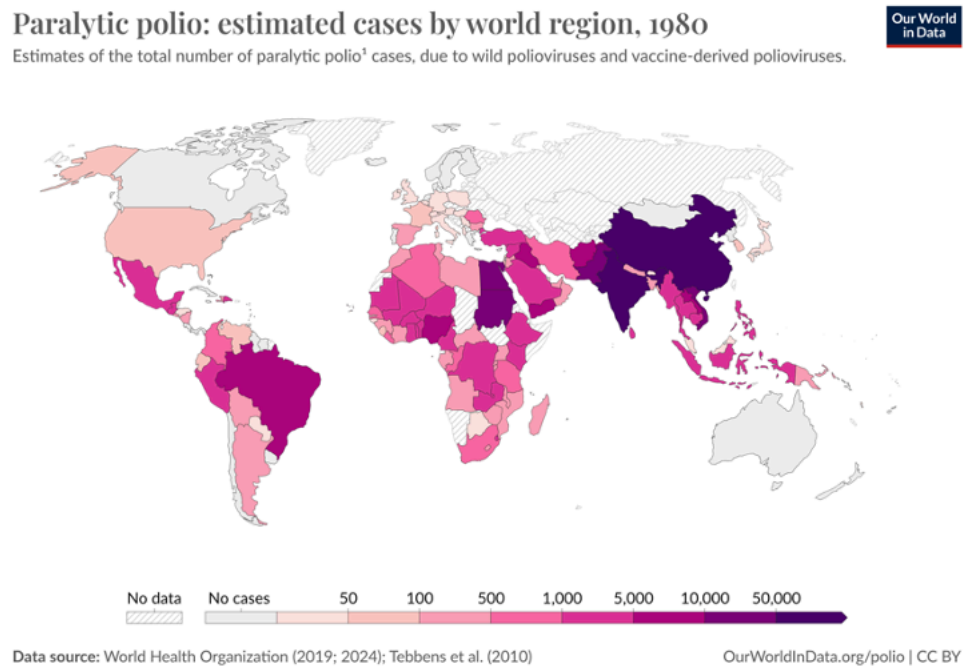
For cVDPVs, post Switch, the number of cVDPV2 outbreaks and the geographical spread has been increasing [49], especially during the years of the COVID-19 pandemic. From January 2020 – April 30, 2022, a total of 1,856 paralytic cVDPV cases across all serotypes were reported worldwide, 399 of which were reported in 2022 alone [48]. Most detections occurred throughout the African continent,

but 2022 also saw cVDPV detection in high income countries previously unaffected by VDPVs. In May 2022, six environmental samples positive for VDPV2 were collected in the United Kingdom and in December 2022, a cVDPV2 case was reported in New York, USA, followed by a total of 30 environmental samples [50]. These detections in New York were then genetically linked to a cVDPV2 isolate detected from two environmental samples in Montreal, Quebec [50, 51].

The viral spread throughout the UK, USA and Canada highlights the emerging risk that VDPVs pose. Also, the response to these poliovirus detections in high-income countries is worth noting. For example, in the UK, VDPV2 isolates that were genetically linked to poliovirus detected in Israel and the US were found in sewage samples collected from the Beckton sewage treatment works. This sewage treatment centre covers a catchment area with a population of about 4 million people across north-east and north-central London. However, the UK declared a *national* enhanced incident response to these detections and recalled unvaccinated and partially vaccinated children under the age of 5 in all of London to receive IPV [52]. Following this initial response, a second targeted catch-up campaign offering IPV and MMR vaccine to unvaccinated or partially vaccinated children aged 1 to 11 years in London was launched in May 2023 [52]. This vaccination response was geographically more widespread than a traditional outbreak response in countries in the WHO African region, for example, highlighting how different countries respond to the perceived risk of polio outbreaks.

Globally, the total number of polio cases caused by cVDPVs decreased from 881 in 2022 to 524 in 2023, but eight new countries reported cVDPV outbreaks than in 2022, highlighting the increasing geographical spread of cVDPVs [53]. As of 5 June 2024, there were 8 WPV1 cases and 62 global cVDPV cases [54].

A



B

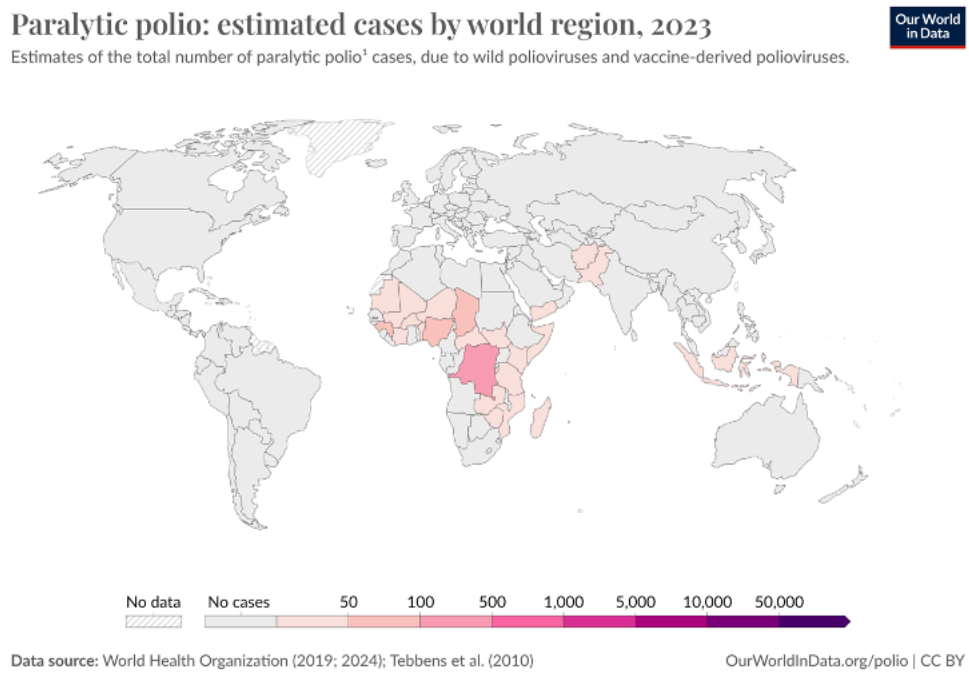


Figure 1. Global distribution of paralytic polio cases *in (A) 1980 and (B) 2023. The darker colours correspond to a greater number of cases. Figures were obtained from Our World in Data: https://ourworldindata.org/estimating-total-global-paralytic-polio-cases (accessed on 6 June 2024).*

1.1.5.2 Measles epidemiology

Measles cases have also dramatically declined since the 1980s, attributed to the success of measles vaccination, Figure 2. Most of the measles burden is now confined to several high-burden countries. For example, India, Nigeria, Indonesia, Ethiopia, China, Philippines, Uganda, DRC, Pakistan, Angola, Madagascar, Ukraine, Malawi, and Somalia represented 78% of the global measles burden in 2022 [55].

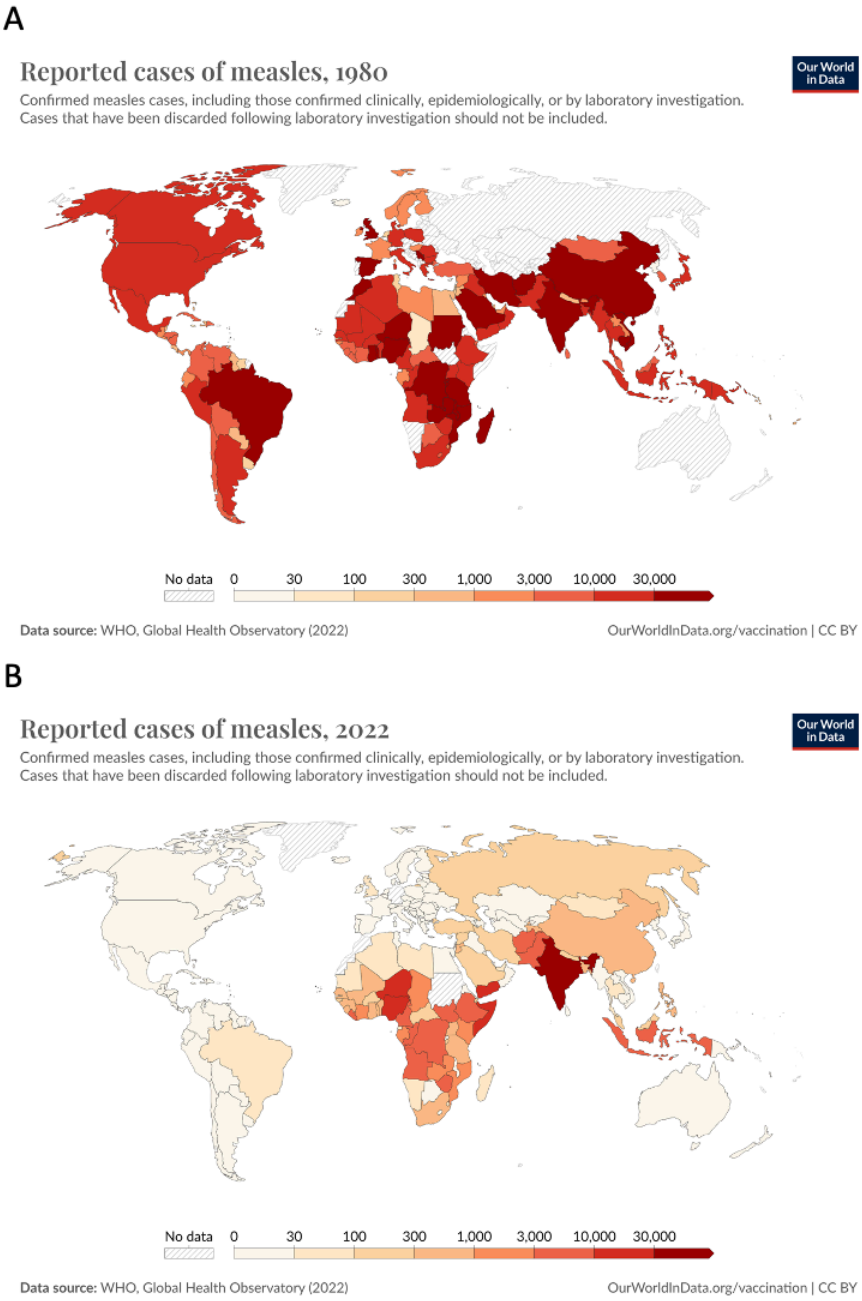


Figure 2. Global distribution of measles cases *in (A) 1980 and (B) 2022. The darker colours correspond to a greater number of cases. Figures were obtained from Our World in Data: https://ourworldindata.org/grapher/reported-cases-of-measles (accessed on 6 June 2024).*

However, because measles is a very transmissible virus, even modest dips in vaccination coverage can result in measles outbreaks. Consequently, despite the global reduction in measles burden since 1980, resurgence of measles is a current issue. For example, in 2018, there was a resurgence in measles cases, with the WHO reporting a 300% increase in measles cases compared to the previous year. In 2019, the outbreaks continued and worsened in many parts of the world, and over 869,000 cases of measles were recorded in 2019, the highest number in decades [56]. Factors that contributed to this resurgence included vaccine hesitancy and misinformation campaigns, such as the misinformation spread by Andrew Wakefield's 1998 retracted study that incorrectly supported the claim that the MMR vaccine causes autism [57, 58]. Although vaccine coverage has increased since, vaccine hesitancy and misinformation remain an obstacle for achieving high enough levels of vaccination coverage to interrupt measles transmission and achieve elimination.

1.1.6 Features of measles and polio that makes them amenable to elimination or eradication

Elimination is broadly defined as the reduction to zero cases of infection in a geographical area, although explicit definitions of elimination can vary by pathogen. *Eradication* refers to the permanent reduction to zero of the worldwide incidence of infection. There are certain features of pathogens that make them suitable for eradication (Figure 4) including: scientific feasibility, epidemiological susceptibility, political commitment, availability of effective interventions, such as vaccines, and demonstrated feasibility of elimination [59].

Whilst polio has been targeted for eradication, measles is only targeted for elimination due to several differences that stem from factors related to the biology of the viruses, transmission dynamics, vaccine effectiveness, and public health infrastructure. Measles is a more contagious respiratory virus with a longer infectious period, and though humans are the only known reservoir, its mode of transmission and extreme contagiousness makes achieving eradication more challenging [60]. The virus can spread rapidly in populations with any gaps in immunity. Polio vaccines (OPV and IPV) are highly effective, and their widespread use has led to the elimination of endemic WPV in most of the world (other than Afghanistan and Pakistan). The success of these vaccines, combined with sustained global coordination, has made the goal of polio eradication feasible. Measles vaccines, though very effective, require extremely high coverage (at least 95%) to achieve herd immunity because of the virus's contagiousness. This makes global eradication more difficult, and the focus remains on regional elimination rather than complete eradication. Finally, the global coordination and initiatives for polio eradication are longstanding and have gained political will and support, whilst measles initiatives have been more region specific [61].

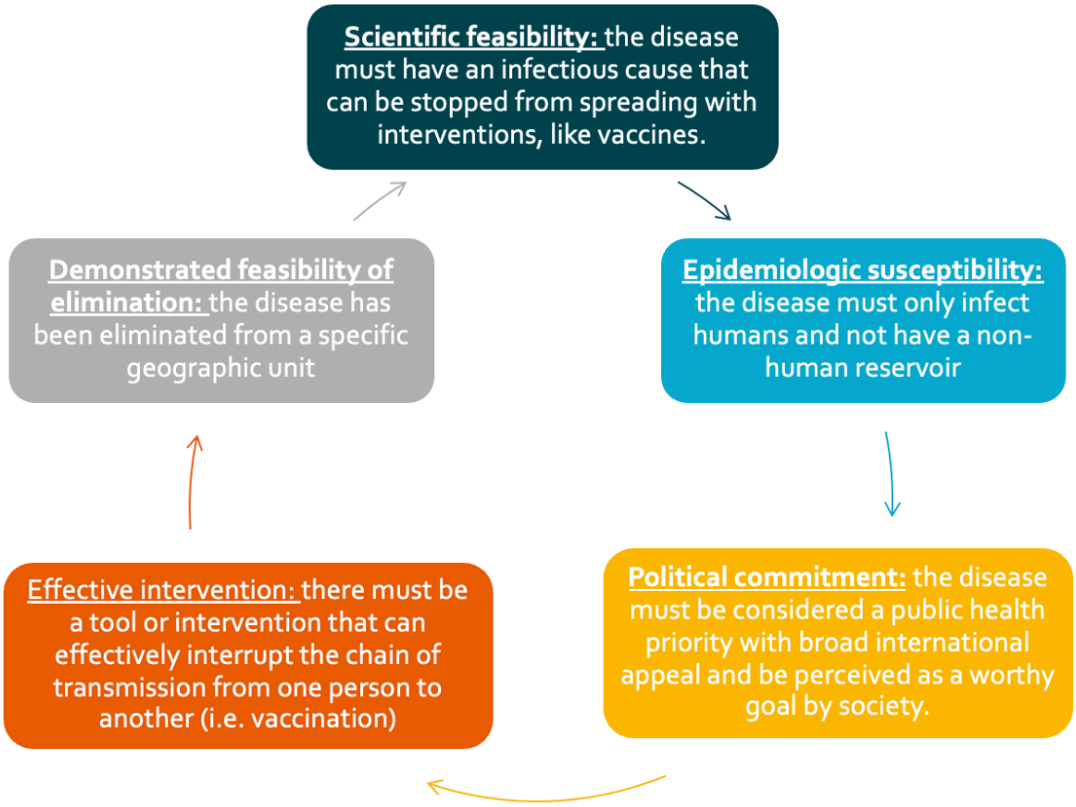


Figure 3. Criterion for disease eradication.

1.1.6.1 Progress towards polio eradication

Whilst the first clinical case description of polio predates the 19th century, research on the virus and its transmission dynamics began to accelerate after the global polio epidemic in the early 20th century. In 1988, when more than 1,000 children were paralysed from polio every day, the World Health Assembly (WHA) passed a resolution to eradicate polio by 2000.

At this point in time, disease burden was highest across the African continent and a range of Asian countries including Afghanistan, Pakistan and northern India. However, in 1999, the last case of WPV2 was reported in Uttar Pradesh, India, a tremendous feat reinforcing the potential for global eradication [62]. By 2001, the number of endemic countries had decreased from over 100 to less than ten. Most recently, Nigeria was removed from the list of WPV endemic countries at the end of 2019, leaving only Afghanistan and Pakistan with ongoing WPV transmission. With no detections of wild type 3 globally since 2012, certification of type 3 eradication is underway.

Since its inception in 1988 following the WHA's resolution to eradicate polio, the Global Polio Eradication Initiative (GPEI) has set forth a mission to interrupt transmission of WPV and VDPVs. Since

GPEI's inaugural year, the global incidence of polio has decreased by 99.9% and it is estimated that 16 million cases of paralysis and 1.5 million deaths due to severe poliomyelitis have been prevented [63].

The GPEI is facing a critical time where the endgame for polio is in sight and global polio eradication is deemed an attainable feat. Core strategies of the GPEI now focus on interruption of WPV transmission through AFP surveillance, environmental sampling, and vaccination through both RI and SIAs. Implementing these strategies at the subnational level allows for concentrated geographic focus on the most vulnerable and hard to reach populations. Recently, however, global pressures to eradicate polio have been inversely related to budget allocations for vaccination and outbreak response. Arguably, a level of fatigue has been witnessed to complete the final stages of eradication and feared complacency with the global epidemiology has been coupled with ongoing outbreaks [53]. Therefore, as we move towards global certification of eradication, research must continue to improve the effectiveness of vaccination programmes, increase vaccination coverage in the hardest to reach communities, maximise cost-savings, and align synergies between polio eradication efforts and emergency programmes.

1.1.6.2 Progress towards measles elimination

In 1989, the WHA announced a goal of reducing global measles morbidity and mortality by 90% and 95%, respectively, by 1995 [64]. Initial measles elimination targets were set depending on region: elimination from the Americas by 2000, from Europe by 2007 and from the Eastern Mediterranean region by 2010 [65]. In 2010, the WHA revised these goals and set the following targets for measles control by 2015: increase MCV1 RI coverage in children aged 1 year to 90% at the national level and 80% in subnational districts; reduce global annual measles incidence to under 5 cases per 1 million population; and reduce global mortality attributed to measles by 95% from the 2000 estimate of measles mortality [66].

Furthermore, in 2012, the WHA endorsed the Global Vaccine Action Plan to eliminate measles in five of the six WHO regions by 2020 [67], which aligns with the global IA2030 [68]. Since then, the Measles and Rubella Strategic Framework 2021-2030 and the Measles Outbreaks Strategic Response Plan have aligned with these IA2030 goals and emphasise the need for robust measles surveillance systems to identify immunity gaps, explore causes of under-vaccination and prioritise local interventions to increase MCV2 administration [6, 69].

Though the global burden of measles has reduced tremendously since the WHA's initial resolution, in 2018 there was a global resurgence of measles cases and in 2019, the WHO responded to measles outbreaks in all six WHO regions. Since this resurgence, no WHO region has been verified as having eliminated measles [67]. Disruption to health systems during the COVID-19 pandemic further exacerbated the need for catch-up vaccination and mobilisation of resources to vaccinate susceptible populations [69, 70].

1.1.7 Using models to inform vaccine policy – literature reviews

Mathematical and statistical models have been used previously to inform vaccination decisions for the control of both measles and polio. In this section, I highlight three topics of existing literature to align with the objectives of this thesis: (1) economic models have been used to estimate the costs and benefits of polio vaccination strategies, (2) modelling has been used to estimate the impact of measles vaccination strategies, and (3) statistical approaches have been used for evaluating the indirect effects of vaccination with OPV, specifically the seeding and detection of cVDPVs.

1.1.7.1 Polio economic models

Economic considerations for polio began appearing in the literature in the early 1990s, following the WHO's 1988 commitment to polio eradication. Economic models have been used in the past to quantify the cost-effectiveness of achieving polio eradication. I searched PubMed for manuscripts published in English between Jan 1, 1980, and August 29, 2023, that contained the following search terms: (((polio) OR (poliovirus)) OR (poliomyelitis)) AND ((economic*) OR (cost*)) AND (model*). I identified 18 modelling studies that investigated the costs and benefits of vaccination strategies to effectively control poliovirus and included these studies in a risk-of-bias assessment. Several identified studies analysed policy decisions for future control or eradication of polio, including varying assumptions around SIAs. However, to date, most research looking into polio economics has focused on the cost benefit ratios of eradicating polio vs. the cost of controlling endemic polio long term [71-78].

Some researchers believe if polio eradication remains technically achievable, eradication offers lower cumulative costs and a fewer number of cases than adopting a global control strategy [79]. Research by Barrett et al. explored investments in polio eradication and concluded that maintaining a high level of control will never be optimal since the eradication of polio is technically feasible [71]. Zimmerman et al. also assessed the costs of a permanent control strategy vs. eradication of polio. Authors concluded that eradication of polio would be cost-saving compared to permanent control because

eradication will likely have a high return on investment in avoided costs of vaccination [78], i.e., eradication is only deemed cost-effective here because vaccination is assumed to stop. If it is decided that IPV vaccination will be given indefinitely [80], there will be different implications for costs.

In 2020, work by Kalkowska and Thompson et al. modelled risk management scenarios for cVDPVs and recommended aggressive outbreak response SIAs. Cost-effectiveness and affordability were not considered, neither were budget constraints nor the geographical spread of cVDPVs in present day [81], both of which are limitations for current vaccination programming. The same authors published a 2021 analysis investigating whether improving the quality of SIAs in Pakistan and Afghanistan could eliminate endemic WPV1 [82]. Authors concluded that increasing the quality of pSIAs could lead to WPV1 elimination in the first quarter of 2021, a timeline already in the past. Moreover, their definition of 'improved quality' is vague at best and authors do not explicitly state what it takes to increase 'impact level', i.e., what operational components of SIAs would need to change to 'improve quality'? The most recent analysis published by this same team of researchers in 2023 considers the cost-effectiveness of specific operational decisions for pSIAs and oSIAs in a hypothetical population, but only focuses on co-circulation of cVDPVs, and does not consider importations of WPV1 [83]. Therefore, research is needed to expand the scope of cost-effectiveness analyses for polio vaccination strategies.

1.1.7.2 Measles vaccination impact modelling

To evaluate existing literature on modelling measles vaccination strategies, I searched PubMed for manuscripts published in English between Jan 1, 2000, and March 10, 2022, that contained the following search terms: ("measles" or "MCV" or "MCV1" or "MCV2") and ("vaccin*" or "immun*") and ("supplementary immun* activit*" or "campaign" or "catch-up") and "model". 13 modelling studies investigating vaccination strategies to effectively control measles were identified and included in a risk-of-bias assessment. Although several articles recommended that sustaining a high coverage of routine immunisation and campaigns was optimal for measles control, I found only three studies that explicitly addressed the interactions between different delivery strategies of MCV doses.

One modelling study concluded that, in Zambia, an MCV2 vaccination strategy can sustain high levels of population immunity and that frequent, low-coverage SIAs might sustain higher levels of immunity than less frequent, high-coverage SIAs [84]. However, direct comparisons of the incremental differences between strategies were not conducted. The second modelling study assessed the vaccination effects of incrementally introducing MCV1, MCV2, and SIAs compared with a counterfactual scenario without measles vaccination, but also did not directly compare MCV2 with

SIAs [85]. The third modelling study showed that in addition to MCV1, delivering MCV2 was more cost-effective and prevented more cases of measles than SIAs in a hypothetical cohort in the DRC.

1.1.7.3 Evaluating factors associated with cVDPV detection

A scoping review was undertaken to identify cVDPV outbreaks using the search terms: 'vaccine-derived poliovirus* OR VDPV OR circulating vaccine-derived poliovirus* OR cVDPV'. Because poliomyelitis is a notifiable disease, the GPEI and WHO laboratories report all confirmed outbreaks through the Morbidity and Mortality Weekly Reports (MMWR), so most existing literature on cVDPVs is in the form of outbreak reports. Modelling reports on cVDPVs vary in approach from analysing the spatial spread of genetically linked clusters, to evaluating SIAs linked to ongoing cVDPVs. For example, a stochastic mathematical model has shown that the probability of polio elimination is 95% if a case has not been detected for three years, increasing to 99% if after four years no case has been detected [86]. Research by Macklin et al. has shown that six outbreaks in the first year following *The Switch* were seeded before or close to the time of *The Switch*, occurring in DRC, Pakistan and Syria, but no virus was detected later than six months following *The Switch*. In the second year after *The Switch* (May 2017 to April 2018) however, five more outbreaks emerged, one seeded before and four after *The Switch* [49].

Research related to cVDPVs for this thesis was completed between 2020-2021. At the time, a better understanding of time from seeding to detection of historical cVDPV outbreaks was needed. Before November 2020 when nOPV2 was authorised for emergency use, the bulk of existing literature on cVDPVs was concerned with the increasing number of outbreaks alongside geographical spread of genetically linked lineages. Since 2023, cVDPV2 research has been focused on population immunity to serotype 2 post *Switch* [87], and the utility of nOPV2 [88, 89] or IPV in SIAs [90] to control cVDPV2 outbreaks.

1.1.8 Evidence gaps

1.1.8.1 Polio economic models

While some research has concluded polio eradication to be cost-effective, this does not necessarily mean eradication is affordable in the present day, and sometimes, adopting cost-effective interventions requires eliminating other, more beneficial expenditures [91].

Traditional cost-effectiveness analyses (CEAs) are limited in evaluating polio eradication for several reasons, primarily because they are not designed to capture the unique long-term dynamics and

uncertainties associated with eradication efforts. In the case of polio eradication, key factors such as upfront costs, long-term benefits, and the economic implications of cessation strategies are difficult to incorporate into standard CEAs. Polio eradication requires significant upfront costs (e.g., vaccination campaigns, infrastructure, and surveillance) with long-term benefits that might not be realized for years or even decades. Traditional CEAs typically focus on short- to medium-term costs and benefits, which makes it hard to capture the true value of eradication, which includes avoiding future cases, healthcare costs, and maintaining a polio-free world. The benefits of eradication extend into the future, but these are highly dependent on when vaccination can be stopped and when surveillance costs can be scaled back. CEAs struggle to account for the dynamic interplay between ongoing investments and future savings [92].

Also, polio eradication deals with non-linear costs. In a typical vaccination program, cost-effectiveness improves as vaccine coverage increases because the health burden decreases proportionally. However, with polio eradication, the costs increase non-linearly as the goal nears. Eradication requires intensive efforts to reach the last remaining cases in hard-to-reach areas, which incurs disproportionately high costs relative to the number of cases averted in the final stages [92]. Traditional CEAs are not equipped to address these rising marginal costs and may underestimate the resources needed for complete eradication. Finally, the financial success of polio eradication depends on how quickly the financial benefits of stopping vaccination programs can be realised after the virus is eradicated. Traditional CEAs do not usually consider the transition period between cessation of vaccination and recouping the costs of eradication, which includes ongoing expenses for surveillance and emergency preparedness [79].

Considering recent budget pressures, the polio programme could benefit from a better understanding of which programmatic scenarios for SIAs are not only cost-effective, but also affordable. Though several studies have concluded that eradication is cost-effective, we are more than two decades past the initially proposed timeline for polio eradication. Annually, the global polio budget is around $1 billion and recent trends in cVDPV outbreaks have further stretched this budget. Therefore, more research is needed to better understand which scenarios and programmatic interventions can be altered or made more effective.

1.1.8.2 Measles vaccination impact modelling

Knowledge of the incremental health effects of historical measles vaccination policies implemented in high-burden countries is needed. Specifically, the relative roles of MCV1, MCV2, and SIAs in

preventing measles transmission is important as countries rebuild health systems following the COVID-19 pandemic. As countries continue to introduce MCV2, in principle, reliance on SIAs should decrease and eventually stop once high population immunity (i.e., above the herd immunity threshold) can be maintained with a routine two-dose schedule alone. Instead of relying on hypothetical scenarios, using models to directly compare historical vaccination strategies that countries implemented at different time points can add great value to future measles vaccination programming decisions. To achieve high levels of vaccination coverage and meet targets for measles elimination in high-burden areas, SIAs should be strengthened. However, an evidence gap persists in understanding the historical efficiency SIAs in different countries.

1.1.8.3 Evaluating factors associated with cVDPV detection

The capacity of polio infrastructure has been applied to other infectious disease outbreaks in the past to mitigate risk and disease spread [93-95]. However, in the most recent GPEI Endgame Strategy, the GPEI cites the lack of "*systematic collaboration between polio and emergency programmes*" as one of its major challenges in efforts to control cVDPVs. This lack of coordination means that synergies between GPEI and emergency responses often go unrecognised, and consequently, cost-efficiencies and humanitarian needs of communities are not met [96]. As planning for global bOPV cessation is underway, it is important to better understand why the predictions for OPV2 removal did not hold true. Analysing nucleotide divergence and estimated date of seeding of cVDPVs, including historic outbreaks pre-2016, is essential to address this issue.

1.2 Aims and objectives

The overall aim of my thesis is to evaluate the effect of different vaccination strategies for polio and measles using statistical and mathematical models. I hypothesise that the impact and effectiveness of different strategies will depend on population level baseline vaccination coverage and the implementation, quality and frequency of preventative vaccination activities.

The aim is met by the following objectives, each corresponding to a chapter in this thesis:

1. Identify outbreak risk and associated costs and benefits for conducting pSIAs at varying frequencies in a LMIC in sub-Saharan Africa, at risk of WPV1 importation.
2. Evaluate the health impact of different measles vaccination strategies that were implemented at different time points in 14 high-burden countries and identify which strategies were effective and/or efficient in preventing outbreaks and vaccinating unvaccinated children.

3. Identify factors associated with quicker time from emergence to outbreak detection for cVDPVs to understand the indirect effects of vaccination strategies using the OPV.

1.3 Thesis structure

This thesis follows the *research paper style* and includes an introduction chapter, methods chapter, three analyses chapters that include research published as peer-reviewed scientific papers, and a final discussion chapter. Each analysis chapter includes a bridging section that outlines how the analysis relates to the overall aims of this thesis. The three analysis chapters are as follows:

- **Chapter 3: Outbreak risks, cases, and costs of vaccination strategies against wild poliomyelitis in polio-free settings: a modelling study.** This study has been peer-reviewed in BMJ Global Health. This chapter covers thesis objective 1.

- **Chapter 4: Health effects of routine measles vaccination and supplementary immunisation activities in 14 high-burden countries: a Dynamic Measles Immunization Calculation Engine (DynaMICE) modelling study.** This study was peer-reviewed and published in the Lancet Global Health in August 2023. This chapter covers thesis objective 2.

- **Chapter 5: The impact of surveillance and other factors on detection of emergent and circulating vaccine derived polioviruses.** This study was peer-reviewed and published in Gates Open Research in May 2021. This study covers thesis objective 3.

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2. Chapter 2: Methods

This chapter summarises several overarching methods used throughout this PhD and offers a critical appraisal of the strengths and limitations of each methodological approach. Each subsequent research chapter will have an independent methods section outlining explicit methodologies used in each research paper. This chapter provides an overview of the justification for using mathematical modelling, economic evaluation and statistical approaches to evaluate vaccination strategies.

2.1 Using models to evaluate vaccine impact

Historically, mathematical models for infectious disease dynamics were developed nearly a century ago and described in a paper by Kermack and McKendrick in 1927 [1]. Since then, mathematical models for disease dynamics have been used in a wide range of applications, including modelling vaccination events. In this PhD specifically, transmission models are used to model historical measles outbreaks under different vaccination strategies and to predict polio outbreak size and probability given an importation of WPV1 infection.

Transmission models separate the population into different compartments based on epidemiological status. For example, in an SIR model, susceptible individuals are in the 'S' compartment, infectious individuals are in the 'I' compartment and recovered individuals are in the 'R' compartment. Individuals move through these compartments based on predetermined rates that are unique to the disease being modelled. Another commonly used model structure is the SEIR model, which includes an exposure 'E' compartment. It is important to include an 'E' compartment for diseases when there is a significant latent period between exposure and the time when individuals become infectious, for example, COVID-19. During this latent period, individuals are infected but cannot transmit the disease, which should be accounted for in models because it affects the timing of disease transmission.

SIR and SEIR models describe the spread of infectious diseases through a population in time, where the spread of infection depends on parameters such as the transmission rate (β), the duration of infectiousness and recovery rate (γ) [2]. The basic reproduction number R_0 describes the contagiousness or transmissibility of an infectious disease in a fully susceptible population. It represents the average number of secondary infections that one infected person is expected to cause in a population where everyone is susceptible to the infection.

- If R_0>1: Each infected person, on average, infects more than one other person, meaning the infection will likely spread through the population, potentially leading to an outbreak or epidemic.
- If R_0=1: Each infected person, on average, infects exactly one other person, meaning the infection will remain stable in the population without significant growth or decline.
- If R_0<1: Each infected person, on average, infects fewer than one person, meaning the disease will likely die out in the population over time.

Most conventional SIR and SEIR models assume that the rate at which an individual has infectious contacts is constant in time and the proportion of infectious individuals in the population depends on infection prevalence [3]. To calculate the frequency of individuals in each compartment at time (t), three simple ordinary differential equations (ODEs) are used, shown below in Figure 1. In Figure 1, the SIR model structure has been used as a baseline model structure, but the schematic has been extended to illustrate how vaccination, importations of infection, births/deaths and immunity from maternal antibodies could be accounted for.

Several considerations need to be made to include vaccination in an SIR model structure. Conceptually, modelling *all-or-nothing* and *leaky* vaccines involves simulating different ways that a vaccine affects the population, either by fully protecting a proportion of vaccinated individuals or partially reducing susceptibility to the disease or infection in all vaccinated individuals. In an all-or-nothing model, a vaccine either fully protects some individuals or provides no protection at all to others. This means that a proportion of vaccinated individuals is completely immune (not susceptible to infection or disease), while the remaining proportion is just as susceptible as unvaccinated individuals [4]. In a leaky model, a vaccine reduces the probability of infection or disease severity for all vaccinated individuals rather than fully protecting a proportion of the population. In this case, all vaccinated individuals remain susceptible, but the risk of infection or disease is reduced compared to unvaccinated individuals [4].

OPV provides protection against infection and can reduce transmission of the virus in the population by inducing mucosal immunity. Therefore, OPV behaves as an all-or-nothing vaccine that protects individuals from both infection and disease and indirectly reduces transmission in the population through viral shedding. Similarly, MCV provides strong protection against both infection and disease and is also considered an all-or-nothing vaccine.

In Figure 1, the 'M' compartment reflects protection from maternal antibodies. Maternal antibodies are antibodies that are passed from mother to child, either through the placenta during pregnancy or via breastfeeding. These antibodies provide temporary immunity to newborns against certain infections, giving them some degree of protection during the early months of life before their immune system is fully developed or before they can be vaccinated. The duration of this protection varies depending on the disease and the type of antibodies transferred. Over time, however, these antibodies wane, and the child becomes fully susceptible to infection, unless they are vaccinated. Because MCV is typically administered between 9-12 months of age, protection from maternal antibodies is crucial in shielding infants from infection in the early months of life before they are eligible for vaccination. Therefore, in an SIR model for measles, it is important to include an 'M' compartment to accurately model the period during which infants are protected by maternal antibodies. OPV is administered much earlier (6 weeks to 2 months of age) reducing the dependence on maternal antibodies for protection. Consequently, in an SIR model for polio, inclusion of maternal antibodies is less important because early vaccination provides more timely protection.

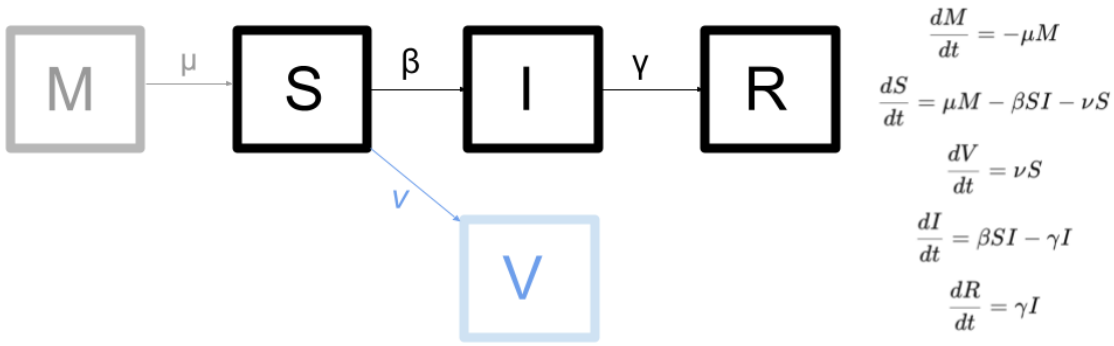

Figure 1. SIR transmission model. *The model compartments shown here are for an SIR model and are accompanied by the rates at which individuals move through the compartments once infected. Individuals start in the M compartment (protected by maternal antibodies), and after their immunity wanes (arrow from M to S), they become susceptible. The rate at which susceptible individuals move into the vaccinated compartment is proportional to the number of susceptible individuals and the vaccination rate v, reflecting an all-or-nothing vaccine.*

Beyond model structure, it is important to note that such models can be either stochastic or deterministic in nature. Deterministic models assume that disease dynamics are fully predictable and governed by fixed parameters and initial conditions. The outcomes of deterministic model simulations are determined entirely by the input parameters, and if the model is run multiple times with the same initial conditions, the results will always be the same. Deterministic models can be less computationally exhaustive, but they do not account for randomness or variability, which can be important in real-world settings. Stochastic models incorporate randomness or probability into model predictions and simulate individual-level events, such as infections or recoveries, that occur

probabilistically based on rates (e.g., a certain probability that one person will infect another in a given time period). Stochastic model outcomes vary between runs, even if the starting conditions are the same [5].

In this methods section, I highlight three strengths and limitations of using mathematical models for vaccine impact estimates and I explain how I address each strength and limitation in the subsequent research chapters.

2.1.1 Strengths

1. *Models can be used in the absence of real-world data*
    a. Transmission models can be useful in projecting the propagation of disease dynamics in the future, or modelling events that have not necessarily occurred [6]. Models can also help to explain disease dynamics in the absence of pharmaceutical therapeutics, or interventions, such as vaccination.
    b. For example, this is the case in Chapter 3. I constructed a model to simulate polio transmission dynamics given an importation of WPV1 into Africa. In this chapter, using a transmission model allowed me to demonstrate risks and benefits under different polio vaccination strategies given a 'hypothetical' importation event that poses public health risk, but has not necessarily occurred in some geographies.
2. *Models can be used to decide between different vaccination policies*
    a. Deciding between different vaccination policies can be challenging as a delicate balance between preventing disease and the costs associated with disease prevention needs to be considered. Models allow for risks and benefits of different vaccination scenarios to be compared alongside, ahead of real-world implementation.
    b. This strength was highlighted in both Chapters 3 and 4, where recommendations for future polio and measles SIAs were made based on model simulations of risks and benefits of different strategies.

2.1.2 Limitations

1. *Models can be overly complex and rely on assumptions*
    a. Parameters, such as the rates described above in Figure 1, can be informed by the natural history of a disease, but often the natural history of disease can vary by individual or geographical location, or in the case of polio, can also depend on hygiene

[7]. Consequently, model assumptions can result in varying accuracy of model outputs.

b. Advancements in computational techniques and computational capacity for disease modelling has improved over the years, but also allows for construction of very large and complex models [8]. Validating overly complex models can be challenging.

c. Uncertainties in underlying model assumptions should not be overlooked and to ameliorate the effect of these assumptions, my subsequent research chapters are explicit about the inherent limitations in the models used.

2. *"All models are wrong, but some are useful"*

   a. This aphorism coined by George Box, encapsulates the pros and cons of using modelling to inform decision making. There is weight in the first part of his statement about all models being wrong. It is impossible to accurately predict all human interactions and behaviours – people do not always act in rational ways, which in turn can affect disease dynamics.

   b. While assumptions are made in modelling that, in theory, should account for the uncertainties of human behaviour and natural disease progression, there will implicitly be elements of models that are not entirely accurate.

   c. Communicating these uncertainties through sensitivity analyses, where model outputs are evaluated using different parameter assumptions, is one way to address model limitations. My research chapters that use mathematical modelling include many sensitivity analyses to evaluate model outputs under alternative parameter assumptions. For example, later in chapter 3, I conduct sensitivity analyses for the following parameters: WPV1 importation rate, basic reproductive number (R_0), SIA coverage, vaccine wastage, costs of pSIAs and oSIAs and cost discounting assumptions.

3. *Models can elicit scepticism and criticism from the public, stakeholders and policymakers*

   a. Because of the first two limitations described, communicating the outputs and implications of mathematical models to the public, stakeholders and policymakers can be challenging.

   b. To bridge the gap between model outputs and vaccine policy, measles and polio stakeholders were involved in model conceptualisation, analysis of outputs and communication of results in both projects featured in Chapters 3-4. For Chapter 3 specifically, polio stakeholders were involved in an iterative process of model

refinement and validation that spanned several years and results were presented to global decision-making task teams that implement polio vaccine interventions.

c. During and alongside this PhD, I was also involved in mathematical modelling and qualitative stakeholder engagement for the newly licenced chikungunya vaccine. I used the Evidence to Recommendation framework for vaccine introduction to guide this research and learned about the applicability of this criterion to inform vaccine decision-making across a range of diseases. As part of my continued academic pathway, I learned how to communicate mathematical models and model outputs to stakeholders and further engaged in conversations around models being used to inform vaccine policy. An example of this stakeholder engagement can be read in Appendix section 7.1.1.

2.2 Evaluating vaccination strategies

2.2.1 Defining vaccine impact

Vaccine impact can estimate disease burden averted by vaccination by calendar year, birth year and year of vaccination [9]. In this PhD, I estimate vaccine impact by comparing the number of cases, deaths and disability-adjusted life years (DALYs) associated with measles infection in the same population for the counterfactual vaccination scenarios in comparison to a baseline strategy (such as no vaccination).

2.2.2 Effectiveness vs. efficiency

The effectiveness of a vaccine refers to the protection provided by immunisation and considers both direct (vaccine-induced) and indirect (population-related) protection. The effectiveness of a vaccine depends on vaccination coverage, alongside other factors that may affect the target population. In this PhD, efficiency addresses the number of individuals that need to be vaccinated to control a disease, i.e., measles. There are several ways to measure the efficiency of vaccination. In this PhD, I use two metrics to measure vaccine efficiency: (1) the incremental number of doses needed to vaccinate (NNV) to prevent an additional measles case and (2) the ability of a vaccination strategy to keep the size of the susceptible population of children younger than five years below the size of the birth cohort. The latter is a rule of thumb that has been used historically in measles vaccination programming.

NNV is considered a measure of efficiency in the context of vaccination programs, as it helps quantify the effectiveness and efficiency of a vaccine in preventing disease in a population. A lower NNV means fewer vaccinations are required to prevent a case, making the vaccination program more resource efficient. High NNV values suggest that many vaccinations are required to prevent a single case, which may be less efficient in terms of cost or logistics.

2.2.3 Economic models and checklists

Using health economics is another way to evaluate vaccination strategies. Economic evaluation involves comparisons of alternative vaccination approaches in terms of both costs and health outcomes. According to the WHO Guide for Standardization of Economic Evaluations of Immunization Programmes, several economic models are typically deployed for economic evaluation of childhood vaccination [10], including:

- Cost-minimization analysis (CMA): used to assess two or more interventions with identical health outcomes
- Cost-effectiveness analysis (CEA): used to compare different interventions or scenarios and usually considers the additional cost of providing a health care intervention in relation to additional health benefits [9]. Health outcomes are measured in natural health units (cases averted, deaths averted, life-years gained)
- Cost-utility analysis (CUA): reflects preferences for one intervention over another and often expresses the different outcomes in terms of quality-adjusted life years (QALYs) and DALYs.
- Cost-benefit analysis (CBA): converts programme benefits in all forms into a monetary value for comparison to show the broader benefits of an intervention (e.g. human capital or labour market), however, expressing health outcomes in monetary terms is controversial.

In Chapter 3, I use a CEA because I aim to compare vaccination strategies with different frequencies of preventative SIAs to a baseline strategy that relies only on RI and outbreak response. I consider the additional costs of SIAs in relation to the additional health benefits, specifically cases of paralytic polio averted. I adhered to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 framework for my CEA [11]. Next, I outline the components of the CHEERS checklist and provide commentary on why certain checklist items are pertinent to polio economic modelling.

2.2.3.1 CHEERS Checklist

The CHEERs checklist is integral to using economic models in decision making. The reporting guidelines ensure that economic evaluations follow a specific format and are transparent in assumptions made

and methods followed. The checklist includes the following items: title, abstract, background and objectives, health economic analysis plan, study population, setting and location, comparators, perspective, time horizon, discount rate, measurement and valuation of outcomes, valuation of resources and costs, currency, rationale of model, analytics and assumptions, heterogeneity, uncertainties, public engagement, study parameters, main results, findings, and generalisability [10].

The entire CHEERs checklist (used in Chapter 3) is included in Appendix pp 238-239, but here I choose to highlight several checklist items that strongly influence polio economic evaluations, specifically, (1) perspective(s), (2) time horizon, (3) comparators, and (4) heterogeneity.

- *Perspectives*:
    - This refers to the view or perspective adopted for the health economic analyses. Or, who pays for the intervention and accounts for the DALYs incurred? Some examples of perspectives include payer, health system, funder, global or societal perspectives.
    - For polio, the perspective adopted for an economic analysis in an LMIC can greatly influence the findings and conclusions—the health system in many LMICs at risk of a poliovirus outbreak typically incurs the costs associated with paralytic polio cases, but the GPEI often funds vaccination interventions, such as outbreak response and pSIAs. Also, the governments of LMICs typically receive financial support from GAVI (Global Alliance for Vaccines and Immunization) in the form of reduced costs on certain polio vaccine doses [12]. So, one would need to consider both the health system and funder perspectives to make recommendations on polio vaccination strategies.
    - These financing patterns are greatly shifted in high income countries, however. In high income countries, the governments pay for their own polio vaccine doses administered via RI, but given a low perceived risk of polio outbreaks, high income countries usually do not fund pSIAs. This keeps polio budgets relatively low in comparison to other health expenditures. However, high income countries that donate money towards international development funds, and in turn support global polio eradication efforts in other at-risk LMICs, also have a stake in financing of polio eradication activities.
    - The global perspective is equally important to consider in polio economic evaluations, as just one case of poliovirus can threaten eradication. From the global perspective, investing in preventative polio vaccination results in a greater probability of polio elimination and eradication, but still requires justification in a pragmatic environment of finite resources. These motivations align with the game theoretic approach

proposed by Barret et al. such that global eradication only succeeds if the country with the weakest elimination programme is successful, and that success depends on mutual assurance [13]. Many non-endemic countries in sub-Saharan Africa have an incentive to maintain elimination of polio, but domestic funding is limited and GPEI is left to support the budget gaps in polio programming. Well-resourced countries that have eliminated polio have an incentive to financially support or incentivise less resourced endemic countries to eliminate polio to realise the full potential of their investments already made, and therefore financially support GPEI.

- *Time horizon*:
    - The current GPEI strategic plan 2022-2026 has set out to eradicate polio by 2026, although this timeline has been revised several times since the WHA's initial commitment to eradicate polio in 1988. If all vaccination is assumed to stop once polio eradication has been achieved, economic analyses need to consider a longer time horizon to account for the costs saved by halting vaccination. However, to address shorter term financial needs and budget expenditures, a shorter time horizon may be appropriate. In Chapter 3, I model a five-year time horizon, in line with the current GPEI strategic plan to demonstrate imminent costs and benefits of different vaccination strategies.
- *Comparators*:
    - Comparators refers to the health interventions being compared in an economic analysis. In many economic analyses for vaccination, the baseline strategy is 'no vaccination', as was done in Chapter 4 for estimating measles vaccine impact. This is an important CHEERS checklist item for polio because the baseline strategy for polio vaccination may differ from other diseases. For example, even just one polio case triggers an outbreak response [14], therefore it is sensible if the baseline strategy against which other vaccination strategies are compared accounts for baseline RI plus outbreak response (if an outbreak were to occur), not 'no vaccination.' If a longer time horizon is considered for polio eradication cost-effectiveness, the baseline comparator may be 'no vaccination'. So, the appropriate comparators also depend on the selected time-horizon.
- *Heterogeneity*:
    - Heterogeneity in the CHEERS checklist refers to differential health outcomes in different subgroups of the target population or in different geographical areas. For polio, heterogeneity can affect vaccination coverage, transmission of virus and

exposure to infection. If subnational geographies within a country have different vaccination coverage levels, immunity against poliovirus may also vary. This is an important consideration for economic analyses as it may affect the costs of interventions in different regions. The analysis in Chapter 3 assumes a homogenous population, and whist the limitations of this approach are outlined in the discussion, this was a sensible assumption due to existing knowledge gaps on subnational polio SIA coverage.

2.3 Tying it all together

This is an interdisciplinary PhD, with methodological approaches ranging from epidemiology, and mathematical modelling to health economics and statistics. Each subsequent research chapter includes in-depth explanations of specific methods used to answer the objectives of this PhD. Despite the interdisciplinary approaches used in this PhD, all methods tie together with the fundamental aim of evaluating vaccination strategies for measles and polio: Chapter 3 uses mathematical modelling and economic evaluation for polio vaccination strategies, Chapter 4 uses mathematical modelling and vaccine impact estimates for measles vaccine evaluation, and Chapter 5 uses epidemiological and statistical analyses to evaluate VPDVs, seeded by vaccination.

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3. Chapter 3: Vaccination strategies against wild poliomyelitis in polio-free settings: outbreak risk modelling study and cost-effectiveness analysis

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3.1 Research paper cover sheet

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RESEARCH PAPER COVER SHEET

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SECTION A – Student Details

Student ID Number	1604063	**Title**	Ms
First Name(s)	Megan		
Surname/Family Name	Auzenbergs		
Thesis Title	Mathematical and statistical modelling to inform polio and measles vaccination programming		
Primary Supervisor	Dr. Kathleen M O'Reilly & Dr. Kaja Abbas		

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

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	BMJ Global Health
Please list the paper's authors in the intended authorship order:	Megan Auzenbergs, Kaja Abbas, Arend Voorman, Corey M Peak, Mark Jit, Kathleen M O'Reilly
Stage of publication	Peer-reviewed, with editor

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I worked on: conceptualisation, methodology, formal analysis, visualisation, and writing - original draft

SECTION E

Student Signature	[redacted]
Date	30 May 2024

Supervisor Signature	[redacted]
Date	31 May 2024

3.2 Bridging section

This paper was peer-reviewed in *BMJ Global Health* in June 2024. This research evaluates the risk of outbreaks and associated costs with differing frequencies of pSIAs for a LMIC in sub-Saharan Africa where polio is not endemic, but there is a risk of WPV1 importation. pSIAs increase population immunity and prevent outbreaks but are also costly interventions. Consequently, many countries in sub-Saharan Africa have not conducted a pSIA in several years. Do these countries have high enough levels of RI coverage to prevent an outbreak given an importation of WPV1? This work estimates removal of pSIAs in countries with RI coverage <67% would have high risk of outbreaks following a WPV1 importation, however, in countries where RI coverage is >67%, reducing the frequency of pSIAs could still maintain a low risk of large outbreaks. Further, this work adopts several perspectives for economic outputs: health system, GPEI and a combined health system and GPEI perspective. From all perspectives, annual and biennial pSIAs are cost-saving and avert disability adjusted life years (DALYs) when RI coverage is low, but above 67% RI coverage, pSIAs become less cost-effective. These findings are extremely timely given current timelines for polio eradication and the GPEI strategic plan. The outputs from this research are being used as a guide to plan pSIAs ahead of bOPV cessation in consequential geographies at high risk of poliovirus outbreaks.

This work was conducted entirely on my own. I developed the underlying model, coded all vaccination strategies, validated, processed and analysed all model outputs, conducted the cost-effectiveness analysis, and wrote up the final manuscript. I received input from the GPEI Strategic Group of Modellers and GPEI colleagues based at the BMGF throughout the research process and presented this work at GPEI stakeholder meetings and the Institute for Disease Modelling symposium in 2023.

3.3 Abstract and author summary

3.3.1 Abstract

The 2021 importation of wild poliovirus serotype 1 (WPV1) into Malawi with subsequent international spread represented the first WPV1 cases in Africa since 2016. Preventing importations and spread of WPV1 is critical, and dependent on population immunity provided through routine immunisation (RI) and supplementary immunisation activities (SIAs). We aim to estimate outbreak risk and costs given an importation of WPV1 for non-endemic countries in the WHO AFRO region. We developed a stochastic mathematical model of polio transmission dynamics to evaluate the probability of an outbreak, expected number of poliomyelitis cases, costs, and incremental cost-effectiveness ratios under different vaccination strategies. Across variable RI coverage, we explore three key strategies:

RI+outbreak SIAs (oSIAs), RI+oSIAs+annual preventative SIAs (pSIAs), and RI+oSIAs+biennial pSIAs. Results are presented in 2023 USD over a five-year time horizon from the Global Polio Eradication Initiative (GPEI) and health system perspectives. The annual pSIA strategy has the greatest probability of no outbreaks in comparison to other strategies: under our model assumptions, annual pSIAs result in 80% probability of no outbreaks when routine immunisation coverage ≥50%. The biennial pSIA strategy requires RI coverage ≥65% to achieve equivalent risk of no outbreaks. The strategy with no pSIAs requires ≥75% RI coverage to achieve equivalent risk of no outbreaks. For the health system, when RI coverage is between 35-60%, both pSIA strategies are cost-saving. For the GPEI, below 65% RI pSIA strategies are cost-effective, but the biennial pSIA strategy incurs higher costs in comparison to annual pSIAs due to more oSIAs. Prioritisation of pSIAs must balance outbreak risk against implementation costs, ideally favouring the smallest manageable outbreak risk compatible with elimination. We infer that there are few short-term risks due to population immunity from RI, but without pSIAs, long-term risks accumulate and can result in outbreaks with potential for international spread.

3.3.2 Author summary

While previous modelling analyses have deemed polio eradication cost-effective, they were conducted under prior polio eradication timelines and/or modelled only trivalent oral polio vaccine (tOPV) since they were conducted before the switch from trivalent to bivalent OPV in 2016. There are current concerns of WPV1 importation in Africa that impact future planning and funding of polio vaccination activities. We simulate WPV1 importations in our model and estimate outbreak risk and costs for non-endemic countries in the WHO AFRO region. At low levels of RI coverage, pSIAs are cost-effective in reducing the probability and size of an outbreak following an importation of WPV1. To achieve low probability of a WPV1 outbreak, RI coverage and the frequency of pSIAs should be increased. If high levels of RI coverage have been maintained overtime, even in the absence of pSIAs, a country can remain at low risk of an outbreak following a WPV1 importation. Our study inferences can be mapped to different geographies in the WHO AFRO region to infer varying levels of outbreak risk from WPV1 importations. Without preventive supplementary immunisation activities, if routine immunisation coverage is above 70–80%, the risk of polio outbreaks is considerably less and a feasible and cost-effective approach for many non-polio endemic LMICs in sub-Saharan Africa.

3.4. Introduction

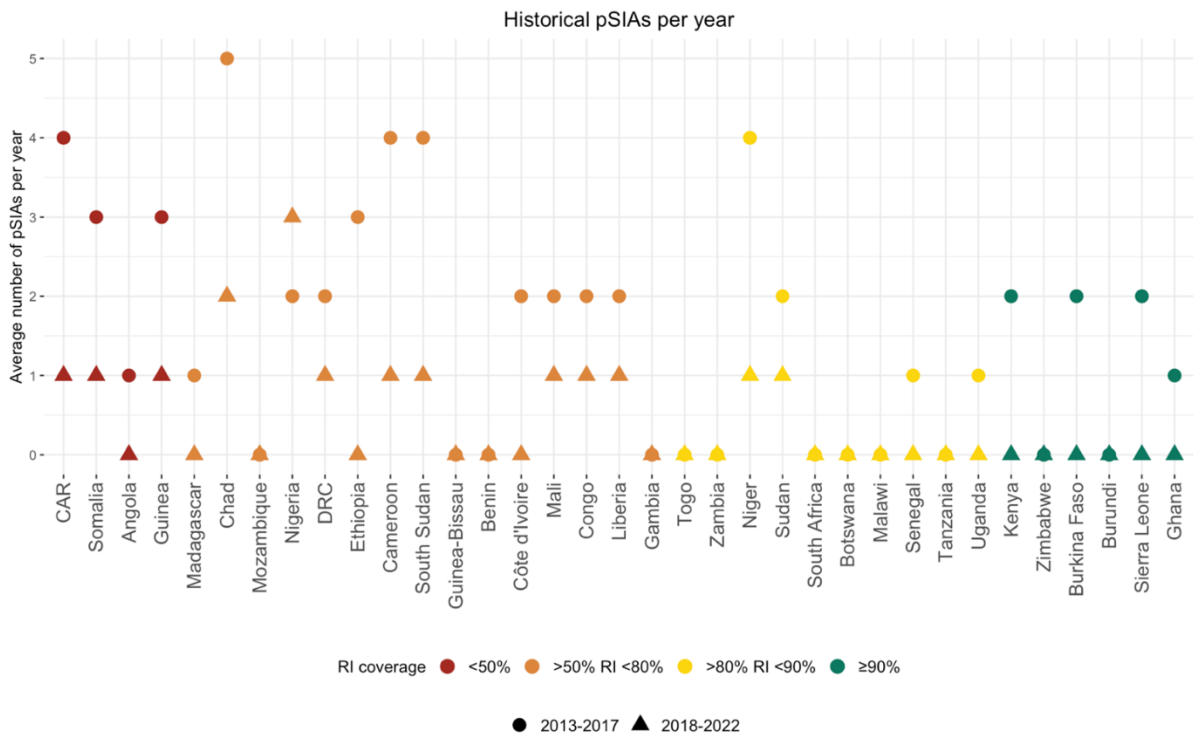
In 2019, the African Region was certified free from endogenous transmission of wild poliovirus (WPV), with the last clinical case reported in Nigeria in August 2016 [1]. However, in late 2021 and early 2022, Malawi and Mozambique reported WPV serotype 1 (WPV1) cases, respectively, linked to ongoing circulation in Pakistan [2]. The geographic distribution and genetic linkage of these WPV1 cases suggest missed transmission of an unknown geographic extent [2]. These WPV1 cases highlight the importance of ensuring high and homogeneous levels of population immunity despite decreasing global incidence and elimination in the African continent.

Poliovirus infection typically initiates in the gut, and approximately one in every 200 infections of serotype 1 may go on to infect the central nervous system and the spinal cord, resulting in paralytic disease known as poliomyelitis, or polio. Since 2016, the recommended routine immunisation schedule is with bivalent oral polio vaccine (bOPV) and at least 1 dose of the inactivated polio vaccine (IPV). OPV induces mucosal immunity and protects against infection (and transmission), whilst IPV only protects against poliomyelitis and does not induce mucosal immunity. OPV is integral to eradication as it prevents infection and transmission. However, variable routine immunisation (RI) coverage leads to differential population immunity across countries.

The Global Polio Eradication Initiative (GPEI) is responsible for the coordination of activities to support polio eradication. The activities include surveillance for acute flaccid paralysis (AFP) which includes poliomyelitis and other infectious and non-infectious causes, environmental surveillance for poliovirus, and providing polio vaccinations through both supplementary immunisation activities (SIAs) and RI (through the Expanded Programme for Immunisation). SIAs typically aim to vaccinate all children under five years old, including those hard-to-reach children otherwise missed by RI. Despite an annual expenditure of around one billion USD, decision makers within polio eradication often must make complex decisions in allocating resources amid decreases in the global budget [3]. Alongside, the frequency of preventative supplementary immunisation activities (pSIAs) has decreased in almost all countries in Africa since 2017 (Figure 1) [4].

Figure 1. Historical pSIAs and RI coverage in African countries. (A) Mean number of pSIAs per year from 2013–2017 and 2018–2022 and (B) year of last pSIA and WUENIC estimates of Diphtheria Tetanus Toxoid and Pertussis vaccine third dose (DTP3) coverage, an indicator of vaccination via RI as the DTP vaccine is administered concurrently with OPV in the routine immunisation series. Preventative SIAs were defined as either a national or subnational immunisation day (NID, SNID) with bOPV (or tOPV pre-2016) and did not occur within 365 days after a WPV1 or VDPV1 detection, to distinguish historic pSIAs from oSIAs. Any SIAs that occurred within 365 days of a WPV1 or VDPV1 outbreak were not included in the pSIA count. Country selection represents low, lower middle and upper middle-income sub-Saharan African countries. CAR = Central African Republic; DRC = Democratic Republic of the Congo.

A



B

Country	DTP3 coverage 2022	Year of last pSIA
RI coverage <50%		
CAR	42%	2021
Somalia	42%	2021
Angola	42%	2018
Guinea	47%	2021
>50% RI coverage <80%		
Madagascar	57%	2019
Chad	60%	2021
Mozambique	61%	2011
Nigeria	62%	2021
DRC	65%	2021
Ethiopia	65%	2021
Cameroon	68%	2021
South Sudan	73%	2021
Guinea-Bissau	74%	2018
Benin	76%	2007
Côte d'Ivoire	76%	2018
Benin	76%	2018
Mali	77%	2019
Congo	78%	2021
Liberia	78%	2019
Gambia	79%	2014
>80% RI coverage <90%		
Togo	82%	2014
Zambia	82%	2009
Niger	84%	2019
Sudan	84%	2019
South Africa	85%	2010
Botswana	86%	2004
Malawi	86%	2010
Senegal	88%	2016
Tanzania	88%	2010
Uganda	89%	2019
≥90% RI coverage		
Kenya	90%	2019
Zimbabwe	90%	2007
Burkina Faso	91%	2016
Burundi	91%	2011
Sierra Leone	91%	2019
Ghana	99%	2015

The GPEI annual budget exists of contributions from donors and is used to support the GPEI's objectives. This budget is divided into pSIAs and outbreak response, and additional budget lines (not considered further in this study). Outbreak response includes outbreak response SIAs (oSIAs), whilst pSIAs are planned to prevent outbreaks in polio-free settings and raise population immunity in at-risk areas to stop transmission. Operationally, pSIAs and oSIAs differ both in the target populations for vaccination as well as the funding and planning for activities – oSIAs must be implemented soon after outbreak detection and require more resources for rapid mobilisation. pSIAs are planned well ahead of implementation and are less costly because logistics do not require rapid mobilisation, but as their need is not always acute, this can result in de-prioritisation.

Since the World Health Assembly's 1988 resolution to eradicate polio by the year 2000, economic analyses have informed strategies to progress towards this goal [5-7]. However, few studies distinguish between pSIAs and oSIAs, which is important because they have different strategic goals and funding approaches. Furthermore, of the economic analyses that include modelling of different vaccination strategies, several assume eradication will have already occurred [6, 8], include limited geographies [6, 9], or model populations where WPV1 is endemic [10]. One economic analysis that considers the cost-effectiveness of operational decisions for pSIAs and oSIAs does not consider importations of WPV1 [11]. Therefore, we provide a modelling approach for low-and-middle income countries (LMICs) in sub-Saharan Africa to compare strategies of differing frequencies of pSIAs to identify at what levels of RI the risks of outbreaks and polio cases may outweigh the associated costs of implementing pSIAs, given the risk of WPV1 importations. In this study, we consider only the risks of WPV1 outbreaks in a polio-free settings that are representative of LMICs in sub-Saharan Africa. This is an evidence gap identified by stakeholders involved in OPV cessation planning that is important to address as we approach the final stages of WPV1 transmission [12].

3.5 Methods

We evaluated different vaccination strategies for a hypothetical population of 8 million children under five years of age, reflecting a mean population size across twenty-five LMICs in sub-Saharan Africa (Appendix pp 218-219). Model outputs from each strategy include probability of an outbreak, estimated cases of paralytic poliomyelitis and vaccine associated paralytic polio (VAPP), number of outbreaks and disability-adjusted life years (DALYs). The Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) reporting guidance was used in the development of this analysis [13], Appendix pp 238-239.

3.5.1 Vaccination strategies

We explored three vaccination strategies (Table 1). We assume that vaccination via RI follows a sequential immunisation schedule that includes 3 doses of bOPV given orally and 1 dose IPV administered intramuscularly or subcutaneously.

***Table 1. Polio vaccination strategies**. The target population for SIAs is children missed by RI. For example, both pSIAs and oSIAs vaccinate 25% of the population of children missed by RI. RI = Routine Immunisation, oSIA = outbreak response supplementary immunisation activity, pSIA = preventative supplementary immunisation activity. An outbreak response was only conducted if a simulation had at least 1 case of paralytic polio. Additional assumptions for R_0, SIA target populations and importation rate are explored in sensitivity analyses (Appendix pp 233-235).*

Vaccination strategy	**RI coverage levels modelled**	**oSIA** ***% of target population vaccinated***	**pSIA** ***% of target population vaccinated***	**pSIA frequency**	**R_0**	**WPV1 importations**
Baseline strategy	25%–100% in 5% increments	25%	no pSIAs	No pSIAs	3	2 per year
Annual pSIA strategy	25%–100% in 5% increments	25%	25%	Annual		
Biennial pSIA strategy	25%–100% in 5% increments	25%	25%	Every 2 years		

In all strategies, we define an outbreak as at least one case of paralytic polio. An oSIA is conducted in all simulations where at least one case was detected within any 90-day interval, in line with standard operating procedures [14]. oSIAs continue until all cases are stopped over the five-year time horizon. We do not account for case detections through environmental surveillance in this analysis. We assume that all SIAs reach 25% of children missed by RI, as prior evidence suggests that SIA coverage varies across locations and analysis with higher coverage assumptions for zero-dose children resulted in unrealistically high population immunity when compared to empirical data [15]. A sensitivity analysis of different SIA assumptions is on Appendix p 233.

3.5.2 Model structure

We developed a stochastic SIR model to simulate polio transmission dynamics, whereby infectious individuals develop either asymptomatic or symptomatic infection, both of which are assumed to be infectious. We specify vaccine induced immunity based on OPV and IPV doses. In the model, children under the age of 5 years are either susceptible, fully vaccinated and protected from poliovirus infection, or have received an incomplete vaccination series (less than 3 bOPV doses + 1 IPV dose). Each subsequent dose of vaccine corresponds to additional protection and an opportunity for a child to seroconvert and be considered fully protected from infection (Appendix pp 213-215).

Whilst bOPV also has protective effects against poliovirus serotype 3, we only consider the vaccine's protective effects for serotype 1 for this analysis due to the greater risk of WPV1 given recent importations. Outbreaks of circulating vaccine-derived poliovirus (cVDPV) serotype 2 require alternative vaccines and assumptions and are therefore beyond the scope of this analysis. cVDPV serotypes 1 and 3 are also outside of the scope of this analysis due to the specific mechanisms of emergence.

3.5.3 Model assumptions

The modelled time horizon is five years, in line with the current GPEI strategic plan 2022-2026 where a central aim is to interrupt all WPV transmission in the coming years [16]. R_0 is the basic reproductive number and estimates the expected number of secondary poliovirus infections in an immunologically naïve population. We have used an R_0 of 3, supported by data driven work exploring variable R_0 values in a non-endemic setting in Africa for children under five years of age [17] and higher R_0 assumptions were explored in sensitivity analysis (Appendix p 234). The proportion of children vaccinated with one dose of IPV is assumed to be equal to the third dose of bOPV RI coverage, in line with the joint assessment of immunization coverage by UNICEF and WHO (WUENIC) data [18] (Appendix p 218).

We assume a randomly mixed population of children under five with no heterogeneity in the probability of a child being vaccinated in an SIA or in transmission of poliovirus. Data shows a low mean age of wild poliomyelitis infections with under-5s accounting for more than 80% of cases in non-endemic settings [19]. Older children and adults are thought to play a minor role in WPV transmission (with a few notable exceptions) [15, 19], therefore, we focus only on children under five for this analysis. Simulations were run for 50 years before virus introduction allowing for historical pSIAs, then one infection was introduced into the population at the start of the simulation and further WPV1 importations were assumed to occur at a Poisson distributed rate of two importations per year.

Different importation rates and seasonality are addressed in a sensitivity analysis (Appendix p 235). The models were repeated for 10,000 stochastic simulations and run using the R package SimInf in R version 4.2.2 [20].

3.5.4 Outbreak probability

The probability of an outbreak was calculated using the proportion of stochastic simulations that resulted in at least one paralytic polio case (i.e., a polio AFP case) following an importation of WPV1. This definition is not directly comparable to the WHO criteria for elimination status [21] but is useful for understanding outbreak risk. For example, the WHO criteria for elimination refers to the reduction to zero of the incidence of infection caused by a poliovirus in a defined area [21].

3.5.5 DALYs

DALYs were calculated assuming that in LMICs, the mean discounted lifetime DALYs associated with one paralytic poliomyelitis case, with no age-weighting, is 14 DALYs per paralytic case [5], assuming that one in 200 infections leads to irreversible paralysis and among those paralysed, 5–10% die when respiratory muscles become paralysed [22] and long-term mortality is approximately 20% higher in paralytic polio cases than the general population [23]. The proportional contribution of YLD (years lost to disability) and YLL (years of life lost due to premature mortality) assuming a mean of 14 DALYs per case is 60% YLDs in addition to 40% YLLs per case [24]. After importation of infection, we assume no further international transmission during outbreaks for calculations of DALYs.

3.5.6 Health and economic outcomes

Incremental costs and DALYs averted were used to estimate incremental cost-effectiveness ratios (ICERs) under each pSIA strategy, calculated as follows:

$$ICER = \frac{(costs\ of\ pSIA\ strategy - costs\ of\ baseline\ strategy)}{(DALYs\ averted\ by\ pSIA\ strategy)}$$

We compare the ICER to three thresholds determined by Pichon-Riviere et al. 2023 [25] representing the lowest, median and highest cost-effectiveness thresholds among the sub-Saharan African countries used in the sample size calculation (appendix pp 218-219). We used a 3% discount rate for costs and 0% for health with no age-weighting [26], with other discounting assumptions explored on Appendix p 229. We do not include indirect costs of vaccination, such as opportunity costs of time spent for vaccination.

3.5.7 Perspectives

Incremental costs are analysed from both the GPEI and health system perspectives and a combined perspective for both the health system and GPEI. The GPEI perspective is valuable for strategic planning and future programming as well for domestic health systems in their overall polio programming activities. For discounting, costs are calculated annually for each model simulation and then aggregated over all simulations and the 5-year time horizon.

The total costs for the health system perspective are calculated as follows:

*(Cost per AFP case * AFP cases) +*

*(Cost per VAPP case * VAPP cases) +*

*(RI coverage * (Newborns eligible for bOPV vaccination* total doses received per child) * (Cost per dose of bOPV + RI delivery cost per dose of bOPV) * (1 + (bOPV wastage rate for RI / (1 – bOPV wastage rate for RI)))*

The total costs for the GPEI perspective are calculated as follows:

*(SIA coverage * (Target population[†] * Number of pSIAs) * (Cost per dose of bOPV + pSIA delivery cost per dose of bOPV) * (1 + bOPV wastage rate for SIAs)) +*

*(SIA coverage * (Target population[†] * Number of oSIAs) * (Cost per dose of bOPV + oSIA delivery cost per dose of bOPV) * (1 + (bOPV wastage rate for SIAs / (1 – bOPV wastage rate for SIAs))) +*

*(RI Coverage * (Newborns eligible for IPV vaccination) * (Cost per dose of IPV + RI delivery cost per dose of IPV) * (1 + (bOPV wastage rate for RI / (1 – bOPV wastage rate for RI)))*

[†] Target population for pSIAs and oSIAs refers to all children under five years of age

3.5.8 Vaccine costs

Vaccine costs per dose for bOPV and IPV in Gavi supported countries were obtained from the latest UNICEF update in 2023 USD, with a mean cost of $0.18 and $2.00, respectively [27, 28] and costs associated with RI (administration, procurement and storage) were obtained from previous research [29], Appendix pp 220. All costs have been adjusted to 2023 USD. The main analysis assumes 10%

wastage for OPV in SIAs, 13% wastage for OPV in RI and 13% for IPV [30, 31]. Further wastage assumptions are on Appendix p 230.

3.5.9 SIA data and costs

The Polio Information System (POLIS) was used to obtain SIA data from 2013–2022 and further analysis was done to distinguish pSIAs from oSIAs (Appendix p 210). The cost per child for pSIAs and oSIAs was obtained from GPEI data (Appendix p 236) and ranged from USD2023 $0.28 - $1.12 for pSIAs and USD2023 $0.22 – 2.79 for oSIAs. We assume oSIAs cost twice the cost of a pSIA and explore a range of proportional costs between pSIAs and oSIAs (Appendix pp 231). The stochasticity of outbreaks, which affects total estimated costs, is variable and contributes to the variability in expected costs across all strategies (Appendix p 222).

3.5.10 Adverse events

The expected risk of adverse events, such as VAPP in countries using OPV is 1 case of VAPP per 0.9 million doses of bOPV administered and declines with subsequent doses [32]. A VAPP case was considered equivalent to a case of wild-acquired paralytic polio for calculation of the expected costs of VAPP and DALYs.

3.5.11 Ethics

Ethical approval for this project was received from the London School of Hygiene and Tropical Medicine, project ID 15873.

3.5.12 Patient and public involvement

Patients were not involved in this research.

3.6 Results

Across all simulations, the mean expected number of WPV1 cases over five years is greatest in the baseline strategy and least in the annual pSIA strategy (Figure 2A). The annual pSIA strategy is the strategy under which the fewest number of outbreaks occur across all RI coverage levels. Under the base case assumptions (including R_0 and proportion of zero dose children reached by SIAs) annual pSIAs achieve and maintain >80% probability of no outbreaks when baseline RI coverage is 50% (Figure 2B). The biennial pSIA strategy achieves >80% probability of no outbreaks when RI is above 65% and the baseline strategy requires ≥75% RI coverage to achieve >80% probability of no outbreaks.

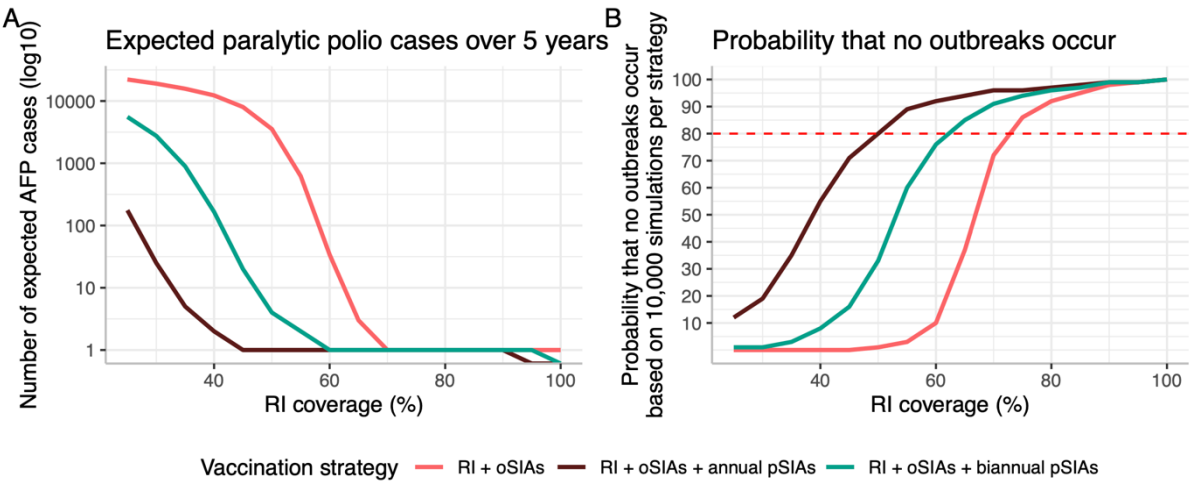


Figure 2. Estimated number of paralytic polio cases and probability that no outbreaks occur over five years. (A) number of expected paralytic polio cases (presenting as a polio AFP case). The solid line represents the mean estimate of 10,000 simulations, and (B) probability of no outbreaks occurring across all vaccination strategies. Outbreak probability was based on 10,000 simulations per vaccination strategy. The red dashed line corresponds to 80% probability that no outbreaks occur.

The annual pSIA strategy had the greatest expected VAPP cases over five years, since it was the strategy with the greatest number of vaccine doses administered and resulted in the fewest expected WPV1 cases over five-years. Estimated costs are shown in Figure 3 and Appendix pp 225-227. Calculating herd immunity as $(1 - 1/R_0)$, when RI coverage is below 66.6%, the point when herd immunity is achieved in this simple homogenously mixed model, total costs from all perspectives are highest in the baseline strategy. Above the herd immunity threshold, costs for the health system perspective are comparable across all strategies, due to fewer paralytic cases and increase with increasing RI coverage. From the GPEI perspective, from 25-40% RI coverage, costs are highest in the biennial pSIA strategy, driven by more oSIAs than the annual pSIA strategy. When RI coverage is 45-60%, the baseline strategy has the greatest costs due to a greater number of oSIAs required to stop outbreaks. When RI coverage exceeds the herd immunity threshold, costs are highest in the annual pSIA strategy due to the high costs associated with annual campaigns and increase with increasing RI coverage. From the combined health system and GPEI perspective, below the herd immunity

threshold, costs are highest in the baseline strategy, due to the large number of AFP cases. Above the herd immunity threshold, the annual pSIA strategy becomes the costliest strategy.

Figure 3. Health system and GPEI estimated total costs over five years. The size of the circle is proportional to the mean number of expected paralytic polio cases across all model simulations. The solid circles correspond to >80% probability the strategy had no outbreaks over a five-year period.

For the health system (Figure 4A and Table 2), when RI coverage is below 66.6%, both pSIA strategies are cost-saving at the country-level upper, median and lower bounds (see Appendix p 237 for further explanation of the quadrants of a cost-effectiveness plane). At 65% RI and above, no DALYs are averted by either pSIA strategy, instead more DALYs are incurred with pSIAs due to VAPP, hence the negative ICERs. From the GPEI perspective, when RI is 25-30% the ICERs for annual pSIAs are USD$15 and USD$7 per DALY averted, but then the strategy becomes cost-saving between 30-60% RI (Figure 4B and Table 3). For biennial SIAs, the strategy is more costly when RI coverage is 25-40% and cost-saving from 45-60% RI coverage. When the health system and GPEI perspectives are combined, both pSIA strategies are cost-saving when RI coverage is below the herd immunity threshold (Figure 4C and Table 4). When RI coverage approaches 66.6%, the point when herd immunity is achieved, the ICERs for all perspectives (Tables 2-4) are negative for both annual and biennial pSIAs due to increased VAPP cases in comparison to the baseline strategy. However, even if the pSIA strategies are not cost-effective at >66.6% RI coverage and present challenges for VAPP, both pSIA strategies continue to avert outbreaks as RI coverage increases, which is important as a single outbreak under any vaccination strategy has implications for global polio eradication (Appendix p 228).

Table 5 outlines implications for decision making. When RI coverage falls below 50%, the annual pSIA strategy averts many cases, so removal of pSIAs entirely would create substantial risk. Countries with 50–90% RI coverage have a higher probability of no outbreaks occurring. However, the risk of an outbreak is not removed entirely until the probability of no outbreaks reaches 100% (when WPV1 transmission is interrupted globally). All strategies require >95% coverage for 100% probability that no outbreaks occur, however, above 80% RI coverage, outbreak probability is low and, if an outbreak does occur, the expected number of cases is low.

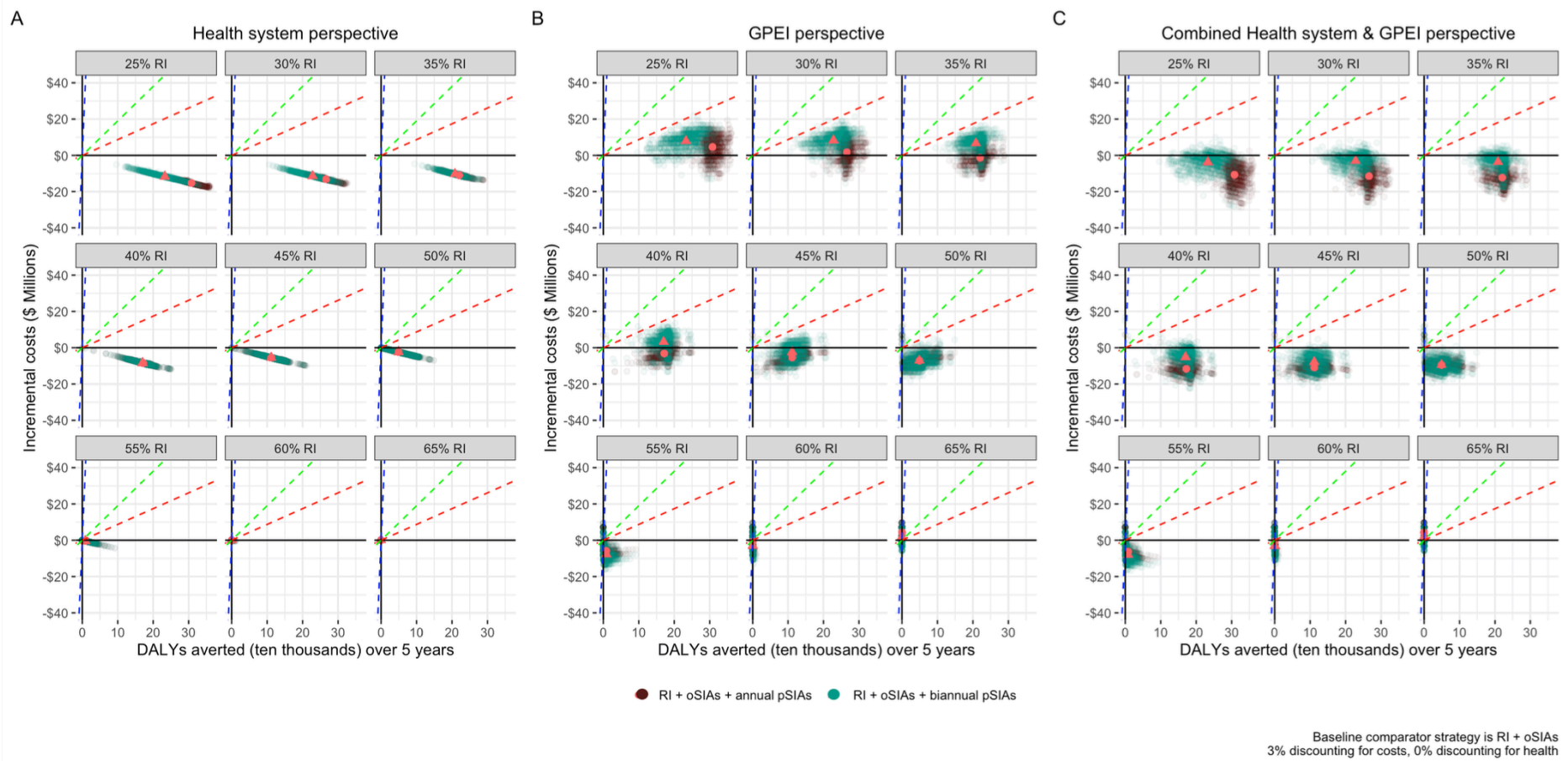


Figure 4. Cost-effectiveness planes for the annual and biennial pSIA vaccination strategies. Incremental costs and DALYs averted under the annual pSIA (RI+oSIAs+annual pSIAs) and biennial pSIA (RI+oSIAs+Biennial pSIAs) strategies are compared to the baseline strategy (RI+oSIAs). The pink circle is the mean estimate for the annual pSIA strategy and the pink triangle is the mean estimate for the biennial pSIA strategy. Each individual model simulation is represented as a single dot. The dashed lines represent three cost-effectiveness thresholds (representing the lowest (red=Democratic Republic of the Congo), median (green=Benin) and highest (blue=South Africa) country thresholds) among low, lower middle and upper middle-income sub-Saharan African countries.

Table 2. Health system perspective - DALYs averted and differential costs between each pSIA strategy and the baseline strategy. *Interpretation of the ICERs is provided in the commentary column. Negative ICERs are usually cost saving, but >65%, negative ICERs are due to VAPP.*

RI coverage	pSIA strategy	DALYs averted	Cost difference	ICER	Commentary
25	Annual pSIAs	307907	-15311684	-50	Cost saving
30	Annual pSIAs	265881	-11656192	-50	
35	Annual pSIAs	220350	-13204856	-50	
40	Annual pSIAs	171969	-11384118	-50	
45	Annual pSIAs	111684	-10904822	-49	
50	Annual pSIAs	49157	-10327265	-50	
55	Annual pSIAs	8172	-8492658	-49	
60	Annual pSIAs	185	-8392864	-49	
65	Annual pSIAs	-237	-5487803	-49	No DALYs averted, instead more DALYs incurred with pSIAs due to VAPP, hence the negative ICER
70	Annual pSIAs	-287	-5480087	-49	
75	Annual pSIAs	-309	-2392834	-49	
80	Annual pSIAs	-327	-2394881	-49	
85	Annual pSIAs	-345	-392734	-48	
90	Annual pSIAs	-362	-396638	-48	
95	Annual pSIAs	-379	-8804	-48	
100	Annual pSIAs	-397	-13386	-47	
25	Biennial pSIAs	232850	11382	-48	Cost saving
30	Biennial pSIAs	228148	6353	-49	
35	Biennial pSIAs	208311	13775	-48	
40	Biennial pSIAs	169876	8351	-49	
45	Biennial pSIAs	111523	14832	-48	
50	Biennial pSIAs	49200	9052	-49	
55	Biennial pSIAs	8255	15716	-48	
60	Biennial pSIAs	283	9594	-48	
65	Biennial pSIAs	-130	16560	-48	No DALYs averted, instead more DALYs incurred with pSIAs due to VAPP, hence the negative ICER
70	Biennial pSIAs	-172	10095	-49	
75	Biennial pSIAs	-186	17387	-48	
80	Biennial pSIAs	-198	10584	-49	
85	Biennial pSIAs	-208	18204	-48	
90	Biennial pSIAs	-218	11065	-49	
95	Biennial pSIAs	-228	19053	-48	
100	Biennial pSIAs	-238	11569	-49	

Table 3. GPEI perspective - DALYs averted and differential costs between each pSIA strategy and the baseline strategy. *Interpretation of the ICERs is provided in the commentary column. When RI coverage is 25 and 30% for the annual pSIA strategy, the strategies are more costly than the baseline because the baseline strategy results in explosive outbreaks that deplete susceptibles, resulting in the pSIA strategy requiring more total pSIAs throughout the time horizon.*

RI coverage	pSIA strategy	DALYs averted	Cost difference	ICER	Commentary
25	Annual pSIAs	307907	4668615	15	More costly
30	Annual pSIAs	265881	1792608	7	
35	Annual pSIAs	220350	-1312169	-6	Cost saving
40	Annual pSIAs	171969	-3140650	-18	
45	Annual pSIAs	111684	-5392966	-48	
50	Annual pSIAs	49157	-7111413	-145	
55	Annual pSIAs	8172	-5878933	-719	
60	Annual pSIAs	185	-681367	-3683	
65	Annual pSIAs	-237	4331306	-18276	No DALYs averted, instead more DALYs incurred with pSIAs due to VAPP, hence the negative ICER
70	Annual pSIAs	-287	6416874	-22358	
75	Annual pSIAs	-309	6888407	-22293	
80	Annual pSIAs	-327	7022112	-21474	
85	Annual pSIAs	-345	7095951	-20568	
90	Annual pSIAs	-362	7127935	-19690	
95	Annual pSIAs	-379	7127872	-18807	
100	Annual pSIAs	-397	7157937	-18030	
25	Biennial pSIAs	232850	7945495	34	More costly
30	Biennial pSIAs	228148	8352947	37	
35	Biennial pSIAs	208311	6679133	32	
40	Biennial pSIAs	169876	3259477	19	
45	Biennial pSIAs	111523	-2327649	-21	Cost saving
50	Biennial pSIAs	49200	-7150458	-145	
55	Biennial pSIAs	8255	-7643058	-926	
60	Biennial pSIAs	283	-3049671	-10776	
65	Biennial pSIAs	-130	1713497	-13181	No DALYs averted, instead more DALYs incurred with pSIAs due to VAPP, hence the negative ICER
70	Biennial pSIAs	-172	3650380	-21223	
75	Biennial pSIAs	-186	4067384	-21868	
80	Biennial pSIAs	-198	4203660	-21231	
85	Biennial pSIAs	-208	4252305	-20444	
90	Biennial pSIAs	-218	4277093	-19620	
95	Biennial pSIAs	-228	4274782	-18749	
100	Biennial pSIAs	-238	4294966	-18046	

Table 4. Combined health system and GPEI perspective - DALYs averted and differential costs between each pSIA strategy and the baseline strategy. *Interpretation of the ICERs is provided in the commentary column.*

RI coverage	pSIA strategy	DALYs averted	Cost difference	ICER	Commentary
25	Annual pSIAs	307907	-10643069	-35	Cost saving
30	Annual pSIAs	265881	-11412248	-43	
35	Annual pSIAs	220350	-12216992	-55	
40	Annual pSIAs	171969	-11633308	-68	
45	Annual pSIAs	111684	-10880769	-97	
50	Annual pSIAs	49157	-9504247	-193	
55	Annual pSIAs	8172	-6271667	-767	
60	Annual pSIAs	185	-690171	-3731	
65	Annual pSIAs	-237	4342688	-18324	No DALYs averted, instead more DALYs incurred with pSIAs due to VAPP, hence the negative ICER
70	Annual pSIAs	-287	6430649	-22406	
75	Annual pSIAs	-309	6903240	-22341	
80	Annual pSIAs	-327	7037828	-21522	
85	Annual pSIAs	-345	7112511	-20616	
90	Annual pSIAs	-362	7145322	-19738	
95	Annual pSIAs	-379	7146075	-18855	
100	Annual pSIAs	-397	7176991	-18078	
25	Biennial pSIAs	232850	-3710697	-16	Cost saving
30	Biennial pSIAs	228148	-3031171	-13	
35	Biennial pSIAs	208311	-3648131	-18	
40	Biennial pSIAs	169876	-5133387	-30	
45	Biennial pSIAs	111523	-7807735	-70	
50	Biennial pSIAs	49200	-9545339	-194	
55	Biennial pSIAs	8255	-8039696	-974	
60	Biennial pSIAs	283	-3063057	-10824	
65	Biennial pSIAs	-130	1719850	-13230	No DALYs averted, instead more DALYs incurred with pSIAs due to VAPP, hence the negative ICER
70	Biennial pSIAs	-172	3658730	-21272	
75	Biennial pSIAs	-186	4076436	-21916	
80	Biennial pSIAs	-198	4213253	-21279	
85	Biennial pSIAs	-208	4262400	-20492	
90	Biennial pSIAs	-218	4287677	-19668	
95	Biennial pSIAs	-228	4285847	-18798	
100	Biennial pSIAs	-238	4306535	-18095	

Table 5. Policy implications of polio vaccination strategies. *Expected paralytic polio cases are conditional means amongst simulations that resulted in at least one case. DALYs and outbreaks averted are mean and median values across all model simulations, respectively. The probability of no outbreaks occurring is obtained from the proportion of model simulations (out of 10,000 simulations) that resulted in zero paralytic cases. For outbreaks averted, the comparator is the baseline strategy with no pSIAs. The raw data used to create this table, alongside data for additional RI coverage levels is in Appendix pp 225-227. IQR = Interquartile Range.*

RI coverage	Estimated risk with annual pSIAs‡	Estimated risk with Biennial pSIAs‡	Estimated risk relying on oSIAs only‡	Outbreaks averted by annual pSIAs	Outbreaks averted by Biennial pSIAs	Implications for decision making
	Mean‡ polio cases if an outbreak occurs (95% CI) (Probability no outbreaks occur, from 10,000 simulations)			Median (IQR)		
35%	3 (3—4) (35%)	401 (368—434) (3%)	9,191 (8,834—9,547) (0%)	3 (2—4)	-1 (-2—0)	pSIA removal would have high risks and consequences
50%	1 (1—1) (80%)	3 (3—3) (33%)	1,611 (2,526—1697) (1%)	6 (5—6)	5 (3—6)	Removal of pSIAs altogether could lead to a high risk of outbreaks in subsequent years
55%	1 (1—1) (89%)	2 (1—2) (60%)	289 (263—315) (3%)	5 (5—6)	5 (4—6)	
60%	1 (1—1) (92%)	1 (1—1) (76%)	20 (17—23) (11%)	4 (2—4)	3 (2—4)	
65%	1 (1—1) (94%)	1 (1—1) (85%)	3 (2—3) (37%)	1 (0—2)	1 (0—2)	
70%	1 (1—1) (96%)	1 (1—1) (91%)	1 (1—1) (72%)	0 (0—1)	0 (0—1)	Reducing the frequency of pSIAs could still maintain a low risk of large outbreaks
80%	1 (1—1) (97%)	1 (1—1) (96%)	1 (1—1) (92%)	NA	NA	
90%	1 (1—1) (99%)	1 (1—1) (99%)	1 (1—1) (98%)	NA	NA	
100%	0 (0—0) (100%)	0 (0—0) (100%)	1 (1—1) (100%)	NA	NA	Even if pSIAs are removed, there is low to no risk of outbreaks

3.7 Discussion

The key messages of our study include: (i) with higher RI, the probability of outbreaks reduces considerably – under our model assumptions, outbreak size and risk are minimal when RI is above 66.6%; (ii) pSIAs of any frequency avert DALYs and are cost-saving for the combined GPEI and health system perspective below 66.6% RI; (iii) a strategy with only RI and oSIAs implicitly accepts some level of outbreak risk, but if RI is above 70–80%, the risk of outbreaks is considerably less than in other settings where RI is below 70%, which may be a feasible and cost-effective approach for many non-polio endemic LMICs in sub-Saharan Africa.

Our results are generalisable to different geographies. Using the modelled population size as a guide alongside national RI coverage and historical pSIA schedules, many geographies can be mapped to table 5. For countries with population sizes smaller or larger than our modelled population, model estimates can be scaled up or down.

Further, below 66.6% RI both pSIA strategies are cost-effective and avert a substantial number of DALYS, outweighing the increased number of expected VAPP cases. Countries such as Madagascar or Angola where 55% and 42% of the population under five years, respectively, are vaccinated with three or more DTP doses, have many subpopulations that could benefit from regular pSIAs. In Ghana and Sierra Leone, for example, future SIAs would not seem necessary as routine immunisation coverage of three doses of bOPV and 1 dose IPV exceeds 90% without reliance on historic pSIAs, unless there are subpopulations with substantially lower coverage. The proportion of the population in Malawi that has received three doses of bOPV peaked in 2011, but has been unstable since, falling to 83% in 2016 [18], with no historic reliance on pSIAs.

Our study has implications for global polio eradication decision making and health policy. Decisions on vaccination strategies should consider the combined perspective of the health system and GPEI rather than relying solely on one perspective. Despite the high costs and increased VAPP, reduced outbreak probability under annual pSIAs is an important consideration for polio eradication. Should the GPEI adopt an annual pSIA strategy irrespective of estimated RI and importations? Annual pSIAs that include all children under five in LMICs in sub-Saharan Africa would consume most of the GPEI annual budget for activities and would be an inefficient use of funds, potentially reducing funds for other activities (surveillance, vaccination against other serotypes). However, prioritising pSIAs in countries with low RI and perceived risk of introductions is a necessary compromise to which GPEI already adheres, and here we provide a framework to support decision making. Renewed

commitment by donors was requested in 2022 [33] considering the 2022–2026 Strategic Plan, and these commitments remain essential to resource the activities needed to meet the objectives of polio eradication, including interrupting WPV transmission.

Our study has limitations. The main results assume a R_0 of 3 in a homogenous population (both with respect to transmission and population immunity), two imported infections per year and SIAs reaching 25% of children missed by RI. If SIAs reach up to 50% of zero-dose children, the impact of SIAs on reducing outbreak risk is further increased, consequently, for the same costs a better outcome is achieved (Appendix p 233). Assuming a higher R_0 and increasing the frequency of importations would also increase the outbreak risk (Appendix pp 234-235). One of the most uncertain inputs of the analysis is importation rate: as poliovirus infection is typically asymptomatic this is not directly observable, and due to the changing epidemiology of polio globally, the importation rate will vary in time. We have not considered population heterogeneity. If there are pockets of the population with higher rates of transmission and/or lower vaccination coverage, then the probability of an outbreak occurring would increase. We only model children under five given the limited but uncertain extent to which older children and adults contribute to WPV transmission, which may under-estimate total expected cases. Research suggests no evidence of imperfect intestinal immunity in adults and older children in the transmission of WPV across different locations, which supports our modelled target population [15], but in the future, more research is needed to better understand context specific transmission by older ages.

While we have used cost-effectiveness thresholds based on the growth in life expectancy and health expenditures [25] alternative thresholds based on health opportunity costs could be further explored [34-36]. We do not consider the costs of further delaying the eradication timeline through outbreaks, or the societal implications of outbreaks on polio eradication, both of which may further emphasise the need to implement pSIAs even when the outbreak risks are small. We also do not include the impact of joint SIAs that might deliver other interventions or vaccines alongside OPV, as these joint campaigns occur less frequently and are programmed differently than polio specific SIAs. By limiting our analysis to a five-year time horizon, we underestimate the benefits of SIAs (particularly pSIAs) as they will increase the likelihood of eradication, meaning that control efforts after eradication can be scaled back. However, this time-horizon was chosen to specifically align with the current GPEI strategic plan for imminent programming decisions. Further, the pSIA health system costs only consider the geographical remit stated in the model and ignores the potential for further international spread.

International spread would be far more likely with larger outbreaks, consequently the health system costs are under-estimated.

From the global perspective, investing in pSIAs results in a greater probability of polio elimination, but still require justification in a pragmatic environment of finite resources. These motivations align with the game theoretic approach proposed by Barret et al. such that global eradication only succeeds if the country with the weakest elimination programme is successful, and that success depends on mutual assurance [37]. Many non-endemic countries in sub-Saharan Africa have an incentive to maintain elimination of polio, but domestic funding is limited and GPEI supports the budget gaps in polio programming [37]. Well-resourced countries that have eliminated polio have an incentive to financially support or incentivise less resourced endemic countries to eliminate polio to realise the full potential of their investments already made, and therefore financially support GPEI.

In conclusion, we assessed the outbreak risk and cost-effectiveness of different vaccination strategies and critically assessed the risks associated with adopting different strategies given baseline RI coverage. Decisions made solely based on fixed budget, cost-effectiveness or burden reduction may not fully capture all consequences or benefits associated with adopting a particular vaccination strategy. Urgently, as importations of WPV1 remain a threat to the AFRO region, this analysis serves as a valuable tool to estimate risk and plan vaccination activities across a range of settings at risk of importation of WPV1 cases.

3.7.1 Contributors

MA and KMOR conceptualised the study. MA curated the data, conducted the modelling analysis, prepared visualisations of results and wrote the original draft. MA, KMOR and KA independently validated the underlying data in this study and all results. MA, KA, AV, CMP, MJ and KMOR contributed to reviewing results and editing of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors read and approved the final version of the manuscript. The authors alone are responsible for the views expressed in this article and they do not necessarily present the decisions, policy or views of their affiliated organisations.

3.7.2 Data sharing

Simulation code used in the analysis and sample model outputs are publicly available at: https://github.com/mauzenbergs/polio_econ.

3.7.3 Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

3.7.4 Declaration of interests

We declare no conflicts of interest.

3.7.5 Acknowledgements

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4. Chapter 4: Health effects of routine measles vaccination and supplementary immunisation activities in 14 high-burden countries: a Dynamic Measles Immunization Calculation Engine (DynaMICE) modelling study.

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4.1 Research paper cover sheet

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Thesis Title	Mathematical and statistical modelling to inform polio and measles vaccination programming		
Primary Supervisor	Dr. Kathleen M O'Reilly & Dr. Kaja Abbas		

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SECTION E

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4.2 Bridging section

This paper was published in *The Lancet Global Health* in August 2023 following peer-review. The paper evaluates incremental measles cases, deaths and DALYs averted due to different vaccination strategies in 14 high-burden countries. It also measures the effectiveness and efficiency of these vaccination strategies. As many countries rebuild their health systems after the COVID-19 pandemic, quantifying the incremental effects of different vaccination strategies that have historically been implemented is useful. Equally, understanding the incremental effects and efficiency of each strategy can be used to minimise measles burden and maximise the reach of vaccines to children who are unvaccinated and under-vaccinated.

The DynaMICE model used in this analysis was previously developed at LSHTM and is routinely used to evaluate measles burden and measles vaccine impact across a range of projects. Alongside this PhD, I also used the DynaMICE model to produce annual vaccine impact estimates for the Vaccine Impact Modelling Consortium (VIMC). Like most research in academia, this project was a team effort and required good communication and project management skills. Dr. Han Fu is a postdoc who continually validates and improves this in-house model. I initiated the overall approach of this project and developed an analysis plan, then, I collaborated with Dr. Han Fu to use the DynaMICE model. Together, we refined the methodologies used in this paper, but we had different roles and responsibilities throughout the analysis. Dr. Han Fu was responsible for editing the model code and running model simulations. I conducted the literature review to identify evidence gaps, determined which high-burden countries should be modelled, decided on the vaccination strategies for comparison, and wrote the public health implications for efficiency and effectiveness of the vaccination strategies. Alongside the wider study team, Dr. Han Fu and I both contributed to data analysis, interpretation of model outputs, data visualisation and write-up. I identified how measures of effectiveness and efficiency can be used to inform future decision making for measles SIAs, demonstrating my ability to use complex models to answer pressing vaccination policy questions. I also leveraged lessons learned from working on polio to explore trade-offs between RI and SIAs for measles.

4.3 Abstract and author summary

4.3.1 Abstract

Most countries worldwide use routine services to offer a first dose of measles-containing vaccine (MCV1) and later, a second dose of measles-containing vaccine (MCV2). Many countries worldwide conduct supplementary immunisation activities (SIAs), offering vaccination to all people in a specific

age range irrespective of previous vaccination history. We aimed to estimate the relative effects of each dose and delivery route in 14 countries with high measles burden. We used an age-structured compartmental dynamic model, the Dynamic Measles Immunization Calculation Engine (DynaMICE), to assess the effects of different vaccination strategies on measles susceptibility and burden during 2000–20 in 14 countries with high measles incidence (containing 53% of the global birth cohort and 78% of the global measles burden). Country-specific routine MCV1 and MCV2 coverage data during 1980–2020 were obtained from the WHO and UNICEF Estimates of National Immunization Coverage database for all modelled countries and SIA data were obtained from the WHO summary of measles and rubella SIAs. We estimated the incremental health effects of different vaccination strategies using prevented cases of measles and deaths from measles and their efficiency using the incremental number needed to vaccinate (NNV) to prevent an additional measles case. We found that SIAs resulted in larger incremental effects but were less efficient than vaccination strategies with only MCV1 and MCV2.

4.3.2 Author summary

This work demonstrates the impact of vaccination on measles cases, deaths and DALYs from 2000-2020. Compared with no vaccination, MCV1 implementation was estimated to have prevented 824 million cases of measles and 9.6 million deaths from measles, with a median NNV of 1.41 (IQR 1.35–1.44). Adding routine MCV2 to MCV1 was estimated to have prevented 108 million cases and 404 270 deaths, whereas adding SIAs to MCV1 was estimated to have prevented 256 million cases and 4.4 million deaths. Despite larger incremental effects, adding SIAs to MCV1 (median incremental NNV 6.02, 5.30–7.68) showed reduced efficiency compared with adding routine MCV2 (5.41, IQR 4.76–6.11). Vaccination strategies, including non-selective SIAs, reach a greater proportion of children who are unvaccinated and reduce measles burden more than MCV2 alone, but efficiency is lower because of the wide age range targeted by SIAs. This analysis provides information to help improve the health effects and efficiency of measles vaccination strategies. The interplay between MCV1, MCV2, and SIAs should be considered when planning future measles vaccination strategies.

4.4. Introduction

Between 2000 and 2020, deaths from measles were estimated to have decreased by 94% globally [1], which was mostly achieved through routine immunisation and supplementary immunisation activities (SIAs) with measles-containing vaccines (MCVs) [2–5]. According to WHO, the first routine dose of measles-containing vaccine (MCV1) should be given during the first year of life, ideally at age 9 months or age 12 months. The second routine dose of measles-containing vaccine (MCV2) is recommended

to be given between age 15 months and 18 months. SIAs are vaccination campaigns that deliver vaccine doses using strategies other than via routine services and are usually non-selective (i.e., vaccination is offered irrespective of vaccination history). Throughout this chapter, the term SIA indicates non-selective SIAs.

Since the introduction of measles vaccination in high-income countries in the 1960s and in low-income and middle-income countries in the 1970s and 1980s, recommendations around measles vaccination strategies have been revised. Historically, low-income and middle-income countries relied on MCV1 with SIAs to interrupt transmission and reach children who were unvaccinated. In 2009, WHO recommended introducing MCV2 once a country reached 80% MCV1 coverage, retaining an emphasis on aiming for high coverage with MCV1 as soon as possible after a child loses antibodies from the birthing parent. In 2017, this recommendation was revised to state that countries should include MCV2 in routine immunisation schedules regardless of MCV1 coverage. Furthermore, operational support to strengthen routine immunisation infrastructure when incorporating MCV2 should be provided. Partly due to concerns about the sustainability of funding for nationwide, non-selective SIAs and their potential to disrupt routine services [6,7], WHO has proposed that such SIAs can be phased out once countries have more than 95% coverage of both routine doses [8].

The implementation of SIAs over time has been motivated by different goals and needs. SIAs were a major component of the measles elimination strategy implemented widely in the Americas in the 1990s, with high routine MCV1 coverage and occasional follow-up SIAs sustaining elimination since July 2015 [9,10]. In other regions, such as Africa and southeast Asia, SIAs have increased population immunity in countries with low MCV1 or MCV2 coverage. In these countries, SIAs have been a highly effective and equitable strategy for protecting hard-to-reach children who would otherwise be missed by routine immunisation [11,12], although the relative reach of SIAs versus routine immunisation varies between and within countries [13]. To prevent measles transmission and subsequent outbreaks, a commonly used criterion is that a follow-up SIA should be conducted before the cumulative number of susceptible children younger than 5 years approaches the size of a birth cohort (including the newborn population of a year) [14,15]. Historically, this criterion has been influential in informing the timing of SIAs so the number of susceptible children remains less than the size of one birth cohort and measles transmission can be interrupted, and elimination can be achieved [8]. In practice, even if countries recognise that a follow-up SIA is due and correctly identify the age groups with the highest prevalence of susceptibility, delays in obtaining funding or competing priorities, such as other pathogens, might lead to delayed implementation of an SIA or a narrower than ideal age

range targeted, which reduces the effects of the SIA [15]. Outbreak-response SIAs might then be needed, the effects of which depend on the speed of response, geographical extent, and coverage attained [16]. Many countries, therefore, have implemented a mixture of so-called preventive campaigns targeting various age groups at national or subnational levels and reactive campaigns that aim to shorten outbreaks.

In 2012, the World Health Assembly endorsed the Global Vaccine Action Plan, which included a commitment to achieving measles elimination in five of the six WHO regions by 2020. During 2000–10, estimated global MCV1 coverage increased from 72% to 84%, but has since stagnated. However, estimated routine MCV2 coverage has increased from 18% in 2000 to 70% in 2020 [17]. In this retrospective analysis of measles vaccination policies during 2000–20, we aimed to use the Dynamic Measles Immunization Calculation Engine (DynaMICE), a population-based dynamic model of measles transmission, to better understand the effects of different vaccination strategies that have been used in 14 high-burden countries.

4.5 Methods

4.5.1 Data sources

Reported measles cases, collected through the WHO and UNICEF Joint Reporting Form on Immunization, and estimated measles incidence data from the Institute for Health Metrics and Evaluation (IHME), were used to obtain separate rankings of countries by measles incidence from 2010 to 2019 [18,19] We included the ten countries with the highest incidence from each data source (Appendix p 242), which resulted in 14 countries being included in the analysis (i.e., India, Nigeria, Indonesia, Ethiopia, China, Philippines, Uganda, DR Congo, Pakistan, Angola, Madagascar, Ukraine, Malawi, and Somalia). These countries contained 53% of the global birth cohort and 78% of the global measles burden.

Country-specific routine MCV1 and MCV2 coverage data during 1980–2020 were obtained from the WHO and UNICEF Estimates of National Immunization Coverage (WUENIC) database for all modelled countries [20] and SIA data were obtained from the WHO summary of measles and rubella SIAs (Appendix pp 243–248) [21]. Year of MCV2 introduction varied between countries (Appendix p 242). We extracted the start and end dates of SIA implementation, targeted age group, and number of doses given during each SIA. Knowing whether the entire country was covered after phased or subnational SIAs was not always possible, so we calculated country-level coverage for each SIA by comparing

reported SIA doses with the national population in the target age range from World Population Prospects 2019 [22].

4.5.2 DynaMICE model

DynaMICE is an age-structured compartmental model of measles transmission that considers time-varying states of disease (i.e., maternally immune or immune from birthing parent, susceptible, infectious, or recovered) and vaccination (i.e., no doses, one dose, two doses, or three or more doses). The model has been used previously for estimating the effects of measles vaccination [2,7] and a description of the model structure, parameters, and equations has been published [23]. Using the DynaMICE model, we modelled country-level routine immunisation programmes on the basis of historical WUENIC coverage estimates for MCV1 and MCV2 [19] following nationally recommended schedules (Appendix p 242). We modelled each SIA according to the target age group and median date of implementation in each country in the WHO record (Appendix pp 243–248). We assumed that SIA doses are more likely to reach children who had been previously vaccinated by distributing doses randomly among the target population, except for a proportion who are less likely to be reached by current childhood vaccination programmes. This population who are less likely to be reached could only be covered by a campaign when all the other target populations have received an SIA dose. This proportion of children who are less likely to be reached was assumed to be 7.7% of the total country level population in each country on the basis of the population-weighted mean estimate for children aged 1 year who were missing all diphtheria–pertussis– tetanus, BCG, measles-containing, and polio vaccines in 92 low-income and middle-income countries during 2010–19 (Appendix p 252) [24]. In the DynaMICE model, MCV1 efficacy increases linearly by 1.49% per increased month of age, resulting in 78% efficacy for children aged 9 months and 82% efficacy for children aged 12 months [20,25]. MCV2 efficacy depends on the level of MCV1 protection (i.e., the proportion of vaccinated people who are effectively protected) received previously, and two-dose vaccine efficacy is capped at 98%.20,26 The basic reproduction number (R_0) of measles was 15.9 based on a summary estimate taken from endemic settings [27]. Country-dependent and age-dependent social-contact matrices [28] were used to inform the country-specific patterns of measles transmission. To include epidemic patterns since the global implementation of MCV, the model simulation began in 1980.

The coverage data and simulation code used for analysis can be accessed through GitHub (https://github.com/hfu915/dynamice_ph).

4.5.3 Measles vaccination strategies and effect estimates

Using the DynaMICE model, we assessed cases of measles and deaths from measles during 2000–20 across the following vaccination strategies: no vaccination; MCV1 alone; MCV1 and MCV2; MCV1 and SIAs; and MCV1, MCV2, and SIAs. We estimated deaths by multiplying the model estimates of cases of measles with age-specific, year-specific, and country-specific case-fatality ratios [29]; the model did not account for non-measles-specific vaccine effects on preventing deaths. We calculated the annual incidence of measles per 1 million population and compared the susceptible population of children younger than 5 years with the birth cohort, defined as the mid-year population aged 0–1 year, to understand the potential of different delivery strategies to reduce transmission and outbreaks. To estimate the incremental effects of historical measles vaccine strategies, each strategy was compared with a counterfactual strategy that was representative of a historical policy decision for measles vaccination. MCV1 was compared with the alternative of no vaccination, whereas the MCV1 and MCV2 strategy and the MCV1 and SIAs strategy were compared with MCV1 alone. The MCV1, MCV2 and SIAs strategy was compared with the counterfactual strategy of MCV1 and SIAs, as well as separately compared with the MCV1 and MCV2 strategy. Although the same comparator strategies were evaluated across countries, countries adopted varying policies, such as year of MCV2 introduction or frequency of SIAs. For each strategy, historical coverage data were used, and for each pair of comparisons we estimated the health effects of an additional delivery strategy by calculating the cumulative vaccine-prevented cases and deaths, and the efficiency of adding a delivery strategy by calculating the incremental number of doses needed to vaccinate (NNV) to prevent an additional measles case during 2000–20.

4.5.4 Sensitivity analysis

We modelled vaccine effects if MCV2 had been introduced in 2000 under fast or gradual roll-out (Appendix p 251). For each year during 2000–20, we assumed that the alternative MCV2 coverage was either 10% lower than the MCV1 coverage of each country or equal to the MCV2 coverage of each country in that year, whichever was larger. Moreover, we modelled two alternative assumptions about the likelihood of receipt of an SIA dose according to past vaccination history (Appendix p 255). In this sensitivity analysis, we defined the so-called zero-dose population as children receiving no MCV doses. One assumption is that SIA doses preferentially reach children who are already vaccinated and that any remaining doses after all children who are already vaccinated are reached are then given to children in the zero-dose population. However, the other assumption is that a strategy reaches children in the zero-dose population first, and the remaining doses are then given to children who are already vaccinated.

4.5.6 Role of the funding source

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

4.6 Results

Between the 14 analysed countries, there were notable differences in MCV1 and MCV2 coverage during 2000–20 (figure 1)—some countries had not introduced MCV2 as of 2020 (i.e., Uganda, Somalia, and DR Congo) or introduced MCV2 much later in time (i.e., Madagascar, Ethiopia, Nigeria, and Angola). Comparatively, some countries introduced MCV2 early and sustained high coverage (i.e., India, Pakistan, and China), whereas in others, MCV2 coverage fluctuated over time (i.e., Indonesia and Ukraine).

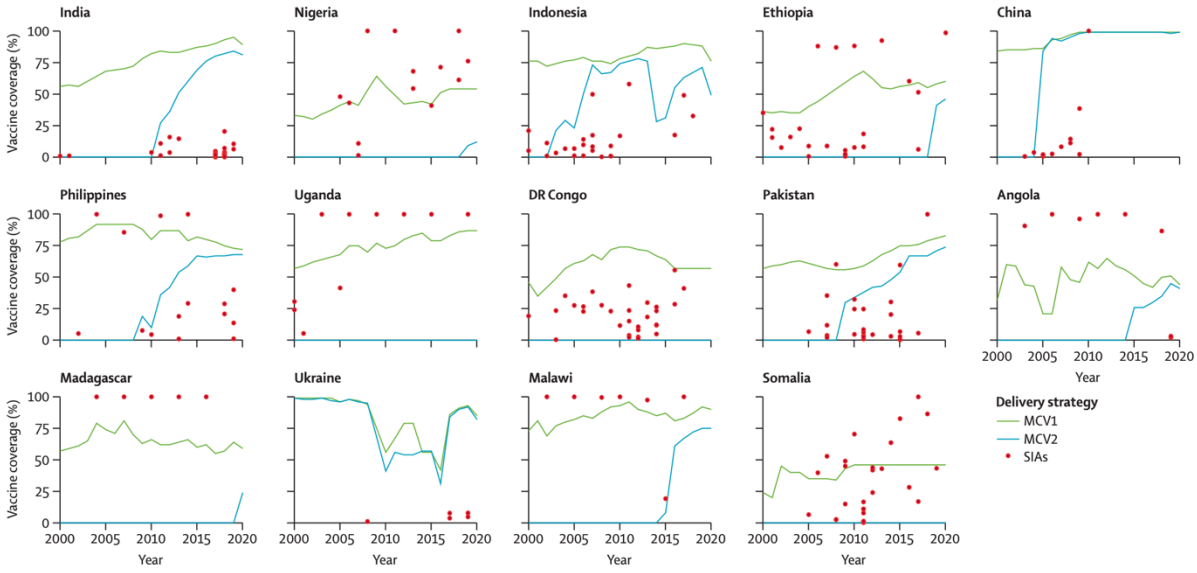

Figure 1. Immunisation coverage for MCV1, MCV2, and SIAs (2000–20)
SIA coverage was calculated from reported numbers of doses administered and national populations in the SIA target age group. As of 2020, Uganda, DR Congo, and Somalia had not implemented MCV2. Additional years of MCV2 introduction for other countries are available (Appendix p 242). MCV1=the first routine dose of measles-containing vaccine. MCV2=the second routine dose of measles-containing vaccine. SIA=supplementary immunisation activity.

Compared with the no vaccination strategy, measles incidence rates declined substantially in all 14 high-burden countries in strategies with MCV1 only (figure 2). In the strategy in which MCV1 and MCV2 were used without SIAs, the annual burden of measles declined slowly over time and endemic transmission continued. With MCV1 and SIAs, there was a more rapid decline in measles burden, but large-scale outbreaks were predicted (figure 2). The largest absolute burden reduction attributable to MCV1, MCV2, and SIAs in comparison with no vaccination during 2000–20 was in India, China, and

Nigeria (Appendix p 253), which are the countries with the highest global IHME measles incidence estimates and largest population sizes of the 14 analysed countries. There are several countries (i.e. Pakistan, Angola, Ukraine) where an SIA vaccination strategy can lead to a higher incidence than the no vaccination strategy (figure 2). Following a large outbreak or a large-scale, targeted SIA, the susceptible population could be 'cleared' by measles transmission or vaccination, which could affect a wider population and increase the population-level immunity. However, this protective effect may only last short term—if high levels of routine immunisation coverage are not sustained, the susceptible population will accumulate and later on lead to a large outbreak. Before the overshooting happened in the vaccination scenarios, there was neither intense transmission (following previous outbreaks or large-scale SIAs) nor high-coverage routine immunisation to boost population immunity and close the susceptibility gap, while in the no-vaccination scenario, there was persistent transmission to sustain the population immunity (recovery from infection) at a certain level.

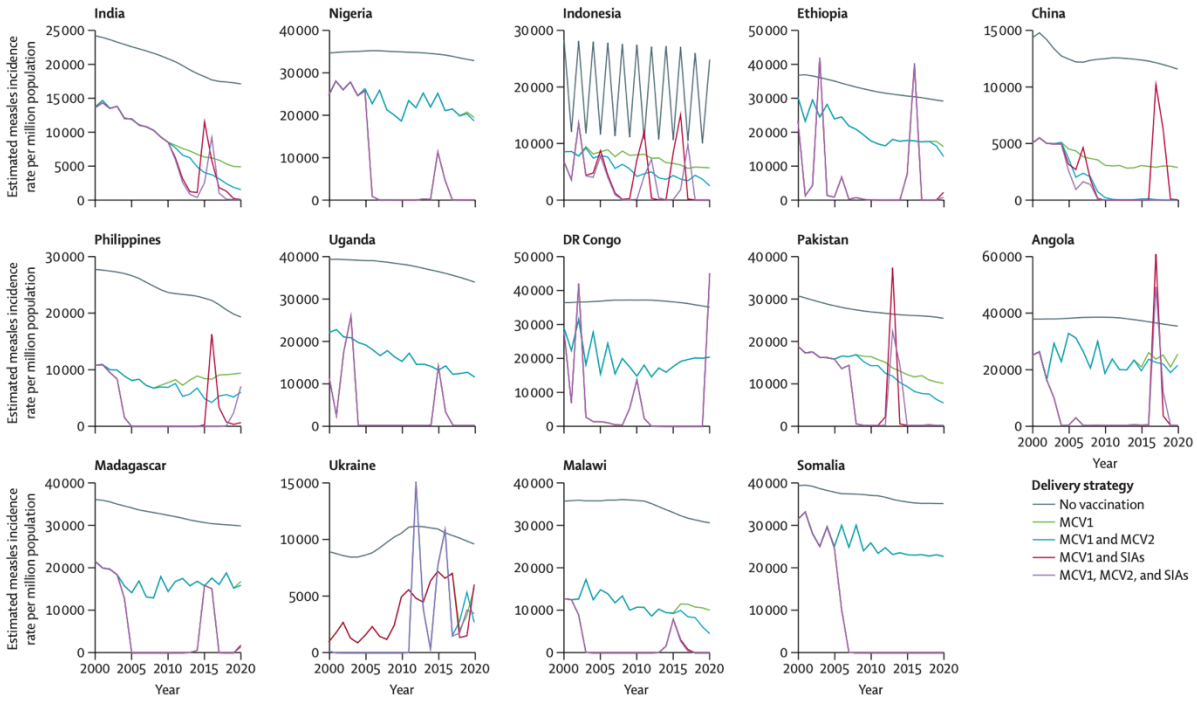

Figure 2. Estimated annual measles incidence rate per million population across different vaccination delivery strategies (2000–20)

Temporal trends in measles incidence rates vary by different vaccination delivery strategies; the measles burden decreases with additional vaccination delivery strategies. For countries that have not yet introduced MCV2 (i.e., Uganda, DR Congo, and Somalia), there are overlapping trends for incidence rates for the delivery strategies of MCV1 and MCV2 (blue lines) and MCV1 only (green lines) and the delivery strategies of MCV1, MCV2, and SIAs (purple lines) and MCV1 and SIAs (red lines). Overlapping trends are also seen in most analysed years in countries that introduced MCV2 after 2017 (i.e., Nigeria, Ethiopia, and Madagascar). In Indonesia, the fluctuations seen in the no vaccination strategy are the result of dynamic sizes of the susceptible population over time, jointly affected by measles seasonality, transmissibility (R_0), and the age-related contact structure. The incidence in the no vaccination strategy declines in time due to demographic transition. As the size of the aging population increases, children under 5 years of age, who are at a higher risk of measles infection, represent a smaller proportion of the total population, hence the decline in incidence over time per million population. MCV1=the first routine dose of measles-containing vaccine. MCV2=the second routine dose of measles-containing vaccine. SIA=supplementary immunisation activity.

Compared with no vaccination, we estimated that MCV1 alone prevented 824 million measles cases and 9.6 million deaths from measles during 2000–20 in the 14 countries (table 1; Appendix p 250). SIAs conducted in these countries were estimated to have prevented a further 256 million cases and 4.2 million deaths compared with MCV1 alone. MCV2, as used by these countries, was estimated to have prevented 108 million cases and 404 000 deaths compared with MCV1 alone. SIAs showed more effects on burden reduction than MCV2 when added to MCV1, as indicated by the increased number of prevented cases and deaths in all countries except China and Ukraine. Furthermore, the strategy of MCV1, MCV2, and SIAs was predicted to have incrementally averted 303 million cases and 4.4 million deaths compared with MCV1 alone.

Table 1. Estimated number of prevented cases, in thousands, across different vaccination delivery strategies reported by each country (2000–20). *Five pairs of strategies were compared with two comparator strategies to assess the health effects of additional vaccination delivery strategies as reported by each country. MCV2 effects begin in the year when WUENIC first reports MCV2 coverage (Appendix p 242). Note that the strategy of MCV1, MCV2, and SIAs compared with no vaccination (represented in the first column of data) does not depict an actual historical policy implementation for vaccination strategies. Countries are presented in order of their introduction year of MCV2 and magnitude of measles burden (Appendix p 242). Sums of the prevented cases in the 14 countries are presented in the last row of the table. Entries with no value correspond to options involving MCV2 in the three countries that have not yet introduced MCV2 (i.e., Uganda, DR Congo, and Somalia), so prevented cases cannot be estimated. MCV1=the first routine dose of measles-containing vaccine. MCV2=the second routine dose of measles-containing vaccine. SIA=supplementary immunisation activity. WUENIC=WHO and UNICEF estimates of national immunisation coverage.*

	Compared with no vaccination		Compared with MCV1 alone		
	MCV1, MCV2, and SIAs	MCV1 alone	MCV1 and SIAs	MCV1 and MCV2	MCV1, MCV2, and SIAs
MCV2 introduction before 2017					
India	349481	295563	41272	28182	53918
Indonesia	83082	61350	16176	9902	21732
China	321262	257140	32643	57289	64122
Philippines	42549	29887	11448	3164	12661
Pakistan	76409	49163	26681	7070	27246
Angola	15515	6780	8651	433	8735
Ukraine	7306	6090	102	1132	1217
Malawi	9944	7003	2926	313	2941
MCV2 introduction during 2017-20					
Nigeria	93009	39343	53667	251	53667
Ethiopia	49569	23045	26357	484	26525
Madagascar	12033	6935	5087	25	5098
No MCV2 introduction until 2020					
Uganda	23922	15024	8898	..	8898
DRC	40965	23429	17537	..	17537
Somalia	7634	2931	4703	..	4703
Total	1132682	823682	256146	108245	309000

Compared with no vaccination, incremental NNVs for MCV1 ranged between 1.27 and 1.46, with a median NNV of 1.41 (IQR 1.35–1.44) across the 14 analysed countries. In comparison with MCV1 alone, SIAs had a median NNV of 6.02 (IQR 5.30–7.68), which was greater than including MCV2 in seven of the 11 countries that have introduced MCV2 (median NNV 5.41, IQR 4.76–6.11; table 2). The opposite trend of incremental NNV was observed in Nigeria, Ethiopia, Angola, and Madagascar, where frequent SIAs took place and MCV2 had only been introduced in 2015 at the earliest (Appendix p 242).

Furthermore, including SIAs when both MCV1 and MCV2 were used led to a median NNV of 6.44 (IQR 5.36–9.78), whereas including MCV2 when both MCV1 and SIAs were used resulted in a median NNV of 17.0 (IQR 9.34–42.33). There is diminishing return in efficiency for including an additional vaccination delivery strategy when multiple strategies are already in use.

Table 2. Incremental NNV to prevent a measles case across different vaccination delivery strategies (2000–20). *Data are NNV. Incremental NNV is defined as the ratio of additional doses given to incremental prevented cases in a vaccine delivery strategy compared with its comparator. The median NNVs among countries with applicable values for the five comparison pairs are presented in the last row of the table. Entries with no NNV value correspond to options involving MCV2 in the three countries that have not yet introduced MCV2 (i.e., Uganda, DR Congo, and Somalia), so NNV cannot be estimated. As MCV2 did not contribute to burden reduction in these three countries, the incremental NNV values are the same between the MCV1, MCV2, and SIAs strategy vs the MCV1 and MCV2 strategy, and the MCV1 and SIAs strategy vs the MCV1 strategy. For the MCV1, MCV2, and SIAs strategy vs the MCV1 and SIAs strategy, the incremental NNV in Nigeria is exceptionally large due to a small number of prevented cases from MCV2 introduction in 2019. MCV1=the first routine dose of measles-containing vaccine. MCV2=the second routine dose of measles-containing vaccine. NNV=number needed to vaccinate to prevent a case. SIA=supplementary immunisation activity.*

	MCV1 vs no vaccination	MCV1and SIAs vs MCV1	MCV1 and MCV2 vs MCV1	MCV, MCV2, and SIAs vs MCV1 and SIAs	MCV1, MCV2, and SIAs vs MCV1 and MCV2
MCV2 introduction before 2017					
India	1.35	10.20	5.41	11.57	16.13
Indonesia	1.27	7.54	4.73	7.75	10.00
China	1.34	8.23	4.59	7.57	35.73
Philippines	1.33	5.57	4.39	10.92	6.65
Pakistan	1.44	6.95	4.80	57.52	9.12
Angola	1.45	4.48	5.32	27.14	4.66
Ukraine	1.26	12.51	6.10	6.17	14.72
Malawi	1.36	7.72	6.59	132.46	8.55
MCV2 introduction during 2017-20					
Nigeria	1.46	4.53	5.78	918368.12	4.55
Ethiopia	1.42	5.21	6.12	17.03	5.27
Madagascar	1.40	3.67	8.16	17.84	3.68
No MCV2 introduction until 2020					
Uganda	1.41	6.22	..	..	6.22
DRC	1.44	5.61	..	..	5.61
Somalia	1.45	5.83	..	..	5.83
Median	1.40 (1.35–1.44)	6.02 (5.30–7.68)	5.41 (4.76–6.11)	17.03 (9.34–42.33)	6.44 (5.36–9.78)

The estimated total number of susceptible children younger than 5 years shows varying patterns by vaccination delivery strategy (figure 3). Historical coverage rates with MCV1 and MCV2 reduced measles susceptibility compared with the counterfactual scenario with no vaccination, but the numbers of susceptible children remained higher than one birth cohort in 11 (73%) of the analysed countries by 2020. China was an exception, where high MCV1 and MCV2 coverage successfully kept the susceptible population under the threshold of one birth cohort since 2007. Furthermore, sustained high MCV2 coverage in India resulted in the number of susceptible children being less than one birth cohort from mid-2017 onwards. Despite several rebounds of the susceptible population (i.e., when the susceptible population is larger than the size of one birth cohort) during 2000–20, MCV1 and SIAs had more potential to reduce the number of susceptible children than MCV1 and MCV2. However, we estimated that in two countries (i.e., India and Ukraine), MCV1 and SIAs would not have reduced the number of susceptible children to below the birth cohort in any year (Appendix p 249). Overall, measles vaccination strategies as reported by these countries were estimated to have reduced the number of susceptible children below the birth cohort in a median 24% (14–37) of years between 2000 and 2020.

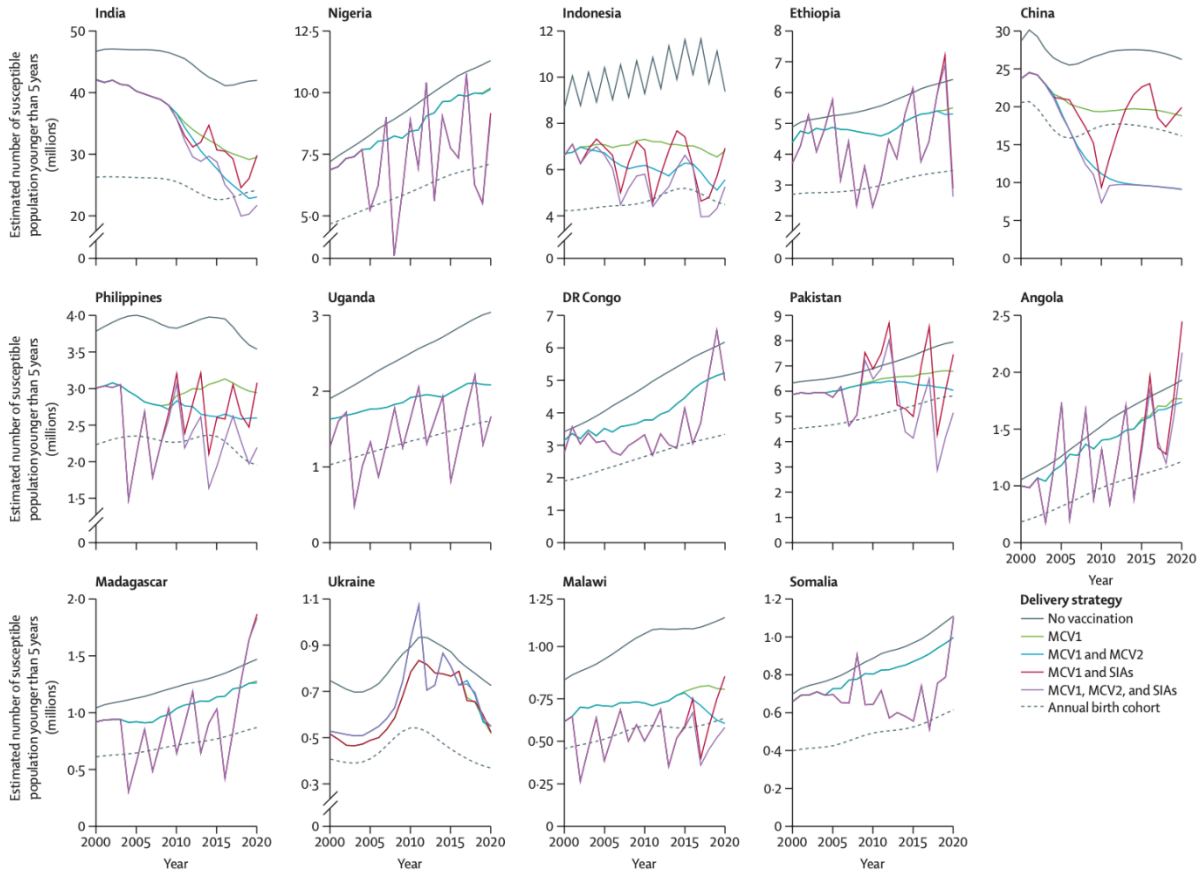

Figure 3. Figure 3: Susceptible population younger than 5 years by vaccination delivery strategy (2000–20)
Estimated total numbers of susceptible people younger than 5 years under different vaccination delivery strategies compared with the size of birth cohort. For countries that have not yet introduced MCV2 (i.e., Uganda, DR Congo, and Somalia), there are overlapping trends for incidence rates for the delivery strategies of MCV1 and MCV2 (blue lines) and MCV1 only (green lines) and the delivery strategies of MCV1, MCV2, and SIAs (purple lines) and MCV1 and SIAs (red lines). Overlapping trends are also seen in most analysed years in countries that introduced MCV2 in 2017 or later (i.e., Nigeria, Ethiopia, and Madagascar). In Indonesia, the fluctuations seen in the no vaccination strategy are the result of dynamic sizes of the susceptible population affected by natural seasonality of measles transmission. MCV1=the first routine dose of measles-containing vaccine. MCV2=the second routine dose of measles-containing vaccine. SIA=supplementary immunisation activity.

We estimated prevented cases and incremental NNVs under alternative assumptions for MCV2 early introduction and SIA dose distribution (figure 4; Appendix pp 254–257). Compared with MCV1 alone, early introduction of MCV2, either under fast or gradual rollout, would have prevented more cases than occurred when MCV2 was actually introduced, resulting in a further estimated reduction of 75–97 million measles cases across the 14 analysed countries. Only a slight improvement in efficiency was seen from early MCV2 introduction, with a median NNV reducing from 5.41 (IQR 4.76–6.11) to 5.09 (IQR 4.71–5.25). The distribution of SIA doses between zero-dose and already-vaccinated populations had a strong effect on the incremental effects and efficiency of vaccination. When MCV1 was already in use, successfully directing SIA doses first to children in the zero-dose population then to children who were already vaccinated was estimated to prevent more cases of measles than early MCV2 introduction in all countries except China. This observation was particularly apparent when MCV1 coverage was low, so there was a greater proportion of children in the zero-dose population who were

eligible for vaccination with an additional dose via an SIA. Prioritising the zero-dose population for SIA doses was estimated to improve efficiency (median NNV 4.84 [IQR 4.09–5.40] vs 6.02 [IQR 5.30–7.68] in the main analysis) for countries with low routine-immunisation coverage, such as Nigeria and DR Congo. Conversely, when SIA doses first reached children who were already vaccinated, the median NNV increased to 8.32 (IQR 5.97–8.81) and was estimated to substantially reduce the number of prevented cases of measles compared with the main analysis.

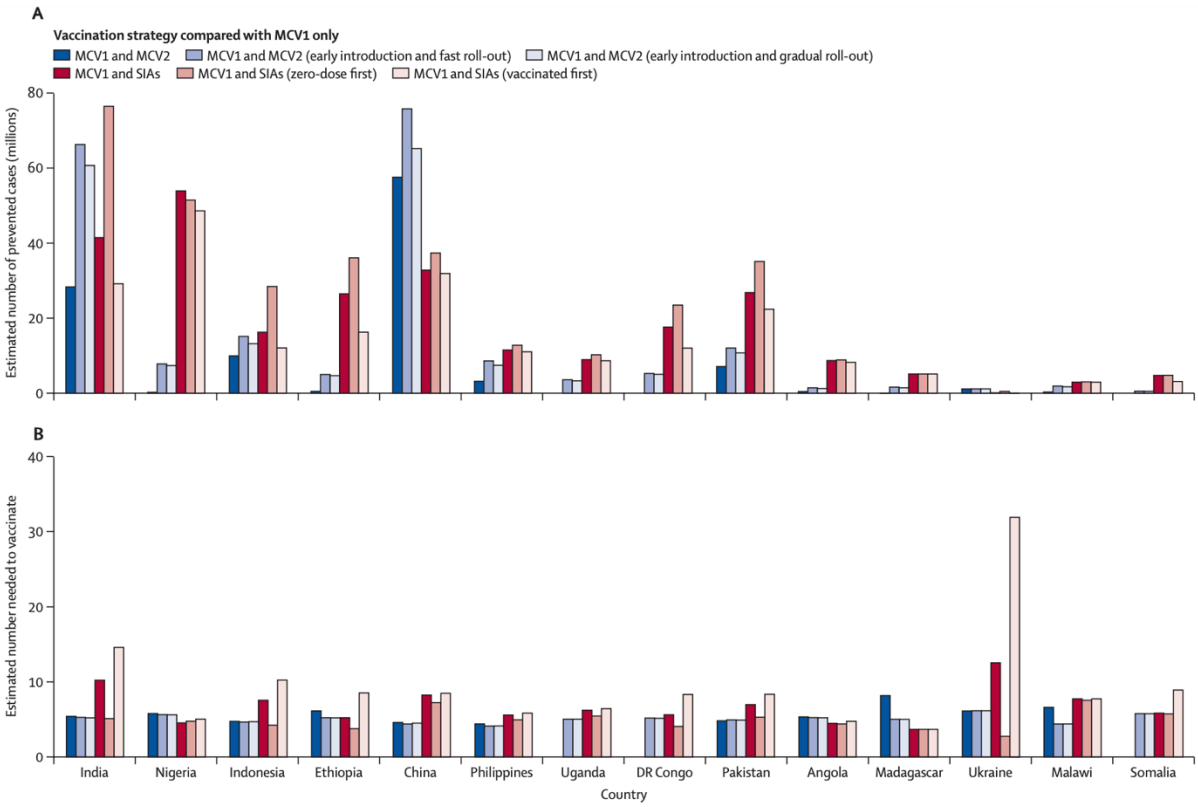

Figure 4. Prevented cases and number needed to vaccinate to prevent a measles case under alternative assumptions for early MCV2 introduction and different SIA dose distribution

(A) Prevented cases. (B) Number needed to vaccinate to prevent a measles case. In the sensitivity analysis, we modelled the incremental effect and efficiency of vaccination under the alternative assumptions of MCV2 introduction and SIA distribution. The incremental effects of each of the strategies were compared with the strategy in which MCV1 was already in use. The incremental effects of each of the strategies are compared with the strategy in which MCV1 was already in use. In the main analysis, MCV2 was introduced on the basis of its historical WUENIC coverage (dark blue) and SIAs were distributed with an assumption that 7·7% of children were less likely to be reached by vaccination than the rest of the targeted population (red). The alternative MCV2 assumption indicates early introduction of MCV2 in 2000 with coverage inputs from the appendix (p 251; light blue). Three countries that have not yet introduced MCV2 (i.e., Uganda, DR Congo, and Somalia) have missing estimates for the original strategy with MCV1 and MCV2. Two alternative assumptions for SIA distribution were evaluated, including prioritisation of children who had not received any MCV doses (pink) and prioritising children who had been previously vaccinated (dark red). MCV=measles-containing vaccine. MCV1=the first routine dose of measles-containing vaccine. MCV2=the second routine dose of measles-containing vaccine. SIA=supplementary immunisation activity. WUENIC=WHO and UNICEF Estimates of National Immunization Coverage.

4.7 Discussion

Using MCV coverage data from 2000 to 2020, we investigated and estimated the relative effects and efficiency of different MCV strategies in 14 countries with high measles burden that include a wide range of socioeconomic, demographic, and immunisation-service settings.

The use of MCV1 resulted in the highest relative health effects of any dose and the best efficiency in reducing measles burden. The strategy of MCV1 and SIAs can more effectively keep the susceptible population size less than the size of one birth cohort and had a bigger effect on predicted measles incidence than MCV1 and MCV2 together, when both strategies were compared with MCV1 alone. Overall, SIAs reduced the susceptible-population size more than MCV1 and MCV2, whereas the efficiency of SIAs, as assessed by NNV, to prevent a measles case was lower than the efficiency of MCV2. However, there was variation between countries in the relative efficiency of each incremental strategy. The strategies used between 2000 and 2020 in the 14 included countries substantially reduced measles burden compared with a no vaccination strategy but, other than in China, were not predicted to prevent large outbreaks. This finding is consistent with other analyses in low-income and middle-income countries [30].

The high effects but reduced efficiency of SIAs could also be interpreted from the viewpoint of dose delivery—although SIAs could be delivered to more people than MCV1 and MCV2, many doses were predicted to reach children who had previously been vaccinated (Appendix p 254). Repeated vaccinations were seen more often in countries with high routine immunisation coverage than in countries with low routine immunisation coverage, such as Madagascar, where SIAs remained an important strategy to reach children who were unvaccinated. Compared with SIAs, MCV2 showed relatively less effect in countries with low MCV2 coverage such as DR Congo, Nigeria, Angola, Ethiopia, and Somalia, even under the assumption of early MCV2 introduction, compared with countries with higher sustained MCV1 coverage such as China and Malawi. Accompanied by better reach of SIAs to children in the zero-dose population, early introduction of MCV2 could have substantially reduced incidence over time. In countries that implemented routine MCV2 early and maintained high levels of coverage, such as China and India, there was little difference in estimated measles incidence rate between historical strategies and optimal assumptions for MCV delivery when MCV2 was introduced in 2000, and SIA doses were given first to children in the zero-dose population (Appendix p 255). This finding suggests that, in the future, SIAs might be needed less often if high coverage of MCV2 can be successfully attained, maintained, and aligned with WHO recommendations [8]. These results might also be generalisable to other vaccine preventable diseases; for example, similar findings have been

shown for polio, such that if high baseline routine immunisation can be maintained, SIA frequency can be reduced with low probability of an outbreak [31].

WHO advises countries that have not yet introduced rubella-containing vaccine (RCV) to do so via nationwide, non-selective SIAs of measles–rubella vaccine until at least age 15 years. Once RCV has been introduced, the timing and extent of further SIAs depends on the epidemiology of measles, which has higher transmissibility than rubella. The Measles and Rubella Strategic Framework 2021–2030 emphasises shifting from a so-called one-size-fits-all approach to focus on effective local approaches for vaccinating hard-to-reach populations with MCV [32]. For high-burden countries to achieve high levels of coverage and meet targets for measles elimination, SIAs should be strengthened but could be made more efficient and designed to fit local demand. If SIA efficiency is low in a particular setting, as shown by a high predicted NNV to prevent a case, but SIAs consistently result in a greater burden reduction than MCV2, investing in mechanisms to improve efficiency through improved surveillance and coverage data to target SIAs and improving so-called mop-up activities in specific areas where the virus is known or suspected to be circulating immediately after a campaign [33] will be valuable. Mop-up activities involve going to areas where the reported number of doses administered in the SIA was lower than the target population, or to places where a rapid-coverage evaluation shows low coverage and conducting special vaccination activities to increase coverage (e.g., going to each house to identify and vaccinate any children who have not been reached).

We did not explore potential differences in effectiveness and efficiency between selective and non-selective approaches [34]. Some countries have implemented selective SIAs, but further empirical data are needed on the feasibility of this approach in a range of contexts. Further studies should also assess the combined effectiveness and efficiency of integrated campaigns [35], which deliver multiple vaccines or include other interventions, such as nutritional screening.

Our study has limitations. First, SIA doses were assumed to be randomly delivered to their target population, except for a fixed proportion of children who were assumed to be less likely to be reached by childhood immunisation programmes [24]. The extent to which in-practice doses are correlated with, or independent of, previous vaccination status is unknown because only a minority of countries report high-quality, post-campaign-coverage surveys to WHO and even fewer surveys report SIA coverage and previous measles vaccination status [36]. Other household surveys, such as Demographic and Health Surveys, try to capture specific information on measles vaccination [37], but the ability to compare SIA dose receipt among children in the zero-dose population or children who

were previously vaccinated is constrained by the low proportion of children with documentation of routine vaccination and potential misclassification of routine or SIA vaccination when relying on parental recall [37]. For each measles vaccination campaign, however, the size of zero-dose population reached by SIAs varies depending on local routine coverage and SIA-implementation approach [36]. Furthermore, SIA coverage reported in the WHO record might be overestimated [36,38,39], possibly due to vaccinating non-target populations or not capturing unreached populations in the denominator.

Second, MCV2 effect based on historical coverage could be underestimated, given our purposeful selection of high-burden countries that mostly had low coverage. Moreover, differences exist between MCV2 recommended policies and vaccination in practice. For example, lessons learned from MCV2 routine immunisation introduction in Africa found that, in practice, to reduce vaccine wastage, vaccinations were only administered on days when 10 or more children were present, missing opportunities for vaccination [40]. Furthermore, the interplay between MCV1, MCV2, and SIAs should be considered when planning future measles vaccination strategies. Third, although DynaMICE is a dynamic transmission model that captures the indirect effect (e.g., herd immunity) of vaccination, it does not capture international case importation. Furthermore, due to model limitations in simulating measles outbreaks in subnational areas, differentiation between outbreak response SIAs and preventive SIAs was not explored in our analysis. Additionally, accurately accounting for the effect of subnational SIAs and subnational variations in both routine immunisation and SIA coverage remains a challenge as subnational data on SIAs are not regularly collected. The potential effects of subnational variation in key determinants of measles transmission, such as birth rates, routine and SIA vaccination coverage, and migration, were also not assessed.

Finally, NNV is not applicable for comparison between strategies when an alternative strategy does not prevent additional cases and there is no established threshold to establish whether the efficiency of an immunisation programme is acceptable [41]. Further data, such as the costs of vaccine procurement and delivery, will be useful in understanding the cost-effectiveness of immunisation programmes.

The resources required for SIAs, including economic and human resources and logistical challenges, can be major deterrents to their implementation. Despite several unknowns regarding interpretation of estimated NNVs, our results show that routine MCV2 is not always more efficient than SIAs. Furthermore, the current trend towards including multiple interventions in a single SIA or integrating

many of the components of SIA planning across different interventions might increase efficiency, although monitoring the effectiveness of integrated campaigns will be important [42,43]. There is a need to improve the evaluation of SIAs to identify how they could increase efficiency, transfer best practices between countries, and ensure adequate and timely funding for SIA implementation and evaluation.

We assessed the incremental effects and efficiency of different measles vaccination strategies to inform future decisions about vaccination planning and policies. Understanding the relative effects and efficiency of the first routine dose, the second routine dose, and SIAs of MCV will assist stakeholders in assessing the value of measles vaccination programmes and further identify improved pathways towards measles elimination.

4.7.1 Acknowledgements

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5. Chapter 5: The impact of surveillance and other factors on detection of emergent and circulating vaccine derived polioviruses

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5.1 Research paper cover sheet

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5.2 Bridging section

This paper was published in *Gates Open Research*. The work was completed between June 2020 and April 2021 and revised following peer review in April 2022.

This research ties into the overall theme of this thesis because it evaluates an indirect effect of polio vaccination strategies, seeding future cVDPVs. Also, this analysis provides important considerations for global cessation of the OPV and eradication certification timelines. In this chapter, I demonstrate my understanding of the delicacy and complexity of polio vaccination policy decisions and how statistical methods can be utilised for identifying outbreak risks. Chapter 3 focused on vaccination approaches for mitigating *WPV1* outbreaks, whilst this chapter focuses on *cVDPV* outbreaks, demonstrating my understanding of the different challenges that exist within polio programming.

This work was a joint effort with Holly Fountain. I was Holly's supervisor for her MSc student project in 2020 and supervised her work creating a database of nucleotide mutations for historical cVDPV outbreaks. Holly was responsible for database creation and approved the final publication but did not have any involvement in the statistical analysis or write-up. I conducted the entire statistical analysis for this work, including estimating time from emergence to outbreak detection and the regression analysis identifying factors associated with time to detection. I led manuscript write-up, disseminated the results and made all corrections following peer-review.

5.3 Abstract and author summary

5.3.1 Abstract

Circulating vaccine derived poliovirus (cVDPV) outbreaks remain a threat to polio eradication. To reduce cases of polio from cVDPV of serotype 2, the serotype 2 component of the vaccine has been removed from the global vaccine supply, but outbreaks of cVDPV2 have continued. The objective of this work is to understand the factors associated with later detection to improve detection of these unwanted events. The number of nucleotide differences between each cVDPV outbreak and the oral polio vaccine (OPV) strain was used to approximate the time from emergence to detection. Only independent emergences were included in the analysis. Variables such as serotype, surveillance quality, and World Health Organization (WHO) region were tested in a negative binomial regression model to ascertain whether these variables were associated with higher nucleotide differences upon detection. In total, 74 outbreaks were analysed from 24 countries between 2004-2019. For serotype 1 (n=10), the median time from seeding until outbreak detection was 572 (95% uncertainty interval (UI) 279-2016), for serotype 2 (n=59), 276 (95% UI 172-765) days, and for serotype 3 (n=5), 472 (95% UI 392-603) days. Considerable variation in the time between emergence and detection of VDPVs were apparent, and other than surveillance quality and inclusion of environmental surveillance, the reasons for this remain unclear. Therefore, maintaining surveillance for poliomyelitis even after achieving local elimination is essential to quickly respond to both emergence of VDPVs and potential importations as low-quality AFP surveillance causes outbreaks to continue undetected.

5.3.2 Author summary

I used nucleotide differences of cVDPVs to determine the time from emergence to outbreak detection. Significant improvement in the time to detection was found with increasing surveillance of non-polio acute flaccid paralysis (AFP) and adequate stool collection. cVDPVs remain a risk and all WHO regions have reported at least one VDPV outbreak since the first outbreak in 2000. Exacerbating the issue, outbreak response campaigns using monovalent OPV type 2 risk seeding future outbreaks. In this analysis, we show that some emergences took >3 years to detect. This has implications for the polio endgame strategy and certification of polio eradication because to confidently certify global polio eradication, the global community needs to be certain that there is no risk of virus emergence. If time to detection exceeds four years but circulation remains unknown, then eradication may be declared prematurely. Moreover, for successful removal of other serotypes from OPV, it is important to better understand why the predictions for OPV2 removal did not hold true. Analysing nucleotide divergence and estimated date of seeding of cVDPVs, including historic outbreaks pre-2016, is important to address this issue.

5.4 Introduction

Polio has been targeted for eradication since 1988 when countries represented within the World Health Assembly committed to eradication [1]. Whilst the initial goal to eradicate all poliovirus by 2000 was not achieved, two of the three wild serotypes have been eliminated, most recently type 3 in 2018 [2-4]. The main driver in this reduction of cases has been vaccination achieved through both routine and supplementary immunisation activities (SIAs), largely with the oral polio vaccine (OPV), a live attenuated vaccine. OPV is important for polio eradication, as it provides both humoral and intestinal immunity. However, the genetic instability of the attenuated virus can result in mutations that increase transmissibility and neurovirulence of infections [5,6]. Consequently, circulating vaccine-derived polioviruses (cVDPVs) can arise and cause paralysis in affected individuals. Prior to 2000, these outbreaks had not been reported in any countries using OPV [7], and recent analysis has suggested that cVDPV emergence and spread is more common in populations with low to moderate mucosal immunity against poliovirus [8,9].

Since observing this unwanted effect of OPV vaccination, along with vaccine-associated paralytic polio (VAPP) and immunodeficiency-associated VDPVs (iVDPVs), removal of OPV from use has been prioritised within the Global Polio Eradication Initiative (GPEI) [10,11]. Especially for serotype 2, the risks of OPV have begun to outweigh the benefits because OPV use can seed additional outbreaks in susceptible populations, and the continued use of OPV2 was deemed unnecessary [12]. The Switch from trivalent OPV (tOPV) to bivalent OPV (bOPV), removing serotype 2, was accomplished globally in a two-week period at the end of April 2016 [13]. Instead of the anticipated decrease in circulating VDPVs, in the third- and fourth-years post-Switch, outbreaks and geographic spread of outbreaks have increased.

The strategy for eradication described in the 2013–2018 GPEI Strategic Plan outlines that wild poliovirus should be interrupted whilst strengthening immunization systems, including the introduction of inactivated polio vaccine (IPV) [10]. Alongside, considerable investment has been made towards transition to a polio-free world that includes containment of all polioviruses, including minimising the risks of unintended release from laboratory facilities, and eventual removal of the OPV (known as cessation) [14]. This transition phase is needed to ensure that the chances of poliovirus transmission in a susceptible population would be as low as manageable, and that populations would remain protected from outbreaks. The Polio Post-Certification Strategy [14], describes the many facets of containing polioviruses, protecting populations, cessation of the OPV and detecting and responding to a polio threat. The Switch from tOPV to bOPV provided the first trial of removing one of the

serotypes from the global vaccine supply. Within the Polio Post-Certification Strategy, the pre-cessation (zero-to-one-year post-certification) and immediate post-cessation (two to five years post-certification) were regarded as the time periods where VDPVs were most likely to emerge, where the risk was thought to be highest 12–18 months after (in the most recent example) bOPV withdrawal. The time until detection is based on modelling which suggests that the cumulative probability of detecting circulating poliovirus is over 99.9% by four years [15], but the modelling did not account for weaknesses in surveillance or include specific aspects of VDPV transmission.

cVDPVs are of particular concern in areas with low to moderate OPV induced immunity, as the virus can emerge and maintain transmission [9,16]. In (mostly high-income) countries with no OPV vaccination, there is minimal risk of VDPV emergence because the source is largely absent, transmission risk is lower, and vaccination coverage with the IPV is usually high. However, other risk factors for cVDPVs include continued OPV use at low rates of coverage, prior elimination of the corresponding wild poliovirus serotype, insensitive acute flaccid paralysis (AFP) surveillance, and use of monovalent OPV (mOPV) and bOPV in SIAs due to the emergent risk of the live attenuated vaccine [6,8,17]. A novel, genetically stable OPV2 that is a modified version of the existing OPV2 but better retains attenuation is currently in development and has been approved and deployed for emergency use as of 2021 to mitigate these risk factors [18,19].

Here we provide a retrospective analysis of cVDPV outbreaks between 2004 and 2019 and estimate the time from emergence to detection using publicly available data. We explore the differences in time to detection across VDPV serotypes and examine the effect of AFP surveillance and other factors on the time to detection. The aim is to provide useful information on the time to detection of VDPV outbreaks by serotype and the factors that affect this, to inform future cessation planning.

5.5 Methods

Detection of poliomyelitis outbreaks are dependent upon global surveillance for AFP and the Global Polio Laboratory Network where clinical specimens are investigated to identify poliovirus as the causative agent. To confirm poliovirus infection, at least two stool specimens should be collected 24–48 hours apart and within 14 days of the onset of AFP in affected individuals [20]. All samples undergo confirmatory testing and genetic sequencing at laboratories that are part of The Global Polio Laboratory Network (GPLN) following a standardised protocol to minimise contamination and maximise sensitivity [21]. Sequencing of the VP1 region of the viral genome is used to classify poliovirus; if the sample differs from the parental OPV strain by 1–15% (or from 0.6% for serotype 2),

the case is defined as a VDPV [9,22]. However, this definition changed in 2010 for serotype 2 only, such that prior to 2010, 10 nucleotide mutations in the VP1 region constituted a VDPV, but later, the cut-off dropped to 6 nucleotide mutations. Therefore, we exclude type 2 outbreaks prior to 2010 (n=16) to account for this change as historic type 2 outbreaks where the isolate had <10 nucleotide mutations would not have been counted as a cVDPV.

By definition, cVDPV refers to VDPV isolates for which there is evidence of person-to-person transmission in the community and 'genetically linked VDPVs' are isolated from at least two individuals who do not live in the same household, or from one individual and ≥1 environmental surveillance (ES) sample reported through the comprehensive surveillance network [11]. Within the GPEI surveillance network, cVDPV outbreaks that spread across country borders are treated as separate outbreaks (requiring a response within each country). Here we are only interested in the emergence of new cVDPV outbreaks and exclude outbreaks because of international spread. For example, an emergence first detected in Jigawa State, Nigeria, which has spread to several countries in West Africa is only included once in the dataset. Where possible, the lineage code for each cVDPV2 emergence is provided (Appendix pp 259-262 [23]).

Poliomyelitis is a notifiable disease, and as part of global surveillance for poliomyelitis, the GPEI and WHO laboratories report all confirmed outbreaks through the Morbidity and Mortality Weekly Reports (MMWR). Consequently, we use these reports to compile a spreadsheet of all cVDPV outbreaks from 2000 to February 2020. Outbreaks were first identified using MMWR reports and then country and year(s) of the outbreak were searched using the search terms: 'vaccine-derived poliovirus* OR VDPV OR circulating vaccine-derived poliovirus* OR cVDPV'. This search criterion is not a systematic review of all literature for polio outbreaks within the period, but due to the nature of disease surveillance for poliomyelitis, resulted in a comprehensive list of outbreaks. The number of nucleotide sequences that are different to the Sabin 2 strain at first detection (referred to as 'VP1 divergence') and the dates of the first and last isolates of the outbreak were also collated through the literature search. As per exclusion criteria, we did not include outbreaks that did not meet the aforementioned cVDPV definition or were the result of international spread. The annual country-level non-polio acute flaccid paralysis (AFP) rate and percentage of adequate stool specimens collected, both indicators of surveillance quality, were extracted for each outbreak and year corresponding to the start of the outbreak. In order examine the effect of environmental sampling as a supplement to AFP surveillance, the mechanism via which the first isolate was detected (AFP or ES) was ascertained for each outbreak. Additionally, we included WHO region, Diphtheria-tetanus-pertussis vaccine dose

3 (DTP3) coverage (which is often used as a marker for routine immunisation coverage), and whether the outbreak was detected before/after 2016. Multiple independent emergences observed within the same country-year unit of observation were treated as multiple observations even if the associated surveillance data and outbreak response remained the same.

Variables associated with the number of nucleotide differences were explored using a negative binomial model. A negative binomial model was selected because the variance of the reported number of nucleotide differences was larger than the mean and the data was highly dispersed. The minimum number of mutations was 9 for serotypes 1 and 3, and 6 for serotype 2, and the outcome variable was shifted-left so that the minimum number was 0. Separate datasets were created for serotype 2 and serotypes 1 and 3 to account for the small sample size of types 1 and 3 outbreaks and because of the similar case to infection ratio for serotypes 1 and 3 [24]. The data set for types 1 and 3 retained a covariate for serotype. Preliminary analysis illustrated that outbreak with nucleotide mutations ≥30 (n=4) affected the fit of the model to the data (due to overdispersion that could not fully be accounted for) and were removed from the dataset as outliers. A multivariate regression model was built using stepwise removal by comparing differences in the Akaike information criteria (AIC) between candidate models and estimating the negative binomial dispersion parameter (θ). Interactions between the non-polio AFP rate and the percentage of stool samples adequately collected were also examined. The negative binomial regression model can be written in terms of the expected nucleotide differences $\mathrm{E(Y)}$, which is linked to the predictors through a logarithmic link function, where β_0 is the intercept and $\sum_{i=1}^{k} \beta_i \chi_i$ represents the additive effects of κ predictor variables $\chi_1, \chi_2 \ldots \chi_k$, each with its own coefficient β_i:

$$\ln\big(E(Y)\big) = \beta_0 + \sum_{\iota=1}^{\kappa} \beta_i \chi_i$$

For every VDPV outbreak, we estimate the time to detection using the following methods. Each VDPV outbreak has included with it the number of VP1 mutations associated with the first case(s) and is used to estimate the time to detection. The first VP1 mutation of the Sabin strain is assumed to be instantaneous, and each subsequent mutation follows an average rate of 1.14×10^{-2} nucleotides per site per year [25,26]. The VP1 RNA gene consists of 906 nucleotides, so we would expect approximately 1 nucleotide change every 35 days under a constant clock model. We assume that the viral evolution rate is the same across all serotypes [27,28]. Each independent mutation was modelled using an exponential distribution and the sum of waiting times as an Erlang distribution, as done for a previous analysis of cVDPVs [26]. By treating each VDPV detection as a random sample of the

population parameter for the time to detection, we use bootstrapping of the sample estimates of time to detection to provide robust estimates for serotype 2 and serotypes 1 and 3. The empirical distribution function of the bootstrapped samples were used to calculate the probability of VDPV outbreaks being detected within one and four years. All analyses were carried out in R version 4.0.3. This project received ethical approval from the London School of Hygiene & Tropical Medicine (LSHTM) on 29th June 2020: project ID 21929. The source code for this project is publicly available from: https://github.com/mauzenbergs/polio_vdpv.

5.6 Results

5.6.1 Independent cVDPV outbreaks

Review of MMWR reports identified a total of 96 outbreaks in 28 countries. However, once outliers were excluded and the change of cVDPV2 definition was accounted for and cVDPV2 outbreaks pre-2010 were removed, a total of 75 cVDPV outbreaks due to independent emergences were analysed from 24 countries (Table 1). cVDPV type 2 was the most frequent serotype isolated, accounting for 80% of outbreaks, followed by serotypes 1 and 3, accounting for 13% and 7% of outbreaks, respectively. Of the 75 outbreaks, 18 (24%) were first detected via ES.

Table 1. Summary of all circulating vaccine derived polioviruses (cVDPVs) included in the analysis split by serotype.
**Median and **range provided if there was more than 1 outbreak, otherwise a single value was provided. WHO = World Health Organization; NPAF P= non-polio acute flaccid paralysis; CI = confidence interval; PNG = Papua New Guinea; CAR= Central African Republic; DRC = Democratic Republic of Congo.*

WHO Region	Country	Number of outbreaks	Median* duration days (range**)	Median* nucleotide difference from Sabin strain of the first isolate (range**)	Mean NPAFP rate (per 100,000 children <15) (95% CI)	Mean % adequate stool samples (95% CI)
			Serotype 1			
AFR	MADAGASCAR	1	338	20	4.2	85.6
AFR	MOZAMBIQUE	1	112	27	2.7	87.2
AMR	DOMINICAN REPUBLIC	1	190	17	-	-
EUR	UKRAINE	1	7	20	2.7	97.4
SEAR	INDONESIA	1	139	10	2.4	85.5
SEAR	MYANMAR	2	258 (59, 458)	19.5 (14, 25)	2.8	92.7
WPR	CHINA	2	55 (51, 59)	11 (9, 13)	1.9	92.2
WPR	LAOS	1	269	21	2.6	57.1
WPR	PNG	1	193	14	7.9	44.7
Global Type 1 total		11	125.5 (7, 458)	17 (9, 27)	3.2 (1.9, 4.5)	82.7 (70.2, 95.2)
			Serotype 2			
AFR	ANGOLA	5	195 (39, 288)	7 (6, 10)	5.0	85.1
AFR	CAR	7	99 (0, 275)	7 (6, 10)	9.2	71.1
AFR	CHAD	2	184 (97, 270)	6 (6)	10.2	84.6
AFR	DRC	12	173 (1, 473)	8 (6, 19)	7.7	84.2
AFR	ETHIOPIA	4	94 (41, 151)	12 (10, 18)	2.9	90.8
AFR	GUINEA	1	475	12	2.6	96.6
AFR	MOZAMBIQUE	1	57	6	3.4	88.5
AFR	NIGERIA	9	84 (0, 637)	10 (6, 16)	11.9	95.4
AFR	SOUTH SUDAN	1	3	9	4.2	94.4
AFR	TOGO	1	78	13	4.6	70.2
AFR	ZAMBIA	1	71	9	3.8	84.3
EMR	AFGHANISTAN	1	1295	8	11.0	92.6
EMR	PAKISTAN	9	58 (8, 654)	6 (6, 9)	17.7	87.1
EMR	SYRIA	1	202	22	3.6	80.4
EMR	YEMEN	1	179	6	3.4	91.5
SEAR	MYANMAR	1	172	13	2.5	93.2
WPR	CHINA	2	300 (113, 487)	10 (6, 13)	2.0	92.3
Global Type 2 total		59	105 (0, 1295)	8 (6, 22)	8.9 (7.3, 10.4)	86.2 (84.2, 88.2)
			Serotype 3			
AFR	ETHIOPIA	1	556	12	2.6	79.0
AFR	MADAGASCAR	1	32	13	1.3	89.4
EMR	SOMALIA	1	183	14	4.8	97.7
EMR	YEMEN	1	454	18	4.3	93.2
WPR	CAMBODIA	1	50	17	2.0	95.8
Global Type 3 total		5	255	14 (12, 18)	3.0 (1.2, 4.8)	91.0 (81.3, 100)
Total Outbreaks		**75**	**109 (0, 1295)**	**9 (6, 27)**	**7.7 (6.3, 9.0)**	**86.0 (83.8, 88.2)**

For serotype 1 (n=11), the median nucleotide divergence for the first isolate of the outbreak was 17 (range: 9, 27) and the mean non-polio AFP rate was 3.2 cases per 100,000 of the population under 15 years of age (95% confidence interval (CI): 1.9-4.5) (Table 1). Half (50%) of type 1 outbreaks were contained or closed within 120 days. For serotype 2 (n=59), the median nucleotide divergence for the first isolate of the outbreak was 8 (range: 6, 22) and the mean non-polio AFP rate was 8.9 cases per 100,000 of the population under 15 years of age (95% CI: 7.3, 10.4). Most type 2 outbreaks (54%) were contained within 120 days. For serotype 3 (n=5), the median nucleotide divergence for the first isolate of the outbreak was 14 (range: 12, 18) and the mean non-polio AFP rate was 3.0 (95% CI: 1.2, 4.8) cases per 100,000 of the population under 15 years of age. In total, 40% of type 3 outbreaks were contained within 120 days.

For serotype 2, a regression model of the number of nucleotide differences of the first isolate for each outbreak suggests a decrease in nucleotide difference with increasing non-polio AFP rate and percentage of adequate stool samples collected (incidence rate ratio (IRR) 0.18, 95% CI 0.06-0.49, p<0.01 and IRR 0.91 95% CI 0.84-0.99, p=0.05, respectively), but no significant difference between classification (AFP or ES) (p=0.07), Table 2. Despite the non-significant p-value and wide confidence interval that crosses 1.00, the IRR (2.15 95% CI: 0.93, 5.4) provides weak evidence that rate of nucleotide mutations of outbreaks identified via ES is greater when compared to outbreaks first identified through AFP surveillance. Interaction between non-polio AFP rate and percentage of adequate stool samples was significant for both serotype 2 and serotypes 1 and 3 (IRR 1.02 95% CI 1.01-1.04, p<0.01 and IRR 1.01 95% CI 1.0-1.03, p=0.03, respectively). A regression model was attempted for the 15 outbreaks that were either type 1 or 3, but low sample size prevents meaningful interpretation (Appendix p 263 [23]). The mean estimates of the regression terms for serotypes 1 and 3 were similar in value to serotype 2 estimates, for example, there was no significant difference in surveillance classification for serotypes 1 and 3 (IRR 0.22, 95% CI 0.04-1.28, p=0.08), but the confidence intervals of the regression estimates were wide, likely due to low sample size.

Table 2. Final regression model of factors associated with the number of nucleotide differences of the first isolate of vaccine derived poliovirus (VDPV) outbreaks.

*Sample size and dispersion parameter (ϑ) for the serotype 2 model are reported. AFP = acute flaccid paralysis; ES = environmental surveillance; CI = confidence interval; *IRR=incidence rate ratio, used to compare the relative rates between each of the variables and the intercept, or baseline comparator.*

Variable	Serotype 2 (n = 59) θ = 0.99 Factor	IRR*, multivariable (95% CI)	P-value
Intercept	-	-	
Unit increase of non-polio AFP rate (cases per 100,000 children aged <15 years old) Mean (95% CI): 8.9 (7.3, 10.4)	Linear term	0.18 (0.06, 0.49)	<0.01
Percent of stool samples adequately collected Mean (95% CI): 86.2 (84.2, 88.2) <80%: n = 9 (15%)	Linear term	0.91 (0.84, 0.99)	0.047
Unit increase of non-polio AFP rate * Percent of stool samples adequately collected	Interaction term	1.02 (1.01, 1.04)	<0.01
Type of surveillance via which first isolate was detected (AFP case or ES) AFP: n = 42 (71.1%) ES: n = 17 (28.8%)	ES (vs. AFP)	2.15 (0.93, 5.4)	0.069

The effects of non-polio AFP rate on nucleotide differences are shown in Figure 1, where the negative binomial regression model for serotype 2 is used to predict counts of nucleotide differences. To illustrate the interaction between non-polio AFP rate and percentage of adequate stool samples, Figure 1a illustrates that as both non-polio AFP rate and percentage of adequate stool increases, predicted nucleotide differences decline. Although the type of surveillance via which the first isolate was detected (AFP case or ES) was not significant in the final model and could act as a confounder, in Figure 1b, predicted nucleotide differences decrease as non-polio AFP rate increases for both surveillance mechanisms, but to a greater extent for AFP at low rates of non-polio AFP surveillance.

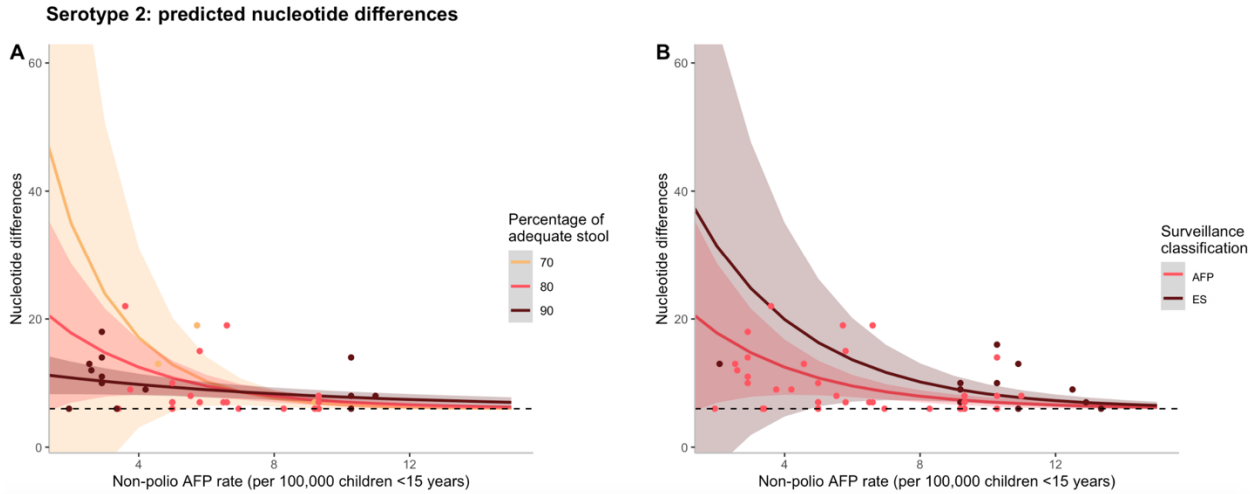

Figure 1. Predicted nucleotide differences for serotype 2.
(A) Predicted counts of nucleotide differences for serotype 2 based on the final negative binomial regression model vs. non-polio AFP rate (per 100,00 children <15 years of age). The different colour lines correspond to varying percentages of adequate stool samples collected and the shaded regions represent a 95% confidence interval of model predictions. The different colour points also correspond to varying percentages of adequate stool samples collected but represent data from a particular cVDPV2 outbreak. (B) Predicted counts of nucleotide differences for serotype 2 based on the final negative binomial regression model vs. non-polio AFP rate (per 100,00 children <15 years of age). The different colour lines correspond to the type of surveillance via which the first isolate was detected, and the shaded regions represent a 95% confidence interval of model predictions. The different colour points also correspond to the type of surveillance via which the first isolate was detected but represent data from a particular cVDPV2 outbreak. In both figures, the black dashed line represents the minimum threshold cut-off of nucleotide differences (n=6) to be considered a cVDPV2.

Model residuals (Figure 2a) for the serotype 2 model support an appropriate model structure as the plot illustrates homoscedasticity of the residuals. The Q-Q plot (Figure 2b) further supports the assumed theoretical distribution for the final models as most values are centred along the Q-Q line, but the extreme values illustrate deviation from the assumed normal distribution of residuals. Figure 2c provides a visual comparison of expected vs. observed frequencies of nucleotide mutations. For serotype 2, outbreak frequencies corresponding to 6, 13, 19 and 22 nucleotide mutations are under-estimated by the model. Similar figures for serotypes 1 and 3 can be found on Appendix p 264 [23].

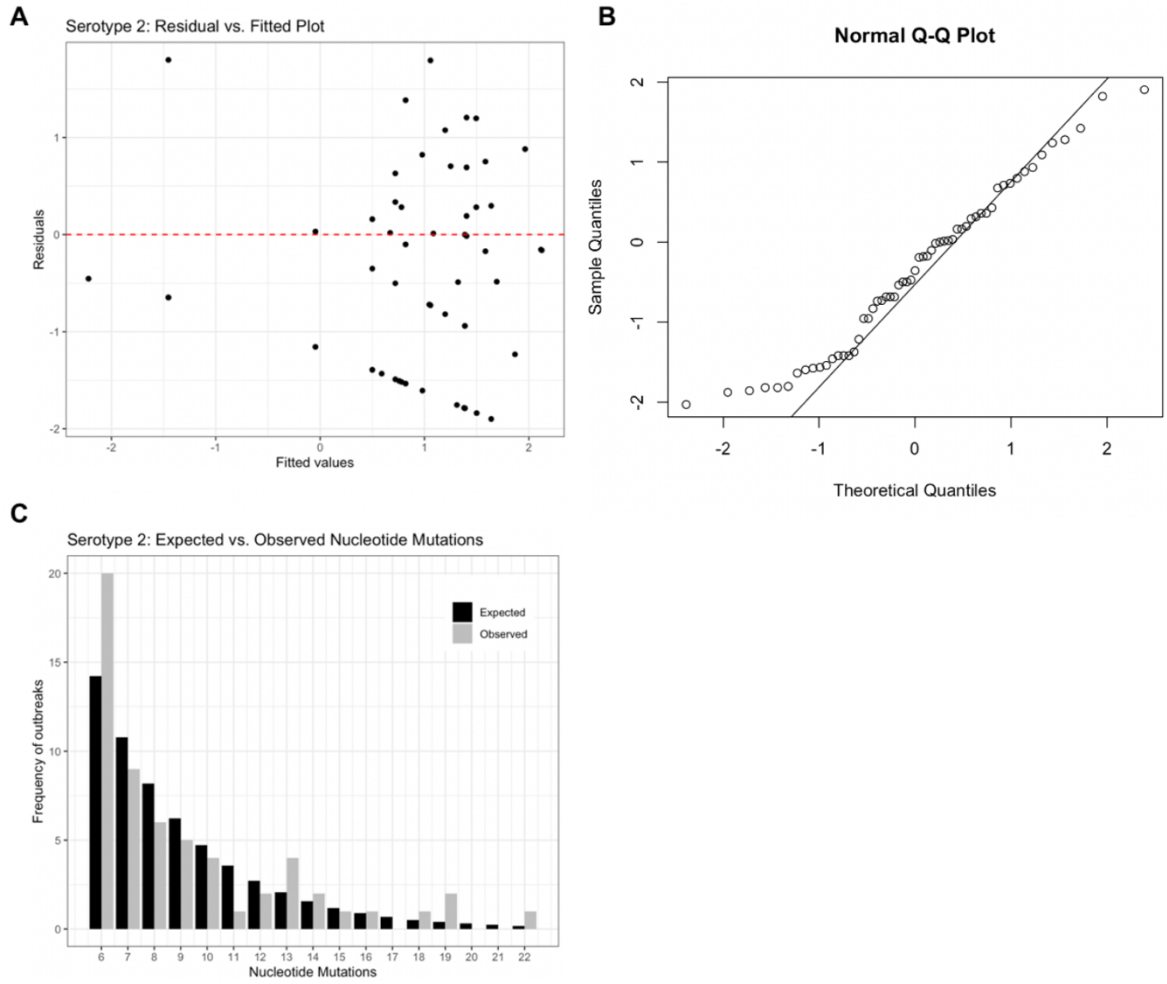

Figure 2. Serotype 2 diagnostic plots. *(A) residual vs. fitted values, (B) Normal Q-Q plot and (**C**) Expected vs. observed frequencies of nucleotide mutations assuming a negative binomial distribution. Figure 2A shows how far the fitted values vary from the residual values, the closer to the red dashed line, the better fit. Figure 2B is used to analyse the distribution of the data. Because several points at the bottom left of the figure deviate from the Q-Q line, the data is positively skewed towards lower nucleotide mutations.*

5.6.2 Estimating the time to outbreak detection

The time to detection was estimated for each outbreak, including uncertainty intervals (Figure 3). Using the bootstrap method, the median time from seeding until outbreak detection for serotype 1 (n=10), was 572.3 (95% UI 279.1 - 2015.8) days and it was estimated that 91.5% of outbreaks would be detected within four years. The median time from seeding until outbreak detection for serotype 2 (n=59) was 276.1 (95% UI 172.3-764.8) days and 99.7% of outbreaks are estimated to be detected within four years. For serotype 3 (n=5), the median time from seeding until outbreak detection was 472.4 (95% UI 392.1-603.1) days and it was estimated that 100% of outbreaks would be detected within four years. Using the full uncertainty of the estimated time to detection, 20 of the 59 (34%)

outbreaks of serotype 2 were detected under one year, whereas no serotype 1 or 3 outbreaks were detected within one year.

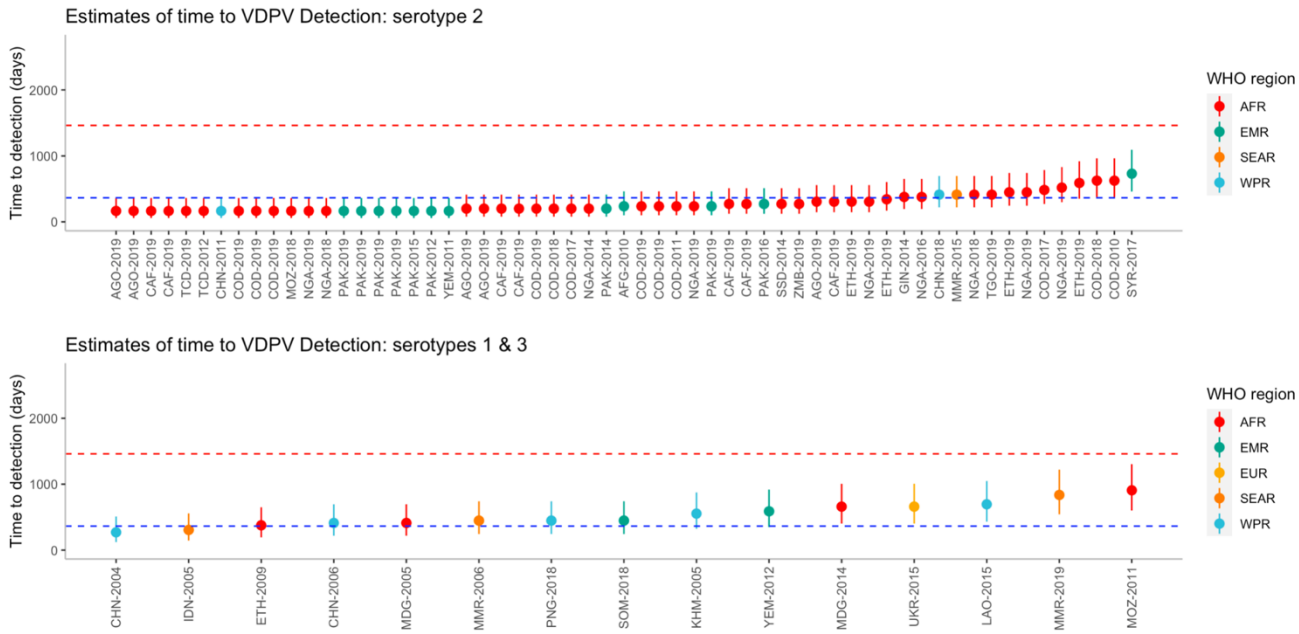

Figure 3. Estimated time to detection of each outbreak from the reported number of nucleotide differences from the Sabin strain, by serotype and region. *Outbreaks are ordered on the x-axis by increasing time to detection, where uncertainty in the estimates are shown using 95% uncertainty intervals. Dashed lines represent one year (blue) and four years (red). Country names along the x-axis have been abbreviated using a country's corresponding United Nations ISO 3166-1 alpha-3 code and year of first detection.*

5.7 Discussion

Polio eradication has been deemed an achievable undertaking, but with timeline and budget pressures ever present, it is importance to better understand the risks associated with cessation strategies and how to better plan for unwanted events. Emerging and circulating VDPVs are one of many threats to eradication, and detecting cVDPVs early to respond and limit transmission in communities will be important throughout the final stages of eradication.

This analysis illustrates several observations about cVDPV outbreaks. cVDPVs caused by serotype 2 have been more commonly detected than outbreaks caused by serotypes 1 and 3. This observation was apparent between 2000–2015 when the trivalent OPV was in use, as well as in subsequent years. When children are vaccinated with the OPV, the serotype 2 strain is more competitive in the gut mucosa [29,30], resulting in increased 'take' by vaccinated individuals and subsequently a higher rate of secondary spread. The increased rate of spread was exacerbated post-Switch as a larger proportion of populations were not vaccinated with the serotype 2 strain due to the strategy of cessation. Additionally, a recent modelling study using inference from data on several clinical trials suggests that

the order of transmissibility within equivalent populations is in the descending order of serotype 2, 1, and 3, which would further explain the observed frequency of each serotype-specific VDPV outbreak [31].

The number of nucleotide differences at the time of detection did not significantly vary between serotypes. For serotype 1, it has between estimated that there are approximately 200 infections for every case, 2000 infections for a serotype 2 case, and 1000 infections for a serotype 3 case [32]. Based on differences in the asymptomatic rate, one might expect nucleotide differences of type 1 and 3 to be lower than serotype 2 when first detected, which was not observed. Based on the data from reported outbreaks, detection of cVDPVs does not seem sensitive to differences in symptomatic reporting that is associated with serotype but may be influenced by unknown differences in where serotype specific detections emerge, which in-turn are affected by surveillance efforts within these countries.

In countries where ES is present, detection of emergent cVDPVs has previously been shown to be quicker than if surveillance relied on AFP alone [33]. Here, we identified weak evidence that outbreaks detected through ES had higher nucleotide divergence, which is contradictory. However, ES is likely placed in locations with known risks of poliovirus transmission and potential challenges in AFP reporting, which may potentially bias findings. Although WHO region did not account for differences in detection time, ES is more commonly implemented across the AFR and EMR regions in comparison to other WHO regions. The total number of active ES sites across AFR, EMR and SEAR WHO regions was 620 in 2020, a 15% increase in the number of reported active ES sites in 2019 [34], but the percentage of the population within a catchment area remains comparatively low and poorly measured. While ES remains a useful source for detecting circulating viruses, its low coverage will mean that ES can only supplement AFP surveillance to enable rapid detection of VDPVs.

The relationship between non-polio AFP rate and time to detection illustrates that in order to detect VDPVs early, a country needs to maintain a high rate of non-polio AFP surveillance. Now that wild poliovirus has been eliminated from the African continent, there may be incentive to reduce the intensity of non-polio AFP surveillance in the region. However, in line with the Global Polio Eradication Initiative Strategic Plan 2019–2023, which calls for closing gaps and strengthening global surveillance, this analysis has illustrated the importance of maintaining a high rate of non-polio AFP surveillance, especially for timely detection of cVDPVs [11]. While higher NPAFP rates well beyond the minimal threshold for quality are more predictive of earlier cVDPV detection, this does not necessarily mean

that the surveillance standard is too low. Instead, this suggests that while standards are in place, they perhaps do not accurately capture localised issues that may mitigate surveillance sensitivity. Accurate rates of clinical syndrome that are not associated with poliovirus (i.e., Guillain-Barré syndrome) would need to be detected with greater sensitivity to ensure true cases of poliovirus are not missed [35]. The most recent GPEI protocol for responding to poliovirus outbreaks describes NPAFP goals and how recommended levels of surveillance may vary across high-risk areas versus smaller areas with fewer children under 15 years of age [36]. Therefore, as cVDPVs remain a threat, AFP surveillance must remain high in all areas with OPV use and/or suboptimal IPV coverage. Low rates of NPAFP surveillance that persist across many settings coupled with the low case to infection rate for polio means undetected transmission is possible in many areas, jeopardising the attainment of polio eradication. As the risk of importation of infection across the African continent increases following the 2021 WPV1 importation in Malawi [37], adopting strategies to improve surveillance are increasingly important.

Adequate stool describes both the timeliness and quality of the samples (i.e., collected within 14 days of paralysis onset, 24–48 hours apart, and arrival at the laboratory in "good" condition) and current WHO guidelines state that at least 80% of AFP cases should have stool collection described as adequate, which this analysis further supports [38]. However, while the mean percentage of adequate stool specimens in this analysis exceeds 80% for all serotypes, 15% and 20% of outbreaks of serotypes 2 and serotypes 1 and 3, respectively, fall below this targeted 80%. Also, this indicator is often reported at the national level while research suggests that percentage of adequate stool specimens is not only disparate at subnational levels, but age groups are not well-covered by the surveillance system and some countries report inaccurate rates of adequate stool specimen collection [39]. After accounting for factors other than WHO regions, WHO region did not remain a significant explanatory variable, suggesting region specific differences do not account for nucleotide divergences as much as surveillance quality (both non-polio AFP rate and percentage of adequate stool samples collected).

Of the cVDPV2 outbreaks that were seeded post-Switch, the source of about 95% of isolates was found to be consistent with mOPV2 outbreak response campaigns [26]. This has been due to the inherent nature of mOPV2, and likely poorly implemented campaigns, and because children recently vaccinated with mOPV2, or their contacts, travelled outside the response zones to areas where children born after the Switch were fully susceptible to infection [40]. The need to improve these response campaigns has been recognised with an addendum to the Polio Endgame Strategy 2019–2023, whereby the strategy is to implement actions such as enhanced outbreak response campaigns and ensure sufficient supply of mOPV2 to diminish immunisation gaps [10]. The novel OPV2 vaccine

replaced the mOPV and received WHO prequalification approval in December 2023 for use under the Emergency Use Listing regulatory pathway [41]. This new vaccine reduces the risk of cVDPV2 emergence [41]. As illustrated in this analysis, emergences of cVDPV2 from mOPV2 are likely to continue for up to four years after the last mOPV2 campaign, meaning that nOPV2 use in outbreak response will be required for at least this period.

A weakness of our approach is that we assume that VDPV mutations occur at a constant and independent rate. In reality, multiple mutations may result in a reduction in nucleotide divergence (through back mutations). Consequently, our estimates may under-estimate the time to detection. Additionally, we have not used data on ambiguous (aVDPVs – progenitors to cVDPVs) to observe the frequency of detection across WHO regions. Inclusion of this data may provide further insight on factors associated with detection but is reliant on consistent laboratory reporting of aVDPVs across WHO regions. Additionally, this analysis was a retrospective analysis of cVDPV outbreaks where few countries have included IPV into routine immunisation, meaning that we were unable to explore any effects of IPV on VDPV detection. Furthermore, this analysis was done at the national level, where no relationship between RI coverage and time to detection was observed. We recognise that at a smaller geographical level, the relationship between RI coverage may have a stronger relationship with time to detection, highlighting a potential type 1 error and limitation to this analysis.

In conclusion, this analysis of cVDPV outbreaks illustrates that surveillance for AFP—ensuring a high non-polio AFP rate with adequate stool collection—can result in quick detection of cVDPV outbreaks, having the potential to prevent transmission and subsequent cases in populations. In all regions, undetected circulation of poliovirus will remain an issue until the current OPV vaccines are no longer necessary.

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6. Chapter 6: Discussion

6.1 Summary of findings

6.1.1 Understanding risks and benefits of different polio vaccination strategies to avert outbreaks following WPV1 importations

This work highlights the risks and benefits of vaccination strategies with varying frequencies of pSIAs to mitigate and prevent an outbreak following a WPV1 importation into Africa. I conclude that areas with low levels of RI coverage (<67%) would benefit from doing annual or Biennial pSIAs to prevent a WPV1 outbreak—both annual and Biennial pSIAs are cost-effective at this RI threshold. Given a limited annual budget alongside difficult decisions about vaccination programming, this work demonstrates that in areas with high levels of RI coverage (>85%), pSIAs could be removed entirely from vaccination programming and a low outbreak risk would persist. To inform the polio endgame strategy, an increasing amount of focus is centred around consequential geographies. These geographical areas may be at an increased risk of an outbreak given low vaccination coverage and low population immunity, or migratory patterns may result in an increased risk of an importation or spread of virus across country borders. Given these considerations for future polio programming, it is important that the combined health system and GPEI perspectives is considered to analyse costs alongside risks of outbreaks and DALYs.

This chapter aligns with the aims and objectives of this PhD—it involved complex mathematical modelling of polio transmission dynamics and incorporated health economic methodologies to conduct a cost-effectiveness analysis. Lessons learned from this work have taught me the delicate balance between costs of vaccination programmes and risk of outbreaks when planning vaccination interventions for diseases near eradication. The skills obtained during this work are directly transferrable to a career in vaccine epidemiology and health economics.

6.1.2 Which measles vaccination strategies have resulted in the greatest impact over time?

Analysing historic measles vaccination strategies deployed at different time across different countries offers a unique perspective of evaluating the impact and efficiency of the different strategies. For example, in countries with low routine immunisation coverage, such as Madagascar, SIAs remained an important strategy to reach children who were unvaccinated. However, MCV2 showed relatively less effect than SIAs in countries with low MCV2 coverage such as DR Congo, Nigeria, Angola, Ethiopia, and Somalia, even under the assumption of early MCV2 introduction, compared with countries with

higher sustained MCV1 coverage such as China and Malawi. This direct comparison of strategies highlights that differences exist even between some bordering countries and that going forward, a 'one-size-fits-all' approach for SIA planning would fail to account for country level differences in strategy implementation.

This work uses the indicator NNV to evaluate the efficiency of strategies to deliver vaccine doses, for example, uncovering if doses are more likely to go to previously vaccination children or zero-dose children. In the IA2030 strategy alongside the Measles and Rubella Strategic Plan, addressing zero-dose populations is a priority. If SIA efficiency is low in a particular setting, as shown by a high predicted NNV to prevent a case, but SIAs consistently result in a greater burden reduction than MCV2, investing in mechanisms to improve efficiency could be used to help target zero-dose populations.

This chapter aligns with the aims and objectives of this PhD because alongside mathematical modelling of measles vaccination strategies, it demonstrates my ability to use different metrics to evaluate the incremental impact of SIAs in addition to RI. This chapter also showcases my ability to apply similar methodologies to different pathogens and the collaborative nature of the project has prepared me for future work in vaccine impact modelling.

6.1.3 Determining the importance of surveillance in quickly detecting cVDPVs

Learning from mistakes made during *The Switch* that led to pockets of susceptibility and subsequent increased spread of cVDPVs in important going forward in the polio endgame. For example, in 2023, a bOPV cessation task team was formed to evaluate existing literature on cessation risks and timelines for withdrawing global use of bOPV. To be well-informed ahead of global bOPV cessation, accurate estimates of time from cVDPV emergence to detection are crucial… declaring eradication and withdrawing bOPV from use prematurely could result in a catastrophe that undermines the entire polio programme. Chapter 5 of this thesis contributes to global literature on detection and circulation of cVDPVs. I identify the importance of high-quality AFP and environmental surveillance in detecting cVDPVs quickly. For example, the relationship between non-polio AFP rate and time to detection illustrates that to detect VDPVs early, a country needs to maintain a high rate of non-polio AFP surveillance. I also demonstrate an upper uncertainty interval approaching 4-years from emergence to detection, which highlights that in the absence of quality surveillance, undetected virus could circulate for a substantial amount of time. As we approach the timelines for bOPV cessation, this work has the potential to greatly influence cessation policy decisions.

This chapter's research aligns with the aims and objectives of this PhD because the epidemiological approaches showcase my ability to conduct statistical analyses with different forms of data (i.e. nucleotide mutations) that may have different distributions and variances across different virus serotypes. This work required in-depth knowledge of polio surveillance methods and an understanding of the history of cVDPVs. Conclusions from this work are important for my future career plans in vaccine epidemiology—understanding the adverse or indirect effects of vaccination strategies (i.e. seeding future VDPVs with use of OPV) is important for vaccination programming and policy making.

6.2 Strengths and limitations

Each research chapter in this thesis includes a discussion section outlining specific limitations of my research. Here, I will focus on the overall strengths and limitations of this thesis.

6.2.1 Strengths

6.2.1.1 Using real-world data

In the measles chapter, the novelty of the work is the direct comparison of historical vaccination strategies implemented at different times across high-burden countries, rather than comparing only hypothetical scenarios about coverage. Previous analyses of measles vaccine impact [1, 2] failed to analyse the incremental impact of different vaccination strategies between countries as the strategies deployed between countries were not always directly comparable—even neighbouring countries introduced strategies and vaccines (i.e., MCV2) at different points in time. By using historical vaccination data, we can provide meaningful comparators across countries and time.

In the cVDPV chapter, nucleotide mutation data obtained from actual cVDPV isolates was used to estimate the time from seeding to outbreak detection. Using real-world lab confirmed data on nucleotide mutations allowed us to produce accurate estimates of time from seeding to detection. Previous analyses that used the polio SIA calendar to estimate the date of likely seeding events are limited because they only provide rough estimates of circulation time and operate on limitations inherent in SIA reporting, for example, dates of the campaign, number of doses delivered, and proportion of the target population vaccinated. Using nucleotide data obtained from cVDPV isolates allows for a more accurate estimate of circulating time to be estimated and a direct comparison in time from emergence to detection across all serotypes.

6.2.1.2 Application across different diseases

I have demonstrated in this thesis that similar policy questions around vaccination strategies can be used across both measles and polio to achieve respective elimination and eradication programmatic goals. Even though the vaccination interventions vary slightly between polio and measles, for example house-to-house vs. fixed post SIAs, questions around efficiency, impact and costs associated with the varying strategies are similar across both diseases.

Skills acquired during this PhD research allowed me to research vaccination strategies for other diseases, such as chikungunya, for which global introduction of a new vaccine is now occurring. In November 2023, the United States Food and Drug Administration approved IXCHIQ, the first chikungunya vaccine developed by Valneva. To navigate the complexities of introducing this vaccine, stakeholder engagement is crucial for devising effective vaccination strategies, deciding on the optimal timing for vaccination, establishing vaccine stockpiles, and pinpointing target populations. I therefore conducted a stakeholder evaluation study, guided by Evidence to Recommendation (EtR) criteria used by National Immunisation Technical Advisory Groups (NITAGs).

This stakeholder engagement spanned four global regions at risk of chikungunya outbreaks and identified gaps in EtR criteria around unknown disease burden, stemming from diagnostic challenges, the unpredictable nature of outbreaks and lack of disease specific passive surveillance. Stakeholders also grappled with the disease's high morbidity yet lower mortality, which complicates disease prioritisation amidst competing health threats, like dengue and other febrile illnesses. Furthermore, there is ambiguity surrounding the target population for the vaccine, with logistical challenges in rollout, uncertainty about age-specific targeting, and deployment strategies, further exacerbated by socioeconomic factors of populations most at risk of chikungunya infection. The full-text published manuscript can be read in the Appendix section 7.1.1. To address in part the evidence gaps highlighted in the stakeholder analysis, I then collaborated on a systematic review, meta-analysis, and modelling study to estimate chikungunya seroprevalence, force of infection, and prevalence of chronic disability after infection in endemic and epidemic settings [3].

During this PhD, I also collaborated with the Vaccine Impact Modelling Consortium to estimate the health effects of COVID-19-related immunisation disruptions against 14 pathogens in 112 low-income and middle-income countries during 2020-30 [4]. Specifically, I co-generated the health impact estimates for vaccines against measles, *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and rotavirus. These estimates by used by key stakeholders (Gavi, the Vaccine Alliance and the Bill and

Melinda Gates Foundation) for decision-making on resource allocation strategies, further highlight that skills gained during this PhD are transferrable to other diseases and research questions.

I have also used the skills gained during this PhD to collaborate on research that evaluates different computational approaches and software for evaluating polio and other diseases, specifically Salmonella typhimurium in pigs [5]. This work demonstrates my understanding of computational considerations for disease modelling and my ability to collaborate on cross-cutting research spanning different diseases, species and disciplines. The full text of this work can be read in Appendix section 7.1.2.

6.2.2 Limitations and remaining gaps in knowledge

6.2.2.1 Modelling homogenously mixed synthetic populations

In Chapter 3's polio economic modelling, the modelled population is assumed to mix homogenously, which is a limitation. In the real world, population mixing contributes to disease transmission and heterogenous vaccination overage and population immunity create pockets of susceptibility within countries. If an imported virus were to enter a geography with low population immunity, there would be a greater risk of an outbreak than if an importation were to arrive in an area with higher population immunity. I modelled a hypothetical LMIC in Africa but assume baseline RI coverage is the same across the entire population. The research findings in Chapter 3 still have important implications for policy, especially as the model assumptions and outputs are coherent and easy to understand. But, to provide improved risk estimates, future research could account for subnational variations in population immunity, which could be used to improve costs assumptions and associated benefits of SIAs.

6.2.2.2 Limited time horizons

Each of the research chapters present work over a defined period: Chapter 3 focuses on a 5-year modelled time horizon from 2023-2028, Chapter 4 analyses historical strategies from 2000-2020 and Chapter 5 analyses cVDPVs from 2010-2020.

Firstly, estimates from Chapter 3's polio economic modelling align with the 2023 GPEI strategic plan, but do not allow for consideration of the costs associated with further delaying the polio eradication timeline through outbreaks, or the societal implications of outbreaks on polio eradication. By limiting the analysis to a five-year time horizon, the benefits of SIAs (particularly pSIAs) are under-estimated as they will increase the likelihood of eradication. Next, in Chapter 4's measles vaccine impact modelling, evaluating vaccination strategies only up to 2020 means that effects of the COVID-19

pandemic on vaccination were not modelled. Research has demonstrated the disruption caused to both RI and SIAs during the pandemic [6], so more research is needed to understand if NNV and efficiency of different strategies have rebounded after pandemic disruptions.

6.2.2.3 Assumptions for SIA target populations and data reporting biases

In the measles vaccine impact modelling work, I did not explore potential differences in effectiveness and efficiency between selective and non-selective approaches—the former referring to SIAs that vaccinate only children with no previous history of vaccination and the latter referring to vaccination during an SIA regardless of doses previously received. Polio SIAs are usually non-selective. Measles SIAs can vary in selection criteria for the target population. Some countries have implemented selective measles SIAs, but more empirical data are needed to assess the feasibility of this approach in a range of geographies.

In both polio and measles modelling chapters, SIA doses were assumed to be randomly delivered to the target population, with an exception in the measles work where a fixed proportion of children who were assumed to be less likely to be reached by childhood immunisation programmes were not allocated doses. In practice, however, the random distribution of doses may vary in reality for several reasons: mother's recall of previous vaccination may be incorrect, accessibility issues may mean the entire target radius cannot be reached by vaccinators, mother's may refuse vaccination on behalf of their children, vaccine supply issues may cause changes or disruptions to the designated area or population for vaccination, amongst other logistical challenges that occur in the field [7, 8]. Therefore, the assumptions made in the polio and measles modelling chapters around random dose allocation during SIAs may vary in practice, causing the modelled estimates to be over or under-estimated.

6.2.2.4 Multi-intervention SIAs

Multi- intervention SIAs refer to SIAs that combine multiple interventions, such as OPV + MCV, OPV + de-worming medication, OPV + Vitamin A supplementation, MCV or OPV + bed net distribution [9]. Although multi-intervention SIAs occur less frequently and vary across regions, the indirect effects of SIAs are important for vaccine impact modelling and economic analyses. For example, if an SIA combines multi-interventions, the DALYs averted associated with this intervention may increase by protecting against multiple pathogens. Further studies are needed to assess the combined effectiveness and efficiency of integrated campaigns. The measles and polio modelling chapters do not consider the impact of multi-intervention SIAs due to limited data availability on combined campaigns. Also, because funding is usually disease specific, (i.e. GPEI funds are used only for polio

SIAs, not measles SIAs), the economic work on the cost-effectiveness of multi-intervention campaigns is limited in scope and geography [10]. By not considering multi-intervention SIAs in either of my models, the estimated impact of polio and measles vaccination strategies may under-estimate the true reach or potential of SIAs.

6.3 Feasibility of polio eradication

This PhD has given me perspectives into the complexities of disease control programmes and the delicate balance between elimination and eradication efforts, scientific innovation and political will. In the following sections, I critically summarise the feasibility of polio eradication and measles elimination given current timelines given the knowledge and insights I acquired during this PhD.

Efforts towards polio eradication alongside the GPEI have faced numerous challenges, especially in recent years, leading to critiques of the feasibility of global polio eradication. While substantial progress has been made in reducing the worldwide incidence of infection to zero, various issues have hindered complete eradication, resulting in a divide between those who believe eradication is still achievable and those who argue it may not be possible under current conditions.

6.3.1 Criticisms of global polio eradication efforts

The widespread use of the OPV and the vaccine's unintended consequence has raised concerns over the sustainability of eradication efforts as the emergence and geographical spread of VDPVs is increasing [11]. Even after the recent use of nOPV2 in response to cVDPV2 outbreaks, the epidemiology of cVDPV2 outbreaks in 2024 is concerning. A total of 532 cVDPV2 cases were confirmed in 26 countries during January 2023–June 2024 [12]. As of August 2024, there were 13 independent cVDPV2 emergences detected globally, including detections in July 2024 in Gaza Strip [12]. Most recently, as of 9 October 2024, cVDPV2 was detected in Barcelona, representing the first time that cVDPV2 was reported in Spain [13].

While type cVDPV2 outbreaks have been the most widespread, cVDPV1 and cVDPV3 cases are also increasingly reported, particularly in areas with gaps in immunisation coverage, where the virus can spread undetected and evolve further [14]. From January 2023–June 2024, a total of 140 cVDPV1 cases were confirmed, (111 of which were in DRC), 106 (75%) in 2023, and five (5%) in the first half of 2024 [12]. No new cVDPV3 emergences were detected during January 2023–June 2024. The ongoing transmission of multiple types of cVDPVs highlights vulnerabilities in global immunity levels and suggests that, despite advances, eradication efforts face considerable setbacks due to the need for

OPV in high-risk regions, which perpetuates the cycle of VDPV emergence. This evolving epidemiology underscores the importance of maintaining robust vaccination and surveillance programmes, even in regions that are polio-free, to prevent re-emergence and address immunity gaps that drive these outbreaks. The ongoing circulation of VDPVs raises doubts about the ability to achieve complete eradication. Research suggests that as long as OPV is used in some capacity, there remains a risk of VDPVs emerging, which may necessitate continued vaccination and surveillance indefinitely [15].

6.3.1.1 Security and accessibility challenges

Eradication efforts have been hindered by conflict and political instability in endemic regions, particularly in WPV endemic countries, Afghanistan and Pakistan. In these areas, vaccination workers often face significant security threats, making it challenging to reach all children [16, 17]. These issues have contributed to a persistence of susceptibility reservoirs in inaccessible populations. As of 29 October 2024, the total number of WPV1 cases in 2024 is 64, compared to 10 for the same period in 2023 and a total of 12 reported WPV1 cases in all of 2023 [13]. Until WPV1 transmission is interrupted in Afghanistan and Pakistan, importations of infection will remain a concern, which has risks and consequences, as I have outlined in Chapter 3.

6.3.1.2 Cost and resource allocation

Some experts argue that the costs of continued eradication efforts are becoming prohibitive, diverting resources from other critical health needs in LMICs [11, 18]. Given the high financial demands of the polio eradication programme, it is uncertain whether these resources might achieve better overall health outcomes if redirected to broader health infrastructure [19]. I agree with these arguments because in my experience, emphasising the importance of preventative SIAs has proven difficult. Whilst there is a clear benefit of doing preventative vaccination, other competing health priorities (for example, COVID-19) have required attention in recent years and ongoing polio efforts are sometimes seen as disruptive of other ongoing outbreaks that need attention.

6.3.1.3 Vaccine hesitancy, misinformation and challenges for the future

In recent years, vaccine hesitancy and misinformation have become more pronounced, particularly in regions with socio-political challenges. In Pakistan, for instance, misinformation regarding the polio vaccine has led to refusals and violent reactions against health workers, undermining eradication efforts [17]. Vaccine hesitancy has contributed to the persistence of polio in areas where community cooperation is critical for programme success [20].

Other challenges for the post-eradication period are containment of the virus and asymptomatic carriers. Thompson et al. cautions that, even if eradication were achieved, the risk of laboratory or environmental reintroduction of poliovirus would necessitate ongoing precautions, making the "end" of polio a costly, perpetual goal [18, 21]. The maintenance of virus containment and biosecurity adds further complexity to the eradication target. Some critics argue that eradication is a highly complex goal that may be unattainable with current tools and strategies, especially with the added challenge of asymptomatic carriers who can unknowingly transmit the virus [22]. This hidden transmission complicates eradication efforts by making it difficult to identify all cases and interrupt the virus's spread fully.

6.3.2 Support for the feasibility of polio eradication

Despite these challenges, some researchers and public health experts continue to support the goal of polio eradication. Innovations in vaccine formulation, such as the new monovalent OPV, offer hope that eradication is still possible by minimising the risk of VDPVs [23]. These vaccines provide immunity without the risks associated with live attenuated vaccines, making them safer options for widespread use in polio-free areas [23]. The GPEI has reduced polio cases by over 99% since its inception, demonstrating that eradication strategies have been effective in most regions [24]. Continued success in maintaining polio-free status in previously endemic areas suggests that, with increased efforts, eradication remains a viable goal.

From an economic perspective, achieving eradication has the potential to yield significant long-term cost savings by eliminating the need for ongoing vaccination and surveillance programmes [25]. Eradication proponents argue that the financial benefits of stopping polio entirely outweigh the current costs of control measures [26]. Alongside the research used to justify the sustained feasibility of polio eradication, non-governmental or charitable organisations, such as the Gates Foundation and Rotary International, remain optimistic. Renewed contributions from donors, such as high-income governments (i.e. via the UK's Department for International Development or the United States AID programme) are crucial for addressing budget gaps and sustaining high energy and motivation for reaching the final stages.

6.4 Feasibility of measles elimination

Measles has been targeted for elimination rather than eradication due to several key factors that make complete eradication challenging. Moreso than polio, measles is an extremely contagious virus with an R_o value between 12 and 18, the highest of any known infectious disease [27]. This high

transmissibility means that even a small number of susceptible individuals can maintain measles transmission within a population, making the achievement of global herd immunity harder to sustain [28]. The complexity of reaching such high vaccination coverage worldwide, along with challenges such as vaccine hesitancy, has led to measles being targeted for regional elimination rather than complete eradication, unlike polio.

6.4.1 Why measles elimination is still feasible

Despite these challenges, measles elimination remains feasible in many regions due to the availability of the highly effective vaccines and strong regional public health initiatives. Various regions, including the Americas, have historically achieved prolonged periods of measles elimination, showing that with sufficient political commitment and sustained vaccination efforts, elimination is possible on a large scale [29, 30]. Successful elimination in regions such as the Americas provides a framework that can be adapted by other regions, particularly through the WHO Measles and Rubella Partnership.

Also, in contrast to polio eradication strategies, measles elimination can be achieved with high two-dose coverage because of the very high VE of measles vaccines, or, in settings with suboptimal RI, with periodic measles SIAs implemented every 3–5 years [31]. Multiple repeated SIAs targeting the same age groups (as done in polio SIAs with the OPV), will not be required for measles [32]. Thus, measles elimination can move forward with a 'diagonal approach,' using measles surveillance data to identify areas missed by vaccination and using efforts to achieve high vaccination coverage to strengthen the wider health system [32, 33] versus focusing only on measles in a vertical approach.

6.4.2 Challenges for measles elimination given current timelines

Maintaining measles elimination has proven difficult, and current timelines for global elimination may not be achievable due to challenges like vaccine hesitancy and inadequate health infrastructure in certain regions. Vaccine hesitancy, driven by misinformation and distrust in vaccines, has led to declines in immunisation uptake in regions where measles had previously been controlled or eliminated [34]. This hesitancy, coupled with resource constraints and limited access to vaccines in LMICs, has enabled measles outbreaks to resurge in countries with previously high coverage [30]. The global response has been hindered further by competing public health priorities and insufficient funding for SIAs, as measles control efforts have often had to share resources with other pressing health needs [35]. These factors make it challenging to achieve and sustain the high levels of coverage required for elimination in all regions, especially given the contagious nature of measles.

Furthermore, the COVID-19 pandemic has disrupted vaccination programmes worldwide, exacerbating the challenges of maintaining measles elimination. The pandemic has led to the postponement of both RI and SIAs, increasing the number of susceptible individuals in many regions and raising the risk of large-scale outbreaks [6]. Additionally, measles elimination requires a well-coordinated global surveillance system capable of rapid outbreak detection and response, but many regions lack the infrastructure and resources needed for this [36-38]. With these persistent issues and shifting public health priorities, the goal of global measles elimination within the original timelines set by public health agencies may be difficult to achieve, and efforts may need to be reassessed to account for these evolving barriers. Historically, the global coordination of modellers that exist within GPEI for polio has not been as well coordinated for measles modelling research. Recognition of this shortcoming has led to the creation of a new Measles Analytics Hub within the VIMC, which aims to: (i) facilitate technical discussions and innovation in measles modelling and analytics, (ii) improve communication and collaboration between modelers and stakeholders to deliver research with policy impact and (iii) be inclusive of researchers in high measles burden countries [39.] With improved coordination of measles modelling research, I believe that the important GPEI working groups that have been established for polio eradication can be mimicked for measles research and this will be important for elimination programming.

6.5 The polio legacy and global health programmes

One consideration of disease eradication is the legacy that will be left behind once eradication has been achieved. Following smallpox eradication in 1980, the EPI emerged from the lessons learned and legacy of smallpox eradication, which has proven its value alongside the power of vaccines [40]. One example of the polio legacy being used to improve other public health needs is in Ethiopia. The government successfully used GPEI funding to enhance disease surveillance networks, improve the supply chain and expand human resources for health programmes [41, 42]. As we approach global polio eradication, it is important to further document lessons learned and the infrastructure accumulated by the GPEI to address other health priorities.

The Polio Legacy Management Group aims to both to protect a polio-free world and to ensure that investments in polio eradication will contribute to other health goals after polio is eradicated [40, 43]. For example, legacy planning aims to ensure the innovations that have helped the world achieve polio eradication can be adapted and applied to the EPI and surveillance for other vaccine preventable diseases. The polio legacy also hopes to enable long-term transitions to country ownership of public health activities and innovations historically provided through the GPEI. This includes things such as

the execution of SIAs, including robust planning and mapping of SIA target areas using geospatial technologies, mechanisms and personnel used to deliver vaccines to hard-to-reach areas and using finger-marking and independent monitoring, including lot quality assurance sampling, to monitor SIA quality [43].

However, there are criticisms of the vertical nature of the polio programme as the GPEI's commitment to and focus on polio eradication has taken precedence over strong collaborations with other global health programmes. In many countries with ongoing VPDVs that were more recently WPV-endemic (i.e. WHO AFRO region), the GPEI's approach over the years had not fostered strong relationships with RI and programme administrators for other vaccine preventable diseases [44]. Uncertainty also exists around who should be responsible for the transition process—which agencies will pay for and deliver polio-funded activities [40]? Despite these challenges, I believe that the polio infrastructure has public health importance that will be valuable long after polio eradication is achieved.

One example of a global health programme that could benefit from the polio legacy is measles elimination. Transitioning polio assets to measles elimination efforts could accelerate progress toward measles elimination, increase measles vaccination coverage and improve vaccine equity [31].

Several strategies for measles elimination are similar to those for polio eradication and could be included in a post-eradication transition, such as: (1) achieving and maintaining high levels of population immunity through vaccination via both RI and SIAs (2) using effective surveillance mechanisms to monitor disease; (3) maintaining outbreak preparedness and timely outbreak response; (4) engaging with stakeholders to enhance public confidence in immunisation programmes; and (5) implementing research and innovation to improve the disease programmes [45]. However, there are some differences in delivery of polio and measles vaccines that make some aspects of the polio legacy less applicable to measles elimination. For example, the OPV can be easily administered via drops in the mouth, which has historically made the polio programme heavily reliant on SIAs. Measles vaccines require a cold chain, injectable equipment and trained health care workers to administer the injections. Therefore, measles efforts must have a greater focus on strengthening RI service delivery because of the 'diagonal approach' required to strengthen overall EPI vaccine delivery systems [31].

6.6 Implications of this PhD and future work

The research I have presented in this thesis has implications for further study of vaccine preventable diseases. I demonstrated in Chapter 3 that baseline RI coverage can be used as an indicator of outbreak risk given an importation of WPV1. By using baseline RI coverage and date of last pSIA, policymakers can make informed decisions about the best SIA strategy for different geographies. Additionally, the economic results presented in Chapter 3 also identify potential costs and risks associated with adopting different pSIA strategies. The total costs presented for annual pSIAs vs Biennial pSIAs have implications for future economic evaluations when countries need to decide how to proceed with polio vaccination in the future. For example, since publication, this work has been discussed with colleagues in South Africa who are interested in country-level economic estimates required to raise population immunity and prevent importations, given WPV1 outbreaks in nearby countries.

Using indicators such as NNV to estimate the efficiency of measles vaccination strategies, as done in Chapter 4, offers a framework that can be applied to other measles research. For example, the work from Chapter 4 laid the foundation for my post-doctoral research, investigating the impact of expanding the upper age limit for measles SIAs. Additionally, work from Chapter 4 has been discussed with researchers at the World Bank focused on supply chain logistics, for which NNV and efficiency of SIAs have major implications. The impact and efficiency of different strategies covered in Chapter 4 is also important for other vaccine preventable diseases that are lesser studied. For example, understanding the efficiency of oSIA vs. pSIA strategies was highlighted by global stakeholders as an important consideration for rolling out the first ever chikungunya vaccine, as documented in the stakeholder analysis (Appendix section 7.1.1).

Because timelines for global cessation of bOPV are now under discussion, the work presented in Chapter 5 on time from emergence to detection of cVDPVs has the potential to inform cessation planning. More work that complements this research is currently being done to evaluate genetic lineages of cVDPVs in Africa and the likely movements of the viruses following specifics SIAs [46].

6.7 Concluding remarks

6.7.1 Continued academic pathway

This PhD has prepared me for a career in vaccine epidemiology. I have developed an appreciation for the intersection between epidemiology, health economics, infectious disease modelling and health

policy. I have demonstrated a well-rounded knowledge base across methodologies and diseases and have applied skill learned during this PhD to other academic work. Alongside this PhD, I have conducted other research relevant to a career in vaccine epidemiology. The full-text version of two articles for which I was the lead author are included in Appendix Section 7.1 and other selected publications that I was involved in are listed below:

- Vaccine impact modelling for other antigens
    - Hartner, A. M., Li, X., Echeverria-Londono, S., Roth, J., Abbas, K., Auzenbergs, M., ... & Gaythorpe, K. A. (2024). Estimating the health effects of COVID-19-related immunisation disruptions in 112 countries during 2020–30: a modelling study. *The Lancet Global Health*, *12*(4), e563-e571. https://doi.org/10.1016/s2214-109x(23)00603-4
- Estimating the impact of COVID-19 on childhood vaccination
    - Abbas, K., Procter, S. R., van Zandvoort, K., Clark, A., Funk, S., Mengistu, T., ... & Medley, G. (2020). Routine childhood immunisation during the COVID-19 pandemic in Africa: a benefit–risk analysis of health benefits versus excess risk of SARS-CoV-2 infection. *The Lancet Global Health*, *8*(10), e1264-e1272. https://doi.org/10.1016/s2214-109x(20)30308-9
- Evaluating the role of climate on COVID-19 mitigation strategies
    - O'Reilly, K. M., Auzenbergs, M., Jafari, Y., Liu, Y., Flasche, S., & Lowe, R. (2020). Effective transmission across the globe: the role of climate in COVID-19 mitigation strategies. *The Lancet Planetary Health*, *4*(5), e172. https://doi.org/10.1016/s2542-5196(20)30106-6
- Estimating the seroprevalence of chikungunya ahead of vaccine introduction
    - Kang, H., Auzenbergs, M., Clapham, H., Maure, C., Kim, J. H., Salje, H., ... & Abbas, K. (2024). Chikungunya seroprevalence, force of infection, and prevalence of chronic disability after infection in endemic and epidemic settings: a systematic review, meta-analysis, and modelling study. *The Lancet Infectious Diseases*. *24(5):488-503. https://doi.org/10.1016/s1473-3099(23)00810-1*

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7. Appendices

7.1 Other published work to supplement this PhD research

Alongside this PhD, I have published two additional studies relevant to the methodologies used in this PhD: (1) Stakeholder engagement for introduction of the newly licenced Chikungunya vaccine and (2) Using BUGS for statistical modelling of infectious diseases.

These manuscripts are included here to provide additional justification for the methods used in the research chapters of this thesis and they also demonstrate my continued academic pathway in vaccine research. This PhD has given me an appreciation for the intersection between disease modelling and vaccine policy and these two select publications demonstrate this synergy alongside my ability to use interdisciplinary methods in vaccine research and policymaking.

7.1.1 Programmatic considerations and evidence gaps for chikungunya vaccine introduction in countries at risk of chikungunya outbreaks: Stakeholder analysis

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7.1.1.1 Research paper cover sheet – Chikungunya stakeholder research

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SECTION A – Student Details

Student ID Number	1604063	**Title**	Ms
First Name(s)	Megan		
Surname/Family Name	Auzenbergs		
Thesis Title	Mathematical and statistical modelling to inform polio and measles vaccination programming		
Primary Supervisor	Dr. Kathleen M O'Reilly & Dr. Kaja Abbas		

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

SECTION B – Paper already published

Where was the work published?	PLOS Neglected Tropical Diseases		
When was the work published?	April 2024		
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Have you retained the copyright for the work?*	Yes	Was the work subject to academic peer review?	Yes

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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I worked on: conceptualisation, methodology, formal analysis, visualisation, and writing - original draft

SECTION E

Student Signature	[redacted]
Date	30 May 2024

Supervisor Signature	[redacted]
Date	31 May 2024

7.1.1.2 Abstract

Chikungunya can have longstanding effects on health and quality of life. Alongside the recent approval of the world's first chikungunya vaccine by the US Food and Drug Administration in November 2023 and with new chikungunya vaccines in the pipeline, it is important to understand the perspectives of stakeholders before vaccine rollout. Our study aim is to identify key programmatic considerations and gaps in Evidence-to-Recommendation criteria for chikungunya vaccine introduction. We used purposive and snowball sampling to identify global, national, and subnational stakeholders from outbreak prone areas, including Latin America, Asia, and Africa. Semi-structured in-depth interviews were conducted and analysed using qualitative descriptive methods. We found that perspectives varied between tiers of stakeholders and geographies. Unknown disease burden, diagnostics, non-specific disease surveillance, undefined target populations for vaccination, and low disease prioritisation were critical challenges identified by stakeholders that need to be addressed to facilitate rolling out a chikungunya vaccine. Future investments should address these challenges to generate useful evidence for decision-making on new chikungunya vaccine introduction.

7.1.1.3 Author Summary

The first vaccine to prevent chikungunya fever has been recently approved in November 2023 by the US FDA and multiple chikungunya vaccine candidates are in different phases of the development pipeline. These will be the first-ever vaccines against an alphavirus and offer new technologies for vaccine development against other viruses of the same family that may cause future epidemics. We interviewed stakeholders from areas at risk of chikungunya outbreaks across Latin America, Asia and Africa, and identified gaps in Evidence-to-Recommendation criteria that should be addressed alongside vaccine introduction. Our findings show that stakeholders from different regions prioritised chikungunya differently, but all stakeholders agreed that the unknown burden of disease, undefined target populations for vaccination and non-specific disease surveillance were challenges that needed to be addressed imminently. To address these gaps, the involvement of stakeholders in all phases of vaccine development and rollout will be crucial to uncover future challenges and to ensure vaccine equity.

7.1.1.4 Introduction

Chikungunya is a mosquito-borne neglected tropical disease (NTD) caused by the chikungunya virus (CHIKV), an alphavirus spread by the mosquito vectors Aedes aegypti and Aedes albopictus. Symptoms associated with chikungunya fever are often mild, but can be associated with severe morbidities, such

as persistent arthralgia, reported in 88% of cases up to one month after infection [1] and severe chronic arthralgia lasting years after infection [2, 3]. The severe, chronic morbidities associated with chikungunya fever can have longstanding effects on health and quality of life.

The stochastic transmission dynamics of CHIKV make it difficult to predict when the next outbreak will occur or if CHIKV will become endemic in any specific setting. Chikungunya cases have historically been clustered in tropical areas with warm, humid climates where the vectors thrive and cause recurring outbreaks of chikungunya fever. In a related systematic review and modelling study, we inferred subnational heterogeneity in the force of infection and transmission dynamics as well as identified both endemic and epidemic settings coexisting within countries such as Brazil, Ethiopia, and India [4]. However, the increasing spread of the vector to more geographic regions due to climate change poses a greater risk of CHIKV to more people in the future [5, 6]. CHIKV-carrying mosquitoes are currently endemic in the Americas, parts of Africa, and Southeast Asia [7]. These geographical regions are at high-risk of infection and carry the greatest burden of global chikungunya cases.

On November 9, 2023, the first ever chikungunya vaccine, Ixchiq, was approved by the US Food and Drug Administration (FDA) [8]. The vaccine was developed by Valneva, alongside investment from The Coalition for Epidemic Preparedness Innovations (CEPI) [9, 10]. The vaccine was approved for use in individuals 18 years and older who are at an increased risk of exposure to CHIKV. Currently the vaccine is a one-dose vaccine and is estimated to cost US $350 per dose for US travellers with a discounted cost of US$10–20 per dose in low- and middle-income countries [11]. Whilst chikungunya was not included in the Global Alliance for Vaccines and Immunisation (GAVI) Vaccine Investment Strategy for 2024, a learning agenda will be developed to identify the gaps which need to be addressed before such an investment can be considered. CEPI's support for the chikungunya vaccine development alongside GAVI's learning agenda [12] for this vaccine provides a pathway towards equitable access for chikungunya vaccines in countries at risk of chikungunya outbreaks [13]. A schematic showing the chikungunya vaccine development to introduction pathway is presented in Fig 1.

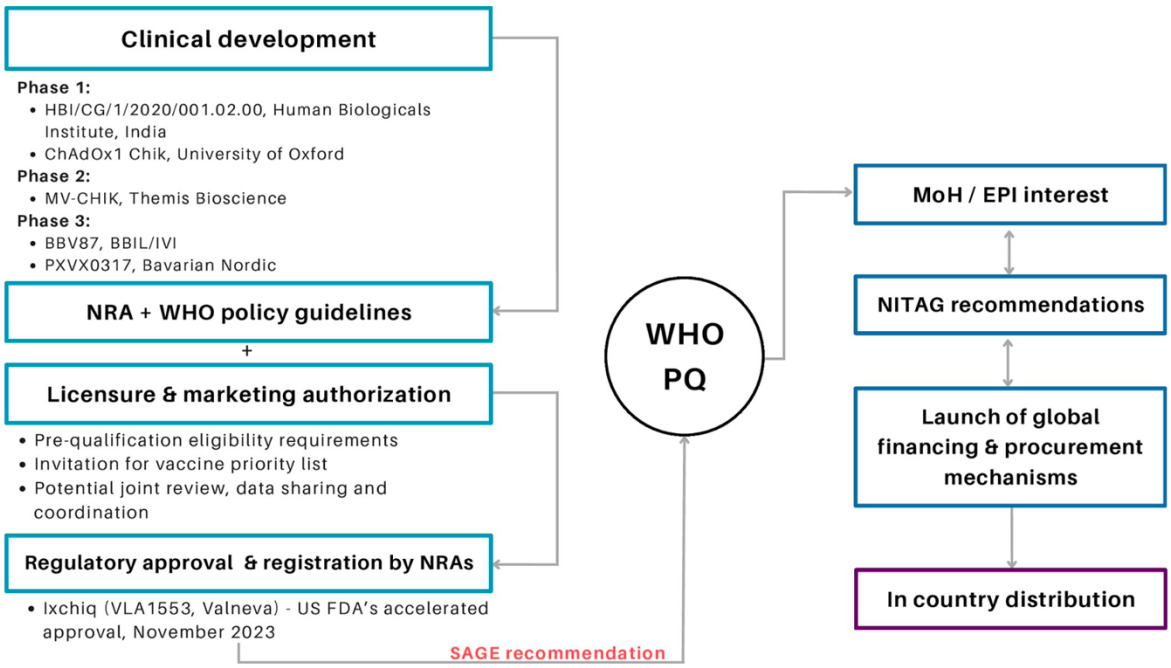

Fig 5. Chikungunya vaccine development to introduction pathway. *Schematic showing the vaccine development process for the chikungunya vaccine alongside stages of licensure and evidence-based recommendations for policy making decisions. WHO–World Health Organization; MoH–Ministry of Health, NRA—National Regulatory Agencies, SAGE–Strategic Advisory Group of Experts, EPI–Expanded Program for Immunization, NITAG–National Immunization Technical Advisory Group, PQ-Pre-qualification.*

A chikungunya vaccine provides primary value in reducing global burden of CHIKV and long-term disabilities associated with CHIKV infection. It also provides additional significant value since this is the first vaccine against an alphavirus genus in the family Togaviridae, thereby enabling a novel vaccine development platform against emerging alphaviruses in the family Togaviridae [14]. As the risk of emerging infections increases with global travel and climate change, having an existing mechanism for developing a vaccine against an emerging pathogen expedites global outbreak response and vaccine development, as was done with mRNA and viral-vector vaccines during the COVID-19 pandemic [15].

The chikungunya vaccine value profile provided a high-level holistic assessment of available evidence to inform the potential public health, economic, and societal value of chikungunya vaccines in the development pipeline [16]. However, evidence to recommend chikungunya vaccine introduction is needed, including the disease burden, benefits and harms of chikungunya vaccination, values and preferences of the target population, acceptability to stakeholders, resources use and economic impact, equity, and feasibility [17]. As the global risk of CHIKV infection increases alongside introduction of the first chikungunya vaccine, we urgently need to understand the target populations for the new vaccine in addition to context specific social, logistical and financial barriers to rolling out

the vaccine [18]. To date, qualitative research on chikungunya has been limited to patient experience, specifically quality of life and coping strategies following infection [19, 20]. Further, there is a lack of research exploring cultural explanations and conceptualizations of CHIKV aetiology in different geographical areas [21].

We aim to identify gaps in the Evidence-to-Recommendation (EtR) criteria needed to assess the introduction of chikungunya vaccine. To our knowledge, this is the first study to synthesise stakeholder perceptions on chikungunya outbreaks and vaccination by interviewing a diverse sample of global, national and subnational stakeholders involved in different elements of chikungunya epidemiology, policy, outbreak control and vaccinology. We provide timely implications for decision-making alongside qualitative data from a robust sample of stakeholders to inform introduction of the first available and licensed chikungunya vaccine.

7.1.1.5 Methods

Ethics statement

Ethical approval for this project was received from the London School of Hygiene and Tropical Medicine in January 2023, project reference number 28292. Written consent was obtained from all stakeholders ahead of the interviews.

Stakeholder selection

We conducted a scoping review on chikungunya epidemiology to identify geographical regions at risk of chikungunya outbreaks alongside countries with ongoing clinical trials of chikungunya vaccine candidates. The regions of Latin America, Africa and Asia were prioritised for stakeholder identification. From here, a diverse list of contacts was created using purposive and snowball sampling of organisational databases, search engines and input from project coordinators at the International Vaccine Institute who oversee several clinical trial networks for chikungunya. At the end of all interviews, we requested stakeholders to recommend colleagues that would be also interested in taking part in an interview, to which a follow-up invite was sent. Further explanation of the stakeholder sampling framework can be found in S1 Fig. Participants were first grouped into geographical categories and then grouped into one of three hierarchical categories: global, national or subnational stakeholders, referred to later as stakeholder tiers. From all geographical regions sampled, global stakeholders included experts from international organisations focused on immunisation and academics with a focus on arbovirus research in one of the aforementioned high-burden regions. National stakeholders included experts working at country-level ministries of health

or within a policy sector for vaccine regulatory approval and oversight. Subnational stakeholders included clinicians, laboratory scientists and community health workers with experience working with chikungunya patients or in high-burden areas. Participants were geographically representative of chikungunya burden and evenly split across stakeholder tiers.

Data collection

We developed a semi-structured interview questionnaire (S1 Table) through consultations with experts in vaccine epidemiology and reviewed existing studies evaluating the perception of stakeholders on other vaccine introductions and rollouts. Questions were focussed on perception of chikungunya outbreak risk, barriers to chikungunya vaccination, and pathways to advance the chikungunya vaccine agenda in the future. At the time of the interviews, there was no licensed chikungunya vaccine, although several vaccine candidates had ongoing or completed phase III clinical trials. As interviews were conducted, questions were revised to reflect new topics that emerged. Biweekly meetings with the research team occurred to ensure the interviews were going smoothly and new themes that emerged through data collection were discussed.

Data analysis

We conducted qualitative semi-structured interviews via video call during which detailed notes were transcribed. We analysed the interview data through an iterative process using MAXQDA 2022 (VERBI Software, 2021) for data analysis and codebook development was done following the methods discussed in MacQueen et al. [22]. We use inductive and deductive coding to analyse the raw interview data. We categorised the coded data into themes. Thematic differences between geographical regions were first identified and then stakeholder tiers were analysed.

Identification of evidence gaps

Guidance on the EtR used by national immunization technical advisory groups (NITAGs) [17] was used to identify evidence gaps in current chikungunya knowledge and research, as shown in Fig 2. EtR criteria were then aligned with stakeholder perspectives and grouped by geo- graphical region to highlight regional evidence gaps.

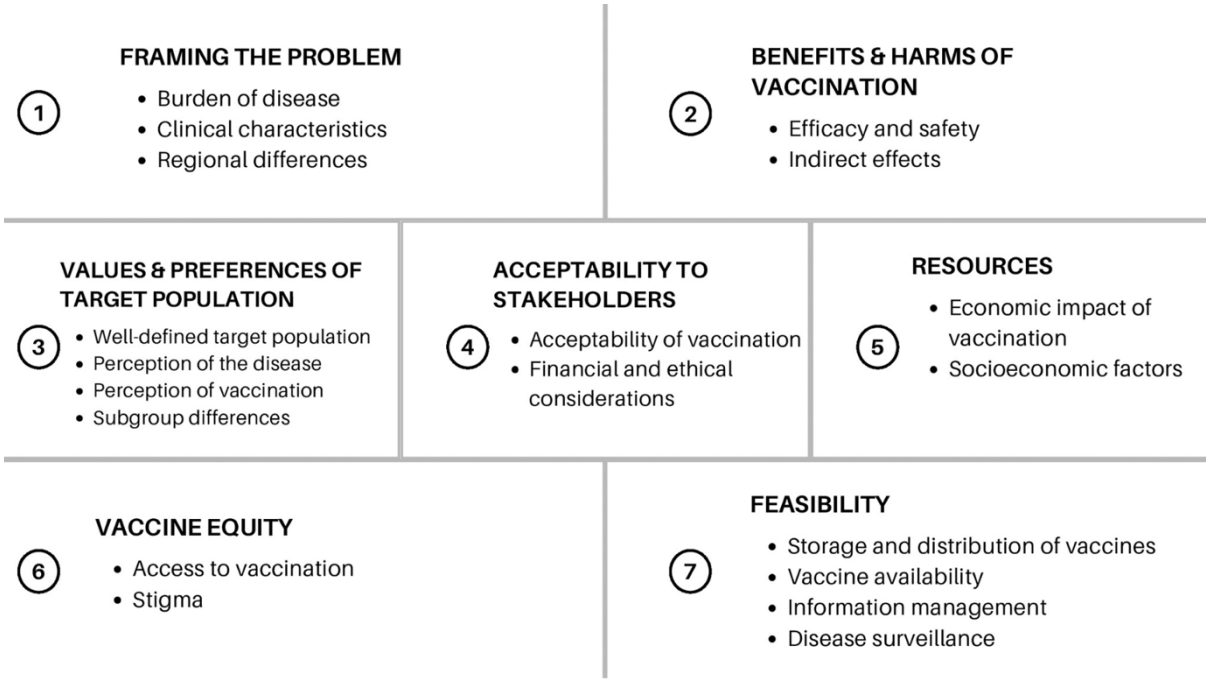

Fig 2. Evidence-to-Recommendation criteria for chikungunya vaccine introduction. *The Evidence-to-Recommendation criteria for chikungunya vaccine introduction is based on the World Health Organization's Guidance on an adapted Evidence-to-Recommendation Process for National Immunization Technical Advisory Groups.*

7.1.1.6 Results

Participant characteristics

Between January-February 2023, approximately 60 stakeholders were emailed and invited to take part in an interview. Overall, a total of 18 stakeholder interviews were conducted via video call between February and July 2023 (see Table 1).

Table 1. Participant characteristics by geographical region and type of stakeholder.

Geographical region	Country	Type of stakeholder	Number of interviewees
Latin America	Brazil	National	3
		Subnational	1
	Guatemala	Subnational	1
	Colombia	National	2
		Subnational	2
Asia	Thailand	National	2
	India	National	1
		Subnational	1
Africa	Kenya	Subnational	2
International		Global	3
		Total	18

Implications for decision making

We identified several themes for challenges associated with chikungunya vaccine introduction. Notable differences exist within stakeholders in different organisation tiers and by geographical regions (see Table 2).

Unknown burden of disease

The disease burden of chikungunya is unknown in many settings, which was the most frequently mentioned barrier to uptake of a chikungunya vaccine reiterated by stakeholders across all organisation tiers and geographical regions, alongside awareness of the unpredict- ability of chikungunya outbreaks.

Stakeholders partially attribute the unknown burden to non-specific or insensitive surveillance as surveillance for CHIKV is often done alongside other arboviral diseases, such as dengue and Zika. Surveillance for CHIKV is also often based on clinical cases, so passive surveillance only, which stakeholders believe results in under-reporting as surveillance systems usually only capture the cases that seek medical attention. Because this type of case detection relies on symptomatic patients reporting to health systems, passive surveillance excludes less severe or asymptomatic infections.

Without a comprehensive understanding of disease burden, quantifying the economic burden, including direct and indirect costs of acute but also chronic symptoms, is difficult. This barrier primarily affected national and global level stakeholders as countries cannot advocate for interventions, such as vaccination, without a cost-effectiveness and risk benefit analysis.

Table 2. Themes and challenges presented by stakeholders in different organisation tiers and by geographical regions.

Theme	Challenges presented by stakeholders in different organisation tiers			Challenges presented by stakeholders in different geographical regions			
	Subnational level	National level	Global level	Latin America	Asia	Africa	International
Unknown burden of disease	A lack of diagnostic sensitivity and laboratory capacity in the most affected areas results in an under diagnosis and under reporting of chikungunya	Surveillance for chikungunya is lacking in areas, which makes it difficult to understand which areas are most affected, detect outbreaks and respond accordingly	Without a good understanding of disease burden, demonstrating the economic burden of chikungunya or economic impact of a vaccine is challenging	Non-specific disease surveillance makes it difficult to distinguish the burden of disease between CHIKV, dengue and zika	Unknown chikungunya burden makes it difficult to advocate for CHIKV prevention and vaccination over dengue	Inability to detect actual CHIKV cases amongst other febrile illnesses, such as malaria, results in a large under-estimation in disease burden	Prioritisation of the vaccine in certain geographical regions is uncertain, making investment case for the vaccine difficult
Chikungunya has a high burden of morbidity, but not mortality making disease prioritisation uncertain	Public perception around chikungunya can be lacking in areas with endemic dengue circulating	It is difficult to prioritise chikungunya over other pathogens (specifically dengue or zika) when it comes to investing in developing improved laboratory and surveillance methods	Country buy-in is important for future vaccine investment strategies	Despite co-circulation of chikungunya with other arboviruses and lower mortality rates, the chikungunya vaccine is a priority, and countries are preparing for vaccine rollout	Lack of buy in from national vaccine policymakers to prioritise the chikungunya vaccine over the dengue vaccine	Prioritisation of other diseases with higher mortality rates means chikungunya is rarely discussed, and public awareness about the disease is lacking	Varying levels of prioritisation and support for the vaccine makes it difficult to plan for vaccine introduction
Target population for the chikungunya vaccine is not well defined	Vaccine confidence and public perception of a chikungunya vaccine would affect the success of a vaccine roll-out	Ensuring that the right infrastructure is in place to deliver the vaccine is difficult because the exact target population and delivery method (outbreak response or routine immunisation) is unknown	Understanding the exact use of the vaccine and the target populations are important for stockpile estimates, which are part of a global vaccine investment strategy	Anticipated use in outbreak response and affected areas, but approval of the current vaccine only for use in 18-years and older individuals means uncertainty if/when children can be vaccinated	Disease burden varies greatly within some countries, so subnational infrastructures would need to be in place to improve diagnostics and support vaccination at the local level	Research shows a high burden amongst children, but lack of age-specific serodata makes it hard to define a target population, the vaccine has also not been evaluated in children	Following the safety approvals for the vaccine and recommended age groups may make outbreak trajectory uncertain if outbreak data shows high burden amongst children

Chikungunya has specific climate or vector factors to consider	Different disease burdens are experienced by different sub-populations because of vector exposure	As vector epidemiology changes, chikungunya may become endemic in some countries, this has implications for vaccine stockpiles and roll-out	The technology behind the chikungunya vaccine may aid vaccine development of other alphaviruses in the *Togaviridae* family	Chikungunya and dengue cocirculate and concurrent outbreaks have occurred. It is important to understand how to deploy both the dengue and chikungunya vaccines in outbreak settings	Vector viability can differ within the same country, so sometimes local prevention measures and vaccination would be preferred over national programmes or campaigns	The animal reservoir in Africa demonstrates sylvatic transmission and viral evolution, so global chikungunya prevention should be concerned with natural origins of the virus	As global travel patterns and climate change affect viability of settings for the chikungunya vector, epidemic trends and spatial epidemiology may shift

"We need to better understand the burden of disease, disability adjusted life years (DALYs) lost, the benefits of a vaccine in terms of reducing morbidity and work loss."

-Programme lead for chikungunya, international organisation

"We don't have good chikungunya surveillance, and it is usually paired with surveillance for dengue and Zika. Surveillance can be coupled with dengue and Zika, but a good surveillance system should look for mild cases of chikungunya, not just severe cases that will look for medical attention. A lot of mild chikungunya cases are not found or not reported"

-Paediatric infectious disease specialist, Guatemala

Geographical variations in disease burden

We observed regional differences in stakeholder perceptions around chikungunya burden. For African countries, other febrile illnesses make fevers associated with chikungunya difficult to accurately detect.

"The burden of disease is not well defined for chikungunya. We do not understand the nature of outbreaks and the burden of disease in African nations because it is hidden in other febrile illnesses (malaria, etc.)."

-Programme lead for chikungunya, international organisation

In South America, stakeholders attribute unknown burden mostly to passive surveillance and the fact that outbreaks of chikungunya and dengue sometime occur concurrently.

"There is lots of under-reporting because current chikungunya surveillance is based on clinical cases, passive surveillance only, not active case detection, so we are only capturing cases that seek medical help, not community level cases."

-Neglected tropical diseases division, national organisation, Brazil

In India, the subnational burden of disease is of concern if a chikungunya vaccine were to be rolled out. This is of particular importance given the large population size of India and infra- structure needed to manufacture enough vaccine doses and deliver these doses to many people.

> *"There are subnational variations in burden within India. It is a question if the vaccine would be rolled out as a pan-national vaccine, or if it would be like the Japanese Encephalitis vaccine, which is restricted to only a few areas. Burden is limited in some parts of India, except for big states, like Delhi, Uttar Pradesh."*
>
> *-Infectious disease clinician, India*

Diagnostics

Subnational stakeholders identify additional concerns around improving laboratory diagnostics and not overloading laboratory capacity alongside vaccine interventions. At the subnational level, stakeholders expressed concerns on diagnostic sensitivity and capacity since some diagnostic tests are unable to detect CHIKV infections early enough, and that many high-risk areas are not well-equipped with the laboratory equipment required for CHIKV diagnosis and samples therefore are shipped elsewhere [23, 24].

> *"The amazon region of Brazil does not have good laboratory capacity for diagnostics, most samples are shipped to São Paulo, so most local diagnoses are left to clinical diagnoses. Enhanced serological testing for burden estimates would not be possible because of the remoteness of the area."*
>
> *-Nurse and laboratory specialist, Amazon region, Brazil*

> *"You need to know both the symptomatic and asymptomatic burden of chikungunya—we will need to determine the asymptomatic burden and confirm what genotypes are circulating. To do this, we require: good serology kits for IgM and IgG, good PCR that will detect the different circulating strains and a well working lab team."*
>
> *-Virology laboratory specialist, India*

Unpredictable outbreaks

In places where chikungunya is not endemic, outbreaks are unpredictable. The unpredictability of outbreaks affects stockpiling of vaccine as it is difficult to estimate the time, duration and number affected during each outbreak.

> *"Chikungunya tends to come in waves, but not predictable waves within regions and countries, the prioritisation and national public health interest (and therefore funding) is low because the waves only come once in a while and are unpredictable, so it is difficult to maintain attention to efforts."*
>
> *-Programme lead for chikungunya, international organisation*

In other regions, policy stakeholders believe chikungunya would have to become an endemic disease for priority to be given to the chikungunya vaccine.

> *"Even if we have an efficacious [chikungunya] vaccine, there are a number of challenges for public use. In comparison to dengue, chikungunya would need to be endemic in our region [Southeast Asia]. However, from the epidemiology, we see the number of chikungunya cases occurring per year are less than dengue."*
>
> *-Vaccine policy & safety, national organisation, Thailand*

Prioritisation of chikungunya over other arboviral diseases

Because chikungunya has a high burden of morbidity, but not mortality in many regions, stakeholders admit it is currently not a high-priority disease. Since countries with the greatest burden of chikungunya also have high burdens of other arboviral diseases, specifically dengue, there are often competing priorities. For example, stakeholders in India and Southeast Asia mostly prioritised chikungunya lower than dengue. One stakeholder from Thailand even refused to partake in an interview because they saw the promotion of a chikungunya vaccine to detract from resources being allocated to dengue vaccine roll-out. Despite this perceived competition, stakeholders in Latin and South America overall had the greatest interest in the chikungunya vaccine and were confident in vaccine roll-out despite concurrent dengue out- breaks, albeit with some concerns about public perception of the vaccine due to lack of perceived risk of morbidities associated with chikungunya.

"Now that the dengue vaccine is about to be licenced globally in the very near future, dengue may be a higher priority in the same countries where chikungunya is also a problem, so dengue will probably be ahead of chikungunya in the priority list. Latin America is the region that has the most interest in chikungunya, the most concern and high prioritisation. Certain sectors in India may be interested, but overall, broadly, prioritisation in India is lower, they will prioritise dengue over chikungunya"

-Programme lead for chikungunya, international organisation

"The size of morbidity and mortality is lower for chikungunya than dengue, moreover, we rarely see a mortality rate from chikungunya that is similar to that of dengue, particularly in children, so severity (DALYs) is less, burden is less than dengue. The number of cases of chikungunya does not ring a bell and there is a longer duration between outbreaks, which is hard to predict. We [Thailand] have a number of competitive health problems and we have many things on the priority list".

-Vaccine policy & safety, national organisation, Thailand

"There will be challenges rolling out the chikungunya vaccine. On an individual level, people won't see it as an important vaccine because there is a feeling that chikungunya is a mild dis- ease. The perception is that it is not as important as other diseases. People won't be as eager to get the vaccine, which is different from dengue. Lots of people have seen severe dengue, so if you see people in the hospital with dengue, you know it is a severe disease. But with chikungunya, people usually don't go to the hospital and if they do, they usually don't die from chikungunya."

-Paediatric infectious disease specialist, Guatemala

Stakeholders state that the lack of vaccine evaluation and an underinvestment in chikungunya research in Africa perpetuates vaccine inequity. Whilst some stakeholders in Latin America have a better understanding of how a chikungunya vaccine would be rolled out, other stakeholders in Africa are concerned about the lack of knowledge about the disease in their geographical region.

"Chikungunya was discovered in Tanzania, there has never been a vaccine trial anywhere in Africa, there are no discussions about vaccine evaluations in Africa.

And yet suddenly, we have all these advanced programmes for chikungunya and the chikungunya pipeline is very healthy, but none of those products actually have a strategy for evaluation in Africa, as far as I am aware . . .. This promotes inequity."

-Vaccinologist and One Health expert, Kenya

Because of prioritisation of other diseases, the community engagement process to raise awareness about chikungunya is lacking. This concern is emphasised by African stakeholders, where the lack of awareness about the disease poses challenges for future interventions and highlights evidence gaps associated with perception of the disease and stigma.

"Chikungunya is known, but it is stereotyped as a disease that came from spirits from the ocean, or is linked to witchcraft, they think that a treatment is drinking boiled papaya leaves. People know this thing (chikungunya) exists, but general knowledge about chikungunya is lacking. Most people know about malaria, what symptoms are, they know about malaria treatment, but if you talk about chikungunya they laugh at you because public engagement has not been done for chikungunya."

-Academic researcher, Kenya

Target population for the chikungunya vaccine is not well defined

The target population for a vaccine includes individuals within defined demographics and geographies that are eligible for a vaccine intervention. The unknown target population for the chikungunya vaccine presents challenges to all tiers of stakeholders. For global stakeholders, the biggest implication for unknown target population is the impact this has on industry manufacturing.

"Things have already been done and spearheaded by individual vaccine manufacturers to push the [chikungunya vaccine] development path forward. The biggest impediment for chikungunya vaccine development has not been technical, but defining what the market is for a chikungunya vaccine. There is not a huge amount of public funding for chikungunya vaccine development because of morbidity and mortality and burden issues. The commercial market is limited. Big players are not vaccine multinationals, but more intermediate developers, or ones located in endemic countries . . . the biggest impediment has been what is the commercial market that makes it worth developing?"

-Programme lead for chikungunya, international organisation

For national and subnational stakeholders, the undefined target population presents more concerns for vaccine roll-out logistics in their countries.

> *"What we see in the Paraguay outbreak is that more children have been infected and there have been more fatalities in children, so we need more information on this. The diagnostics and surveillance previously available have been weak to detect the type of infection some of these children have . . . Maybe children were not affected so much in previous outbreaks, but going forward we need to be aware of child infections. For example, from which age should we vaccinate?"*
>
> *-Physician and clinical researcher, Colombia*

Additionally, concerns around vaccine hesitancy and vaccine equity highlight the need for identification of target populations ahead of vaccine roll-out and ensuring that vaccine roll-out is packaged alongside advocacy campaigns.

> *"Some important questions that need to be addressed soon, include: if vaccine supplies are limited, which population groups are considered priority groups? The purpose of vaccination is to achieve what objective? To ensure equity in vaccine distribution, what steps do we need to take?"*
>
> *-Neglected tropical diseases division, national organisation, Brazil*

Climate sensitivity of Chikungunya vectors

Sub-populations experience different disease burdens because of differences in exposure to mosquito bites. Stakeholders explain that variations in vector exposure is an important consideration in vaccine roll-out because certain populations are disproportionately affected. As climate change impacts vector and virus population dynamics, CHIKV may become endemic in some countries, this has implications for vaccine stockpiles and roll-out.

> *"In Guatemala, we have a lot of areas of high rain, humidity and areas for mosquitoes to grow. Alongside, our population is growing, and we have a large urban population, so more people in small places, which makes the perfect conditions for an outbreak."*
>
> *-Paediatric infectious disease specialist, Guatemala*

"Africa is the only continent that has reported sylvatic circulation, between primates and mosquitoes. This is the natural reservoir for chikungunya virus, so we need to do a thorough study of chikungunya in Africa because even if the vaccine is rolled out elsewhere and people are protected, we don't know what strains will come again from the natural habitat for the virus, especially as climate changes the evolution of viruses. So, these viruses, as much as you can control them elsewhere, these viruses will again spread from their original source. So, to address challenges for chikungunya, it is better to address them from the source."

-Academic researcher, Kenya

Existing evidence gaps

Regional stakeholder perspectives were aligned with EtR criteria to highlight existing gaps in knowledge. Where stakeholders believed an EtR criterion was a current challenge or a gap in knowledge, it was recorded in Table 3. If no annotation was made for any of the criterion, this means the topic was not discussed during the stakeholder interviews or the topic was not identified as a current evidence gap.

Table 3. Mapping stakeholder perspectives with Evidence-to-Recommendation criteria. *Stakeholder perspectives were aligned with Evidence-to-Recommendation cri- teria to highlight existing gaps in knowledge. Cells in the table without data mean these topics were not discussed by any of the stakeholders.*

Evidence-to-Recommendation Criteria		Stakeholders identifying a specific criterion as a knowledge gap or challenge				Implications
		Africa (n=2)	Asia (n=4)	Latin America (n=9)	International (n=3)	
1. Framing the problem	Burden of disease	2/2	4/4	7/9	2/3	Unknown burden of disease leads to unknown epidemiology and lower prioritisation of the disease
	Clinical characteristics	2/2		4/9		Misdiagnosed cases result in under-reporting
2. Benefits and harms of vaccination	Vaccine efficacy and safety	2/2	3/4	1/9	2/3	Vaccine efficacy is based on neutralizing antibodies as a potential immune correlate of protection against chikungunya infection. The first and only chikungunya vaccine (VLA1553) currently under regulatory review has demonstrated good immunogenicity profile.
	Indirect effects of vaccination	1/2				Broader benefits include chikungunya vaccine serving as a prototype vaccine for other alphaviruses
3. Values and preferences of target population	Well-defined target population	2/2	3/4	5/9	2/3	Unknown burden leads to unknown target populations and risk areas
	Perception of the disease	1/2	2/4	4/9	1/3	Variable awareness about the disease can affect public perception of risk
	Perception of vaccination	1/2	3/4	6/9		Variable risk perception can affect willingness to get vaccinated
	Differences in subgroups	2/2	2/4	8/9	1/3	The vector and disease affect certain subgroups disproportionately

4. Acceptability of the vaccine	Financial & ethical considerations	2/2	1/4	3/9		Government prioritisation of disease may affect willingness to pay for the vaccine versus private market availability in country
5. Resources	Economic impact of vaccination	1/2	2/4	1/9	3/3	Unknown disease burden leads to evidence gaps in economic evaluation
	Socioeconomic factors			4/9		People living in poverty are disproportionately affected
	Diagnostics and laboratory capacities	2/2	2/4	4/9	1/3	Non-specific diagnostics and non-detection of asymptomatic infections leads to misreporting and underreporting
6. Vaccine equity	Access to vaccination	1/2		6/9		If the vaccine is not available without out-of-pocket charges, those affected by the disease may not be able to or willing to pay privately
	Stigma	1/2				Lack of public communication about the disease leads to stigmatising misconceptions
7. Feasibility	Storage and distribution	1/2	2/4	6/9	2/3	Understanding how the vaccine will be delivered (i.e. outbreak response) is important
	Vaccine availability	1/2	1/4	1/9		If the vaccine will be used in outbreak response, considerations for vaccine stockpile are necessary
	Information management	2/2	2/4	6/9	1/3	The vaccine should be rolled-out in parallel to a communications package to raise awareness about both the disease and vaccine
	Disease surveillance	2/2	2/4	4/9	1/3	Non-specific disease surveillance can result in under-reporting or unknown disease burden

7.1.1.7 Discussion

We infer from our stakeholder analysis that unknown disease burden, diagnostics, non-specific disease surveillance, undefined target populations for vaccination, and low disease prioritisation are critical challenges that need to be addressed to facilitate rolling out a chikungunya vaccine. Future investments should address these challenges to generate useful evidence for decision-making on new chikungunya vaccine introduction.

Both disease burden and surveillance were highlighted as gaps in the Evidence-to-Recommendation criteria across all geographical regions, further stressing these as major issues that need addressing ahead of vaccine rollout. Paucity of data and research illustrating the disease burden of chikungunya, exacerbated by non-specific disease surveillance presents several challenges. The disease burden of chikungunya remains unknown and likely under- estimated in many high burden settings due to a lack of chikungunya-specific disease surveillance [25]. Laboratory capacity and existing diagnostics for detecting chikungunya infection are limited in some high burden settings [26]. Passive surveillance methods currently used in many settings only pick up clinical cases of chikungunya presenting to hospital, resulting in an under diagnosis of asymptomatic and less severe infections. Analysis of age-stratified seroprevalence data is a useful method for estimating long-term average infection burden [4]. In some African settings, misdiagnosis of chikungunya as another febrile illness, such as malaria, is common, which is concerning, given that research shows a higher burden of chikungunya in children [27]. Accurate detection and surveillance of alphaviruses in vectors is especially important in Africa (and other malaria endemic areas) where existing zoonotic reservoirs exist and there has been an increasing frequency of chikungunya detection in recent years [28]. Accordingly, stakeholders in Africa highlighted the indirect effects of vaccination as a current evidence gap that would be valuable to address alongside cross- protections from chikungunya and other viruses.

The unknown disease burden also affects prioritisation of chikungunya, both in terms of national vaccine policy decisions [25] and public perception of chikungunya risk [21]. Several stakeholders highlighted that by focusing on chikungunya vaccination, resources are taken away from dengue vaccination and prevention, which many stakeholders, especially those in South and Southeast Asia, believe is a higher priority on country agendas. In contrast, stake- holders in Latin America affirmed a higher prioritisation of chikungunya in national vaccine policy agendas, but voiced concerns that public perception of chikungunya risk was skewed by a greater awareness about dengue, including symptoms, transmission and infection risk. Because chikungunya is often seen as a disease with low

mortality, stakeholders voiced con- cerns in the public perception of risk [21,29]. Lower prioritisation of chikungunya is concern- ing because the long-term chronic disability of chikungunya such, as arthritis, can be debilitating, putting stress on health care systems and diminishing economic productivity. These health deficits for chikungunya are not usually captured in global health assessments despite the large populations currently at risk [30]. By illustrating the true burden of chikungunya and its long-term health and economic impact, stakeholders were confident that prioritisation and public perception of chikungunya risk can be increased.

Concern for social factors affecting vaccine rollout were varied across geographical regions. Stakeholders in Africa and Latin America identified vaccine perception and hesitancy, information management and socioeconomic factors affecting vaccine uptake as current challenges more often than stakeholders in Asia. This could be attributed to the overall perception and prioritisation of chikungunya—stakeholders in Latin America saw chikungunya as a higher priority disease whilst stakeholders in Asia stated other diseases with competing interests were a higher priority. This differential prioritisation could affect concern for social factors around vaccination, showing a greater level of thought has been put into chikungunya vaccine equity amongst stakeholders that see the vaccine as more favourable. Stakeholders discussed synergies with other vaccination programmes, specifically citing lessons learned from distribution and administration of COVID-19 vaccines. Stakeholders in Latin America and Asia believed les- sons learned during the COVID-19 pandemic could be leveraged for the chikungunya vaccine, however, stakeholders in Africa saw the ongoing inequity of COVID-19 vaccines in Africa to perpetuate concerns about chikungunya vaccine equity in the African continent.

New chikungunya vaccines provide broader value beyond the direct benefits of lowering the chikungunya disease burden. These will be the first-ever vaccines against an alphavirus and thereby offer new platforms for vaccine development against other alphaviruses of the family *Togaviridae* that may emerge to cause epidemics and potential for pandemics. Further, the lessons learned, and technologies developed by the chikungunya vaccine will pave the way for new regulatory approval processes as vaccines can be approved based on immunogenicity data estimated by measures of neutralizing antibodies as potential immune correlates of protection, instead of vaccine efficacy estimates based on disease events [31].

Our study has limitations. By limiting our analysis to stakeholders in regions at risk of chikungunya outbreaks, stakeholders in regions at future risk of chikungunya invasion due to climate change were

excluded from our interview sample. We used a limited number of organisational databases that so possibly not all relevant stakeholders were identified. Despite contacting over 60 stakeholders, the response rate was low, especially in Africa. When stakeholders were referred by other stakeholders, they were more likely to participate, suggesting that use of purposive sampling in addition to the low response rate could result in selection bias. The sample of interviewees is geographically representative of current willingness to roll-out the chikungunya vaccine, but the number of participants by region is not necessarily proportional to disease burden. For example, Latin America had the greatest number of participants across all geographies and it was also the region with the most eagerness to rollout the vaccine; however, the burden of disease in Africa is estimated to be relatively high, especially in children [27], and this burden was not proportional to the sample size of stakeholders from the African region included in our study. This limited sample size for Africa could be attributed to topics mentioned in interviews with stakeholders who expressed concern that chikungunya epidemiology is not currently well documented and disease awareness is low across the African region. Despite the low sample size, we were still able to interview stakeholders from three different high burden geographical regions, six different countries, and across the international, national and subnational organisation tiers, lending to diverse perspectives that will be valuable in making future decisions about chikungunya vaccine introduction and delivery strategies.

Especially given shifts in global travel patterns, urbanisation and climate change, as vector viability changes, public health officials must collaborate to improve surveillance, prevention, and control programmes for arboviral diseases [32–34]. In July 2023, the European Centre for Disease Prevention and Control (ECDC) announced an increasing risk of mosquito-borne dis- ease in Europe following the spread of *Aedes* mosquito species capable of transmitting CHIKV [35]. While our analysis focused on perspectives in regions at current risk of chikungunya out- breaks and excluded Europe, the rising concern of transmission-competent mosquito populations in Europe highlights just one aspect of how changing climate patterns can shift the future epidemiology of chikungunya outbreaks. To address these evolving patterns, the involvement of stakeholders in all phases of vaccine development and rollout alongside risk assessment and climate sensitivity of chikungunya will be crucial to uncover challenges and gaps to be addressed in the future.

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7.1.1.8 References

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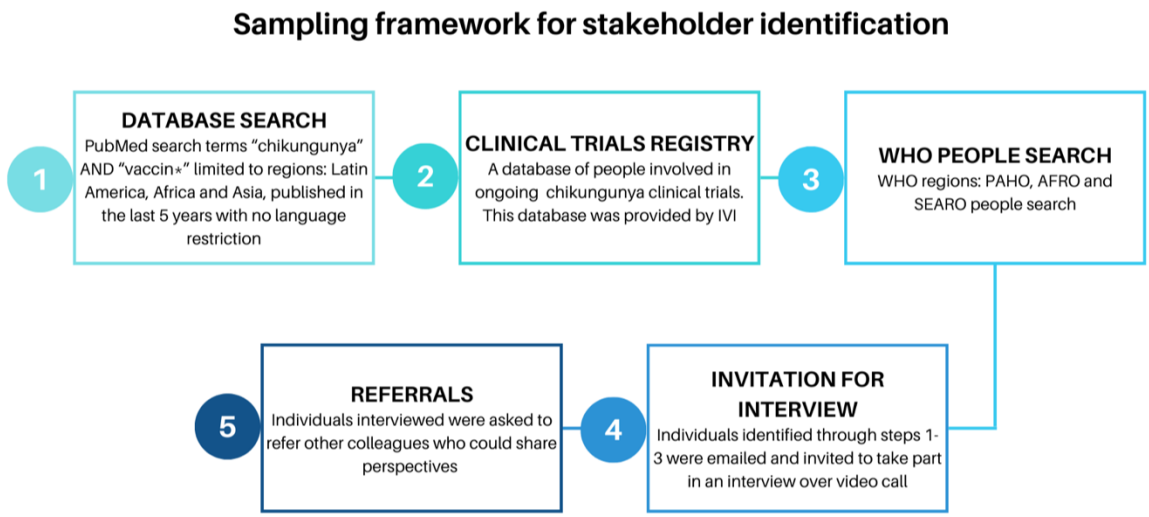
7.1.9 Supporting information



S1 Fig. Sampling framework used to identify individuals invited for the stakeholder inter- views. *First, articles on chikungunya vaccination were identified from a PubMed search, limited to geographical regions with a high risk of chikungunya outbreaks. There was no language restriction on articles, but the publication date was limited to the last five years, in line with chikungunya vaccine development. Next, a database of individuals involved in chikungunya vaccine clinical trials were added to the list of stakeholders to contact. Third, WHO regional websites were used to identify individuals working*

on chikungunya in the AFRO, PAHO and SEARO regions. Individuals identified in steps 1–3 were then invited to partake in a stakeholder interview. If successful contact was made, during the interview stakeholders were invited to refer colleagues that would also be interested in sharing perspectives.

S1 Table. Interview questionnaire used in the semi-structured interviews. *These questions were used to guide the interviews, but participants were invited to speak freely and structure the interview how they saw best.*

#	Question
Q1	Please introduce yourself, explain your role within your organisation and summarise your work related to chikungunya
Q2	Based on your experience, what is your perception of (your region's) current risk of a chikungunya outbreak?
Q3	Do you think a chikungunya vaccine (in your region) would be feasible?
Q4	What are the potential barriers in chikungunya vaccine uptake?
Q4b	If not covered in Q4, what political, social, financial, logistical barriers would affect the roll-out of chikungunya vaccine in (your area)? What other factors would affect the feasibility of vaccination?
Q5	Is there any other information you think would be useful for us to know? Is there anything else unique to your experience in your region that you would like to share?

7.1.2 Desirable BUGS in models of infectious diseases

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7.1.2.1 Research paper cover sheet

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Surname/Family Name	Auzenbergs		
Thesis Title	Mathematical and statistical modelling to inform polio and measles vaccination programming		
Primary Supervisor	Dr. Kathleen M O'Reilly & Dr. Kaja Abbas		

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Where was the work published?	Epidemics		
When was the work published?	December 2019		
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SECTION E

Student Signature	[redacted]
Date	30 May 2024

Supervisor Signature	[redacted]
Date	31 May 2024

7.1.2.2 Abstract

Bayesian inference using Gibbs sampling (BUGS) is a set of statistical software that uses Markov chain Monte Carlo (MCMC) methods to estimate almost any specified model. Originally developed in the late 1980s, the software is an excellent introduction to applied Bayesian statistics without the need to write a MCMC sampler. The software is typically used for regression-based analyses, but any model that can be specified using graphical nodes are possible. Advanced topics such as missing data, spatial analysis, model comparison and dynamic infectious disease models can be tackled. Three examples are provided; a linear regression model to illustrate parameter estimation, the steps to ensure that the estimates have converged and a comparison of run-times across different computing platforms. The second example describes a model that estimates the probability of being vaccinated from cross-sectional and surveillance data, and illustrates the specification of different models, model comparison and data augmentation. The third example illustrates estimation of parameters within a dynamic Susceptible-Infected-Recovered model. These examples show that BUGS can be used to estimate parameters from models relevant for infectious diseases, and provide an overview of the relative merits of the approach taken.

7.1.2.3 Introduction

BUGS is a software for Bayesian inference using Gibbs sampling [1]. The software is now in its third decade, and has undergone several developments in its use and application. Although the software is sufficiently generic that it can be used within many data-driven fields, perhaps due to the affiliations of its developers BUGS is often used in medical sciences, but has also been widely used in social sciences, ecology and environmental sciences.

For a full description of the developments of BUGS see the article by Lunn et al. [2] and the associated commentaries at the end of the article. The rationale behind developing BUGS was a need to make Bayesian analysis more accessible. Whilst the 1970-2000s saw many developments in Bayesian analysis, markov chain monte carlo (MCMC) analysis was largely restricted to models in closed form where a conjugate prior was required for specification of the model (where a conjugate prior is part of the same family of probability distributions as the posterior). A simple example of using conjugacy to estimate parameters from a model is the estimation of probability of occurrence from data. The likelihood is assumed to be binomially distributed where the data consists of k successes from n trials, $Pr(x = k|p,n) = (n\ k)\ p^k(1 - p)^{n-k}$. To estimate the posterior distribution of the probability of success (p) we first specify the posterior from Bayes rule; $Pr(p|n,k) \propto Pr(n,k|p)Pr(p)$ where Pr(p) is assumed to be a beta prior with parameters α and β. The probability density function of a beta distribution is Pr(p) =

$p^{\alpha-1}(1 - p)^{\beta-1}$. Conjugacy occurs in this circumstance because the prior and posterior have the same distributional form, and the posterior can be sampled using $p \sim B(\alpha + k,\beta + n - k)$ as $Pr(p|n,k) \propto p^{\alpha+k}(1 - p)^{\beta+n-k}$ [3]. However, a closed form posterior distribution is unusual for most problems and additional (often impractical) mathematical manipulation is required to identify the posterior distribution, which prevents widespread use. The solution developed by Lunn et al. [2] makes use of graphical modelling theory [4], and the development of the BUGS language to specify models. The network of nodes define the model where each node is either data or a parameter, and the edges between each node define the dependencies between the nodes. The dependencies illustrate the conditional probabilities assumed between nodes (which are usually directed), and is a core element of Bayesian inference. Additionally, the specification of directed acyclic graphs (DAGs) and automated translation to code means that scientists without a statistics or programming background are able to develop their own models.

As opposed to other languages that require considerable translation of equations into code [5], the language used to specify models in BUGS has a much lower learning curve for scientists to translate theory into practice. The original WinBUGS software has been available since the 1990s [1]. Programming developments, applications and interest within the scientific community has grown steadily since. The estimation procedures within the software expanded from using a Gibbs sampler to a self-tuning Metropolis updater, to increase the flexibility of the full conditional probability that can be specified and increase the efficiency of the estimation procedure. Additional modules were developed for specific applications; PkBUGS for application to pharmacokinetic models [6] and the associated complex functions, and GeoBUGS for spatial modelling and the use of structured random errors [7]. Over 30 years of development has led to multiple software platforms performing very similar tasks. In the early 2000s clones and suitable alternatives of the original software were developed; first OpenBUGS [8] and then JAGS (just another gibbs sampler [9]), both of which facilitated use of the software by linux and MacOS users. To make use of multi-core processors (common to most computers) and reduce the run-time of MCMC estimation, multiBUGS was released in 2017 [10]. Small but important differences between them (Table 1) mean that all versions are likely to be in use for the foreseeable future. Integration with other software such as R is facilitated by calling the software within bespoke libraries (eg. BRugs [8], R2WinBUGS [11], runJAGS [12]). Development of additional custom distributions within JAGS is possible and requires a working knowledge of C++ [13].

Table 1: *The available BUGS software and current scope of each for analysing data*

	WinBUGS	OpenBUGS	JAGS	multiBUGS
First available	Mid 1990s	2006	2008	2017
Operating system	MS Windows	MS Windows / Linux / Mac[1]	MS Windows, Mac, Linux	Windows (Linux under development)
Extensions	PkBUGS, glm, GeoBUGS	GeoBUGS, glm, MultiBUGS	glm, geoBUGS[2]	glm, GeoBUGS

[1] But note that OpenBUGS hasn't been fully tested within the Mac OS. [2] GeoBUGS has not yet been fully tested within JAGS.

There are now a vast number of worked BUGS examples and applications, which are available via affiliated websites, tutorials, peer-reviewed papers and books. Most applications are centred on the analysis of data where variation in the response requires explanation. Examples include the classic linear and generalised linear model structure, as well as mark-capture, markov-models, non-linear functions, and differential equations. Useful reference books include; Kery [14], Kery and Schaub [15], and McCarthy [16], Lawson [17] and Kruschke [18] as they explain the statistical details well and provide examples including code.

There are several reasons for choosing BUGS over other modelling options. First, BUGS fits data within a Bayesian context (for an introduction to Bayesian analysis see the first few chapters of Kery [14]). Second, the language and almost absence of additional coding required to implement models and estimate parameters brings the model structure to the front of what the researcher does. From the beginning of learning BUGS and Bayesian analysis the researcher is encouraged to consider what form the data takes, for example by asking what distribution approximates the response variable, and what corresponding parameters (and data) determine this distribution. It is then a relatively simple process to translate this equation to the BUGS code and a few clicks or lines of code later a posterior distribution of the parameter(s) are available to examine [19]. This is especially important when learning statistical modelling and in developing models that are different to those 'off the shelf' varieties which may, for example, require the researcher to make invalid assumptions about the data or removing data points because they are not fully observed. The model specification within BUGS makes it a useful stepping-stone into Bayesian analysis and model construction [19]; to this end BUGS is used in many postgraduate epidemiology courses [20, 21]. Whilst the estimation procedure is largely automated, knowledge of the appropriate MCMC parameters to select is needed to ensure that the posterior target distribution is stationary (i.e. a random sample of the posterior of sufficient size that additional samples will not influence its shape or summary statistics). An ability to assess the MCMC chains for convergence is required and some practical advice is given in this article. Data

simulation from a BUGS model is possible with only a small number of alterations, making model checking and validation a more natural process when compared to other software.

The rest of this paper provides working examples of common applications of BUGS to models of infectious disease, how to sensibly assess the output of a model, and a commentary on the relative merits and disadvantages elicited within each example.

7.1.2.4 Case studies

A linear model, associated output and comparison of run time between software

Model specification

A simple linear regression model assumes that the response variable $Y = \{Y_i, i = 1,...,N\}$ is normally distributed with mean value μ and variance σ (ie. $Y_i \sim N(\mu,\sigma)$). We assume that an explanatory variable $X = \{X_i, i = 1,...,N\}$ explains some of the variation in Y. We assume that the model takes the form $\mu = \alpha + \beta X$, which introduces two additional parameters that require estimation. Within a Bayesian setting priors are assigned to these parameters; both are assumed to be normally distributed with mean 0 and precision (τ) of 0.5, which can be written as $\alpha \sim N(0,0.5)$ and $\beta \sim N(0,0.5)$. These priors are regarded as minimally informative as they can encompass a wide range of values and consequently the posterior will largely be informed by the data. Selection of appropriate priors can be a challenging process and it is important to examine priors and understand the influence of priors on the posterior distribution [22]. Additionally, specification and estimation of the standard deviation is often more intuitive than use of precision for a parameter, and additional code may be used to specify the standard deviation instead of precision. This model can be written either as a DAG (Figure 1) or directly within the BUGS language;

```
model{
    for(i in 1:N){
        y[i] ~ dnorm(mu[i],tau)
        mu[i] <- alpha + beta*x[i]
    }
    alpha ~ dnorm(0,0.5)
    beta ~ dnorm(0,0.5)
    log.sigma ~ dunif(0,100)
    sigma <- exp(log.sigma)
    sigma.sq <- pow(sigma,2)
    tau <- 1/sigma.sq
}
```

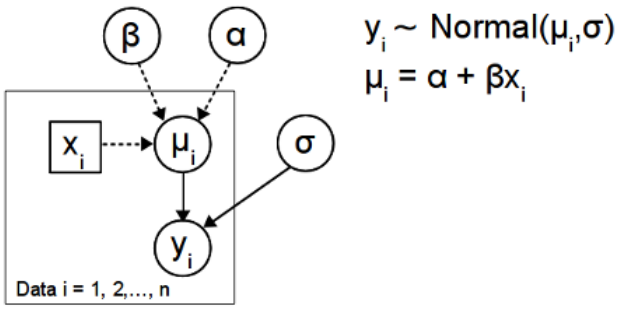

Figure 6. *Directed acyclic graph (DAG) for the linear model example.*

The code is deliberately similar to the mathematical equations, creating a natural bridge from equations to code and vice versa. Note that BUGS specifies a normal distribution using the mean (μ) and precision (τ). For a generalised linear model structure it is also possible to specify the model using the standard lme-4 style syntax within R through loading the runjags package [12];

model <- template.jags(y ~ x, data, n.chains=3, family='gaussian').

Continuing with the linear model example above, this model is used to generate simulated data with sample sizes ranging from 100 to 10,000 to examine the differences between software and platforms. In MS Windows the models were run on a 4-core machine consisting of 3.40 GHz and 8 processors with 16GB of RAM. In the Mac operating system the models were run on a 3.2 GHz Intel core i5 machine with 4 processors consisting of 16GB of RAM. Estimation of the posterior distribution was implemented by specifying the number of MCMC iterations, the number of initial iterations that will be discarded (i.e. burn-in), the extent of thinning (i.e. extracting every j^{th} iteration of the MCMC), and the number of MCMC chains. The general principal of specifying these settings is to obtain a stationary target posterior distribution. There is no certain way to assess when the stationary distribution has been reached, but rather there are techniques to establish when it has not been reached [23]. It is ideal to obtain the equivalent of 1,000 independent samples of the posterior distribution, and given that autocorrelation of MCMC chains is common, generating at least 10,000 samples per chain should be considered a minimum value. Some software provides estimates of the effective sample size which provides an estimate of the equivalent number of independent samples (for example the coda package in R [24]), and this value should exceed 1,000 for all parameters. Chain convergence can be assessed visually by plotting the sampled value against its number in the chain. Running several chains with different starting values and comparing the sampled values on the same figure will illustrate whether enough burn-in has been specified (more noise in early iterations may be identified) and that the chains have converged to a common mean value, if convergence has been achieved. To assess convergence, the Multivariate Potential Scale Reduction Factor (also known as the Gelman-Rubin

statistic [25]) can be applied. The Gelman-Rubin statistic compares the variance between the chains to the variance within the chains of each parameter, and if these are similar (indicating convergence) then its value should be less than 1.05. Autocorrelation plots can be used to assess the extent of autocorrection in MCMC chains and further inform the extent of thinning that needs to be specified.

Model results and interpretation

For this example each model was specified in an identical form and 15,000 MCMC iterations were run within each of three chains. The first 5,000 iterations were regarded as 'burn-in' and discarded. The Gelman-Rubin statistic was applied to an initial round of samples where values were <1.01 which suggests that the between-chain variance is low and consistent with convergence of the chains (Figure 2). The autocorrelation plot illustrated a lag to approximately 5, so the model was re-run (10,000 iterations with 5,000 burn-in) and the output was thinned to every 10^{th} iteration. The time-series and density plots of the subsequent output (Figure 2) illustrate consistent values across the chains. The effective sample size of the 10,000 iterations was at least 1,435.

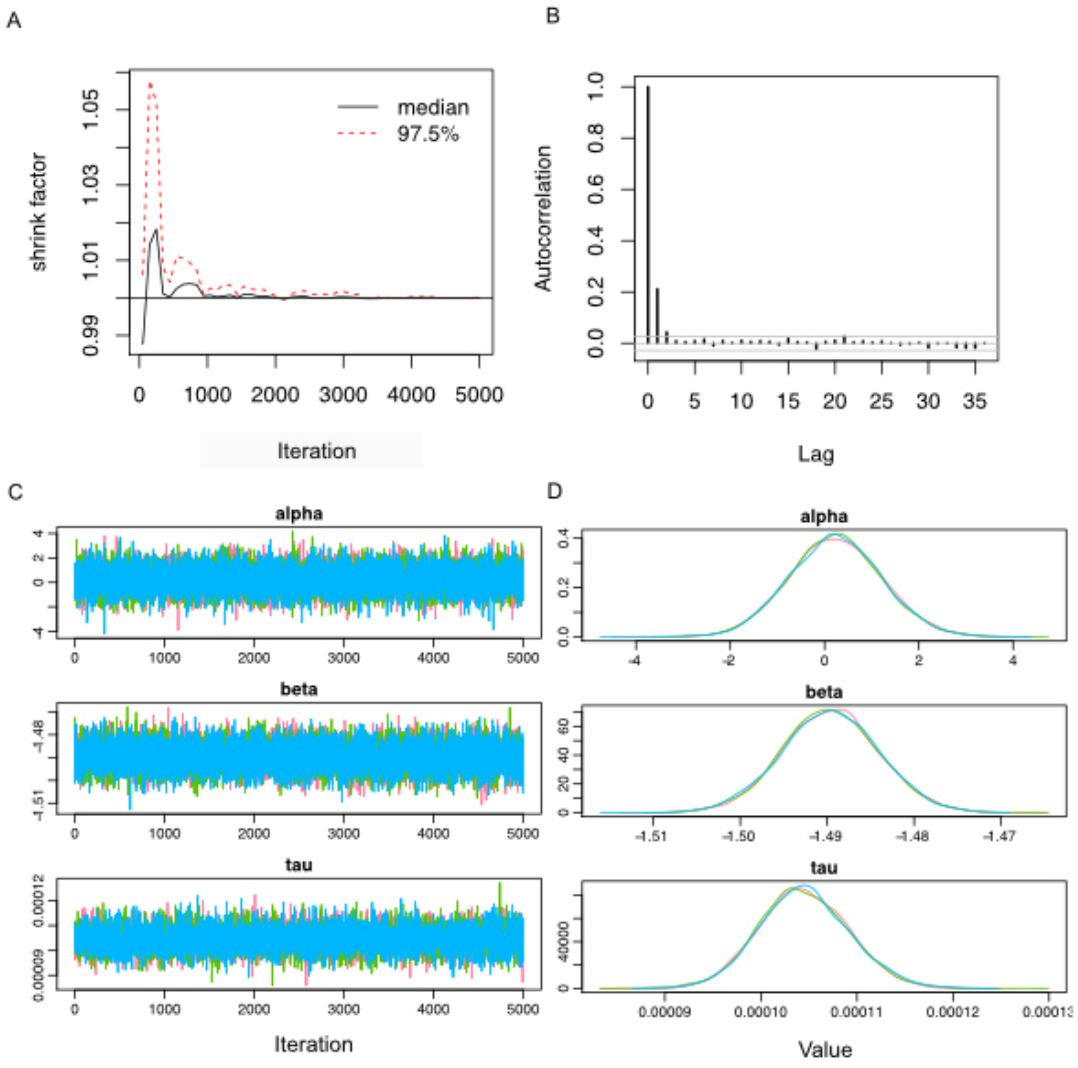

Figure 2. *MCMC output from example 1 illustrating visual diagnostics used to assess whether a stationary distribution for each of the parameters has been reached. A) Gelman-Rubin diagnostic plot, B) autocorrelation plot of the un-thinned MCMC iterations, c) time-series plots of each of the parameters estimated, d) posterior density plots.*

Table 2 illustrates that the run-time for each version of BUGS is linear with the size of the data for WinBUGS, JAGS and OpenBUGS. Whilst the run time also increases with models that have more parameters, the size of the data is usually the limiting factor for medical problems (especially when considering that the number of parameters should be much less than the number of observations within data). The relatively slow run time associated with the MCMC estimation has perhaps limited more widespread use of BUGS [19], but these issues are not unique to BUGS but are common to most MCMC estimation approaches. Recent developments of the R library Nimble enables conversion of BUGS code to C++ code, which in the example above, has improved the run time by a factor of approximately 25. Inclusion of Nimble into the model construction adds additional programming complexity, but a suitable model can be developed within BUGS on a subset of a large dataset, and

once developed, then specified within Nimble. Using multiBUGS to run the models resulted in a faster run time than JAGS, openBUGS and winBUGS and did not require any additional coding.

***Table 2**: Runtime (in seconds) of the linear regression model according to the size of the dataset. (all models were run for 100,000 iterations using 3 chains).*

Dataset size	WinBUGS	OpenBUGS	JAGS	Nimble	multiBUGS
100	6	15	15	<5	11
1000	31	194	175	29	92
5000	1565	1083	1157	135	452
10000	3500	2314	2970	214	937
run time of 1,000 independent samples from the dataset of 1,000	332	414	189	3	98

Spatio-temporal analysis of data: Estimating vaccine effectiveness

Analysing polio vaccination data from Ethiopia shows how BUGS is particularly useful for combining multiple data sources into a statistical model. The aim of the analysis was to estimate the probability that a child aged 12 months would be vaccinated with the oral polio vaccine (OPV), and examine whether there was evidence for spatial or temporal variation in this estimate of vaccination coverage. Three different data sources were used: (1) Demographic and Health Survey (DHS) 2011; (2) DHS 2016; and (3) non-polio Acute Flaccid Paralysis (AFP) surveillance data for 2005-2016 from the WHO Polio Information System [26]. Within the DHS data, the number of OPV doses were reported for each child aged < 5 years of age included in each cross-sectional survey. For the non-polio AFP data, cases of non-polio AFP were assumed to be an opportunistic sample of children aged <5 years of age within Ethiopia where OPV vaccination histories were recorded as part of the case investigation. The non-polio AFP data have been previously used to estimate country- and province-level probabilities of being immunised with 3+ doses, where higher values were previously associated with a lower probability of reporting poliomyelitis outbreaks [27, 28], but its predictive ability may be affected by the uncertainty in the estimates. With the addition of DHS data estimates of vaccine effectiveness are likely to be more representative and reliable.

Model formulation

The reported number of OPV doses were converted to a response variable of whether 3+ OPV doses had been received ($y_i(d)$ where i refers to a child's index and d refers to the dataset origin, which is

omitted from further equations for clarity), and explanatory variables included in the model were year of vaccination according to the Gregorian calendar (t_i, which was inferred from the child date of birth and that routine OPV doses in Ethiopia are administered at 6, 10 and 14 weeks [29]), district of residency (z_i), number of eligible supplementary immunisation activities (SIAs, s_i) extrapolated from an OPV SIA calendar and exposure to routine immunisation (r_i) using Diptheria-Tetanus-Pertussis (DTP) vaccination information (the DTP vaccine is administered concurrently with OPV drops in the routine immunisation series). Dose history of DTP vaccination was included within the DHS surveys and was used to augment DTP vaccination data for AFP cases, as DTP vaccination is not included in the AFP surveillance data in Ethiopia.

The model was used to test the hypothesis that estimates of vaccination coverage vary across districts and in time and that SIAs increase the probability of a child being 'fully vaccinated' (ie. receiving 3+ OPV doses). Additionally, each data source is assumed to have an associated reporting factor to account for small changes in how the survey question is asked, differences in the sampled populations and potential reporting bias [30], modelled using an adjustment factor β_d. We assume a binomial model for the response with associated regression coefficients as described above and mechanistic variables that describe individual vaccination histories from the data. The response variable $Y_{\cdot} = \{Y_{i,\cdot}, i = 1,...,N\}$ takes the value of 0 or 1 according to whether 3+ OPV were reported by data source (Y_a: AFP, Y_{d1}: DHS 2011, Y_{d6}: DHS 2016) while z_i, t_i, d_i are covariates used to explain the variation (in district, time and dataset, respectively) and s_i are the number of SIA campaigns inferred from the child's birth date and interview date and dtp_i are the number of OPV doses received via routine immunisation. The parameters β_s and β_r correspond to the parameters associated with SIAs and DTP OPV doses, β_z and β_t are the corresponding variables for the covariates. The effectiveness (ie. the probability of receiving 3+ OPV doses associated with each incremental increase in SIA or DTP) is 1 - ($1/\exp(\beta_s)$) and 1 - ($1/\exp(\beta_r)$). The model is as follows;

$$Y_i \sim binomial(\mu_i, 1)$$

$$logit(\mu_i) = \beta_z z_i + \beta_t t_i + \beta_d d_i + \beta_s sia_i + \beta_r dtp_i$$

Developing the model in BUGS allowed for changes in the model structure such as inclusion of interaction terms and adaptation of the model beyond a standard generalised linear model framework to be made with relative ease. For example, data on OPV doses provided via routine immunisation was not available within the AFP dataset so it was augmented [15] from the spatial-temporal patterns in the DHS data assuming,

$$dtp_i \sim binomial(\mu_{r,i}, 1)$$

$$logit(\mu_{r,i}) = \alpha_t t_i \,.\, \gamma_z z_i \,.\, \log(age_i)$$

To complete the model, we specify minimally informative priors where the regression coefficients were assigned β_z, β_t, β_d, β_s, $\beta_r \sim N(0,\tau)$ and $\tau \sim U(0.1,1)$ so that the posterior was largely influenced by the data. In this circumstance selection of these and alternative priors resulted in consistent posterior distributions but sometimes the posterior is unidentifiable and different variances were selected [?]. The model was implemented in JAGS and the outputs examined within R. We generated three MCMC chains of length 10,000 iterations with a burn-in of 5,000 and thinning to every 10th to obtain 1,500 samples from the joint posterior distribution. To transform the model parameters into more interpretable outputs, the parameters were used to estimate the district-level probabilities of receiving 3+ doses of OPV through routine immunization and the probability of a child 12 months of age receiving 3+ OPV doses through both routine immunization and scheduled SIAs for 2011, along with estimates of vaccine effectiveness.

Different models were run in order to assess district estimates of vaccination in the presence of different covariates. The deviance information criteria (DIC) was used to compare the fit of each model and the model with the smallest DIC was assumed to provide the best fit to the data. At least two runs of the model were generated to compare the DICs to ensure consistency of the outputs.

Model results and interpretation

A model was developed to account for district of residency and year of vaccination as explanatory variables, and was compared to including the impact of the number of SIAs (by adding β_s) and whether this impact varied by district, year, or both. The DIC values illustrate increased evidence for inclusion of the SIA exposure histories into the models (DIC 22679.3 compared to 22842.8, respectively). Further model developments included augmented data so it was not possible to directly compare DIC values. Outputs of the probability of being vaccinated via routine immunisation and overall vaccination probabilities show that OPV vaccination coverage in Ethiopia varies spatially (Figure 3), and vaccination has steadily improved since 2012 (Table 3). The effectiveness of the first SIA was estimated to be 0.44 (95% CI 0.34-0.53), and subsequent SIAs were estimated to further improve the chances of being fully vaccinated but with diminishing returns (DIC of constant effectiveness model = 36348.8 vs. DIC of per-dose model = 36285.9, difference = 62.9). The model also suggests that the source of vaccination data impacts estimates of vaccination coverage, with DHS data typically reporting a lower odds of a child 12 months of age being vaccinated with 3+ doses of OPV than the AFP data (odds ratio associated with DHS data 0.35 (95% CI 0.32-0.38)).

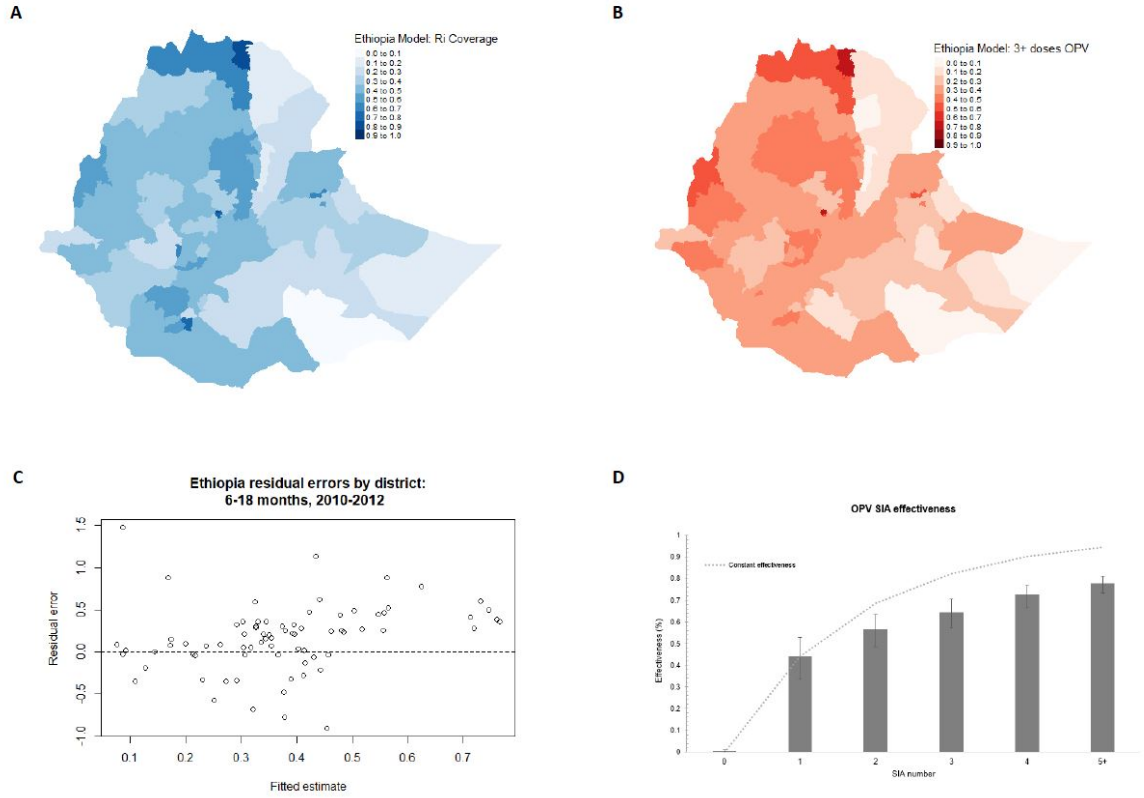

Figure 3. Predicted probability of a child aged 12 months of age reporting A) 3+ OPV doses received via routine immunisation B) 3+ OPV doses irrespective of mechanism, C) estimated residuals by fitted estimates for each district, D) Comparison of SIA effectiveness estimated within the constant dose model and the per-dose model.

Table 3. Summary of the outputs from the polio vaccination model applied to Ethiopia.

Value	Relation to equations	Estimated value (95% CI)
Scalar of output associated with DHS data	OR of β_{d1}, β_{d2}	0.35 (0.33, 0.38)
Mean value of district variation	mean(β_z)	-0.09 (-0.25, 0.06)
Mean probability of receiving 3+ OPV doses in 2005	$\text{logit}^{-1}(t_1)$	0.35 (0.16, 0.57)
2006	$\text{logit}^{-1}(\beta_t(2)$	0.33 (0.26, 0.41)
2007	$\text{logit}^{-1}(\beta_t(3))$	0.26 (0.21, 0.33)
2008	$\text{logit}^{-1}(\beta_t(4))$	0.26 (0.2, 0.32)
2009	$\text{logit}^{-1}(\beta_t(5))$	0.3 (0.23, 0.36)
2010	$\text{logit}^{-1}(\beta_t(6))$	0.22 (0.17, 0.27)
2011	$\text{logit}^{-1}(\beta_t(7))$	0.15 (0.12, 0.19)
2012	$\text{logit}^{-1}(\beta_t(8))$	0.29 (0.22, 0.38)
2013	$\text{logit}^{-1}(\beta_t(9))$	0.34 (0.27, 0.41)
2014	$\text{logit}^{-1}(\beta_t(10))$	0.42 (0.34, 0.5)
2015	$\text{logit}^{-1}(\beta_t(11))$	0.43 (0.36, 0.51)

2016	$\text{logit}^{-1}(\beta_t(12))$	0.36 (0.3, 0.43)
2017	$\text{logit}^{-1}(\beta_t(13))$	0.43 (0.36, 0.51)
2018	$\text{logit}^{-1}(\beta_t(14))$	0.36 (0.3, 0.43)
Effectiveness of first SIA	$1 - (1/(e^{\beta_2}))$	0.44 (0.34, 0.53)
second SIA	$1 - (1/(e^{\beta_3}))$	0.57 (0.49, 0.64)
third SIA	$1 - (1/(e^{\beta_4}))$	0.64 (0.57, 0.7)
forth SIA	$1 - (1/(e^{\beta_5}))$	0.73 (0.67, 0.77)
fifth and subsequent SIAs	$1 - (1/(e^{\beta_6}))$	0.78 (0.74, 0.81)

Comments as a first-time user

Building the model in JAGS was relatively straightforward and existing example code (from similar applications) was easily replicable, which made the process behind building the model easier. Because adjusting priors and parameters within the JAGS model could be done with ease, the model could be built in a stepwise manner for each dataset by adding one covariate and corresponding prior at a time until the final model with all the data was constructed. Once all data was added to the final model, it was straightforward to parameterise the model and easy to apply the aforementioned minimally informative priors. In an effort to fit the best model to the data, a conditional autoregressive model (CAR model [17]) was trialed using spatial adjacency data and implemented in OpenBUGS (as the GeoBUGS module has not yet been fully tested in JAGS). This model takes into account spatial autocorrelation between neighbouring areal units and uses a spatial covariance matrix to assess spatial correlation that cannot be explained by the other model covariates alone, assuming that v[1 : N] ~ car.normal(adj[],weights[],num[],τ_r) where adj is a spatial matrix describing the neighbourhood structure, weights are the corresponding weights for the neighbourhood structure, num is the sum of all neighbours and τ_r is the standard deviation. Here, the adjacency weights were taken to be simple binary values; 1 if district d_i has a common boundary with d_j and 0 otherwise.

In comparison to the model implemented in JAGS, making changes to the openBUGS model was more difficult. Priors needed adjusting each time a new covariate or parameter was added into the model (to prevent the model from crashing) and the run time was much longer than when run in JAGS. OpenBUGS trap windows pop up each time an unsatisfactory model is run and deciphering the convoluted error messages can be difficult and time consuming to amend. JAGS errors appear directly in the R Console and contain more constructive feedback, such as indicating exactly which line of code contains the error. We found the model without the CAR structure had a much better fit to the data (difference in DIC >100) so the CAR model was discarded.

Mechanistic (as opposed to statistical) transmission models are extremely useful in understanding disease dynamics. In particular, the class of Susceptible-Infectious-Resistant (SIR) models are widely used to estimate transmission and test the efficacy of control measures. SIR models describe the spread of infectious disease through a population in time, and the extent of spread depends on natural history parameters such as the transmission rate and the duration of infectiousness [31, 32]. Such parameters are traditionally assumed known, however with appropriate (i.e. detailed) data, these can be estimated exploiting the flexibility of Bayesian modelling to allow for flaws in the data, and to fully quantify the associated uncertainty.

Here, we consider data on occurrence of Salmonella typhimurium in pigs, using simulated data based on Correia-Gomes et al. [33]. The data consists of bi-weekly counts (over 18 weeks so that t=1,...,9) of animals that are either classified as susceptible (S) or infectious (I) or resistant/carrier (R), for 8 pig cohorts. These classifications of infection state were based on imperfect tests, a point we return to later.

Model formulation

Most conventional SIR models assume that the rate at which an animal has infectious contacts is constant in time and proportional to the density of infectious animals. The constant of proportionality β is called the transmission rate parameter. Assuming contacts between animals are random, the number of infections in a bi-weekly time step is Poisson distributed with mean $\lambda_t = \beta(I_t/N_t)$, where N_t is the total number of animals. The probability of no infectious contacts per animal is then $\exp(-\beta(I_t/N_t))$ so that the probability of infection is $p_t = 1 - \exp(-\beta(I_t/N_t))$. The number of new cases assumed to be $C_t \sim \text{Binomial}(S_t, p_t)$. To allow for cohort variability (j=1,...,8) as well as temporal variation due to external factors, we include a zero mean random cohort-time effect, so that $p_{jt} = 1 - \exp(-\beta(I_{jt}/N_{jt}))\exp(r_{jt})$. As such, we can formulate the model for new infections at the end of time period t as

$$
\begin{aligned}
C_{jt} &\sim \text{Binomial}(S_{jt}, p_{jt}) \\
p_{jt} &= 1 - \exp\{ -\beta(I_{jt-1}/N_{jt-1})\exp(r_{jt})\} \\
\text{cloglog}(p_{jt}) &= \log(\beta) + \log(I_{jt-1}) - \log(N_{jt-1}) + r_{jt} \\
r_{jt} &\sim N(r_{j,t-1}, \sigma_r^2) \text{ for } t>1,\ j=1,\ldots,8 \\
r_{j1} &\sim N(0, 100)
\end{aligned}
$$

so that for each cohort, j, the effects r_{jt} capture the any unobserved but structured (modelled by a random walk) effects in time.

Recall however, that the detection of the infection was based on imperfect tests (serological and bacteriological), whose parallel specificity (true negatives) can nonetheless be assumed 100%. However, the sensitivity (true positives) of both tests is not 100% and as such the observed number of infected animals $Iobs_{jt}$, are a lower bound of the true (unobserved) number I_{jt}. We can then write I_{jt} = $Iobs_{jt}$ + Iob_{jt} where $Inob_{jt}$ is the number of false positives. This can be modelled as:

$$Inob_{jt} \sim Binomial(N_{jt}, pND)$$

Where the probability of not detecting an infected case pND = (1 - SenC)(1 - SenE), with SenC and SenE representing the sensitivity probability of each test (and perfect specificity [34, 35]). Treating $Inob_{jt}$ as unobserved allows formal quantification of the uncertainty due to the test sensitivity. Historical information on the sensitivity of both tests ([34, 35]) was used to construct informative beta prior distributions for SenC and SenE, namely SenC ~ Beta(48.5,50.5) and SenE ~ Beta(58.5,27.5).

To model the transition from infectious to resistant we can use similar arguments as before (see Correia-Gomes et al. [33] for details) and write

$$Rnew_{jt} \sim Binomial(I_{jt}, pR_j)$$
$$cloglog(pR_j) = log(\alpha) + s_j$$
$$s_j \sim N(0,\sigma_s^2)$$

Where $Rnew_{jt}$ is the number of (new) animals that become resistant at the end of t, and pR_j is the probability that an animal becomes resistant. Parameter α is the associated recovery rate, while s_j is a cohort random effect allowing for cohort heterogeneity.

Finally, considering the transition from resistant to infectious we use the following model

$$Inew_{jt} \sim Poisson(\mu_{jt})$$
$$log(\mu_{jt}) = log(v) + log(R_{j,t-1}) + q_j$$
$$q_j \sim N(0,\sigma_q^2)$$

again using similar arguments to before, but replacing the binomial with a Poisson on the basis that this transition is a very rare event and that a Poisson distribution is a good approximation to the binomial distribution for small values of p [3]. $Inew_{jt}$ is the number of new infectious animals (from this transition) in cohort j at end of time t, while v is the transmission rate parameter from resistant to infectious. $R_{j,t-1}$ is the number of resistant animals in the previous time step, so its logarithm is used an as offset. Lastly, q_j is another cohort random effect.

Model implementation and results

To complete the model, we use minimally informative priors for the inverse of the three variance parameters ($1/\sigma_r^2$,$1/\sigma_s^2$,$1/\sigma_q^2$ ~ Gamma(0.5,0.005)). This prior has mean 100 and variance 20000 so it is still a flat prior. Unlike conventional Gamma priors with mean 1, the larger mean of 100 can avoid

the chains getting stuck at very low values. Also, we use flat priors N(0,100) for log(β), log(α) and log(ν) (note the large standard deviation). The model was written in the BUGS language, but implemented in the Nimble package within R [36]. The run-time using Nimble was 20 minutes on a 16GB RAM laptop with an i7-8550U CPU. Three MCMC chains were ran for 300,000 iterations, and 200,000 of those were discarded as the burn-in. Only one in ten samples were collected to improve mixing, resulting in a total of 30,000 samples. Here the maximum Gelman-Rubin statistic (across 94 quantities) was 1.03, implying the chains had likely converged to the posterior.

The median estimates of the transmission parameters and the R_0 from this case study are within what is expected for this infectious disease (i.e. Salmonella is an agent that mainly spreads via the faecal-oral route). These estimates are also comparable with estimates from other simulation studies [37, 38] and very similar to what is known from experimental and field studies [39, 40]. The estimate of the transition rate (β) is slightly higher than that reported in Lurette et al. [38]. For a more detailed discussion please see [33].

The top three panels of Figure 4 show the posterior distributions of the three transmission parameters β,α and ν . These are the parameters of interest, and point estimates of these can be used to run SIR models, noting that the associated uncertainty can also be propagated by using the MCMC samples. The bottom left panel shows the posterior density of $R_0 = \beta/\alpha$, the basic reproduction ratio which quantifies the number of secondary cases to which a primary case gives rise during the infectious period. If $R_0 < 1$ then the disease is receding, but $R_0 > 1$ implies the disease is spreading. The bottom middle panel shows the posterior mean and 95% credible intervals of r_1 given the data. This is the temporal random effect that captures any latent temporally varying effects in the transition from susceptible to infectious, in cohort 1. Lastly, the bottom right plot shows the posterior density of the probability of not detecting an infected case, pND, showing that although it is small, it is non-zero. As expected both tests are imperfect as bacteriology lacks sensitivity given intermittent shedding of Salmonella by infected pigs, and there is a delay between infection and expression of antibodies detected by serology. It was consequently important to include test sensitivity within the model as not accounting for this lack of sensitivity could generate a lower transmission rate [33].

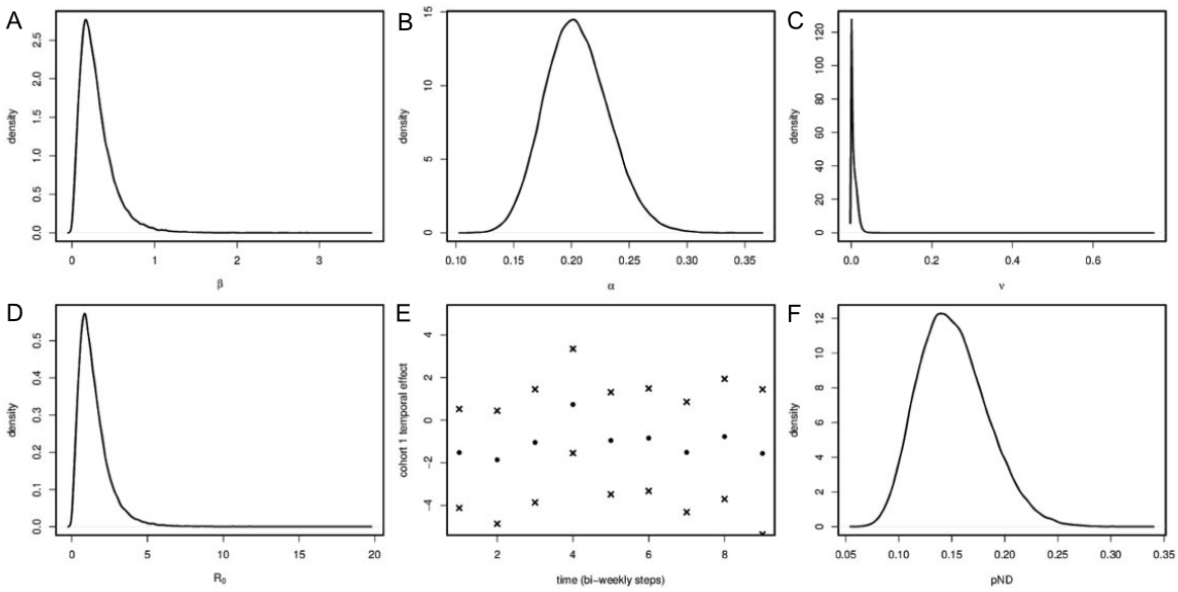

Figure 4. *Plots of posterior estimates from the transmission model from the Salmonella dataset. Top three panels (A, B, C) show posterior densities of the three transmission parameters. Lower panels show D) the posterior density of R_0, E) the temporal effect in the transmission from susceptible to infectious for cohort 1, and F) the posterior probability distribution of not detecting an infected case.*

Comments as a first-time user

Building the model in WinBUGS was relatively straightforward, existing example code from different models were easily replicable, which made the process behind building the model easier. We have started with a simpler model (without cohort effects) and then step-by-step incorporated additional complexity. At each step the priors and parameters had to be adjusted to prevent the model from crashing. As mentioned previously the WinBUGS trap windows pop up each time an unsatisfactory model is run and deciphering the convoluted error messages can be difficult and time consuming to amend the model.

7.1.2.5 Conclusions

The BUGS language is a useful way to put the theory of Bayesian inference into practice due to the clear distinction between model specification and model implementation (MCMC). BUGS has adapted to current best practice in statistical inference (through additional software development) applied to infectious diseases and many other medical fields. All versions of BUGS continue to gain popularity in research. Typing “WinBUGS Bayesian”, “OpenBUGS Bayesian” or “JAGS Bayesian” into Google Scholar returns >24,700 >4,800 and >8,400 hits respectively. Using R to run BUGS models is preferred because of the ease in data manipulation, efficiency in running models and manipulation of the outputs.

For complex models applied to large datasets, model implementation can become increasingly slow. However, the option of using BUGS with R for model implementation, and the recent availability of multiBUGS have made BUGS more computationally efficient. The process behind model development and implementation was illustrated using the examples in this article. However, once the software becomes limiting, it is likely that alternative programming languages that enable alternative implementation to MCMC, or are just faster, would need to be considered. Moderate speed is not an issue unique to BUGS, so the choice of programming language becomes a trade-off between mode run-time and user friendliness.

This article aims to illustrate the utility of using BUGS rather than being an exhaustive list of models that can be implemented, but some additional frameworks are worth mentioning. Accounting for correlation between parameters and non-independent data are important for spatiotemporal analyses, for which several methods are available, such as the CAR model that was trialled using the OPV data. This class of auto-regressive models have been used to account for spatial infectious disease data and covariates not being fully independent, and enables a robust analysis (for example see Lawson [17] and a specific application to dengue modelling by Lowe et al. [41]). If it is not possible to specify a model using the distributions provided within BUGS, the likelihood function can be specified using the 'ones' or 'zeros' trick (and the log-likelihood minimised [42]) and the MCMC machinery used to estimate the posterior distribution (example provided in the SI).

The versatility, ease of use and implementation of Bayesian analysis makes BUGS an excellent tool in infectious disease modelling. For the authors, this means that BUGS has been used for over 10 years and will continue to be used in both teaching and research.

Acknowledgements

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7.1.2.6 References

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7.1.2.7 Supplementary material

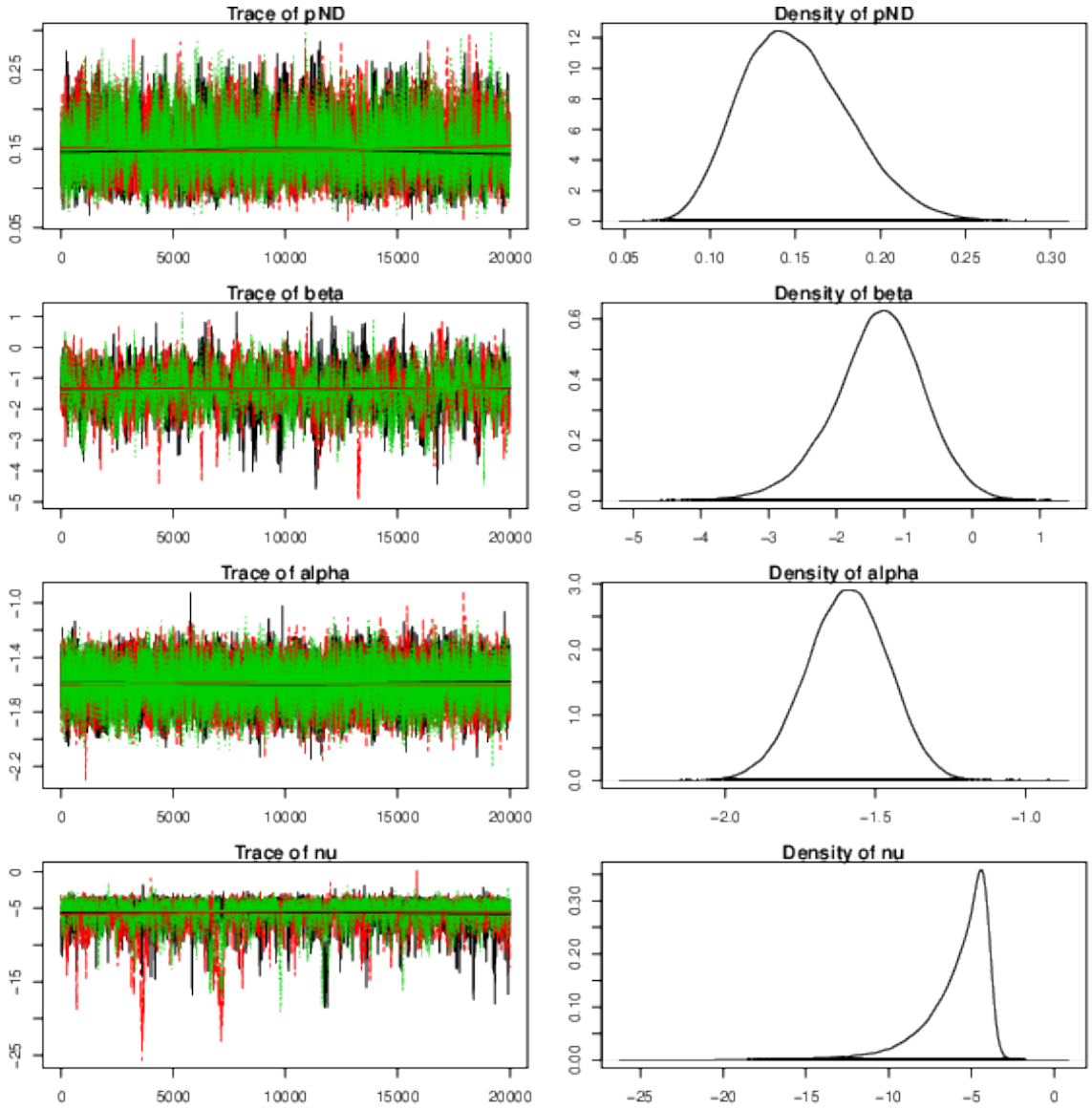


Figure S1. *Trace plots of the following parameters; probability of not detecting an infected case (pND), the transmission rate (β), the recovery rate (α), the reinfection rate (ν).*

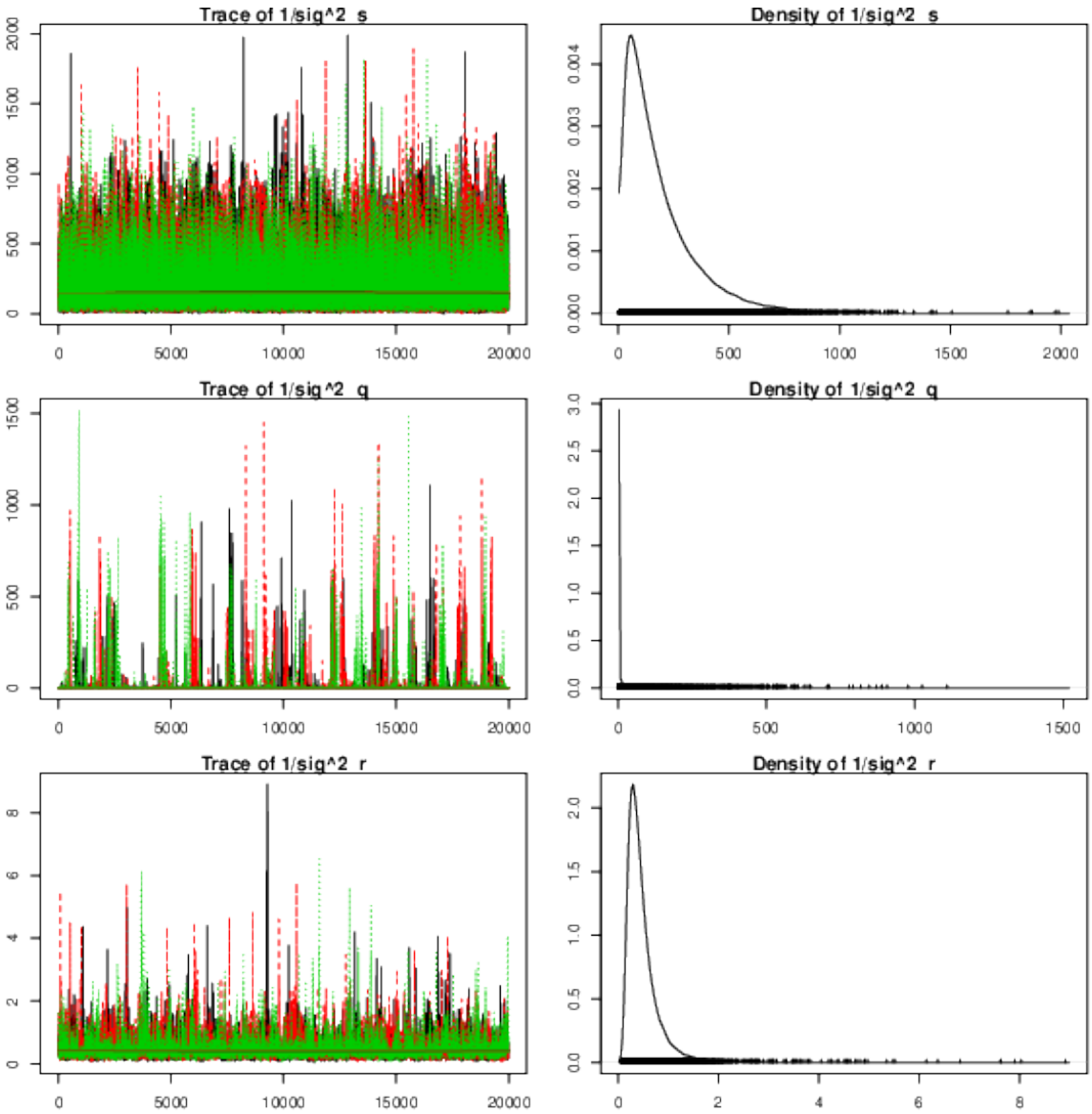


Figure S2. *Trace plots of the variance parameters; cohort heterogeneity (σ_s), cohort random effect (σ_q), time random effect (σ_r).*

7.2 Chapter 3 appendix

Section 1: Model structure, parameters and limitations

Execution of pSIAs and oSIAs

SIAs, including both pSIAs and oSIAs include door-to-door delivery of OPV to children under five years of age. Before an SIA occurs, a target population for the activity is set and vaccinators operate within this target geography for the activity. OPV does not require a cold chain and therefore allows for vaccinators to vaccinate hard-to-reach children who would otherwise be missed by routine immunisations. Once a child has been vaccinated, the dose is recorded on a health card or the child's finger is marked with ink to indicate to the vaccinators that the child has already received a dose during the SIA. This prevents vaccinators from vaccinating the same children twice. This process is used in both pSIAs and oSIAs. Therefore, the transition of a child between model compartments following a vaccine dose is identical for pSIAs and oSIAs. The parameters such as SIA coverage, vaccine efficacy and seroconversion are the same for pSIAs and oSIAs

The difference between pSIAs and oSIAs is how they are funded and planned. oSIAs are emergency responses to outbreaks and therefore, occur rapidly following an outbreak (at least within 90 days) only in areas affected by the outbreak. Sometimes, a buffer area, or a geography surrounding the outbreak, can also be vaccinated during an oSIA. pSIAs occur as National Immunisation Days (NIDs) or Subnational Immunisation Days (SNIDs) and usually cover a larger geographical area than oSIAs. These funding and planning differences are important for the economic aspects of this analysis, but do not alter any model transitions in the SIR model below. For calculation of historical SIAs, we assumed that pSIAs included NIDs or SNIDs with bOPV (or trivalent OPV (tOPV) pre-2016) that did not occur within 365 days of a WPV1 or VDPV1 detection by AFP surveillance or ES. Any SIA that occurred within this interval was not included in the overall count of pSIAs.

Geographical setting modelled

In this analysis, we model a hypothetical geography for a non-polio endemic LMIC in sub-Saharan Africa with a population size of approximately 8 million children under five years of age. There are a few reasons we did not model a specific country. Firstly, WPV1 importation into Africa is not, in 2024, a common occurrence. Therefore, we cannot fit this model to actual WPV1 importation data in many geographies. We saw an unexpected, albeit understandable, importation event in 2021, which highlighted the need for other non-endemic countries in AFRO to evaluate their current vaccination strategies given baseline RI coverage and importation risk, given onward transmission from the

Malawi importation event. One benefit of using a hypothetical setting is that the implications of this model can be applied to a range of countries even in the absence of an importation to predict risk and understand the benefits and risks of adopting different SIA strategies.

Model structure

A stochastic non-linear mathematical model was used to simulate polio transmission dynamics, whereby infectious individuals develop either asymptomatic (I, or infectious, compartment), or symptomatic infection (C, or case, compartment), both of which are assumed to be infectious. Both infections and cases recover to the Rn compartment. In the model, children are either susceptible (S0 compartment), fully vaccinated and protected from poliovirus infection (Rv compartment) or have received an incomplete vaccination series (less than 3 bOPV doses + 1 IPV dose, modelled separately). Children who were not vaccinated via RI, can receive additional doses of bOPV vaccine through either pSIAs or oSIAs. Each subsequent dose of vaccine corresponds additional protection and an opportunity for a child to seroconvert and be considered fully protected from poliovirus infection (corresponding to each of the Sn tiers).

The left side of Appendix Figure 1 corresponds to children missed by RI who have an opportunity for additional bOPV doses via SIAs. Progression through the model to different Sn compartments happens only at the time of an SIA.

The right side of Appendix Figure 1 corresponds to RI and happens daily, when life births enter the population. Vaccination via RI is assumed to occur upon entering the model. Children vaccinated via RI are assumed to receive a sequential schedule of both bOPV and IPV, whereby they are assumed to seroconvert and be protected from poliovirus (transitioning to Rv compartment). Only children previously vaccinated via RI are eligible for vaccination with IPV and IPV is provided alongside the third dose of bOPV via RI in most African countries.

To guide understanding of the model diagram, the compartments correspond to the following:

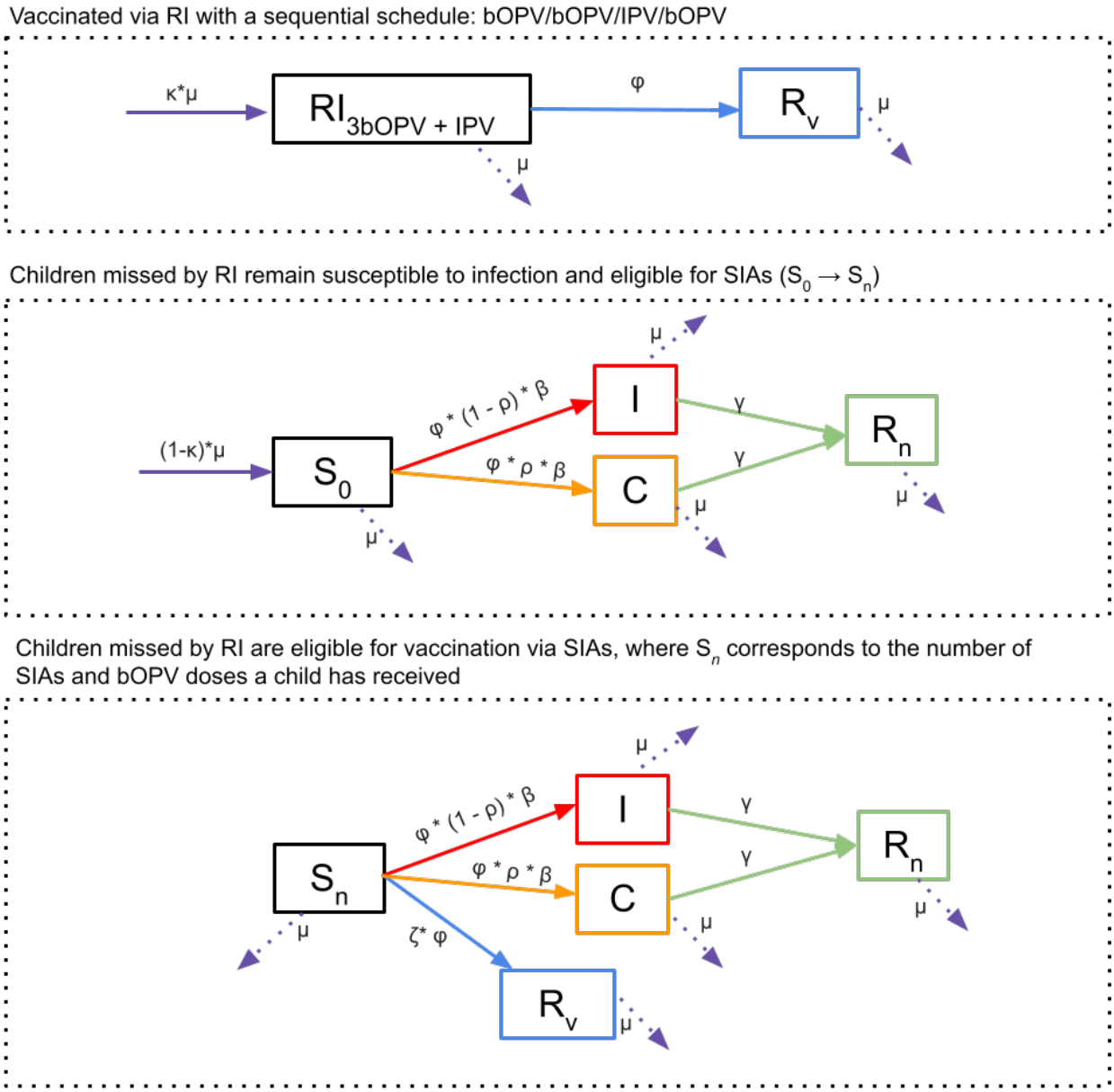
- S0 = susceptible to poliovirus, no vaccine received
- I = infectious, but asymptomatic
- C = infectious and polio (AFP) case
- Rn = recovery via natural infection
- S_n = susceptible to poliovirus infection, but have received *n* bOPV doses via SIAs (S_{3sia} explicitly refers to children who received the 3rd bOPV dose via SIAs not RI)
- $RI_{3bOPV + IPV}$ = vaccinated with 3 bOPV doses + IPV at birth via RI
- $S3_{ri}$ = vaccinated with bOPV, but missed IPV dose

Event table for the SIR model

Appendix table 1 shows transitions and transition probabilities in the stochastic SIR model. The compartments and probabilities correspond to Appendix figure 1 and Appendix Table 3.

Appendix Table 1. Model transitions and transition probabilities in the stochastic SIR model

$S0 \rightarrow ((1-\rho) * \phi) * (\beta * S0 * (I + C)) / (S0 + S_n + RI_{3bOPV+IPV} + Rv + I + C + Rn) \rightarrow I$
$S0 \rightarrow \rho * \phi * (\beta * S0 * (I + C)) / (S0 + S_n + RI_{3bOPV+IPV} + Rv + I + C + Rn) \rightarrow C$
$S_n \rightarrow ((1-\rho) * \phi) * (\beta * S_1 * (I + C)) / (S0 + S_n + RI_{3bOPV+IPV} + Rv + I + C + Rn) \rightarrow I$
$S_n \rightarrow \rho * \phi * (\beta * S_1 * (I + C)) / (S0 + S_n + RI_{3bOPV+IPV} + Rv + I + C + Rn) \rightarrow C$
$RI_{3bOPV+IPV} \rightarrow ((1-\rho) * \phi) * (\beta * RI_{3bOPV+IPV} * (I + C)) / (S0 + S_n + RI_{3bOPV+IPV} + Rv + I + C + Rn) \rightarrow I$
$RI_{3bOPV+IPV} \rightarrow \rho * \phi * (\beta * RI_{3bOPV+IPV} * (I + C)) / (S0 + S_n + RI_{3bOPV+IPV} + Rv + I + C + Rn) \rightarrow C$
$I \rightarrow \gamma * I \rightarrow Rn$
$C \rightarrow \gamma * C \rightarrow Rn$



Appendix Figure 1. Model structure of the extended SIR model. Births enter the population either via the S0 compartment or the $S3_{ri}$ compartment, assuming vaccination with three bOPV doses occurs via RI at the time of birth. Children can exit the population from any compartment via death. Children missed by RI at birth remain in the S0 compartment, with potential for vaccination with one dose of bOPV via pSIA or oSIA. Each of the SIA tiers (S_n), where n corresponds to the number of bOPV doses received via an SIA, allow for potential seroconversion and transition to the Rv compartment according to assumed bOPV vaccine efficacy. Children who do not seroconvert following bOPV during an SIA progress to the next vaccination tier, n+1, and await subsequent SIA vaccination. Each of the SIA tiers remain susceptible to infection. In this model we assume that bOPV coverage = IPV coverage.

Model compartments and transitions

A review of the immunogenicity of vaccination schedules with both IPV and three doses of bOPV indicate high rates of seroconversion alongside some geographical variability [1] and sustained protection against paralytic poliomyelitis [2]. Accordingly, we assume seroconversion and transition to the Rv compartment is 100% for children who received three doses of bOPV and one dose of IPV and no waning of protection. The assumptions described here about vaccination activities provide a 'steady state' immunity profile which we use to explore the effects of polio introductions. We assume that once five years of age is reached, children are no longer relevant to poliovirus transmission, due to the high likelihood of immunity against infection due to vaccination.

Appendix Table 2. Model compartments and corresponding explanation of compartmental transitions and assumptions

Compartment	Assumption
S_0	Susceptible individuals in this compartment have not been vaccinated, i.e., zero doses received of both bOPV and IPV. The proportion of unvaccinated individuals born into this compartment depends on assumed RI coverage. From S_0, individuals exposed to 1 dose of bOPV via an SIA progress to S_n. Individuals who stay in S_0 remain susceptible to infection.
S_n	Individuals in this compartment have received *n* doses of bOPV via an SIA. From each S_n compartment, a certain proportion will seroconvert after vaccination and transition to Rv, according to bOPV vaccine efficacy (see parameter ϕ below). While those that did not seroconvert stay in S_n and remain susceptible to infection (adjusted by a factor of ϕ for protection received by *n* doses) and are eligible for future vaccination in a subsequent SIA. After 4 bOPV doses, all children are assumed to seroconvert and transition to Rv after completing a full series of vaccinations.
$RI_{3bOPV + IPV}$	Assuming bOPV coverage = IPV coverage. Children in this compartment are vaccinated via RI with a sequential schedule of OPV/OPV/IPV/OPV. It is assumed after 3 doses of bOPV and 1 dose IPV 100% of children seroconvert and transition to the Rv compartment and are also protected from paralysis.
$S3_{ri}$	Individuals in this compartment received 3 doses of bOPV at birth via RI. From $S3_{ri}$, a certain proportion will seroconvert after 3 doses and transition to Rv, according to bOPV vaccine efficacy (see parameter ϕ below in Appendix Table 3). Of those vaccinated with IPV, 100% are assumed to seroconvert and transition to Rv.
I	Individuals in this compartment are infectious, but asymptomatic. They can spread infection to others but are not a paralytic case of polio. Importations of infection who enter the population enter via this compartment.
C	Individuals in this compartment are a paralytic case of polio. They can spread infection to others and trigger an outbreak response campaign in the baseline strategy.
Rn	Individuals in this compartment have recovered from natural infection and are assumed immune to subsequent infection.
Rv	Individuals in this compartment have received sufficient vaccination to result in seroconversion and are assumed immune to subsequent infection.

Model parameters, assumptions and transition probabilities

Appendix Table 3. Table of model parameters and corresponding values and assumptions

Parameter	Value	Assumption
γ	1/8	γ = recovery rate – the infectious period for polio is between 7-10 days before AND after symptoms. Here, we took the average, 8 days that an individual can remain in the I or C compartment, before transitioning to R_n
R_o	3	Basic reproductive number. For polio, the basic reproductive number, R_0, can vary substantially between locations depending on sanitation and hygiene conditions [3].
β	0.375	The effective contact rate, which affects the transition from the susceptible compartment to the infected compartment, and the rate of recovery, which affects the transition from the infected compartment to the recovered compartment. If, $R_o = β / γ$ Then, if R_o is 3, and γ is 1/8, then β is 0.375
ρ	1/200	Case to infection ratio for WPV. The WPV1 case to infection ratio was assumed to be 1:200, which is consistent with estimates for poliovirus serotype 1 [4].
κ	Varied between 0.25 – 1.0	Proportion that received 3 doses of bOPV via RI
ζ	0.25	Proportion of the target population reached by the SIA, those missed by the campaign are represented by 1- ζ
ω	Varied between 0.25 – 1.0	Proportion exposed to IPV vaccination
ϕ	$1 – ((1 – 0.5)^{doses})$	Vaccine effectiveness of bOPV for protection against serotype 1, i.e., the proportion of the population that seroconvert and transition to Rv assuming vaccine efficacy (VE) is 50%
μ	$5*10^{-4}$ * population	Birth rate = death rate 4,000 live births per day in a country of 8 million is the average number of live births across African countries, assumptions on the equal birth and death rate are in line with other research using a similar hypothetical population [5]
Herd immunity	$1-1/R_0$	Using an R_0=3, the herd immunity threshold would be assumed to be reached at 66.67% RI coverage

Model framework

It is important to discuss the model framework used in this analysis and associated pros and cons of the simplistic model structure and assumptions. Model simplicity allows for easy interpretation and is applicable to a range of settings. Here, we model a hypothetical population size for a LMIC in sub-Saharan Africa using certain fixed parameters, but the simple model structure can be easily adapted to fit specific countries, or even subnational populations. The model compartments and transitions are easy to understand by a wide range of audiences, not just mathematical modellers and the SimInf package allows for easy adaptation of scheduled vaccination activities to local contexts. SimInf uses continuous-time Markov chains using the Gillespie stochastic simulation algorithm (SSA) to integrate infection dynamics and incorporates available data such as births, deaths or vaccination as scheduled events.

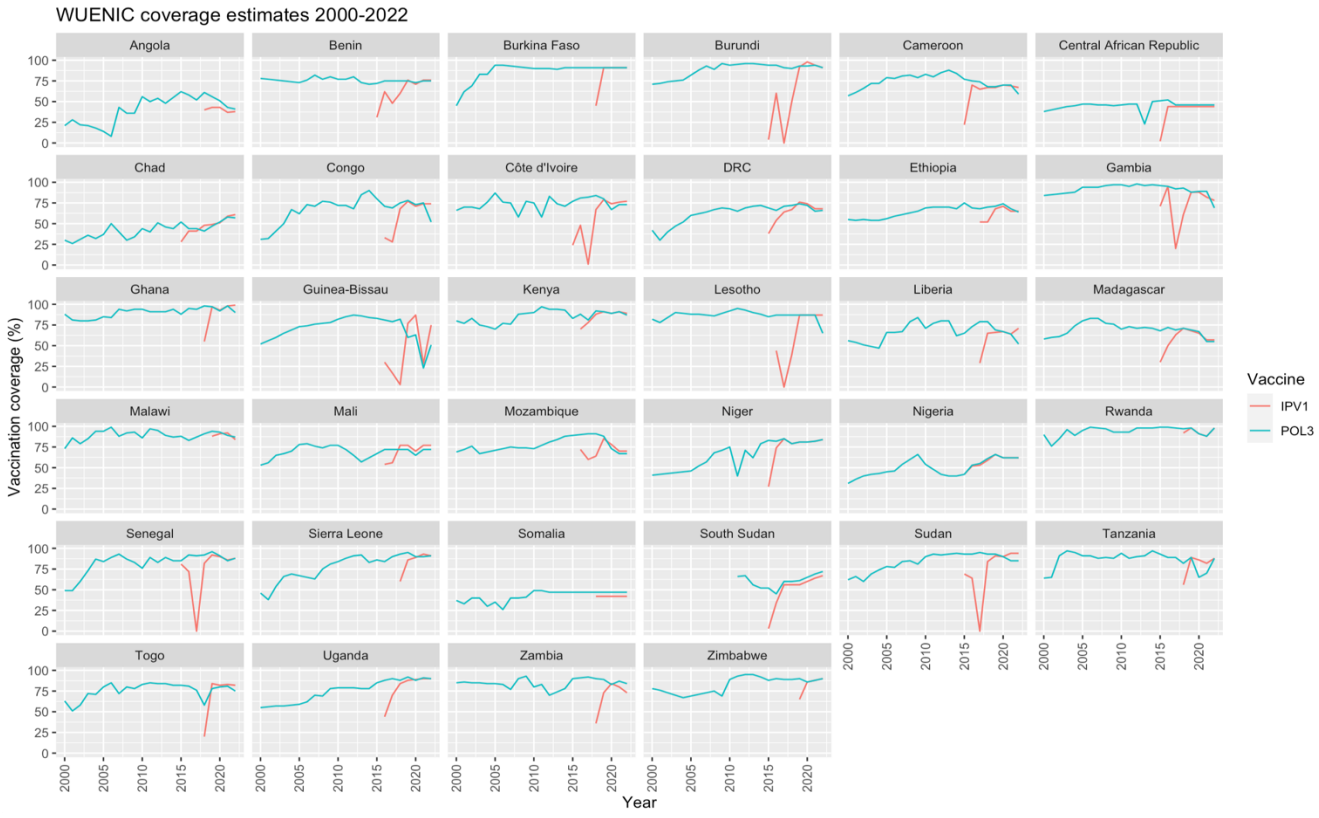
The simplicity of the model does give rise to several limitations. In this model, we assume homogenous mixing, assume that the same polio programme has been in place for 50 years prior to model initiation, assume SIAs reach 25% of children unvaccinated by RI, assume a single value for R_0 and other model parameters with no uncertainty. Of particularly importance is heterogeneity in the population structure. If there are pockets with higher rates of transmission or lower vaccination coverage (or both) then this would increase the likelihood of outbreaks and thus decrease the likelihood that eradication will be achieved. Sensitivity analyses in Appendix Section 4 further explore varying assumptions about SIA target population, importation rate and R_0. In summary, under different assumptions, model outputs across vaccination strategies are only affected when RI coverage is very low and therefore, support the assumptions used in the main analysis.

Further, the model structure assumes that children are vaccinated when they are born into the population, not accounting for infection prior to vaccination. Because the average age of infection with poliomyelitis occurs after the vaccination schedule of bOPV given at 6, 10 and 14 weeks of age alongside the effect of maternal antibodies, this limitation is unlikely to impact the expected number of AFP cases. However, because the size of the birth cohort vaccinated may be overestimated in the absence of infant mortality assumptions, the costs of RI may be over-estimated here. Additionally, we do not include indirect costs of vaccination, such as opportunity costs of time spent for vaccination, which may result in an underestimation of costs across all strategies. The indirect benefits of these additional interventions (such as productivity increases from averting polio cases) are also not quantified in the costs and benefits of SIAs described here, therefore the deaths and burden averted are polio specific and exclude indirect economic effects, in contrast to some other analyses.

Section 2: Model and cost assumptions

IPV and OPV coverage estimates

This WEUNIC data shows the relationship between IPV and OPV3 coverage (three doses of bOPV vaccine) for twenty-five countries in sub-Saharan Africa. IPV was introduced later in time in all countries, and although at the time of introduction IPV coverage was lower than OPV3 coverage in most countries, in 2021, IPV and OPV3 coverage was roughly equal across all countries. This data supports the model assumption that IPV coverage = OPV3 coverage, or all children that receive a third dose of bOPV, also received IPV via RI.



Appendix Figure 2. WUENIC coverage estimates 2000-2021 for OPV3 and IPV1 across Sub-Saharan African countries. The strong correlation between OPV3 and IPV1 coverage estimates in 2020 and 2021 (when scale-up of IPV implementation was reached) support model assumptions that OPV coverage is equal to IPV coverage. DRC = Democratic Republic of Congo.

Sample size calculation

The United Nations World Population Prospects (WPP) data was used in our sample size calculation [6]. We used WPP data from 2021 to calculate the mean under-5 population size in 25 Sub-Saharan countries: Burundi, Guinea, Benin, Zimbabwe, Senegal, Malawi, Zambia, Somalia, Chad, Burkina Faso, Mali, Madagascar, Côte d'Ivoire, Cameroon, Ghana, Niger, Mozambique, South Africa, Angola, Kenya, Sudan, Uganda, United Republic of Tanzania, Democratic Republic of the Congo, Ethiopia, Nigeria. The

mean under-5 population size was 8,000,000 and the range of the data was (2,500,000 – 41,000,000). Given this large range of population sizes across countries, we chose to use the mean under-5 sample size amongst these countries as our target-population size for this modelling. Historical pSIAs and RI coverage of an additional 10 countries with smaller under-5 populations are referenced in the manuscript to give regional context and our results are still relevant for these geographies, but absolute cases and costs need to be scaled according to population size.

Cost assumptions

We assume costs of SIAs are the same across the entire modelled time horizon. Costs associated with vaccine doses and the number of children vaccinated during an SIA are estimated using the entire target population of eight million children under five years of age, even though in practice, the true proportion of children reached during SIAs is often much lower due to operational challenges and other logistical shortcomings [7]. As model outputs captured the variability across all stochastic simulations, costs for each individual simulation were calculated across all strategies. The average expected costs for each strategy were then obtained by taking the mean cost across all simulations for each corresponding strategy. The GPEI costs include those associated with SIAs and IPV in RI. Treatment costs associated with paralytic polio (including VAPP) are paid for by the country and included as health care system costs; specific equations used in the costing estimates can be found below in Appendix Table 4.

Literature has shown that costs associated with RI administration can vary across RI coverage for different antigens [8, 9], but usually the threshold cut-off is below and above 80% RI coverage and explicit evidence of this differential for polio is not well documented. Accordingly, we use one value for costs associated with RI administration for polio as documented by Kalkowska et al.

Appendix Table 4. Table of cost inputs and corresponding values and assumptions

Item	Value (USD$2023)	Assumption / reference
bOPV dose	$0.18	Average cost for a GAVI country [9], price per dose in a 10-dose vile
IPV dose	$2.00	For a GAVI country 10-dose vile and translated into USD$2023 [10]
RI OPV admin	$1.06*3 doses	Costs associated with administration, procurement and storage of OPV for use in RI. 2019 costs were obtained from appendix Table A1 [11]. We assume costs and wastage are based on the size of the entire birth cohort.
RI IPV admin	$2.00	Costs associated with administration, procurement and storage of IPV for use in RI. 2019 costs were obtained from appendix Table A1 [11]. We assume costs and wastage are based on the size of the entire birth cohort.
pSIA	$0.50/child	Includes operational costs, social mobilisation and administration. We assume that SIAs are planned to reach 100% of the population and costed accordingly but the actual population vaccinated is 25% due to operational challenges. Costs are obtained from GPEI
oSIA	$1.0/child Range: $0.50 – $1.50/child	Includes costs associated with emergency response to an outbreak. We assume that SIAs are planned to reach 100% of the population and costed accordingly but the actual population vaccinated is 25% due to operational challenges. Costs are estimated based on GPEI costs for pSIAs
VAPP rate	Dependent on dose and vaccination schedule	1st dose: 0.9 VAPP cases/1 million bOPV doses administered, a 6.6-fold greater risk than following subsequent doses [12] The risk of VAPP following OPV vaccination is reduced if IPV has been received. We assume no risk of VAPP associated with IPV vaccination and a 53% reduction in VAPP cases following bOPV if IPV has already been received
DALY	14/paralytic case	Assume AFP case = VAPP case
Paralytic case	$700/case	Assume AFP case = VAPP case, cost is for a low-income country [8]
bOPV wastage RI	Range 10-20%	Range of estimated wastage of bOPV in RI [13, 14]
bOPV wastage SIA	Range 5-15%	Range of estimated wastage of bOPV in both pSIAs and oSIAs [13, 14]
IPV wastage RI	Range 5-20%	Range of estimated wastage of IPV in routine settings. Range varies based on vial size and setting [13, 14]
Health care system & non-GPEI costs		Treatment costs (red) + RI OPV costs (blue) *(Cost per AFP case * AFP cases) +* *(Cost per VAPP case * VAPP cases)* *+* *(RI coverage *(New-borns eligible for bOPV vaccination * total doses received per child) * (Cost per dose of bOPV + RI delivery cost per dose of bOPV) * (1 + bOPV wastage rate for RI))*

GPEI costs		pSIA costs (green) + oSIA costs (purple) + RI IPV costs (orange) *(SIA coverage * (Target population† * Number of pSIAs) * (Cost per dose of bOPV + pSIA delivery cost per dose of bOPV) * (1 + bOPV wastage rate for SIAs))* + *(SIA coverage * (Target population† * Number of oSIAs) * (Cost per dose of bOPV + oSIA delivery cost per dose of bOPV) * (1 + bOPV wastage rate for SIAs))* + *(RI coverage * (New-borns eligible for vaccination) * (Cost per dose of IPV + RI delivery cost per dose of IPV) * (1 + IPV wastage rate for RI))* † Target population for pSIAs and oSIAs refers to all children under five years of age

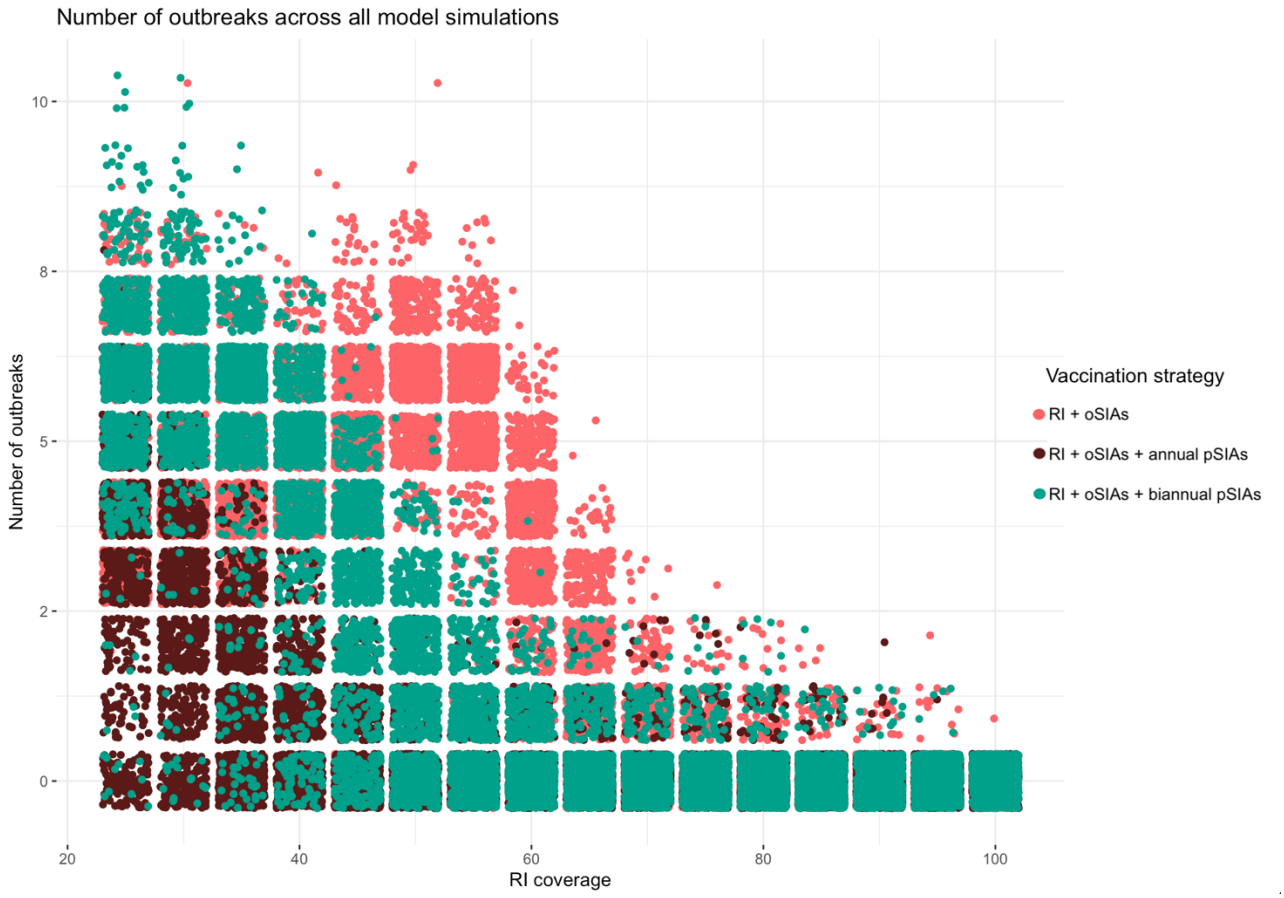
Calculation of Incremental Cost-Effectiveness Ratios (ICERs)

ICERs were calculated using the following equation:

$$ICER = \frac{(costs\ of\ pSIA\ strategy - costs\ of\ baseline\ strategy)}{(DALYs\ averted\ by\ pSIA\ strategy)}$$

Mean ICERs were calculated using the mean costs and DALYS of each vaccination strategy for each RI coverage level across all model simulations. Then to get uncertainty, we calculated an ICER for each of the simulations. We extracted the lowest (Democratic Republic of the Congo), median (Benin) and highest (South Africa) cost-effectiveness thresholds among the 25 low, lower middle and upper middle-income sub-Saharan African countries used in our sample size calculation from supplementary table 3 by Pichon-Riviere A et al. 2023 [15]. The results are provided not to drive a specific investment decision within a health technology assessment (HTA) or other decision-making framework (as a cost-effectiveness analysis for a new drug or vaccine would be), but to provide general evidence to inform policy making. GDP data was obtained from the World Bank database [16].

Variable number of outbreaks across all strategies



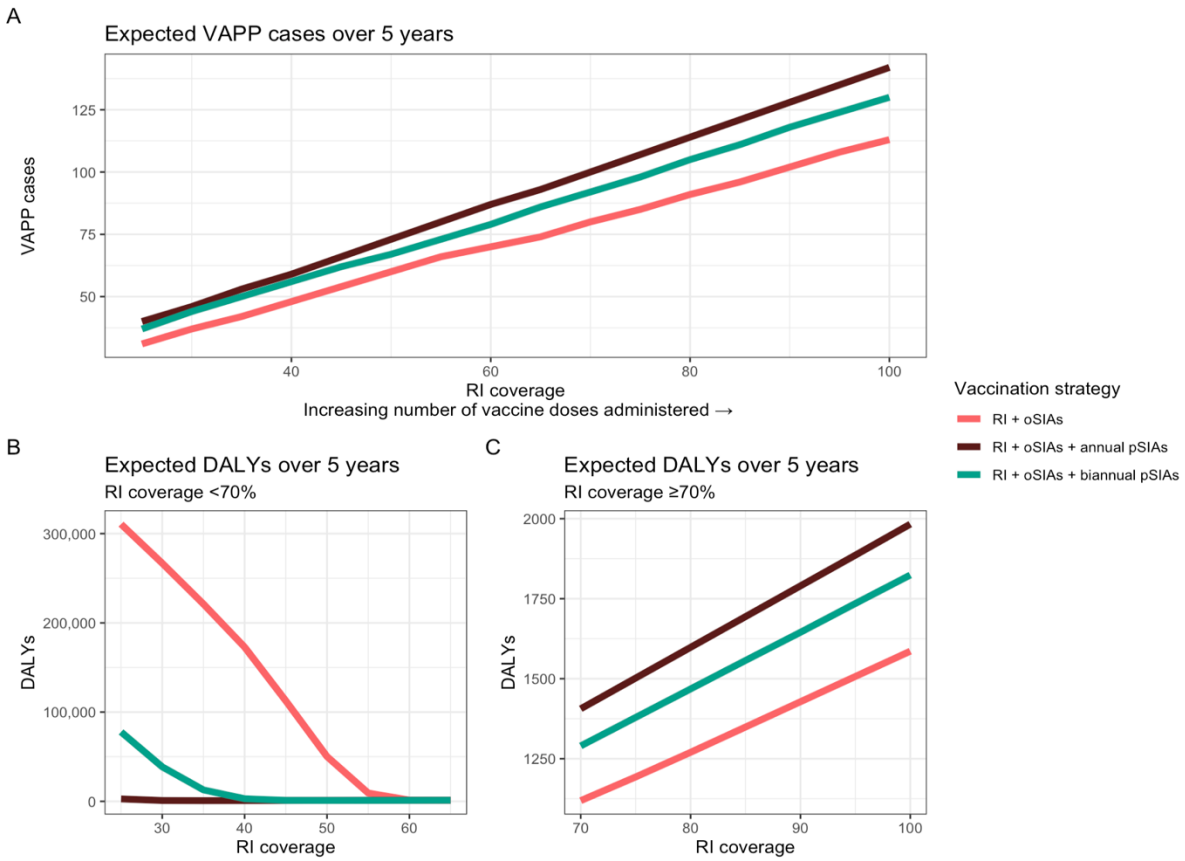
Appendix Figure 3. Number of outbreaks in each individual model simulation for each vaccination strategy, among simulations with ≥1 paralytic polio case. The low number of outbreaks at RI coverage levels >70% correspond to a lower probability of an outbreak, which was lowest in the annual pSIA strategy.

The stochasticity of epidemics means that there is considerable variability in outcome for identical assumptions focussing on simulations that had ≥1 paralytic polio case (Appendix Figure). We define an outbreak as at least one case of paralytic poliomyelitis, which we assume would present as acute flaccid paralysis (AFP). To count the total number of outbreaks, all cases that occurred within 90 days of the first case were considered part of the same outbreak. Cases that occurred in subsequent intervals of 90 days were considered part of different independent outbreaks. Even though some cases that are allocated to different outbreaks may in fact be linked or a part of the same outbreak, the 90-day threshold aligned with the schedule of oSIAs and was used as a consistent unit to count outbreaks across strategies. This method of counting outbreaks may incorrectly attribute linked cases from the same outbreak as independent outbreaks but was taken to reduce model complexity. As

standard operating procedures for polio outbreaks recommend an oSIA in affected areas within 90-days of the first case, if an outbreak is not stopped or subsequent cases arise later, this would trigger a subsequent oSIA, a chronology which is accurately accounted for in this analysis. In the absence of having uniquely identifiable outbreaks within the model, simplifying the outbreak count by using a 90-day cut-off is a limitation that may over-estimate the total number of outbreaks, however, the counting methodology is consistent across all evaluated strategies.

Trends in VAPP and DALYs

Vaccine associated paralytic polio (VAPP) occurs when a strain of poliovirus that has genetically mutated from the original attenuated vaccine strain contained in OPV causes paralysis [17]. VAPP can occur following vaccination with OPV, or it can also occur in a close unvaccinated or non-immune contact of a vaccine recipient who excretes the mutated virus [17]. VAPP rate across settings with and without SIAs has been shown to vary [18], although this variation is not well understood or documented. OPV administration following IPV receipt is associated with a further risk reduction of VAPP [12] and is accounted for in model assumptions (Appendix Table 4). Expected VAPP cases over the same interval are greatest in the annual pSIA strategy, corresponding to the strategy with the greatest number of vaccine doses administered (Appendix Figure 4). The annual pSIA strategy administers the greatest number of vaccine doses and is the strategy that results in the fewest expected WPV cases over five-years (main text figure 2A). At RI coverage levels below 70%, DALYs incurred are greatest in the baseline strategy, the strategy with the greatest number of expected AFP cases. However, at RI coverage levels >70%, the average number of VAPP cases exceeds the number of WPV1 cases in all pSIA strategies, which drives these two strategies to have a greater number of estimated DALYs lost than the RI strategy alone. Expected DALYs in the annual pSIA strategy are greatest when RI coverage exceeds 70% because the number of pSIAs remains constant over time, resulting in more VAPP cases and consequently, a greater number of DALYs incurred. In contrast, above 70% RI coverage, the baseline strategy has fewer WPV1 cases and no or fewer oSIAs, resulting in fewer VAPP cases and therefore fewer expected DALYs incurred.



Appendix Figure 4. Average number of expected VAPP cases and DALYs per capita over 5 years amongst model simulations that reported at least one outbreak. The increase in VAPP cases is related to the increase in vaccine doses administered.

Appendix Table 5. Health system perspective: table of cases, VAPP, DALYS and costs across all strategies. Uncertainty in cases and associated costs is presented as 95% credible intervals (CI). Here, the mean values are obtained from taking the mean across all model simulations, not just amongst the simulations with an outbreak (as was done in table 2 in the main text).

RI (%)	Strategy	Mean cases	Cases lwr 95% CI	Cases upr 95% CI	Mean outbreaks (range)	Mean VAPP	Mean DALYS	Mean total costs ($)	Total costs ($) lwr 95% CI	Total costs ($) upr 95% CI
25	Annual pSIA	156	129	183	4 (0—8)	40	2742	8065554	7955389	9028399
30	Annual pSIA	20	16	24	2 (0—6)	46	930	9560618	9545889	9652046
35	Annual pSIA	3	3	4	1 (0—5)	53	784	11139031	11136390	11150405
40	Annual pSIA	1	1	1	1 (0—3)	59	843	12727687	12726890	12730621
45	Annual pSIA	0	0	0	0 (0—3)	66	931	14317772	14317391	14319951
50	Annual pSIA	0	0	0	0 (0—3)	73	1024	15908119	15907891	15909613
55	Annual pSIA	0	0	0	0 (0—2)	80	1118	17498506	17498392	17499412
60	Annual pSIA	0	0	0	0 (0—2)	87	1214	19088967	19088893	19089831
65	Annual pSIA	0	0	0	0 (0—2)	93	1310	20679448	20679394	20680270
70	Annual pSIA	0	0	0	0 (0—2)	100	1406	22269934	22269894	22270717
75	Annual pSIA	0	0	0	0 (0—2)	107	1502	23860434	23860395	23861221
80	Annual pSIA	0	0	0	0 (0—2)	114	1598	25450918	25450896	25451599
85	Annual pSIA	0	0	0	0 (0—1)	121	1694	27041413	27041397	27041399
90	Annual pSIA	0	0	0	0 (0—1)	128	1790	28631903	28631897	28631899
95	Annual pSIA	0	0	0	0 (0—1)	135	1886	30222399	30222398	30222399
100	Annual pSIA	0	0	0	0 (0—0)	142	1983	31812928	31812928	31812928
25	Biennial pSIA	5520	5351	5689	6 (0—10)	37	77800	11818435	8287477	15535884
30	Biennial pSIA	2718	2577	2859	6 (0—10)	44	38663	11447281	9561613	14853006
35	Biennial pSIA	866	797	935	5 (0—9)	50	12822	11740950	11133068	13865749
40	Biennial pSIA	154	137	171	4 (0—8)	56	2936	12832320	12723213	13448221
45	Biennial pSIA	16	15	18	3 (0—7)	62	1093	14325840	14313359	14387991
50	Biennial pSIA	3	2	3	1 (0—5)	67	981	15905929	15903505	15915663
55	Biennial pSIA	1	1	1	1 (0—4)	73	1035	17494354	17493651	17497300
60	Biennial pSIA	0	0	0	0 (0—4)	79	1116	19084100	19083798	19085739
65	Biennial pSIA	0	0	0	0 (0—2)	86	1203	20674109	20673944	20674993
70	Biennial pSIA	0	0	0	0 (0—2)	92	1290	22264176	22264091	22265056
75	Biennial pSIA	0	0	0	0 (0—2)	98	1379	23854299	23854237	23855158
80	Biennial pSIA	0	0	0	0 (0—2)	105	1468	25444422	25444384	25445241
85	Biennial pSIA	0	0	0	0 (0—2)	111	1557	27034555	27034531	27035333
90	Biennial pSIA	0	0	0	0 (0—1)	118	1645	28624688	28624677	28624679
95	Biennial pSIA	0	0	0	0 (0—1)	124	1735	30214829	30214824	30214825
100	Biennial pSIA	0	0	0	0 (0—0)	130	1824	31804991	31804991	31804991
25	Baseline	22158	22071	22246	4 (2—9)	31	310649	23460911	21665597	25612092
30	Baseline	19021	18938	19105	4 (3—10)	37	266811	22854690	20515728	25133539
35	Baseline	15753	15664	15842	4 (3—8)	42	221134	22156506	19692406	24125425
40	Baseline	12296	12182	12409	5 (0—9)	48	172812	21326123	18539293	23184345
45	Baseline	7990	7859	8120	5 (0—9)	54	112616	19901986	16503382	22298018
50	Baseline	3524	3399	3649	6 (0—10)	60	50181	18365947	15986096	21224605
55	Baseline	598	546	650	5 (0—8)	66	9290	17907087	17486193	19487919
60	Baseline	30	26	34	3 (0—7)	70	1399	19098238	19075847	19199688
65	Baseline	2	2	2	1 (0—5)	74	1073	20667602	20665501	20674099
70	Baseline	0	0	0	0 (0—3)	80	1119	22255585	22255155	22257731
75	Baseline	0	0	0	0 (0—3)	85	1193	23844979	23844808	23845898
80	Baseline	0	0	0	0 (0—2)	91	1270	25434546	25434462	25435474
85	Baseline	0	0	0	0 (0—2)	96	1349	27024160	27024116	27025050
90	Baseline	0	0	0	0 (0—1)	102	1428	28613790	28613770	28613770
95	Baseline	0	0	0	0 (0—2)	108	1507	30203435	30203424	30203424
100	Baseline	0	0	0	0 (0—1)	113	1586	31793079	31793078	31793078

Appendix Table 6. GPEI perspective: table of cases, VAPP, DALYS and costs across all strategies. Uncertainty in cases and associated costs is presented as 95% credible intervals (CI). Here, the mean values are obtained from taking the mean across all model simulations, not just amongst the simulations with an outbreak (as was done in table 2 in the main text).

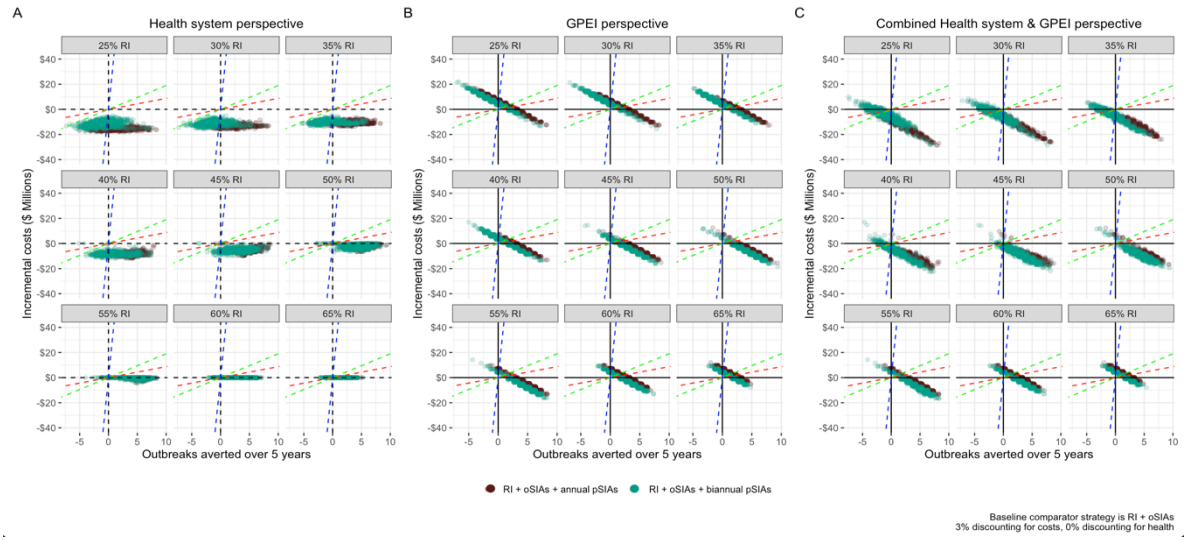
RI (%)	Strategy	Mean cases	Cases lwr 95% CI	Cases upr 95% CI	Mean outbreaks (range)	Mean VAPP	Mean DALYS	Mean total costs ($)	Total costs ($) lwr 95% CI	Total costs ($) upr 95% CI
25	Annual pSIA	156	129	183	4 (0—8)	40	2742	25173474	15992148	31700148
30	Annual pSIA	20	16	24	2 (0—6)	46	930	23728011	17672577	30762577
35	Annual pSIA	3	3	4	1 (0—5)	53	784	22400359	19353007	29825007
40	Annual pSIA	1	1	1	1 (0—3)	59	843	22627798	21033436	28887436
45	Annual pSIA	0	0	0	0 (0—3)	66	931	23512356	22713866	27949866
50	Annual pSIA	0	0	0	0 (0—3)	73	1024	24954547	24394295	29630295
55	Annual pSIA	0	0	0	0 (0—2)	80	1118	26365323	26074725	28692725
60	Annual pSIA	0	0	0	0 (0—2)	87	1214	27959358	27755154	30373154
65	Annual pSIA	0	0	0	0 (0—2)	93	1310	29595282	29435584	32053584
70	Annual pSIA	0	0	0	0 (0—2)	100	1406	31239059	31116013	33734013
75	Annual pSIA	0	0	0	0 (0—2)	107	1502	32919489	32796443	35414443
80	Annual pSIA	0	0	0	0 (0—2)	114	1598	34544941	34476873	34542323
85	Annual pSIA	0	0	0	0 (0—1)	121	1694	36207044	36157302	36157302
90	Annual pSIA	0	0	0	0 (0—1)	128	1790	37858676	37837732	37837732
95	Annual pSIA	0	0	0	0 (0—1)	135	1886	39520779	39518161	39518161
100	Annual pSIA	0	0	0	0 (0—0)	142	1983	41198591	41198591	41198591
25	Biennial pSIA	5520	5351	5689	6 (0—10)	37	77800	28308100	23428148	33900148
30	Biennial pSIA	2718	2577	2859	6 (0—10)	44	38663	30355049	22490577	35580577
35	Biennial pSIA	866	797	935	5 (0—9)	50	12822	30613905	16317007	34643007
40	Biennial pSIA	154	137	171	4 (0—8)	56	2936	29262690	17997436	33705436
45	Biennial pSIA	16	15	18	3 (0—7)	62	1093	26707196	19677866	32767866
50	Biennial pSIA	3	2	3	1 (0—5)	67	981	24900449	21358295	31830295
55	Biennial pSIA	1	1	1	1 (0—4)	73	1035	24489097	23038725	30892725
60	Biennial pSIA	0	0	0	0 (0—4)	79	1116	25446958	24719154	29955154
65	Biennial pSIA	0	0	0	0 (0—2)	86	1203	26818464	26399584	29017584
70	Biennial pSIA	0	0	0	0 (0—2)	92	1290	28305161	28080013	30698013
75	Biennial pSIA	0	0	0	0 (0—2)	98	1379	29927995	29760443	32378443
80	Biennial pSIA	0	0	0	0 (0—2)	105	1468	31556065	31440873	34058873
85	Biennial pSIA	0	0	0	0 (0—2)	111	1557	33191988	33121302	35739302
90	Biennial pSIA	0	0	0	0 (0—1)	118	1645	34835766	34801732	34801732
95	Biennial pSIA	0	0	0	0 (0—1)	124	1735	36495251	36482161	36482161
100	Biennial pSIA	0	0	0	0 (0—0)	130	1824	38162591	38162591	38162591
25	Baseline	22158	22071	22246	4 (2—9)	31	310649	20023450	16256148	29346148
30	Baseline	19021	18938	19105	4 (3—10)	37	266811	21510147	17936577	28474027
35	Baseline	15753	15664	15842	4 (3—8)	42	221134	23381691	19617007	30089007
40	Baseline	12296	12182	12409	5 (0—9)	48	172812	25499326	21297436	31769436
45	Baseline	7990	7859	8120	5 (0—9)	54	112616	28753174	25595866	33449866
50	Baseline	3524	3399	3649	6 (0—10)	60	50181	32067235	27276295	37748295
55	Baseline	598	546	650	5 (0—8)	66	9290	32310383	18484725	36810725
60	Baseline	30	26	34	3 (0—7)	70	1399	28568934	20165154	35873154
65	Baseline	2	2	2	1 (0—5)	74	1073	24979330	21845584	29699584
70	Baseline	0	0	0	0 (0—3)	80	1119	24431841	23526013	28762013
75	Baseline	0	0	0	0 (0—3)	85	1193	25612233	25206443	27824443
80	Baseline	0	0	0	0 (0—2)	91	1270	27104167	26886873	29504873
85	Baseline	0	0	0	0 (0—2)	96	1349	28685112	28567302	31185302
90	Baseline	0	0	0	0 (0—1)	102	1428	30302710	30247732	30247732
95	Baseline	0	0	0	0 (0—2)	108	1507	31964813	31928161	31928161
100	Baseline	0	0	0	0 (0—1)	113	1586	33611209	33608591	33608591

Appendix Table 7. Combined health system and GPEI perspective: table of cases, VAPP, DALYS and costs across all strategies. Uncertainty in cases and associated costs is presented as 95% credible intervals (CI). Here, the mean values are obtained from taking the mean across all model simulations, not just amongst the simulations with an outbreak (as was done in table 2 in the main text).

RI (%)	Strategy	Mean cases	Cases lwr 95% CI	Cases upr 95% CI	Mean outbreaks (range)	Mean VAPP	Mean DALYS	Mean total costs ($)	Total costs ($) lwr 95% CI	Total costs ($) upr 95% CI
25	Annual pSIA	156	129	183	4 (0—8)	40	2742	33239028	23947537	40236483
30	Annual pSIA	20	16	24	2 (0—6)	46	930	33288629	27218467	40387381
35	Annual pSIA	3	3	4	1 (0—5)	53	784	33539389	30489397	40966777
40	Annual pSIA	1	1	1	1 (0—3)	59	843	35355485	33760326	41617075
45	Annual pSIA	0	0	0	0 (0—3)	66	931	37830128	37031257	42269292
50	Annual pSIA	0	0	0	0 (0—3)	73	1024	40862666	40302187	45539473
55	Annual pSIA	0	0	0	0 (0—2)	80	1118	43863829	43573117	46192137
60	Annual pSIA	0	0	0	0 (0—2)	87	1214	47048326	46844047	49462985
65	Annual pSIA	0	0	0	0 (0—2)	93	1310	50274730	50114978	52733854
70	Annual pSIA	0	0	0	0 (0—2)	100	1406	53508993	53385908	56004730
75	Annual pSIA	0	0	0	0 (0—2)	107	1502	56779923	56656838	59275664
80	Annual pSIA	0	0	0	0 (0—2)	114	1598	59995859	59927768	59993922
85	Annual pSIA	0	0	0	0 (0—1)	121	1694	63248457	63198699	63198701
90	Annual pSIA	0	0	0	0 (0—1)	128	1790	66490579	66469629	66469630
95	Annual pSIA	0	0	0	0 (0—1)	135	1886	69743179	69740559	69740560
100	Annual pSIA	0	0	0	0 (0—0)	142	1983	73011519	73011519	73011519
25	Biennial pSIA	5520	5351	5689	6 (0—10)	37	77800	40126535	34251252	45144180
30	Biennial pSIA	2718	2577	2859	6 (0—10)	44	38663	41802331	32529975	46294381
35	Biennial pSIA	866	797	935	5 (0—9)	50	12822	42354854	27450074	47107075
40	Biennial pSIA	154	137	171	4 (0—8)	56	2936	42095010	30720649	47450549
45	Biennial pSIA	16	15	18	3 (0—7)	62	1093	41033036	33991225	47139598
50	Biennial pSIA	3	2	3	1 (0—5)	67	981	40806378	37261800	47739817
55	Biennial pSIA	1	1	1	1 (0—4)	73	1035	41983451	40532376	48388857
60	Biennial pSIA	0	0	0	0 (0—4)	79	1116	44531058	43802952	49040867
65	Biennial pSIA	0	0	0	0 (0—2)	86	1203	47492573	47073528	49692577
70	Biennial pSIA	0	0	0	0 (0—2)	92	1290	50569337	50344104	52963070
75	Biennial pSIA	0	0	0	0 (0—2)	98	1379	53782294	53614680	56233601
80	Biennial pSIA	0	0	0	0 (0—2)	105	1468	57000487	56885257	59504114
85	Biennial pSIA	0	0	0	0 (0—2)	111	1557	60226543	60155833	62774635
90	Biennial pSIA	0	0	0	0 (0—1)	118	1645	63460454	63426409	63426410
95	Biennial pSIA	0	0	0	0 (0—1)	124	1735	66710080	66696985	66696986
100	Biennial pSIA	0	0	0	0 (0—0)	130	1824	69967582	69967582	69967582
25	Baseline	22158	22071	22246	4 (2—9)	31	310649	43484360	38992552	52597540
30	Baseline	19021	18938	19105	4 (3—10)	37	266811	44364837	40580950	51953897
35	Baseline	15753	15664	15842	4 (3—8)	42	221134	45538197	42218881	52444894
40	Baseline	12296	12182	12409	5 (0—9)	48	172812	46825449	44354110	51747400
45	Baseline	7990	7859	8120	5 (0—9)	54	112616	48655160	46132766	53020230
50	Baseline	3524	3399	3649	6 (0—10)	60	50181	50433183	45595353	54122545
55	Baseline	598	546	650	5 (0—8)	66	9290	50217470	35970918	55186699
60	Baseline	30	26	34	3 (0—7)	70	1399	47667172	39241001	54975934
65	Baseline	2	2	2	1 (0—5)	74	1073	45646932	42511085	50379689
70	Baseline	0	0	0	0 (0—3)	80	1119	46687426	45781168	51019444
75	Baseline	0	0	0	0 (0—3)	85	1193	49457212	49051251	51670341
80	Baseline	0	0	0	0 (0—2)	91	1270	52538712	52321335	54940346
85	Baseline	0	0	0	0 (0—2)	96	1349	55709272	55591418	58210352
90	Baseline	0	0	0	0 (0—1)	102	1428	58916499	58861502	58861502
95	Baseline	0	0	0	0 (0—2)	108	1507	62168248	62131585	62131585
100	Baseline	0	0	0	0 (0—1)	113	1586	65404287	65401669	65401669

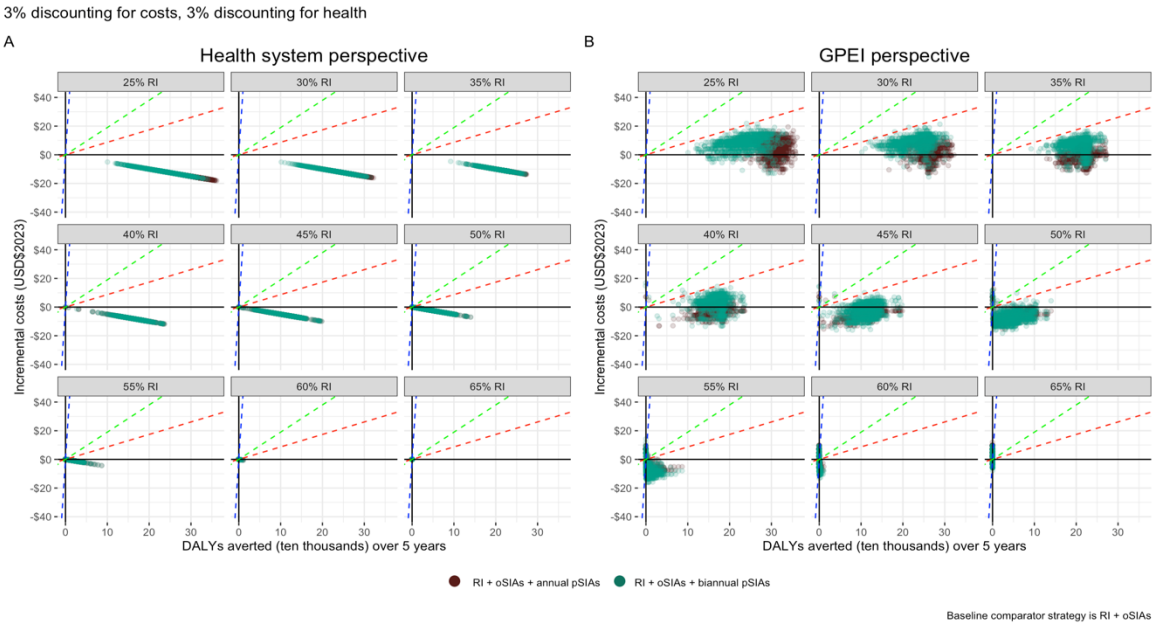
Incremental costs per outbreak averted

Incremental costs per outbreak averted capture the global perspective of polio eradication as a single outbreak under any vaccination strategy has implications for global polio eradication. It is important to note that the figure below does not suggest that the baseline strategy is better performing at low RI coverage levels. Instead, negative (or no) outbreaks averted by both pSIA strategies at low levels of RI coverage correspond to two phenomena: (i) the baseline strategy has larger explosive outbreaks when RI coverage is low, so the susceptible population is depleted quicker, whilst the pSIA strategies have much smaller, albeit more frequent, outbreaks when RI coverage is low.



Appendix Figure 5. Incremental costs per outbreak averted. Incremental costs and outbreak averted under the annual pSIA (RI+oSIAs+annual pSIAs) and biennial pSIA (RI+oSIAs+Biennial pSIAs) strategies in comparison to the baseline strategy (RI+oSIAs) assuming a 3% discount rate for costs and 0% discount rate for health. The points correspond to 10,000 model simulations. Here, it is assumed that the cost per child in an oSIA is two times the cost per child in a pSIA. An outbreak is defined as at least one case of paralytic polio. It is important to note that this figure does not suggest that the RI+oSIAs strategy is better performing at low RI coverage levels. Instead, negative (or no) outbreaks averted by both pSIA strategies at low levels of RI coverage correspond to two phenomena: (i) the RI+oSIA strategy has larger explosive outbreaks when RI coverage is low, so the susceptible population is depleted quicker, whilst the pSIA strategies have much smaller, albeit more frequent, outbreaks when RI coverage is low.

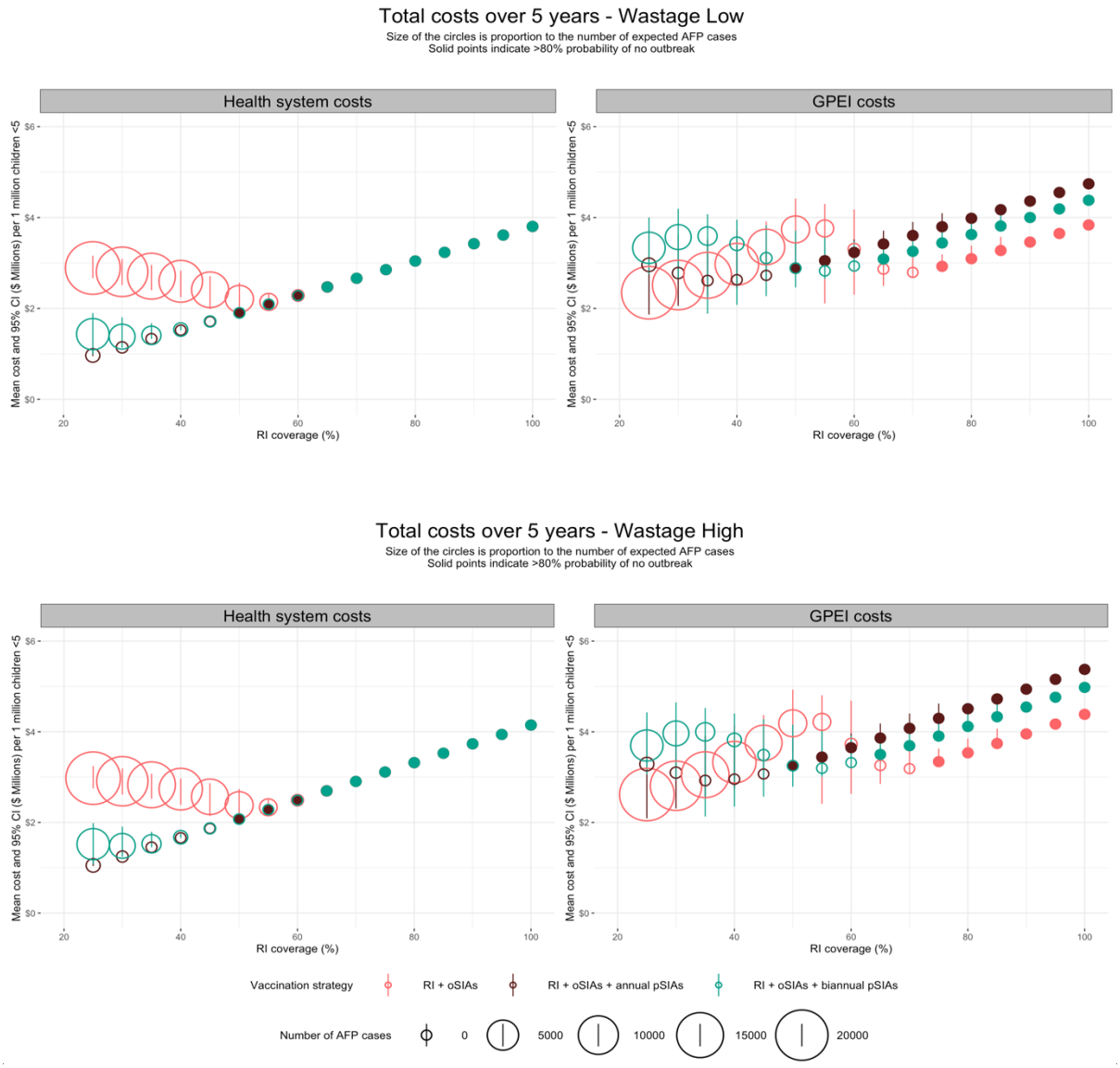
Sensitivity analysis—discounting for health



Appendix Figure 6. Incremental costs per DALY averted under the annual pSIA and biennial pSIA strategies in comparison to the baseline strategy assuming a 3% discount rate for costs and 3% discount rate for health. Incremental costs are split between health system/non-GPEI perspective and GPEI perspective and the plots are facetted by RI coverage level. Each individual model simulation is represented as a single dot. The dashed lines represent three cost-effectiveness thresholds (representing the lowest (red=Democratic Republic of the Congo), median (green=Benin) and highest (blue=South Africa) country thresholds) among low, lower middle and upper middle-income sub-Saharan African countries.

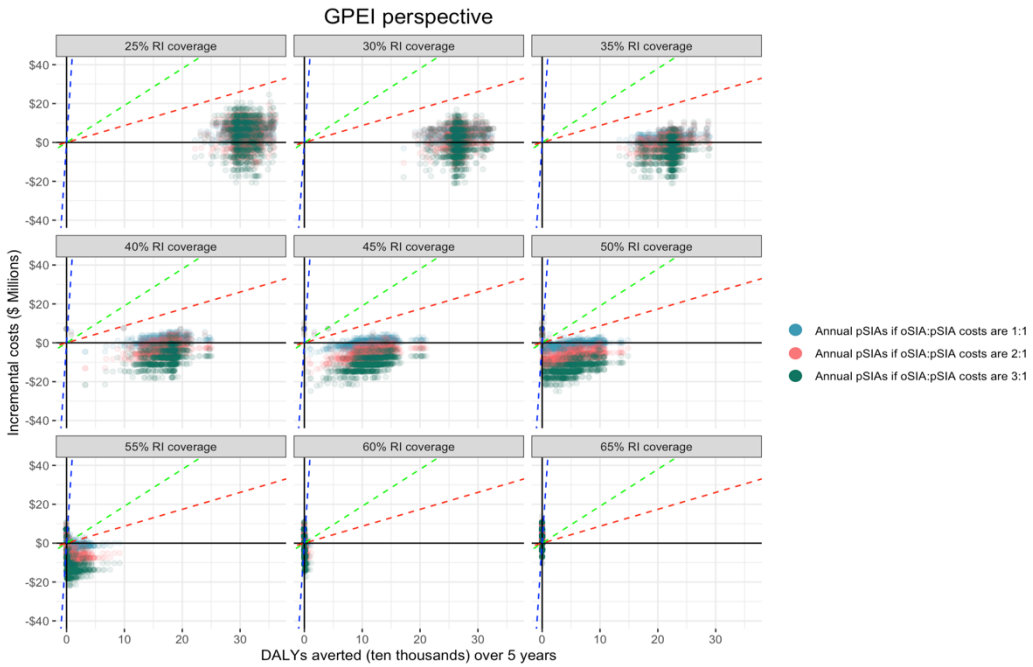
Sensitivity analysis – different assumptions about vaccine wastage

GPEI estimates OPV wastage ranges from 5-15% in SIAs and wastage is lower in SIAs than in RI [13]. Estimates of IPV wastage vary between 5-20% in the literature [14] and country-specific analyses from Nigeria and The Gambia suggest IPV wastage can even be higher in practice, exceeding 20% for IPV wastage in some instances [19, 20]. Accordingly, the main analysis assumes an average of 10% wastage for OPV in SIAs, 13% for OPV in RI and 13% for IPV.



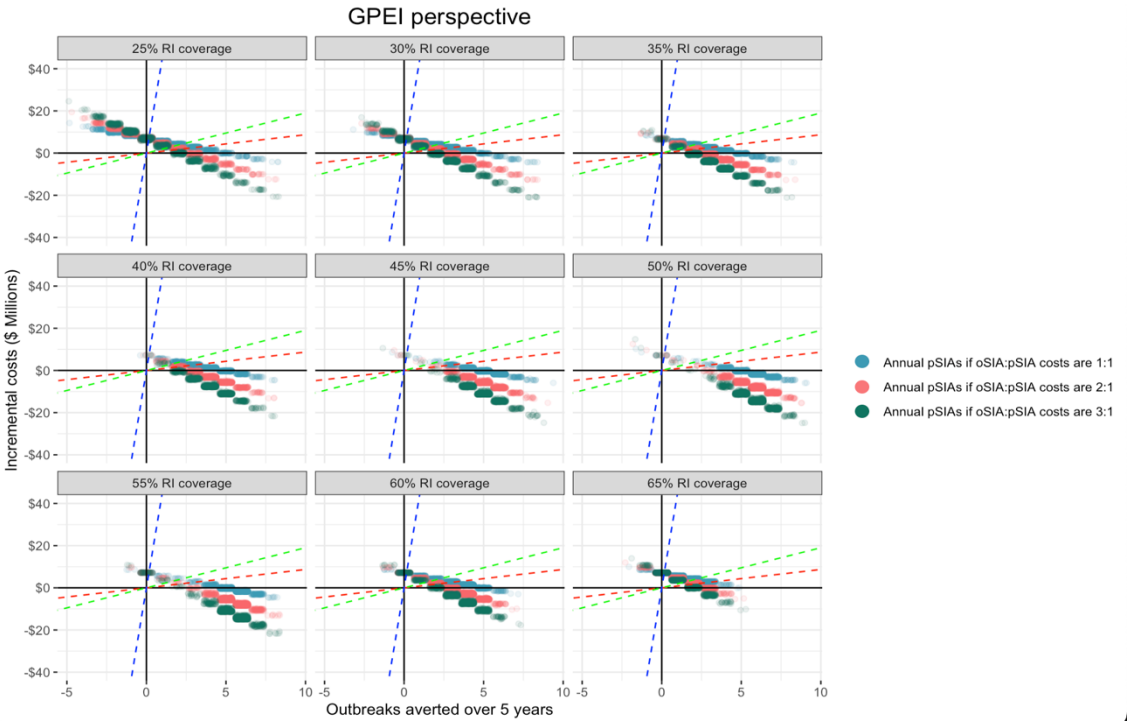
Appendix Figure 7. Total costs over five years under different wastage assumptions. The top plots represent conservative estimates of wastage using the lowest limit of the range of published wastage rates for both OPV and IPV vaccination via RI and SIAs while the bottom plots use the highest limit of the range of published wastage rates.

Sensitivity analysis – different proportional costs between pSIAs and oSIAs



Appendix Figure 8. Sensitivity analysis exploring incremental costs per DALY averted under variable assumptions about oSIA costs. The different colours represent different proportional differences between annual pSIAs and oSIAs. For example, "Annual pSIAs if oSIA:pSIA costs are 3:1" presents the incremental costs and DALYs averted by annual pSIAs if oSIAs cost three times as much as pSIAs. Each individual model simulation is represented as a single dot. The dashed lines represent three cost-effectiveness thresholds (representing the lowest (red=Democratic Republic of the Congo), median (green=Benin) and highest (blue=South Africa) country thresholds) among low, lower middle and upper middle-income sub-Saharan African countries.

A sensitivity analysis explored incremental costs under variable assumptions about the proportional difference in costs between oSIAs and annual pSIAs. The main analysis assumed the cost per child for an oSIA was twice the cost per child for a pSIA, but available outbreak response cost data suggests a range across African countries. In the sensitivity analysis, two alternative cost assumptions were explored: (I) the cost per child in an oSIA equalled the cost per child in a pSIA (1:1) and (II) the cost per child of an oSIA was three times the cost per child in a pSIA (3:1). This sensitivity analysis answers the question, under what cost assumptions are annual pSIAs more cost-effective than oSIAs? Appendix Figure 8 shows the incremental costs per DALY averted across all oSIA assumptions and Appendix Figure 9 shows incremental costs per outbreak averted from the GPEI perspective as GPEI costs include SIA costs. When RI coverage exceeds the herd immunity threshold, the number of outbreaks, and consequently, the number of oSIAs required substantially decreases causing the GPEI incremental costs to be aligned across all oSIA cost assumptions.



Appendix Figure 9. Sensitivity analysis exploring incremental costs per outbreak averted under variable assumptions about oSIA costs. The different colours represent different proportional differences between pSIAs and oSIAs. For example, "Annual pSIAs if oSIA:pSIA costs are 3:1" presents the incremental costs and outbreaks averted by annual pSIAs if oSIAs cost three times as much as pSIAs. Each individual model simulation is represented as a single dot. The dashed lines represent three cost-effectiveness thresholds (representing the lowest (red=Democratic Republic of the Congo), median (green=Benin) and highest (blue=South Africa) country thresholds) among low, lower middle and upper middle-income sub-Saharan African countries.

Sensitivity analysis – different assumptions about proportion of children reached by SIAs

The true effectiveness of SIAs (defined as the product of coverage and vaccine efficacy) remains uncertain in practice; although vaccine efficacy is well described in clinical trials, it is known to vary by population, and the population coverage achieved is uncertain resulting in variable effectiveness. For example, mathematical modelling demonstrates a dramatic range of SIA effectiveness estimates in Tajikistan versus the Republic of Congo: in Tajikistan, SIA effectiveness in response to a localised outbreak was estimated to be 69% (95% CI 55-80%) while in the Republic of Congo, SIA effectiveness was estimated to be 0.4% (95% CI 0.0-14.0%) per SIA [21]. In this analysis we define the SIA target population as children missed by RI. As research suggests that SIA effectiveness is highly variable in different locations, this model assessed outcomes under the assumption that all pSIAs and oSIAs reach 25% of the population missed by RI and bOPV vaccine efficacy is 50%. In the sensitivity analysis below (Appendix Table 7), we explore the average number of expected AFP cases over five years and the probability of an outbreak if SIAs reached 50% of the target population, or 50% of children under five years of age who were missed by RI.

Appendix Table 8. Expected average number of AFP cases and expected probability of an outbreak if each SIA were expected to reach 50% of the target population instead of the 25% assumption in the main analysis. Assumptions about vaccine efficacy are the same across all models. Expected AFP cases were calculated by taking the average number of AFP cases across all stochastic model simulations that had ***at least one AFP case.***

RI coverage	SIA strategy	If SIAs vaccinate 25% of the target population		If SIAs vaccinate 50% of the target population	
		Average number of expected AFP cases over 5 years	Expected probability of an outbreak	Average number of expected AFP cases over 5 years	Expected probability of an outbreak
25%	RI + oSIA + annual pSIA	176	88%	1	16%
35%	RI + oSIA + annual pSIA	5	65%	1	9%
50%	RI + oSIA + annual pSIA	1	20%	1	6%
75%	RI + oSIA + annual pSIA	1	4%	1	2%
25%	RI + oSIA + biennial pSIA	5,564	99%	15	83%
35%	RI + oSIA + biennial pSIA	894	97%	3	56%
50%	RI + oSIA + biennial pSIA	4	67%	1	17%
75%	RI + oSIA + biennial pSIA	1	6%	1	6%
25%	RI + oSIA	22,158	100%	18,093	100%
35%	RI + oSIA	15,753	100%	9,851	100%
50%	RI + oSIA	3,549	99%	602	99%
75%	RI + oSIA	1	14%	1	14%

Sensitivity analysis – different R_0 assumptions

As the true value of R_0 for polio is unknown and depends on geographical settings, sanitation and hygiene, and age. In the main analysis, we assume an R_0 of 3, which is in line with other research and the target population of children under five years of age living in an LMIC in Africa. However, in the sensitivity analysis below (Appendix Table 9) we explore the average number of expected AFP cases over five years and the probability of an outbreak if R_0 = 6. As shown the table, when RI coverage >50%, a higher R_0 only increases the probability of an outbreak slightly in the annual pSIA strategy but has a bigger effect on outbreak probability for the biennial pSIA and baseline strategies.

*Appendix Table 9. Expected number of AFP cases and expected probability of an outbreak under different R_0 assumptions. Expected AFP cases were calculated by taking the average number of AFP cases across all stochastic model simulations that had **at least one AFP case.***

RI coverage	SIA strategy	R_0 = 3		R_0 = 6	
		Average number of expected AFP cases over 5 years	Expected probability of an outbreak	Average number of expected AFP cases over 5 years	Expected probability of an outbreak
25%	RI + oSIA + annual pSIA	176	88%	16,379	100%
50%	RI + oSIA + annual pSIA	1	20%	3,837	100%
75%	RI + oSIA + annual pSIA	1	4%	1	19%
25%	RI + oSIA + biennial pSIA	5,564	99%	24,403	100%
50%	RI + oSIA + biennial pSIA	4	67%	9,542	100%
75%	RI + oSIA + biennial pSIA	1	6%	4	68%
25%	RI + oSIA	22,158	100%	37,069	100%
50%	RI + oSIA	3,549	99%	20,229	100%
75%	RI + oSIA	1	14%	2,046	99%

Sensitivity analysis – different importation rates

When RI coverage exceeds 50%, model assumptions for the importation rate of WPV infection have little effect on the expected number of AFP cases and expected probability of an outbreak across all vaccination strategies. This reiterates the importance of baseline RI coverage, which remains an important underlying factor that greatly influences the number of expected AFP cases and outbreak probability, more so than importation rate or assumptions around the proportion of children reached by SIAs.

Seasonality, with peaks in infection usually seen around late summer and autumn, has been observed for WPV in Northern Hemisphere endemic settings (Afghanistan and Pakistan), but remains a phenomenon not well explored for geographies in the Southern Hemisphere [22]. Furthermore, here outbreaks are dependent on WPV1 importations, which can occur at any time. To better understand if any trends in importations exist, better data on migration and travel patterns into African countries from endemic settings is needed.

Appendix Table 10. Expected number of AFP cases and expected probability of an outbreak if the rate of WPV importation is one importation of WPV infection every year and three importations every year, rates that are under and over the rate used in the main analysis (two importations per year). Expected AFP cases were calculated by taking the average number of AFP cases across all stochastic model simulations that had ***at least one AFP case.***

RI coverage	SIA strategy	1 importation every year		3 importations every year	
		Average number of expected AFP cases over 5 years	Expected probability of an outbreak	Average number of expected AFP cases over 5 years	Expected probability of an outbreak
25%	RI + oSIA + annual pSIA	42	71%	49	96%
50%	RI + oSIA + annual pSIA	1	11%	1	27%
75%	RI + oSIA + annual pSIA	1	2%	1	5%
25%	RI + oSIA + biennial pSIA	5,353	95%	5,363	100%
50%	RI + oSIA + biennial pSIA	4	45%	5	78%
75%	RI + oSIA + biennial pSIA	1	3%	1	8%
25%	RI + oSIA	22,327	99%	22,236	100%
50%	RI + oSIA	3,430	91%	3,399	100%
75%	RI + oSIA	1	9%	1	20%

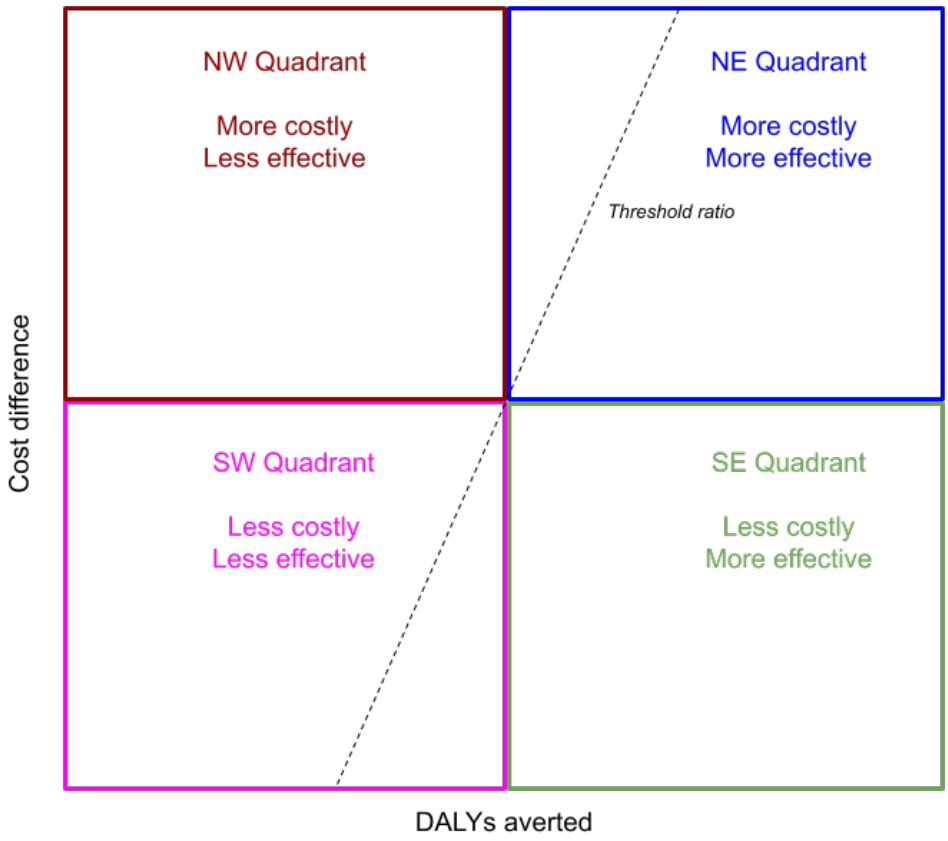
Section 5: Supporting information

Raw data used to inform proportional differences between pSIA and oSIA costs

*Appendix Table 11. Country level SIA data showing the differences in costs between oSIAs and pSIAs. The rightmost column shows the proportional difference between oSIAs and pSIAs for operational costs. *pSIA cost data was available pre COVID-19 pandemic and given in USD$2019, therefore, estimates have been calculated for USD$2023 assuming 2019$1 = 2023$1.18. oSIA cost data for bOPV has historically been less readily available. Therefore, to estimate the proportional differences between oSIAs and pSIAs, oSIA cost data from campaigns administering novel OPV2 (nOPV2) was used, and we assume that while the vaccine costs may differ, the oSIA operational costs are similar.*

Country	bOPV cost (USD$)	pSIA - cost per child $2019	pSIA - cost per child $2023*	oSIA (nOPV) - cost per child $2023	proportional difference - *operational only*
Benin	0.17	0.31	0.37	0.73	2.0
Burkina Faso	0.15	0.27	0.32	0.65	2.0
Cameroon	0.17	0.33	0.39	0.86	2.2
Central African Republic	0.17	1.09	1.29	2.79	2.2
Chad	0.16	0.45	0.53	0.42	0.8
Congo	0.16	0.44	0.52	2.29	4.4
Côte d'Ivoire	0.14	0.15	0.18	0.67	3.8
DR Congo	0.15	0.48	0.57	1.28	2.3
Eritrea	0.18	0.95	1.12	1.00	0.9
Ethiopia	0.17	0.89	1.05	0.56	0.5
Gabon	0.16	0.77	0.91	1.00	1.1
Gambia	0.18	0.60	0.71	0.78	1.1
Ghana	0.18	0.29	0.34	1.32	3.9
Guinea	0.19	0.26	0.31	1.23	4.0
Kenya	0.18	0.59	0.70	1.02	1.5
Liberia	0.20	0.83	0.98	1.58	1.6
Madagascar	0.17	0.37	0.44	0.53	1.2
Malawi	-	-	0.00	1.00	
Mali	0.17	0.24	0.28	0.52	1.8
Mauritania	0.12	0.81	0.96	1.00	1.0
Mozambique	-	-	0.00	0.80	
Niger	0.19	0.36	0.42	0.57	1.3
Nigeria	0.21	0.32	0.38	0.22	0.6
Senegal	0.18	0.29	0.34	0.47	1.4
Sierra Leone	0.16	0.46	0.54	0.92	1.7
South Sudan	0.17	0.78	0.92	1.17	1.3
Sudan	0.15	0.58	0.68	0.65	0.9
Tanzania	0.17	0.93	1.10	1.00	0.9
Togo	0.17	0.27	0.32	0.73	2.3
Uganda	0.18	0.48	0.57	1.00	1.8
Zambia	-	-		2.78	
Zimbabwe	-	-		1.76	
Average	**$0.17**	**$0.52**	**$0.61**	**$1.04**	**$1.7**

Cost-effectiveness plane



Appendix Figure 10. Quadrants comprising a cost-effectiveness plane for interpretation of incremental costs and DALYs averted under each vaccination strategy. This figure was adapted for this analysis from Briggs et al. 2006 [23]. If the ICER (cost differences / DALYS averted) for a particular vaccination strategy falls below the threshold ratio (dashed line – which represents the willingness-to-pay), then the strategy represents a cost-effective option.

Appendix Table 12. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) checklist. The checklist has been taken from Husereau et al. and adapted to this analysis [24].

Section/topic	Item No	Guidance for reporting	Reported in section
Title			
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	Heading
Abstract			
Abstract	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses	Heading
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Introduction
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available	Methods paragraphs 1 & 2
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Methods paragraph 2
Settings and location	6	Provide relevant contextual information that may influence findings	Methods paragraph 2
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Methods: "vaccination strategies"
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Methods: "Perspectives"
Time horizon	9	State the time horizon for the study and why appropriate.	Methods: "Time horizon and model assumptions"
Discount rate	10	Report the discount rate(s) and reason chosen.	Methods: "Health and economic outcomes"
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Methods: "Probability of an outbreak occurring" & "DALYS"
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Methods: "Health and economic outcomes" & "Adverse events"
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Methods: "Time horizon and model assumptions"
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Methods: "Vaccine costs" & Appendix section 2
Currency, price data and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Methods: "Vaccine costs"
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Methods: "Model structure" & Appendix sections 1 & 2
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Methods: "Time horizon and model assumptions" & Appendix sections 1 & 2

Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	We assume a homogenous population
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	We assume SIAs reach hard-to-reach children otherwise missed by RI
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Appendix section 4
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	GPEI stakeholders were involved in the analysis from project inception
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Results table 2
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Results paragraph 1
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Appendix section 4
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	This project has been presented at conferences and stakeholder meetings and was well received
Discussion			
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Discussion
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis.	Acknowledgements
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Declaration of Interests

7.2.1 References - Chapter 3 appendix

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7.3 Chapter 4 appendix

Table S1. Number of cases across modelled countries 2010-2019 and vaccination schedules

Country	Reported number of cases (WUENIC)	Estimated number of cases (IHME)	Nationally recommended age for MCV1	Nationally recommended age for MCV2	Year of MCV2 introduction
India	192566	112263832	9–12 months	16–24 months	2011
Nigeria	169394	15381229	9 months	15 months	2019
Indonesia	115974	15373892	9 months	18 months	2003
Ethiopia	59824	10108569	9 months	15 months	2019
China	213832	6171658	8 months	18 months	2005
Philippines	149325	6050672	9 months	12–15 months	2009
Uganda	20029	4555096	9 months	-	-
DRC	791259	3976920	9 months	-	-
Pakistan	74209	3271893	9 months	15 months	2009
Angola	30564	3246826	9 months	15 months	2015
Madagascar	234682	2966145	9 months	15–18 months	2020
Ukraine	129608	154625	12 months	6 years	2000
Malawi	118775	852873	9 months	15 months	2015
Somalia	80769	2440208	9 months	-	-

Table S1. For countries without available data on the recommended MCV2 schedules, we assumed the age at vaccination to be 15–18 months old. In China and Philippines, where multiple types of vaccines are in use, we adopted the vaccination schedules from the two doses of MMR (measles-mumps-rubella). Year of MCV2 introduction was assumed to be the first year a country has available coverage data in the WUENIC database.
(-) indicates a country has not yet introduced MCV2 and therefore, does not have a recommended age for MCV2 vaccination. In the model, MCV1 is assumed to deliver to unvaccinated infants at 9 months old in most countries, and MCV2 to previously vaccinated children at the recommended age of each country. IHME: Institute for Health Metrics and Evaluation. MCV1: the first routine dose of measles-containing vaccine. MCV2: the second routine dose of measles-containing vaccine. WUENIC: WHO and UNICEF Estimates of National Immunization Coverage.

Table S2. Supplementary immunisation activities in 14 countries, 2000-2020.

Year	Month	Target age group	Target population size	Reached doses	Coverage - target	Coverage - country-level
India						
2000	-	9-59m	974034	739417	75.9%	0.7%
2001	-	9-59m	1384891	962474	69.5%	0.9%
2010	Dec	9m-10y	10469901	9367822	89.5%	3.6%
2011	Apr	9m-10y	3375785	2709014	80.2%	1.0%
2011	Dec	9m-10y	30751228	27919442	90.8%	10.7%
2012	Mar	9m-9y	9416352	8215227	87.2%	3.5%
2012	Dec	9m-9y	40717834	36976587	90.8%	15.7%
2013	Jun	9m-9y	36012805	33639706	93.4%	14.4%
2017	Feb	9m-15y	16033000	15845000	98.8%	4.2%
2017	Feb	9m-15y	320000	312000	97.5%	0.1%
2017	Apr	9m-15y	16000	12000	75.0%	0.0%
2017	Apr	9m-15y	17605000	16953000	96.3%	4.5%
2017	Apr	9m-15y	304000	266000	87.5%	0.1%
2017	Aug	9m-15y	11854000	11458000	96.7%	3.0%
2017	Aug	9m-15y	114000	115000	100.9%	0.0%
2017	Aug	9m-15y	58000	62000	106.9%	0.0%
2017	Sep	9m-15y	9001000	9148000	101.6%	2.4%
2017	Sep	9m-15y	310000	301000	97.1%	0.1%
2017	Sep	9m-15y	1774000	1808000	101.9%	0.5%
2017	Dec	9m-15y	2836000	2876000	101.4%	0.8%
2017	Dec	9m-15y	7655000	6488000	84.8%	1.7%
2018	Feb	9m-15y	438000	443000	101.1%	0.1%
2018	Mar	9m-15y	11225000	11037000	98.3%	3.0%
2018	May	9m-15y	324000	324000	100.0%	0.1%
2018	May	9m-15y	818000	793000	96.9%	0.2%
2018	Jun	9m-15y	83000	78000	94.0%	0.0%
2018	Jul	9m-15y	6964000	6684000	96.0%	1.8%
2018	Jul	9m-15y	7438000	7364000	99.0%	2.0%
2018	Sep	9m-15y	15157000	14560000	96.1%	3.9%
2018	Oct	9m-15y	10602000	10257000	96.7%	2.7%
2018	Oct	9m-15y	1156000	1107000	95.8%	0.3%
2018	Oct	9m-15y	9209000	9028000	98.0%	2.4%
2018	Nov	9m-15y	7778000	7792000	100.2%	2.1%
2018	Nov	9m-15y	3762000	3757000	99.9%	1.0%
2018	Nov	9m-15y	449000	439000	97.8%	0.1%
2018	Nov	9m-15y	956000	897000	93.8%	0.2%
2018	Dec	9m-15y	76403000	75720000	99.1%	20.3%
2018	Dec	9m-15y	29052000	25866000	89.0%	6.9%
2019	Feb	9m-15y	37757000	38415000	101.7%	10.4%
2019	Feb	9m-15y	23245000	22822000	98.2%	6.1%
Nigeria						
2005	Dec	9m-15y	29500000	28538974	96.7%	47.8%
2006	Oct	9m-15y	31630011	26353793	83.3%	42.9%
2007	Jan	9-59m	2583480	2308527	89.4%	10.7%
2007	Mar	6y-17y	662164	517410	78.1%	1.2%
2008	Dec	9-59m	29828229	28848102	96.7%	130.4%
2011	Feb	9-59m	28272893	28435589	100.6%	119.3%
2013	Oct	9-59m	15957208	17004058	106.6%	68.0%
2013	Nov	9-59m	13344281	13575608	101.7%	54.3%
2015	Nov	6m-10y	23967617	24069024	100.4%	40.8%

2016	Jan	9-59m	14577013	19065787	130.8%	71.2%
2018	Feb	9-59m	37412277	40044875	107.0%	144.4%
2018	Mar	9-59m	15969475	16955354	106.2%	61.1%
2019	Nov	9-59m	20531083	21417932	104.3%	76.1%
Indonesia						
2000	-	6-12y	6665950	6341407	95.1%	20.8%
2000	-	6-59m	1142183	948012	83.0%	4.9%
2002	Sep	0-59m	166087	155101	93.4%	0.8%
2002	Nov	9-59m	2667343	2031029	76.1%	11.0%
2003	Oct	6-12y	1030445	980754	95.2%	3.1%
2004	-	6-12y	2180918	2062556	94.6%	6.5%
2005	Feb	6m-15y	4836094	4642650	96.0%	6.6%
2005	-	6m-15y	679230	615577	90.6%	0.9%
2006	Jan	6-12y	3161323	3049844	96.5%	9.6%
2006	May	6m-5y	234528	220777	94.1%	0.9%
2006	Aug	6m-5y	3743568	3440698	91.9%	13.9%
2007	Feb	6-59m	11237274	10099534	89.9%	49.7%
2007	Feb	6m-12y	2692912	2863068	106.3%	5.0%
2007	Aug	6y-12y	2569350	2609301	101.6%	8.2%
2007	Aug	6-59m	3679318	3499242	95.1%	17.2%
2008	Oct	1-3y	11203	8730	77.9%	0.1%
2009	Oct	9-59m	141685	126800	89.5%	0.6%
2009	Oct	9-59m	219765	126699	57.7%	0.6%
2009	Oct	9-59m	1763122	1700834	96.5%	8.7%
2010	Oct	9-59m	3619024	3294315	91.0%	16.7%
2011	Nov	9-59m	11989559	11365665	94.8%	57.8%
2016	Aug	9-59m	4222172	3638183	86.2%	17.3%
2017	Aug	9m-15y	34964384	35307148	101.0%	48.9%
2018	Oct	9m-15y	31963154	23453882	73.4%	32.5%
Ethiopia						
2000	Jul	9-59m	3800000	3610000	95.0%	35.0%
2001	Jan	9-59m	3026147	2346464	77.5%	21.9%
2001	Dec	9-59m	2166232	1646336	76.0%	15.4%
2002	Nov	9m-14y	2316214	2277988	98.3%	7.4%
2003	Aug	6m-14y	5605502	5101007	91.0%	15.8%
2004	Apr	6m-14y	8835802	7422074	84.0%	22.4%
2005	-	6m-14y	198456	136935	69.0%	0.4%
2005	Sep	9-59m	1073066	987221	92.0%	8.6%
2006	Apr	9-59m	11688720	10169187	87.0%	87.9%
2007	Nov	6-59m	1117345	1072701	96.0%	8.7%
2008	Nov	6-59m	11791819	10848474	92.0%	86.9%
2009	Jan	6-59m	773910	662168	85.6%	5.2%
2009	Jan	6-59m	279102	264134	94.6%	2.1%
2009	Jan	6-59m	62504	57762	92.4%	0.5%
2009	Jun	6-59m	285644	266621	93.3%	2.1%
2010	Mar	6-59m	1057327	961798	91.0%	7.5%
2010	Oct	9-47m	7656367	8171534	106.7%	88.1%
2011	Feb	9-47m	774658	757421	97.8%	8.1%
2011	Oct	6m-14y	7326463	7034264	96.0%	18.3%
2013	Jun	9-59m	11873928	11609484	97.8%	92.3%
2016	Apr	6m-<15y	25706550	24986589	97.2%	60.1%
2017	Mar	9m-14y	22035787	21225199	96.3%	51.3%
2017	Aug	6-179m	2579178	2524841	97.9%	6.0%
2020	Jul	9-59m	14135353	13970822	98.8%	98.5%

China						
2003	Nov	8m-12y	831600	819732	98.6%	0.4%
2004	Nov	8m-12y	10000000	7791796	77.9%	3.5%
2005	Mar	8m-14y	4222349	4032343	95.5%	1.5%
2005	May	8m-25y	2410000	2289500	95.0%	0.4%
2005	Jul	1-14y	5193749	4300424	82.8%	1.7%
2005	Sep	8m-14y	8000000	4800000	60.0%	1.8%
2006	Mar	8m-14y	6200000	5900000	95.2%	2.3%
2007	Sep	8m-14y	20400000	20100000	98.5%	8.1%
2008	Jul	8m-14y	35705379	34983574	98.0%	14.2%
2008	Nov	8m-6y	11842830	11570750	97.7%	11.0%
2009	Apr	8m-14y	5114101	5008565	97.9%	2.0%
2009	Jul	8m-14y	96487581	94167415	97.6%	38.4%
2010	Sep	8m-4y	106060935	102300000	96.5%	140.1%
Philippines						
2002	Jun	9-59m	507463	500897	98.7%	5.3%
2004	Mar	9m-7y	18394880	17291555	94.0%	108.0%
2007	Nov	9-48m	8648864	8201862	94.8%	85.7%
2009	Aug	15-23m	787693	459682	58.4%	7.8%
2010	Jul	9-59m	-	420129	-	4.5%
2011	May	9-95m	18651791	15649907	83.9%	98.8%
2013	Nov	6-59m	-	1937471	-	19.0%
2013	Dec	6-59m	-	108783	-	1.1%
2014	Jan	6-36m	2183971	1695930	77.7%	29.3%
2014	Sep	9-59m	11485540	10402489	90.6%	107.3%
2018	May	6-59m	4205517	2893466	68.8%	28.9%
2018	Oct	6-59m	6604059	2089432	31.6%	20.9%
2019	Apr	6-59m	3784099	3920103	103.6%	40.1%
2019	Jul	5-12y	8575452	2457514	28.7%	13.7%
2019	Jul	13y-100y	2179336	947677	43.5%	1.2%
Uganda						
2000	Mar	9-59m	1596240	1218737	76.4%	30.7%
2000	Nov	9-59m	1030490	957876	93.0%	24.2%
2001	Oct	9m-14y	503904	614156	121.9%	5.4%
2003	Oct	6m-14y	12861020	13457127	104.6%	108.8%
2005	Feb	9-23m	389696	557869	143.2%	41.5%
2006	Aug	6-59m	5263090	5239221	99.5%	103.9%
2009	Jun	9-47m	4699748	4893634	104.1%	122.7%
2012	May	6-59m	6314309	6283441	99.5%	107.0%
2015	Oct	6-59m	6658881	6349182	95.3%	101.0%
2019	Oct	9m-<15y	18200969	19432256	106.8%	100.2%
DRC						
2000	Oct	9-59m	1926879	1395451	72.4%	19.3%
2003	Jan	6m-15y	5774245	5554824	96.2%	23.5%
2003	Feb	6m-15y	100000	108000	108.0%	0.5%
2004	Oct	6m-15y	10055523	8604754	85.6%	35.3%
2005	Oct	6m-15y	7817076	6957653	89.0%	27.6%
2006	Aug	6-59m	2189069	2158329	98.6%	22.9%
2006	Nov	6m-15y	7164815	6966200	97.2%	26.7%
2007	Aug	6-59m	3736672	3768794	100.9%	38.5%
2008	Nov	6-59m	2852430	2811092	98.6%	27.8%
2009	Nov	6-59m	2593478	2412168	93.0%	23.1%
2010	Jan	6-59m	1226792	1259363	102.7%	11.7%
2011	Feb	6-59m	1673147	1701315	101.7%	15.2%

2011	Mar	6-59m	2672338	2649574	99.1%	23.7%
2011	Apr	6-59m	415909	430571	103.5%	3.8%
2011	May	6-59m	5227315	4864554	93.1%	43.4%
2011	Jun	6-59m	272392	266811	98.0%	2.4%
2012	Jan	6-59m	845002	948237	112.2%	8.2%
2012	Jan	6-59m	314283	303786	96.7%	2.6%
2012	Jan	6-59m	1253230	1239803	98.9%	10.7%
2012	Aug	6-59m	170530	175467	102.9%	1.5%
2013	Sep	6m-9y	6794574	6813783	100.3%	29.9%
2013	Dec	6m-9y	4087697	4213293	103.1%	18.5%
2014	Mar	6m-9y	5346158	5482612	102.6%	23.3%
2014	May	6m-9y	6137295	6211685	101.2%	26.4%
2014	Jun	6m-9y	2883624	2803550	97.2%	11.9%
2014	Jul	6m-9y	1196822	1163251	97.2%	4.9%
2014	Aug	6m-9y	2858403	2878785	100.7%	12.2%
2016	Aug	6-59m	7081288	7212977	101.9%	55.7%
2016	Oct	6-59m	3725998	3708843	99.5%	28.6%
2017	Feb	6-59m	5291916	5466923	103.3%	41.2%
Pakistan						
2005	Dec	12-59m	1600000	1232000	77.0%	6.8%
2007	Mar	9m-15y	2571536	2511837	97.7%	3.8%
2007	Jul	9m-13y	1219364	1282232	105.2%	2.2%
2007	Aug	9m-13y	6890603	6906376	100.2%	11.9%
2007	Nov	9m-13y	21262960	20566497	96.7%	35.5%
2008	Mar	9m-13y	34123305	35315375	103.5%	60.3%
2010	Feb	9m-<13y	15209539	13740906	90.3%	24.8%
2010	Sep	6-59m	7359790	6991065	95.0%	32.5%
2010	Oct	6-59m	988224	1007195	101.9%	4.7%
2011	Jan	9-59m	1401269	1299618	92.7%	6.3%
2011	Jan	9-59m	872287	784337	89.9%	3.8%
2011	Jan	9-59m	5143498	5098071	99.1%	24.8%
2011	Feb	9-59m	2028374	1744206	86.0%	8.5%
2011	Jul	9-59m	225947	205551	91.0%	1.0%
2011	Nov	9-59m	570538	547716	96.0%	2.7%
2012	Dec	9m-9y	1918267	1954175	101.9%	4.5%
2014	May	6m-9y	13418263	14026013	104.5%	30.4%
2014	May	6m-9y	9346563	9432492	100.9%	20.4%
2014	Dec	6m-9y	1438492	1439892	100.1%	3.1%
2015	Feb	6m-10y	29670753	30633406	103.2%	59.7%
2015	Feb	6m-10y	240921	227762	94.5%	0.4%
2015	Feb	6m-10y	165355	204308	123.6%	0.4%
2015	Apr	6m-10y	3474044	3512771	101.1%	6.8%
2015	May	6m-10y	414494	413695	99.8%	0.8%
2015	Aug	6m-10y	1607543	1519242	94.5%	3.0%
2017	Aug	9-59m	1355202	1279819	94.4%	5.7%
2018	Oct	9-59m	35199413	37131234	105.5%	161.4%
Angola						
2003	May	9m-14y	7642739	7226105	94.5%	90.8%
2006	Jul	9-59m	3218676	3210160	99.7%	100.2%
2009	Jun	9-59m	3430913	3469806	101.1%	96.3%
2011	Sep	9-59m	5472822	4635248	84.7%	119.1%
2014	Sep	6m-9y	7829940	9169335	117.1%	104.8%
2018	Apr	6m-14y	12858213	12001436	93.3%	86.7%
2019	May	6m-4y	108673	127740	117.5%	2.5%

2019	May	6m-4y	84101	110280	131.1%	2.2%
2019	Jun	6m-4y	141802	164410	115.9%	3.2%
Madagascar						
2004	Sep	9m-14y	7626090	7546229	99.0%	100.5%
2007	Oct	9-59m	3123163	3053702	97.8%	112.0%
2010	Oct	9-47m	2603510	2415792	92.8%	108.7%
2013	Oct	9-59m	3610265	3316542	91.9%	109.8%
2016	Oct	9-59m	3715133	3547466	95.5%	111.6%
Ukraine						
2008	May	15-29y	8000000	113000	1.4%	1.1%
2017	Oct	1-9y	287240	163782	57.0%	3.7%
2017	Oct	6-9y	231102	154430	66.8%	7.7%
2019	Apr	1-18y	506232	387731	76.6%	4.7%
2019	Apr	6-18y	618756	462407	74.7%	7.8%
Malawi						
2002	Aug	9-59m	1583664	1906985	120.4%	106.8%
2005	Sep	9-59m	1851176	2137152	115.4%	111.3%
2008	Oct	9-59m	2120557	2087375	98.4%	99.5%
2010	Aug	9m-15y	6370409	6785428	106.5%	101.9%
2013	Nov	6-59m	2297546	2405018	104.7%	97.5%
2015	May	9-59m	436257	453202	103.9%	19.2%
2017	Jun	9m-14y	7991666	8132788	101.8%	109.9%
Somalia						
2005	Nov	9m-15y	384725	319321	83.0%	6.5%
2006	May	9m-15y	2266917	2019717	89.1%	39.7%
2007	Jun	9m-15y	3191161	2774178	86.9%	52.9%
2008	Mar	9m-15y	150000	142654	95.1%	2.6%
2008	Dec	9m-15y	238355	138205	58.0%	2.6%
2009	Mar	9-59m	1483134	909687	61.3%	49.0%
2009	Apr	9-59m	1117384	835927	74.8%	45.0%
2009	Aug	9-59m	380911	276994	72.7%	14.9%
2010	Mar	9-59m	1562336	1335892	85.5%	70.4%
2011	Apr	9-59m	-	2924	-	0.1%
2011	Jul	6m-15y	90000	71653	79.6%	1.2%
2011	Jul	9-59m	169414	151279	89.3%	7.8%
2011	Jul	9-59m	380911	323986	85.1%	16.6%
2011	Aug	6m-15y	745234	656226	88.1%	10.9%
2011	Sep	6m-15y	86373	74300	86.0%	1.2%
2011	Oct	6m-14y	672054	626625	93.2%	11.0%
2012	Mar	6-59m	578457	509042	88.0%	24.0%
2012	Mar	6m-4y	1012879	886033	87.5%	41.8%
2012	Oct	9-59m	959424	872230	90.9%	43.8%
2013	Dec	6m-4y	1029870	923580	89.7%	43.0%
2014	Oct	9-59m	1483574	1306426	88.1%	63.6%
2015	Dec	9m-9y	3884554	3518358	90.6%	82.7%
2016	Aug	9-59m	676557	602136	89.0%	28.2%
2017	Feb	6-59m	4700000	4400000	93.6%	189.4%
2017	May	6m-5y	503812	472033	93.7%	16.9%
2018	Jan	6m-10y	4745484	4424261	93.2%	86.5%
2019	Nov	6-59m	1149117	1061064	92.3%	43.3%

Table S2. WHO records for measles SIAs with a confirmed status of implementation between 2000–2020 in the 14 countries were extracted. We excluded SIAs for the purpose of outbreak response, since they were usually driven by emergency events and restricted in a local area. (-) indicates missing information in the records. Year and month denote the mid-point of each campaign and July 1st is assigned for SIAs with missing dates. Two

coverage estimates are presented: one is calculated from the number of target population reported in each SIA (sub-national), and the other is based on the country-level population from the World Population Prospects 2019 at the target age group (national). When there is no information on target population in the WHO records, the sub-national coverage estimates are assumed to be the same as national ones in the analysis. DRC: Democratic Republic of the Congo. SIA: supplementary immunisation activity.

Table S3. Percentage of years over 2000–2020 showing a smaller number of susceptible children than the birth cohort size

Country	No vaccination	MCV1	MCV1+ MCV2	MCV1+SIAs	MCV1+MCV2+SIAs
India	0%	0%	9.5%	0%	14%
Nigeria	0%	0%	0%	24%	24%
Indonesia	0%	0%	0%	9.5%	24%
Ethiopia	0%	0%	0%	14%	14%
China	0%	0%	67%	19%	67%
Philippines	0%	0%	0%	24%	38%
Uganda	0%	0%	0%	38%	38%
DRC	0%	0%	0%	14%	14%
Pakistan	0%	0%	0%	19%	33%
Angola	0%	0%	0%	24%	24%
Madagascar	0%	0%	0%	29%	29%
Ukraine	0%	0%	0%	0%	0%
Malawi	0%	0%	4.8%	48%	57%
Somalia	0%	0%	0%	4.8%	4.8%
Median (25^{th}—75^{th} percentiles)	0% (0%—0%)	0% (0%—0%)	0% (0%—0%)	19% (11%—24%)	24% (14%—37%)

Table S3. This table presents the percentage of years over the analysis period that had an outbreak potential among different vaccination strategies. The outbreak potential in a year is indicated by a larger size of susceptible population under 5 years old compared to the size of birth cohort in each country. The median and 25^{th} and 75^{th} percentiles of percentage among 14 countries are shown in the bottom row. DRC: Democratic Republic of the Congo. MCV1: the first routine dose of measles-containing vaccine. MCV2: the second routine dose of measles-containing vaccine. SIA: supplementary immunisation activity.

Table S4. Averted deaths (thousands) across different vaccination strategies from 2000–2020

Country by MCV2 introduction year	Comparator: no vaccination		Comparator: MCV1 alone		
	MCV1 + MCV2 + SIAs	MCV1 alone	MCV1 + SIAs	MCV1 + MCV2	MCV1 + MCV2 + SIAs
MCV2 < 2017					
India	2392	2223	125	84	169
Indonesia	373	308	48	30	65
China	1544	1377	91	149	168
Philippines	199	160	35	9.82	38
Pakistan	1368	989	365	94	379
Angola	531	262	266	9.93	269
Ukraine	56	50	0.18	5.84	6.01
Malawi	337	264	72	5.69	73
MCV2 > 2017					
Nigeria	2918	1475	1443	5.19	1443
Ethiopia	1712	858	852	9.45	854
Madagascar	192	135	57	0.21	57
No MCV2					
Uganda	798	546	252	0	252
DRC	1352	841	511	0	511
Somalia	229	110	119	0	119
Total	14002	9598	4237	404	4403

Table S4. This table presents the total deaths averted in the 5 pairs of vaccination delivery strategies for comparison. Sums of the averted deaths in the 14 countries are shown in the last row of the table. DRC: Democratic Republic of the Congo. MCV1: the first routine dose of measles-containing vaccine. MCV2: the second routine dose of measles-containing vaccine. SIA: supplementary immunisation activity

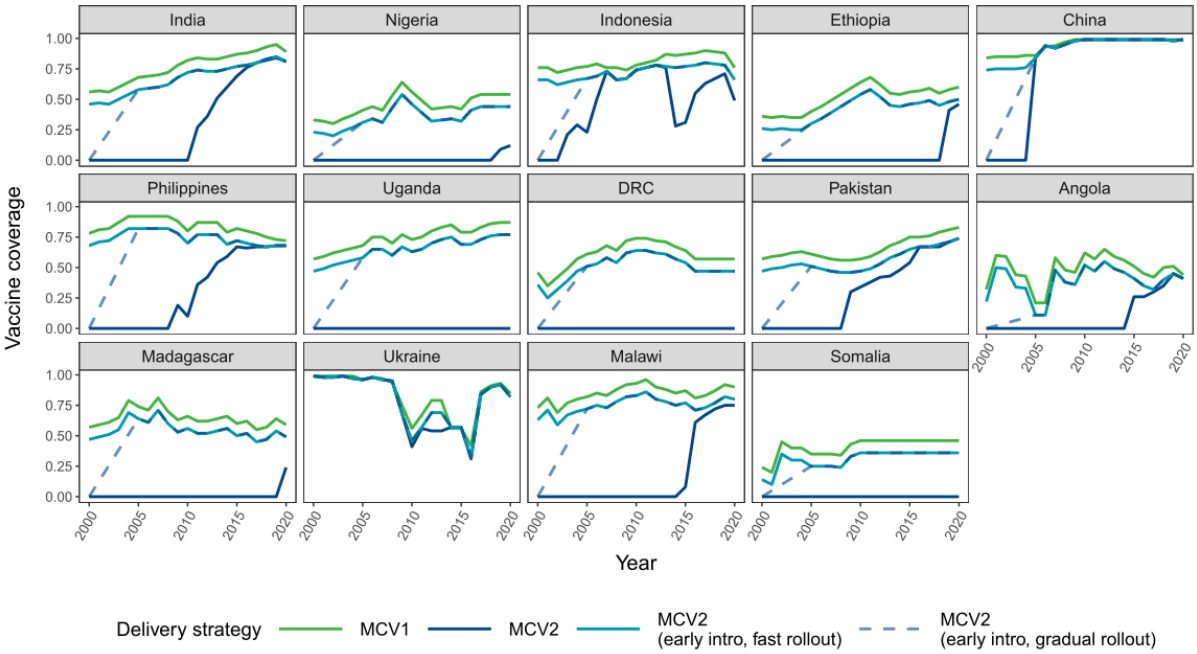

Figure S1. Immunisation coverage for early introduction of MCV2 over 2000–2020.
In the sensitivity analysis, all countries were assumed to introduce MCV2 early in 2000, with each year's coverage 10% lower than MCV1 coverage, or the same as the country's actual MCV2 coverage in that year, whichever was larger. Under fast rollout, MCV2 coverage would reach the assumed level in 2000, whereas MCV2 coverage would increase linearly over 2000–2005. DRC: Democratic Republic of the Congo. MCV1: the first routine dose of measles-containing vaccine. MCV2: the second routine dose of measles-containing vaccine.

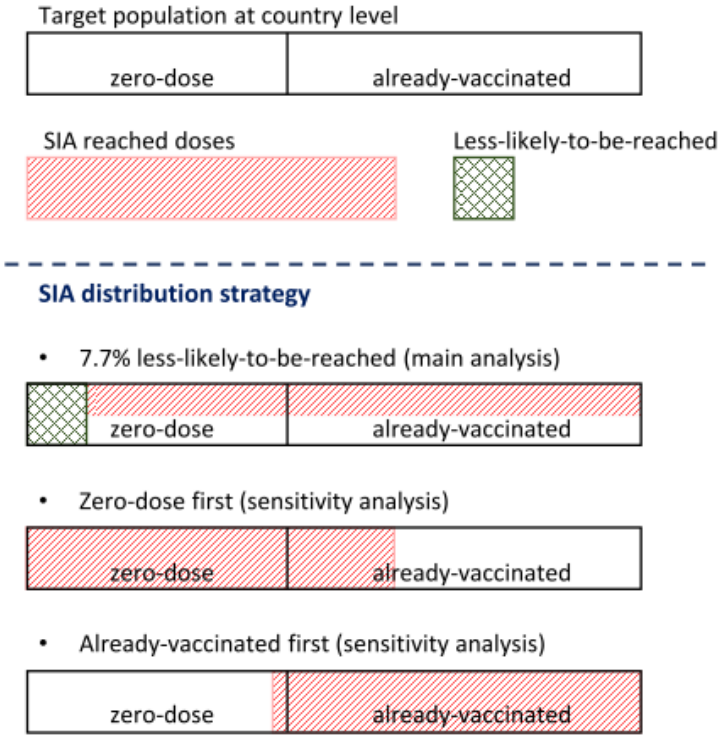

Figure S2. Distribution strategies of SIAs included in the analysis.
In the main analysis, 7.7% of target population are assumed less likely to receive MCV doses through current immunisation programmes and SIAs doses are given randomly to the rest of population. In addition, the distribution strategies to direct SIA doses first to MCV zero-dose and already-vaccinated children are assessed respectively in the sensitivity analysis. MCV: measles-containing vaccine. SIA: supplementary immunisation activity.

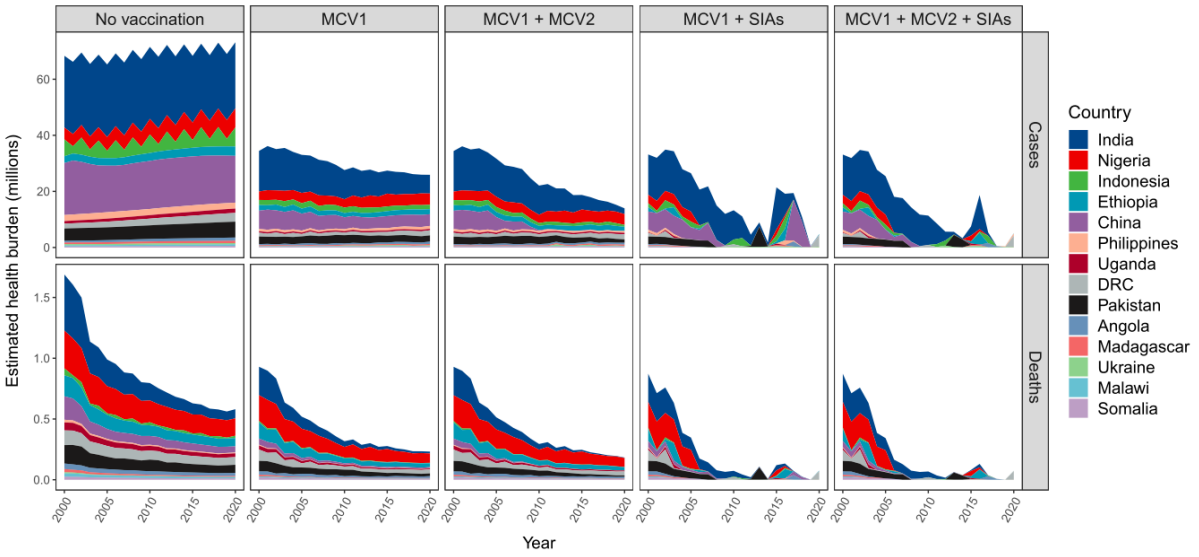

Figure S3. Annual number of measles cases (top row) and deaths (bottom row) across different vaccination delivery strategies over 2000–2020.

Country measles burden is present in different colours and stacked over time. The measles burden decreases with adding vaccination delivery strategies. DRC: Democratic Republic of the Congo. MCV1: the first routine dose of measles-containing vaccine. MCV2: the second routine dose of measles-containing vaccine. SIA: supplementary immunisation activity.

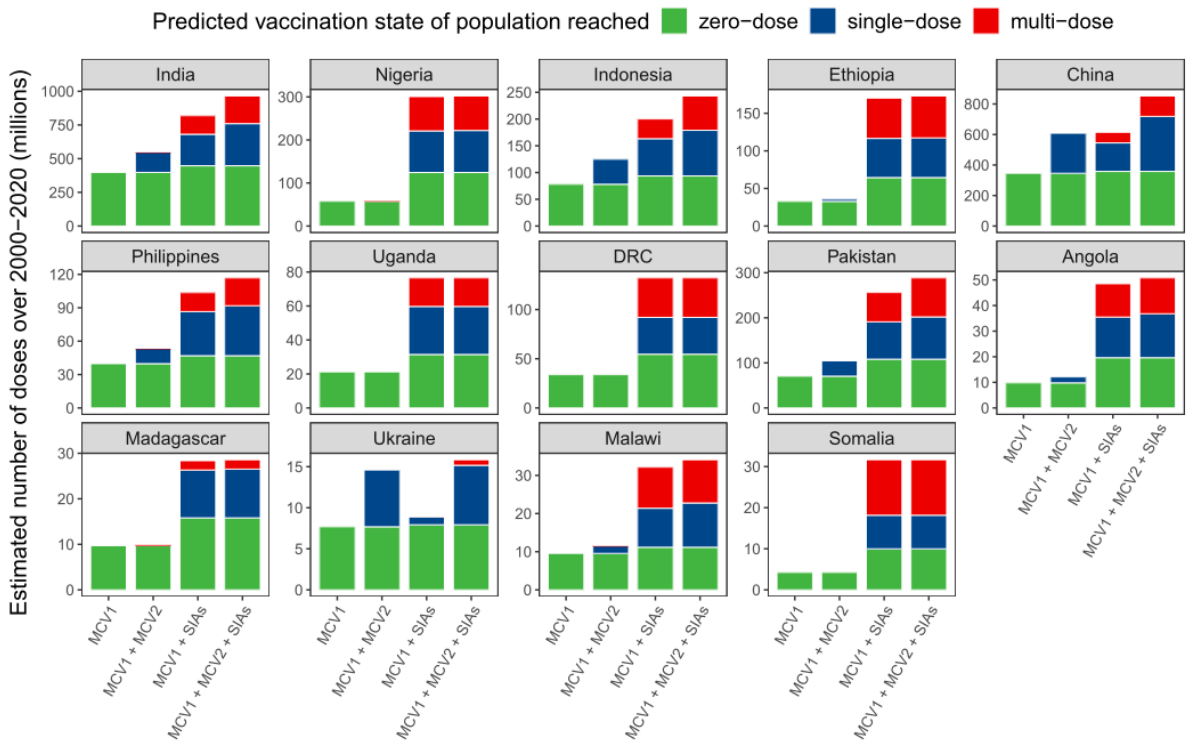

Figure S4. Doses reaching zero-dose, single-dose, and multiple-dose children across different vaccination delivery strategies

Total vaccine doses administrated over 2000–2020 are aggregated by estimated vaccination state of the target children reached. DRC: Democratic Republic of the Congo. MCV1: the first routine dose of measles-containing vaccine. MCV2: the second routine dose of measles-containing vaccine. SIA: supplementary immunisation activity.

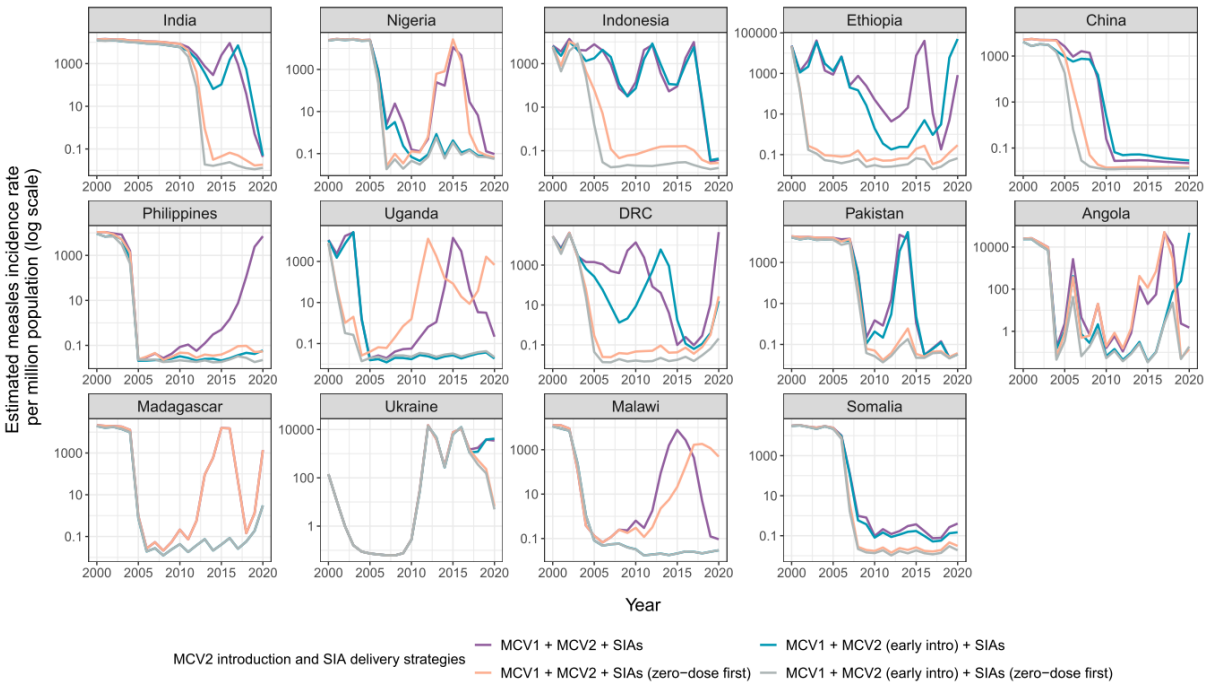

Figure S5. Estimated measles incidence rate (per million) under alternative assumptions of delivering MCV2 and SIAs over 2000–2020.

To estimate the impact of "optimal" vaccination impact (though not changing assumed MCV1 coverage or overall SIA coverage), we combined the alternative assumptions of early MCV2 introduction and SIA dose allocation prioritised for zero-dose populations. Incidence rates for different strategies are in different colours. Note that the y-axis is on the log scale. DRC: Democratic Republic of the Congo. MCV1: the first routine dose of measles-containing vaccine. MCV2: the second routine dose of measles-containing vaccine. SIA: supplementary immunisation activity.

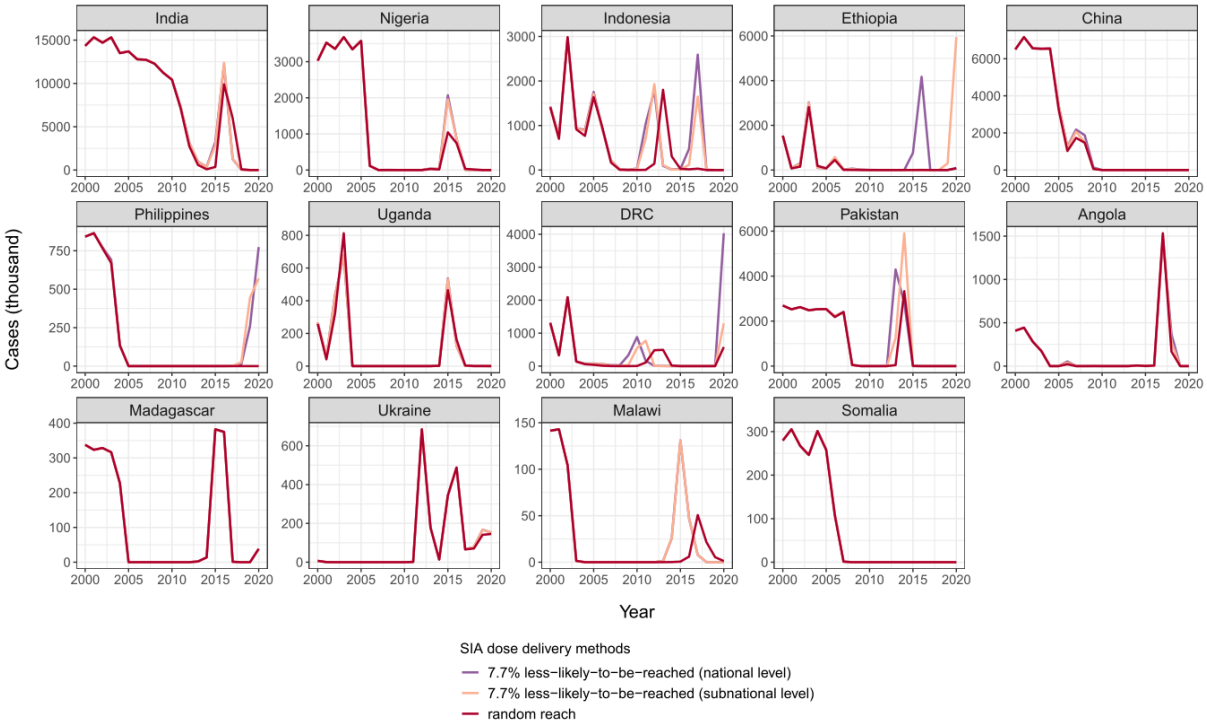

Figure S6. Estimated measles cases (thousands) under different assumptions of SIA dose distribution over 2000–2020.

This figure shows estimated measles cases using three SIA dose delivery methods based on historical coverage of MCV1, MCV2, and SIAs over 2000–2020. In the main analysis, we used the national SIA coverage and assumed SIA doses to be distributed equally to the zero-dose and already-vaccinated populations except for 7.7% of children who are considered less likely to be reached under current immunisation programmes. Alternatively, distributing SIA doses at the subnational level while holding the 7.7%-less-likely-to-be-reach assumption would result in fewer estimated measles cases. Random distribution of SIA doses leads to the lowest burden among the three delivery methods due to better targeting the zero-dose population. DRC: Democratic Republic of the Congo. MCV1: the first routine dose of measles-containing vaccine. MCV2: the second routine dose of measles-containing vaccine. SIA: supplementary immunisation activity.

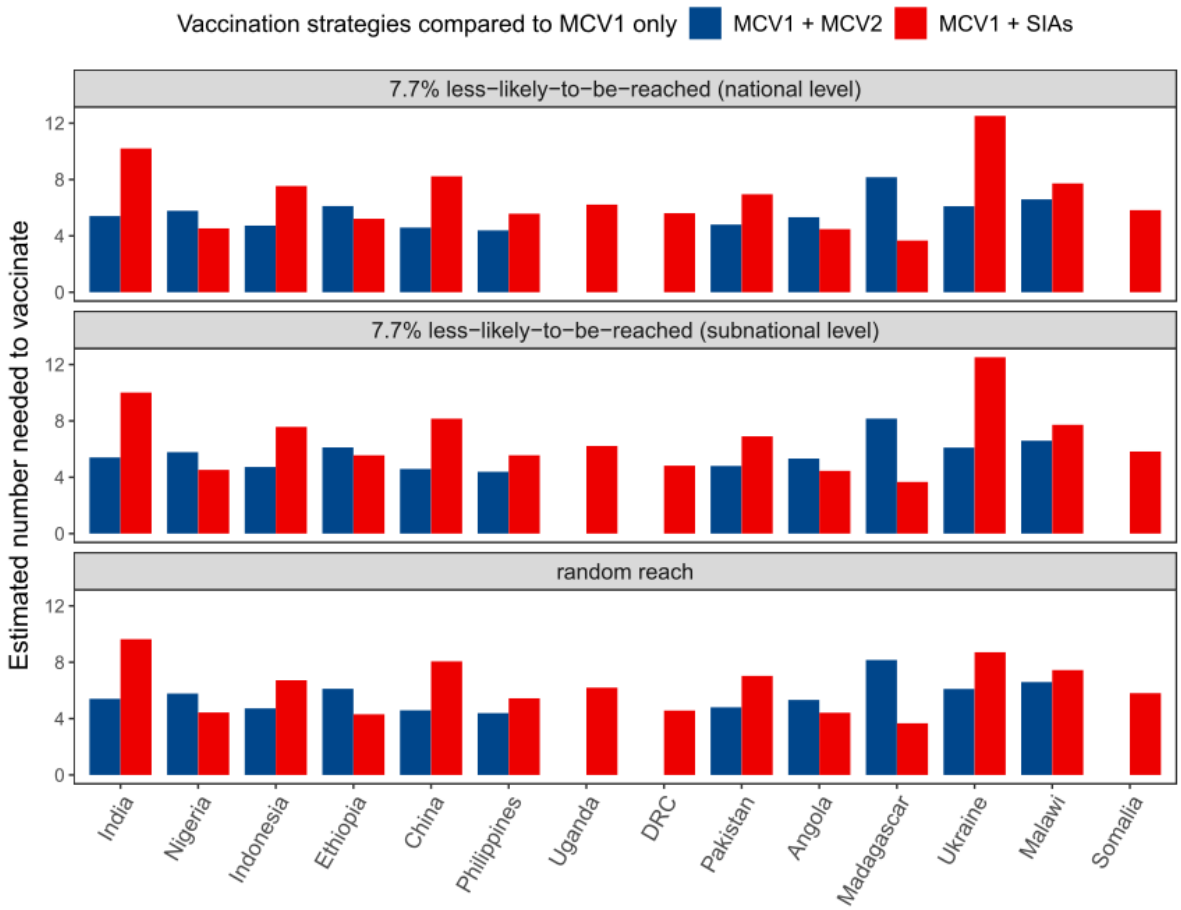

Figure S7. Estimated number needed to vaccinate to avert a measles case under different assumptions of SIA dose distribution over 2000–2020.

The number needed to vaccinate is calculated by dividing the number of additional doses by the number of averted measles cases. The comparator vaccination strategy of MCV1 only was used. DRC: Democratic Republic of the Congo. MCV1: the first routine dose of measles-containing vaccine. MCV2: the second routine dose of measles-containing vaccine. SIA: supplementary immunisation activity.

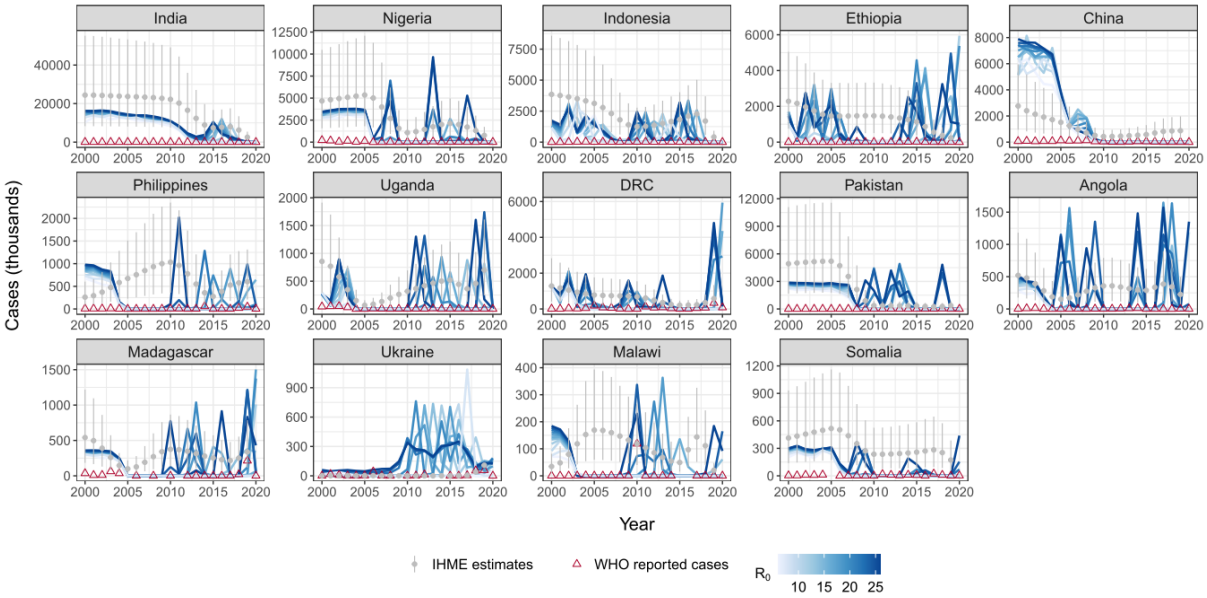

Figure S8. Estimated measles cases and reported cases under different values of R_0 over 2000–2020.
Blue solid lines denote model estimates of measles cases by different values of R_0, based on historical coverage of MCV1, MCV2, and SIAs over 2000–2020. WHO data for reported measles cases and IHME incidence estimates from the Global Burden of Disease 2019 study are included for comparison. The magnitude and trend of our model burden estimates show similarities to the IHME estimates. However, these case estimates are substantially different from the WHO country notifications, which suffer from underreporting and varying capacity for surveillance and diagnosis over time. DRC: Democratic Republic of the Congo. IHME: Institute for Health Metrics and Evaluation. MCV1: the first routine dose of measles-containing vaccine. MCV2: the second routine dose of measles-containing vaccine. SIA: supplementary immunisation activity.

7.4 Chapter 5 appendix

Table 1. Database of all cVDPVs 2000-2019 (n=96). Note that for the final analysis, outliers and serotype 2 outbreaks pre-2010 were removed.

Country	Region	Date first isolate collected	Date last isolate collected	Type	AFP Cases	Isolates	First NC[1]	Smallest NC	Largest NC	NPAFP[2]	Estimated seed date	Days to detect	Emergence lineage[3]	Reference(s)
DOMINICAN REPUBLIC	AMR	24/07/2000	30/01/2001	1	13	21	17	17	23	-	16/01/1999	554	-	(1,2)
PHILIPPINES	WPR	28/03/2001	23/09/2001	1	3	4	28	28	32	-	27/08/1998	943	-	(2,3)
MADAGASCAR	AFR	21/03/2002	12/04/2002	2	4	6	23	23	27	0.30	13/02/2000	766	-	(4,5)
CHINA	WPR	16/06/2004	06/08/2004	1	3	7	9	9	11	1.85	18/09/2003	271	-	(6,7)
DRC	AFR	01/01/2005	31/08/2005	2	7	7	9	6	9	5.10	04/04/2004	271	-	(8–10)
MADAGASCAR	AFR	22/04/2005	24/05/2005	3	1	8	13	9	16	1.30	05/03/2004	413	-	(2,9,11)
MADAGASCAR	AFR	16/06/2005	07/09/2005	2	4	9	21	10	24	1.30	21/07/2003	696	-	
INDONESIA	SEAR	09/06/2005	26/10/2005	1	46	46	10	10	20	2.41	06/08/2004	307	-	(12,13)
NIGERIA	AFR	05/07/2005	08/06/2006	2	3	3	10	-	-	6.50	01/09/2004	307	-	(7,9,14)
CAMBODIA	WPR	26/11/2005	15/01/2006	3	2	2	17	17	22	2.09	20/05/2004	554	-	(9,15)
CHINA	WPR	18/03/2006	16/05/2006	1	1	7	13	13	20	1.99	29/01/2005	413	-	(16,17)
MYANMAR	SEAR	19/04/2006	21/07/2007	1	4	11	14	14	20	2.11	26/01/2005	448	-	(15,17)
NIGERIA	AFR	19/05/2006	04/03/2015	2	384	527	6	6	-	6.60	04/13/2005	165	-	(14,17–22)
NIGERIA	AFR	05/07/2006	07/02/2008	2	6	6	9	-	-	6.60	06/10/2005	271	-	
NIGERIA	AFR	17/07/2006	17/10/2006	2	2	2	15	-	-	6.60	20/03/2005	483	-	
NIGERIA	AFR	26/02/2007	05/03/2009	2	6	6	13	-	-	5.30	09/01/2006	413	-	
SOMALIA	EMR	01/07/2008	09/01/2013	2	19	19	6	6	36	3.96	17/01/2008	165	-	(10,18–20,22–24)
DRC	AFR	19/01/2008	02/03/2009	2	14	14	8	8	16	6.09	28/05/2007	236	-	(8,10,18,19)
DRC	AFR	29/07/2008	25/02/2009	2	5	5	12	10	16	6.09	17/07/2007	377	-	
ETHIOPIA	AFR	04/10/2008	16/02/2009	2	4	4	10	10	11	3.00	02/12/2007	307	-	(20,25)
NIGERIA	AFR	01/12/2008	25/05/2010	2	7	7	12	-	-	6.59	19/11/2007	377	-	(14,19–21)
NIGERIA	AFR	20/04/2009	02/06/2009	2	2	2	17	-	-	7.00	13/10/2007	554	-	(14,19–21)
ETHIOPIA	AFR	27/04/2009	04/11/2010	3	7	7	12	12	28	2.59	14/04/2008	377	-	(20,25)

Country	Region	Date first isolate collected	Date last isolate collected	Type	AFP Cases	Isolates	First NC[1]	Smallest NC	Largest NC	NPAFP[2]	Estimated seed date	Days to detect	Emergence lineage[3]	Reference(s)
AFGHANISTAN	EMR	29/07/2009	13/02/2013	2	15	23	8	8	50	10.99	05/12/2008	236	-	(20,22,26)
INDIA	SEAR	19/10/2009	31/01/2010	2	16	16	9	9	14	9.53	20/01/2009	271	-	(20,25)
DRC	AFR	09/08/2009	24/09/2010	2	5	5	12	12	32	4.68	27/07/2008	377	-	(8,20)
DRC	AFR	20/04/2010	13/10/2010	2	9	9	19	11	19	5.72	03/08/2008	625	-	
MOZAMBIQUE	AFR	10/02/2011	02/06/2011	1	2	2	27	27	39	2.68	16/08/2008	908	-	(20,27)
YEMEN	EMR	09/04/2011	05/10/2011	2	9	11	6	6	14	3.35	25/10/2010	165	-	
DRC	AFR	17/10/2011	04/04/2012	2	30	30	8	6	32	5.53	23/02/2011	236	-	(22,27,28)
CHINA	WPR	18/10/2011	08/02/2012	2	3	4	6	6	11	1.94	05/05/2011	165	-	(23,24,29)
YEMEN	EMR	27/04/2012	25/07/2013	3	4	6	18	18	27	4.26	15/09/2010	589	-	(23,24,30)
CHAD	AFR	15/08/2012	12/05/2013	2	16	16	6	6	16	6.95	02/03/2012	165	-	(23,24,30,31)
PAKISTAN	EMR	30/08/2012	15/06/2014	2	81	87	6	6	33	8.28	17/03/2012	165	-	(30,32–34)
NIGERIA	AFR	16/08/2014	28/05/2015	2	1	6	7	7	13	12.9	27/01/2014	201	-	(33,35–37)
GUINEA	AFR	06/09/2014	25/12/2015	2	6	13	12	12	27	2.60	24/08/2013	377	-	(36–38)
SOUTH SUDAN	AFR	09/09/2014	12/09/2014	2	2	2	9	9	9	4.20	11/12/2013	271	-	(33,36)
MADAGASCAR	AFR	29/09/2014	02/09/2015	1	11	24	20	20	30	4.20	07/12/2012	660	-	(33,35–37)
PAKISTAN	EMR	13/12/2014	28/03/2015	2	1	30	7	7	19	6.50	26/05/2014	201	-	
PAKISTAN	EMR	01/02/2015	09/02/2015	2	2	2	6	6	6	9.20	19/08/2014	165	-	(35,37)
MYANMAR	SEAR	16/04/2015	05/10/2015	2	2	2	13	13	15	2.54	27/02/2014	413	-	
UKRAINE	EUR	30/06/2015	07/07/2015	1	2	2	20	20	26	2.67	07/09/2013	660	-	(35,39,40)
LAO PEOPLE'S DEMOCRATIC REPUBLIC	WPR	07/09/2015	02/06/2016	1	14	43	21	21	35	2.61	11/10/2013	696	-	(35,39)
PAKISTAN	EMR	20/10/2016	28/12/2016	2	1	5	9	9	18	12.5	22/01/2016	271	PAK-QTA-1	(41,42)
NIGERIA	AFR	28/10/2016	24/11/2016	2	1	2	12	12	16	21.2	16/10/2015	377	NIE-SOS-2	
DRC	AFR	20/02/2017	08/06/2018	2	27	37	15	14	29	5.80	25/10/2015	483	-	(43–46)
DRC	AFR	26/03/2017	18/04/2017	2	2	3	7	7	9	5.80	06/09/2016	201	-	(43–46)
SYRIA	EMR	03/03/2017	21/09/2017	2	74	113	22	22	33	3.60	03/03/2015	731	SYR-1	(43,44)
SOMALIA	EMR	22/10/2017	04/02/2020	2	10	61	38	33	58	6.30	04/04/2014	1297	-	(43,44,47–51)

Country	Region	Date first isolate collected	Date last isolate collected	Type	AFP Cases	Isolates	First NC[1]	Smallest NC	Largest NC	NPAFP[2]	Estimated seed date	Days to detect	Emergence lineage[3]	Reference(s)
NIGERIA	AFR	10/01/2018	09/10/2019	2	46	191	13	13	33	10.90	23/11/2016	413	NIE-JIS-1	(44,47,48)
NIGERIA	AFR	30/01/2018	24/03/2019	2	1	18	6	6	14	10.90	17/08/2017	165	NIE-SOS-3	
SOMALIA	EMR	08/03/2018	07/09/2018	3	7	24	14	14	23	4.80	15/12/2016	448	SOM-BAN-2	(43,44,47,49)
CHINA	WPR	18/04/2018	18/08/2019	2	1	5	13	13	33	2.08	01/03/2017	413	CHN-XXX	(44,47)
PAPUA NEW GUINEA	WPR	25/04/2018	04/11/2018	1	26	41	14	13	24	7.90	01/02/2018	448	PNG-MOR-1	(43,44,47)
DRC	AFR	26/04/2018	29/10/2018	2	11	21	19	18	26	6.60	09/08/2016	625	RDC-MON-1	
DRC	AFR	06/10/2018	07/10/2018	2	2	2	7	7	8	6.60	19/03/2018	201	RDC-HKA-1	
MOZAMBIQUE	AFR	21/10/2018	17/12/2018	2	1	3	6	6	10	3.40	08/05/2018	165	MOZ-ZAM-2	
INDONESIA	SEAR	27/11/2018	13/02/2019	1	1	3	58	58	60	2.40	02/06/2013	2004	IDN-PAP-1	
DRC	AFR	08/02/2019	17/03/2019	2	1	3	6	6	7	9.31	26/08/2018	165	RDC-KAS-1	(47,48,50–52)
DRC	AFR	10/02/2019	13/12/2019	2	20	26	8	8	15	9.31	19/06/2018	236	RDC-HLO-2	
NIGERIA	AFR	18/03/2019	10/06/2019	2	0	3	16	16	20	10.27	15/10/2019	519	NIE-SOS-4	
DRC	AFR	03/04/2019	22/06/2019	2	4	5	6	6	11	9.31	19/10/2018	165	RDC-KAS-2	
ANGOLA	AFR	05/04/2019	14/05/2019	2	1	2	7	7	10	4.99	16/09/2018	201	ANG-LNO-2	
DRC	AFR	21/04/2019	30/11/2019	2	32	35	6	6	16	9.31	06/11/2018	165	RDC-SAN-1	
ANGOLA	AFR	27/04/2019	09/02/2020	2	78	105	6	6	16	4.99	12/11/2018	165	ANG-HUI-1	
CENTRAL AFRICAN REPUBLIC	AFR	02/05/2019	20/11/2019	2	5	22	10	7	19	9.19	29//06/2018	307	CAR-BAM-1	
CENTRAL AFRICAN REPUBLIC	AFR	06/05/2019	29/06/2019	2	2	3	9	9	11	9.19	07/08/2018	271	CAR-BIM-1	
CENTRAL AFRICAN REPUBLIC	AFR	06/05/2019	05/02/2020	2	9	22	6	6	17	9.19	21/11/2018	165	CAR-BNG-1	
NIGERIA	AFR	20/05/2019	20/06/2019	2	1	2	14	14	15	10.27	26/02/2018	448	NIE-SOS-5	
CENTRAL AFRICAN REPUBLIC	AFR	27/05/2019	27/05/2019	2	0	3	6	6	6	9.19	12/12/2018	165	CAR-BAM-2	
CENTRAL AFRICAN REPUBLIC	AFR	28/05/2019	11/09/2019	2	0	16	9	9	20	9.19	29/08/2018	271	CAR-BIM-2	
ANGOLA	AFR	01/06/2019	25/12/2019	2	15	16	10	10	20	4.99	29/07/2018	307	ANG-LNO-1	(47,48,50–52)
DRC	AFR	03/06/2019	08/03/2020	2	21	27	8	8	20	9.31	10/10/2018	236	RDC-KAS-3	(47,48,50–52)
PAKISTAN	EMR	10/06/2019	10/02/2020	2	41	124	6	6	18	24.49	26/12/2018	165	PAK-GB-1	(47,48,50–52)

Country	Region	Date first isolate collected	Date last isolate collected	Type	AFP Cases	Isolates	First NC[1]	Smallest NC	Largest NC	NPAFP[2]	Estimated seed date	Days to detect	Emergence lineage[3]	Reference(s)
ANGOLA	AFR	15/06/2019	27/12/2019	2	34	51	6	6	14	4.99	26/02/2019	201	ANG-LUA-1	(47,48,50–52)
MYANMAR	SEAR	23/06/2019	21/08/2019	1	5	12	25	25	33	3.43	08/03/2017	837	-	(47,48,51,53)
PHILIPPINES	WPR	26/06/2019	24/01/2020	2	14	50	61	61	70	4.30	14/09/2013	2110	PHL-NCR-1	(47,48,51,52)
DRC	AFR	27/06/2019	14/08/2019	2	1	2	7	7	7	9.31	08/12/2018	201	RDC-TPA-1	
PAKISTAN	EMR	01/07/2019	28/08/2019	2	0	3	6	6	12	24.49	07/11/2018	236	PAK-GB-2	
PAKISTAN	EMR	01/07/2019	22/08/2019	2	1	2	8	8	9	24.49	16/01/2019	165	PAK-KOH-1	
PHILIPPINES	WPR	01/07/2019	28/11/2019	1	1	24	30	30	40	4.30	20/09/2016	1014	PHL-NCR-2	(48,54)
ZAMBIA	AFR	16/07/2019	25/09/2019	2	1	3	9	9	10	3.75	17/10/2018	271	ZAM-LUA-1	(48,50–52)
NIGERIA	AFR	22/07/2019	26/01/2020	2	3	9	8	8	14	10.27	28/11/2018	236	NIE-KGS-1	
CENTRAL AFRICAN REPUBLIC	AFR	30/07/2019	23/08/2019	2	2	9	7	7	14	9.19	10/01/2019	201	CAR-BIM-3	
NIGERIA	AFR	07/08/2019	17/08/2019	2	2	5	6	6	10	10.27	22/02/2019	165	NIE-KGS-2	
ETHIOPIA	AFR	30/08/2019	30/12/2019	2	0	3	14	14	14	2.91	08/06/2018	448	ETH-SOM-1	
CENTRAL AFRICAN REPUBLIC	AFR	31/08/2019	08/12/2019	2	3	7	7	7	11	9.19	11/02/2019	201	CAR-BER-1	
NIGERIA	AFR	11/09/2019	11/09/2019	2	0	1	10	10	10	10.27	08/11/2018	307	NIE-SOS-6	
ETHIOPIA	AFR	14/09/2019	12/02/2020	2	11	15	10	10	23	2.91	11/11/2018	307	ETH-ORO-1	
ANGOLA	AFR	15/09/2019	18/12/2019	2	12	14	7	7	14	4.99	26/02/2019	201	ANG-MOX-1	
PAKISTAN	EMR	15/09/2019	12/11/2019	2	1	4	6	6	12	24.49	02/04/2019	165	PAK-GB-3	
CHAD	AFR	31/10/2019	05/02/2020	2	8	21	6	6	23	13.35	18/05/2019	165	CHA-NDJ-1	
PAKISTAN	EMR	15/11/2019	03/01/2020	2	2	10	6	6	14	24.49	02/06/2019	165	PAK-TOR-1	
TOGO	AFR	15/11/2019	01/02/2020	2	3	5	13	13	17	4.57	28/09/2018	413	TOG-SAV-1	
ETHIOPIA	AFR	16/12/2019	26/01/2020	2	3	3	11	11	14	2.91	05/05/2018	589	ETH-ORO-2	
ETHIOPIA	AFR	16/12/2019	21/02/2020	2	1	2	18	18	20	2.91	08/01/2019	342	ETH-ORO-3	

[1] Nucleotide divergence of the first isolate
[2] NPAFP rate (per 100,000 children <15) for the first year of the outbreak
[3] Reporting of emergence lineage only began in 2016. Lineage is reported only where data is available

Table 2. Final regression model of factors associated with the number of nucleotide differences of the first isolate of VDPV outbreaks. Sample size and dispersion parameter (θ) for the serotypes 1 and 3 model are reported.

Serotypes 1 & 3 (n = 15) θ = 3.91			
Variable	Factor	IRR, multivariable (95% CI)	P-value
Intercept	-	-	
Type of surveillance via which first isolate was detected (AFP case or ES) AFP: n = 14 (93.3%) ES: n = 1 (6.7%)	ES (vs. AFP)	0.22 (0.04, 1.28)	0.077
Unit increase of non-polio AFP rate (cases per 100,000 children aged <15 years old) Mean (95% CI): 3.1 (2.2, 4.0)	Linear term	0.49 (0.21, 1.02)	0.087
Percent of stool samples adequately collected Mean (95% CI): 85.5 (77.1, 93.9) <80%: n = 3 (20%)	Linear term	0.98 (0.95, 1.02)	0.415
Unit increase of non-polio AFP rate * Percent of stool samples adequately collected	Interaction term	1.01 (1.0, 1.03)	<0.05

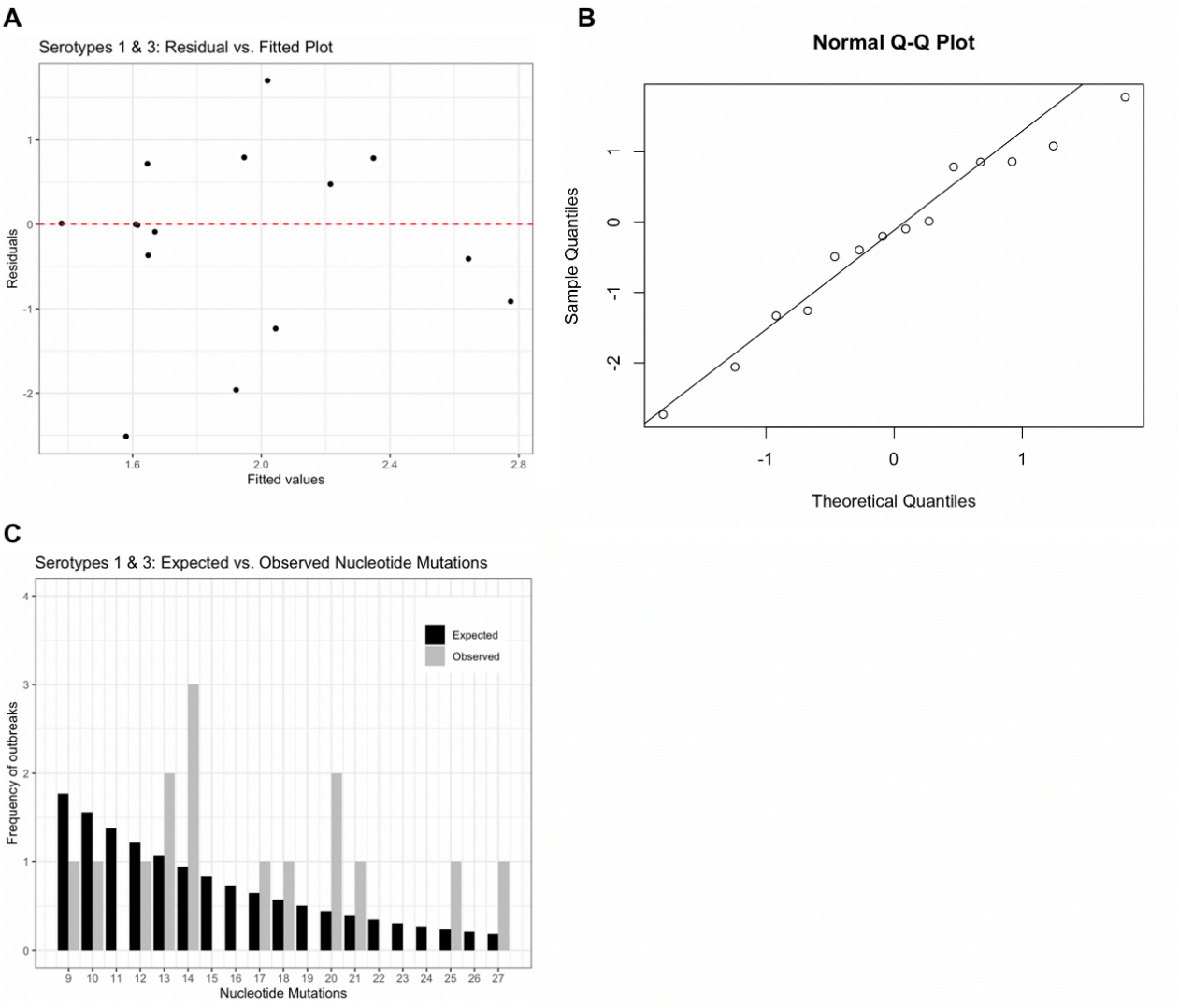

Figure 1. Serotypes 1 & 3 diagnostic plots: (A) residual vs. fitted values, (B) Normal Q-Q plot and (C) Expected vs. observed frequencies of nucleotide mutations assuming a negative binomial distribution. Model residuals (Figure 1a) for the serotypes 1 and 3 model support an appropriate model structure as the plot illustrates homoscedasticity of the residuals. The Q-Q plot (Figure 1b) further supports the assumed theoretical distribution for the final model as most values are centred along the Q-Q line, but the extreme values illustrate deviation from the assumed normal distribution of residuals. Figure 1c provides a visual comparison of expected vs. observed frequencies of nucleotide mutations. For serotypes 1 and 3, some outbreak frequencies corresponding to ≥13 nucleotide mutations are under-estimated while smaller mutations (9-10) are over-estimated by the model.

7.4.1 References - Chapter 5 appendix

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