Epidemiology and vaccination strategies against type-2 vaccine-derived poliovirus

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Abstract

In 1988, the World Health Assembly passed a resolution to eradicate poliomyelitis, a disease which was endemic in 125 countries and paralyzed 350,000 children per year. Primarily through the large-scale use of oral poliovirus vaccine (OPV), two of the three wild poliovirus (WPV) serotypes (types 2 and 3) have been declared as globally eradicated and transmission of type 1 remains uninterrupted only in Afghanistan and Pakistan.

Unknown at the time of declaring eradication, vaccine-derived poliovirus (VDPVs)— strains that have genetically mutated from the poliovirus contained in OPV, pose a major challenge to eradication. Outbreaks of circulating VDPV (cVDPVs), mostly caused by the type 2 strain of OPV, have become particularly difficult to interrupt in recent years after the elective, globally synchronized cessation of routine use of type 2-containing live poliovirus vaccine. In the context of on-going outbreaks and declining population immunity, optimal vaccination strategies to prevent and control cVDPV2s are uncertain.

The aims of this thesis are to evaluate the epidemiology of type 2 cVDPVs and synthesize optimal vaccination strategies: firstly, through generating evidence on the immunogenicity of alternative routine immunization schedules to understand population immunity; secondly, to understand the origin and dynamics of type 2 VDPV outbreaks; and finally, by incorporating the findings of these analyses into a compartmental transmission model, to evaluate outbreak response vaccination strategies with the novel type 2 oral poliovirus vaccine (nOPV2). This thesis has been targeted to inform the evolving policy questions of the Global Polio Eradication Initiative through generation of original evidence.

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Behind this individual stands a team: any and every accomplishment is only made possible by Margaret, Kevin and Rebecca Macklin through their endless and selfless support.

List of publications

Below is a list of publications on work that has been conducted during the period of my

PhD. Articles and Papers

Macklin GR, Grassly NC, Sutter RW, Mach O, Bandyopadhyay AS, Edmunds WJ, O'Reilly KM. Vaccine schedules and the effect on humoral and intestinal immunity against poliovirus: a systematic review and network meta-analysis. The Lancet Infectious Diseases. 2019 Oct 1;19(10):1121-8.

Macklin GR, O'Reilly KM, Grassly NC, Edmunds WJ, Mach O, Santhana Gopala Krishnan R, Voorman A, Vertefeuille JF, Abdelwahab J, Gumede N, Goel A. Evolving epidemiology of poliovirus serotype 2 following withdrawal of the serotype 2 oral poliovirus vaccine. Science. 2020 Apr 24;368(6489):401-5.

Bandyopadhyay AS and **Macklin GR**. Final frontiers of the polio eradication endgame. Current Opinion in Infectious Diseases. 2020 Oct 1;33(5):404-10.

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Macklin GR, Goel A, Mach O, Tallis G, Ahmed J, O'Reilly KM, Grassly NC, and Diop O. Epidemiology of type 2 Vaccine-Derived Poliovirus Outbreaks between 2016 – 2021. Vaccine. Status: In Press.

Mirzoev, A., **Macklin, G. R**., Zhang, Y., Mainou, B. A., Sadykova, U., Olsavszky, V. S., ... & Mach, O. Impact of Vaccination Campaigns with Novel Oral Polio Vaccine on Seroprevalence of Antibodies–Immunogenicity Study in Tajikistan 2021. The Lancet Global Health. Available at SSRN 4090413. Status: Under Review.

Book Chapters

Bandyopadhyay AS and **Macklin GR**. Global Polio Eradication: Progress and Challenges. In Human Viruses: Diseases, Treatments and Vaccines 2021 (pp. 629-649). Springer, Cham.

Estivariz CF, Burns C and **Macklin GR**. Poliovirus Vaccine–Live. In Plotkin's Vaccines, Eighth Edition (Chapter 50). Elsevier. Status: In Press.

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Introduction

The control of an infectious disease can be defined as the reduction of disease incidence, prevalence, morbidity or mortality to a locally acceptable level because of deliberate efforts, with continued intervention measures required (1). For some diseases, sustained intervention measures can result in the elimination and eradication of disease, the ultimate goal for public health. A hierarchy of public health outcomes in dealing with infectious diseases can be set out as follows (1):

- *Elimination of disease:* Reduction to zero of the incidence of a specified disease in a defined geographical area as a result of deliberate efforts; continued intervention measures are required.
- *Elimination of infections:* Reduction to zero of the incidence of infection caused by a specific agent in a defined geographical area as a result of deliberate efforts; continued measures to prevent re-establishment of transmission are required.
- *Eradication:* Permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts; intervention measures are no longer required.

In 1998, Dowdle defined three principle indicators of eradicability for human diseases: first, an effective intervention is available to interrupt transmission of the agent; second, practical diagnostic tools with sufficient sensitivity and specificity are available to detect levels of infection that can lead to transmission; and third, that humans are essential for the life-cycle of the agent, which has no other vertebrate reservoir and does not amplify in the environment (1). In addition to biological feasibility, it is evident that adequate public health infrastructure, sufficient funding and sustained political and societal will are essential to achieve eradication (2).

To date, the World Health Organization (WHO) has only declared the eradication of two diseases: the human disease smallpox caused by variola virus and the animal disease rinderpest caused by the rinderpest virus. For both, vaccination was the key intervention to interrupt transmission and was globally established before the initiation of eradication campaigns. Since

the eradication of smallpox, several human diseases have been considered as potential candidates for eradication, but the WHO has targeted only two other diseases for global eradication: poliomyelitis and dracunculiasis (Guinea worm)(3).

The World Health Assembly passed a resolution to eradicate poliomyelitis in 1998 (3). At that time, there were an estimated 350,000 cases of paralytic poliomyelitis reported annually across 125 countries. Building on the lessons learnt from smallpox, and in accordance with Dowdle's principal indicators of eradicability, polio eradication efforts have been centered on vaccination with oral poliovirus vaccine (OPV) in routine immunization and supplemental immunization actives (SIAs), alongside surveillance (4, 5).

By 2022, sustained efforts in polio vaccination worldwide have resulted in more than 99.9% decrease in the number of reported paralytic cases caused by wild poliovirus (WPV) and a reduction in the number of endemic countries from 125 to just two (Afghanistan and Pakistan). The last cases of poliomyelitis caused by WPV type 2 (WPV2) and 3 (WPV3) were reported in October 1999 (India) and November 2012 (Nigeria) respectively (6, 7). Subsequently, the Global Commission for Certification of Poliomyelitis Eradication declared the eradication of WPV2 and WPV3 on 20 September 2015 and 24 October 2019, respectively. In addition, four out of five WHO regions have been certified to have interrupted transmission of all wild polioviruses; the most recent being the African region in August 2020 (8).

Despite such progress, the objective of permanent reduction to zero of the worldwide incidence of poliomyelitis remains elusive. In addition to wild poliovirus, the live, attenuated Sabin polioviruses contained in oral poliovirus vaccines (OPV) have been identified as causes of paralytic poliomyelitis. Due to the inherent genetic instability, Sabin polioviruses can lose their attenuating mutations through reversion (9, 10) . These strains, termed vaccine-derived poliovirus (VDPV), can re-acquire transmissibility and neurovirulence equivalent to wild poliovirus in areas with low vaccination coverage and where epidemiologic conditions favor poliovirus transmission (e.g., low socioeconomic status, poor hygiene/sanitation, and crowding) and result in outbreaks of circulating VDPV (cVDPV) (10, 11). Since the first documented paralytic poliomyelitis outbreak of cVDPV between 2000 and 2001, they have been acknowledged as a barrier to achieving eradication (12).

Due to the risk of VDPV and vaccine-associated paralytic poliomyelitis (VAPP), the cessation of Sabin OPV is required for eradication of all poliomyelitis (5, 12). The end-game strategy is to replace OPV with inactivated poliovirus vaccine (IPV), with the first phase the removal of type-2 containing OPV (13). In April 2016, there was a globally synchronized change from trivalent OPV (tOPV, containing types 1, 2 and 3) to bivalent OPV (bOPV, containing types 1 and 3) – termed 'the Switch' – and the addition of at least one dose of IPV in all OPV-using routine immunization schedules to provide protection against paralysis from type-2 poliovirus. In this thesis, I focus on the epidemiology of type-2 cVDPV (cVDPV2) in the period after the Switch and vaccination strategies for prevention and control.

In Chapter 1, I provide a background review of polio eradication to best frame my thesis.

In Chapter 2, I address the levels of high population immunity against each of the three serotypes through routine immunization. Several vaccine schedules and formulations have been considered and assessed through randomized control trials, associated with the change in routine immunization through the removal of tOPV and global introduction of IPV. Here, I use a Bayesian network meta-analysis to synthesize policy-informing evidence on the differing pattern of mucosal and humoral immunogenicity induced by alternative schedules of IPV and OPV.

Following the global removal of tOPV and the use of Sabin type-2 OPV only in outbreak control, it was expected that the number of cVDPV2s would decrease substantially. In chapter 3, I review the epidemiology of cVDPV2 since the Switch, and through statistical analysis of genetic sequences, I explore the origin of cVDPV2 outbreaks. Here, I demonstrate that the new emergences of cVDPV2 outbreaks are seeded through inadequate Sabin type-2 OPV response to outbreaks.

To address the risks of generating VDPVs, OPVs that are more genetically stable are urgently needed (14). The type 2 novel oral poliovirus vaccine (nOPV2), engineered to have a lower risk of reversion compared to the current Sabin mOPV2, received recommendation under WHO Emergency Use Listing (EUL) in November 2020 (15, 16). During the period of EUL application and immediately after, I worked for WHO Polio Eradication to support the roll-out of

nOPV2 alongside undertaking my PhD. In Chapter 4, I document the accelerated development process and policy considerations for rolling out a vaccine in a Public Health Emergency of International Concern.

For my final chapter, I had a desire to expand beyond epidemiology and develop skills in mathematical modelling. One of the critical factors for consideration in Chapter 4 is the need to monitor the safety and effectiveness of nOPV2 during its use in outbreak response. In the absence of phase III clinical trial data, it is essential to evaluate vaccine performance in the target population in a timely manner. Building on the evidence generated from previous chapters, in Chapter 5 I develop a mathematical model for a cVDPV2 outbreak and OPV outbreak response, which can be applied to evaluate the effectiveness of nOPV2 vaccination campaigns.

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Chapter 1: Global Polio Eradication - Progress and Challenges

1.1 Chapter publication status

This chapter has been published with the following full bibliographic information:

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This was an invited book chapter for Human Viruses: Diseases, Treatments and Vaccines. I was one of two authors in the publication of this chapter and made the following author contributions according to the CRediT checklist: Conceptualization, Investigation and Writing – original draft.

*Note that the epidemiology section of this thesis chapter has been altered from the published book. The published version also contains an overview of more recent epidemiology (2017-2020), including details of my analyses that form later chapters in this thesis. In this version, the epidemiology is focused on the time up to the commencement of my PhD in 2017, which provides context to the status of the eradication programme at that time.

1.2 Abstract

In 1988, the World Health Assembly passed a resolution to eradicate poliomyelitis, a disease which was endemic in 125 countries and paralyzed 350,000 children per year. Primarily through the large-scale use of oral poliovirus vaccine (OPV), as of 2020, two of the three wild poliovirus serotypes (types 2 and 3) have been eradicated and transmission of type 1 remains only in Afghanistan and Pakistan. Unknown at the time of declaring eradication, vaccine-derived poliovirus (VDPVs) - rare strains that have genetically mutated from the poliovirus contained in OPV – pose a major challenge to eradication. In this chapter, we discuss the basic principles for eradication of poliomyelitis, the epidemiology over time and prospective scientific and strategic developments.

1.3 Introduction

Eradication of human diseases continues to be a major area of interest for global health practice (1). The idea of permanent reduction of global incidence of a disease to zero has triggered several attempts to identify pathogens suitable for eradication over the past several decades. However, with smallpox being the only human disease to be ever eradicated, it is evident that even though the benefits of disease eradication are well acknowledged, the likelihood of success is complicated by a range of social, political and economic factors that go beyond the virologic or immunologic dimensions of disease control (2).

Galvanized by the success of smallpox eradication, understanding of biologic feasibility of poliovirus eradication and the initial success in controlling polio transmission in the World Health Organization (WHO) Region of Americas, the World Health Assembly passed a resolution in 1988 to eradicate polio by the year 2000 (3). Twenty years from the target of eradication, several major milestones have been achieved. There has been a dramatic, more than 99.99% reduction in incidence of poliomyelitis and all but two WHO Regions have now been certified free of wild poliovirus transmission (4). Also, out of the three serotypes of polio, only the wild type 1 continues to circulate (4).

Despite such progress, the aim to stop all transmission everywhere has not been achieved. Circulation of wild poliovirus within the two endemic countries of Pakistan and Afghanistan has expanded in the recent years with cases of paralytic polio on a steady rise – marking a reversal of consistent trend of decline over the decades (4). Moreover, the expanding nature of outbreaks of circulating vaccine-derived polioviruses (cVDPVs) has become a major concern. Such outbreaks of cVDPVs, mostly caused by the type 2 strain of Sabin oral polio vaccine (OPV) have become particularly difficult to interrupt in the recent past with the elective, globally synchronized cessation of all routine use of type 2 containing OPV(5).

Innovations on vaccine, operations and diagnostic fronts spiked in the past decade to address the evolving need of the endgame. Among several promising vaccine-related initiatives, a novel OPV type 2 (nOPV2) that is genetically more stable with less risk of reversion to neurovirulence

compared to the current Sabin OPV type 2 is at the fore-front of new tools to be introduced in the program in the near-term (6, 7). Direct detection and novel sequencing methodologies hold the promise of making the outbreak response faster and more efficient. Understanding the social, political and economic dimensions of disease control in remaining areas of circulation remains key though to enable the existing and new tools to reach the last reservoirs of transmission.

1.4 Main Text

Polio: Basic Characteristics

Poliomyelitis is a viral disease caused by infection with any of the three poliovirus serotypes. Infection results in one of four clinical outcomes: inapparent infection without symptoms (72%), minor illness (24%), aseptic meningitis (nonparalytic poliomyelitis) (4%), or paralytic poliomyelitis (< 1%) (8).

Humans are the only known natural host of poliovirus that are able to sustain transmission, which typically occurs by person-to-person spread, through faecal-oral or oral-oral routes, with infants and young children driving virus transmission in most settings (8). Polioviruses establish initial infection in the gastrointestinal tract and replicate in the oropharyngeal and intestinal mucosa. From these primary sites of replication, the virus is excreted in the faeces and saliva and can drain into lymph nodes and to the blood, causing a temporary viremia. Most human infections end at this stage and are asymptomatic, with some having minor disease comprising nonspecific symptoms such as sore throat, fever, and malaise. Rarely, however, the virus can spread to the central nervous system. Viral replication in motor neuron cells in the spinal cord cause cell destruction and flaccid paralysis in the muscles the neurons innervate. Infection of the brainstem in rare cases results in paralysis of respiratory muscles, which can be fatal (bulbar paralysis) (8).

People remain most infectious immediately before and two weeks after infection, although virus is typically excreted in the feces for around 3-6 weeks and 2 weeks in saliva (8). The incubation period between infection and mild illness is 3 to 6 days, and from infection to onset of paralytic

disease is usually 7-21 days (8). In immunodeficient individuals, an inability to mount an immune response can lead to prolonged viral replication and shedding in faeces (8).

Polioviruses are classified as enteroviruses and belong to the family Picornaviridae. The viral genome, a single-stranded plus-strand RNA is enclosed in a non-enveloped capsid composed of four viral capsid proteins: VP1, VP2, VP3, and VP4 (9). There are three antigenic serotypes (serotype 1, serotype 2 and serotype 3), which differ in their capsid proteins and induce serotype-specific immunity. For each of the three poliovirus serotypes, are two broad categories of polioviruses: (1) wild polioviruses (WPV), or the naturally occurring strains not linked with the live attenuated vaccine viruses, and (2) vaccine-related polioviruses (10).

Vaccine-related viruses for each of the three serotypes are categorized based on the divergence of the genetic sequence in the VP1 gene from the original OPV strain: (1) Sabin-like, which have limited divergence from their parental OPV strains and are ubiquitous wherever OPV is used, and (2) vaccine-derived polioviruses (VDPV), whose higher level of divergence from their parental OPV strains (>1% [types 1 and 3] or >0.6% [type 2]) indicates prolonged replication (or transmission) of the vaccine virus (9, 10).

VDPVs resemble wild polioviruses phenotypically, can cause paralytic polio in humans and have the potential for sustained circulation (9, 10). The clinical signs and severity of paralysis associated with VDPV and wild poliovirus infections are indistinguishable. VDPVs are categorized as (1) circulating VDPVs (cVDPVs), when there is evidence of person-to-person transmission in the community; (2) immunodeficiency-associated VDPVs (iVDPVs), which are isolated from persons with primary immune deficiencies (PIDs) who have prolonged VDPV infections; and (3) ambiguous VDPVs (aVDPVs), which do not fit into the previous two types, and are typically either clinical isolates from persons with no known immunodeficiency or sewage isolates where the primary source may be unknown (9, 10).

Polio: Control and Eradication

The key biological characteristics that indicated poliovirus could be eradicated were (a) absence of a persistent carrier state (b) virus spread is by person-to-person transmission, (c) active immunization interrupts virus transmission, (d) absence of any nonhuman reservoir hosts capable of sustaining virus transmission, and (e) finite virus survival time in the environment (9). The strategy to achieve polio eradication has been focused on high vaccination coverage of infants and young children through routine immunisation and supplementary immunization activities (SIAs) and sensitive surveillance to detect poliovirus.

Vaccines

Over the past six decades, two types of vaccines have been used to protect against polio. The inactivated poliovirus vaccine (IPV), developed by Salk, is an injectable vaccine consisting of all three poliovirus serotypes (11). The OPV, developed by Sabin, is an oral vaccine composed of live attenuated polioviruses, and can be monovalent (mOPV, type-specific), bivalent (bOPV, types 1 and 3), or trivalent OPV (tOPV, all serotypes) (8). OPV has been extensively used in routine immunization and SIAs due to the ease of administration, ability to induce intestinal immunity (which is critical to limit faecal-oral transmission), low cost and ability to provide immunity through secondary exposure (9).

Despite its many advantages, the live attenuated vaccine strains in OPV (Sabin strains) may re-acquire neurovirulence leading to vaccine-associated paralytic poliomyelitis (VAPP) in the vaccine recipient or close contacts, or generation of VDPVs (8, 9). In settings of persistently low immunization coverage, VDPVs can circulate in the community and cause paralytic outbreaks of cVDPV (8). The estimated average rate of VAPP is about 4.7 per million births globally (12). Immunocompromised individuals with B cell deficiencies are at the highest risk of VAPP with >3,200 times the risk of VAPP compared to the general population. Type 3 virus is the most commonly isolated virus in people with VAPP who do not have immunodeficiencies and type-2 virus is the most commonly isolated virus in those with immunodeficiencies (12).

The pattern of immunogenicity and factors affecting it vary between IPV and OPV (8, 11). Humoral immunity, assessed by serological responses and considered predictive of protection

from paralytic poliomyelitis, is consistent across geographies and populations with IPV, in contrast to OPV where per dose immunogenicity has been low in developing countries, attributed to several factors including malnutrition and enteropathy (8). On the other hand, maternally derived antibodies in early weeks of life are known to be the biggest risk factors for lack of vaccine take with IPV (13). For induction of mucosal immunity, the impact of IPV remains less clear compared to the proven effect of OPV (11, 14, 15). Based primarily on OPV challenge studies, IPV is considered comparable to OPV in reducing oro-pharyngeal excretion; however, it is inferior to OPV in inducing primary intestinal mucosal immunity (16, 17).

Given the understanding that fecal – route drives transmission in areas with persistent poliovirus circulation, the lack of a meaningful impact on primary intestinal mucosal immunity is considered a critical limitation of IPV for the purposes of its use for polio eradication. Increasing antigen content or dose alone does not appear to have any favorable impact on IPV induced intestinal immunity, although higher doses do translate into a rise in titers of serum neutralizing antibodies (16, 18, 19). In contrast, several recent studies demonstrated a measurable reduction in virus excretion when IPV was administered to OPV-primed children: the impact on intestinal immunity was comparable to or no less than what was observed with an additional dose of OPV(20-22). This is encouraging for wider use of IPV beyond routine immunization and as an extension, analyses of acute flaccid paralysis and environmental surveillance data from Nigeria and Pakistan showed that compared to the traditional approach of OPV-only SIAs, a combined IPV – OPV campaigns had a bigger impact on interrupting VDPV and WPV transmission respectively (23, 24).

Given the near ten-fold cost differential per dose between IPV and OPV, several initiatives have focused on feasibility of dose sparing options such as administering a fractional dose (1/5th of the normal dose) through the intradermal (ID) or more recently, intramuscular (IM) route (25, 26). Overall, based primarily on the age at first dose and number of doses administered, fractional dose administration of IPV has generally shown encouraging results for seroconversion (16). Some of the difficulties of ID administration, such as specific training of vaccinators, could be overcome with the use of jet injector devices or with the option of IM administration. A recent randomized controlled clinical trial conducted in Cuba reported non-

inferior seroconversion rates for all three serotypes for fractional IPV administered via IM route compared with fractional IPV administered via the ID route after two doses, given at 4 and 8 months old infants (25). Further exploration of immunogenicity of fractional dose IPV administered intramuscularly in different age groups and settings will be important for possible policy impact of this option.

Surveillance

The primary means of detecting poliovirus is through identifying cases of paralytic poliomyelitis via surveillance of acute flaccid paralysis (AFP). An AFP case for the purposes of polio surveillance is defined as a child under 15 years of age presenting with recent, sudden onset of floppy paralysis or muscle weakness due to any cause, or any person of any age with paralytic illness if poliomyelitis is suspected by a clinician (27). For identified AFP cases, collection of adequate stool specimens and viral isolation is required to distinguish the case as poliomyelitis or non-polio AFP (27).

In many locations, AFP surveillance is supplemented by environmental surveillance (ES), the regular collection and testing of sewage to detect polioviruses (28). Functioning environmental surveillance is a mechanism to detect poliovirus circulation in the absence of paralytic cases and provide information on the extent of circulation.

Laboratory testing of stool specimens and environmental samples is conducted by the Global Polio Laboratory Network (GPLN), which includes 146 WHO-accredited poliovirus laboratories in all WHO regions. The GPLN member laboratories follow standardized protocols to 1) isolate poliovirus, 2) conduct intratypic differentiation and 3) conduct genomic sequencing of the VP1 region to distinguish Sabin-like, VDPV and WPV types (29).

Epidemiology: Wild poliovirus

In 1988, when the World Health Assembly passed a resolution to eradicate poliomyelitis, poliovirus was endemic in over 100 countries and paralyzed an estimated number of 350,000 children per year. Between 1988 and 2001, polio incidence declined by 99%, primarily due to

administration of tOPV through large-scale vaccination campaigns. The reported number of cases reduced from 35,000 to 3,000, and the number of polio endemic countries from 125 to 10 (Figure 1)(30). The WHO regions of the Americas and the Western Pacific were certified polio-free in 1994 and 2000 respectively, and the European Region in 2002 (30). In addition, the last indigenous case of WPV2 occurred in 1999 in Aligarh, India (31).

In the early millennium, there was an expectation that global eradication of wild poliovirus was imminent. However, in 2006, polio types 1 and 3 continued to persist in four endemic countries: India, Nigeria, Pakistan, and Afghanistan (32). The co-circulation of WPV1 and WPV3 was difficult to control due to requiring frequent interchange of tOPV, mOPV1, and mOPV3 during immunization activities. As the type 2 component of Sabin vaccine is more immunogenic than the other types, the immune response to type 1 and type 3 from tOPV was suboptimal. To overcome this challenge, development of bOPV that had superior immunogenicity compared with tOPV and non-inferiority compared with mOPV1 and mOPV3, was critical (33).

After the introduction of bOPV in vaccination campaigns in 2009-2010, it was possible to simultaneously sustain reduction in WPV1 and WPV3 cases (34). India achieved a level of population immunity adequate to interrupt transmission, with the last confirmed WPV3 and WPV1 cases in October 2010 and January 2011, respectively (34). India, which was once considered the most difficult setting to achieve polio elimination, was removed from the list of endemic countries and the South East Asian Region was declared polio-free (34). Subsequently, the last case of WPV3 was detected on November 10, 2012, in Yobe, Nigeria (35).

In 2013, WPV1 was the only wild-type poliovirus serotype circulating, and was endemic in three countries: Nigeria, Pakistan and Afghanistan (32, 35). However, importation of WPV1 lead to polio cases reported from previously polio-free countries: from Nigeria into the Horn of Africa resulted in 217 cases (9 in Ethiopia, 14 in Kenya, and 194 in Somalia); from Pakistan into Syria resulted in 35 cases; and from Nigeria to Cameroon resulted in 4 cases (32, 35, 36).

The number of WPV1 cases in each of the three endemic countries continued to decline between 2013 and 2016: from 37 to 13 in Afghanistan, 93 to 20 in Pakistan and 53 to 4 in Nigeria (Figure 1)(36). In Nigeria, no cases of WPV1 were reported for two years (from July of 2014 until June

2016). However, in July 2016, four WPV1 cases were reported, and genetic sequencing of the excreted virus indicated that it might have been circulating undetected in Nigeria for 5 years (37). Subsequently, there were major efforts to improve access and surveillance in Northern Nigeria. There has been no detection of WPV1 since 2016 and Nigeria has been removed from the list of endemic countries.

Between 2017 and 2020, transmission of WPV1 has persisted in Pakistan and Afghanistan. In Pakistan, this has primarily been attributed to a failure to vaccinate children at the doorstep (38). The spread of misinformation and propaganda, fueled by social media, has resulted in a mistrust in the polio vaccine and community resistance to vaccination (38, 39). Community fatigue towards repeated polio vaccination is present in those communities that are deprived of other basic services (38, 39). In Afghanistan, insecurity and bans on vaccination campaigns have severely affected the ability of the program to reach children. Kandahar City continues to be main source of transmission, with continuous detection of poliovirus through environmental surveillance, with ongoing gaps in campaign quality due to high numbers of refusals 30% and 43% (38, 39).

Epidemiology: circulating vaccine-derived poliovirus (cVDPV)

The first documented outbreak of cVDPV occurred in the Dominican Republic and Haiti, between 2000–2001 and was associated with the type 1 Sabin strain, likely originating from OPV dose given in 1998–1999 (40). The 21 confirmed cases occurred in communities with very low (7 to 40%) rates of coverage with OPV, with 20/21 individuals either unvaccinated or incompletely vaccinated (40).

Following their discovery, cVDPVs have been acknowledged as a cause of paralytic poliomyelitis outbreaks in certain settings and a barrier to achieving eradication (9, 41). Between January 2000 and December 2016 there were a total of 810 paralytic cVDPV cases reported: 86% (697/810) cVDPV2, 13% (103/810) cVDPV1, and 1% (10/810) cVDPV3 (Figure 1). These cases were from 42 genetically unique cVDPV outbreaks: 20 occurring in the African Region (Nigeria, Democratic Republic of Congo, Madagascar, Chad and Guinea); 11 in the Eastern

Mediterranean Region (Ethiopia, Somalia, Afghanistan, Yemen, Pakistan and South Sudan); 5 in the Western Pacific Region (Philippines, China, Cambodia, Lao People's Democratic Republic); 4 in South East Asian Region (Indonesia, Myanmar and India); 1 in the European Region (Ukraine) and 1 in the American Region (Dominican Republic and Haiti) (42).

The most significant risk factor for cVDPV outbreaks is insufficient population immunity and inadequate OPV vaccination coverage over time: using data from 2003-2016, significant risk factors associated with an increased probability of cVDPV outbreaks were the percentage of unimmunized children, the percentage of the population displaced, and the numbers of children born per year (42). The prior elimination of indigenous poliovirus circulation also increases the risk, as nonimmune individuals accumulate rapidly in the absence of high vaccination coverage or naturally acquired immunity (9).

In April 2016, the first phase of OPV cessation occurred, with the removal of type 2 OPV from routine immunisation and a synchronized switch from tOPV (containing types 1, 2 and 3) to bOPV (containing types 1 and 3) – termed 'the Switch'(45). The type 2 component was the first to be removed as it was responsible for most VDPV outbreaks, whilst the WPV2 had been certified as eradicated in 2015, with the last indigenous WPV2 case in 1999 (31). As a risk mitigation strategy, at least one dose of IPV was introduced into routine immunization in all OPV-only using countries, to protect against paralysis from serotype 2 in case of re-introduction of WPV2 or persistence of VDPV2 (45). However, due to IPV supply shortages, many countries had to delay IPV introduction or faced stock-outs of IPV (45).

Prior to the Switch, large-scale campaigns were conducted with tOPV to increase population immunity against type 2 poliovirus (46). Some cVDPV2 outbreaks were expected and a global stockpile of monovalent OPV2 (mOPV2) was created for outbreak response. However, any use of mOPV2 retains a risk of creating new VDPV2 emergences, which increases with time since the switch due to declining population immunity (47).

Since the removal of type 2 OPV from routine immunization use in April 2016, there has been a substantial change in the epidemiology with a notable increase in cVDPV2 outbreaks, which is analyzed in detail in chapter 3. For cVDPV1 and cVDPV3, which are not discussed further in

this thesis, there have been 38 and 7 cases reported, respectively, between 2017 and 2019: cVDPV1 outbreaks have been reported in Indonesia (2018 – 2019), Malaysia (2019), Myanmar (2019), Papua New Guinea (2018), and Philippines (2019) and a cVDPV3 outbreak in Somalia (2018) (43, 44).

Looking Forward

Policy and endgame strategy

In accordance with the complexity of evolving epidemiology and timelines, the GPEI have produced several strategic plans, which outline the key goals to achieve and sustain a world free from polioviruses and are summarised below (48-50):

1: Interrupt transmission
The first objective is to stop all wild poliovirus transmission and control new outbreaks of cVDPV within 120 days of confirmation of the index case.

2: Containment of polioviruses
Following interruption of WPV transmission globally, the safe handling and containment of infectious materials in laboratory and vaccine production facilities will be essential to minimize the risk of reintroducing WPV into the population. A reintroduction of WPV from a poliovirus facility would risk the potentially serious consequences of re-establishing WPV circulation. Additionally, after the cessation of all OPV use, the reintroduction of an OPV/Sabin virus strain from a poliovirus facility would risk the emergence of a cVDPV, and again the potentially serious consequences of re-establishing its circulation.

Most facility-associated poliovirus risks can be eliminated through the destruction of WPV and OPV/Sabin infectious and potentially infectious materials. However, poliovirus facilities will be necessary in several countries to continue essential functions, including IPV production, OPV

stockpile management, vaccine quality assurance, diagnostic reagent production, virus reference functions and research.

3: Certification of eradication of WPV

The Global Certification Committee (GCC) will be responsible for global certification of WPV, following the successful certification of all six WHO regions. The primary requirements for certifying a WHO region as free of WPV are: the absence of any WPV detection for a minimum of three years in all countries of the region; the presence of certification standard surveillance in all countries during that three-year period; the completion of Phase I biocontainment activities for all facility-based WPV stocks. Currently, mathematical modelling is being used to determine whether the three-year period will be suitable for global certification, and the interplay between the period of time without a detection and surveillance sensitivity.

4: Complete OPV withdrawal.

The complete cessation of OPV use from routine immunisation and SIAs is essential to decisively eliminate the risk of VDPVs and VAPP. Global OPV cessation is planned approximately one year following certification of WPV eradication and would be followed by period of IPV-only vaccination. The first phase of OPV cessation was conducted in April 2016, with the globally synchronised withdrawal of the type 2 OPV component from routine immunisation and switch from trivalent OPV use to bivalent OPV use. However, the evolving epidemiology after the Switch and lessons learned will be key to informing future policy.

5: Validation of absence of cVDPVs.

Following complete OPV cessation, there should be no new cVDPV outbreaks seeded. After a period without of detection and high-quality surveillance, the absence of cVDPV outbreaks can be verified. Any iVDPV excretors that were infected prior to OPV cessation and continue to excrete will require monitoring and treatment.

Research and development

We identified the following research and development areas that could have major policy implications to facilitate both interruption of transmission of all polioviruses and maintain polio-free status for long-term.

OPV with less risk of VAPP/VDPVs: A central priority of polio vaccine development is to develop OPV strains that are significantly more genetically stable compared to Sabin strains. Enhanced genetic stability as a result of stabilizing key areas of the vaccine virus genome would translate into less risk of losing the attenuations that are known to be linked with reversion to neurovirulence. Two such novel OPV type 2 (nOPV2) candidates have been under pre-clinical and clinical development with heightened focus in accelerated clinical development over the recent past given the rapidly deteriorating cVDPV2 situation. The modifications in nOPV2 candidates include changes ribonucleic acid (RNA) sequence in the 5' untranslated region (5' UTR), the non-structural protein 2C, the capsid protein coding region (P1), and the polymerases (51, 52). Pre-clinical development that begun early in the past decade has been successfully completed, and the first-in-human study was implemented under contained conditions in Belgium in 2017 with promising results confirming safety and immunogenicity with enhanced genetic and phenotypic stability of the novel strains (6, 53, 54). Following this, phase II studies and manufacturing processes have been accelerated with the WHO Executive Board in February 2020 urging for review and assessment of nOPV2 through the Emergency Use Listing (EUL) procedure of WHO – a process to expedite the availability of unlicensed medical products for PHEICs (7, 55).

IPV with mucosal immunogenicity: Although the novel OPV strains have shown significant promise to reduce the risk of generating VAPP and VDPV cases, a live attenuated vaccine strain would still carry some risk of reversion, recombination and potentially neurovirulence on prolonged excretion or circulation. A new or modified IPV with intestinal immunogenicity has therefore been considered an "ideal" solution to the issue of vaccine-related poliovirus disease and circulation. In recent times, IPV adjuvanted with enterotoxin-based mucosal vaccine antigens such as the double-mutant heat-labile enterotoxin (dmLT) has demonstrated rise in fecal IgA secretion and upregulation of expression of the intestinal homing receptor $\alpha 4\beta 7$, indicating

potential induction of mucosal immunity in pre-clinical studies (56, 57). Human clinical data are awaited and would be key in informing the next phases of development.

IPV with easier delivery tools: A major issue restricting the broader use of IPV in SIAs or house-to-house campaigns has been the requirement of trained personnel for administering injections and managing associated logistics. Alternative modes and options for IPV administration such as needle-free, jet injector devices and microarray patches (MAP) hold the promise of making IPV more usable in the peripheral settings, outside of immunization clinics (58). Several studies have reported the user dynamics, safety and immunogenicity with such devices, and tools such as the MAPs are under further evaluation for technological and scientific merit and the potential to enhance equitable vaccine access for in low- and middle-income countries (59-62).

Minimizing risk of containment failure: As successive types of WPVs are eradicated, any potentially infectious poliovirus material stored in laboratories, and vaccine production facilities will continue to have a risk of reintroduction of the homotypic poliovirus into communities. Several recent examples of containment failures from manufacturing sites in emphasize the importance of timely implementation of poliovirus containment measures to prevent potential long-lasting, damaging fall out of re-establishment of poliovirus transmission in the post-eradication era, especially when population immunity against poliovirus is expected to be on the decline (63). Major new initiatives in developing IPV and novel laboratory assays from non- or less- infectious materials or constructs have been reported in the recent past, including attenuated Sabin strains or S19 strains, that could significantly reduce the public health impact of any accidental containment failure of polio-essential facilities (63-66).

Treating immunodeficient excretors: A unique challenge for long-term maintenance and completeness of polio eradication comes from individuals with the rare, inherited immunodeficiency disorders who are at risk of prolonged excretion of polioviruses and thus could give rise to polio outbreaks in communities (67, 68). At least two drugs are under advanced stages of development to mitigate this risk in individuals with specific immunodeficiency disorders. Pocapavir, a capsid inhibitor with proven efficacy demonstrated in human OPV challenge study and V-7404, a 3C protease inhibitor, are in clinical development

with initial trends suggesting the need of a combination product for effective virus clearance and to reduce development of resistance (69-71). Building a robust surveillance system to identify and track such individuals at risk of prolonged shedding will be a key contributory step to the success of these anti-viral agents.

Faster, easier detection: In addition to considerations for expanded and risk-based deployment of environmental surveillance sites for poliovirus detection, use of newer tools such as water-quality probes to evaluate physical attributes of sewage collection sites and tools with potential advantages of sample shipment and higher sensitivity of detection such as the Bag-mediated filtration system (BMFS) could be important for the final phases of eradication (72-74). Wider, more targeted use of principles of molecular epidemiology to interpret sequencing results of poliovirus isolates could play a pivotal role in planning effective scale of outbreak response. The importance of using advanced molecular technologies to expedite the process of poliovirus detection and final classification of the isolates has been emphasized in recent reviews (75). For example, methodologies with nested PCR with nanopore sequencing protocols have demonstrated promising sensitivity for detection of WPVs, VDPV2 and Sabin-like viruses in a pilot conducted in Pakistan, generating sequencing information in less than 3 days from the time of initiation of sample, compared to 2-4 weeks with the current, culture-based method (76).

1.5 Conclusion

In 1988, when the World Health Assembly declared its commitment to eradication and the Global Polio Eradication Initiative (GPEI) was formed in pursuit of this goal, there were 350 000 annual cases of WPV in 125 countries. By 2020, only two countries remain endemic (Afghanistan and Pakistan) and two of the three WPV serotypes have been certified as eradicated. Unknown at the time of declaring eradication, VDPVs - rare poliovirus strains that have genetically mutated from the poliovirus contained in OPV – have been discovered and pose a major challenge. Now the GPEI must confront a dual emergency: interrupting WPV1 in the two remaining endemic countries and stopping outbreaks of VDPVs.

The barriers to reaching WPV eradication Afghanistan and Pakistan are not an exclusive matter of science or virology anymore; they are instead social and political realities that impede the delivery of polio vaccine in these settings. The programme has not been able to vaccinate every child for several reasons, including inaccessibility of some areas due to geographical isolation, insecurity or bans on vaccination activities by political or religious leaders. Even when the programme does have access, pockets of vaccine refusals are growing due to misinformation, mistrust, cultural beliefs, fatigue or other, urgent, health priorities (such as access to water and basic healthcare).

The problems of VDPV, on the other hand, are more biological and require scientific innovation and strategies for improved program implementation. It remains clear that cessation of Sabin OPV use is essential to stop all cases of paralytic poliomyelitis. However, the epidemiology that has evolved since Sabin OPV2 removal has implications for existing strategies outlined for total OPV cessation, which need urgent attention.

In 2019, we have observed the largest numbers of outbreaks and countries experiencing cVDPV2 transmission to date, primarily due to new emergences of cVDPV2 outbreaks seeded through inadequate mOPV2 response to outbreaks. It is not currently possible to control cVDPV2 outbreaks without inducing intestinal mucosal immunity through mOPV2 use; however, any sub-optimal use of mOPV2 risks generating cVDPV2. The spread of cVDPV2 is increasing over time as the immunity of the global population against type 2 poliovirus rapidly decreases.

The GPEI is currently awaiting the introduction of nOPV2, developed to be more genetically stable and less likely to revert to a neurovirulent genotype than Sabin OPV2. However, uncertainty remains about when nOPV2 will be rolled out for widespread use in outbreak response and how effective they will be in interrupting outbreaks in high-risk areas of polio transmission.

Several modelling groups have developed prospective mathematical models to inform and evaluate the endgame strategic plans including a recent global model update that emphasised that the GPEI is not on track to achieve WPV1 eradication prior to 2024 without improved

implementation, or to successfully stop the transmission of VDPV2 viruses using current tools (77). This indicates the current trajectory of the polio endgame will continue to have significant challenges.

In the final phases of the global eradication program, it would be important to maintain high population immunity against all three WPV serotypes through strengthening of routine and supplementary immunization delivery systems (78, 79). Alongside, effective and urgent incorporation of technological advances such as use of novel, more genetically stable vaccine options and innovative program strategies to have better and faster outbreak response will be necessary to complete and sustain eradication of all types of polioviruses.

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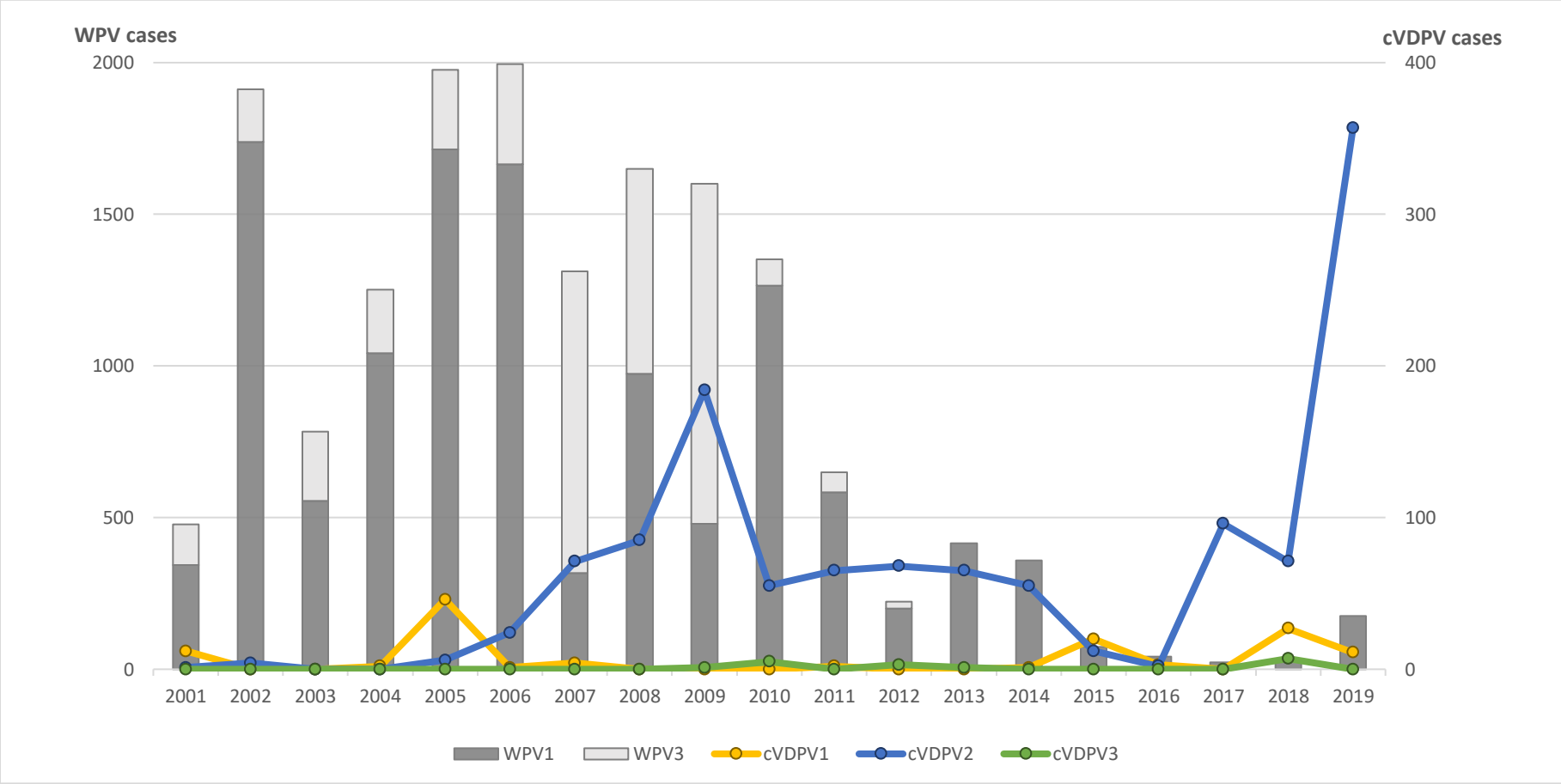
1.7 Figures and Tables

Figure 1: Annual incidence of reported wild poliovirus (WPV) and circulating vaccine-derived poliovirus (cVDPV) cases, by year and serotype isolated, 2001-2019. Data as of August 2020 (36, 80).



Chapter 2: A Network Meta-analysis of Vaccine Schedules and the Effect on Humoral and Intestinal Immunity Against Poliovirus

2.1 Chapter publication status

This chapter has been published in *The Lancet Infectious Diseases* with the following full bibliographic information:

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2.2 Abstract

The eradication of wild and vaccine-derived poliovirus requires the global withdrawal of oral poliovirus vaccine (OPV) and replacement with inactivated poliovirus vaccine (IPV). The first phase was the removal of serotype 2 vaccine in April 2016, with a switch from trivalent OPV to bivalent OPV. The aim of this study was to produce comparative estimates of humoral and intestinal mucosal immunity associated with different routine immunization schedules.

We performed a single effect meta analysis and network meta-analysis in a Bayesian framework, to synthesise direct and indirect evidence. We searched MEDLINE and Cochrane Library Central Register of Controlled Trials for randomised trials published up to 01 November 2018, comparing poliovirus immunisation schedules in a primary series. The first outcome was seroconversion against poliovirus serotypes 1, 2 and 3 and the second outcome was intestinal immunity against serotype 2, measured by absence of shedding poliovirus after challenge OPV dose.

We identified 17 studies and eight studies, with 8279 and 4254 infants, eligible for humoral and intestinal immunity outcomes, respectively. For serotype 2, the risk ratio (RR) of seroconversion after three doses of bivalent OPV was 0·14 [95% credible intervals (CrI): 0·11, 0·17] compared with three doses of trivalent OPV. The addition of one or two full doses of IPV after bivalent OPV increased RR to 0·85 [95%CrI: 0·75, 1·0] and 1·1 [95% CrI: 0·98, 1·4], respectively. However, this addition of IPV to bivalent OPV schedules did not significantly increase intestinal immunity from RR 0·33 [95% CrI: 0·18, 0·61], compared to trivalent OPV. For serotype 1 and 3, pooled seroconversion estimates were $\geq 80\%$ and $\geq$ 88% for all vaccine schedules, respectively.

The immunogenicity of alternative vaccination schedules can be assessed using network meta-analysis. For the polio eradication programme, the addition of one IPV dose for all birth cohorts should be prioritized to protect against type 2 poliovirus; however, this will not prevent transmission or circulation in areas with faecal-oral transmission.

2.3 Introduction

In 1988 the World Health Assembly passed a resolution which committed the World Health Organisation (WHO) to eradicate poliomyelitis. The eradication effort has been centred on mass vaccination campaigns and achieving high routine immunisation (RI) coverage with oral poliovirus vaccines (OPV) and inactivated poliovirus vaccines (IPV)(1, 2). More than 150 countries have relied on OPV to eliminate poliovirus transmission and maintain a polio-free status; however, the cessation of all OPV use and replacement by IPV is necessary due to the risk of vaccine-derived poliovirus (VDPV) and vaccine-associated paralytic poliomyelitis (VAPP) associated with the OPV vaccine.(3) The first phase of this cessation was completed in April 2016, with the global withdrawal of Sabin type 2 OPV and a switch from the trivalent (tOPV) to bivalent OPV (bOPV) formulation. In addition, the Strategic Advisory Group of Experts on Immunisation (SAGE) recommended that at least one dose of IPV was introduced into all RI schedules to protect against poliomyelitis caused by serotype 2(4). However, constraints on IPV supply resulted in 39 countries having to delay IPV introduction or interrupt routine use, with some countries adopting the use of intradermal (ID) fractional-dose IPV (fIPV).(5)

After OPV withdrawal, the post-eradication schedule will comprise a minimum of 2 IPV doses, given after 14 weeks.(6) There is a portfolio of approaches to develop affordable IPV options including: limiting the number of IPV doses in RI to two; reducing the volume of each dose through ID administration; reducing the antigen content of each dose through use of adjuvants; and reducing the cost of production through developing IPV from attenuated Sabin vaccine strains of poliovirus.(7, 8) This has resulted in the development of alternative formulations to conventional intramuscular (IM) Salk IPV, including fIPV, adjuvanted-IPV, monovalent type 2 IPV (mIPV2) and Sabin-IPV (sIPV).

Accordingly, a multitude of clinical trials have been conducted to evaluate the immunogenicity of different vaccine schedules. It is essential to develop a comprehensive overview of immunity induced by different RI schedules against the three poliovirus serotypes. Standard meta-analysis approaches combine information from multiple studies to estimate the overall effectiveness of an intervention, but do not compare effectiveness between interventions that have not been explicitly trialled. In contrast, network meta-analysis (NMA) uses the relatedness of interventions to estimate both the direct and indirect

effects.(9, 10) While NMA are used increasingly in comparisons of drugs, they have not been widely adopted to compare vaccine schedules.(11, 12)

In this paper, we describe a systematic review and network-meta analysis to provide an estimate of the relative immunogenicity of the different OPV and IPV RI schedules to induce humoral and intestinal immunity against poliovirus. This knowledge will be used to inform global policy.

2.4 Methods

Study design and selection

Eligible studies were randomised controlled trials that compared the immunogenicity of primary immunisation schedules of poliovirus vaccines in healthy infants and provided vaccine efficacy outcomes (see outcomes 1 and 2). Interventions of IPV-only, IPV-bOPV combination and bOPV-only vaccine schedules were included, in comparison with each other or a tOPV-only schedule. Interventions were included if the age of administration of the first vaccine dose (excluding birth dose) was between four and eight weeks of age. A full study protocol outlining the Population, Intervention, Comparison and Outcome (PICOs) criteria used is available in Web Appendix 1. We searched MEDLINE and Cochrane Library Central Register of Controlled Trials for randomised clinical trials from January 01, 1980, to November 01, 2018, using the search terms: (Polio OR poliovirus) AND vaccine AND (primary series OR routine OR infants) AND (seropositive OR seroconversion OR antibody OR mucosal immunity OR intestinal immunity). The search was last updated on November 13, 2018. Trials were excluded if they were conducted in Western Europe or North America, due to differences in vaccine immunogenicity and schedules in these high-income settings,or if there was variation in age-schedules between study arms, to ensure consistency within the network. The most relevant or inclusive data for a given study, with no differentiation between vaccine manufacturer, were chosen. We follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting of the NMA within this paper.

Two investigators (GM and KO) independently reviewed studies and extracted data. The number of individuals in each study arm were recorded by serotype and time of sample collection. Additional data included study location, age at administration, route of administration, vaccine antigen content, and challenge vaccine and timing (where applicable).

We assessed the risk of bias in accordance to the The Cochrane Collaboration's tool for assessing risk of bias in randomised trials, for individual elements from five domains (selection, performance, attrition, reporting, and other) and the overall certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation framework(13).

Outcomes

Included studies reported on one of two pre-defined outcome:

Seroconversion against poliovirus serotypes 1, 2 and 3, measured four weeks after the last vaccine dose. Seroconversion was defined as a change from non-detectable (< 1:8) to detectable (≥ 1:8) antibody titre, or a ≥ four-fold increase in antibody titre over the expected decline of maternally-derived antibodies (assuming a half-life of 28 days) (14).

Development of intestinal immunity against serotype 2. This was measured as the absence of shedding of type 2 poliovirus, seven days after a challenge dose of OPV containing Sabin 2.

Statistical analysis

A random-effect meta-analysis of single proportions was performed, using an inverse variance pooling method and logit transformation, in the 'meta' package in R (version 3.4.3). A random-effect NMA was developed for each endpoint, with a binomial likelihood and log-link function and computed in a Bayesian framework using the GeMTC package in R (version 3.4.3).(15) Markov chain Monte Carlo (MCMC) simulations estimated posterior distributions of relative treatment effects and standard deviation, with vague uniform priors. Four independent Markov chains were run with 10,000 burn-in iterations and 60,000 inference-iterations per chain. Convergence of Markov chains was evaluated using the Gelman–Rubin–Brooke diagnostic and time-series plots. Autocorrelation plots were assessed to detect auto-correlation in the chains. Additional analysis included network meta-regression to explore the effect of study-level covariates including the estimated under-five child mortality rate due to diarrhoeal disease in the country of study location.(16)

Between-intervention relative effects were summarised as risk ratios (RR), reported as the median of the posterior distribution with 95% credible intervals (CrIs). Differences between treatments are considered significant (at the five percent level) if confidence intervals do not overlap the no-effect line. The RR between treatments are presented relative to a tOPV comparator and relative effect tables between treatments.

Model fit was measured by deviance information criterion, residual deviance and leverage(17). We display the standard deviation of the random-effects model (known as tau (τ)), as a measure of heterogenicity in the network, where τ^2 is the between-study variance of the true effect size. A node-splitting model was generated to assess inconsistency within the network.(10)

Role of the funding source

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

2.5 Results

A literature search in MEDLINE and CENTRAL registers identified 437 unique studies and 53 were retrieved for full-text assessment. A total of 17 studies describing 47 study-arms and eight studies describing 25 study-arms met inclusion criteria and were included in the NMA for humoral and intestinal immunity, respectively (Figure 1, Web Appendix 2). We determined a low to moderate risk of bias for individual studies and a moderate to high quality of evidence for each outcome (Web Appendix 3). Seven vaccine formulations were included in the analysis: tOPV; bOPV; Salk IPV (referred to as IPV), administered IM; mIPV2, administered IM; fIPV ($1/5^{th}$ Salk IPV dose) administered ID; sIPV, administered IM; and aluminium-adjuvanted IPV (IPV-Al, $1/10^{th}$ Salk IPV dose) administered IM.

Humoral Immunity

There were 19 unique vaccination schedules identified, which each formed a node in the network (Figure 2A), with corresponding age of schedules (Figure 2B). The network was serperated into two sub-groups - studies without a birth dose (14 nodes, 15 studies) and those with a birth dose (5 nodes, 2 studies). In total, 8254, 8241 and 8279 infants were included in the analysis for seroconversion against serotype 1, 2 and 3, respectively.

<u>Serotype 2</u>

The pooled proportion of individuals that seroconverted ranged from 13% to 100% between different vaccine schedules.

In the NMA, the criteria for adequate model fit was satisfied with no significant inconsistency between any direct and indirect estimates ($P < 0{\cdot}05$ for all comparisons) and low between-trial heterogeneity ($\tau = 0{\cdot}05$ [95% CrI: 0·009, 0·15]) (Web Appendix 4-5).

All vaccine schedules achieved higher seroconversion RR against serotype 2 than bOPV alone (Figure 3a). Compared with the standard three tOPV doses, three bOPV doses had a seroconversion RR of 0·14 [95% CrI: 0·11, 0·17]. The addition of one or two doses of IPV to a 3 dose bOPV schedule at age 18 and 36 weeks, increased the seroconversion RR to 0·85 [95% CrI: 0·75, 1·0] and 1·1 [95% CrI: 0·98, 1·4], respectively. A pairwise analysis of studies that directly compared seroconversion from three bOPV + two IPV to three bOPV + one IPV gave a pooled RR of 1·25 [95% CrI: 1·07, 1·47] (Web Appendix 7).

Combined bOPV-IPV schedules where IPV administration preceded bOPV, had a lower RR than where IPV succeeded bOPV . The seroconversion RR of one IPV + two bOPV and two IPV + one bOPV were 0·62 [95% CrI: 0·50, 0·71] and 0·80 [95% CrI: 0·68, 0·91], respectively, compared to tOPV (Figure 3a).

IPV-only schedules were compared for both two and three doses, with a table of the relative effects shown in Web Appendix 6. There was no significant difference between the seroconversion achieved by two doses of Salk IPV or ID fIPV (RR 0·88 [95%CrI: 0·74, 1·02]). Adding a third dose to the schedule gave no significant increase: the RR was 0.96 [95% CrI: 0·81, 1·15] and 1·01 [95% CrI: 0·85, 1·20] for two versus three doses of Salk IPV and ID fIPV, respectively. Additionally, there was no significant difference between three doses of any alternative IPV formulation with Salk IPV: fIPV (0.92 [95% CrI: 0·83, 1·0]), sIPV (1·01 [95% CrI: 0·93, 1·10]) or IPV-Al (0·96 [95% CrI: 0·83, 1·11]) .

For schedules including a birth dose from the full network analysis, the addition of one or two doses of IPV following a four dose bOPV-only schedule increased seroconversion (Figure 3b). The RR increased from 0·21 [95% CrI:0·13, 0·32] to 0·63 [95% CrI:0·42, 0.93] and 0·99 [95% CrI:0·59, 1·7], for bOPV only, bOPV + one IPV and bOPV + two IPV, respectively, compared to four doses of tOPV.

<u>Serotype 1 and 3</u>

For serotypes 1 and 3, the network meta-analysis had substantial inconsistency between direct and indirect effects (for 1 and 6 comparisons, respectively) and high between-trial heterogenicity τ= 0·23 [95% CrI: 0·11, 0·34]) and τ= 0·17 [95% CrI: 0·10, 0·32], respectively (Web Appendix 4-5). Therefore, we present the results of the individual trial data and pooled estimates only: all vaccine schedules had pooled estimates for seroconversion ≥ 80% for serotype 1 and ≥ 88% for serotype 3 (Figure 4a and 4b). For both serotypes, 3 doses of bOPV alone gave high seroconversion: 0·98 [95% CrI: 0·96, 0·99] and 0·96 [95% CrI: 0·92, 0·98] for serotype 1 and 3, respectively. In addition, there was no significant difference between 3 doses of IPV, fIPV, sIPV or IPV-Al, or between 2 doses of IPV and fIPV (Figure 4A and 4B).

Intestinal mucosal Immunity

There were 15 unique vaccination schedules identified for intestinal immunity against serotype 2. The single-proportion meta-analysis of the 15 schedules is shown in Web Appendix 8. The average proportion of individuals who developed intestinal immunity was 0·91 [95% CI: 0·70, 0·98] following three tOPV doses; 0·30 [95% CI: 0·17; 0·48] following three bOPV doses; 0·25 [95% CI: 0·22, 0·29] following three bOPV + one IPV dose; and 0·28 [95% CI: 0·22,0·29] following three bOPV + two IPV doses. Heterogeneity was high between studies, and was statistically significant for schedules of three tOPV doses, three bOPV doses and four bOPV + one IPV dose ($p < 0·01$).

Only four RI schedules had data from multiple studies: 3 tOPV, 3 bOPV, 3 bOPV + IPV and 3 bOPV + 2IPV. Therefore, a smaller network was generated out of these nodes, which was directed at a programmatic question of the added benefit of IPV to intestinal immunity (Figure 5A). Intestinal immunity was significantly lower for all schedules than 3 doses of tOPV (Figure 5B). Following 3 doses of bOPV, the RR was 0·33 (95% CrI: 0·18, 0·61) compared to tOPV. This did not increase through the addition of one or two doses of IPV: RR 0·33 (95% CrI: 0·18, 0·63) and 0·35 (95% CrI: 0·19, 0·65), respectively.

2.6 Discussion

We report the first application of NMA to assess the immunogenicity of vaccine schedules against poliomyelitis and provide a single, comprehensive analysis of polio RI schedules for humoral and intestinal outcomes. We found that for humoral immunity: (1) The addition of one dose of IPV to bOPV schedules reduces the immunity gap against serotype type 2; (2)

There is no difference in relative immunogenicity of IPV variants (Salk IPV, sIPV, ID fIPV, IPV-Al); (3) The order (timing) of the IPV dose in bOPV-IPV schedules is associated with immunogenicity. Potentially the most important finding of this study is for mucosal immunity: as there is no evidence of (4) increased intestinal immunity against serotype 2 associated with an addition of IPV to a bOPV-only schedule.

The clinical trials conducted thus far have provided valuable information to inform policy, but are limited by specific head-to-head schedule-comparisons, small sample sizes and generation of country-specific data. Previously published literature reviews and meta-analysis have been targeted at specific questions: Hird *et al* investigated mucosal immunity induced by OPV vs IPV in 2012;(18) Grassly *et al* investigated the humoral immunity of one versus two doses of IPV in 2014;(19) and Anand *et al* reviewed the immunogenicity of two doses of fIPV in 2017.(20) More recently, a review and meta-analysis have been conducted to compare the immunogenicity of bOPV-IPV mixed schedules and IPV alone.(21, 22) In agreement with our results, Tang *et al* found no significant difference between IPV only and IPV-OPV in seroconversion against serotype 1 and 3.(22) However, the meta-analysis only included six trials, two different schedule groups – IPV only and IPV/OPV mixed schedule – and provided no data on mucosal immunity. Therefore, our analysis goes beyond what has been previously conducted.

After the switch from tOPV to bOPV, SAGE recommended the introduction of at least one dose of IPV at age ≥14 weeks to provide an immunity base to type 2 poliovirus. As expected, our results confirmed that individuals vaccinated with bOPV-only schedules have negligible immunity against poliovirus 2 (likely from passive type 2 exposure or antibody cross-neutralisation from type 1 and 3).This highlights that the estimated 43 million children across 33 countries that did not recieve IPV, due to supply shortages, have no protection(23). Notably, the addition of a single dose of IPV (at 14 weeks), closed much of the humoral immunity gap against serotype 2, whilst a second dose (at 18 or 36 weeks) had a smaller impact, and a single mIPV2 dose provided equivalent immunogenicity to two doses of trivalent IPV. Our results also highlight that the order and timing of the IPV dose in mixed schedules is important, with a reduced immunogenicity against type 2 where IPV preceded bOPV. This is likely due to an earlier age of administration for IPV and the influence of maternal antibodies. (24)

Of note, the addition of IPV has negligable impact on the development of intestinal immunity against serotype 2. Whilst the ability of IPV to induce humoral immunity is undisputed, IPV has a more complicated role in mucosal immunity. It is established that IPV-only schedules provide inadequate intestinal immunity and do not prevent shedding following a challenge dose, whilst the quantity and duration of virus shedding may be reduced.(25, 26) However, IPV has been shown to significantly boost mucosal protection in OPV-primed individuals. Our results provide evidence that the prime-boost model established for IPV works in a serotype-specific manner with limited evidence for heterotypic intestinal mucosal immunity. Our findings have several limitations. Consistency is a fundamental assumption of network meta-analysis, which was not met for serotypes 1 and 3, where heterogenicity and inconsistency persisted through sub-group and regression analysis (Web Appendix 4-5). The geographical-variation in the type, schedule and immunogenicity of poliovirus vaccines has been established. The studies in this analysis were carried out in Eastern-Mediterranean and Latin America countries with a primary vaccine schedule where the first (non-birth) dose is administered between 4 and 8 weeks; therefore, our results are useful for policy makers in these settings.(3) The geographical and age-schedule variation in absolute immunogenicity is incorporated as NMA models the relative effects between vaccines, which eliminates differences in baseline immunogenicity of comparator schedules.(27)

The most widely adopted measure of poliovirus mucosal immunity is through administration of a challenge dose of OPV and collection of subsequent stool samples. There are limitations with extrapolating intestinal immunity and transmission impact based on the absence of shedding seven days following a challenge dose, which does not capture the duration of shedding, quanitity of virus shed or nasopharengeal immunity and have been discussed elsewhere(18, 25). However, this is the best proxy for intestinal immunity to poliovirus available from clinical trial data. Finally, our analysis only provides estimates on protection within the timescale of the trials.

There are research gaps highlighted in the modelled networks, particularly the evaluation of mucosal immunity in more studies. A schedule of 3 bOPV doses followed by fIPV has not been included in randomised control trials, yet this has been adopted in India and Sri-Lanka(6). Future research is needed to compare IPV-only vaccine schedules in a post-eradication setting and address the need for development a more genetically stable live vaccine. Currently in clinical trials is a novel oral poliovirus vaccine, a live attenuated

vaccine with a lower risk of reversion than the standard OPV, and IPV + dmLT adjuvant, for dose sparing and induction of mucosal immunity .(6, 28, 29)

The findings of this comprehensive analysis demonstrate that NMA is effective to evaluate multi-arm vaccination studies. Our results support with policy recommendations from the SAGE for the addition of IPV into RI and the adoption of affordable IPV approaches. We demonstrate a single dose of IPV reduces most of the humoral immunity gap against type 2 and suggest that in times of IPV supply constraints, equitable distribution of a single dose of IPV should be prioritised over cohorts receiving a second dose, taking into account country risk. However, we highlight that this IPV addition will be unlikely to prevent faecal-oral transmission of the virus, but provide individual protection against paralytic disease.

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2.8 Figures and Tables

Figure 1: Systematic review profile

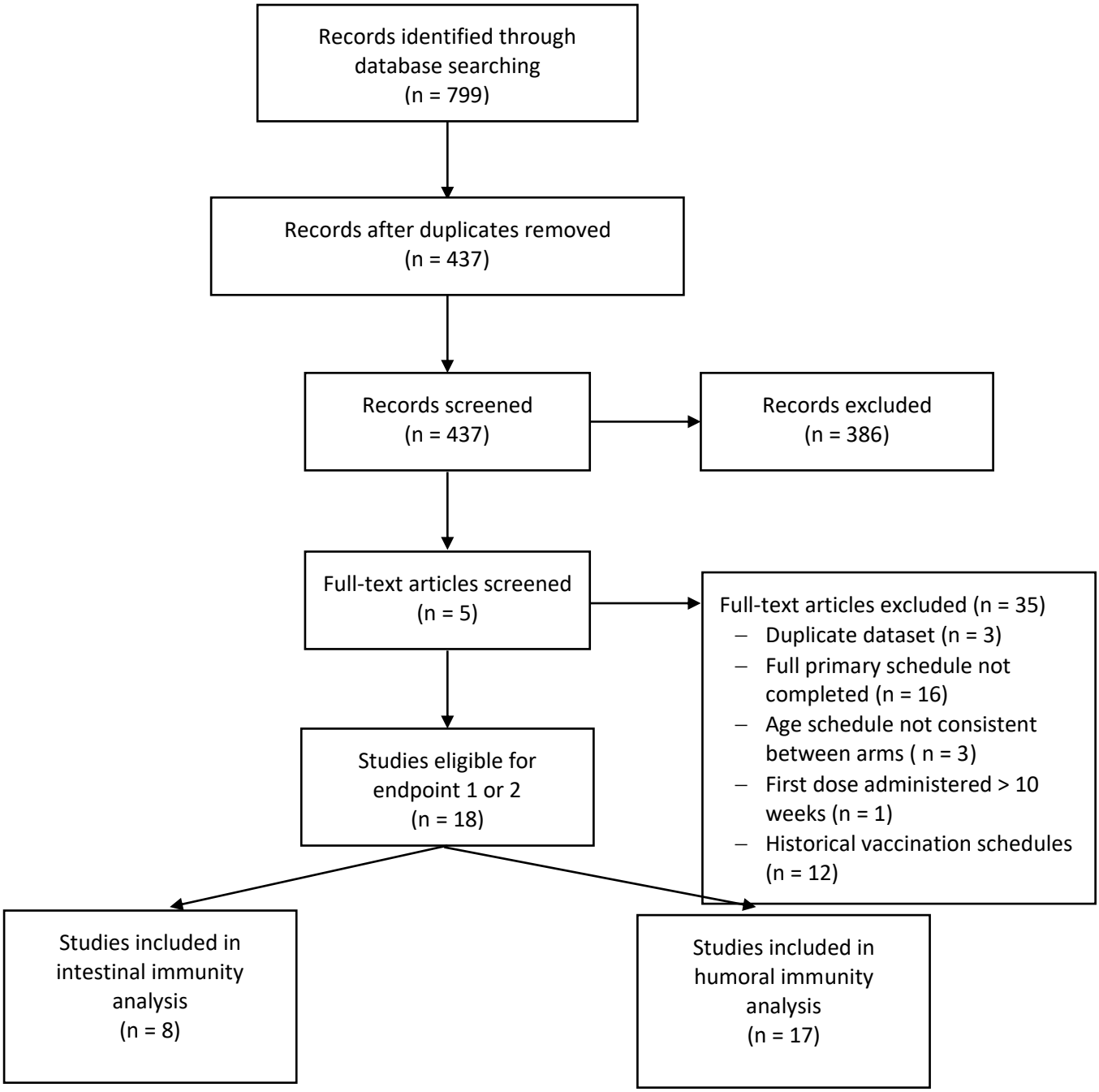
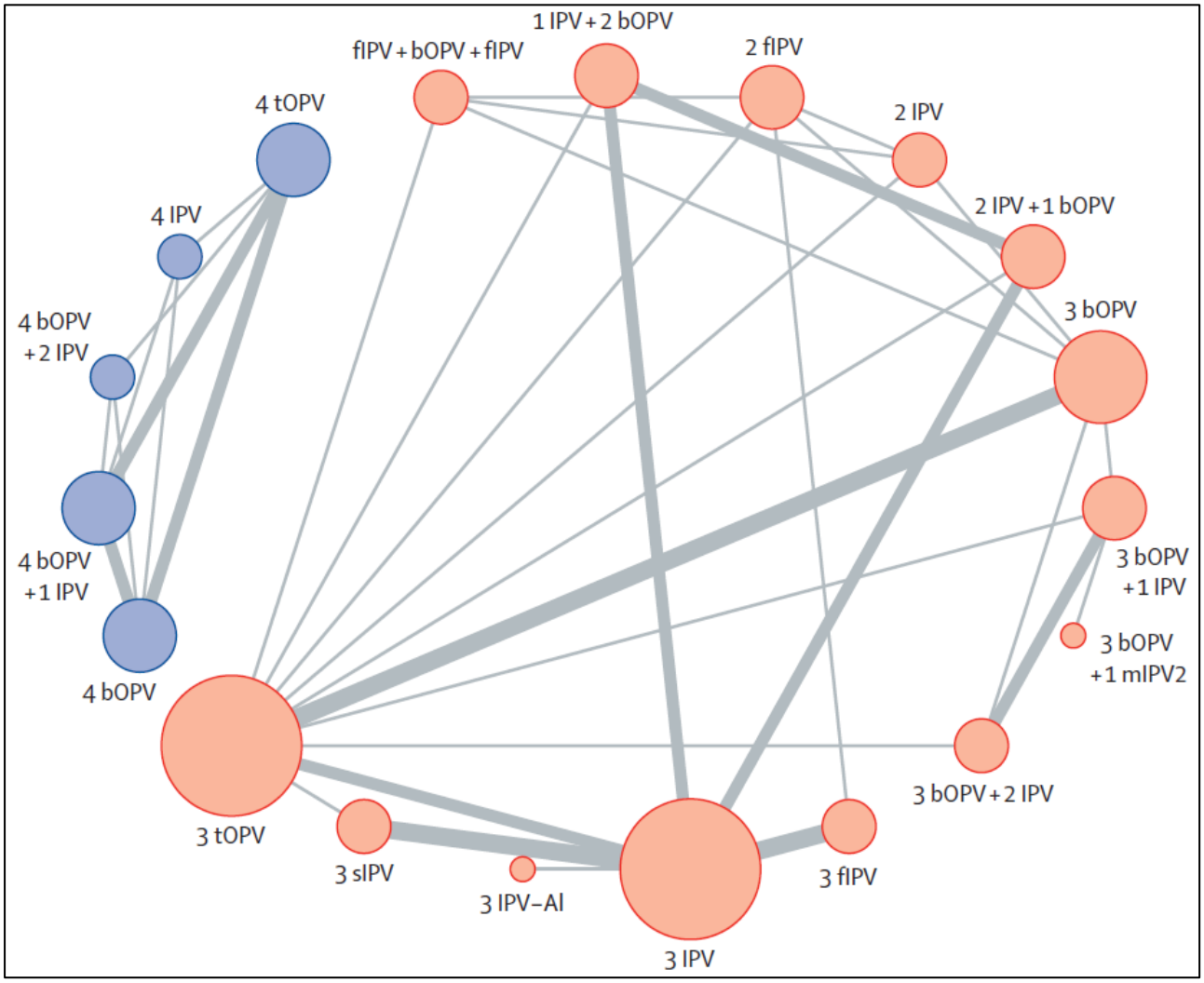


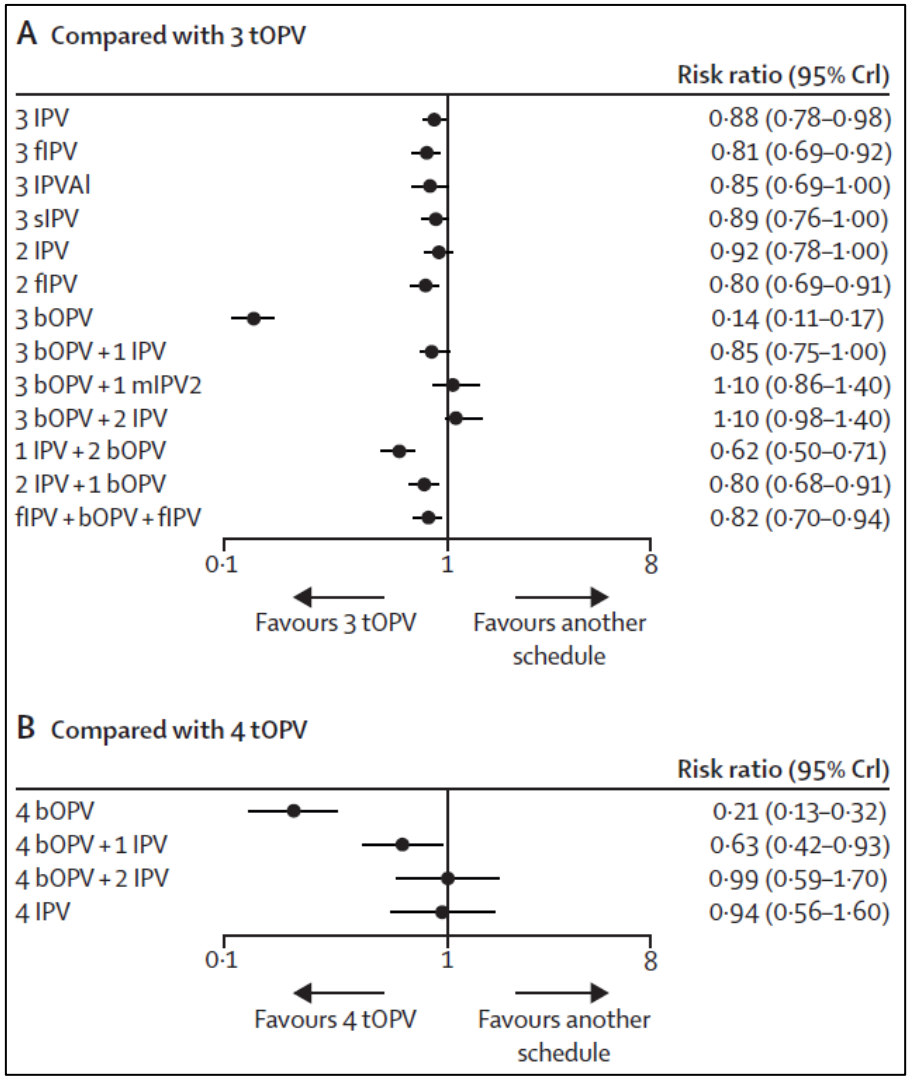
Figure 2: Networks of eligible comparisons for vaccination schedules inducing humoral immunity against poliovirus serotypes 1, 2, and 3.

Each node represents a vaccine schedule and the lines are direct comparisons. The width of the lines is proportional to the number of trials compared and the node size is proportional to the number of trials that include that schedule. Blue schedules include a birth dose and orange schedules do not.



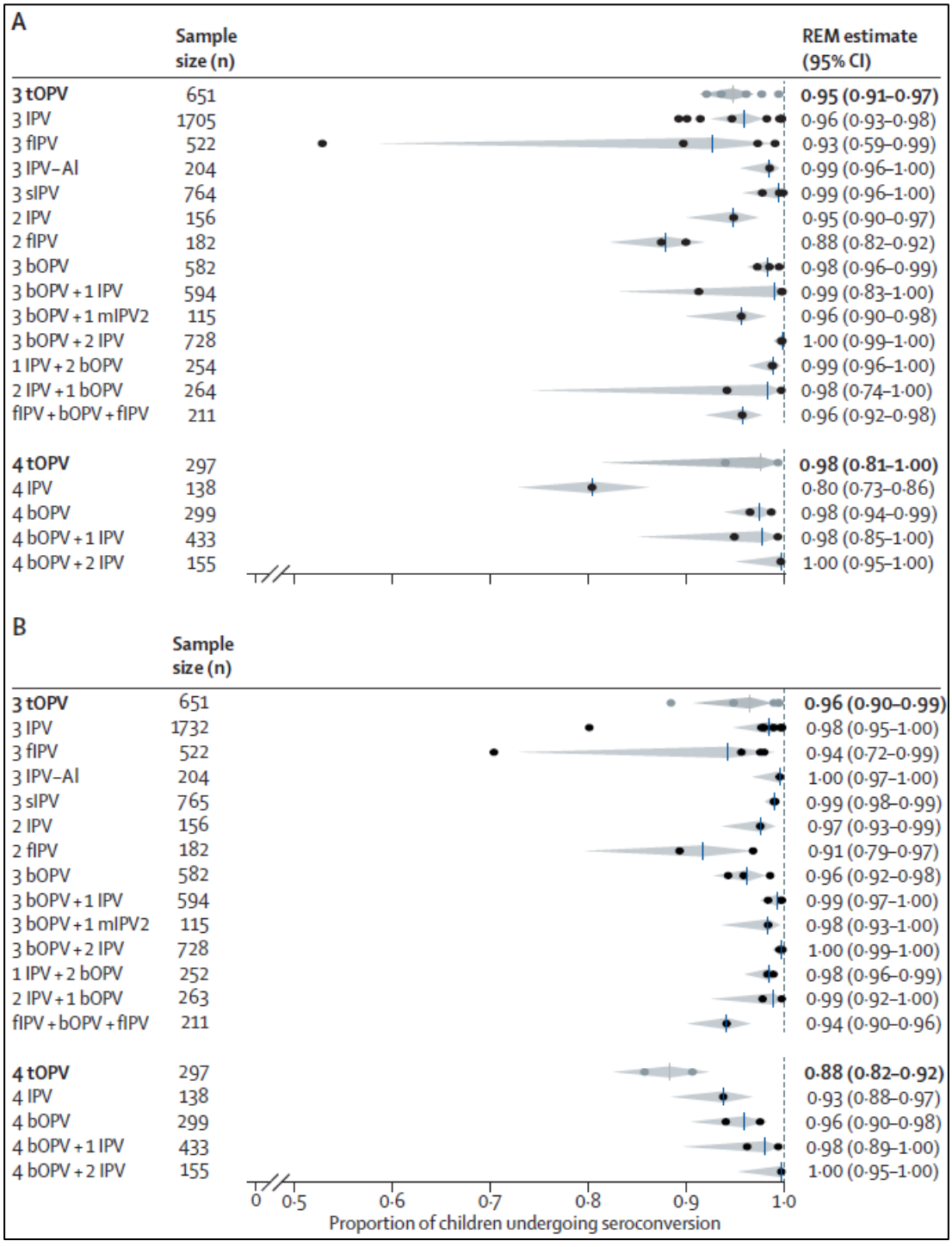
Abbreviations: bOPV=bivalent oral poliovirus vaccine. fIPV=fractional inactivated poliovirus vaccine. IPV=conventional inactivated poliovirus vaccine. IPV-Al=aluminium hydroxide adjuvanted inactivated poliovirus vaccine. mIPV2=monovalent serotype 2 high-dose inactivated poliovirus vaccine. sIPV=Sabin inactivated poliovirus vaccine. tOPV=trivalent oral poliovirus vaccine.

Figure 3: Relative immunogenicity of vaccine schedules for seroconversion against poliovirus serotype 2 schedules with no birth dose and schedules with a birth dose. Between-trial heterogeneity for (A) schedules without a birth dose (τ=0·05, 95% CrI 0·009–0·15) and (B) those with a birth dose (0·23, 0·026–1·31).



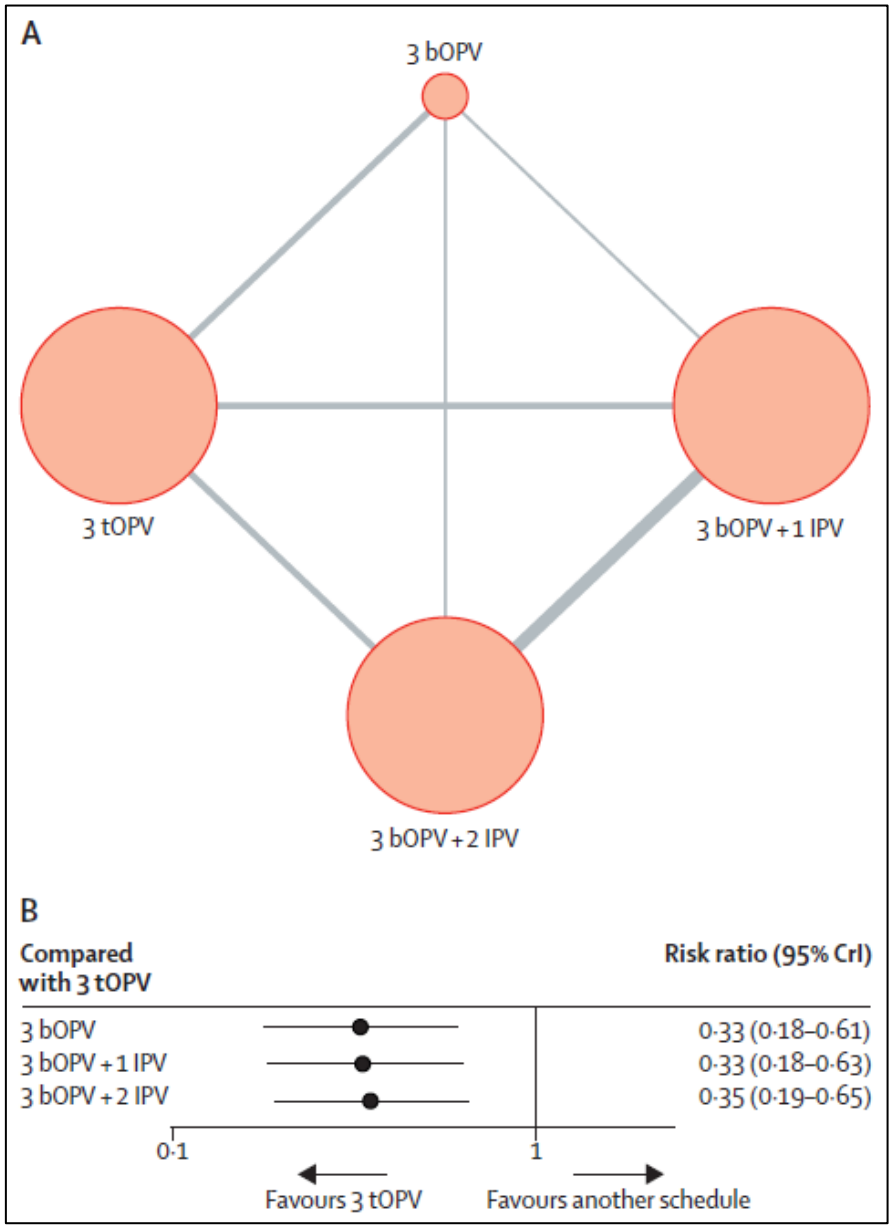
Abbreviations: bOPV=bivalent oral poliovirus vaccine. CrI=credible interval. fIPV=fractional inactivated poliovirus vaccine administered intradermally (one-fifth dose of IPV). IPV=conventional inactivated poliovirus vaccine. IPV-Al=aluminium hydroxide adjuvanted inactivated poliovirus vaccine (one-tenth reduced dose of IPV). mIPV2=monovalent serotype 2 high-dose inactivated poliovirus vaccine. sIPV=Sabin inactivated poliovirus vaccine. tOPV=trivalent oral poliovirus vaccine.

Figure 4: Random-effect single-proportion meta-analysis estimate of the proportion of children undergoing seroconversion against serotypes 1 (A) and 3 (B). Overall REM estimates and heterogeneity were 0·97 (95% CrI 0·96–0·98) and τ^2=1·66 for serotype 1 and 0·97 (0·96–0·98) and τ-squared=1·38 for serotype 3. Individual studies are shown as dots, with the overall estimated proportion as a vertical line through each dot and 95% CrI as shading.



Abbreviations: bOPV=bivalent oral poliovirus vaccine. CrI=credible interval. fIPV=fractional inactivated poliovirus vaccine administered intradermally (one-fifth dose of IPV). IPV=conventional inactivated poliovirus vaccine. IPV-Al=Aluminium hydroxide adjuvanted inactivated poliovirus vaccine (one-tenth reduced dose of IPV). mIPV2=monovalent serotype 2 high-dose inactivated poliovirus vaccine. REM=random effect model. sIPV=Sabin inactivated poliovirus vaccine. tOPV=trivalent oral poliovirus vaccine

Figure 5: Network meta-analysis of routine immunisation schedules for intestinal immunity against serotype 2. (A) Network plot. Each node represents a vaccine schedule and the lines are direct comparisons. The width of the lines is proportional to the number of trials compared and the node size is proportional to the number of trials that include that schedule. (B) Relative risk of absence of shedding vaccine-derived poliovirus after challenge, compared with three tOPV doses. Data are risk ratio (95% CrI).



Abbreviations: bOPV=bivalent oral poliovirus vaccine. CrI=credible interval. IPV=conventional inactivated poliovirus vaccine. tOPV=trivalent oral poliovirus vaccine.

Table 1*:* Vaccine schedules by approximate age of administration included for each node of the network meta-analysis for humoral immunity.

Vaccine schedule	Age of administration
IPV + 2 bOPV	8, 12, 16 or 8, 16, 24
2 fIPV*	6, 14
2 IPV	6, 14
2 IPV + bOPV	8, 12, 16 or 8, 16, 24
3 bOPV	6, 10, 14
3 bOPV + IPV	6, 10, 14, 14
3 bOPV + mIPV2†	6, 10, 14, 14
3 bOPV + 2 IPV	6, 10, 14, 14, 36
3 fIPV*	6, 10, 14 or 8, 16, 24
3 IPV	6, 10, 14; 8, 12, 16; or 8, 16, 24
3 IPV-Al‡	6, 10, 14
3 sIPV§	8, 12, 16
3 tOPV	6, 10, 14 or 8, 12, 16
4 bOPV	Birth, 6, 10, 14
4 bOPV + IPV	Birth, 6, 10, 14, 14
4 bOPV + 2 IPV	Birth, 6, 10, 14, 18
4 IPV	Birth, 6, 10, 14
4 tOPV	Birth, 4, 8, 12 or birth, 6, 10, 14
fIPV* + bOPV + fIPV*	6, 10, 14

Abbreviations: bOPV=bivalent oral poliovirus vaccine. fIPV=fractional inactivated poliovirus vaccine. IPV=conventional inactivated poliovirus vaccine. IPV-Al=aluminium hydroxide adjuvanted inactivated poliovirus vaccine. mIPV2=monovalent serotype 2 high-dose inactivated poliovirus vaccine. sIPV=Sabin inactivated poliovirus vaccine. tOPV=trivalent oral poliovirus vaccine. *One-fifth full IPV dose administered intradermally. †32 D-antigen content for serotype 2 administered intramuscularly.‡One-tenth full IPV dose administered intramuscularly. §30, 32, and 45 D-antigen content for serotype 1, 2, and 3, respectively, administered intramuscularly.

Chapter 3: Epidemiology of type 2 vaccine-derived poliovirus

Chapter 3 is made up of two publications, both applying the same methodology to analyze the epidemiology of cVDPV2 outbreaks, over different time-periods. The initial publication – Chapter 3.1. – was followed up by a sequential publication – chapter 3.2 – two years later.

Chapter 3.1: Evolving epidemiology of poliovirus serotype 2 following withdrawal of the serotype 2 oral poliovirus vaccine

3.1.1 Chapter publication status

This chapter has been published in Science with the following full bibliographic information: Macklin GR, O'Reilly KM, Grassly NC, Edmunds WJ, Mach O, Santhana Gopala Krishnan R, Voorman A, Vertefeuille JF, Abdelwahab J, Gumede N, Goel A. Evolving epidemiology of poliovirus serotype 2 following withdrawal of the serotype 2 oral poliovirus vaccine. Science. 2020 Apr 24;368(6489):401-5.

I was the lead author in this publication and made the following author contributions according to the CRediT checklist: Conceptualization, Methodology, Visualization, Formal analysis, Writing – original draft. The formatting of this chapter has been slightly adjusted due to the non-standard layout of the publications in Science.

A research paper cover letter for this chapter is found in the Appendix.

3.1.2 Abstract

While there have been no cases of type-2 wild poliovirus for over 20 years, transmission of type-2 vaccine-derived poliovirus (VDPV2) and associated paralytic cases in several continents represent a threat to eradication. The withdrawal of the type-2 component of oral poliovirus vaccine (OPV2) was implemented in April 2016 to stop VDPV2 emergence and secure eradication of all poliovirus type 2. Globally, children born after this date have limited immunity to prevent transmission. Using a statistical model, we estimate the emergence date and source of VDPV2s detected between May 2016 and November 2019. Outbreak response campaigns with monovalent OPV2 are the only available method to induce immunity to prevent transmission. Yet, our analysis shows that using monovalent OPV2 is generating more paralytic VDPV2 outbreaks with the potential for establishing endemic transmission. The novel OPV2 is urgently required, alongside a contingency strategy if this vaccine does not materialize or perform as anticipated.

3.1.3 Introduction

Ever since the oral poliovirus vaccine (OPV) was first identified in 2000 as the source of a paralytic poliomyelitis outbreak, vaccine-derived polioviruses (VDPV) have been a known obstacle to achieving polio eradication (1, 2). Despite the global withdrawal of the serotype 2 component of OPV (OPV2), paralytic poliomyelitis cases associated with serotype 2 VDPV (VDPV2) have been reported in expanding global geographies. This is important as there is now a global cohort of children without immunity against serotype 2 that would prevent transmission, which could result in established endemicity of the virus. The inactivated poliovirus vaccine (IPV) can protect against paralysis but provides limited intestinal immunity to stop transmission (3). Therefore, the method to control VDPV2 transmission is through vaccination campaigns with the monovalent OPV2 (mOPV2) (4). However, any use of mOPV2 carries the risk of seeding more VDPV2 (5).

After the eradication of the serotype 2 wild poliovirus (WPV), vaccination continued with OPV2 as part of the trivalent vaccine (tOPV, containing serotypes 1, 2 and 3) (Figure S1), resulting in periodic outbreaks of VDPV2 (as well as VDPV1 and VDPV3) and cases of vaccine-associated paralytic poliomyelitis (VAPP) (6). This is because the attenuated virus strains contained in OPV can mutate and re-acquire factors associated with causing paralytic disease and transmission (7). Populations with low immunization coverage are particularly at risk of spread (7). Once the eradication of the serotype 2 WPV was certified, it was decided to withdraw the OPV2 to prevent paralysis caused by type 2 poliovirus (Figure S1) (6). In April 2016, the Global Polio Eradication Initiative (GPEI) coordinated a globally synchronized switch from tOPV to bivalent OPV (bOPV, containing Sabin 1 and 3) in all routine and supplemental immunization activities, commonly referred to as ‘the Switch’, (Figure S1) (8). As a risk mitigation strategy, countries began to introduce a dose of inactivated poliovirus vaccine (IPV) into routine immunization schedules to protect against paralysis from type 2 poliovirus (9). However, an estimated 143 million children have not received IPV since April 2016 due to supply shortages (43 million) and poor routine immunization coverage (100 million) (10).

It was predicted that after the Switch, circulation of type 2 polioviruses would steadily disappear. Some VDPV2 outbreaks were expected, largely from prior widespread tOPV use in immunization campaigns (approximately 1.5 billion doses in the 12 months before the

Switch) (11, 12). The response to any outbreaks was to conduct campaigns with mOPV2, from a finite global stockpile of vaccine (4). While the virus disappeared from most geographies, eradication did not occur (13). More recently, outbreaks of VDPV2 have been increasing in frequency and geographic spread (Figure 1). At present, WHO classifies circulating VDPV2 (cVDPV2) outbreaks as Public Health Emergencies of International Concern (14). Here we investigate the epidemiology and source of VDPV2 outbreaks through a retrospective analysis of poliovirus surveillance and mOPV2 campaign data between 01 May 2016 and 01 November 2019.

3.1.4. Methods

We obtained data on virus isolates from acute flaccid paralysis (AFP) cases and environmental samples through the surveillance network of the Global Polio Laboratory Network (GPLN) on 1 November 2019. We estimated the date of seeding interval (i.e., 95% confidence intervals for the date that the infectious OPV dose was administered) on the basis of the date of detection and the number of nucleotides divergent from the OPV2 virus in the viral protein 1 (VP1) gene. We assumed that the first VP1 mutation is instantaneous and that each subsequent mutation follows an average rate, previously estimated at $1.14 \times 10–2$ nucleotides per site per year, that corresponds to one nucleotide change observed after approximately 35 days (15). The time to each independent mutation was modeled using an exponential distribution, and the sum of waiting times as an Erlang distribution. A detailed description of data and statistical analysis methods are provided in supplementary materials.

3.1.5. Results

Global VDPV2 detections and source

Between 01 May 2016 and 01 November 2019, the GPLN had detected 859 isolates of VDPV2 across 26 countries, including 325 cases of AFP (Figure 1). The AFP cases had a median age of 1.75 years (range 0.2-12 years) and 27.0% of cases reported receiving no previous polio vaccine doses.

We calculate that 65.5% (548/837) of sequenced VDPV2 viruses detected since April 2016 have a ≥ 90% probability of being seeded after the Switch (Figure 2A). For isolates with a ≥90% probability of being seeded after the Switch, we identified whether a mOPV2 campaign was conducted within the same geographic region during the estimated seeding

interval. We demonstrate that the source of 71.5% (392/548) of these isolates are consistent with mOPV2 outbreak response campaigns conducted within the country of emergence and 24.6% (135/548) consistent with mOPV2 campaigns conducted within a neighboring country (Figure 2B).

Circulating VDPV2 (cVDPV2) outbreaks

VDPV emergences are classified as cVDPV2, when there is evidence of person-to-person transmission (isolates are genetically linked to a previously detected isolate) or ambiguous VDPV (aVDPV) events, when there is no evidence of transmission and after ruling out primary immunodeficiency in infected individuals (16, 17).

Since the Switch, we identify 62 aVDPV2 events and 41 independent cVDPV2 outbreaks (Figure 3 and Table S1). The 41 cVDPV2 outbreaks emerged in Angola (n = 7), Central African Republic (CAR) (n = 6), China (n = 1), DRC (n = 10), Mozambique (n = 1), Nigeria (n = 9), Pakistan (n = 3), Philippines (n = 1), Somalia (n = 1), Syrian Arab Republic (Syria) (n = 1) and Zambia (n = 1). International spread of cVDPV2s has led to transmission in Benin, Cameroon, Chad, Côte d'Ivoire, Ethiopia, Ghana, Kenya and Togo. The countries where these outbreaks occur are mainly characterized by suboptimal health systems with low routine immunization coverage, inaccessible/active conflict affected areas and low sanitation and hygiene (Table S1).

A total of 126 post-Switch mOPV2 campaigns have been conducted in response to these outbreaks, utilizing more than 300 million doses of the mOPV2 vaccine (Table S2), primarily in Nigeria (59%) and DRC (15%). These campaigns are consistent with seeding 27 of 41 outbreaks (Table S2).

Evolving situation over time

In the first year after the Switch (May 2016- April 2017), our analysis shows that there were six cVDPV2 outbreaks, seeded before (n = 5) or close to the time of the Switch (n = 1), likely through immunization with tOPV (Figure 3 and Table S1). This was consistent with the predictions made, including from mathematical modelling groups (11, 18). These outbreaks, which occurred in Nigeria (n = 2), DRC (n = 2), Pakistan (n = 1) and Syria (n = 1) were rapidly controlled through mOPV2 use (Table S1) mention (19).

Interestingly, we observe that no virus was detected later than 6 months following the Switch in the American, European and South-East Asian Regions of WHO: no cVDPV2 outbreaks occurred and the rare detection of aVDPV2 in the first 6 months in these regions was limited likely because of generally high pre-switch intestinal mucosal immunity, good sanitation standards and post-switch IPV use (13, 20).

In the second year after the Switch (May 2017 to April 2018), 5 more outbreaks emerged (Table S1). We calculate that 1/5 were seeded before and 4/5 were seeded after the Switch (Figure 2). In two of these outbreaks (SOM-BAN-1 and NIE-JIG-1 emergences), failure to control the virus has resulted in spread across national borders to establish transmission in neighboring countries: from Somalia to Kenya and Ethiopia, and from Nigeria to Niger, Cameroon, Ghana, Benin, Chad, Togo and Côte d'Ivoire (Table S1). These two outbreaks, which have not yet been controlled, are the longest in duration, with transmission detected for periods of 22 and 21 months, respectively (Table S1).

In the third and fourth years after the Switch (May 2018 to November 2019), it was expected (and planned) that there would be a substantial reduction in the number of outbreaks (18). However, we demonstrate the highest frequency of outbreaks has been in this period: 10 outbreaks emerged between May 2018 and April 2019, and 20 in the period from May 2019 to November 2019 alone. Our analysis shows that all except one of these emergences were seeded after the Switch (Figure 1).

There has been a shift in epidemiology observed over this period, characterized by the emergence of several cVDPV2s in 2019 with low nucleotide divergence in geographies without preceding mOPV2 use (Figure 3). There have been six cVDPV outbreaks in the Central African Republic and seven in Angola (Table S1), which are consistent with seeding from mOPV2 responses in the neighboring Democratic Republic of Congo. Additionally, two low divergence cVDPV2s have emerged in Pakistan, a country where mOPV2 had not been used in outbreak response for more than one year prior to the estimated seeding date (Table S1). On-going investigations are exploring hypotheses of outbreak source, including multiple international importations from mOPV2-using areas and inadvertent mOPV2/tOPV use. However, established transmission of cVDPV2 now exists in these populations and as such, the geographic scope of detections is expanding rapidly (Figure 2).

The detection of two highly divergent cVDPV2s in China and the Philippines in 2019 confirms transmission in the Western Pacific Region (Table S1). In the Philippines, the cVDPV2 was first detected in an AFP case in June 2019, with 64 nucleotides divergence from OPV2, suggesting the virus was seeded in 2014 (Figure 3). Subsequently, an individual with primary immunodeficiency was detected excreting virus genetically linked to the outbreak; however, the role of this case in the outbreak is not clear. It seems unlikely that the virus would circulate undetected for 5 years, although serotype 2 is thought to have approximately 2000 infections for every paralytic case, yet these examples emphasize the need for continuing high-quality surveillance and expanding environmental surveillance (21).

Using logistic regression, we demonstrate the probability that a new VDPV2 emergence (i) was seeded after the Switch, is increasing over time (regression coefficient = 1.99, $P < 0.001$, intercept = –1.66); and (ii) establishes person-to-person transmission, is increasing over time (regression coefficient = 0.88, $P < 0.001$, intercept = –2.27).

3.1.6 Discussion

At this juncture, we show that polio eradication is battling both the new emergences of cVDPV outbreaks seeded after the Switch— largely through mOPV2 use in response to outbreaks—and outbreaks seeded before the Switch that had delayed detection. In 2019, we have observed the largest numbers of outbreaks and countries experiencing cVDPV2 transmission to date. We conclude that the GPEI is in a paradoxical situation: On one hand, it is not currently possible to control the outbreaks without inducing intestinal mucosal immunity through mOPV2 use, but on the other hand, the use of mOPV2 is generating VDPV2. The risk of VDPV2 circulation is increasing over time as the immunity of the global population rapidly decreases (5).

Since the Switch more than 4 years ago, the epidemiology of serotype 2 poliovirus has developed in directions that were neither expected nor planned. This has policy implications for polio. Although the Switch has largely eliminated the incidence of serotype 2 VAPP and immunodeficiency-related VDPV cases, it has not achieved the major objective—that is, the eradication of the last serotype 2 polioviruses (those originating from the oral poliovirus vaccine) in all populations. The question remains as to what the GPEI should do next.

In 2010, the GPEI initiated the development of two candidates for serotype 2 novel oral poliovirus vaccine (nOPV2), which are currently completing phase II clinical trials (21). The nOPV2s are designed to provide intestinal immunity similar to that of the current OPV while being more genetically stable. Therefore, the major advantage of nOPV2 use in outbreak control would be a lower risk of seeding new VDPV2 (and cVDPV2 outbreaks). In 2020, there are efforts to rapidly accelerate the clinical development of one candidate for this vaccine and pursue World Health Organization regulatory approval though the Emergency Use Listing procedure (22).

A strategy for the response to cVDPV2s has been developed for 2020–2021. In the time before nOPV2 is available, the approach is to conduct enhanced outbreak response campaigns with the current mOPV2 to contain cVDPV2 spread. Capacity to conduct aggressive, rapid, and high-quality campaigns is essential: Persistent delays and pockets of low coverage will continually hinder the impact of outbreak responses with any vaccine, whether the nOPV2 or mOPV2. Strengthening routine administration of IPV and strategic vaccination with remaining available IPV doses (to ensure that missed children in areas at high risk are reached) will be used as a paralysis prevention method.

When the nOPV2 vaccine becomes available in sufficient quantities, it will be rolled out to eventually replace mOPV2 in outbreak response. In the situation that nOPV2 does not materialize or perform as anticipated, or incurs substantial delays, the GPEI would have to implement a contingency plan. The reintroduction of preventive vaccination with mOPV2 or tOPV, either through preventive campaigns or routine immunization, would have to be considered. However, this approach would require quantities of mOPV2 or tOPV doses that are currently not available.

It is critical that cVDPV2 outbreaks be managed as national public health emergencies in line with the declaration of a Public Health Emergency of International Concern by WHO (14). All GPEI partners, member state governments, and agencies must fully operationalize their emergency frameworks to prevent the reestablishment of endemic transmission of serotype 2 poliovirus in the form of cVDPV2. It remains clear that OPV removal is essential to stop all cases of paralytic poliomyelitis. However, the epidemiology that has evolved since OPV2 removal has implications for existing strategies outlined for total OPV cessation, which need urgent attention (23).

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3.1.8 Figures and Tables

Figure 1: Geographic location of vaccine-derived poliovirus type 2 isolates detected after the removal of type 2 oral poliovirus vaccine (OPV2), between 01 May 2016 and 01 November 2019. The color of points illustrates the date of isolate detection. Data as of 01 Novemeber 2019.

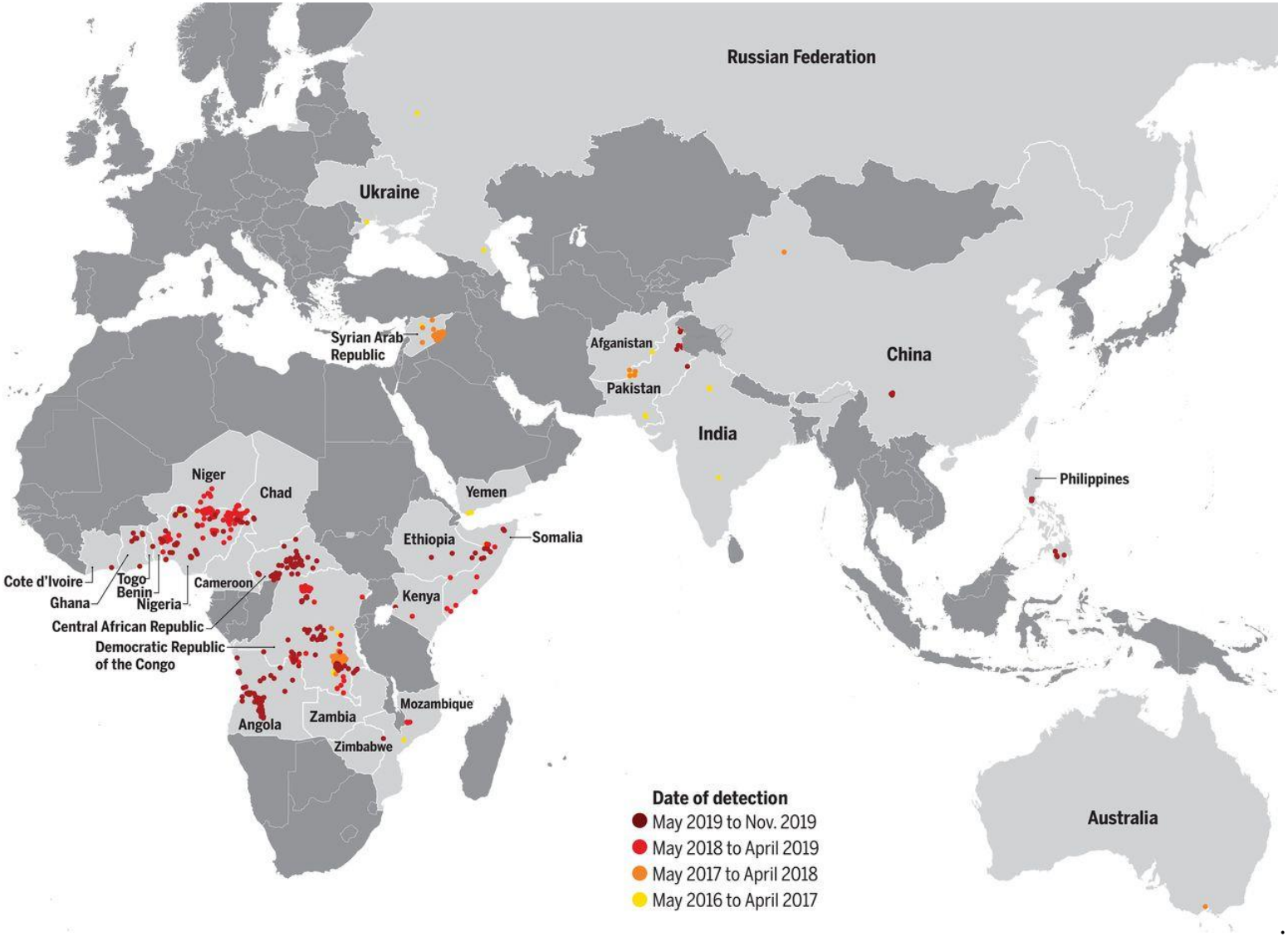


Figure 2: Incidence of detected vaccine-derived poliovirus type 2 isolates between 01 May 2016 and 01 November 2019. (A) The probability that isolate was seeded after the Switch (01 May 2016) was calculated based on the 95% CI of the estimated seeding date, estimated by the number of nucleotides divergence from the poliovirus vaccine strain, in the viral protein 1 gene of the position, assuming a model for the mutation rate (See supplementary materials). (B) For all isolates with >0.9 probability of post-switch seeding, the color demonstrates whether there was a corresponding mOPV2 campaign within estimated dates of seeding and the same or adjacent country.

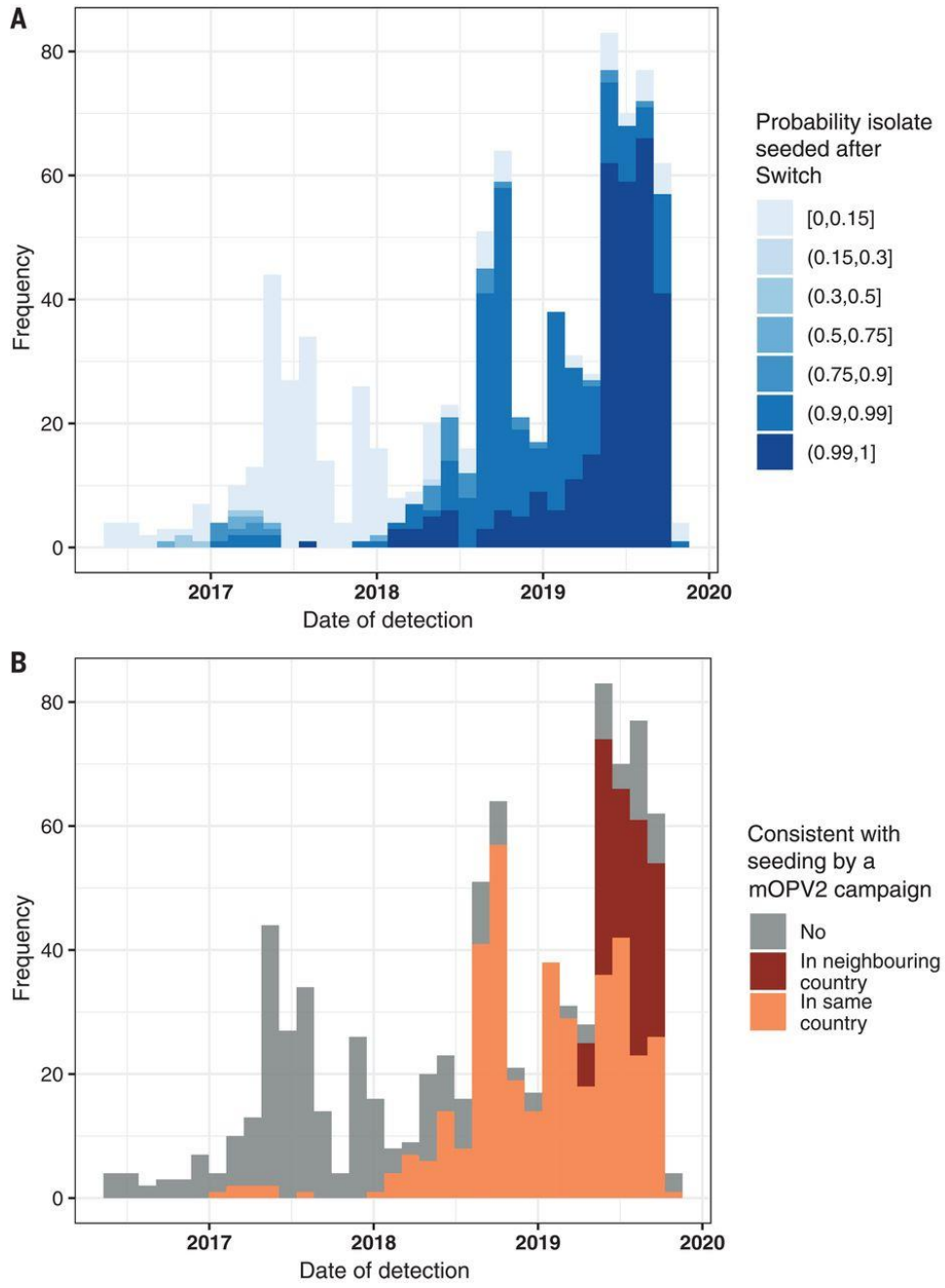
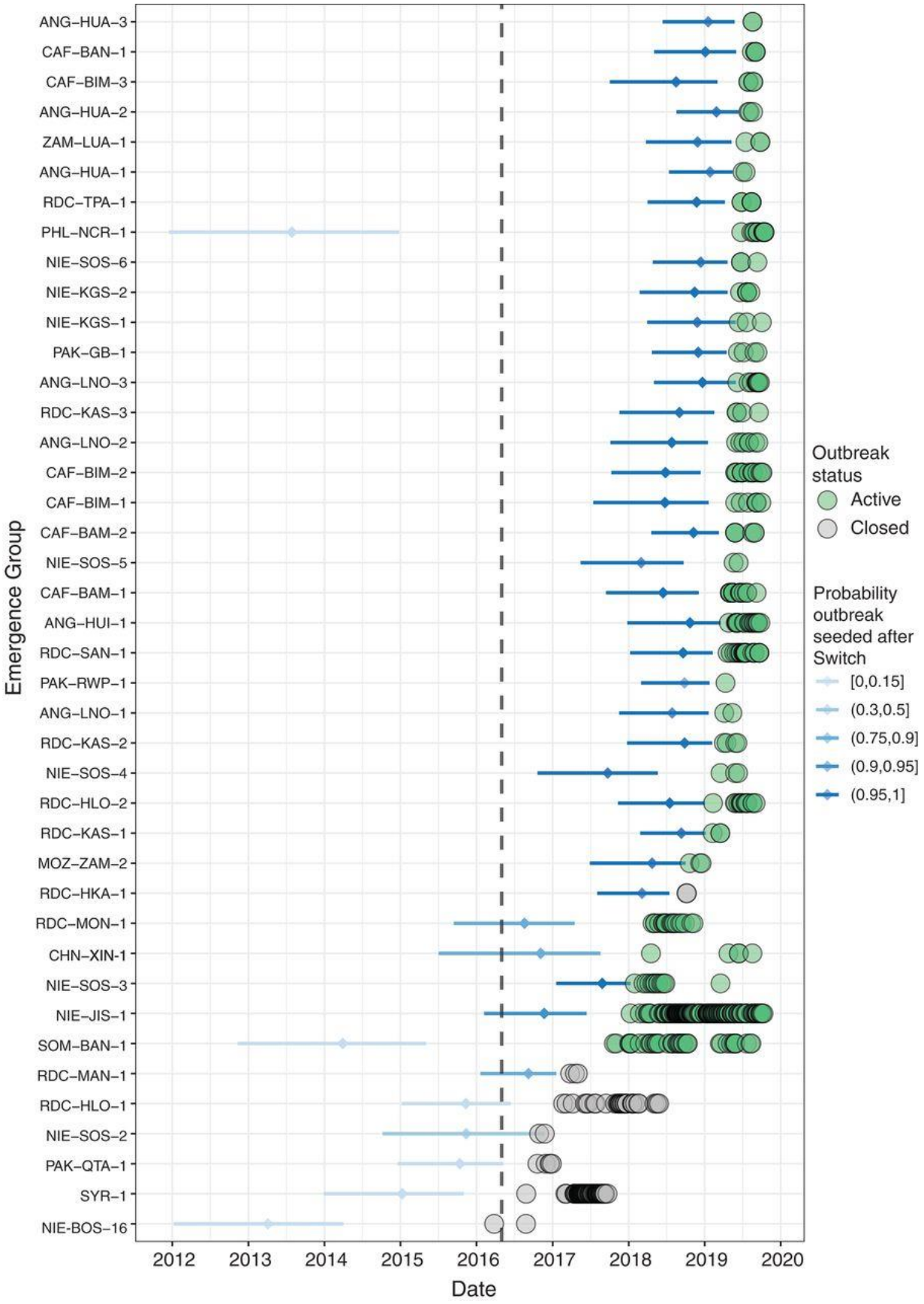


Figure 3: Timeline of circulating VDPV2 outbreaks reported between 01 May 2016 and 01 November 2019, ordered by the date of first isolate detection. The estimated seeding date (i.e., the date that infectious OPV dose was administered) and 95% confidence intervals are given by horizontal bars, colored by the probability that date of seeding was after the Switch on the 01 May 2016 (date of switch illustrated by a dashed black line). Detected virus isolates shown by colored circles, with the color indicating whether the outbreak is assumed active (detection within previous 12 months) or closed (no detection in previous 12 months). Data as of 01 November 2019. NIE-BOS-16: This outbreak was genetically linked to a cVDPV2 emergence originating in Chad in 2012.


ANG–HUA–3
CAF–BAN–1
CAF–BIM–3
ANG–HUA–2
ZAM–LUA–1
ANG–HUA–1
RDC–TPA–1
PHL–NCR–1
NIE–SOS–6
NIE–KGS–2
NIE–KGS–1
PAK–GB–1
ANG–LNO–3
RDC–KAS–3
ANG–LNO–2
CAF–BIM–2
CAF–BIM–1
CAF–BAM–2
NIE–SOS–5
CAF–BAM–1
ANG–HUI–1
RDC–SAN–1
PAK–RWP–1
ANG–LNO–1
RDC–KAS–2
NIE–SOS–4
RDC–HLO–2
RDC–KAS–1
MOZ–ZAM–2
RDC–HKA–1
RDC–MON–1
CHN–XIN–1
NIE–SOS–3
NIE–JIS–1
SOM–BAN–1
RDC–MAN–1
RDC–HLO–1
NIE–SOS–2
PAK–QTA–1
SYR–1
NIE-BOS–16
Emergence Group
2012
2013
2014
2015
2016
2017
2018
2019
2020
Date
Outbreak status
Active
Closed
Probability outbreak seeded after Switch
[0,0.15]
(0.3,0.5]
(0.75,0.9]
(0.9,0.95]
(0.95,1]

Chapter 3.2 Epidemiology of type 2 Vaccine-Derived Poliovirus Outbreaks between 2016 - 2021

3.2.1 Chapter publication status

This chapter has been accepted for publication in *Vaccine* as part of a special edition with the following full bibliographic information:

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A research paper cover letter for this chapter is found in the Appendix.

I was the lead author in this publication and made the following author contributions according to the CRediT checklist: Conceptualization, Methodology, Visualization, Formal analysis, Data Curation, Writing – original draft, Writing – review & editing.

3.2.2 Abstract

The number and geographic breadth of circulating vaccine-derived poliovirus type 2 (cVDPV2) outbreaks detected after the withdrawal of type 2 containing oral polio vaccine (April 2016) have exceeded forecasts. Using Acute Flaccid Paralysis (AFP) investigations and environmental surveillance (ES) data from the Global Polio Laboratory Network, we summarize the epidemiology of cVDPV2 outbreaks. Between 01 January 2016 to 31 December 2020, a total of 68 unique cVDPV2 genetic emergences were detected across 34 countries. The cVDPV2 outbreaks have been associated with 1596 acute flaccid paralysis cases across four World Health Organization regions: 962/1596 (60.3%) cases occurred in African Region; 619/1596 (38.8%) in the Eastern Mediterranean Region; 14/1596 (0.9%) in Western-Pacific Region; and 1/1596 (0.1%) in the European Region. As the majority of the cVDPV2 outbreaks have been seeded through monovalent type 2 oral poliovirus vaccine (mOPV2) use in outbreak responses, the introduction of the more stable novel oral poliovirus vaccine will be instrumental in stopping emergence of new cVDPV2 lineages.

3.2.3 Introduction

The Polio Eradication Endgame Strategic Plan 2013-2018 outlined a phased approach of oral polio vaccine (OPV) cessation, due to the risk of vaccine-associated paralytic poliomyelitis (VAPP) and reversion of OPV to vaccine-derived poliovirus (VDPV) (1). In April 2016, there was global removal of type 2 containing OPV and a synchronised switch from trivalent OPV (tOPV, containing types 1, 2 and 3) to bivalent OPV (bOPV, containing types 1 and 3) vaccine. As a risk mitigation strategy, the World Health Organization's (WHO) Strategic Advisory Group of Experts (SAGE) recommended that at least one dose of inactivated poliovirus vaccine (IPV) should be used in routine immunization in all countries to protect against paralysis from all poliovirus, including serotype 2 (2).

Prior to the switch, supplementary immunisation activities (SIAs) were conducted with tOPV vaccine to increase population immunity against serotype 2 (3) (4) (5). As OPV is the only currently available tool to prevent faecal-oral transmission of poliovirus, a global stockpile of monovalent OPV type 2 (mOPV2) was created for emergency use in response to cVDPV2 outbreaks (6). However, mOPV2 use retains a risk of generating new VDPV2 emergences, particularly in outbreak response areas with low quality campaigns (3) (7).

Due to the unprecedented nature of OPV2 withdrawal, there has been enhanced monitoring of the epidemiology of type 2 poliovirus isolates (5). Outbreaks reported within a year of OPV2 removal were associated with low routine immunization and population immunity, consistent with previously identified risks (5, 8, 9). Low coverage in mOPV2 outbreak response campaigns and the mixing of outbreak response target population and unvaccinated individuals from surrounding areas has resulted in persistence of Sabin 2-like virus transmission after outbreak response with mOPV2 and subsequent reversion of the Sabin-like virus into a neurovirulent VDPV2. Accordingly, an increasing number of new cVDPV2 outbreaks are attributable to mOPV2 use and geographical spread of established cVDPV2 emergences is rapidly increasing with declining population immunity. To supplement the data analyses presented on cases between 2016 and 2019 (10); five years after OPV2 cessation, this assessment of cVDPV2 epidemiology and outbreak origin is valuable for future management.

3.2.4 Methods

Data

The primary poliovirus surveillance sources of the Global Polio Eradication Initiative (GPEI) are cases of acute flaccid paralysis (AFP) targeted towards children aged <15 years. As part of the case investigations stool specimens are collected to determine poliovirus infection. As part of the Global Environmental Surveillance Expansion Plan (11), environmental surveillance (ES) has been established within more than 30 countries where wastewater samples are collected from high-risk areas/populations and tested for polioviruses. Additional surveillance activities include contact sampling and community sampling (6, 12). All collected samples are tested in Global Polio Laboratory Network (GPLN) laboratories per World Health Organization (WHO) protocols to isolate, differentiate and characterize polioviruses to identify WPV, Sabin-like (vaccine) poliovirus, and VDPV (13, 14). Data on poliovirus isolates and reported AFP cases are stored in the GPEI Polio Information System (PolIS) database

Polioviruses isolates are subsequently sequenced and classified by comparing the nucleotide sequence of the coding region for the 903 nucleotide viral capsid protein (VP1) with the corresponding vaccine strain: for serotype 2, Sabin-like virus have > 1 and < 6 nucleotides divergence; and VDPV2s have > 6 nucleotides divergence to Sabin 2 (13). VDPVs are further classified as 1) cVDPV, when evidence of person-to-person transmission in the community exists; 2) immunodeficiency-related VDPV (iVDPV), when they are isolated from persons with primary immunodeficiencies; and 3) ambiguous VDPV (aVDPV), when they are clinical isolates from persons with no known immunodeficiency and no evidence of transmission, or they are sewage isolates that are unrelated to other known VDPVs and whose source is unknown (15). cVDPV2s are further classified into genetic emergence groups defined as viruses sharing four or more nucleotide mutations in VP1, compared to Sabin 2.

Data on poliovirus isolates with date of sample collection or onset of paralysis between 01 January 2016 and 31 December 2020 were exported from the GPEI PolIS database. Data is as of 27 July 2021. In this paper, we classify an outbreak by country and genetic emergence group: a

new cVDPV2 outbreak is either a new genetic emergence or detection of an existing emergence group in a new geographical location (country).

Statistical analysis

The date of seeding of VDPV2 is defined as the date that the infectious OPV2 dose was administered which subsequently evolved into cVDPV2. The date of seeding for each isolate was estimated with 95% confidence interval by back-calculating from the date of sample collection (either AFP case or ENV), based on the number of nucleotide differences in the VP1 coding sequence from the Sabin 2 strain and VP1 mutation rates of approximately 1% per year as described in previous chapter (10).

For case-control analysis to estimate the effectiveness of IPV, controls were selected from AFP cases that had no poliovirus detected in stool samples (non-polio AFP case) from the same period of time. Controls were matched to cases on the year of AFP onset, age of child (to closest full year) and location at the Admin 1 level (subnational: province/state).

3.2.5 Results

A total of 2973 cVDPV2 isolates have been detected between 01 January 2016 and 31 December 2020. These isolates have been detected from multiple surveillance sources: 54% (1596/2973) were through AFP surveillance, 27% (789/2973) through environmental surveillance, and the remaining 19% through stool sampling of case contacts, community members and healthy children.

The cVDPV2 viruses are classified into unique genetic emergence groups through the pattern of nucleotide mutations in VP1 genome. During this period, there have been 68 unique genetic emergence groups identified in 34 countries, resulting in 109 individual outbreaks. The number of cVDPV2 outbreaks, cVDPV2 AFP cases, unique genetic emergences and geographical extent of transmission for each year between 2016 and 2020 are summarised in Table 1.

Outbreaks

The 109 cVDPV2 outbreaks detected between 01 January 2016 and 31 December 2020 are described in Table S1. They have been detected across 34 countries from the WHO African, Eastern Mediterranean, European and Western Pacific regions (Figure 1): Afghanistan (n=3), Angola (n=5), Benin (n=1), Burkina Faso (n = 2), Cameroon (n=4), Central African Republic (n = 8), Chad (n = 3), China (n = 1), Congo (n = 3), Cote d'Ivoire (n=2), DRC (n = 15), Egypt (n = 1), Ethiopia (n = 9), Ghana (n =1), Guinea (n =1), Iran (n= 1), Kenya (n = 1), Liberia (n=1), Malaysia (n = 1), Mali (n = 2), Mozambique (n = 1), Niger (n = 1), Nigeria (n = 12), Pakistan (n = 15), Philippines (n = 1), Senegal (n = 1), Sierra Leone (n = 1), Somalia (n = 3), South Sudan (n = 1), Sudan (n = 2), Syrian Arab Republic (n = 1), Tajikistan (n = 1), Togo (n = 2), and Zambia (n = 2).

There are 39/109 outbreaks that have not had a detection within 12 months (since 01 January 2020) and are considered as closed, whilst 70/109 outbreaks are active with detection within the previous 12 months (Table S1).

Genetic Emergences

For each of the 68 genetic cVDPV2 emergences detected in the period 2016 to 2020, we estimate the date of seeding, shown in Figure 2. We estimate that 7/68 (10.3%) emergences were seeded prior to the removal of tOPV in May 2016, and 61/68 (89.7%) emergences were seeded after May 2016, most likely though use of mOPV2 in outbreak response.

In 2016, three cVDPV2 emergences were detected in Nigeria (n=2) and Pakistan (n=1), that were seeded by pre-switch tOPV use (Table 1, Figure 2). These emergences were rapidly controlled through mOPV2 outbreak response, with no subsequent detections beyond 2016. In 2017 and 2018, four and six new emergences were detected, respectively: 1/4 (25%) in 2017 and 6/6 (100%) in 2018 were seeded early after the Switch. Many of the emergences in this period (2017-2018) were not controlled: the NIE-JIS-1 and SOM-BAN-1 emergence groups have been circulating for over three years and have spread across borders causing outbreaks across 14 and 3 countries, respectively (Table 2).

In 2019, there were 40 new cVDPV2 new emergence groups detected, which 39/40 (97.2%) were seeded after the switch (Table 1). In 2020 there have been only 15 new emergence groups detected, with 15/15 (100%) seeded after the switch (Table 1).

The trend in geographic expansion of cVDPV2 outbreaks is evident in both the number of countries reporting outbreaks, and the number of infected provinces within countries. In 2020 there were 30 countries that reported cVDPV2 transmission, compared to 19 in 2019, 7 in 2018, 3 in 2017 and 2 in 2016 (Table 1). Furthermore, there were 202 infected provinces in 2020 compared to 105 in 2019, 26 in 2018, 7 in 2017 and 3 in 2016 (Table 1).

Paralytic cVDPV2 cases

Between 01 January 2016 and 31 December 2020 there have been 1596 AFP cVDPV2 cases reported: 962/1596 (60.3%) cases occurred in African Region; 619/1596 (38.8%) in the Eastern Mediterranean Region; 14/1596 (0.9%) in Western-Pacific Region; and 1/1596 (0.1%) in the European Region. There were 2, 96, 71, 365 and 1062 AFP cases reported in 2016, 2017, 2018, 2019 and 2020, respectively (Table 2).

The age of cases was available for 1582/1596 AFP cases, with a median age of 1.92 [95% CI: 0.5, 7.0] years. The median age has not significantly changed over time, despite increasing susceptibility in older age cohorts: the median age was 1.92 [95% CI: 1.36, 2.47] years in 2016; 1.33 [95% CI: 0.45, 5.84] years in 2017; 2.0 [95% CI: 0.5, 8.75] years in 2018; 2.0 [95% CI: 0.5, 6.01] years in 2019; and 2.0 [95% CI: 0.45, 7.21] years in 2020. In total, 85% (1343/1582) cVDPV2 AFP cases with age information available were born after the switch.

The number of IPV doses received were unknown in 55.2% (881/1596) of AFP cases, zero doses in 37.9% (605/1596) of AFP cases, one dose in 5.2% (83/1596), and more than one dose reported in 2% (27/1596) of AFP cases (Table 2). There were 1033 cVDPV2 AFP cases that could be matched with non-polio AFP cases by geographic location, age at onset and paralysis onset date. In recall doses histories for children with cVDPV2 AFP cases, 550 investigations reported zero or one IPV dose, and 616 control investigations reported zero or one IPV dose. The proportion of IPV vaccinated cVDPV2 AFP cases was 16.5% (91/550), compared to 32.3% (199/616) of

controls. This provides a vaccine effectiveness of one dose of IPV equal to 58.5% [95% CI: 40.0% – 72.4%].

3.2.6 Discussion

The international spread of poliovirus is declared a Public Health Emergency of International Concern (PHEIC) under the International Health Regulations (IHR) 2005, relating to WPV1 and cVDPV. At the meeting in February 2021, the emergency committee of IHR concluded a rising risk of cVDPV2 spread based on the increasingly large number of cases, environmental detections, and documented exportations across borders; the decreasing intestinal mucosal immunity against poliovirus type 2 since the withdrawal of tOPV in 2016; the impact of the COVID-19 pandemic; and lack of access to susceptible children (16).

As our analysis shows, after a gradual increase in the incidence of outbreaks between 2016 and 2018, the number of cVDPV2 outbreaks amplified considerably in 2019. This was characterised by a large number of unique genetic emergences, that were seeded after the switch, likely from exposure to mOPV2 in outbreak response. In 2020, there have been substantially fewer new genetic emergences, but widespread transmission of established genetic lineages that have not been stopped by outbreak response. This geographic expansion has occurred both within the countries beyond the initial geographic areas identified for outbreak response with mOPV2, and across national borders into neighbouring countries. In 2020, the substantial increase in the number of AFP cVDPV2 cases and number of infected provinces, especially evident in Pakistan and Afghanistan, was notable given that the sensitivity of surveillance was impacted by the COVID-19 pandemic.

The increasing geographic expansion over time is likely linked to the rapidly declining population intestinal mucosal immunity levels against serotype 2 poliovirus, and more recently in 2020, the abrupt interruption of field activities due to the COVID-19 pandemic. Since March 2020, close to 60 scheduled preventive bOPV and outbreak response mOPV2 polio vaccination campaigns were delayed in more than 30 countries in compliance with global guidance on the

pandemic. In addition, essential immunization activities were severely affected and the sensitivity of surveillance for polioviruses and field investigations significantly reduced.

The GPEI recommends that the response to cVDPV2 outbreaks should be at least two high-quality immunization campaigns with OPV within eight weeks of notification (6). Whilst this is based on experience prior to the switch was that two rounds with type 2 OPV are effective at stopping cVDPV2 transmission, we document that the majority of emergences have spread beyond the initial outbreak response zone and established transmission in neighboring areas. The scope of outbreak response with mOPV2 has been restricted due to balancing the risk of seeding new cVDPV2 outbreaks and accounting for the limited vaccine supply available in the global stockpile. Our analysis suggests that reducing escape of the virus should be higher priority, especially as population immunity declines further, which would require larger geographic scope of response in the future.

Based on our case-control analysis, a single dose of IPV in routine immunization has provided around 60% protection against paralytic disease, similar to immunogenicity data in clinical trials (17). However, low coverage and delays in IPV introduction following the switch has left a large proportion of children unvaccinated. In October 2020, the SAGE recommended a second IPV dose to be introduced into routine immunization schedule (18). Vigorous efforts should be made to improve IPV coverage in locations at risk of cVDPV2 outbreaks reduce the number of children susceptible to paralysis before outbreaks can occur, especially in the context of reduced coverage caused by the COVID-19 pandemic (19). However, IPV is not recommended for cVDPV2 outbreak response because evidence demonstrates that IPV campaigns are unlikely to reach children not reached with OPV campaigns, have limited impact on stopping transmission and have a high programmatic cost (18). The priority of outbreak response is to stop transmission; therefore, activities should focus on rapidly achieving high coverage with type-2 containing OPV.

A critical tool for cVDPV2 outbreak response is novel OPV2 (nOPV2), which received recommendation under WHO Emergency Use Licensure in November 2020 (20). nOPV2 is a modified version of the Sabin mOPV2 strain, with enhanced genetic stability as a result of

stabilizing key genomic segments of the vaccine virus. Therefore, this vaccine is expected to have significantly reduced risk of reversion to VDPV (21, 22). The vaccine has demonstrated comparable protection against poliovirus and increased genetic stability in Phase I and II clinical trials (23-25). If nOPV2 performs as expected, it will be an imperative resource for controlling cVDPV2s.

In addition, in April 2020, SAGE recommended that the option of tOPV is available for cVDPV2 outbreak response in subnational areas with co-circulation or high risk of co-circulation of cVDPV2 with cVDPV1, cVDPV3 or WPV1(26). Since October 2020, tOPV has been used for cVDPV2 outbreak response the WPV1 endemic countries of Pakistan and Afghanistan, to avoid the need to conduct dual mOPV2 and bOPV campaigns.

In the context of multiple vaccination options for cVDPV2 outbreak response, SAGE recommends that countries should avoid delay and prioritize rapid, high-quality cVDPV2 outbreak response with whichever oral polio vaccine is available to them (19). Conducting rapid and high-quality campaigns of sufficient scope will be essential to control and stop outbreaks. Persistent delays in responding and poor-quality campaigns will continue to obstruct the impact of outbreak responses with any vaccine.

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3.2.8 Figures and Tables

Figure 1: Map of cVDPV2 AFP cases (circles) and ES positives (squares) detected 01 January 2016 to 31 December 2020.

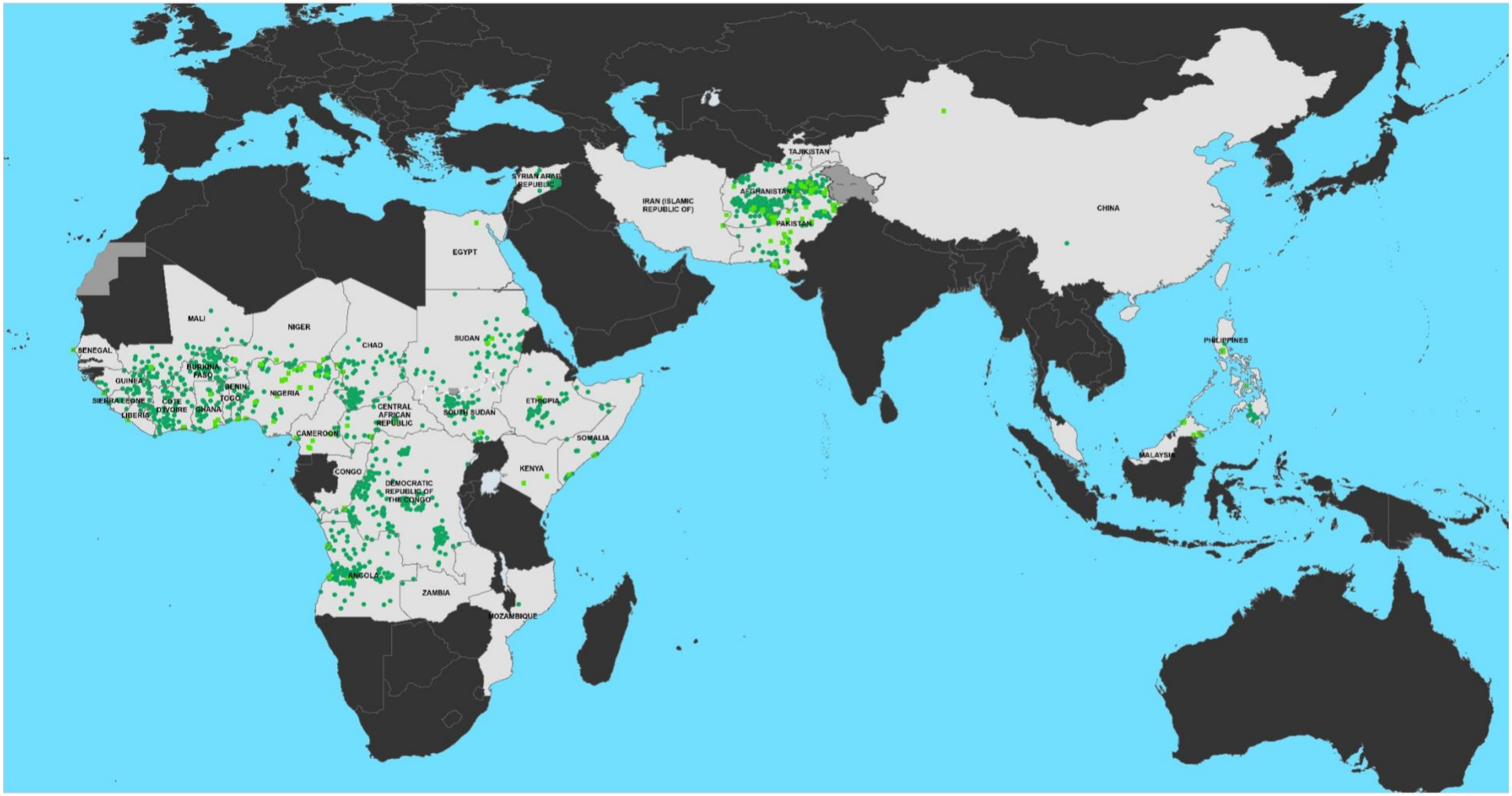

Figure 2: Timeline of cVDPV2 emergences reported between 1 January 2016 and 31 December 2020, ordered by the date of first isolate detection. Each emergence is categorised by a probability >0.5 that the date of seeding was after the Switch on 1 May 2016, shown by colour of circles.

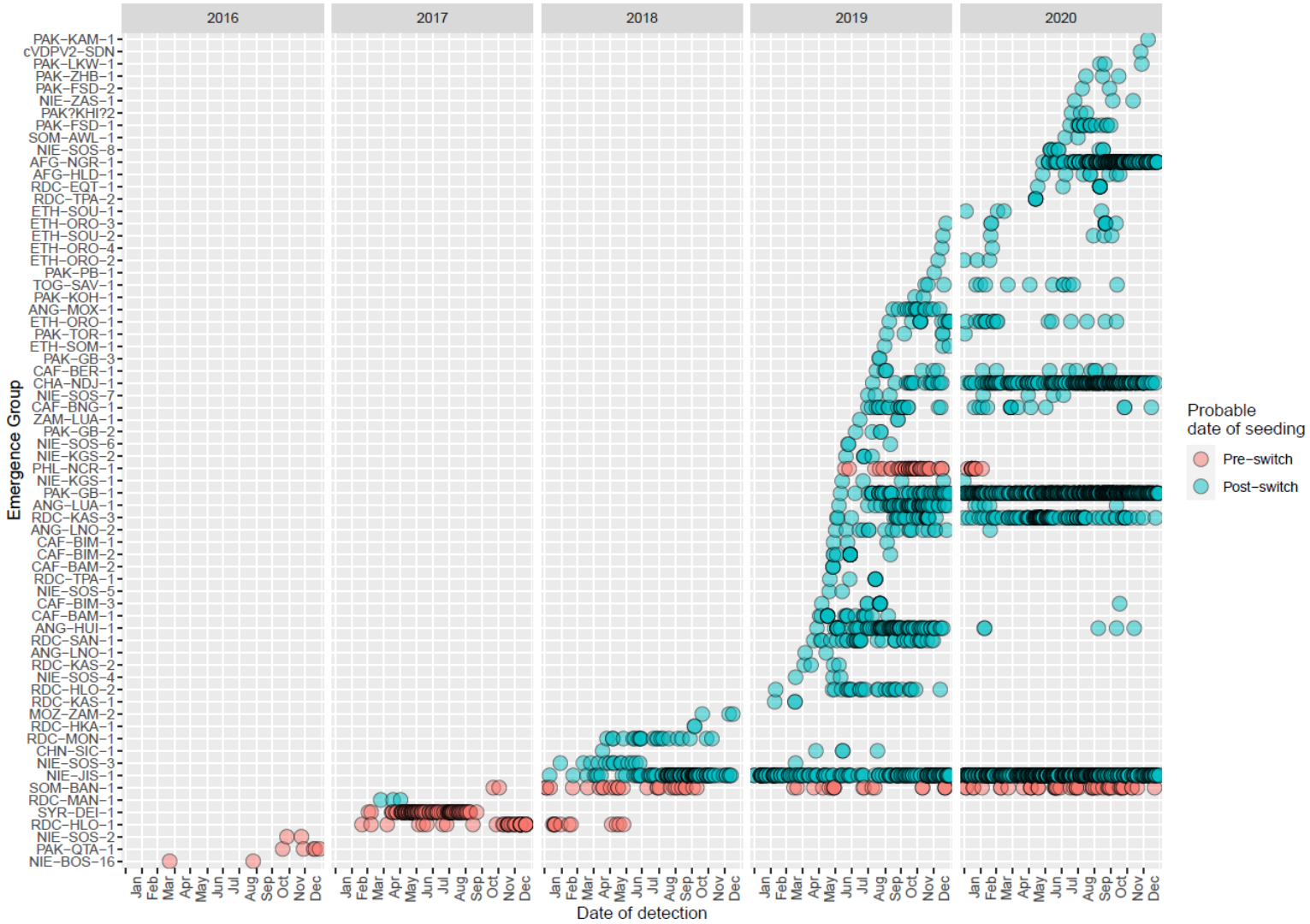

Table 1: Prevalence of cVDPV2s, 01 January 2016 to 31 December 2020.

Year	**Number cVDPV2 outbreaks detected**			**Number of new genetic emergences**	**Number of countries**	**Number of provinces**	**Number of AFP cases**
	New outbreaks	Continuing outbreaks	Total				
2016	3	0	3	3	2	3	2
2017	4	0	4	4	3	7	96
2018	8	2	10	6	7	26	71
2019	52	5	57	40	19	105	365
2020	42	29	71	15	30	202	1062

Abbreviations: AFP = Acute flaccid paralysis; cVDPV2 = circulating vaccine-derived poliovirus type 2.

Table 2: Demographics of cVDPV2 acute flaccid paralysis (AFP) cases reported between 01 January 2016 to 31 December 2020.

Variable	Number of cases (%)
Total	1596
WHO Region	
African	962 (60.3)
Eastern-Mediterranean	619 (38.8)
European	1 (0.1)
Western Pacific	14 (0.9)
Year of onset	
2016	2 (0.2)
2017	96 (6.0)
2018	71 (4.4)
2019	365 (22.9)
2020	1062 (66.5)
Gender	
Female	702 (44.0)
Male	877 (54.9)
Unknown	17 (1.1)
Age in years	
(0,1]	341 (21.4)
(1,2]	594 (37.2)
(2,3]	328 (20.6)
(3,5]	232 (14.5)
(5,15]	87 (5.5)
NA	14 (0.9)
Median age in years (95% CI)	*1.9 [0.5, 7.0]*
Number of IPV doses reported	
0	605 (37.9)
1	83 (5.2)
>1	27 (3.8)
Unknown	881 (55.2)

Abbreviations: IPV = Inactivated poliovirus vaccine; WHO –=World Health Organisation.

Chapter 4: Enabling accelerated vaccine roll-out for Public Health Emergencies of International Concern (PHEICs): Novel Oral Polio Vaccine type 2 (nOPV2) experience

4.1 Chapter publication status

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A research paper cover letter for this chapter is found in the Appendix.

I was the lead author in this publication and made the following author contributions according to the CRediT checklist: Methodology, Visualization, Writing – original draft, Writing – review & editing.

This chapter is based on work I performed alongside my PhD working for World Health Organisation, co-ordinating the policy for the use type 2 novel oral poliovirus vaccine (nOPV2) and developing the framework for the phased roll-out of nOPV2 under EUL, summarised in this paper and endorsed by the WHO Strategic Advisory Group of Experts on Immunization (SAGE). This is a policy paper to provide context to the above work and is included here as a prelude to Chapter 5.

4.2 Abstract

To address the evolving risk of circulating vaccine-derived poliovirus type 2 (cVDPV2), Global Polio Eradication Initiative partners are working closely with countries to deploy an additional innovative tool for outbreak response – novel oral polio vaccine type 2 (nOPV2). The World Health Organization's (WHO) Prequalification program issued an Emergency Use Listing (EUL) recommendation for nOPV2 on 13 November 2020. The WHO's EUL procedure was created to assess and list unlicensed vaccines, therapeutics, and diagnostics to enable their use in response to a Public Health Emergency of International Concern. nOPV2 was the first vaccine to receive an EUL, paving the way for other emergency vaccines. In this report, we summarise the pathway for nOPV2 roll-out under EUL.

4.3 Introduction

Whilst the wild-type poliovirus type 2 (WPV2) has been eradicated, the surge of circulating vaccine-derived poliovirus type 2 (cVDPV2) outbreaks is considered to be a major a challenge for the Global Polio Eradication Initiative (GPEI). In 2020, there were 1054 cVDPV2 paralytic poliomyelitis cases reported from 33 countries across four World Health Organisation (WHO) regions - African, Eastern-Mediterranean, Western-Pacific and European regions.

The current Sabin oral poliovirus vaccine (OPV) strains can lose their attenuating mutations over time, particularly when transmitted from person-to-person (1). Rarely, this results in vaccine-associated paralytic poliomyelitis (VAPP) in vaccine recipients and close contacts, or generation of vaccine-derived polioviruses (VDPV) with transmissibility and neurovirulence characteristics similar to wild poliovirus. In settings of low population immunity, VDPVs can persist in the community and result in outbreaks of circulating VDPVs (cVDPVs) (2). The strategy of responding to cVDPV2 with monovalent oral poliovirus vaccine type 2 (mOPV2) has been largely successful in stopping transmission of cVDPV2; however, due to the genetic instability described above and waning population immunity following the global cessation of routine use of type 2 Sabin OPV, an increasing number of new cVDPV2 outbreaks are attributable to mOPV2 use (3). While inactivated poliovirus vaccine (IPV) used in routine immunization and occasionally in outbreak response protects against paralytic disease from type 2 polioviruses, it provides limited primary intestinal mucosal immunity necessary to stop outbreaks of cVDPV2 or prevent their emergence following type 2 Sabin OPV use (4).

A central priority of GPEI is to develop oral poliovirus vaccine strains that are more genetically stable than Sabin OPV (5). The novel oral polio vaccine type 2 (nOPV2) strains are modified versions of the Sabin mOPV2 with enhanced genetic stability (6), (7). Therefore, nOPV2 is anticipated to have a significantly reduced risk of evolution to a VDPV compared to the existing mOPV2.

In 2019, the GPEI established an nOPV2 Working Group to oversee the multifaceted approach for delivering a vaccine for a Public Health Emergency of International Concern (PHEIC) (Box

1). On 13 November 2020, nOPV2 received a recommendation for use under WHO Emergency Use Listing (EUL) and was first used as part of outbreak response in Nigeria on 13 March 2021. In this paper, we summarise the accelerated pathway for clinical development, manufacturing and programmatic introduction of nOPV2.

Box 1: Overview of the nOPV2 Working Group.

The nOPV2 Working Group is a time-limited group established to manage and coordinate across Global Polio Eradication Initiative (GPEI) activities to enable a rapid and effective rollout of nOPV2 as the tool of choice for responding to cVDPV2 outbreaks.

The core nOPV2 working group is composed of representatives from all six GPEI partner agencies (Rotary International, UNICEF, Bill and Melinda Gates Foundation (BMGF), Gavi, the Vaccine Alliance (GAVI), US Centers for Disease Control and Prevention (US-CDC), and World Health Organisation (WHO).

In order to advance work in a several key technical areas, a collection of specific sub-groups that include membership from experts beyond GPEI were established at different time-points: Research, Data Analysis and Modelling; Initial Use Country Support; Manufacturer Support (including regulatory support); Genetic Characterisation; Safety; and nOPV2 WG liaisons for vaccine supply, communications and readiness verification.

In addition, the core nOPV2 working group oversees policy development for nOPV2 and co-ordinates with two independent advisory boards: WHO Strategic Advisory Group of Experts on Immunisation (SAGE) and the Global Advisory Committee on Vaccine Safety (GACVS). In 2021, support for development of nOPV1 and nOPV3 vaccine candidates was also included in the working group's expanded focus areas, transitioning it to be renamed as "nOPV Working Group".

4.4 Main Text

Pre-clinical development

In 2011, a consortium was formed with funding support from the Bill & Melinda Gates Foundation to develop improved OPV virus strains, with the vision that a collaborative effort using a combination of strategies would have the greatest chance of success. Researchers from

the National Institute for Biological Standards and Controls (NIBSC), the US Centers for Disease Control and Prevention (US-CDC), the US Food and Drug Administration (FDA), and the University of California at San Francisco collaborated to design, produce and test several novel OPV strains in a variety of pre-clinical studies. The strains were assessed through intraspinal inoculation in a transgenic mouse neurovirulence model; passaging in cell culture under selective pressure conditions known to lead to reversion of Sabin (such as 37 degrees Celsius in Vero Cells) followed by deep sequencing; and infectious yield measurements. This identified candidates that were at least as attenuated as Sabin type-2 strains, had enhanced genetic stability (reduced potential to revert to a neurovirulent phenotype), and similar antigenicity and immunogenicity (6), (7).

Two candidate nOPV2 strains, referred to as nOPV2-c1 and –c2, were selected based on these pre-clinical studies to take forward to clinical trials (6), (7). The candidates used different combinations of 5 modifications of the Sabin-2 genome, including changes to the ribonucleic acid (RNA) sequence in the 5′ untranslated region of the polio genome (5′ UTR), the capsid protein coding region (P1), the non-structural protein 2C, and the polymerase 3D (6), (7). Full details of the genetic modifications and their purposes are summarized in Table 1.

Clinical development

The clinical development for both nOPV2-c1 and –c2 investigated the safety, immunogenicity, shedding and genetic stability (less reversion to neurovirulence) of the candidates in Phase I and Phase II trials, in Belgium and Panama. A summary of the nOPV2 trials and historical control trials is provided in Fig. 1. Substantial efforts were made to accelerate the clinical development of nOPV2, which are summarised in Box 2.

Phase IV historical control studies were conducted in Panama and Belgium to provide baseline data with mOPV2 before the global withdrawal of type 2-containing OPV in May 2016. As the nOPV2 candidates were not yet available for clinical trials, these were conducted subsequently: to maximize comparability of data, the mOPV2 phase IV trials were designed to parallel the expected design of the phase I and II nOPV2 studies.

The phase I first-in-human study with nOPV2 was conducted in Belgium: 30 healthy adults (aged 18–50 years) previously immunized exclusively with IPV were administered a single dose of nOPV2-c1 or nOPV2-c2 vaccine and isolated for 28 days in a purpose-built containment facility (8), (9). This study provided an initial demonstration of vaccine safety, viral shedding and genetic stability: this allowed progression into the larger phase II study, with administration to non-IPV vaccinated individuals, and was influential in the WHO Containment Advisory Committee recommendation that subsequent studies could be done outside of containment. Additionally, evaluation of intestinal and serum neutralizing antibodies after a single dose of nOPV2 at dose 106 CCID50 (50% cell culture infectious dose) was also conducted (8), (10).

The subsequent, larger, phase II study was conducted in Belgium with 200 previously OPV-vaccinated healthy adults assigned to receive one or two doses of nOPV2-c1 or nOPV2-c2; a further 50 participants, previously vaccinated with IPV, were assigned to nOPV2-c1 nOPV2-c2 or placebo (11). The results demonstrated safety in a larger group of adults and supported the assessment of the vaccine candidates in children and infants.

Two phase II studies were conducted in Panama: one in children between 1 and 5 years of age that had received prior trivalent oral polio vaccine (tOPV) and/or IPV-vaccination, and the second in infants aged 18 weeks that had previously received bOPV and a single dose of IPV (12). The immunogenicity of nOPV2-c1 and nOPV2-c2 was evaluated at low and high dose potencies in these phase II studies (105 CCID50 and 106 CCID50 (high dose, HD)) (11), (12).

Data from the clinical studies show both nOPV2 candidates to be well-tolerated in adults, young children, and infants, with no specific safety concerns identified (8), (11), (12). There have been no serious adverse events considered to be related to vaccination with nOPV2. The most important immunogenicity evaluation was the seroprotection rate and seroconversion rate, 28 days following a single dose, in 18–22-week-old infants. The primary immunogenicity hypothesis of non-inferiority of seroprotection rate to mOPV2 was met for nOPV2-c1 at both the high and low doses; however, it was only met for nOPV2-c2 at the high dose (12).

Additional studies are underway in Bangladesh: a trial in polio-vaccine naive neonates and a concomitant bivalent oral polio vaccine (bOPV)-nOPV2 administration study. In addition, a phase III safety and lot-to-lot consistency trial has been initiated in The Gambia. These studies will further expand the clinical safety database in the target population (children aged 0–5 years old).

All through the clinical development process, several unprecedented challenges were encountered, and innovative mitigation strategies were applied to overcome these issues in a timely manner. Conducting clinical evaluation of a strain of poliovirus that was under containment introduced multiple complexities in the development process, including the insertion of a phase I study under fully contained conditions, and conducting near real-time laboratory and clinical evaluation to inform decision making on subsequent studies without containment. Evaluation of unique endpoints, such as pattern of reversions in key areas of vaccine virus genome and neurovirulence in modified transgenic mice assays necessitated a series of consultations and extensive engagement of technical authorities to ensure the phase II studies were designed in a way that would inform public health and regulatory decision making, based on the unique epidemiologic context. Precedence and prior positioning on some of these factors could have contributed to a further accelerated development process (Figure 2).

Box 2: Summary of clinical development acceleration methods.

1. Implementing five historical control trials in approximately 6 months' time in advance of global cessation of Sabin OPV2 use, to generate comparator data
2. Executing nOPV2 clinical trials in staggered, parallel trials (e.g. age descension from adults to toddlers to infants in the phase II studies)
3. Studying only a high-dose level in participants who have been fully vaccinated against all polio types.
4. Empowering a data and safety monitoring board (DSMB), common to all nOPV2 studies, with decision rights regarding age de-escalation and dose escalation while trials were on-going
5. Using satellite sites for rapid subject enrollment, and real-time data generation by primary lab to inform trial conduct
6. Generating multiple incremental interim trial reports to enable rolling EUL submission and review
7. Major scale up and optimization of laboratory capacity to generate data for EUL submission, with 20,000 stool samples and 5,000 serological samples tested by US Centers for Disease Control and Prevention (US-CDC).

Down-selection of candidates and manufacturing

In 2019, with the cVDPV2 situation worsening and resulting in an urgent need for nOPV2, a decision was made to move forward with at-risk, at-scale production of nOPV2, based on a review of the available clinical and manufacturing data. Based primarily on manufacturing yield information, one of the two candidates - nOPV2 c1 - was prioritised over c2, driven by the projected program need of large number of doses at the earliest timeframe. The low-dose 105 CCID50 of either candidate would allow faster scale up of production, however, initial data suggested nOPV2-c1 would have higher potency at that dose - the high-dose formulation that would likely be required for nOPV2-c2 would preclude sufficient production to meet the epidemiological need. The decision to proceed with nOPV2-c1 was confirmed from subsequent data from the Phase II trial in Panama, which became available in early 2020, demonstrating non-inferiority of immunogenicity of the low dose formulation for c1 but not nOPV2-c2 (12).

The vaccine manufacturer, PT Bio Farma, committed to produce up to 200 million doses of nOPV2 by the end of 2020 to enable the vaccine to be deployed when WHO issued an

emergency recommendation for use. Having a relatively large number of doses available in this timeframe was critical as the vaccine would potentially be needed for outbreak response campaigns of national scale. Bulk and finished product manufacturing was first performed at a pilot plant at BioFarma and then later shifted to commercial facilities, which received regulatory inspections from WHO Prequalification (PQ) inspection team as well as from the Indonesian National Regulatory Authority (Badan POM) to ensure compliance with international good manufacturing practices (GMP) standards. The finished product from the pilot plant was filled in 20 dose vials and is available for study purposes. To maximize production capacity for nOPV2 for field use, a decision was taken to produce the vaccine in the commercial facility in 50 dose vials, which is the presentation that received WHO EUL.

Use of nOPV2 under Emergency Use Listing (EUL)

The WHO PQ team developed the EUL process to expedite the availability of unlicensed medical products needed in public health emergency situations and to assist interested UN procurement agencies and Member States in determining the acceptability of using specific products in the context of a public health emergency of international concern (PHEIC) (13). The EUL procedure involves a rigorous risk-based assessment by an expert advisory committee based on an essential set of available data on quality, safety, and efficacy/immunogenicity/performance (13).

Considering the cVDPV2 outbreaks and continued declaration of polio as a PHEIC, WHO and the Badan POM agreed to focus on potential use of nOPV2 (c1) under an EUL (14). Without EUL, nOPV2 would not be available until at least 2023, due to the timelines for pre-qualification and licensure of vaccines, including requirement of phase III clinical data. Pre-alignment discussions took place between the nOPV2 development team, Badan POM and WHO PQ, which were necessary to align expectations and provide early feedback. It was agreed that an EUL assessment could be undertaken once sufficient data in young children and infants from phase II studies became available and that a rolling submission and evaluation of clinical data would be used, with data being shared as it becomes available; subsequentially, a roadmap was published for the evaluation of nOPV2 under EUL (15).

A positive recommendation for use of nOPV2 under EUL was made on November 13, 2020, with nOPV2 becoming the first vaccine to receive an EUL recommendation from the WHO. Should data from field use further support vaccine safety and effectiveness, nOPV2 use would continue under the EUL until the clinical data are available to support licensure and WHO prequalification of nOPV2.

For vaccines listed under an EUL, post-deployment monitoring measures may be required (13). For nOPV2, these measures include monitoring and analysis of the safety, genetic stability and effectiveness of the vaccine. Any country wishing to deploy nOPV2 under the EUL must meet a set of pre-defined readiness verification criteria, which are assessed by global and regional teams, to ensure they are ready to implement these measures, and are prepared to respond to any unanticipated findings.

Programmatic roll-out: A phased approach

The GPEI have developed a phased approach to the roll-out of nOPV2 under EUL, which was endorsed by WHO Strategic Advisory Group of Experts on Immunization (SAGE). As nOPV2 had never been used outside clinical trials, a strict set of criteria were developed for the first uses of nOPV2, in addition to the mandatory post-deployment monitoring requirements of EUL (Box 3). The initial use period was expected to last for approximately six months. Given that cVDPV2 outbreaks disproportionately affect areas with weaker healthcare systems and inaccessible areas, these criteria were designed to ensure close monitoring of vaccine safety and performance, and the ability to detect any unanticipated events and respond to these quickly and effectively to minimize risk and impact on broader immunization activities.

Box 3: Criteria for the initial use of nOPV2 under EUL, as endorsed by SAGE

Essential criteria:

1. Detection of disease or virus (VDPV2 detection).
2. Capacity to acquire and distribute the vaccine during outbreak response in a timely manner (including accessibility to population and healthcare system).
3. Capacity to respond to an unanticipated finding in a way that minimises risk and impact on the broader immunisation programme (adverse events, vaccine acceptance amongst the population).
4. Adequate surveillance to monitor vaccine behavior (safety and genetic stability) and disease incidence. Specifically, for nOPV2, this includes:
    a. Adverse Event Following Immunization (AEFI) and Adverse Event of Special Interest (AESI) surveillance
    b. Acute flaccid paralysis (AFP) surveillance
    c. Environmental surveillance (ES)
5. At least 12 weeks from type 2 containing Sabin OPV (mOPV2, tOPV) campaign in the same area.

Recommended criteria:

6. At least 6 weeks from bOPV campaigns in the same area.

The proposed intervals between nOPV2 use and other Sabin OPV (tOPV, mOPV2 or bOPV) campaigns during the initial use phase were in place to minimize confounding in assessment of effectiveness of nOPV2 and reduce overlap of any safety signals associated with different vaccines. In addition, this time separation would also reduce the risk of genetic recombination between vaccine viruses. The time period was based on the duration of transmission of Sabin-strain vaccine in the community after a vaccine campaign and duration between exposure and onset of adverse events (16), (17). Routine immunization with bOPV will be un-interrupted for infants, as the level of vaccine virus circulating in the population is substantially lower from routine immunization than following a vaccination campaign (such as national immunization days and outbreak response) (18).

The Global Advisory Committee on Vaccine Safety (GACVS) established a sub-committee on nOPV2 to provide an independent assessment of safety data generated following use of nOPV2 under the EUL. After provision and review of vaccine safety, the initial use criteria was removed in October 2021, enabling nOPV2 to become the vaccine of choice to respond to cVDPV2 outbreaks, as endorsed by SAGE (19), (20). However, countries must still meet the post-deployment monitoring requirements outlined by the EUL until full licensure and WHO prequalification of nOPV2.

Programmatic roll-out: Preparing countries

Any country planning to use nOPV2 under EUL must have in place the required deployment and monitoring requirements, including a national decision and the relevant regulatory approvals for use. Therefore, in February 2020, the WHO Executive Board urged all Member States to expedite processes for authorizing the importation and use of nOPV2 under EUL (21). As use of nOPV2 is only permitted as part of an approved outbreak response to cVDPV2, it was not possible to pre-select the countries that will use nOPV2 during the initial use phase.

To address this, WHO and UNICEF regional offices, with the support of GPEI, began the process of preparing all countries at high risk of cVDPV2 for use of nOPV2 in mid 2020, in advance of the EUL being issued. A set of tools and guidance materials to support these preparations were developed across GPEI; these provided clarification on what the readiness requirements are and how to meet them in key domains such as national decision making, regulatory approvals, communications, safety, surveillance, laboratory, vaccine management and outbreak operations. Due to COVID-related restrictions, trainings and reviews were rolled out virtually both for priority countries but also by technical area, such as across the global polio laboratory network, with National Immunization Technical Advisory Groups (NITAGs) and National Regulatory Authorities (NRAs).

Given the large number of countries that began preparing for nOPV2 use at the same time, priority countries were asked to nominate a national focal point for nOPV2 preparations; GPEI provided funding for the deployment of nOPV2 focal points and facilitators to support

preparations, where needed. Training and onboarding for these focal points was held virtually, to ensure they were familiar with the tools and guidance, as well as support available to them in their role. The aim over the next few years will be to generate, analyze and use field-use data and information from on-going clinical studies to inform policies on outbreak response, and to strengthen the evidence base in support of full licensure and WHO Prequalification of the vaccine, to transition out of the use of nOPV2 under EUL. Detailed evaluation of genetic characteristics of nOPV2 isolates from sewage and clinical specimens through the global polio laboratory network along with assessment of effectiveness and safety of the vaccine from use in outbreak response in real-world settings would help us determine the impact of the vaccination with nOPV2 in interrupting cVDPV2 transmission.

The first campaigns with nOPV2 were carried out in March 2021 as a response to outbreaks of cVDPV2 in Nigeria and Liberia, with further countries soon following with nOPV2 use.

4.5 Conclusion

The WHO EUL recommendation for nOPV2 use is a milestone achievement in global health and has paved the way for the accelerated use of unlicensed vaccines during PHEIC including COVID-19 vaccines. Between the initial submission of nOPV2 regulatory dossier to WHO EUL in February 2020, to recommendation in November 2020, an in-depth assessment of pre-clinical, manufacturing, and clinical data on vaccine safety and effectiveness was conducted by an independent expert review committee engaged by the WHO Prequalification team. The multi-pronged approach implemented by the GPEI and vaccine manufacturer PT Bio Farma in coordination with other partner agencies to develop the EUL submission and prepare countries for roll-out of the vaccine is summarised in this paper and provides many lessons for acceleration of clinical trials and manufacturing.

The use of nOPV2 in outbreak response to cVDPV2 is urgently needed due to the demonstrated risk of reseeding through Sabin mOPV2 use. However, the ability to stop outbreaks with nOPV2 is dependent on the implementation of timely, high-quality outbreak response of sufficient scope.

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4.7 Figures and Tables

Figure 1: nOPV2 Clinical Development Plan. Additional phase II studies and control trials that were not prioritised for EUL data submission are not shown on this figure and are described in the text.

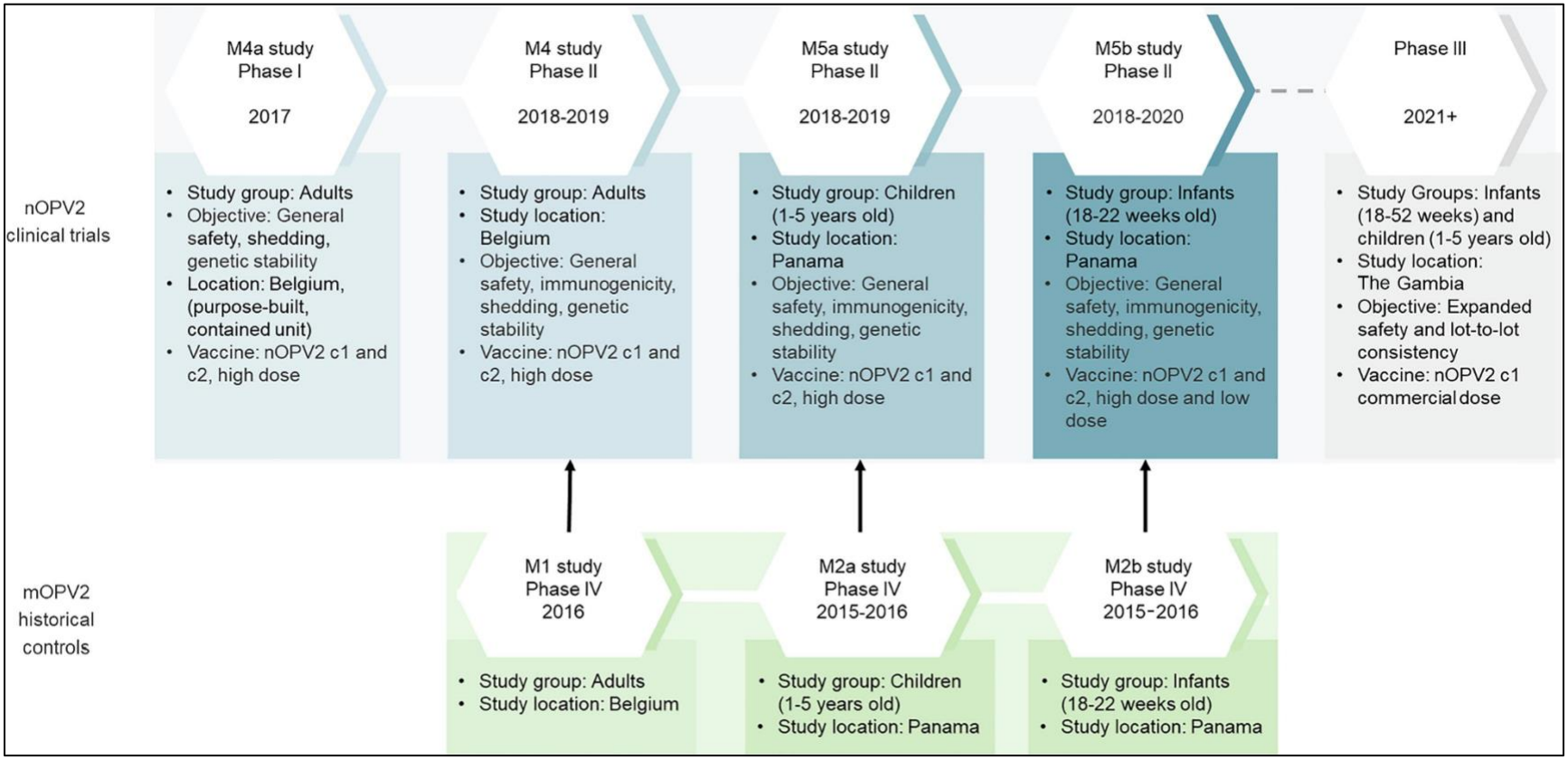

Figure 2: Timeline of nOPV2 development

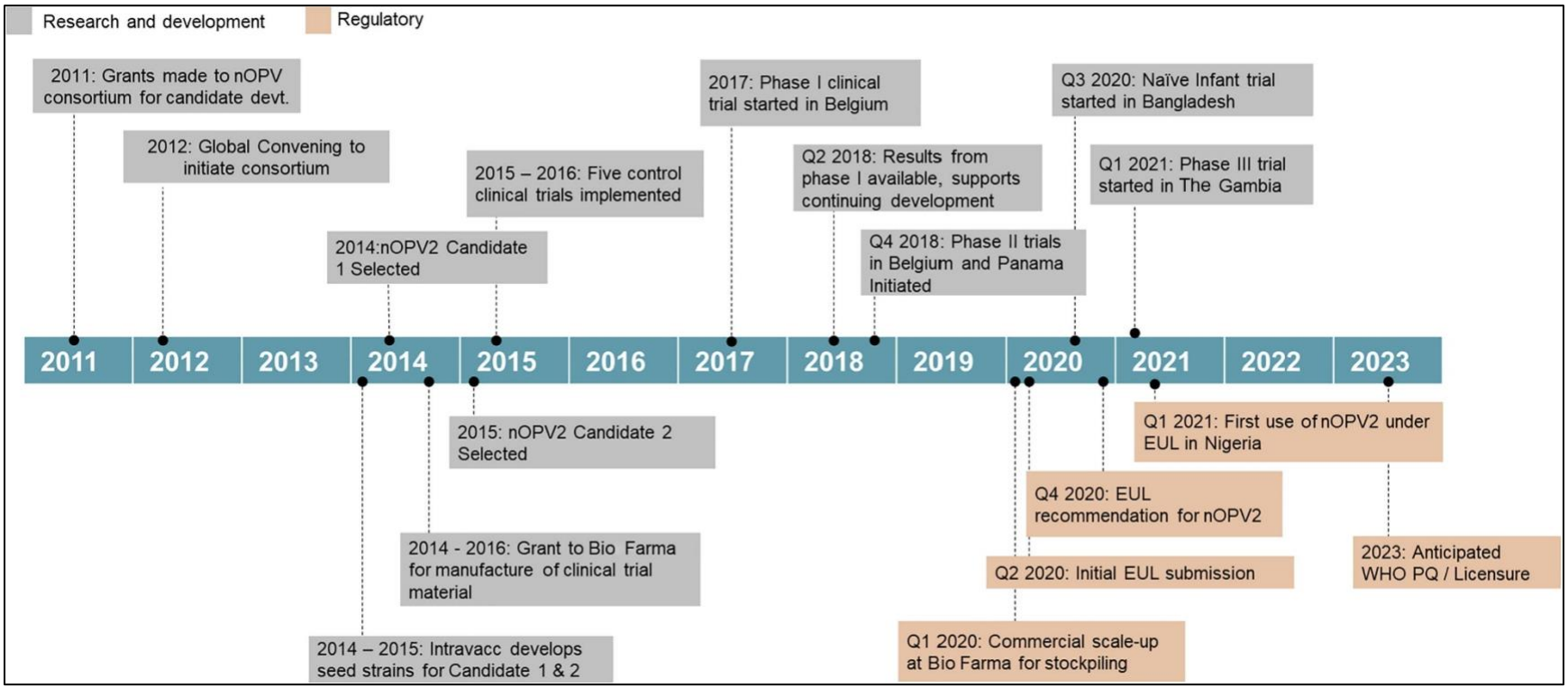

Table 1: Genetic modifications of candidate 1 (c1) and candidate 2 (c2) novel oral poliovirus vaccine type 2 (nOPV2)

Modification	c1*	c2**	Purpose
S15 domain V changes	X	X	• Improved stability of attenuated phenotype. Specifically, improve genetic stability of the domain V attenuating mutation to avoid reversion by single nucleotide changes.
cre relocation	X		• Reduce frequency of recombination events. Specifically, a single recombination event replacing domain V will also remove cre, making virus non-viable and non-infectious.
Polymerase (HiFi):Higher Fidelity changes	X		• Improved stability of attenuated phenotype. Specifically, improved fidelity of replication leading to less genetic drift and reversion.
Polymerase (Rec) changes	X		• Reduce frequency of recombination events thereby reducing ability of population to improve replication fitness.
Capsid P1 region codon deoptimization		X	• Improved stability of attenuated phenotype. • May also reduce transmission (less infectious per particle). • May enhance innate immune response against vaccine. • May increase attenuation.

*Candidate 1 (S2/cre5/S15domV/rec1/hifi3). Strain selected for EUL application.

**Candidate 2 (S2/S15domV/CpG40)

Chapter 5: A model of vaccine-derived poliovirus outbreaks to estimate effectiveness of outbreak response campaigns with a novel oral poliovirus vaccine

5.1 Chapter publication status

This chapter is being prepared as a manuscript, for which I will be the lead author.

5.2 Abstract

The type 2 novel oral poliovirus vaccine (nOPV2) is being rapidly deployed under WHO Emergency Use Listing in outbreak response against circulating vaccine-derived poliovirus (cVDPV2) outbreaks. Whilst phase I and II clinical trials have demonstrated comparable immunogenicity to the traditional Sabin type 2 monovalent oral poliovirus vaccine (mOPV2), nOPV2 performance in the field must be evaluated in a timely manner. This paper presents a generalizable mathematical model of cVDPV2 transmission with outbreak response vaccination campaigns in that can be applied to different settings to estimate vaccine effectiveness, defined as the product of campaign coverage and vaccine immunogenicity. Our results demonstrate vaccine effectiveness of mOPV2 between 37.5% -87.5% in Guinea and 12.5%-17.5% in South Sudan, compared to vaccine effectiveness of nOPV2 between 47.5-100% in Tajikistan, with significant variation between sub-national areas in all three countries. The model will be able to evaluate the effectiveness of vaccination strategies as nOPV2 use continues. The priority for controlling outbreaks should be focused on high quality and timely outbreak response.

5.3 Introduction

Outbreaks of circulating vaccine-derived poliovirus (cVDPV) pose a major barrier to achieving eradication of polio (1). Since the removal of type 2-containing oral poliovirus vaccine (OPV) from routine immunisation in 2016, there has been an increasing incidence of type 2 cVDPV (cVDPV2) outbreaks, largely seeded by monovalent oral poliovirus vaccine type 2 (mOPV2) used in outbreak response (2).

To address the need of a live poliovirus vaccine with reduced risk of reversion, a novel OPV2 (nOPV2) was developed through stabilizing key genomic segments of the vaccine virus (3, 4). Since November 2020, nOPV2 has been recommended under WHO Emergency Use Listing (EUL) for use in outbreak response to cVDPV2 outbreaks (5). In phase I and II clinical trials, nOPV2 has demonstrated comparable immunogenicity and greater genetic stability compared to mOPV2 (6-8). As part of EUL requirements, vaccine effectiveness must be evaluated during the outbreak response.

Evaluating vaccine effectiveness in reactive vaccination campaigns during an outbreak presents several challenges (9). Standard vaccine effectiveness assessment methods include field seroprevalence surveys after campaigns to estimate population immunity, statistical time-series analysis of epidemiological data, and case-control analysis (10-13). However, seroprevalence studies are limited as they cannot distinguish the source of immunity, statistical methods require a longer observation period to accumulate sufficient sample size of datapoints, and inference from reported vaccination history can often be unreliable in these settings (10, 14).

Mathematical models of poliovirus transmission have been developed to quantify the impact of reactive vaccination responses or explore alternative vaccination response situations (15-17). However, to-date, models have been location-specific, where spatial structures have been demonstrated as important for capturing the transmission dynamics (12, 18-20). In contrast, for first-use sites for nOPV2, a model would need to be generalisable to many different locations with potentially limited quantity of data, meaning that a precise spatial structure may not be identifiable.

The objective of this work was to develop a generalisable mechanistic model for cVDPV2 outbreaks based on poliomyelitis case data to estimate vaccine effectiveness, defined as the product of campaign coverage and per-dose immunogenicity. Here, I focus on three different locations with outbreaks during the period 2020-2021: Guinea – a cVDPV2 outbreak with a long delay for outbreak response, allowing us to observe dynamics in the absence of intervention; South Sudan – a cVDPV2 outbreak with a mOPV2 response, allowing us to test the ability of the model to infer mOPV2 effectiveness; and Tajikistan – a cVDPV2 outbreak with an nOPV2 response.

5.4 Methods

Data

Cases of cVDPV2 poliomyelitis are defined by the Global Polio Eradication Initiative (GPEI) as a case of acute flaccid paralysis (AFP) with isolation of cVDPV2 from a stool sample. All cases were identified through the AFP surveillance system, the primary surveillance of the global polio eradication programme, targeted towards children aged <15 years. As part of case investigations, stool specimens are collected to determine poliovirus infection within 14 days of paralysis onset. All collected samples are tested in Global Polio Laboratory Network (GPLN) laboratories per WHO protocols to isolate, differentiate and characterize polioviruses including WPV, Sabin-like (or vaccine-like) poliovirus, and VDPV (21). VDPV are further classified as cVDPV when there is evidence of person-to-person transmission (21).

Vaccination campaign information includes the start date of campaign, the geographic region covered, type of vaccine and estimates of campaign coverage (Table S4). I did not include estimates of campaign coverage in the analysis, as they are known to provide inaccurate and upward-biased estimates of the true coverage achieved (22). However, the estimates are provided in the supplementary materials for use in interpretation. Estimates of administrative coverage are available for all campaigns, and in some instances independent monitoring (IM) and lot-quality assurance sampling (LQAS) assessments of coverage (23). Administrative coverage is a crude estimate calculated by the number of vaccine doses distributed divided by the size of the target

population. IM is conducted after the campaign as a rapid way of checking children's vaccination status, both through house-to-house monitoring and out-of-house monitoring (also known as market surveys). Clustered LQAS is a survey method that combines cluster sampling and the lot quality assurance (LQA) technique to quickly assess immunization performance in defined areas (known as "lots") using a small sample size (24).

Data on AFP cases and polio vaccination campaigns are stored in the GPEI polio information system database. Estimates of the population under 5 years by subnational administrative regions were exported from Humanitarian Data Exchange and are provided in Table S3 (25-27). All data was exported as of March 2022.

Guinea, South Sudan and Tajikistan outbreaks were selected as they met the study criteria that:

- no live type-2 containing vaccine has been used since April 2016 (in routine immunization or outbreak response);
- no cVDPV2 had been detected in these geographies since April 2016;
- and the outbreaks were caused by a single cVDPV2 genetic emergence group.

The study criteria were necessary to ensure fulfil the assumption that the under-five population had negligible intestinal immunity against type-2 poliovirus and were completely susceptible to transmission at the start of the outbreak. In South Sudan and Tajikistan, subnational mop-up vaccination campaigns were conducted after the timeframe of this analysis and are not included here.

Mathematical model

The model was developed in the R package panelPomp by Breto et al, which enables simulating and fitting partially-observed Markov process models (i.e. state-space models) to time series panel data (28) . Each country was modelled as panel data with independent units u, which are denoted as 1, 2…, U and represents a subnational administrative unit (administrative 1 level). Each unit has N_u observations written as $y_{u,1:N_u} = \{y_{u,1} \dots y_{u,N_u}\}$, collected at times $t_{u,n}$.

Observations (reported AFP cases) are modelled as a realisation of a stochastic observable process $Y_{u,1:N_u}$, which is dependent on a latent Markovian process $\{X_u(t), t_{u,0} < t < t_{u,N_u}\}$ (29).The likelihood function for unit u is $l_u(\theta) = f_{Y_{u,1:N_u}}(y^*_{u,N_u};\ \theta)$ and for the entire panel is $l_u(\theta) = \prod_{u=1}^{U} l_u(\theta)$. Any solution $\hat{\theta} = \text{argmax}\ l(\theta)$ is a maximum likelihood estimate (MLE) (28).

Markov process model

The process model is specified by describing the rates at which individuals move between compartments or states, with discrete time-step equal to one day (Figure 1). The state definitions and stochastic equations for the model are fully described in Table S1 and Table S2A, respectively. The model only considers the under-five population because this age group contributes most to poliovirus transmission (16, 30, 31) and specifically for cVDPV2, this age group has substantially lower intestinal immunity against poliovirus type 2 compared to older children and adults since the removal of type-2 containing OPV from routine immunisation in 2016 (32).

The cVDPV2 infection model was adapted from previously published frameworks (15) (29). The under-five population move through compartments susceptible (S) or IPV-vaccinated (V) to Exposed (E) to Infected (I) to Recovered (R) (Figure 1). The number of children moving between states is determined by drawing random numbers from multinomial distributions based on probabilities of model events determined by the transition rates. I did not consider birth and death rates due to the relatively short timing of the poliovirus outbreak. The model assumes homogeneous mixing within units. I assumed the latent and infectious periods for poliovirus to be a mean of 4 and 14 days, respectively (Table S3) (16, 33).

The vaccine-derived poliovirus force of infection was given as:

$$\lambda = \frac{\beta}{N}\ (I(t) + J(t))$$

Where β is the transmission rate, N the population size, I is number of infected individuals and J is the number of visiting infected individuals passing through the population (either 0 or 1), with probability ι (Table S2B). The average basic reproductive ratio, R_0, is defined as the expected number of secondary infections engendered by an infective introduced into a fully susceptible population and can be expressed in terms of β and the recovery rate γ (Table S2B).

A vaccination campaign with OPV vaccine at specified time t is included in the model by moving individuals from compartments S or V to Exposed with Vaccine (Ev), Infected with Vaccine (Iv) and R. All vaccination was assumed to occur on the first day of each SIA. The probability of an individual becoming immunised is the vaccination effectiveness, ε (product of campaign coverage and per-dose immunogenicity). Country administrative coverage levels for each campaign were not used in the model as they provide an indirect measure of the true coverage.

The live attenuated vaccine type 2 OPVs are regarded as infectious (both Sabin mOPV2 and nOPV2) with subsequent transmission of the vaccine to account for the secondary exposure of OPV (18). I assumed a type-2 OPV R_0 value of 0.9 based on evidence that the R_0 of Sabin type-2 OPV is <1, demonstrated by decline of vaccine virus in the environment and AFP cases following OPV withdrawal (15, 34). The duration of latency and infectiousness were assumed equal for cVDPV2 and OPV vaccines (Table S3).

The force of infection for the type-2 OPV vaccine is given as:

$$\lambda_v = \frac{\beta_V(\mathrm{t})}{\mathrm{N}} I_V(t)$$

Markov measurement model

The probability of an infected child being reported as a cVDPV2 AFP case was assumed to follow a binomial distribution:

$$Cases \sim Bin(C, \rho)$$

where is C is the number of children who complete the incubation period and ρ is the probability of becoming a reported AFP case. I assume one reported AFP case for every 2000 infections (35). The incubation period was taken as 16.5 days, based on the timing of independent data from 36 cases of paralytic poliomyelitis with known dates of exposure (36). For the incubation period to follow the Markov property, an Erlang distribution was fitted with a shape of 6 compartments and rate of transitioning between compartments of 0.329 $days^{-1}$ (Table S3) (15). Only individuals that transition from S to E compartments complete the incubation period (C) and can become reported cases: not those from V to E (see below).

IPV-vaccination

Individuals that have immunity from IPV are placed in the V state at the start of the outbreak. We assume one dose of IPV received in routine immunisation as part of a bOPV + IPV schedule provides 60% protection against paralysis (as shown in Chapter 2 and confirmed by case-control analysis of IPV effectiveness of preventing cVDPV2 AFP cases in Chapter 3.2) but negligible mucosal immunity against transmission (37). In the model, this means that individuals with effective IPV vaccination (V state) do not enter the incubation period and cannot become observed AFP cases, yet contribute equally to transmission and progress along the SEIR pathway. The force of infection for VDPV and type-2 OPV is assumed equal for IPV-vaccinated and non-vaccinated individuals.

Initial conditions

As the time of initial introduction of infection into the population was unknown, yet can affect the estimates of $R_{0.}$, it was estimated as follows. The timeseries was first extended to 300 days before the first detected case to capture the likely delay between initial introduction and generation of a first case, for the given case to infection ratio. Subsequently, at each time-step, there is a chance of a single importation into the population, defined by probability ι. The number of imported infections, J, at each time step has a binomial distribution, with probability ι and size 1 (corresponding to either 1 or 0 importations) The probability, ι, was constant over time

and constrained between 0 and 0.1: the upper limit of 0.1 corresponds to a frequency of one importation every 10 days (1/ ι), with the expected first importation event 294 days before the first reported AFP case. The expected timing of the first importation event from the start of the timeseries is calculated by the geometric distribution with probability equal to ι. Sensitivity analysis was conducted to explore the impact taking the timeseries back 400 days before the first cases on parameter estimates, with no significant difference in the 95% confidence interval estimates of vaccine effectiveness (Table S4).

Initial conditions assume that the total under-5 population has no intestinal immunity against type 2 poliovirus transmission. The population is divided into S or V states, depending on immunity from IPV-vaccination (described above). The initial conditions are that 30% the under-5 population have humoral immunity to type 2 poliovirus from IPV vaccination: corresponding to seroprevalence survey data from Tajikistan and Liberia (WHO, unpublished) from 2021 (38). This corresponds to a population IPV coverage of 50% and an estimated one-dose seroconversion of 60%.

Parameter estimation

For each setting I estimated i) the average basic reproductive ratio, R_0, ii) the per-day probability of importation, ι, and iii) vaccination campaign effectiveness, ε, through maximizing the log likelihood of each unit and the total panel. The parameter space was explored using a grid search for parameter combinations over a range of plausible values for each of the three parameters. For each parameter combination, individual unit and total panel likelihood were calculated using particle filter with 1,000 particles and was replicated three times. For individual units the mean loglikelihood and standard error from the 3 replicates were calculated. For the total panel, the loglikelihood and Monte Carlo uncertainty were calculated from the matrix of unit likelihood values using the approach described by Breto et al (28). For each parameter, 95% confidence intervals (CIs) were calculated from profile likelihood, under the assumption that the likelihood surfaces are χ^2distributed (Figure S1-S9) (39). The mid-way point between the parameter values above and below the likelihood line (± standard error) was taken. Panel iterated filtering (PIF) was used to carry out a local search starting at the maximum likelihood parameter combination identified in the grid search (28). However, PIF was not used in the final analysis as it does not

provide a method to calculate the 95% CIs of parameter values, which due to limited amount of data, are substantially more robust than maximum likelihood point estimates.

I compared three models with either shared parameter values between all units, or unit-specific values (i.e. different for each unit) for R_0, ι, and ε, through corrected Akaike Information Criterion (AICc) (39).

Simulations

Five thousand stochastic simulations were run for each unit under the best-fit model (example unit plots shown in Figure S10-S13). The number of cases were calculated by subsetting simulations that resulted in at least one reported case and calculating median and 95% CI. The total number of cases was calculated by taking the sum of a random draw from each panel distribution, repeating 1000 times with replacement, and calculating the median and 95% CI. Using a synthetic control modelling approach, I simulated a counter-factual to the vaccination activities examine the effect of expediting or delaying outbreak responses to further explore the effectiveness of vaccination in the affected countries (40).

All analysis was conducted in R and utilised the pomp and panelPomp packages (41-43). The R code for the analysis is publicly available on: https://github.com/Grace-Ruth/nOPV2.

5.5 Results

Guinea

In Guinea, the cVDPV2 NIE-JIS-1 outbreak was first detected with an AFP cVDPV2 case reported from Kankan region on 20th March 2020. Between 20th March 2020 and 01 April 2021, 50 cVDPV2 AFP cases were detected across seven out of eight regions in the country: Boke, Conakry, Faranah, Kankan, Kindia, Mamou and Nzerekore (Figure 2). The cVDPV2 is from the NIE-JIS-1 genetic group that was first detected in Nigeria in January 2018 and has been circulating in the African Region since. Outbreak response campaigns with mOPV2 were conducted in Kankan, Faranah and Nzerekore in October and December 2020, followed by

subsequent campaigns in Boke, Conakry Kindia and Mamou in February and June 2021 (Figure 2). Administrative estimates of vaccination coverage ranged between 95-106% for all four rounds; whilst independent monitoring estimates were 41% for the first two campaigns, and 79% and 89% for the third and fourth campaigns, respectively (Table S4).

In Guinea, the best fit model was for unit-specific estimates of vaccine effectiveness but shared R0 and iota parameters (AICc 762.4), compared to all three parameters shared (AICc 838.3) or specific (AICc 772.0). The MLE for the shared R0 was 1.25 [95% CI: 1.23-1.28] and ι 0.09 [95% CI: 0.03-0.1] – corresponding to the expected first importation event between 180 and 300 days before the first detected AFP case (Table 1).

The unit-specific 95% confidence intervals for vaccine effectiveness were: 12.5%-100% in Boke, 22.5%-100% in Conakry, 7.5%-32.5% in Faranah, 47.5%-100% in Kankan, 7.5%-100% in Kindia, 12.5%-72.5% in Mamou, 47.5%-100% in Nzerekore: providing a shared maximum likelihood estimate for Guinea between 37.5% and 87.5% (Figure 2A).

When the outbreak was simulated with the vaccination campaign as conducted, the total number of cases across the seven regions was estimated to have a median value of 27 [95% CI: 4-74], compared to the 50 observed cases (Table S5). The difference in simulated and observed cases was largely due to the region Kankan, where there were 20 reported cases compared to a median model estimate of 3 [95% CI: 1, 19] (Figure S11). If the campaign had been conducted one month earlier without any change in coverage, the number of cases was estimated to have been 20 [95% CI: 8- 43] (Table S5).

South Sudan

The first cVDPV2 AFP case was reported with onset of paralysis on 11th June 2020. Between 11th June 2020 and 9th April 2021, there were 58 cVDPV2 cases reported in South Sudan across all ten subnational states in the country, all associated with the CHA-NDJ-1 genetic group that was first detected in Chad in August 2019 (Figure 2). Three subnational vaccination campaigns with mOPV2 were conducted between 10th November 2022 and 16th February 2021 (Figure 2).

Administrative estimates of campaign coverage were 20% for the first round, followed by 87% and 88% for the second and third rounds, respectively, with post-SIA LQAS estimate of 80% after the last campaign (Table S4).

In South Sudan, the best fit model was for unit-specific estimates of vaccine effectiveness but shared R0 and iota parameters (AICc 720.0), compared to all three parameters shared (AICc 1368.0) or specific (AICc 808.8) (Table 2). The MLE for R0 was 1.35 [95% CI: 1.33-1.38] and ι 0.09 [95% CI: 0.085-0.1] – corresponding to the expected importation event between 259 and 300 days before the first AFP case (Table 1).

The 95% CI for vaccine effectiveness for each individual unit were 7.50-32.5% in Central Equatoria, 12.5-100% in Eastern Equatoria, 12.5%-42.5% in Jonglei, 32.5%-100% in Lakes, 32.5%-100% in Northern Bahr El Ghazal, 7.5%-17.5% in Unity, 2.5%-17.5% in Upper Nile, 7.5%-42.5% in Warrap, 7.5%-100% in Western Bahl El Ghazal and 17.5-100% in Western Equatoria. The total (shared) maximum likelihood estimate for vaccine effectiveness in South Sudan was between 12.5% and 17.5% (Figure 3A).

When simulating the outbreak with the vaccination campaign as conducted, I estimate a median of 40 [95% CI: 21-70] total cases across the ten regions (compared to 58 observed): I estimate 29 [95% CI: 16- 47] cases if the campaign had been conducted one month earlier (Table S5).

Tajikistan

In Tajikistan, an outbreak of cVDPV2 resulted in 33 cVDPV2 AFP cases reported between 22nd November 2020 and 26th June 2021 across three out of five regions in the country: Districts of Republican Subordination (DRS), Dushanbe and Khatlon (Figure 2). The Tajikistan outbreak was genetically linked to the PAK-GB-1 emergence, detected earlier in Pakistan and Afghanistan, and was considered as an importation event from one of these countries. Two national vaccination campaigns with nOPV2 were conducted on 31st May and 29th June 2021. The administrative coverage of the two rounds were 99.2% and 99.1% respectively, with post-SIA LQAS results for 2 rounds of 91.67% (Table S4)

The best fit model was for unit-specific estimates of vaccine effectiveness but shared R0 and iota parameters (AICc 294.6), compared to all three parameters shared (AICc 377.2) or specific (AICc 303.6) (Table 2). The shared MLE for R0 was 1.35 [95% CI: 1.23, 1.43]; however, the unit specific estimate for Dushanbe, 1.55 [95% CI: 1.38, 2.03], was significantly higher than in DRS and Khatlon, 1.30 [95% CI: 1.23, 1.43] and 1.35 [95% CI: 1.28, 1.38], respectively. The estimate of per day importation probability, ι was 0.1 [95% CI: 0.05-0.1], and therefore the expected importation event was 229-300 days before the first AFP case (Table 1).

The total effectiveness of the nOPV2 campaigns implemented in Tajikistan was 47.5-100% (Figure 2C): with unit-specific estimates of 12.5-100% in DRS; 7.5-100% in Dushanbe; and 52.5-100% in Khatlon (Figure 2C).

When simulating the outbreak with the vaccination campaign as conducted, using unit-specific coverage estimates, there is a median of 25 [95% CI: 4-74] total cases (in comparison to 33 observed) (Figure 3C). I estimate that without any change in coverage, the number of cases from these three regions alone would have been 17 [95% CI: 3-63] if the vaccination campaign was implemented one month earlier (Table S2).

5.6 Discussion

The substantial increase in cVDPV2 outbreaks after the removal of type 2-containing OPV from routine immunisation is a major burden globally and there is an urgent need for novel outbreak response vaccines (2). I present a generalisable mathematical modelling framework that can be applied to different settings to estimate vaccine effectiveness (the product of coverage and immunogenicity) and compare alternative vaccination strategies that are being implemented. This framework provides a tool to monitor the effectiveness of nOPV2 in outbreak response under WHO EUL in the absence of phase III clinical trial data. The analysis presented here illustrates effectiveness of mOPV2 and nOPV2 in the settings described, but variability between

sub-national regions, likely due to variation in the proportion of susceptible children reached during the campaigns.

As we approach a period when the under-five population globally has negligible intestinal immunity against type 2 poliovirus, we have observed cVDPV2 outbreaks that persist but have not led to the case counts that may be predicted with under the assumption of homogenous mixing at a national level. This is particularly prominent in Guinea, where there was a delay 7 months between the first AFP case and vaccination response with OPV. Our transmission model explains the observed dynamics through transmission persisting in populations at a local level, rather than all under-five children in a country. To capture spatial transmission dynamics, I separated sub-national areas into independent panel timeseries with the same underlying process model. This is supported by genetic analysis where the effective sample size is estimated as commonly small compared to total population. In the outbreaks described here, the independence of sub-national regions is emphasised perhaps due to restrictions on social mixing due to coronavirus.

I demonstrate in my analysis that the R_0 of these outbreaks in our model are between 1.2-1.5. There is little variation in R_0 between subnational areas, with a better model fit using shared parameters of R_0 than unit-specific values, for each of the three countries. In the model, natural stochasticity and population size generates the variance in case numbers seen at sub-national levels as opposed to variation in R_0 or population immunity against type 2 poliovirus. Looking forward, it may not be necessary to account for sub-national variation in transmission, making models simpler and easier to implement.

In this analysis, the ability to determine the effectiveness of an outbreak response from AFP case data depended on the timing of the response. In locations where there was a significant delay from the first case to the outbreak response campaign, the confidence intervals for vaccine effectiveness were very large. Additionally, in a single timeseries, the ability to infer the immunogenicity of the vaccine was limited; it may only be possible only to infer upper or lower limits of vaccine effectiveness. I demonstrate that through combining the likelihoods across subnational administrative regions, it is possible to build up a distribution of plausible values for

vaccine effectiveness. In this way, this work demonstrates that representation of spatiotemporal data through a collection of related units provides the opportunities to study aspects of dynamic systems that cannot be revealed from measurements on a single unit (28).

In the results for the three initial outbreaks, I find significant variation in vaccine effectiveness by sub-national region (as shown by the best fitting model in all three countries having specific parameters for each subnational region). The sub-national variation in vaccine effectiveness (coverage x immunogenicity) is within the expected values from monitoring estimates of vaccine coverage. In Guinea, the initial outbreak response campaigns covered Faranah, Kankan and Nzerekore: we estimate a significantly lower effectiveness for Faranah, which agrees with IM coverage results of 0% in Faranah, compared to 35% and 43% for Kankan and Nzerekore, respectively. In South Sudan, the two regions with the significantly lowest vaccine effectiveness were Unity and Upper Nile, with estimated effectiveness below 17.5%: whilst there were no sub-national estimates of coverage, vaccine supply issues in Unity meant that the campaign was not finished in this region and required a subsequent 'mop-up' campaign after the time period of this analysis.

I did not include vaccine coverage estimates in the analysis to directly infer vaccine immunogenicity due to the variable accuracy of the estimate they provide on true coverage (22). Administrative coverage estimates typically demonstrate close to 100% coverage in all areas, IM methods present issues of bias and lack of random sampling, whilst LQAS assessments are not consistently implemented (24). However, it is worthwhile to discuss the implications of the results in the context of available information on campaign coverage estimates. At a country level:

- For Tajikistan, the model estimates vaccine effectiveness between 47.5-100%: the LQAS coverage estimate of 97% would indicate an immunogenicity of 46-100%;
- For Guinea, the model estimates vaccine effectiveness between 37.5% -87.5%: the out-of-house IM estimates of coverage range from 40% to 90% over the four rounds (average 60%), suggesting an immunogenicity estimate of 62-100%;
- In South Sudan, the model estimates vaccine effectiveness between 12.5%-17.5%: the administrative coverage estimate for the first campaign was 20%, which would indicate an

immunogenicity between 62.5%-87.5%. The estimate of immunogenicity decreases if the administrative coverage estimates of close to 80% for later rounds are accurate.

These estimates are within the expected of mOPV2 and nOPV2 from immunity data, with vaccine immunogenicity expected to be similar for both vaccines. In clinical trials in infants in Panama, the one-dose seroprotection rate was 94% and 93% for mOPV2 and nOPV2, respectively (8). In immunogenicity studies conducted within outbreak response campaigns, one dose of mOPV2 in Mozambique demonstrated an immunogenicity of 60.6% (44), whilst in Tajikistan, one dose of nOPV2 had a seroconversion rate of 67.4% (38).

The simulations of alternative scenarios on total outbreak size emphasise the importance of timeliness and is in agreement with other studies that have shown the importance of fast implementation of SIAs (45). This is in accordance with the WHO Strategic Advisory Group of Experts on Immunisation recommendation that the priority for countries experiencing cVDPV2 outbreaks is to conduct high quality outbreak responses without delay, with whichever oral polio vaccine is available to them (46).

The model framework has several limitations: there is no inclusion of population demographics or movement, the assumption that subnational units are independent and the assumption that vaccine effectiveness is fixed across multiple campaign rounds. Whilst it is likely that vaccine immunogenicity is similar between campaigns, the coverage is known to vary. In addition, I only model subnational areas with detectable cases, whilst are there may be infected areas without detected cases. I assume that the baseline under-5 population is completely susceptible to transmission, with 30% of the proportion protected from paralysis by IPV. Whilst there are national indicators of IPV administration, the difference between these and estimates of immunity from population serological surveys demonstrates they are not reliable (38). I assumed a uniform estimate across countries of 30% based on serological data, while the true value will differ between settings.

Another limitation concerns the introduction time of the virus into the population, which I allow to vary through the probability of importation per time-step. However, this is still constrained by the assumption of introduction less than 300 days before the first detected case. In sensitivity

analysis, extending this time to 400 days did not significantly change the estimates of vaccine effectiveness. If genetic information were made available on the detected isolates, a more precise upper limit on the estimated introduction time could be calculated through establishing a genetic tree of the emergence group and the timing of detection of a last common ancestor. This information is currently not made available. However, plans to do so in the near future provide optimism that this approach can be improved.

To assess the effect of vaccination, I chose to quantify vaccine effectiveness as the combined effect of vaccine efficacy (immunogenicity) and coverage. More precise detail on true estimated coverage could make the model more specific to infer vaccine immunogenicity. Additionally, environmental sampling could be incorporated in settings where this type of surveillance is functional: however, this is often not available in most subnational areas, so would have limited applicability in the panel pomp structure used here.

In conclusion, this chapter demonstrates the development of a generalisable compartmental model for cVDPV2 outbreaks to measure the impact of vaccine effectiveness. This model can be applied to different settings and implements a technique of treating subnational levels of independent timeseries for a panel representation of spatiotemporal data. In this way, vaccine effectiveness can be inferred for different subnational areas to build up a distribution of values to interpret the impact of alternative vaccines. This will be particularly useful for assessing the impact of the nOPV2 vaccine use in the field, in comparison to traditional Sabin OPV-containing vaccines. For future work, I will continue to assess outbreaks and nOPV2 vaccination response to monitor vaccine effectiveness over the EUL period and compare to other evaluation methods, such as serology studies and case-control analysis to provide a holistic overview. Beyond this time, once the immunogenicity of nOPV2 is better established through phase III clinical trials and nested immunogenicity surveys, the model described here could be applied as a framework to estimate vaccination coverage achieved under an assumed vaccine immunogenicity.

5.7 References

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5.8 Figures and Tables

Figure 1: Schematic structure of compartmental cVDPV2 model with type-2 oral poliovirus vaccine (OPV) vaccination. The rectangular squares indicate the states in the mathematical model, defined in Table S1, and the rates at which individuals move between states are provided in Table S2. The blue squares indicate the cVDPV2 infection progress; from IPV-Vaccinated (V) or susceptible (S), to Exposed (E) to Infected (I) to Recovered (R). The green squares indicate the progress after vaccination with type-2 OPV, from V or S to Vaccine Exposed (Ev) to Vaccine Infected (I) to R. Orange squares indicate the AFP case development pathway for individuals enter in parrael to transitioning from S to E, and eventually to completion of the incubation period (C).

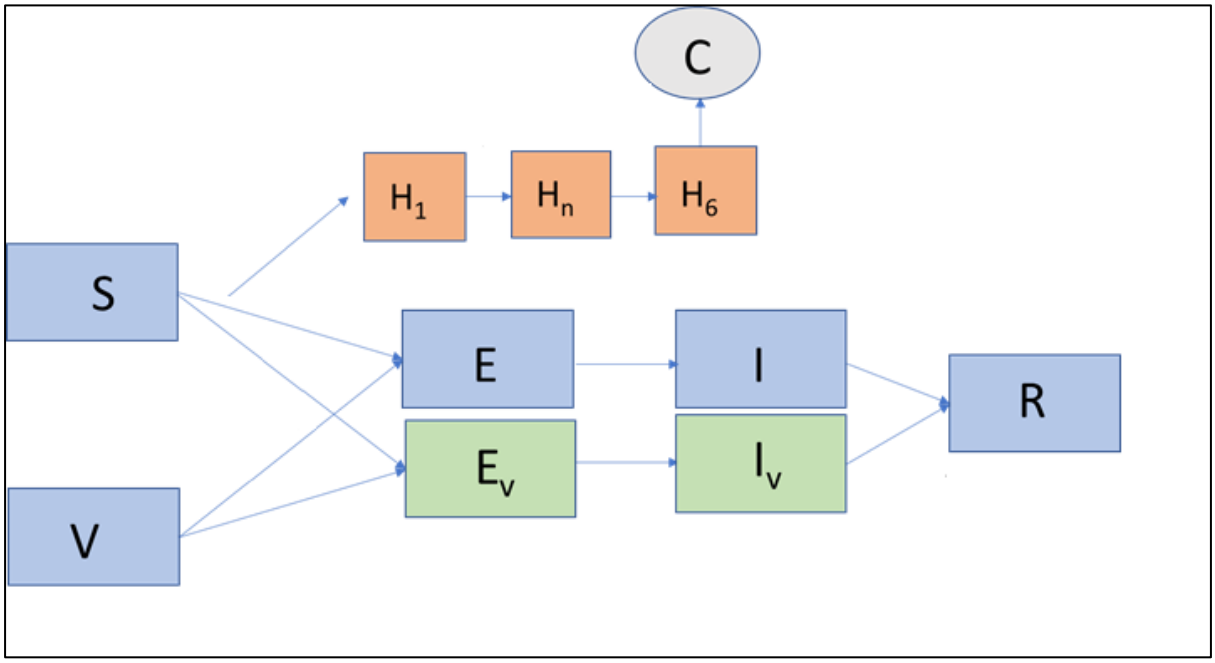


Figure 2: Timeline of cVDPV2 outbreaks and vaccination campaigns by region in Guinea, South Sudan, and Tajikistan. Red circles indicate date of onset of reported Acute Flaccid Paralysis (AFP) cVDPV2 cases, blue and green crosses indicate the start date of vaccination campaigns with mOPV2 and nOPV2 vaccines, respectively. All data exported as of March 2022.

Abbreviations: AFP – acute flaccid paralysis; cVDPV2 – circulating type 2 vaccine-derived poliovirus; DRS – Districts of Republican Subordination; mOPV2 – monovalent oral poliovirus vaccine type 2; nOPV2 – novel oral poliovirus vaccine type 2.

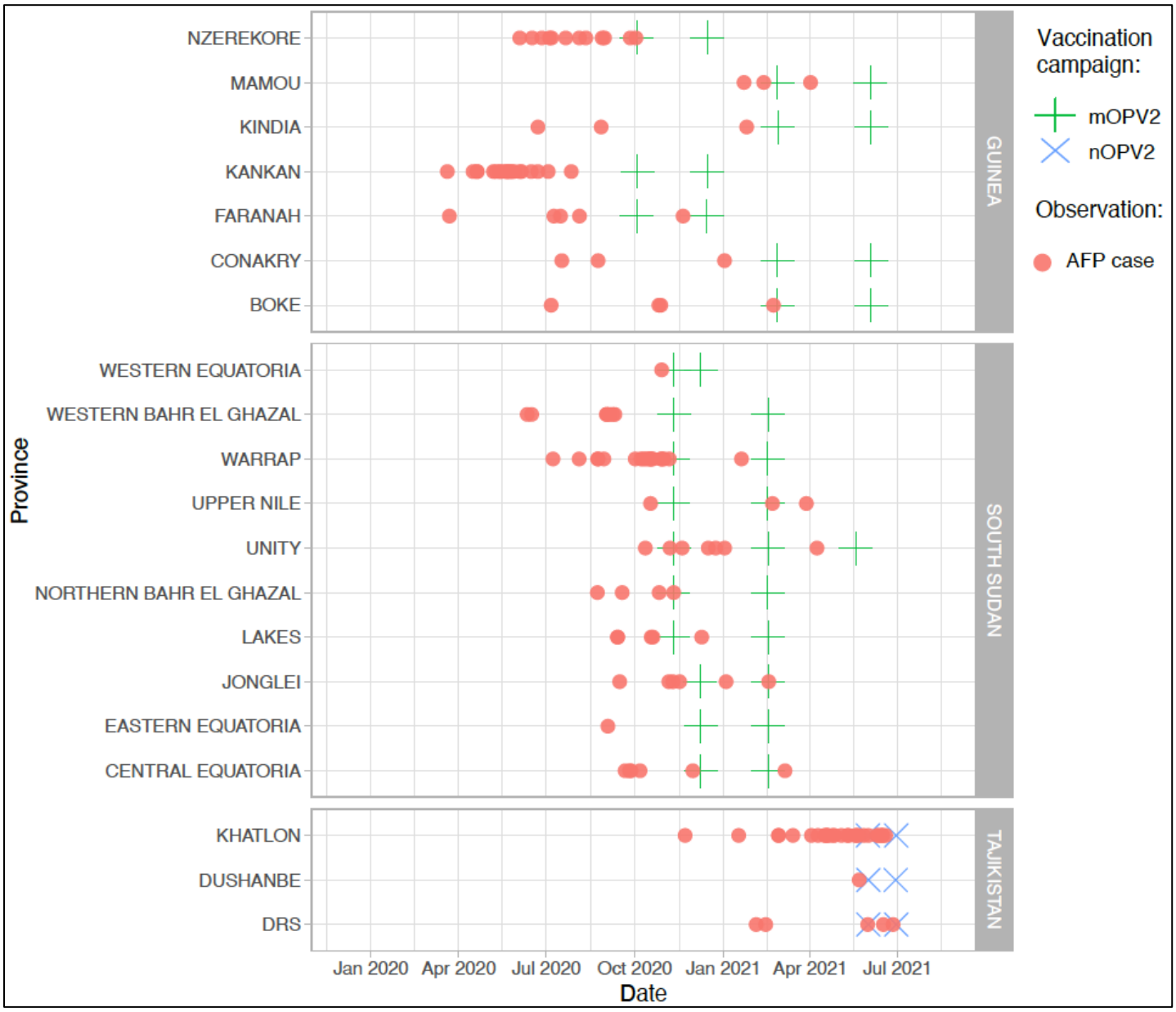
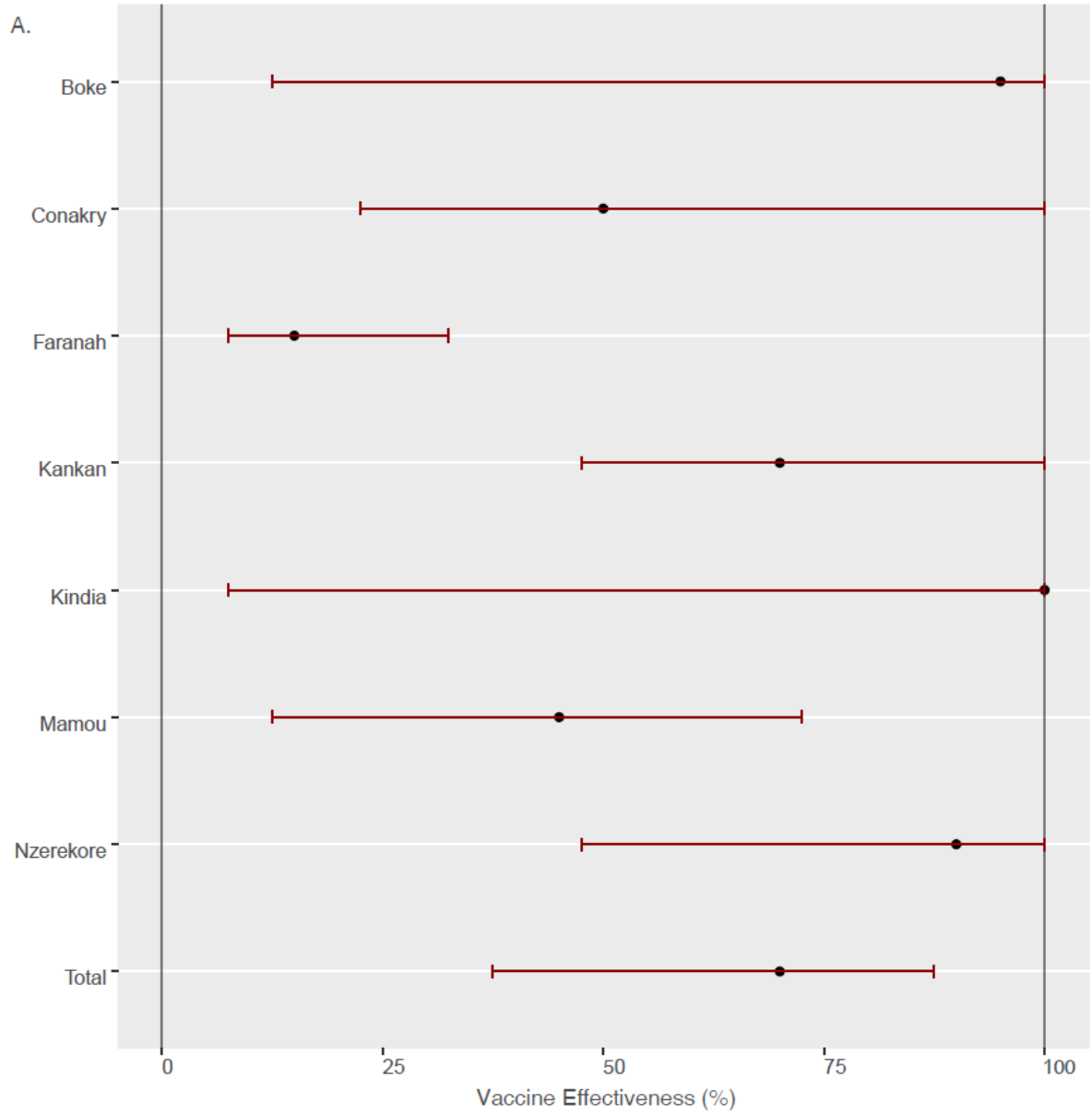
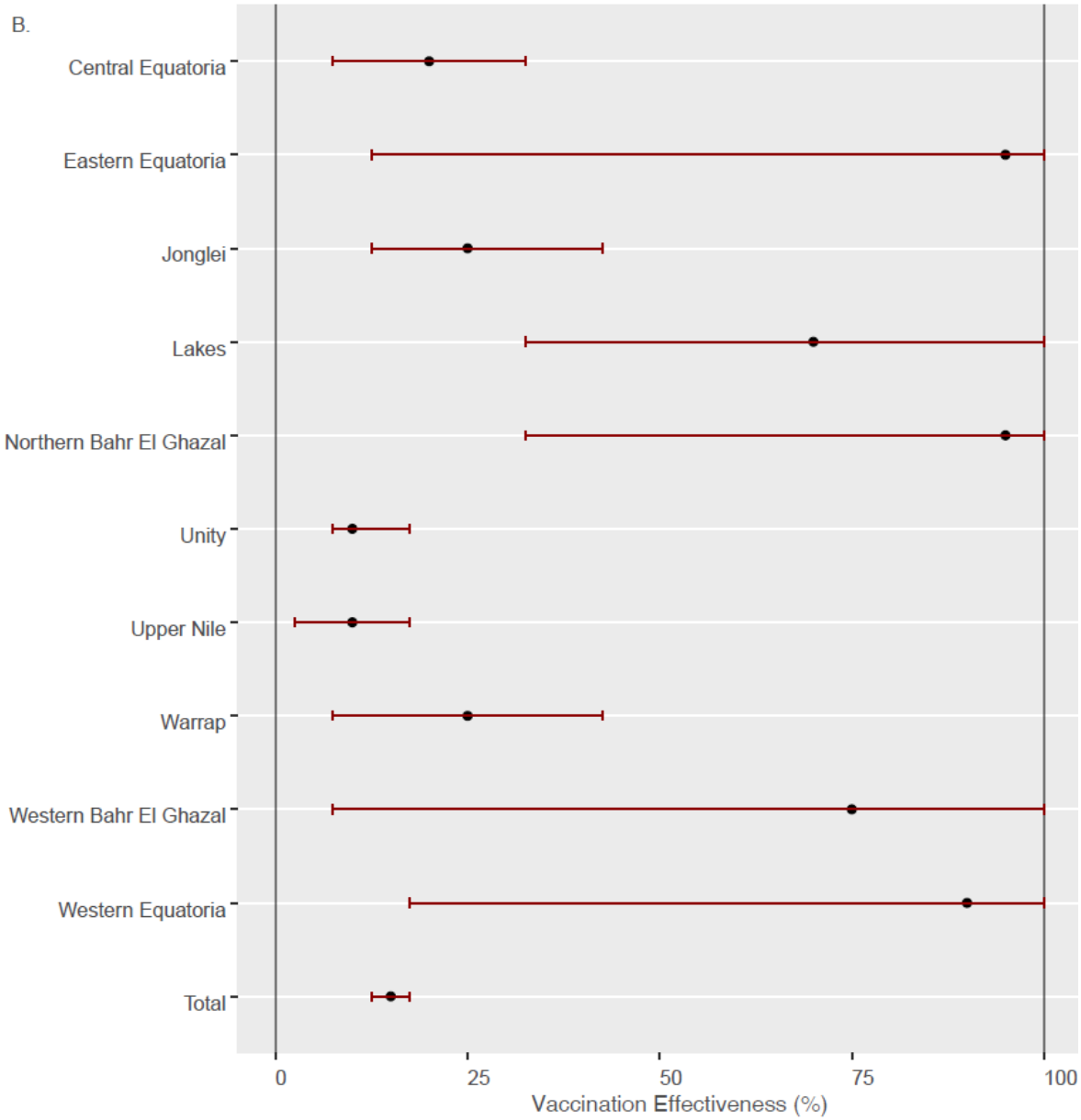


Figure 3: Estimates of vaccine effectiveness (produce of coverage and immunogenicity) for each unit (region) and total panel (country), A. Guinea B. South Sudan and C. Tajikistan. Lines indicate the 95% confidence intervals (CI), and circle indicates the maximum likelihood estimate (MLE). Abbreviation: DRS – Districts of Republican Subordination.




B.
Central Equatoria
Eastern Equatoria
Jonglei
Lakes
Northern Bahr El Ghazal
Unity
Upper Nile
Warrap
Western Bahr El Ghazal
Western Equatoria
Total
0
25
50
75
100
Vaccination Effectiveness (%)

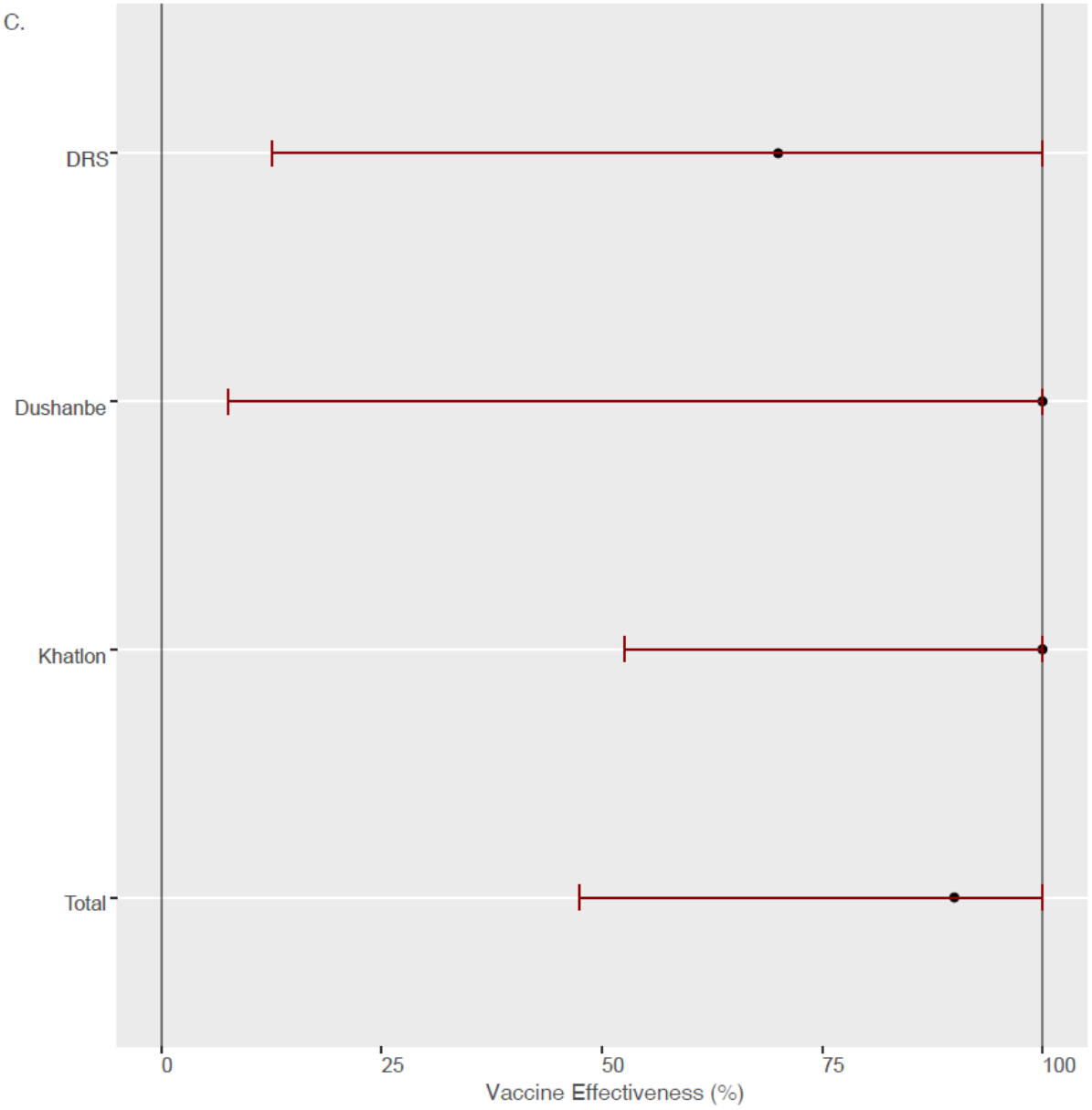

C.
DRS
Dushanbe
Khatlon
Total
0
25
50
75
100
Vaccine Effectiveness (%)

Table 1: Unit-specific and total panel maximum likelihood estimates (MLE) and 95% confidence intervals (CI), for the average basic reproductive ratio, R_0, per-day probability of importation, ι, and vaccination effectiveness, ε.

Country	Unit	Vaccination Effectiveness (ε)			R0			Probability of Importation (ι)		
		Lower CI	Upper CI	MLE	Lower CI	Upper CI	MLE	Lower CI	Upper CI	MLE
Tajikistan	Districts of Republican Subordination	12.5%	100.0%	70.0%	1.23	1.43	1.30	0.01	0.10	0.09
	Dushanbe	7.5%	100.0%	100.0%	1.38	2.03	1.55	0.02	0.10	0.10
	Khatlon	52.5%	100.0%	100.0%	1.28	1.38	1.35	0.01	0.10	0.08
	Total	**47.5%**	**100.0%**	**90.0%**	1.23	1.43	1.35	0.01	0.10	0.10
South Sudan	Central Equatoria	7.5%	32.5%	20.0%	1.28	1.38	1.30	0.02	0.10	0.10
	Eastern Equatoria	12.5%	100.0%	95.0%	1.18	1.43	1.30	0.01	0.10	0.10
	Jonglei	12.5%	42.5%	25.0%	1.23	1.48	1.35	0.01	0.10	0.10
	Lakes	32.5%	100.0%	70.0%	1.33	1.53	1.40	0.01	0.10	0.09
	Northern Bahr El Ghazal	32.5%	100.0%	95.0%	1.28	1.53	1.35	0.02	0.10	0.10
	Unity	7.5%	17.5%	10.0%	1.33	1.58	1.40	0.01	0.10	0.10
	Upper Nile	2.5%	17.5%	10.0%	1.28	1.53	1.40	0.03	0.10	0.09
	Warrap	7.5%	42.5%	25.0%	1.28	1.48	1.35	0.02	0.10	0.10
	Western Bahr El Ghazal	7.5%	100.0%	75.0%	1.23	1.38	1.30	0.02	0.10	0.10
	Western Equatoria	17.5%	100.0%	90.0%	1.33	2.03	1.55	0.01	0.10	0.10
	Total	**12.5%**	**17.5%**	**15.0%**	1.33	1.38	1.35	0.09	0.10	0.09
Guinea	Boke	12.5%	100.0%	95.0%	1.18	1.28	1.20	0.03	0.10	0.08
	Conakry	22.5%	100.0%	50.0%	1.13	1.23	1.20	0.02	0.10	0.10
	Faranah	7.5%	32.5%	15.0%	1.18	1.28	1.20	0.03	0.10	0.05
	Kankan	47.5%	100.0%	70.0%	1.23	1.38	1.30	0.05	0.10	0.10
	Kindia	7.5%	100.0%	100.0%	1.13	1.23	1.20	0.02	0.10	0.09
	Mamou	12.5%	72.5%	45.0%	1.33	1.73	1.50	0.02	0.10	0.10
	Nzerekore	47.5%	100.0%	90.0%	1.23	1.38	1.30	0.01	0.10	0.09
	Total	**37.5%**	**87.5%**	**70.0%**	1.23	1.28	1.25	0.03	0.10	0.09

Table 2: Corrected AIC (AICc), Panel log likelihood and Monte Carlo Standard Error (AICc) alternative models assuming shared or unit-specific estimates of fitted parameters.

Country	Model number	Vaccination Effectiveness (ε)	R_0	Probability of importation (ι)	AICc	Panel log likelihood	Monte Carlo Standard Error
Guinea	1	Shared	Shared	Shared	838.316	-414.714	7.663
	2	Specific	Shared	Shared	762.354	-368.357	2.104
	3	Specific	Specific	Specific	771.981	-345.25	3.647
South Sudan	1	Shared	Shared	Shared	1368.023	-679.634	14.297
	2	Specific	Shared	Shared	720.046	-342.887	1.048
	3	Specific	Specific	Specific	808.8	-335.246	0.341
Tajikistan	1	Shared	Shared	Shared	377.248	-183.91	3.935
	2	Specific	Shared	Shared	294.602	-139.686	0.132
	3	Specific	Specific	Specific	303.561	-136.781	0.087

Chapter 6: Conclusions and future directions

Is polio an eradicable disease? The first requirement for disease eradicability stated by Dowdle in 1998, is an effective intervention available to interrupt transmission of the agent (1). Whilst the oral poliovirus vaccine (OPV) is undoubtedly able to interrupt the transmission of polioviruses, would we consider it an effective intervention, given the reversion and seeding of circulating type 2 vaccine-derived poliovirus (cVDPV2) described in this thesis? The inactivated poliovirus vaccine (IPV) is effective at preventing paralysis, but alone has negligible impact on interrupting intestinal transmission. The novel oral poliovirus vaccine type 2 (nOPV2) is anticipated to have significantly greater genetic stability through a series of genetic modification. However, it is acknowledged that nOPV2 has a non-negligible risk of reversion: only time will discover the magnitude of this risk. Can a combination of these vaccines and innovative strategies in routine immunisation and outbreak response achieve eradication?

The Global Polio Eradication Initiative (GPEI) endgame strategic plan, developed in 2012, aims for the certification of eradication of wild polioviruses (WPV), followed by the complete withdrawal of OPV and replacement with IPV, and subsequently, the validation of absence of VDPVs (2). The first stage of OPV cessation was the removal of type-2 containing OPV from elective use, with replacement of the trivalent OPV (tOPV, types 1, 2 and 3) to bivalent OPV (types 1 and 3) in April 2016, known as the ‘Switch’. My PhD was undertaken during the period immediately after (2017-2022), and the result is a body of research dedicated to better understanding the evolving epidemiology and optimal vaccination strategies to provide an evidence-base for informing global policy.

In this thesis, I have made several significant contributions. Here, I highlight those that I deem to be the most significant:

In Chapter 2, I developed a succinct comparison of the humoral and mucosal immunogenicity induced by different routine immunisation schedules, combining information across clinical trials to provide a single, comprehensive assessment that could advise vaccination policy. I demonstrated the addition of one dose of IPV to bOPV schedules reduces the type 2 humoral

immunity-gap, which is further boosted by a second IPV dose. Additionally, I showed that there is no difference in immunogenicity of IPV variants (Salk IPV, sIPV, ID fIPV, IPV-Al), which provide opportunities address IPV cost and supply constraints. I confirmed the impact of IPV in routine immunisation in Chapter 3.2, with a case-control analysis of cVDPV2 AFP and non-polio AFP cases: estimating 58.5% effectiveness of one dose of IPV in preventing paralysis from cVDPV2. This evidence was presented to the WHO Strategic Advisory Group of Experts (SAGE) and Polio Research Committee as evidence for the recommendation that all countries should add a 2nd IPV dose in their routine immunization schedule(3); as well as recommendations that fractional IPV and Sabin IPV could be used as alternative IPV options (4). Critically, I demonstrated that while the IPV dose in a bOPV + IPV schedule provides humoral immunity protecting against paralysis, it has negligible impact on intestinal mucosal immunity, which is vital to prevent transmission, and has had significant consequences on cVDPV2 epidemiology.

In Chapter 3, I demonstrated the implications of the removal of tOPV from routine immunisation, specifically the increasing incidence and geographic scope of cVDPV2 outbreaks, which have presented a major challenge for the GPEI. In 2016, cVDPV2 transmission was detected in two countries and two cVDP2 AFP cases were reported, which increased to cVDPV2 transmission in 30 countries and 1062 cVDPV2 AFP reported cases in 2020. Since the bOPV + IPV routine vaccination provides negligible intestinal immunity against type 2 poliovirus, there has been a rapid decline in population immunity against transmission, meaning cVDPV2 outbreaks have been increasingly difficult to control. Insufficient outbreak response, due to issues of speed, scope and quality, have resulted in extensive geographic transmission (5). Using statistical analysis based on genetic divergence of cVDPV2 strains from Sabin vaccine virus, I demonstrate that the increasing number of new emergences of cVDPV2s are largely attributable to the use of type 2 monovalent OPV (mOPV2) in outbreak response (6).

The seeding of cVDPV2 outbreaks through use of mOPV2 in outbreak response is one of the biggest challenges in the current phase of polio eradication (6). I presented my findings published in Chapter 2 as a guest on BBC World Service Radio, Science in Action, to a boarder audience, and to WHO SAGE and Global Polio Eradication Advisory Strategy Committee for

policy consideration. My analysis around the source of cVDPV2 outbreaks provided a concrete evidence base to support the accelerated development of the novel oral poliovirus vaccine type 2 (nOPV2), highlighting the urgent need of a more genetically stable vaccine.

In November 2020, the WHO Executive Board emphasised the critical importance of rapid nOPV2 assessment and deployment (7). In November 2020, nOPV2 received recommendation for use in outbreak response to cVDPV2 under the WHO Emergency Use Listing (EUL) procedure – a process to expedite the availability of unlicensed medical products for a Public Health Emergency of International Concern (PHEIC). At this time, working at the WHO Polio Eradication department, I co-ordinated the policy for nOPV2 use, including the framework for nOPV2 roll-out and the post-deployment monitoring plan for evaluating safety and effectiveness. In Chapter 4, I document the considerations for the accelerated development and use of a vaccine under a PHEIC. As the first vaccine to ever receive WHO EUL, this framework has paved the way for the roll-out of other vaccines in the future, including recent COVID-19 vaccine development (8).

In Chapter 5, I developed a generalisable framework to monitor the effectiveness of the nOPV2 vaccine in a timely manner during its use under EUL. I utilised a novel method to incorporate the spatiotemporal dynamics of poliovirus outbreaks, without depending on detailed population demographics or spatial structures incorporated into the model. In the future, this model could include more precise estimates around the introduction time of cVDPV2 into the population, with the incorporation of information on virus genetics and environmental surveillance (ES) detections. The utilisation of molecular epidemiology principles to sequencing results of polioviruses, plays an important role to track geographic origins and patterns of spread of the virus. A recent review by Jorgenson et al highlighted the need of incorporating modern molecular technologies to accelerate poliovirus detection (9).

Through counter-factual simulations, I demonstrated the importance of early response to outbreaks through vaccines. This is in line with the WHO SAGE recommendation that countries should respond rapidly to cVDPV2 outbreaks with whichever type 2 containing OPV is available to them (4). To enable earlier detection and response, it is critical to strengthen existing polio

surveillance systems and adapt them to the evolving epidemiology. The current level of dependence of acute flaccid paralysis (AFP) surveillance to identify transmission will not be maintainable, and expansion of ES must continue (10). The extent of subclinical poliovirus infections, with a case to infection ratio of 1:200 for WPV1 has been a major difference between the endgame success of smallpox and polio eradication, while the case to infection ratio for cVDPV2 (1:2000) is significantly lower (11, 12). As IPV is used more extensively in routine immunisation, the proportion of infections that develop paralysis further reduce; therefore, extensive transmission in the absence of AFP cases will become more frequent (13, 14). The importance of ES has grown in recent years due to its unique role in detecting transmission early, or in the absence of paralytic cases, as well as the programmatic need to monitor Sabin-like viruses for reversion in the post-Switch period (15, 16). ES has practicality beyond poliovirus surveillance and this network can be integrated with broader communicable disease control efforts, such as surveillance for SARs-CoV-2, antimicrobial resistance and cholera control (17-19). Additionally, direct detection of viral RNA using PCR methods has the potential of faster identification of virus transmission, allowing for the initiation of outbreak response activities sooner. A PCR and nanopore sequencing protocol have recently demonstrated high sensitivity for detection of WPVs, VDPV2 and Sabin-like viruses from approximately 150 samples in Pakistan, with sequencing results available in less than 3 days (20).

Despite the intense efforts to accelerate the development and implementation of nOPV2, my modelling analysis in Chapter 5 demonstrates large variability in field effectiveness with estimates as low as 15% in South Sudan due to poor coverage. The practical barriers to delivering vaccines to children in both routine immunisation and supplementary immunisation activities have not been evaluated in this thesis. Yet, it is clear that despite knowing the importance of high-quality campaigns, translation into effective implementation has continued to prove challenging to the GPEI (5). Interestingly, for smallpox eradication, the plan of mass vaccination to achieve population immunity was trialled and brought down cases to low levels (24). However, eradication was only achieved by replacing the strategy of mass vaccination to one of surveillance and ring vaccination for people likely to have been exposed to the virus (24, 25).

While the risk of VDPV2s after withdrawal of tOPV was known, it was under-estimated. On reflection, nOPV2 was developed too late, and if we had this tool prior to April 2016, the epidemiology would undoubtedly look very different today. As of May 2022, the use of nOPV2 under EUL continues with approximately 260 million doses administered across 14 countries; however, sufficient vaccine supply for broader use and demonstration of genetic stability and effectiveness in the field remain unconfirmed. It is clear, however, that even if the vaccine performs as expected, it cannot solve the demonstrated inability to control outbreaks due to poor coverage and delayed outbreak response activities. In addition, as a live vaccine with a risk of reversion, the indefinite use of nOPV2 is not compatible with eradication.

Therefore, the question remains as to whether polio is an eradicable disease. It is difficult at this time, with the tools available or in development, to visualize a feasible endgame that can achieve polio eradication as is currently defined: the reduction to zero of the worldwide incidence of infection of all polioviruses and elimination of the disease they cause (1). The eradication of polioviruses (wild poliovirus and/or vaccine-derived polioviruses) and of the disease (poliomyelitis) should be separated (21). Eradication of wild poliovirus is biologically feasible with the vaccines that are available. The barriers that remain encompass the practicalities of vaccinating every child, including social, political, and financial considerations (5, 22). If these barriers are overcome and WPV eradication is achieved in the next few years, it should be celebrated as a true accomplishment and success in the international health community. Subsequently, the risk of re-introduction of wild poliovirus transmission from laboratories and vaccine production sites would need to be managed and IPVs produced from a non-infectious process, such as virus-like particle vaccines, would become increasingly important (23, 24)

Elimination of poliomyelitis disease as a public health problem is achievable with the vaccines that are available now: a routine programme that maintains high rates of protection against paralytic poliomyelitis from all polioviruses, including vaccine-derived polioviruses. The delivery of vaccines through Expanded Programme on Immunisation (EPI) and sensitive environmental surveillance then should be integrated with other global health programmes (21, 25-27). Use of nOPVs to control outbreaks when detected through sensitive surveillance would

be possible; whether nOPVs would also need to be integrated alongside IPV in routine immunisation, will depend on the epidemiology.

Looking towards the eradication of vaccine-derived polioviruses, it is currently unknown whether nOPV is sufficiently genetically stable that a re-attempt of 'the Switch' (comprising complete cessation of nOPV vaccines) would be successful. It is, however, essential that the programme incorporates the lessons learnt from the Switch: the bOPV vaccine should not removed without the availability of nOVP1 and nOPV3 vaccines. In addition, the Switch was predicted to be successful because it was shown that high levels of population intestinal immunity against type 2 transmission would prevent transmission of OPV vaccine virus and could be effectively boosted by IPV if necessary (28). However, considerable pockets of low population immunity at the time of the Switch contributed to the failure of this strategy (28). Currently, in areas without recent cVDPV2 or type-2 containing OPV use in outbreak response, can be considered to have an under-five population entirely susceptible to transmission, as indicated in my mathematical model. Therefore, mass vaccinations or routine immunisation with nOPV2 may be necessary to increase intestinal immunity before cessation could be attempted again.

If the risks of reversion associated with nOPVs are not sufficiently small, then only the promise of a new vaccine, such as an IPV that can induce intestinal immunity (the 'magic bullet'), would permit the eradication of all polioviruses. However, the development of such a vaccine remains elusive: the most recent hope of an adjuvanted IPV that can stimulate mucosal immune responses was shown to be ineffective at preventing transmission (29). Failing this, the global community must accept a programme as described above that is focused on eliminating poliomyelitis disease as a public health problem, rather than the eradication of all polioviruses.

6.1 Final Remarks

The global polio eradication program is at a decisive juncture in 2022. There has been unprecedented success in eliminating a highly infectious, paralyzing disease from nearly every country in the world, including those with difficult-to-access, high disease burden and densely

populated settings. However, the unique epidemiologic situation following cessation of routine Sabin OPV2 and the inability to effectively control cVDPV2 outbreaks has implications on the broader eradication strategy and puts the global program at risk of failure. Optimal use of the current vaccines and the introduction of genetically stable nOPV vaccine is of paramount importance to control the current situation. However, it is evident that the global polio eradication programme and broader global health community must incorporate the knowledge that has accumulated over recent years and redefine eradication objectives accordingly.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Macklin GR, Grassly NC, Sutter RW, et al. Vaccine schedules and the effect on humoral and intestinal immunity against poliovirus: a systematic review and network meta-analysis. *Lancet Infect Dis* 2019; published online July 23. http://dx.doi.org/10.1016/S1473-3099(19)30301-9.

WEB-APPENDIX

Table of Contents

Web appendix 1: Study protocol

Vaccine schedules and the effect on humoral and intestinal immunity against poliovirus: a systematic review and network meta-analysis

Review questions

1. What is the relative efficacy of different routine vaccination schedules in inducing humoral immunity to poliovirus serotypes one, two and three?

2. What is the relative efficacy of different vaccination schedules in inducing mucosal immunity to poliovirus serotypes one, two and three?

Searches

Eligible trials will be identified by systematic searching of the literature, that will include the following electronic databases: PubMed and Cochrane Central Register of Controlled Trials (CENTRAL). Search results will be restricted to studies in humans. There will be no language restrictions. Studies published between January 1980 and the date the searches are run will be sought. The searches will be re-run just before the final analyses and further studies retrieved for inclusion.

Types of study to be included

Randomized controlled trials only

Condition or domain being studied

Poliovirus vaccine

Participants, Intervention, Comparator, Outcomes (PICOS) criteria

	Included	Excluded
Participants	Infants	Adults, Children
Intervention	Current poliovirus routine immunisation schedules: – IPV-only – bOPV-only – IPV-bOPV only First dose given at birth, or 4-8 weeks	Non-study poliovirus routine immunisation schedules: – tOPV-IPV, tOPV-mOPV or tOPV-bOPV combination schedules – mOPV-only schedules Incomplete routine immunisation schedule Booster vaccination Historical vaccine formulations Variation in age schedule between arms
Comparator	Current poliovirus routine immunisation schedules: – IPV-only – bOPV-only – IPV-bOPV only	

	Historical poliovirus routine schedule, if additionally available: – tOPV-only First dose given at birth, or 4-8 weeks	
Outcome	Seroconversion to serotype 1, 2 and 3 polioviruses AND/OR Shedding serotype 2 polioviruses, seven days after challenge dose with mOPV2 or tOPV.	Report non-serotype-specific outcomes

Primary outcome(s)

1. Development of humoral immunity to poliovirus serotype 1, 2 and 3 (as binary outcome). This will be defined as seroconversion, or a >1:4-fold increase in antibody titers. Blood sample to be taken before and after the full primary vaccination series.
2. Development of intestinal immunity to poliovirus serotype 2 (as binary outcome). This will be defined as the absence of shed virus after challenge dose of OPV. The challenge dose vaccine should be given following the full primary vaccination series. Fecal sample taken seven days after challenge OPV dose.

Data extraction (selection and coding)
One investigator will examine (screening by title and abstract) the records to identify potentially eligible trials. The full texts of potentially eligible trials reports will be retrieved and assessed against the inclusion criteria. Two investigators will extract data using an extraction form and assess the risk of bias.

Risk of bias (quality) assessment
We will assess risk of bias in the included studies using the tool described in the Cochrane Collaboration Handbook as a reference guide. The following domains for each trial will be assessed: sequence generation, allocation concealment, blinding, and incomplete outcome data.

Strategy for data synthesis
For each outcome and serotype, study-arm level data will be used to compute: (1) a random-effect meta-analysis of single proportions and (2) a random-effect network meta-analysis. The network meta-analysis will be running in a Bayesian framework and the relative effects between interventions will summarized as an effect ratio with 95% credible intervals (CrIs). The random effects standard deviation (τ) will be used as a measure of heterogeneity and a node-splitting model will be used to measure network inconsistency.

Analysis of subgroups or subsets
Additional analysis will include network meta-regression and/or sub-group analysis to explore the effect of study-level covariates. If the necessary data are available, study-level covariates may include: country of study, vaccination schedule (birth dose) and if country is polio endemic.

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None known

Language
English

Web appendix 2: References of included studies

2.1 Reference list of studies included in humoral network meta-analysis

Anand et al 2015
Anand A, Zaman K, Estivariz CF, Yunus M, Gary HE, Weldon WC, et al. Early priming with inactivated poliovirus vaccine (IPV) and intradermal fractional dose IPV administered by a microneedle device: A randomized controlled trial. Vaccine. 2015;33(48):6816-22.

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2.2 Reference list of studies included in mucosal network meta-analysis

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Saleem AF, Mach O, Yousafzai MT, Khan A, Weldon WC, Steven Oberste M, et al. Immunogenicity of Different Routine Poliovirus Vaccination Schedules: A Randomized, Controlled Trial in Karachi, Pakistan. J Infect Dis. 2018;217(3):443-50.

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Taniuchi M, Famulare M, Zaman K, Uddin MJ, Upfill-Brown AM, Ahmed T, et al. Community transmission of type 2 poliovirus after cessation of trivalent oral polio vaccine in Bangladesh: an open-label cluster-randomised trial and modelling study. Lancet Infect Dis. 2017;17(10):1069-79.

Web Appendix 3: Data from included studies

Table 1: Characteristics of study arms identified in literature search and included in analysis for humoral immunity against poliovirus serotype 1, 2 and 3, measured as seroconversion.

Study #	Primary Author	Year	Location	Vaccine schedule	IPV route	Age of administration (weeks)[1]	Age at blood draw (weeks)[2]	Type 1 responders	Type 1 sample size	Type 2 responders	Type 2 sample size	Type 3 responders	Type 3 sample size
1	Saleem, A. F.	2018	Pakistan	4 IPV	IM	birth, 6, 10, 14	22	111	138	116	138	129	138
1	Saleem, A. F.	2018	Pakistan	4 bOPV		birth, 6, 10, 14	22	139	144	28	144	135	144
1	Saleem, A. F.	2018	Pakistan	4 bOPV + 1 IPV	IM	birth, 6, 10, 14, 14	22	263	277	142	277	266	277
1	Saleem, A. F.	2018	Pakistan	4 tOPV		birth, 6, 10, 14	22	126	134	125	134	114	134
2	Chu, K.	2018	China	3 sIPV[b]	IM	8, 12, 16	20	104	104	101	104	103	104
2	Chu, K.	2018	China	3 IPV	IM	8, 12, 16	20	110	110	110	110	110	110
3	Rivera, L.	2017	Dominican Republic	3 IPV-Al[c]	IM	6, 10, 14	18	201	204	193	204	203	204
3	Rivera, L.	2017	Dominican Republic	3 IPV	IM	6, 10, 14	18	206	206	203	206	206	206
4	Qiu, J.	2017	China	3 IPV	IM	8, 12, 16	20	75	82	70	82	80	82
4	Qiu, J.	2017	China	1 IPV + 2 bOPV	IM	8, 12, 16	20	85	86	48	86	85	86
4	Qiu, J.	2017	China	3 tOPV		8, 12, 16	20	75	78	76	78	78	78
4	Qiu, J.	2017	China	2 IPV + 1 bOPV	IM	8, 12, 16	20	81	86	71	86	84	86
5	Lopez-Medina, E.	2017	Latin America[a]	3 bOPV + 1 IPV	IM	6, 10, 14, 14	18	285	285	226	285	284	285
5	Lopez-Medina, E.	2017	Latin America[a]	3 bOPV + 2 IPV	IM	6, 10, 14, 14, 36	40	534	535	534	535	534	535
6	Saez-Llorens, X.	2016	Panama	3 bOPV + 1 IPV	IM	6, 10, 14, 14	18	105	115	86	115	113	115

6	Saez-Llorens, X.	2016	Panama	3 bOPV + 1 mIPV2[d]	IM	6, 10, 14, 14	18	110	115	107	115	113	115
7	Asturias, E. J.	2016	Latin America[1]	3 bOPV		6, 10, 14	18	197	198	19	198	195	198
7	Asturias, E. J.	2016	Latin America[1]	3 tOPV		6, 10, 14	18	86	88	86	88	87	88
7	Asturias, E. J.	2016	Latin America[1]	3 bOPV + 1 IPV	IM	6, 10, 14, 14	18	194	194	156	194	194	194
7	Asturias, E. J.	2016	Latin America[1]	3 bOPV + 2 IPV	IM	6, 10, 14, 14, 36	40	193	193	193	193	192	193
8	Liao, G. Y.	2016	China	3 sIPV[b]	IM	8, 12, 16	20	570	570	541	570	564	570
8	Liao, G. Y.	2016	China	3 IPV	IM	8, 12, 16	20	534	564	515	564	552	564
9	Sutter, R. W.	2015	India	4 tOPV		birth, 6, 10, 14	18	162	163	157	163	147	163
9	Sutter, R. W.	2015	India	4 bOPV		birth, 6, 10, 14	18	153	155	29	155	151	155
9	Sutter, R. W.	2015	India	4 bOPV + 1 IPV	IM	birth, 6, 10, 14, 14	18	155	156	107	156	155	156
9	Sutter, R. W.	2015	India	4 bOPV + 2 IPV	IM	birth, 6, 10, 14, 18	22	155	155	155	155	155	155
10	O'Ryan, M.	2015	Chile	1 IPV + 2 bOPV	IM	8, 16, 24	28	166	168	130	168	163	166
10	O'Ryan, M.	2015	Chile	2 IPV + 1 bOPV	IM	8, 16, 24	28	178	178	169	176	177	177
10	O'Ryan, M.	2015	Chile	3 IPV		8, 16, 24	28	175	175	175	175	172	174
11	Estivariz, C. F.	2015	Bangladesh	3 bOPV		6, 10, 14	18-20	179	184	29	184	176	184
11	Estivariz, C. F.	2015	Bangladesh	3 tOPV		6, 10, 14	18-20	175	190	182	190	167	190
12	Anand, A.	2015	Bangladesh	3 tOPV		6, 10, 14	18	190	203	200	203	192	203
12	Anand, A.	2015	Bangladesh	3 bOPV		6, 10, 14	18	197	200	28	200	188	200
12	Anand, A.	2015	Bangladesh	2 IPV	IM	6, 14	18	148	156	142	156	152	156
12	Anand, A.	2015	Bangladesh	2 fIPV[e]	ID	6, 14	18	133	152	123	152	135	152

12	Anand, A.	2015	Bangladesh	fIPV[e] + bOPV + fIPV[e]	ID	6, 10, 14	18	202	211	172	211	198	211
13	Liao, G. Y.	2012	China	3 sIPV[b]	IM	8, 12, 16	20	88	90	84	88	90	91
13	Liao, G. Y.	2012	China	3 tOPV		8, 12, 16	20	92	92	92	92	92	92
13	Liao, G. Y.	2012	China	3 IPV	IM	8, 12, 16	20	82	91	74	82	87	89
14	Cadorna-Carlos, J.	2012	Philippines	3 fIPV[e]	ID	6, 10, 14	18	108	109	103	109	104	109
14	Cadorna-Carlos, J.	2012	Philippines	3 IPV	IM	6, 10, 14	18	112	114	112	114	114	144
15	Mohammed, A. J.	2010	Oman	3 fIPV[e]	ID	8, 16, 24	26	182	187	179	187	183	187
15	Mohammed, A. J.	2010	Oman	3 IPV	IM	8, 16, 24	26	186	186	186	186	186	186
16	Resik, S.	2010	Cuba	3 fIPV[e]	ID	6, 10, 14	18	99	187	159	187	129	187
16	Resik, S.	2010	Cuba	3 IPV	IM	6, 10, 14	18	158	177	169	177	175	177
17	Nirmal, S.	1998	India	2 fIPV[e]	ID	6, 14	18	27	30	21	30	29	30
17	Nirmal, S.	1998	India	3 fIPV[e]	ID	6, 10, 14	18	35	39	31	39	38	39

bOPV = bivalent oral poliovirus vaccine. fIPV = fractional inactivated poliovirus vaccine. ID = intradermal. IM = intramuscular. IPV = conventional inactivated poliovirus vaccine. IPV-Al = Aluminium hydroxide–adjuvanted inactivated poliovirus vaccine. mIPV2 = monovalent serotype 2 high-dose inactivated poliovirus vaccine. sIPV = Sabin inactivated poliovirus vaccine. tOPV = trivalent oral poliovirus vaccine.

[1]Closest approximation time in weeks

[a]Study conducted at four investigational sites in Colombia, Dominican Republic, Guatemala, and Panama

[b]30, 32, and 45 D-Antigen content for serotype 1, 2 and 3, respectively.

[c]1/10th full IPV dose

[d]32 D-Antigen content for serotype 2.

[e]1/5th full IPV dose (0.1m

Table 2: Characteristics of studies identified in literature search and included analysis for intestinal immunity against serotype 2, defined as absence of shedding 7 days after challenge vaccine dose.

Study #	Primary Author	Year	Location	Vaccine schedule	Age of administration[1]	Sample size	Absence of poliovirus in stool, 7 days after challenge dose
1	Saleem, A. F.	2018	Pakistan	4 bOPV	birth, 6, 10, 14	86	57
1	Saleem, A. F.	2018	Pakistan	4 bOPV + 1 IPV	birth, 6, 10, 14	70	47
1	Saleem, A. F.	2018	Pakistan	4 IPV	birth, 6, 10, 14	72	44
1	Saleem, A. F.	2018	Pakistan	4 tOPV	birth, 6, 10, 14	73	69
2	Lopez-Medina, E.	2017	Latin America	3 bOPV + 1 IPV	6, 10, 14, 14	283	72
2	Lopez-Medina, E.	2017	Latin America	3 bOPV + 2 IPV	6, 10, 14, 14, 36	528	161
3	Taniuchi, M.	2017	Bangladesh	3 bOPV + 1 IPV	6, 10, 14, 14	80	19
3	Taniuchi, M.	2017	Bangladesh	3 bOPV + 2 IPV	6, 10, 14, 14, 18	80	20
3	Taniuchi, M.	2017	Bangladesh	3 tOPV	6, 10, 14	69	42
4	Asturias, E. J.	2016	Latin America[a]	3 bOPV	6, 10, 14	384	88
4	Asturias, E. J.	2016	Latin America[a]	3 bOPV + 1 IPV	6, 10, 14, 14	193	53
4	Asturias, E. J.	2016	Latin America[a]	3 bOPV + 2 IPV	6, 10, 14, 14, 18	189	48
4	Asturias, E. J.	2016	Latin America[a]	3 tOPV	6, 10, 14	186	179
5	Saez-Llorens, X.	2016	Panama	3 bOPV + 1 IPV	6, 10, 14, 14	106	23
5	Saez-Llorens, X.	2016	Panama	3 bOPV + 1 mIPV2 [b]	6, 10, 14, 14	108	20
6	Anand, A.	2015	Bangladesh	3 bOPV	6, 10, 14	196	77

6	Anand, A.	2015	Bangladesh	fIPV [c] + bOPV + fIPV [c]	6, 10, 14	211	89
6	Anand, A.	2015	Bangladesh	2 fIPV [c]	6, 14	151	52
6	Anand, A.	2015	Bangladesh	2 IPV	6, 14	156	67
6	Anand, A.	2015	Bangladesh	3 tOPV	6, 10, 14	203	191
7	O' Ryan, M.	2015	Chile	1 IPV + 2 bOPV	8, 16, 24	164	32
7	O' Ryan, M.	2015	Chile	2 IPV + 1 bOPV	8, 16, 24	179	40
7	O' Ryan, M.	2015	Chile	3 IPV	8, 16, 24	171	13
8	Sutter, R. W.	2015	India	4 bOPV + 1 IPV	birth, 6, 10, 14, 14	156	62
8	Sutter, R. W.	2015	India	4 tOPV	birth, 6, 10, 14	160	150

bOPV = bivalent oral poliovirus vaccine. fIPV = fractional inactivated poliovirus vaccine. ID = intradermal. IM = intramuscular. IPV = conventional inactivated poliovirus vaccine. IPV-Al = Aluminium hydroxide–adjuvanted inactivated poliovirus vaccine. mIPV2 = monovalent serotype 2 high-dose inactivated poliovirus vaccine. sIPV = Sabin inactivated poliovirus vaccine. tOPV = trivalent oral poliovirus vaccine.

[1]Closest approximation time in weeks

[a]Study conducted at four investigational sites in Colombia, Dominican Republic, Guatemala, and Panama

[b]32 D-Antigen content for serotype 2.

[c]1/5th full IPV dose (0.1mL)

Web appendix 3: Risk of bias table of included studies

Table 1: Assessment of risk of bias within studies

	Selection bias	Reporting bias	Performance bias	Detection bias		Attrition bias	Comment
Study	Random sequence generation	Allocation concealment	Selective reporting	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	
Qui et al. 2017	Low	Low	Insufficient information	Low	Low (1)	Low (2)	(1) Blinded lab investigators and unblinded statistician using locked database (2) Provided drop-out data
Rivera et al. 2010	Low	Low	Insufficient information	Low	Low	Low	
Resik et al. 2010	Low (1)	Unclear (2)	Insufficient information	Unclear (2)	Unclear (2)	Unclear (2)	(1) Study states participants were "randomised", no other details given (2) Insufficient information
Saez- Llorens et al. 2016	Low	Low	Insufficient information	Low (1)	Low	Low	(1) Not blinded because of different administration techniques (2) Does not provide all details of reasons for withdrawal
Saleem et al. 2018	Low	Low	Insufficient information	Low	Low	Low	
Sutter et al 2015	Low	Low	Insufficient information	Low (1)	Low (2)	Unclear (3)	(1) Not blinded because of different administration techniques (2) Blinded laboratory staff (3) Does not provide all details of reasons for withdrawal
Taniuchi M et al. 2017	Low	Unclear (1)	Insufficient information	Low (2)	Low (3)	Low	(1) Insufficient information provided (2) Field staff could not be blinded because of different administration techniques (3) Blinded laboratory staff
Lopez-Medina et al. 2017	Low (1)	Unclear (2)	Insufficient information	Low	Low	Low	(1) Permuted block randomisation (2) Not described in sufficient detail - allocation was computer generated, but not clear how applied to the population

Asturias et al. 2016	Low	Unclear (1)	Insufficient information	Low	Low (2)	Low	(1) "Block randomisation" used, but no detail given on how individual children were allocated to block (2) Observer-blinded
Cadorna-Carloa et al. 2012	Unclear (1)	Unclear (1)	Insufficient information	Unclear	Unclear (2)	Low	(1) Study states participants were "randomised", no other details given (2) Insufficient information provided
Estivariz et al. 2015	Low (1)	Unclear (2)	Insufficient information	Unclear (2)	Unclear (2)	Low	(1) Carried out by study statistician (2) Insufficient information provided
Liao et al. 2012	Unclear (1)	Unclear	Insufficient information	Unclear (2)	Unclear (2)	Low	(1) Study states participants were "randomised", no other details given (2) Insufficient information given
Anand et al. 2015	Unclear (1)	Unclear (2)	Insufficient information	Unclear (2)	Unclear (2)	Unclear (3)	(1) Infants were "randomly assigned" using block randomisation with no additional details given (2) Insufficient information provided (3) Attrition reported, but reasons not given
Mohammed at al. 2010	Unclear (1)	Unclear (2)	Insufficient information	Unclear	Unclear (2)	Low	(1) Study states participants were "randomised", no other details given (2) Insufficient information given
Nirmal et al. 1998	Unclear (1)	Unclear (2)	Insufficient information	Unclear (2)	Unclear (2)	Low	(1) Study states participants were "randomised", no other details given (2) Insufficient information given
O'Ryan et al. 2015	Low	Unclear (1)	Insufficient information	Low (1)	Low	Low	(1) Insufficient information given (2) Masking considered not feasible

Table 2: The risk of bias across studies for each pairwise comparison for direct effects with contributing evidence from multiple studies. The quality of evidence is rated per Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Network	Serotype	Treatment 1	Treatment 2	Number of studies directly comparing	Study Design	Quality of Data	Risk of Bias	Inconsistency	Publication Bias	GRADE rating[1]
Humoral	1	1IPV + 2bOPV	2IPV + 1bOPV	2	RCT	High	Low	No	No	High
		1IPV + 2bOPV	3IPV	2	RCT	High	Low	No	No	High
		2IPV + 1bOPV	3IPV	2	RCT	High	Low	No	No	High
		3bOPV	3tOPV	3	RCT	High	Low	No	No	High
		3bOPV + 1IPV	3bOPV + 2IPV	2	RCT	High	Low	No	No	High
		3fIPV	3IPV	3	RCT	High	Low	Yes	No	Moderate
		3IPV	3sIPV	3	RCT	High	Low	No	No	High
		3IPV	3tOPV	2	RCT	High	Low	No	No	High
		4bOPV	4bOPV + 1IPV	2	RCT	High	Low	No	No	High
		4bOPV	4tOPV	2	RCT	High	Low	No	No	High
		4bOPV + 1IPV	4tOPV	2	RCT	High	Low	No	No	High
Humoral	2	1IPV + 2bOPV	2IPV + 1bOPV	2	RCT	High	Low	Yes	No	Moderate
		1IPV + 2bOPV	3IPV	2	RCT	High	Low	No	No	High
		2IPV + 1bOPV	3IPV	2	RCT	High	Low	No	No	High
		3bOPV	3tOPV	3	RCT	High	Low	No	No	High
		3bOPV + 1IPV	3bOPV + 2IPV	2	RCT	High	Low	No	No	High
		3fIPV	3IPV	3	RCT	High	Low	No	No	High
		3IPV	3sIPV	3	RCT	High	Low	No	No	High
		3IPV	3tOPV	2	RCT	High	Low	No	No	High
		4bOPV	4bOPV + 1IPV	2	RCT	High	Low	No	No	High
		4bOPV	4tOPV	2	RCT	High	Low	No	No	High
		4bOPV + 1IPV	4tOPV	2	RCT	High	Low	Yes	No	Moderate
Humoral	3	1IPV + 2bOPV	2IPV + 1bOPV	2	RCT	High	Low	No	No	High
		1IPV + 2bOPV	3IPV	2	RCT	High	Low	No	No	High
		2IPV + 1bOPV	3IPV	2	RCT	High	Low	No	No	High
		3bOPV	3tOPV	3	RCT	High	Low	Yes	No	Moderate
		3bOPV + 1IPV	3bOPV + 2IPV	2	RCT	High	Low	No	No	High

		3fIPV	3IPV	3	RCT	High	Low	Yes	No	Moderate
		3IPV	3sIPV	3	RCT	High	Low	No	No	High
		3IPV	3tOPV	2	RCT	High	Low	No	No	High
		4bOPV	4bOPV + 1IPV	2	RCT	High	Low	No	No	High
		4bOPV	4tOPV	2	RCT	High	Low	No	No	High
		4bOPV + 1IPV	4tOPV	2	RCT	High	Low	No	No	High
Intestinal	2	3 bOPV	3 tOPV	2	RCT	High	Low	No	No	Moderate
		3 bOPV + 1IPV	3 bOPV + 2IPV	3	RCT	High	Low	No	No	High
		3 bOPV + 1IPV	3 tOPV	2	RCT	High	Low	Yes	No	Moderate
		3 bOPV + 2IPV	3 tOPV	2	RCT	High	Low	Yes	No	Moderate

GRADE certainty ratings[1]

Very low: The true effect is probably markedly different from the estimated effect
Low: The true effect might be markedly different from the estimated effect
Moderate: The authors believe that the true effect is probably close to the estimated effect
High: The authors have a lot of confidence that the true effect is similar to the estimated effect

Web appendix 4: Assessment of model fit and heterogeneity

Table 1A: Assessment of final models used in analysis, humoral immunity

Model #	Serotype	Model type	Subgroup	Regression variable	Data points	Nodes	Outcome scale for prior distributions[1]	Dbar	pD	DIC	Standard deviation (95% CrI) [2]	Regression coefficient (95% CrI)
1	1	Consistency	No birth dose	NA	39	14	0.5	35.5	22.9	58.4	0.24 (0.12, 0.48)	NA
1	2	Consistency	No birth dose	NA	39	14	2.5	38.4	26.7	65.1	0.05 (0.01, 0.15)	NA
1	3	Consistency	No birth dose	NA	39	14	0.5	38.8	23.9	62.7	0.17 (0.09, 0.32)	
2	1	Consistency	Birth dose only	NA	8	5	0.5	8.8	6	14.8	0.06 (0.004, 0.23)	NA
2	2	Consistency	Birth dose only	NA	8	5	2.5	8	7.4	15.4	0.24 (0.03, 1.3)	NA
2	3	Consistency	Birth dose only	NA	8	5	0.5	8.7	6.8	15.4	0.08 (0.01, 0.2)	NA
3	1	Regression	NA	Diarrhoeal disease[+]	39	14	0.5	35.4	23.1	58.6	0.25 (0.12, 0.48)	0.19 (-0.52, 0.92)
3	2	Regression	NA	Diarrhoeal disease[+]	39	14	2.5	38.1	28.3	66.5	0.06 (0.01, 1.5)	0.16 (-3.74, 6.02)
3	3	Regression	NA	Diarrhoeal disease[+]	39	14	0.5	38.6	23.9	62.5	0.17 (0.10,0.32)	0.40 (-0.14,2.18)

[1] The outcome scale (S) was used to set a vague random effects standard deviation prior and relative effects prior distributions:

- Relative effects ~ normal $(0, (15 \cdot S)^2)$
- Random effects standard deviation ~ uniform (0, S)

[2]The median posterior distribution of the random effects standard deviation, displayed as a measure of heterogeneity Tau (τ) with 95% credible intervals.
CrI: credible intervals. Dbar = mean sum of residual deviance. DIC = deviance information criterion at residual pD = sum of leverage.

Table 1B: Assessment of model used in analysis, mucosal immunity

Model #	Serotype	Model type	Subgroup	Regression variable	Data points	Nodes	Outcome scale for prior distributions[1]	Dbar	pD	DIC	Standard deviation[2] (95% CrI)	Regression coefficient (95% CrI)
1	2	Consistency	NA	NA	11	4	2.5	10.5	10.02	20.6	0.32043 (0.1312, 0.9816)	NA

[1] The outcome scale (S) was used to set a vague random effects standard deviation prior and relative effects prior distributions:

- Relative effects ~ normal (0, $(15 \cdot S)^2$)
- Random effects standard deviation ~ uniform (0, S)

[2]The median posterior distribution of the random effects standard deviation, displayed as a measure of heterogeneity Tau (τ) with 95% credible intervals.
CrI: credible intervals. Dbar = mean sum of residual deviance. DIC = deviance information criterion at residual pD = sum of leverage.

Web appendix 5: Assessment of inconsistency

Table 1: Assessment of inconsistency for network analysis, humoral immunity

Serotype	Outcome	Treatment 1	Treatment 2	Direct effect (95% CI)[1]	Indirect effect (95% CI)[1]	P value
1	Humoral	1 IPV + 2 bOPV	3 tOPV	-0.03 (-0.66,0.59)	4.95 (0.49,14.59)	0.012
1	Humoral	2 fIPV	3 bOPV	0.12 (-0.57,0.81)	0.55 (-0.45,1.75)	0.43
1	Humoral	2 fIPV	3 fIPV	0 (-0.64,0.63)	-0.41 (-1.37,0.32)	0.342
1	Humoral	2 fIPV	3 tOPV	0.07 (-0.62,0.76)	0.52 (-0.37,1.62)	0.379
1	Humoral	2 IPV + 1 bOPV	3 tOPV	0.02 (-0.63,0.66)	-5.43 (-18.58,0.26)	0.086
1	Humoral	3 fIPV	3 IPV	0.28 (-0.07,0.74)	-0.12 (-1.18,0.8)	0.352
1	Humoral	3 IPV	3 tOPV	0.2 (-0.22,0.79)	-0.21 (-1.19,0.68)	0.344
2	Humoral	1 IPV + 2 bOPV	3 tOPV	0.55 (0.28,0.83)	0.5 (0.24,1.05)	0.845
2	Humoral	2 fIPV	3 bOPV	-1.77 (-2.18,-1.39)	-1.65 (-2.1,-1.13)	0.689
2	Humoral	2 fIPV	3 fIPV	0.12 (-0.2,0.47)	-0.03 (-0.32,0.18)	0.407
2	Humoral	2 fIPV	3 tOPV	0.2 (0.01,0.39)	0.36 (0,0.79)	0.41
2	Humoral	2 IPV + 1 bOPV	3 tOPV	0.16 (-0.04,0.38)	0.41 (0.11,0.9)	0.158
2	Humoral	3 fIPV	3 IPV	0.09 (0,0.22)	-0.07 (-0.5,0.32)	0.405
2	Humoral	3 IPV	3 tOPV	0.17 (0.01,0.46)	-0.02 (-0.52,0.42)	0.373
3	Humoral	1 IPV + 2 bOPV	3 tOPV	38.16 (0.85,119.98)	3.52 (-3.61,11.9)	0.126
3	Humoral	2 fIPV	3 bOPV	0.69 (-4.45,5.86)	38.02 (4.27,116.59)	0.02
3	Humoral	2 fIPV	3 fIPV	0.29 (-5.64,6.35)	-21.03 (-65.23,-2.2)	0.031
3	Humoral	2 fIPV	3 tOPV	0.8 (-4.36,5.93)	45.01 (4.45,120.56)	0.019
3	Humoral	2 IPV + 1 bOPV	3 tOPV	35.08 (1.79,117.61)	-30.63 (-108.83,0.91)	0.003
3	Humoral	3 fIPV	3 IPV	1.8 (-1.13,5.24)	-20.95 (-58.3,0.17)	0.029
3	Humoral	3 IPV	3 tOPV	34.76 (3.39,107.79)	-1.51 (-10.44,7.01)	0.02
2	Mucosal	3 bOPV	3 bOPV + IPV	0.17 (-1.1, 1.4)	- 0.30 (-1.8, 1.4)	0.47
2	Mucosal	3 bOPV	3 bOPV + 2 IPV	0.089 (-0.9, 1.1)	-0.097 (-1.4, 1.2)	0.66

[1]Effects are reported as Log Risk Ratio

bOPV = bivalent oral poliovirus vaccine. CrI= credible intervals. fIPV = fractional inactivated oral poliovirus vaccine. IPV = inactivated oral poliovirus vaccine. tOPV = trivalent oral poliovirus vaccine.

Web appendix 6: Relative Effect Tables

Interpretation: The data in relative effect tables provides head to head comparisons of two interventions, rather than all relative to a standard comparator arm (tOPV). Therefore, this data may be simpler to advise policy in the situation that two interventions should be compared directly.

Table 1: The calculated relative effects of all pairwise comparisons among the treatments in network, against serotype 1, reported as log risk ratio with 95% credible intervals. (A) No birth-dose subgroup and (B) birth-dose subgroup.

1A:

	1 IPV + 2 bOPV	2 fIPV	2 IPV	2 IPV + 1bOPV	3 bOPV	3 bOPV + 1 IPV	3 bOPV + 1 mIPV2	3 bOPV+ 2 IPV	3 fIPV	3 IPV	3 IPV-Al	3 sIPV	3 tOPV	fIPV + bOPV + fIPV
1 IPV + 2 bOPV	NA	-0.02 (-0.57, 0.63)	0.13 (-0.49, 0.87)	0.12 (-0.28, 0.7)	0.18 (-0.32, 0.85)	4.65 (0.45, 13.78)	4.68 (0.44, 13.8)	4.65 (0.44, 13.79)	-0.17 (-0.69, 0.39)	0.05 (-0.34, 0.55)	0.04 (-0.6, 0.81)	0.23 (-0.24, 0.95)	0.16 (-0.24, 0.74)	0.14 (-0.48, 0.9)
2 fIPV	0.02 (-0.63, 0.57)	NA	0.15 (-0.39, 0.7)	0.14 (-0.44, 0.79)	0.2 (-0.24, 0.69)	4.65 (0.47, 13.75)	4.7 (0.46, 13.79)	4.66 (0.48, 13.77)	-0.15 (-0.65, 0.3)	0.07 (-0.42, 0.56)	0.06 (-0.68, 0.8)	0.24 (-0.28, 0.92)	0.18 (-0.23, 0.65)	0.16 (-0.36, 0.73)
2 IPV	-0.13 (-0.87, 0.49)	-0.15 (-0.7, 0.39)	NA	0 (-0.69, 0.71)	0.05 (-0.45, 0.58)	4.5 (0.31, 13.58)	4.55 (0.32, 13.6)	4.5 (0.32, 13.59)	-0.3 (-0.97, 0.29)	-0.07 (-0.68, 0.5)	-0.09 (-0.92, 0.73)	0.1 (-0.54, 0.85)	0.04 (-0.46, 0.56)	0.01 (-0.55, 0.59)
2 IPV + 1bOPV	-0.12 (-0.7, 0.28)	-0.14 (-0.79, 0.44)	0 (-0.71, 0.69)	NA	0.06 (-0.53, 0.64)	4.49 (0.32, 13.61)	4.54 (0.29, 13.63)	4.49 (0.31, 13.62)	-0.29 (-0.92, 0.2)	-0.07 (-0.58, 0.36)	-0.09 (-0.84, 0.62)	0.1 (-0.46, 0.74)	0.04 (-0.46, 0.54)	0.01 (-0.7, 0.7)
3 bOPV	-0.18 (-0.85, 0.32)	-0.2 (-0.69, 0.24)	-0.05 (-0.58, 0.45)	-0.06 (-0.64, 0.53)	NA	4.43 (0.28, 13.49)	4.49 (0.28, 13.56)	4.45 (0.29, 13.54)	-0.35 (-0.94, 0.12)	-0.13 (-0.64, 0.31)	-0.15 (-0.9, 0.57)	0.05 (-0.5, 0.67)	-0.02 (-0.34, 0.31)	-0.05 (-0.57, 0.47)
3 bOPV + 1 IPV	-4.65 (-13.78, -0.45)	-4.65 (-13.75, -0.47)	-4.5 (-13.58, -0.31)	-4.49 (-13.61, -0.32)	-4.43 (-13.49, -0.28)	NA	0.04 (-0.52, 0.61)	0 (-0.57, 0.57)	-4.82 (-13.9, -0.62)	-4.58 (-13.7, -0.41)	-4.58 (-13.7, -0.37)	-4.39 (-13.49, -0.2)	-4.46 (-13.55, -0.31)	-4.49 (-13.61, -0.31)
3 bOPV + 1 mIPV2	-4.68 (-13.8, -0.44)	-4.7 (-13.79, -0.46)	-4.55 (-13.6, -0.32)	-4.54 (-13.63, -0.29)	-4.49 (-13.56, -0.28)	-0.04 (-0.61, 0.52)	NA	-0.04 (-0.84, 0.76)	-4.86 (-13.94, -0.63)	-4.63 (-13.71, -0.4)	-4.63 (-13.74, -0.37)	-4.43 (-13.54, -0.19)	-4.5 (-13.56, -0.3)	-4.54 (-13.67, -0.3)
3 bOPV+ 2 IPV	-4.65 (-13.79, -0.44)	-4.66 (-13.77, -0.48)	-4.5 (-13.59, -0.32)	-4.49 (-13.62, -0.31)	-4.45 (-13.54, -0.29)	0 (-0.57, 0.57)	0.04 (-0.76, 0.84)	NA	-4.82 (-13.91, -0.62)	-4.59 (-13.7, -0.41)	-4.58 (-13.7, -0.38)	-4.4 (-13.54, -0.2)	-4.46 (-13.59, -0.31)	-4.5 (-13.64, -0.31)
3 fIPV	0.17 (-0.39, 0.69)	0.15 (-0.3, 0.65)	0.3 (-0.29, 0.97)	0.29 (-0.2, 0.92)	0.35 (-0.12, 0.94)	4.82 (0.62, 13.9)	4.86 (0.63, 13.94)	4.82 (0.62, 13.91)	NA	0.22 (-0.09, 0.59)	0.21 (-0.42, 0.91)	0.4 (-0.03, 1.04)	0.33 (-0.07, 0.86)	0.31 (-0.27, 0.99)

3 IPV	-0.05 (-0.55, 0.34)	-0.07 (-0.56, 0.42)	0.07 (-0.5, 0.68)	0.07 (-0.36, 0.58)	0.13 (-0.31, 0.64)	4.58 (0.41, 13.7)	4.63 (0.4, 13.71)	4.59 (0.41, 13.7)	-0.22 (-0.59, 0.09)	NA	-0.01 (-0.57, 0.56)	0.17 (-0.15, 0.67)	0.11 (-0.23, 0.53)	0.09 (-0.49, 0.71)
3 IPV-Al	-0.04 (-0.81, 0.6)	-0.06 (-0.8, 0.68)	0.09 (-0.73, 0.92)	0.09 (-0.62, 0.84)	0.15 (-0.57, 0.9)	4.58 (0.37, 13.7)	4.63 (0.37, 13.74)	4.58 (0.38, 13.7)	-0.21 (-0.91, 0.42)	0.01 (-0.56, 0.57)	NA	0.19 (-0.45, 0.95)	0.12 (-0.53, 0.83)	0.1 (-0.7, 0.94)
3 sIPV	-0.23 (-0.95, 0.24)	-0.24 (-0.92, 0.28)	-0.1 (-0.85, 0.54)	-0.1 (-0.74, 0.46)	-0.05 (-0.67, 0.5)	4.39 (0.2, 13.49)	4.43 (0.19, 13.54)	4.4 (0.2, 13.54)	-0.4 (-1.04, 0.03)	-0.17 (-0.67, 0.15)	-0.19 (-0.95, 0.45)	NA	-0.07 (-0.6, 0.4)	-0.09 (-0.82, 0.55)
3 tOPV	-0.16 (-0.74, 0.24)	-0.18 (-0.65, 0.23)	-0.04 (-0.56, 0.46)	-0.04 (-0.54, 0.46)	0.02 (-0.31, 0.34)	4.46 (0.31, 13.55)	4.5 (0.3, 13.56)	4.46 (0.31, 13.59)	-0.33 (-0.86, 0.07)	-0.11 (-0.53, 0.23)	-0.12 (-0.83, 0.53)	0.07 (-0.4, 0.6)	NA	-0.02 (-0.54, 0.47)
fIPV + bOPV + fIPV	-0.14 (-0.9, 0.48)	-0.16 (-0.73, 0.36)	-0.01 (-0.59, 0.55)	-0.01 (-0.7, 0.7)	0.05 (-0.47, 0.57)	4.49 (0.31, 13.61)	4.54 (0.3, 13.67)	4.5 (0.31, 13.64)	-0.31 (-0.99, 0.27)	-0.09 (-0.71, 0.49)	-0.1 (-0.94, 0.7)	0.09 (-0.55, 0.82)	0.02 (-0.47, 0.54)	NA

1B:

	4bOPV	4bOPV + 1IPV	4bOPV + 2IPV	4IPV	4tOPV
4bOPV	NA	0 (-0.09, 0.08)	1.22 (0.07, 4.24)	-0.17 (-0.31, -0.05)	0 (-0.1, 0.07)
4bOPV + 1IPV	0 (-0.08, 0.09)	NA	1.22 (0.07, 4.24)	-0.17 (-0.31, -0.04)	0 (-0.09, 0.08)
4bOPV + 2IPV	-1.22 (-4.24, -0.07)	-1.22 (-4.24, -0.07)	NA	-1.39 (-4.42, -0.24)	-1.22 (-4.25, -0.07)
4IPV	0.17 (0.05, 0.31)	0.17 (0.04, 0.31)	1.39 (0.24, 4.42)	NA	0.17 (0.04, 0.3)
4tOPV	0 (-0.07, 0.1)	0 (-0.08, 0.09)	1.22 (0.07, 4.25)	-0.17 (-0.3, -0.04)	NA

bOPV = bivalent oral poliovirus vaccine. CrI = credible intervals. fIPV = fractional inactivated poliovirus vaccine. IPV = inactivated poliovirus vaccine. IPV-al = Aluminium hydroxide–adjuvanted inactivated poliovirus vaccine ($1/10^{th}$ reduced dose). mIPV2 = monovalent inactivated poliovirus vaccine serotype 2. sIPV = Sabin inactivated poliovirus vaccine. tOPV = trivalent oral poliovirus vaccine

Table 2: The calculated relative effects of all pair-wise comparisons among the treatments in network, against serotype 2. Reported as log risk ratio with 95% credible intervals. (A) No birth-dose subgroup and (B) birth-dose subgroup.

2A:

	1 IPV + 2 bOPV	2 fIPV	2 IPV	2 IPV + 1bOPV	3 bOPV	3 bOPV + 1 IPV	3 bOPV + 1 mIPV2	3 bOPV+ 2 IPV	3 fIPV	3 IPV	3 IPV-Al	3 sIPV	3 tOPV	fIPV + bOPV + fIPV
1 IPV + 2 bOPV	NA	0.26 (0.07, 0.49)	0.39 (0.2, 0.63)	0.25 (0.13, 0.41)	-1.5 (-1.77, -1.22)	0.33 (0.14, 0.63)	0.54 (0.3, 0.91)	0.58 (0.4, 0.94)	0.27 (0.11, 0.47)	0.36 (0.22, 0.54)	0.31 (0.12, 0.55)	0.37 (0.21, 0.56)	0.48 (0.34, 0.68)	0.28 (0.09, 0.53)
2 fIPV	-0.26 (-0.49, -0.07)	NA	0.13 (-0.02, 0.3)	-0.01 (-0.2, 0.19)	-1.76 (-2.02, -1.52)	0.06 (-0.11, 0.33)	0.28 (0.04, 0.6)	0.32 (0.15, 0.65)	0.01 (-0.16, 0.19)	0.09 (-0.07, 0.27)	0.05 (-0.16, 0.28)	0.1 (-0.07, 0.29)	0.22 (0.09, 0.38)	0.02 (-0.14, 0.19)
2 IPV	-0.39 (-0.63, -0.2)	-0.13 (-0.3, 0.02)	NA	-0.14 (-0.35, 0.06)	-1.9 (-2.15, -1.66)	-0.07 (-0.24, 0.18)	0.15 (-0.09, 0.47)	0.19 (0.02, 0.5)	-0.12 (-0.32, 0.07)	-0.04 (-0.21, 0.14)	-0.08 (-0.31, 0.15)	-0.02 (-0.22, 0.16)	0.09 (-0.04, 0.25)	-0.11 (-0.27, 0.05)
2 IPV + 1bOPV	-0.25 (-0.41, -0.13)	0.01 (-0.19, 0.2)	0.14 (-0.06, 0.35)	NA	-1.76 (-2.02, -1.5)	0.07 (-0.11, 0.33)	0.29 (0.04, 0.62)	0.33 (0.15, 0.66)	0.02 (-0.14, 0.19)	0.1 (-0.03, 0.26)	0.06 (-0.14, 0.27)	0.11 (-0.04, 0.28)	0.23 (0.09, 0.39)	0.03 (-0.18, 0.24)
3 bOPV	1.5 (1.22, 1.77)	1.76 (1.52, 2.02)	1.9 (1.66, 2.15)	1.76 (1.5, 2.02)	NA	1.83 (1.6, 2.1)	2.05 (1.76, 2.38)	2.09 (1.86, 2.4)	1.78 (1.53, 2.04)	1.86 (1.62, 2.12)	1.82 (1.53, 2.11)	1.87 (1.62, 2.13)	1.98 (1.78, 2.21)	1.79 (1.54, 2.05)
3 bOPV + 1 IPV	-0.33 (-0.63, -0.14)	-0.06 (-0.33, 0.11)	0.07 (-0.18, 0.24)	-0.07 (-0.33, 0.11)	-1.83 (-2.1, -1.6)	NA	0.22 (0.04, 0.4)	0.26 (0.16, 0.42)	-0.05 (-0.31, 0.12)	0.03 (-0.21, 0.19)	-0.01 (-0.3, 0.2)	0.04 (-0.21, 0.21)	0.16 (-0.02, 0.28)	-0.04 (-0.3, 0.14)
3 bOPV + 1 mIPV2	-0.54 (-0.91, -0.3)	-0.28 (-0.6, -0.04)	-0.15 (-0.47, 0.09)	-0.29 (-0.62, -0.04)	-2.05 (-2.38, -1.76)	-0.22 (-0.4, -0.04)	NA	0.05 (-0.16, 0.29)	-0.27 (-0.59, -0.03)	-0.18 (-0.49, 0.05)	-0.23 (-0.58, 0.04)	-0.17 (-0.49, 0.06)	-0.06 (-0.32, 0.15)	-0.26 (-0.58, -0.02)
3 bOPV+ 2 IPV	-0.58 (-0.94, -0.4)	-0.32 (-0.65, -0.15)	-0.19 (-0.5, -0.02)	-0.33 (-0.66, -0.15)	-2.09 (-2.4, -1.86)	-0.26 (-0.42, -0.16)	-0.05 (-0.29, 0.16)	NA	-0.31 (-0.63, -0.14)	-0.23 (-0.52, -0.07)	-0.27 (-0.62, -0.07)	-0.21 (-0.52, -0.05)	-0.1 (-0.35, 0.02)	-0.3 (-0.62, -0.13)
3 fIPV	-0.27 (-0.47, -0.11)	-0.01 (-0.19, 0.16)	0.12 (-0.07, 0.32)	-0.02 (-0.19, 0.14)	-1.78 (-2.04, -1.53)	0.05 (-0.12, 0.31)	0.27 (0.03, 0.59)	0.31 (0.14, 0.63)	NA	0.08 (0, 0.18)	0.04 (-0.12, 0.22)	0.09 (-0.03, 0.22)	0.2 (0.08, 0.37)	0.01 (-0.18, 0.21)
3 IPV	-0.36 (-0.54, -0.22)	-0.09 (-0.27, 0.07)	0.04 (-0.14, 0.21)	-0.1 (-0.26, 0.03)	-1.86 (-2.12, -1.62)	-0.03 (-0.19, 0.21)	0.18 (-0.05, 0.49)	0.23 (0.07, 0.52)	-0.08 (-0.18, 0)	NA	-0.04 (-0.19, 0.1)	0.01 (-0.08, 0.09)	0.12 (0.02, 0.25)	-0.07 (-0.26, 0.11)
3 IPV-Al	-0.31 (-0.55, -0.12)	-0.05 (-0.28, 0.16)	0.08 (-0.15, 0.31)	-0.06 (-0.27, 0.14)	-1.82 (-2.11, -1.53)	0.01 (-0.2, 0.3)	0.23 (-0.04, 0.58)	0.27 (0.07, 0.62)	-0.04 (-0.22, 0.12)	0.04 (-0.1, 0.19)	NA	0.05 (-0.12, 0.22)	0.17 (-0.01, 0.37)	-0.03 (-0.27, 0.21)

3 sIPV	-0.37 (-0.56, -0.21)	-0.1 (-0.29, 0.07)	0.02 (-0.16, 0.22)	-0.11 (-0.28, 0.04)	-1.87 (-2.13, -1.62)	-0.04 (-0.21, 0.21)	0.17 (-0.06, 0.49)	0.21 (0.05, 0.52)	-0.09 (-0.22, 0.03)	-0.01 (-0.09, 0.08)	-0.05 (-0.22, 0.12)	NA	0.11 (-0.01, 0.27)	-0.08 (-0.28, 0.11)
3 tOPV	-0.48 (-0.68, -0.34)	-0.22 (-0.38, -0.09)	-0.09 (-0.25, 0.04)	-0.23 (-0.39, -0.09)	-1.98 (-2.21, -1.78)	-0.16 (-0.28, 0.02)	0.06 (-0.15, 0.32)	0.1 (-0.02, 0.35)	-0.2 (-0.37, -0.08)	-0.12 (-0.25, -0.02)	-0.17 (-0.37, 0.01)	-0.11 (-0.27, 0.01)	NA	-0.2 (-0.36, -0.06)
fIPV + bOPV + fIPV	-0.28 (-0.53, -0.09)	-0.02 (-0.19, 0.14)	0.11 (-0.05, 0.27)	-0.03 (-0.24, 0.18)	-1.79 (-2.05, -1.54)	0.04 (-0.14, 0.3)	0.26 (0.02, 0.58)	0.3 (0.13, 0.62)	-0.01 (-0.21, 0.18)	0.07 (-0.11, 0.26)	0.03 (-0.21, 0.27)	0.08 (-0.11, 0.28)	0.2 (0.06, 0.36)	NA

2B:

	4bOPV	4bOPV + 1IPV	4bOPV + 2IPV	4IPV	4tOPV
4bOPV	NA	1.12 (0.16, 2.01)	20.82 (2.41, 68.18)	1.52 (0.28, 2.67)	1.58 (0.66, 2.49)
4bOPV + 1 IPV	-1.12 (-2.01, -0.16)	NA	19.67 (1.28, 66.93)	0.4 (-0.8, 1.56)	0.47 (-0.48, 1.33)
4bOPV + 2 IPV	-20.82 (-68.18, -2.41)	-19.67 (-66.93, -1.28)	NA	-19.28 (-66.53, -0.88)	-19.22 (-66.47, -0.79)
4 IPV	-1.52 (-2.67, -0.28)	-0.4 (-1.56, 0.8)	19.28 (0.88, 66.53)	NA	0.06 (-1.15, 1.3)
4tOPV	-1.58 (-2.49, -0.66)	-0.47 (-1.33, 0.48)	19.22 (0.79, 66.47)	-0.06 (-1.3, 1.15)	NA

bOPV = bivalent oral poliovirus vaccine. CrI = credible intervals. fIPV = fractional inactivated poliovirus vaccine. IPV = inactivated poliovirus vaccine. IPV-al = Aluminium hydroxide–adjuvanted inactivated poliovirus vaccine ($1/10^{th}$ reduced dose). mIPV2 = monovalent inactivated poliovirus vaccine serotype 2. sIPV = Sabin inactivated poliovirus vaccine. tOPV = trivalent oral poliovirus vaccine.

Table 3: The calculated relative effects of all pairwise comparisons among the treatments in network, against serotype 3, reported as log risk ratio with 95% credible intervals. (A) No birth-dose subgroup and (B) birth-dose subgroup.

3A:

	1 IPV + 2 bOPV	2 fIPV	2 IPV	2 IPV + 1bOPV	3 bOPV	3 bOPV + 1 IPV	3 bOPV + 1 mIPV2	3 bOPV+ 2 IPV	3 fIPV	3 IPV	3 IPV-Al	3 sIPV	3 tOPV	fIPV + bOPV + fIPV
1 IPV + 2 bOPV	NA	0.07 (-0.34, 0.59)	0.23 (-0.23, 0.86)	0.08 (-0.2, 0.44)	0.23 (-0.16, 0.81)	0.38 (-0.09, 1.17)	0.38 (-0.21, 1.27)	0.29 (-0.15, 0.98)	-0.06 (-0.42, 0.3)	0.01 (-0.25, 0.29)	0.01 (-0.47, 0.49)	0.01 (-0.34, 0.36)	0.22 (-0.11, 0.79)	0.19 (-0.26, 0.82)
2 fIPV	-0.07 (-0.59, 0.34)	NA	0.16 (-0.2, 0.57)	0.01 (-0.49, 0.45)	0.16 (-0.15, 0.54)	0.31 (-0.11, 0.94)	0.31 (-0.25, 1.06)	0.22 (-0.18, 0.73)	-0.13 (-0.53, 0.18)	-0.05 (-0.49, 0.28)	-0.06 (-0.66, 0.44)	-0.06 (-0.54, 0.31)	0.16 (-0.13, 0.53)	0.13 (-0.24, 0.53)
2 IPV	-0.23 (-0.86, 0.23)	-0.16 (-0.57, 0.2)	NA	-0.15 (-0.75, 0.35)	0 (-0.35, 0.37)	0.15 (-0.31, 0.76)	0.15 (-0.45, 0.89)	0.06 (-0.38, 0.56)	-0.29 (-0.86, 0.12)	-0.21 (-0.78, 0.19)	-0.22 (-0.92, 0.33)	-0.22 (-0.82, 0.22)	0 (-0.35, 0.37)	-0.03 (-0.43, 0.36)
2 IPV + 1bOPV	-0.08 (-0.44, 0.2)	-0.01 (-0.45, 0.49)	0.15 (-0.35, 0.75)	NA	0.15 (-0.28, 0.72)	0.3 (-0.2, 1.07)	0.3 (-0.31, 1.17)	0.2 (-0.27, 0.88)	-0.14 (-0.54, 0.21)	-0.06 (-0.4, 0.21)	-0.07 (-0.6, 0.4)	-0.07 (-0.47, 0.28)	0.14 (-0.22, 0.7)	0.11 (-0.37, 0.72)
3 bOPV	-0.23 (-0.81, 0.16)	-0.16 (-0.54, 0.15)	0 (-0.37, 0.35)	-0.15 (-0.72, 0.28)	NA	0.15 (-0.2, 0.66)	0.15 (-0.36, 0.8)	0.06 (-0.26, 0.43)	-0.29 (-0.81, 0.06)	-0.21 (-0.73, 0.12)	-0.22 (-0.89, 0.27)	-0.22 (-0.78, 0.14)	0 (-0.22, 0.23)	-0.04 (-0.4, 0.32)
3 bOPV + 1 IPV	-0.38 (-1.17, 0.09)	-0.31 (-0.94, 0.11)	-0.15 (-0.76, 0.31)	-0.3 (-1.07, 0.2)	-0.15 (-0.66, 0.2)	NA	0 (-0.39, 0.39)	-0.09 (-0.47, 0.19)	-0.44 (-1.18, 0)	-0.37 (-1.11, 0.07)	-0.37 (-1.23, 0.18)	-0.37 (-1.15, 0.09)	-0.15 (-0.65, 0.2)	-0.18 (-0.8, 0.27)
3 bOPV + 1 mIPV2	-0.38 (-1.27, 0.21)	-0.31 (-1.06, 0.25)	-0.15 (-0.89, 0.45)	-0.3 (-1.17, 0.31)	-0.15 (-0.8, 0.36)	0 (-0.39, 0.39)	NA	-0.09 (-0.64, 0.39)	-0.44 (-1.3, 0.13)	-0.37 (-1.23, 0.2)	-0.37 (-1.33, 0.29)	-0.37 (-1.25, 0.22)	-0.15 (-0.79, 0.37)	-0.18 (-0.93, 0.41)
3 bOPV+ 2 IPV	-0.29 (-0.98, 0.15)	-0.22 (-0.73, 0.18)	-0.06 (-0.56, 0.38)	-0.2 (-0.88, 0.27)	-0.06 (-0.43, 0.26)	0.09 (-0.19, 0.47)	0.09 (-0.39, 0.64)	NA	-0.35 (-0.98, 0.06)	-0.27 (-0.9, 0.13)	-0.28 (-1.05, 0.26)	-0.28 (-0.94, 0.16)	-0.06 (-0.42, 0.26)	-0.09 (-0.59, 0.33)
3 fIPV	0.06 (-0.3, 0.42)	0.13 (-0.18, 0.53)	0.29 (-0.12, 0.86)	0.14 (-0.21, 0.54)	0.29 (-0.06, 0.81)	0.44 (0, 1.18)	0.44 (-0.13, 1.3)	0.35 (-0.06, 0.98)	NA	0.07 (-0.16, 0.31)	0.07 (-0.39, 0.53)	0.07 (-0.25, 0.39)	0.29 (-0.02, 0.8)	0.26 (-0.15, 0.81)
3 IPV	-0.01 (-0.29, 0.25)	0.05 (-0.28, 0.49)	0.21 (-0.19, 0.78)	0.06 (-0.21, 0.4)	0.21 (-0.12, 0.73)	0.37 (-0.07, 1.11)	0.37 (-0.2, 1.23)	0.27 (-0.13, 0.9)	-0.07 (-0.31, 0.16)	NA	-0.01 (-0.41, 0.39)	-0.01 (-0.23, 0.22)	0.21 (-0.07, 0.71)	0.18 (-0.23, 0.74)
3 IPV-Al	-0.01 (-0.49, 0.47)	0.06 (-0.44, 0.66)	0.22 (-0.33, 0.92)	0.07 (-0.4, 0.6)	0.22 (-0.27, 0.89)	0.37 (-0.18, 1.23)	0.37 (-0.29, 1.33)	0.28 (-0.26, 1.05)	-0.07 (-0.53, 0.39)	0.01 (-0.39, 0.41)	NA	0 (-0.46, 0.45)	0.22 (-0.24, 0.87)	0.18 (-0.37, 0.88)

3 sIPV	-0.01 (-0.36, 0.34)	0.06 (-0.31, 0.54)	0.22 (-0.22, 0.82)	0.07 (-0.28, 0.47)	0.22 (-0.14, 0.78)	0.37 (-0.09, 1.15)	0.37 (-0.22, 1.25)	0.28 (-0.16, 0.94)	-0.07 (-0.39, 0.25)	0.01 (-0.22, 0.23)	0 (-0.45, 0.46)	NA	0.21 (-0.11, 0.76)	0.18 (-0.26, 0.78)
3 tOPV	-0.22 (-0.79, 0.11)	-0.16 (-0.53, 0.13)	0 (-0.37, 0.35)	-0.14 (-0.7, 0.22)	0 (-0.23, 0.22)	0.15 (-0.2, 0.65)	0.15 (-0.37, 0.79)	0.06 (-0.26, 0.42)	-0.29 (-0.8, 0.02)	-0.21 (-0.71, 0.07)	-0.22 (-0.87, 0.24)	-0.21 (-0.76, 0.11)	NA	-0.03 (-0.41, 0.3)
fIPV + bOPV + fIPV	-0.19 (-0.82, 0.26)	-0.13 (-0.53, 0.24)	0.03 (-0.36, 0.43)	-0.11 (-0.72, 0.37)	0.04 (-0.32, 0.4)	0.18 (-0.27, 0.8)	0.18 (-0.41, 0.93)	0.09 (-0.33, 0.59)	-0.26 (-0.81, 0.15)	-0.18 (-0.74, 0.23)	-0.18 (-0.88, 0.37)	-0.18 (-0.78, 0.26)	0.03 (-0.3, 0.41)	NA

3B:

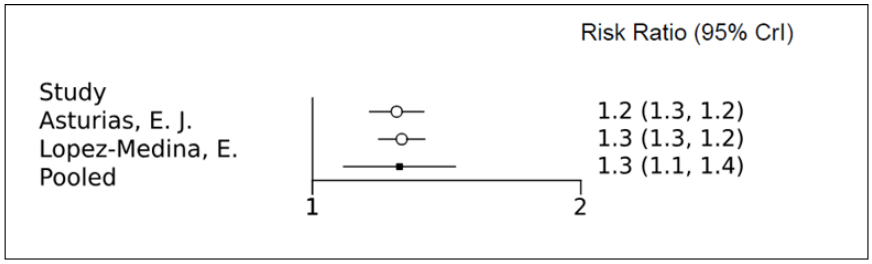
	4bOPV + 1 IPV	4bOPV + 1 IPV	4bOPV + 1 IPV	4bOPV + 1 IPV	4bOPV + 1 IPV
4bOPV	NA	0.02 (-0.05, 0.1)	1.07 (0.06, 4.08)	-0.01 (-0.11, 0.1)	-0.08 (-0.17, -0.01)
4bOPV + 1IPV	-0.02 (-0.1, 0.05)	NA	1.05 (0.04, 4.05)	-0.03 (-0.12, 0.07)	-0.11 (-0.19, -0.03)
4bOPV + 2IPV	-1.07 (-4.08, -0.06)	-1.05 (-4.05, -0.04)	NA	-1.08 (-4.08, -0.07)	-1.15 (-4.16, -0.15)
4IPV	0.01 (-0.1, 0.11)	0.03 (-0.07, 0.12)	1.08 (0.07, 4.08)	NA	-0.08 (-0.19, 0.02)
4tOPV	0.08 (0.01, 0.17)	0.11 (0.03, 0.19)	1.15 (0.15, 4.16)	0.08 (-0.02, 0.19)	NA

bOPV = bivalent oral poliovirus vaccine. CrI = credible intervals. fIPV = fractional inactivated poliovirus vaccine. IPV = inactivated poliovirus vaccine. IPV-al = Aluminium hydroxide–adjuvanted inactivated poliovirus vaccine ($1/10^{th}$ reduced dose). mIPV2 = monovalent inactivated poliovirus vaccine serotype 2. sIPV = Sabin inactivated poliovirus vaccine. tOPV = trivalent oral poliovirus vaccine.

Web Appendix 7: Pairwise analysis

Interpretation: The pairwise analysis looks at the risk ratio from studies that have directly compared the two interventions and estimates the pooled risk ratio result. For 3 bOPV + 1 IPV and 3 bOPV + 2 IPV, the studies that directly compared these interventions were Asturias et al 2016, and Lopez-Medina et al, 2017 and reported risk ratios of 1.2 and 1.3, respectively.

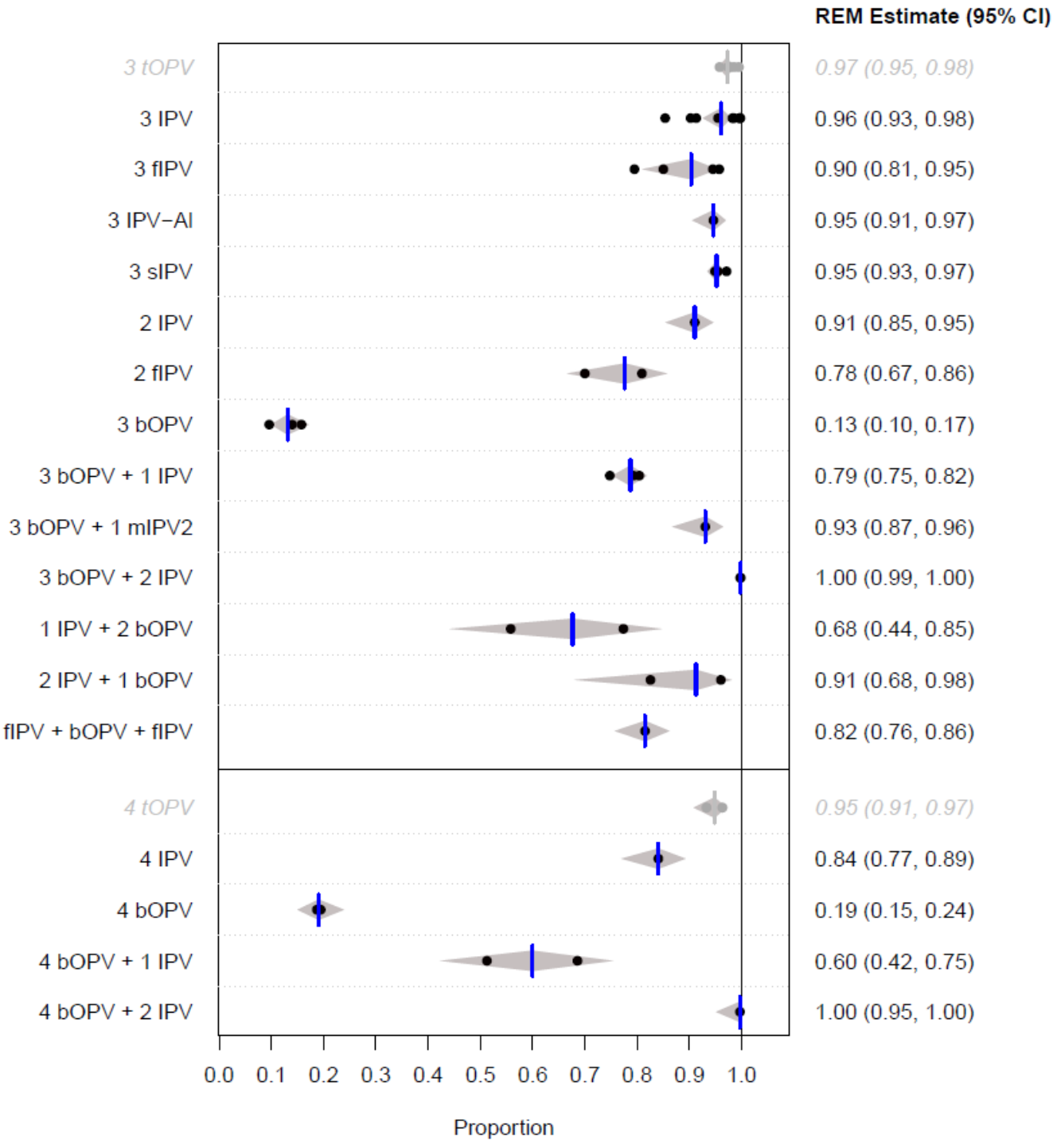
Figure 1: Pairwise meta-analysis of 3 bOPV + 1IPV and 3 bOPV + 2 IPV for outcome seroconversion against serotype 2.



Median posterior estimate of pooled risk ratio is 1.251 (1.064, 1.475) and random effects standard deviation 0.058 (0.002, 0.216). bOPV = bivalent oral poliovirus vaccine. CrI = credible intervals. IPV = inactivated poliovirus vaccine.

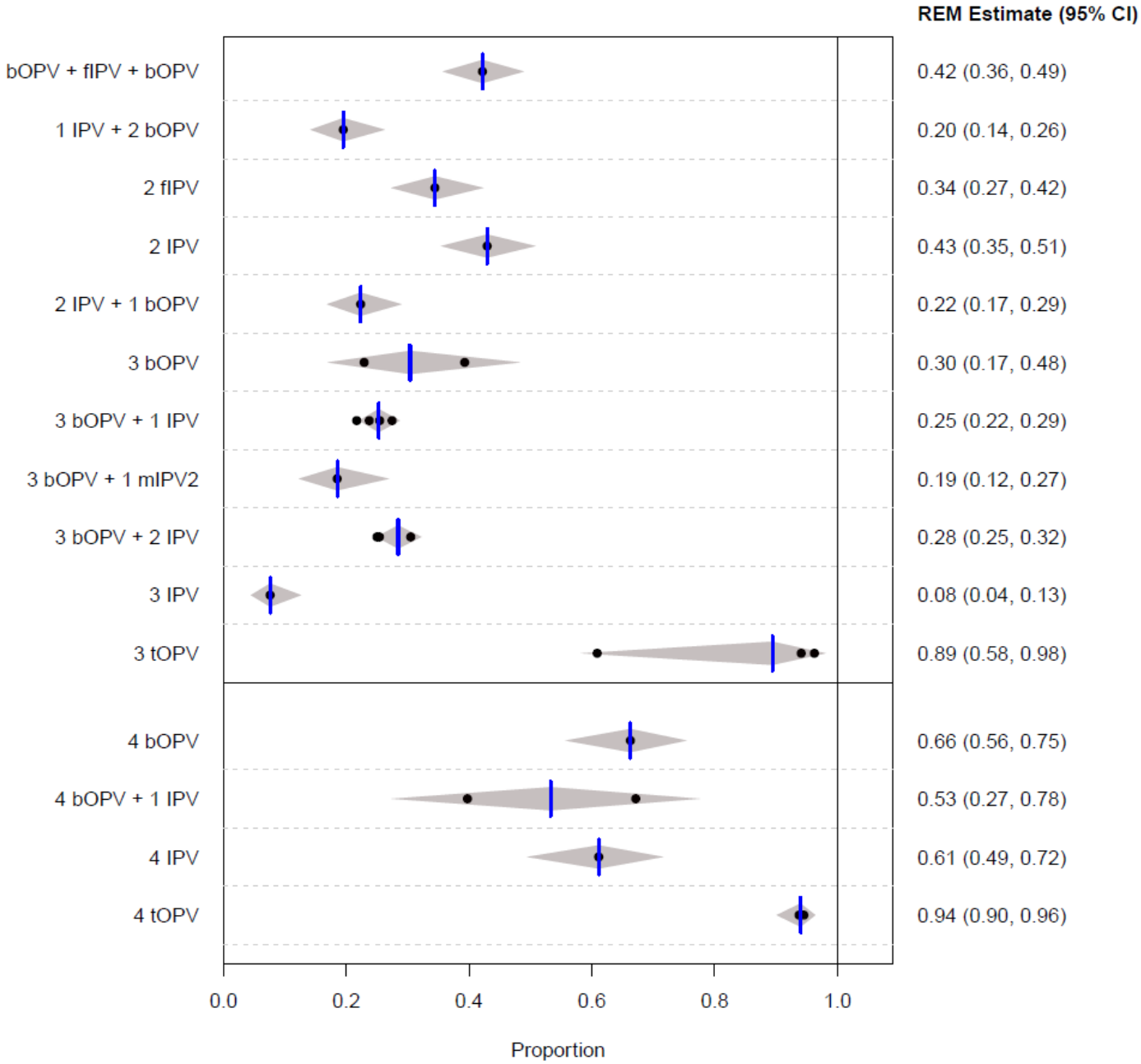
Web Appendix 8: Single proportion meta-analysis

Figure 1: Random-effect single proportion meta-analysis of the proportion seroconversion against serotype 2. Individual study points are shown as black dots, with the overall estimated proportion as a blue line with 95% CrI. Overall random effects model estimate and heterogeneity were (A) 0.89 [0.84; 0.93] and τ-squared = 2.48 .



bOPV = bivalent oral poliovirus vaccine. fIPV = fractional inactivated poliovirus vaccine administered intradermally (1/5th dose of IPV). IPV = conventional inactivated poliovirus vaccine. IPV-Al = Aluminium hydroxide–adjuvanted inactivated poliovirus vaccine (1/10th reduced dose). mIPV2 = monovalent serotype 2 high-dose inactivated poliovirus vaccine. REM = random effect model. sIPV = Sabin inactivated poliovirus vaccine. tOPV = trivalent oral poliovirus vaccine

Figure 2: Random-effect single proportion meta-analysis of the proportion of individuals that develop intestinal immunity against serotype 2 (defined as absence of shedding 7 days after a challenge dose). Individual study points are shown as black dots, with the overall estimated proportion as a blue line with 95% CrI. Overall random effects model estimate and heterogeneity were 0.45 [0.36; 0.55] and τ-squared = 0.88.



bOPV = bivalent oral poliovirus vaccine. fIPV = fractional inactivated poliovirus vaccine administered intradermally (1/5th dose of IPV). IPV = conventional inactivated poliovirus vaccine. IPV-Al = Aluminium hydroxide–adjuvanted inactivated poliovirus vaccine (1/10th reduced dose). mIPV2 = monovalent serotype 2 high-dose inactivated poliovirus vaccine. REM = random effect model. sIPV = Sabin inactivated poliovirus vaccine. tOPV = trivalent oral poliovirus vaccine

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Supplementary Materials for

Evolving epidemiology of poliovirus serotype 2 following withdrawal of the serotype 2 oral poliovirus vaccine

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This PDF file includes:

Materials and Methods

Materials

The primary surveillance sources of the GPEI are cases of acute flaccid paralysis (AFP) among children aged <15 years. As part of the case investigation detailed case histories and stool samples are collected to determine poliovirus infection. Environmental surveillance has been established within more than 30 countries where wastewater samples are collected and tested for polioviruses. Additional surveillance includes outbreak response contact sampling and community sampling [4]. All collected samples are tested in Global Polio Laboratory Network (GPLN) laboratories per WHO protocols with virus isolation, intratypic differentiation (ITD) and genomic sequencing, to identify WPV, Sabin-like (derived from oral poliovirus vaccine) poliovirus, and vaccine-derived polioviruses (VDPV) [24, 25]. Poliovirus isolates are classified by comparing the nucleotide sequence of the coding region of the viral capsid protein 1 (VP1) with the corresponding vaccine strain: for serotype 2, Sabin-like virus are $\geq$ 0 and < 6 nucleotides divergent and VDPV2s are $\geq$ 6 nucleotides divergent from the 903 nucleotide VP1 [24]. VDPVs are further classified as 1) cVDPV, when evidence of person-to-person transmission in the community exists; 2) immunodeficiency-related VDPV (iVDPV), when they are isolated from persons with primary immunodeficiencies; and 3) ambiguous VDPV (aVDPV), when they are clinical isolates from persons with no known immunodeficiency and no evidence of transmission, or they are sewage isolates that are unrelated to other known VDPVs and whose source is unknown [7, 16]. cVDPV2 outbreaks are coded and tracked by a designation of the country, the state or province, and a sequential count of the emergence from that geography (e.g.

the third cVDPV2 outbreak occurring in Sokoto State of Nigeria is coded NIE-SOS-3). The iVDPV cases are excluded from this analysis.

All mOPV2 supplemental immunisation activities conducted between 01 May 2016 and 01 August 2019 were exported from Polio Information System (polIS) database. The exported data included the start and end date of campaign activity, administrative area (Admin 0, Admin 1 and Admin 2 levels) and the number of doses distributed. Geographical information system data for boundaries of administrative areas (Admin levels 0, 1 and 2) were obtained from the World Health Organization. The Admin 0 level is referred to as country. All Sabin-like and VDPV2 poliovirus isolates with date of sample collection between 01 May 2016 and 01 November 2019 were exported from the polIS line list. Extracted data for each isolate included the date of detection (or sample collection), virus classification, surveillance method, and VP1 nucleotide divergence from the Sabin 2 vaccine. The Admin 1 level routine immunisation coverage estimates for all African countries were taken as the estimated coverage of three doses of Diphtheria-tetanus-pertussis (DTP3) in 2016, from Mosser et al [26] (Supplementary Table 1). For countries outside the African continent, routine immunisation coverage was defined as the proportion of non-polio AFP cases in the given Admin 1 region who reported receiving 3 OPV doses through routine immunisation aged between 12-24 months from 2016 to 2019, as used previously [13].

All data was exported as of 01 November 2019.

Methods

For all VDPV2 isolates and outbreaks we estimate the seeding date and likely source from which the virus was seeded after the withdrawal of OPV2 using the following methods. We

define the date of seeding of VDPV2 as the date that the infectious OPV2 dose was administered which subsequently evolved into VDPV2. First, the date of seeding for each isolate was estimated with 95% confidence intervals (CI) by back-calculating from the date of detection (either AFP case or ENV sample) based on the number of nucleotide differences in the VP1 sequence from the Sabin 2 strain. We assumed that the first VP1 mutation is instantaneous and each subsequent mutation follows an average rate, previously estimated at 1.14×10^{-2} nucleotides per site per year, which corresponds to 1 nucleotide change observed after approximately 35 days [15]. The waiting time to each independent mutation is modelled using an exponential distribution that assumes a constant evolution rate, and the Erlang distribution is the sum of the waiting times. The Erlang distribution had a shape parameter equal to n-1, where n is the number of VP1 nucleotide changes of the isolate, and a scale parameter equal to the product of the number of VP1 nucleotides (901) and the average mutation rate (1.14×10^{-2} nucleotides per site per year). For isolates that were part of an emergence group that had > 1 isolate, we estimate the date of seeding for that emergence group by combining data from multiple isolates and then assigning this date of seeding to all isolates in the group (Supplementary Table 1). We selected the earliest three detected isolates of an outbreak and resampled each of their estimated dates of seeding 1000 times to produce a combined distribution with a median date and 95% CI. The analysis was restricted to the nucleotide differences of the first three isolates as using all isolates would have to account for the specific location of nucleotide mutations between isolates, which were not available for analysis. For sensitivity analysis, we repeated the procedure by selecting between one and up to ten of the earliest detected isolates, which did not result in any significant changes (Supplementary Figure 2). The limitations of this analysis are discussed below.

The probability that VDPV isolates were seeded after the switch (taken as 01 May 2016) was calculated using the cumulative probability of the empirical distribution of the estimated seeding date and determining what proportion of this distribution is greater than 01 May 2016. For VDPV isolates with a probability of seeding after the switch above 0.9, the database of mOPV2 campaigns was searched to identify mOPV2 campaigns occurring within the time-frame of the estimated date of seeding (95% CI), within the same state/province (Admin 1 level), country (Admin 0 level) or a neighbouring country. If more than one mOPV2 campaign was within the estimated date of seeding interval, the campaign closest in time (to the median estimated seeding date) was chosen in the nearest geographic area (i.e. 1st - Campaigns in the same Admin 1 level, 2nd - Campaigns from the same Admin 0 level, and 3rd - Campaigns from neighbouring countries).

Generalized linear models (GLMs) were used to quantify the patterns of VDPV emergences over time. For the GLMs, we computed univariate logistic regression (family = binomial, link = logit) on the index isolate of each genetic VDPV emergence. The predictor variable was the time in years between the Switch (taken as 01 May 2016) and date of detection. The binary response variables were: estimated seeding date is post-switch (yes or no); and emergence evolved into a cVDPV2 outbreak (yes or no). For all GLMs we report co-efficient estimates and accompanying P-value.

The limitations of our analysis include the absence of genetic sequencing data from VDPV isolates to inform the estimated date of sequencing. The genetic information available for each isolate was the genetic cluster (emergence group) the virus was associated with and the number of nucleotides divergent from Sabin 2 in the VP1 gene. The ability to construct a phylogenetic tree using genetic sequences would provide more accurate inference. In this

analysis, we have not considered the time between the most recent mutation and time of detection, as this short time is not programmatically significant compared to the uncertainty in the time of seeding (range of 304-1100 days) captured by the 95% confidence intervals.

Table S1. Summary and demography of classified circulating vaccine-derived poliovirus (cVDPV) outbreaks detected between May 2016 and 01 November 2019, data as of 01 November 2019.

Outbreak Code	Country	Date detected	Date of most recent isolate	Number of impacted states (country: states)	Assumed status[1]	Observed duration, months	RI coverage[2], mean estimate (95% CI)	Isolates (n)	AFP cases (n)	Mean case age, months (n)	VP1 nucleotide divergence (range)[3]
NIE-BOS-16	Nigeria	23-Mar-16	26-Aug-16	1 (Nigeria: Borno)	Closed	5	0.29 (0.1, 0.47)	2	0	NaN (0)	32,37
SYR-1	Syrian Arab Republic	27-Aug-16	21-Sep-17	3 (Syrian Arab Republic: Deir Al Zour, Raqua, Homs)	Closed	13	0.31 (0.14, 0.5)	117	74	18.6 (74)	22,34
PAK-QTA-1	Pakistan	20-Oct-16	28-Dec-16	1 (Pakistan: Balochistan)	Closed	2	0.28 (0.19, 0.39)	5	1	16 (1)	10,18
NIE-SOS-2	Nigeria	28-Oct-16	02-Mar-17	1 (Nigeria: Sokoto)	Closed	4	0.04 (0, 0.08)	3	1	30 (1)	7,17
RDC-HLO-1	Democratic Republic of the Congo	20-Feb-17	27-May-18	4 (Democratic Republic of the Congo: Haut Lomami, Tanganika, Haut Katanga, Ituri)	Closed	15	0.62 (0.5, 0.74)	50	27	25.5 (27)	14,29
RDC-MAN-1	Democratic Republic of the Congo	26-Mar-17	02-May-17	1 (Democratic Republic of the Congo: Maniema)	Closed	1	0.51 (0.3, 0.7)	3	2	30 (2)	7,9
SOM-BAN-1	Somalia	22-Oct-17	13-Aug-19	9 (Somalia: Banadir Irobi, Hiran, Gedo, Lower Juba, Sool)	Ongoing	22	0.58 (0.2, 0.88)	44	12	40.6 (10)	37,55
NIE-JIS-1	Nigeria	10-Jan-18	10-Oct-19	24 (Nigeria: Jigawa, Gombe, Yobe, Borno, Katsina, Zinder)	Ongoing	21	0.09 (0, 0.17)	239	65	30.5 (62)	13,35
NIE-SOS-3	Nigeria	30-Jan-18	18-Mar-19	2 (Nigeria: Sokoto, Niger)	Ongoing	14	0.04 (0, 0.08)	15	1	19 (1)	6,14
CHN-XIN-1	China	18-Apr-18	18-Aug-19	2 (China: Xinjiang, Sichuan)	Ongoing	16	1 (0.15, 1.0)[5]	5	1	53 (1)	13,33
RDC-MON-1	Democratic Republic of the Congo	26-Apr-18	08-Nov-18	1 (Democratic Republic of the Congo: Mongala)	Ongoing	6	0.45 (0.3, 0.59)	21	11	14.1 (11)	18,26

RDC-HKA-1	Democratic Republic of the Congo	06-Oct-18	07-Oct-18	1 (Democratic Republic of the Congo: Haut Katanga)	Closed	0	0.73 (0.6, 0.82)	2	2	80.5 (2)	7,8
MOZ-ZAM-2	Mozambique	21-Oct-18	17-Dec-18	1 (Mozambique: Zambezia)	Ongoing	2	0.91 (0.8, 0.97)	3	1	75 (1)	6,10
RDC-KAS-1	Democratic Republic of the Congo	08-Feb-19	17-Mar-19	1 (Democratic Republic of the Congo: Kasai)	Ongoing	1	0.68 (0.5, 0.81)	3	1	24 (1)	6,7
RDC-HLO-2	Democratic Republic of the Congo	10-Feb-19	02-Sep-19	2 (Democratic Republic of the Congo: Haut Lomami, Haut Katanga)	Ongoing	7	0.62 (0.5, 0.74)	16	11	16.5 (11)	8,12
NIE-SOS-4	Nigeria	18-Mar-19	10-Jun-19	1 (Nigeria: Sokoto)	Ongoing	3	0.04 (0, 0.08)	3	0	NaN (0)	16,20
RDC-KAS-2	Democratic Republic of the Congo	03-Apr-19	07-Jun-19	1 (Democratic Republic of the Congo: Kasai)	Ongoing	2	0.68 (0.5, 0.81)	4	4	35 (4)	6,11
ANG-LNO-1	Angola	05-Apr-19	14-May-19	1 (Angola: Lunda Norte)	Ongoing	1	0.22 (0.1, 0.35)	2	1	16 (1)	8,10
PAK-RWP-1	Pakistan	11-Apr-19	11-Apr-19	1 (Pakistan: Punjab)	Ongoing	0	0.85 (0.82, 0.88)	1	0	NaN (0)	7,7
RDC-SAN-1	Democratic Republic of the Congo	21-Apr-19	20-Sep-19	2 (Democratic Republic of the Congo: Sankuru, Kasai Oriental)	Ongoing	5	0.46 (0.3, 0.61)	23	19	21.5 (15)	6,16
ANG-HUI-1	Angola	27-Apr-19	25-Sep-19	5 (Angola: Huila, Cuanza Sul, Kwanza Sul, Huambo)	Ongoing	5	0.33 (0.21, 0.48)	29	15	35 (1)	6,13
CAF-BAM-1	Central African Republic	01-May-19	07-Sep-19	3 (Central African Republic: RS1, RS4, RS7)	Ongoing	4	0.36 (0.1, 0.63)	17	4	33.7 (3)	10,17
NIE-SOS-5	Nigeria	20-May-19	13-Jun-19	1 (Nigeria: Sokoto)	Ongoing	1	0.04 (0, 0.08)	2	1	48 (1)	14,15
CAF-BAM-2	Central African Republic	27-May-19	29-Aug-19	2 (Central African Republic: RS4, RS5)	Ongoing	3	0.44 (0.2, 0.73)	6	1	30 (1)	7,12
CAF-BIM-1	Central African Republic	28-May-19	30-Sep-19	3 (Central African Republic: RS1, RS4, RS7)	Ongoing	4	0.36 (0.1, 0.63)	7	4	33 (1)	6,16

CAF-BIM-2	Central African Republic	28-May-19	05-Oct-19	3 (Central African Republic: RS1, RS7, RS6)	Ongoing	4	0.36 (0.1, 0.63)	21	2	NaN (0)	7,18
ANG-LNO-2	Angola	01-Jun-19	15-Sep-19	5 (Angola: Lunda Norte, Lunda Sul, Malanje, Kwanza Sul, Moxico)	Ongoing	3	0.22 (0.1, 0.35)	7	6	15 (2)	9,15
RDC-KAS-3	Democratic Republic of the Congo	03-Jun-19	18-Sep-19	2 (Democratic Republic of the Congo: Kasai, Kwilu)	Ongoing	4	0.68 (0.5, 0.81)	4	4	22.7 (3)	8,16
ANG-LNO-3	Angola	07-Jun-19	23-Sep-19	3 (Angola: Lunda Norte, Uíge, Luanda)	Ongoing	4	0.22 (0.1, 0.35)	11	8	NaN (0)	6,11
PAK-GB-1	Pakistan	10-Jun-19	11-Sep-19	3 (Pakistan: Punjab, Gilgit Baltistan, Islamabad)	Ongoing	3	0.85 (0.82, 0.88)	6	3	NaN (0)	7,11
NIE-KGS-1	Nigeria	13-Jun-19	02-Oct-19	1 (Nigeria: Kogi)	Ongoing	4	0.46 (0.3, 0.62)	3	2	29 (1)	8,9
NIE-KGS-2	Nigeria	20-Jun-19	08-Aug-19	1 (Nigeria: Kogi)	Ongoing	2	0.46 (0.3, 0.62)	6	2	34.5 (2)	7,10
NIE-SOS-6	Nigeria	24-Jun-19	11-Sep-19	1 (Nigeria: Sokoto)	Ongoing	3	0.04 (0, 0.08)	3	0	NaN (0)	6,10
PHL-NCR-1	Philippines	26-Jun-19	15-Oct-19	3 (Philippines: Armm, Ncr, Southern Mindanao)	Ongoing	4	0.32 (0.16, 0.52)	12	3	NaN (0)	63,71
RDC-TPA-1	Democratic Republic of the Congo	27-Jun-19	14-Aug-19	1 (Democratic Republic of the Congo: Tshuapa)	Ongoing	2	0.41 (0.3, 0.55)	6	0	NaN (0)	7,11
ANG-HUA-1	Angola	02-Jul-19	16-Jul-19	1 (Angola: Huambo)	Ongoing	0	0.45 (0.3, 0.58)	2	2	NaN (0)	6,6
ZAM-LUA-1	Zambia	16-Jul-19	25-Sep-19	1 (Zambia: Luapula)	Ongoing	2	0.84 (0.7, 0.93)	3	1	NaN (0)	9,10
ANG-HUA-2	Angola	30-Jul-19	21-Aug-19	1 (Angola: Huambo)	Ongoing	1	0.45 (0.3, 0.58)	3	2	NaN (0)	6,6
CAF-BIM-3	Central African Republic	30-Jul-19	22-Aug-19	1 (Central African Republic: RS1)	Ongoing	1	0.36 (0.1, 0.63)	4	2	30 (2)	9,15
CAF-BAN-1	Central African Republic	16-Aug-19	03-Sep-19	2 (Central African Republic: RS7, RS2)	Ongoing	1	0.45 (0.2, 0.73)	4	1	NaN (0)	7,9
ANG-HUA-3	Angola	19-Aug-19	19-Aug-19	2 (Angola: Benguela, Huambo)	Ongoing	0	0.31 (0.2, 0.45)	2	2	NaN (0)	7,8

[1]Status is dependent on whether there has been detection of the cVDPV virus in the past 12 months, as of 01 November 2019.

[2]Routine immunisation coverage estimate from the Admin 1 area in which emergence was first detected; see supplementary methods.

[3]Number of nucleotides differences in the viral protein 1 gene (VP1) of the detected poliovirus compared to the Sabin 2 virus in oral poliovirus vaccine.

[4]This outbreak was identified to be genetically linked to a cVDPV2 emergence originating in Chad in 2012.

[5]Routine immunisation coverage estimate provided as a country estimate for China.

Abbreviation: AFP, Acute Flaccid Paralysis; RI, Routine Immunisation; VP1, Viral Protein 1.

Table S2. Outbreak response to circulating vaccine-derived poliovirus serotype 2 (cVDPV2) outbreaks and subsequent isolation of type 2 poliovirus by country, between 01 May 2016 and 01 November 2019.

Country	Number of outbreaks detected since 01 May 2016	Number of rounds	Total mOPV doses (million)	Doses per round (million), median (range)	Number aVDPV events consistent with time of mOPV2 campaign[1]			Number cVDPV outbreaks consistent with time of mOPV2 campaign[1]		
					In the OBRA	In the country	Neighbouring country	In the OBRA	In the country	Outside country
Angola	7	8	4.1	0.35 (0.1-1.18)	0	0	0	0	0	0
Benin	1	1	0.3	0.3 (0.3-0.3)	0	0	0	0	0	0
Cameroon	1	5	4.3	0.24 (0.02-3.68)	0	0	0	0	0	0
Central African Republic	6	2	0.9	0.45 (0.07-0.83)	0	0	0	0	0	0
Chad	1	4	2.3	0.2 (0.19-1.75)	0	0	0	0	0	0
Democratic Republic of the Congo	10	25	35.3	0.72 (0-7.92)	0	1	0	2	5	13[2]
Ethiopia	1	5	2.4	0.52 (0.19-0.59)	0	0	0	0	0	0
Ghana	1	2	2.1	1.05 (0.18-1.92)	0	0	0	0	0	0
Kenya	1	3	6.1	2.42 (0.82-2.88)	1	0	0	0	0	0
Mozambique	1	6	5.3	0.65 (0.5-1.48)	0	0	0	0[3]	0	0
Niger	1	9	17.2	2.52 (0.15-4.63)	0	0	0	0	0	0
Nigeria	9	37	170.6	1.96 (0-38.3)	26	6	0	5	2	0
Pakistan	3	3	3	0.79 (0.51-1.66)	3	0	0	0	0	0
Somalia	1	11	7.6	0.73 (0.05-1.6)	3	0	0	0	0	0
Syrian Arab Republic	1	4	1.6	0.45 (0.15-0.59)	0	0	0	0	0	0
Togo	1	1	0.1	0.14 (0.14-0.14)	0	0	0	0	0	0

[1]We define a VDPV consistent with time of mOPV2 campaigns as a VDPV where the estimated date of seeding 95% confidence interval spans an mOPV2 campaign in a similar geographic region. The geographic region is classified as within outbreak response area (OBRA), within the country (but outside OBRA) or within a neighbouring country to the mOPV2 campaign.

[2]There are 7 cVDPV2 in Angola and 6 in Central African Republic with estimated dates of seeding spanning mOPV2 campaigns conducted in the neighbouring country of Democratic Republic of Congo.

[3]The cVDPV outbreak in Mozambique, Zambezia (MOZ-ZAM-2) is estimated to have been seeded at least 4 months after the mOPV2 campaign in Zambezia.

Fig. S1. Roadmap of the key timepoints in the Global Polio Eradication Initiative Endgame Strategic Plan.

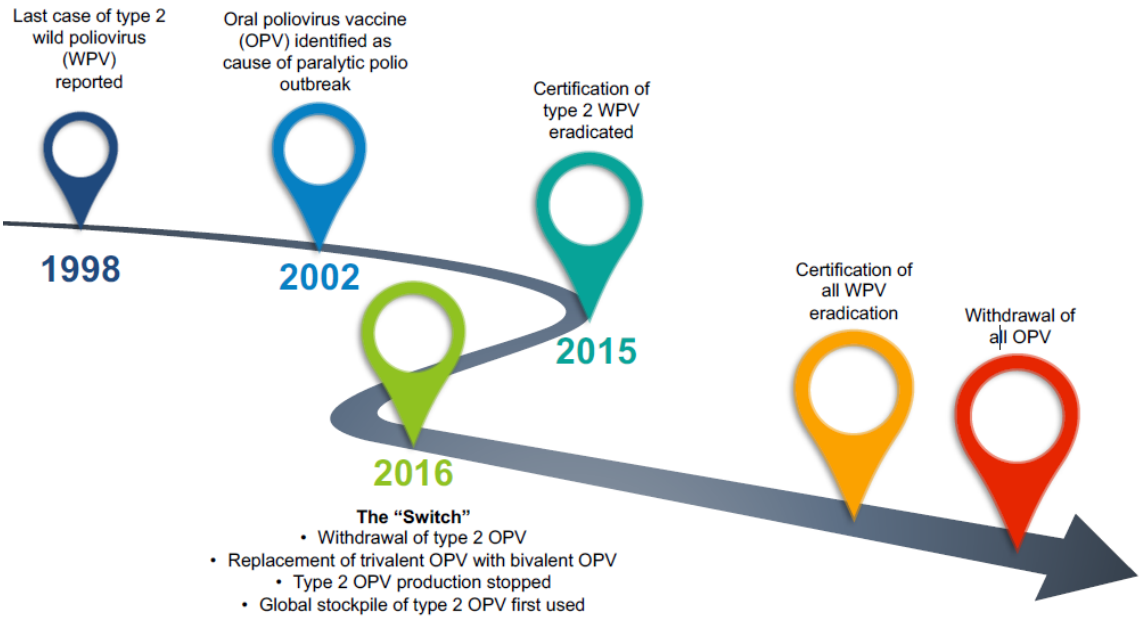
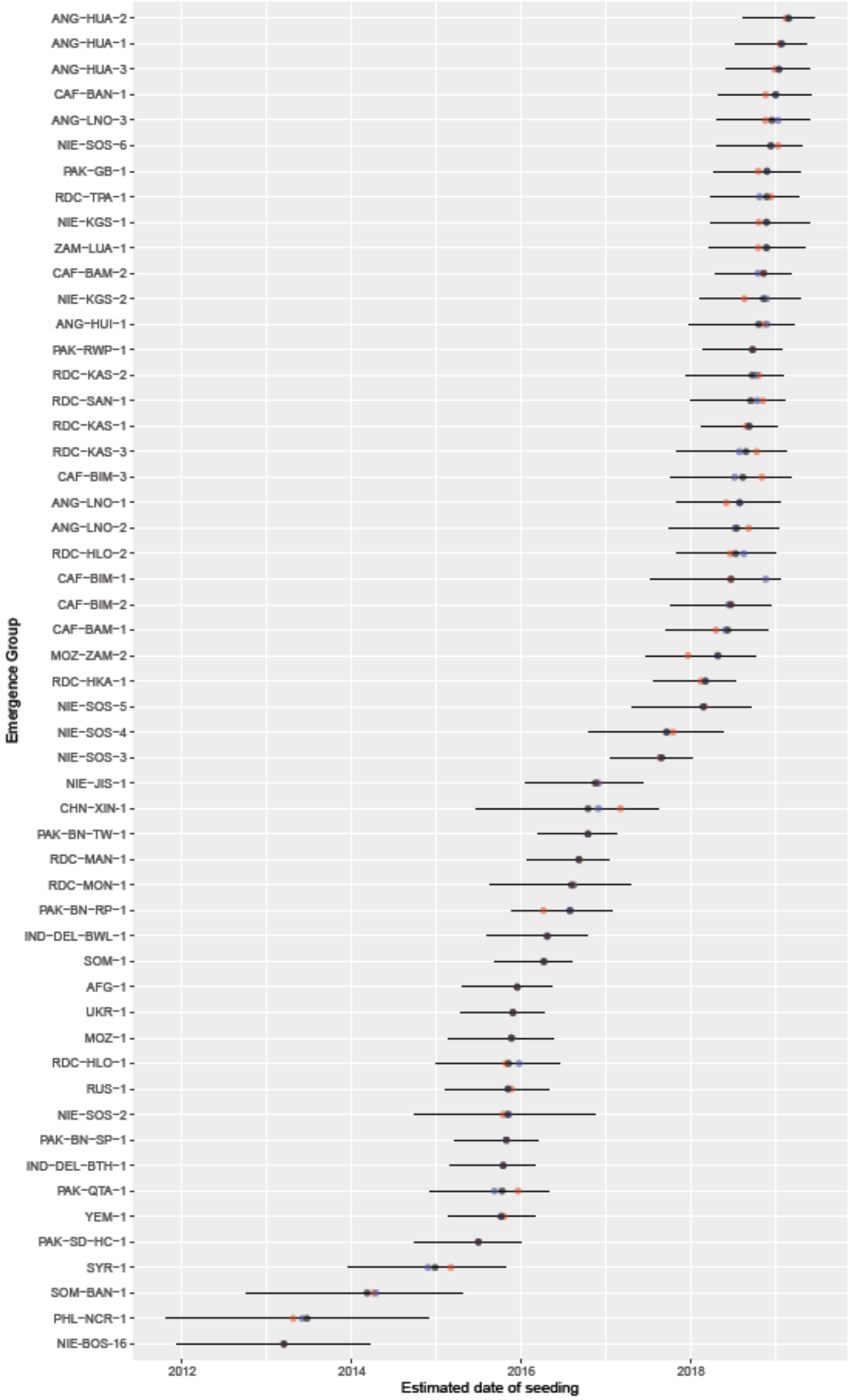


Fig. S2: Sensitivity analysis on the number of isolates selected into generating the estimated date of seeding for a VDPV emergence group. Black circles and horizontal lines indicate the median date of seeding with 95% CI that were used in this manuscript, calculated using from the nucleotide divergence of the first three isolates detected of an emergence group. Coloured circles show the median date of seeding calculated when one (red) or up to ten (blue) of the first detected isolates of an emergence group were used.


ANG-HUA-2
ANG-HUA-1
ANG-HUA-3
CAF-BAN-1
ANG-LNO-3
NIE-SOS-6
PAK-GB-1
RDC-TPA-1
NIE-KGS-1
ZAM-LUA-1
CAF-BAM-2
NIE-KGS-2
ANG-HUI-1
PAK-RWP-1
RDC-KAS-2
RDC-SAN-1
RDC-KAS-1
RDC-KAS-3
CAF-BIM-3
ANG-LNO-1
ANG-LNO-2
RDC-HLO-2
CAF-BIM-1
CAF-BIM-2
CAF-BAM-1
MOZ-ZAM-2
RDC-HKA-1
NIE-SOS-5
NIE-SOS-4
NIE-SOS-3
NIE-JIS-1
CHN-XIN-1
PAK-BN-TW-1
RDC-MAN-1
RDC-MON-1
PAK-BN-RP-1
IND-DEL-BWL-1
SOM-1
AFG-1
UKR-1
MOZ-1
RDC-HLO-1
RUS-1
NIE-SOS-2
PAK-BN-SP-1
IND-DEL-BTH-1
PAK-QTA-1
YEM-1
PAK-SD-HC-1
SYR-1
SOM-BAN-1
PHL-NCR-1
NIE-BOS-16
Emergence Group
2012
2014
2016
2018
Estimated date of seeding

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Supplementary Materials for ‘A model of vaccine-derived poliovirus outbreaks to estimate effectiveness of outbreak response campaigns with a novel oral poliovirus vaccine’

Fig. S1: Profile likelihoods for the parameters corresponding to R0 for Guinea. For units, the points represent the maximized log-likelihood at each fixed value of the parameter: the black points are the median log likelihoods of 3 replicate filters (grey points). For the total country (combined) likelihood, blacks point represents the two maximum panel log-likelihoods at each fixed value of the parameter. The vertical red lines on the point indicate the standard error. The blue point represents the maximum likelihood estimate and the horizontal red lines the 95% confidence interval of the maximum likelihood estimate.

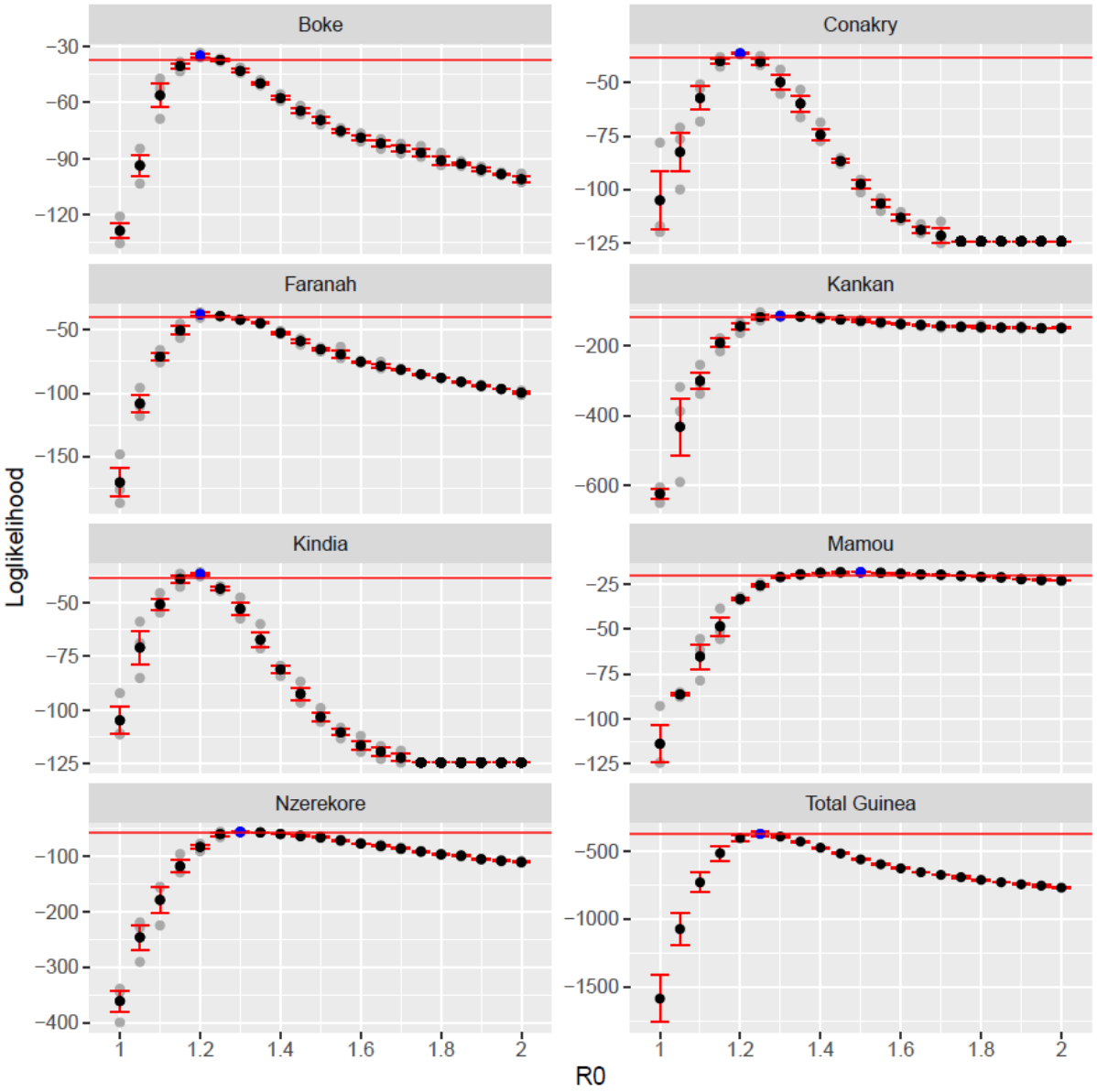


Fig. S2: Profile likelihoods for the parameters corresponding to vaccine effectiveness for Guinea (description as in Figure S1).

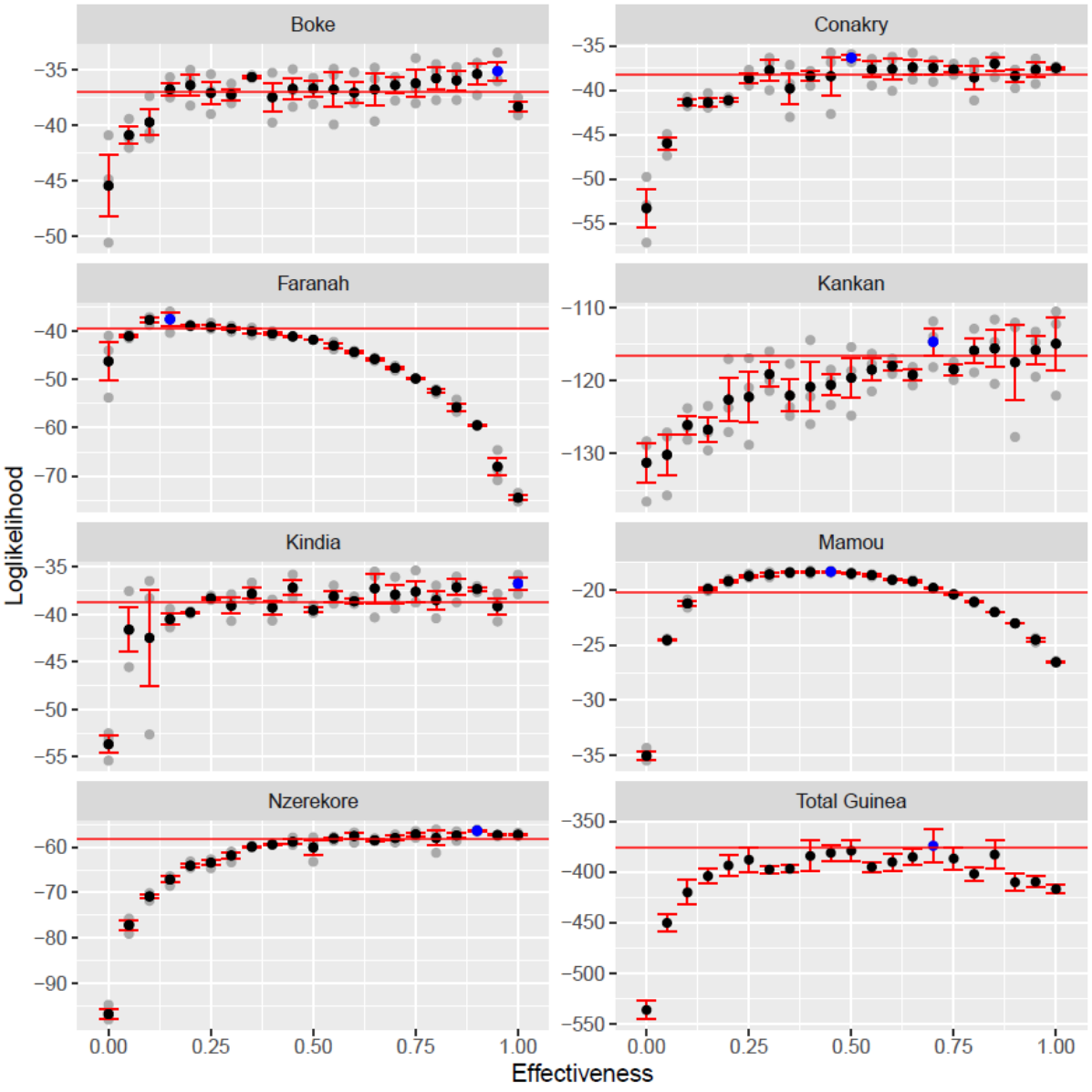


Fig. S3: Profile likelihoods for the parameters corresponding to iota for Guinea (description as in Figure S1).

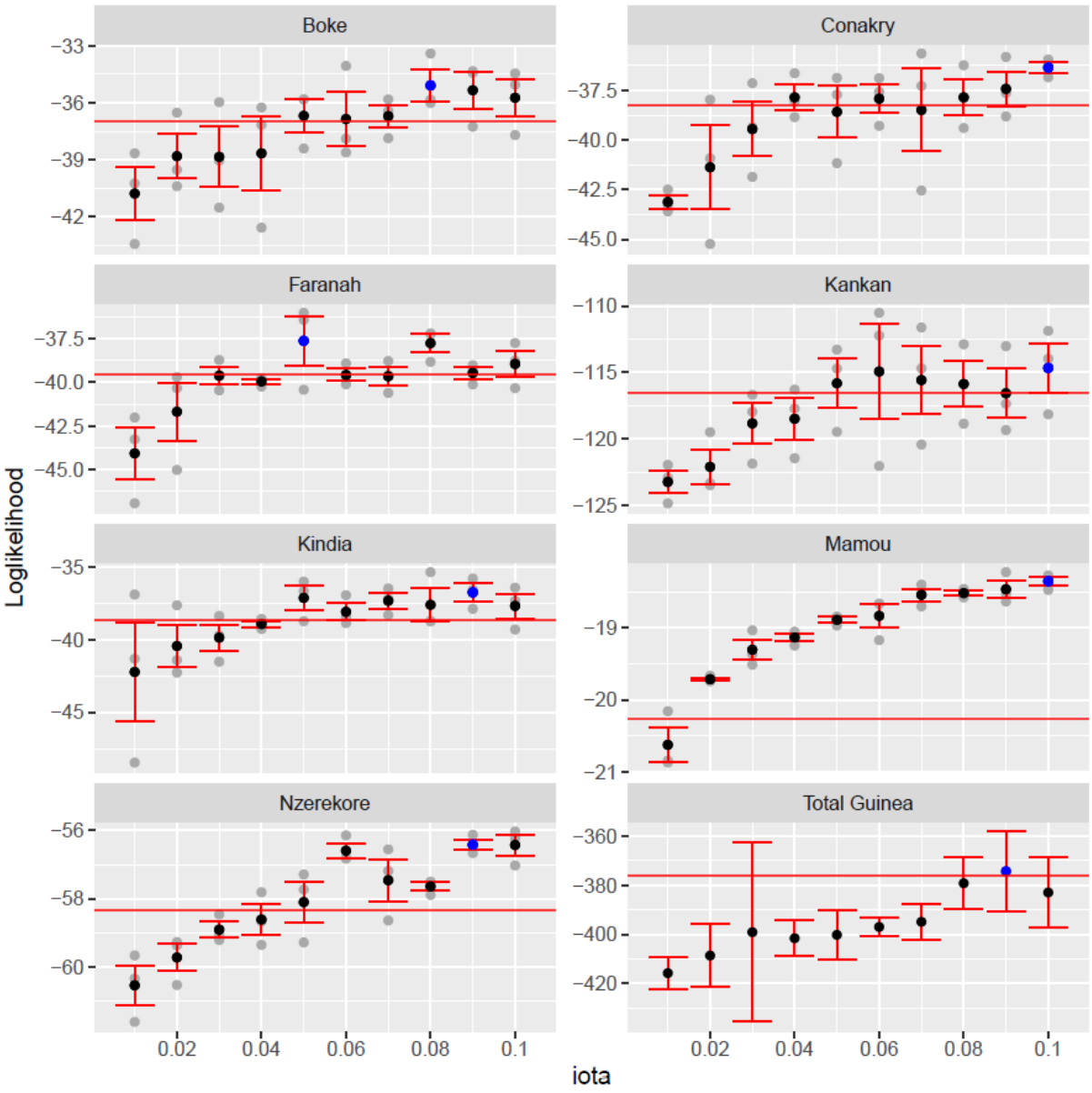


Fig. S4: Profile likelihoods for the parameters corresponding to R0 for South Sudan (description as in Figure S1).

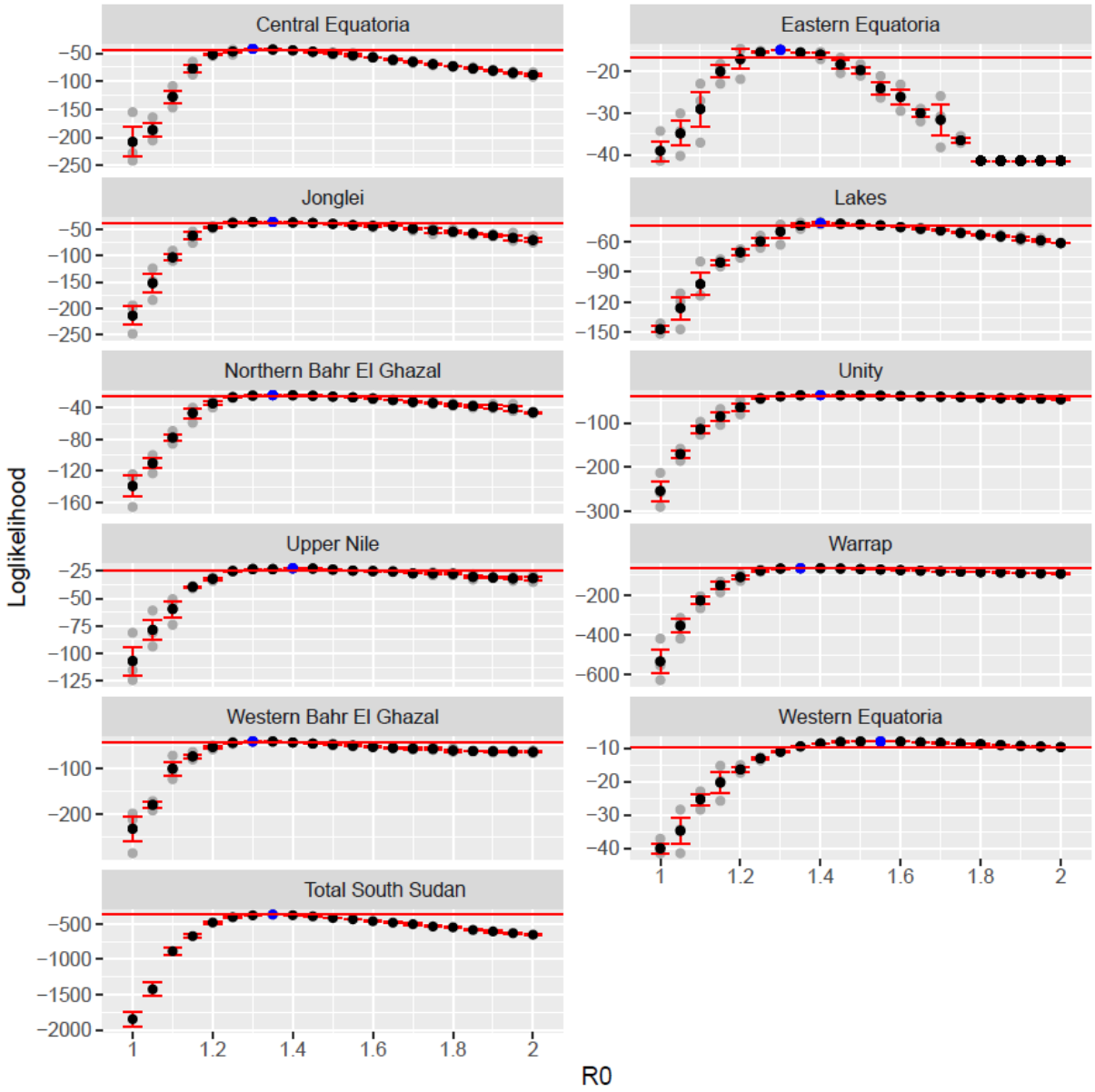


Fig. S5: Profile likelihoods for the parameters corresponding to vaccine effectiveness for South Sudan (description as in Figure S1).

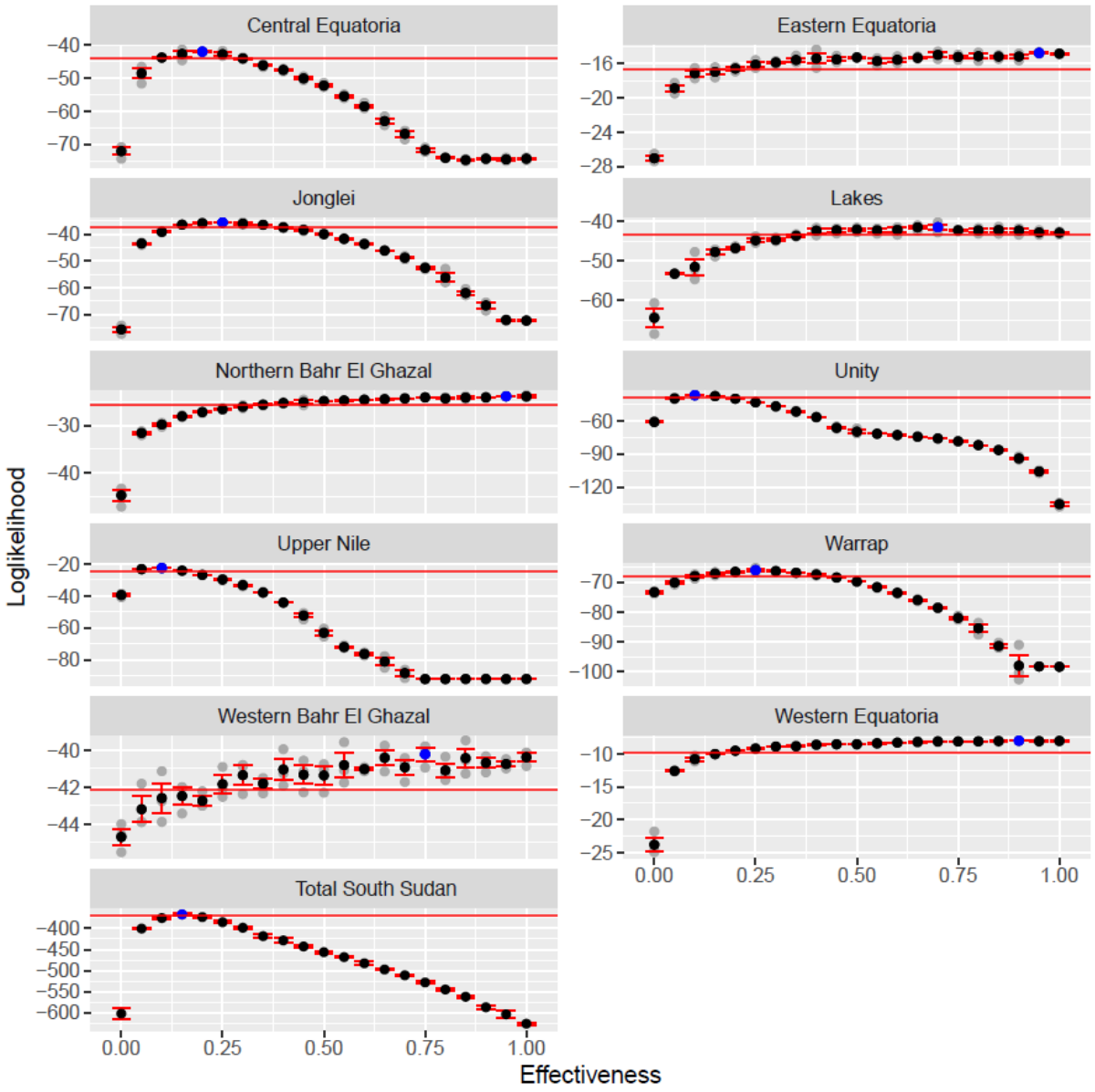


Fig. S6: Profile likelihoods for the parameters corresponding to iota for South Sudan (description as in Figure S1).

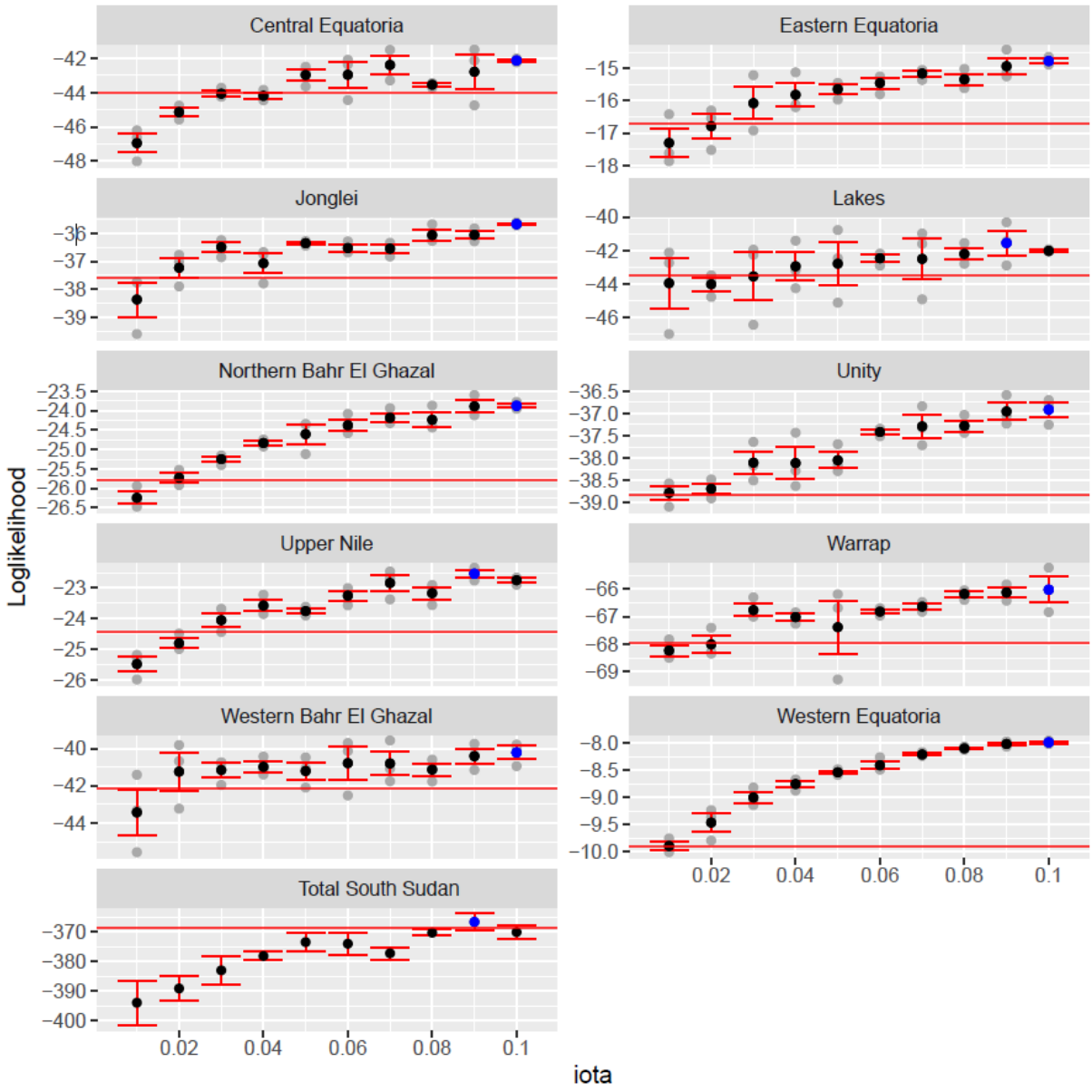


Fig. S7: Profile likelihoods for the parameters corresponding to R0 for Tajikistan (description as in Figure S1).

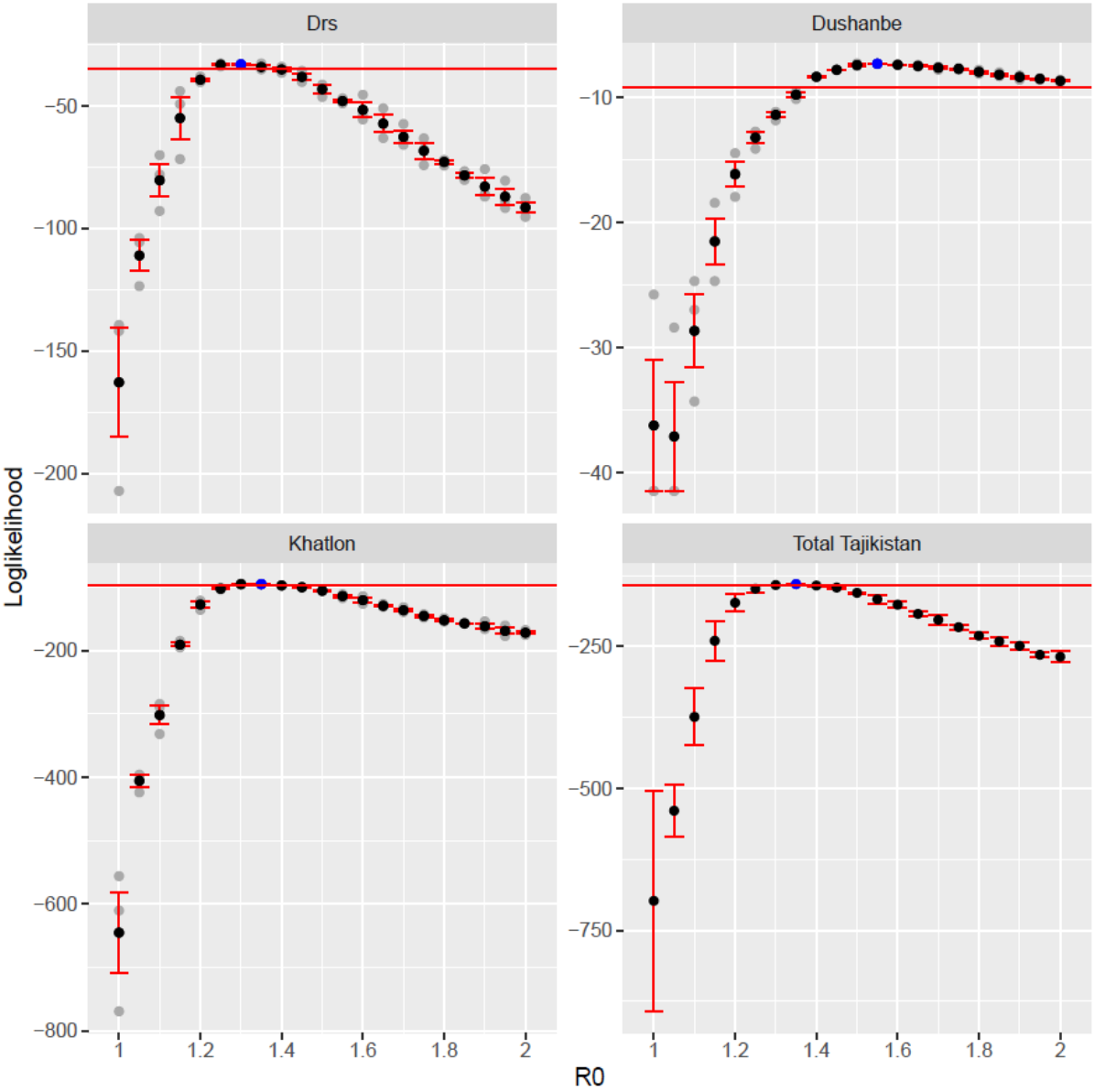


Fig. S8: Profile likelihoods for the parameters corresponding to vaccine effectiveness for Tajikistan (description as in Figure S1).

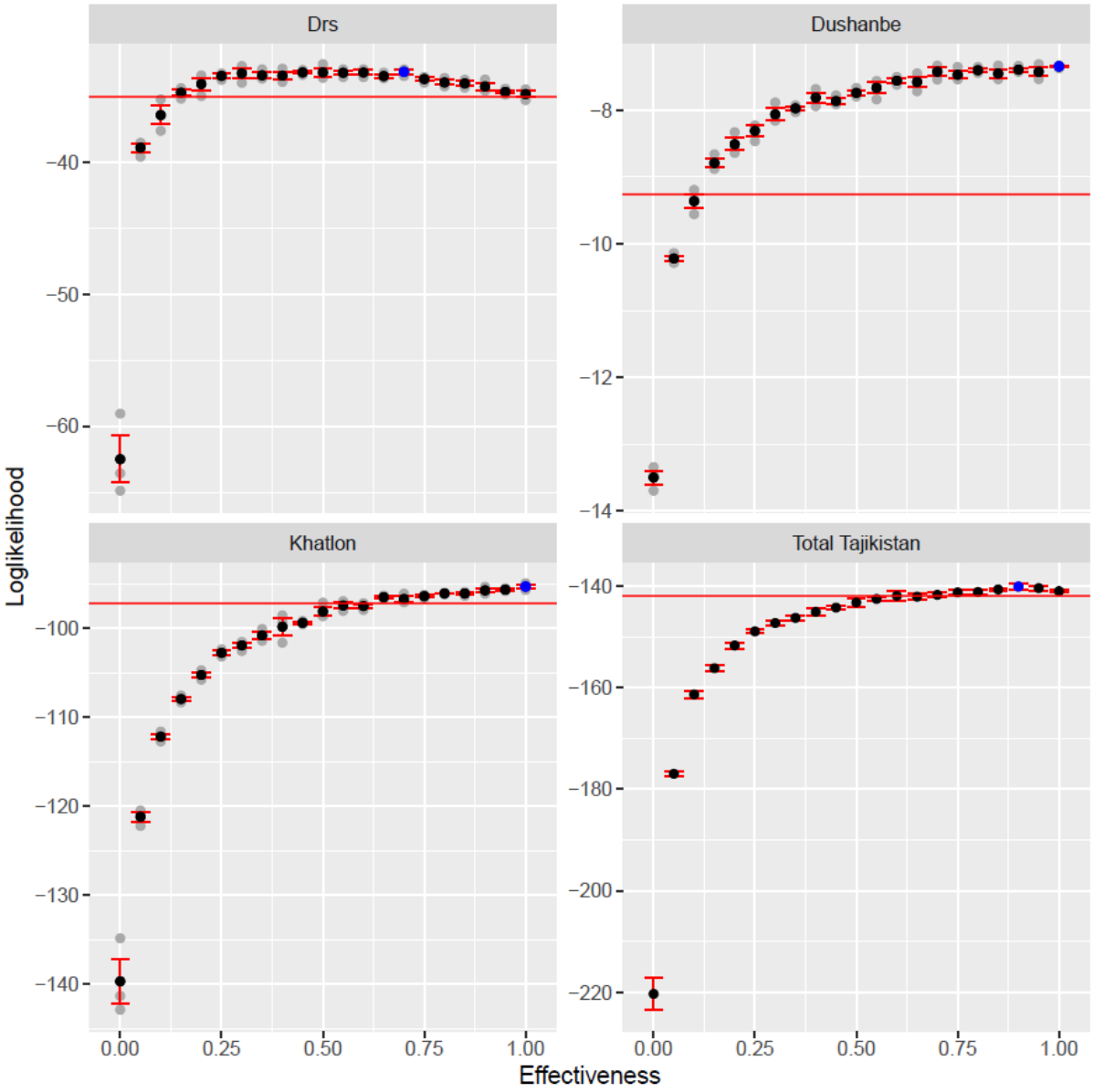


Fig. S9: Profile likelihoods for the parameters corresponding to vaccine effectiveness for Tajikistan (description as in Figure S1).

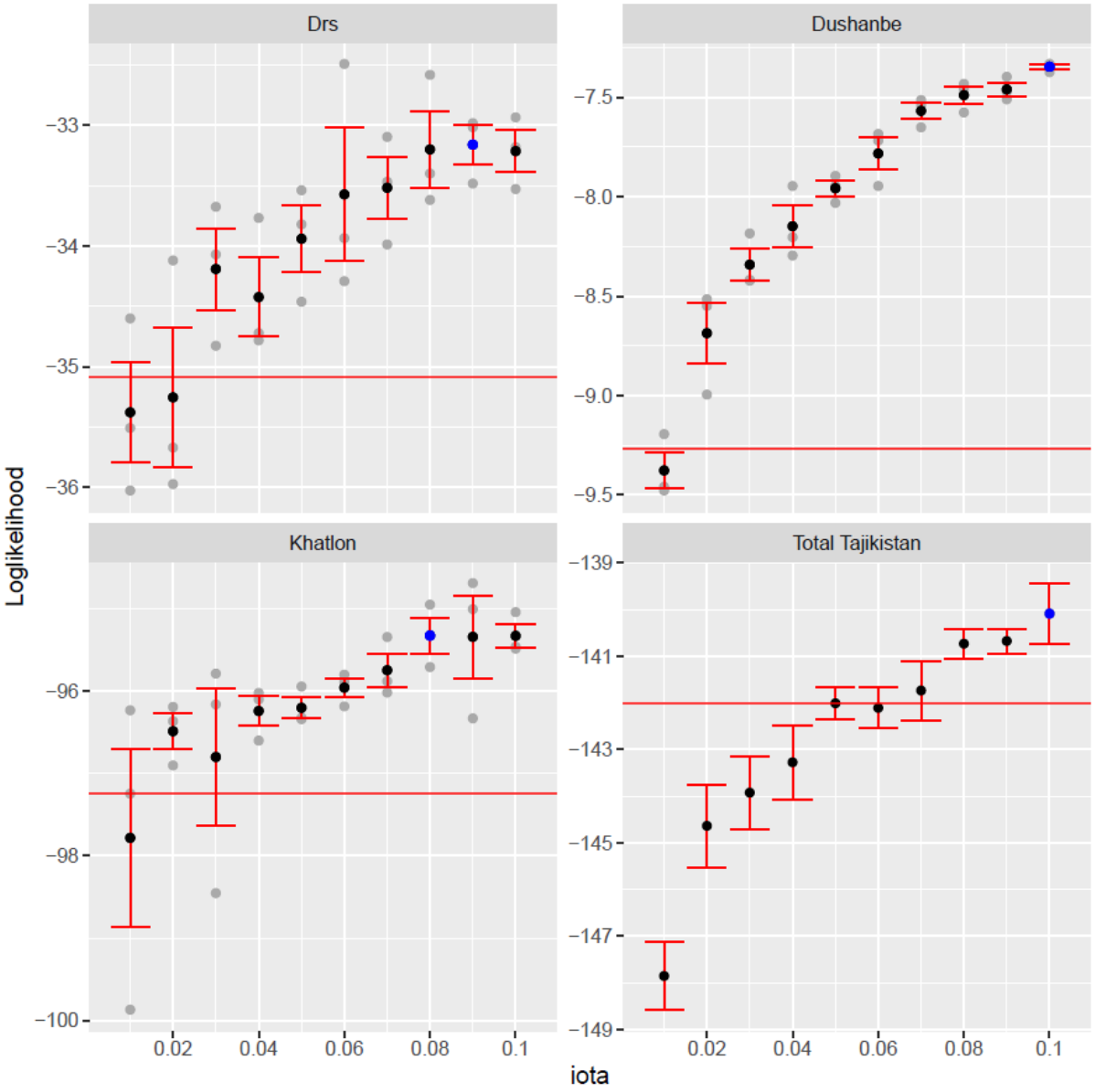


Fig. S10: Plot of 500 random simulations (out 5000) for the unit-pomp model for Guinea, Conakry (Unit 2). The model used the best fit model, with panel shared maximum likelihood estimate for iota and R0, vaccination campaigns on the dates they were implemented, and unit-specific estimated efficacy. Black lines indicate the proportion of the population that is susceptible (either S or V states) at time t. Blue lines indicate the cumulative number of reported AFP cases at time t. Red vertical lines at the top of the plot indicate the minimum time when 5 individuals are in the exposed to cVDPV2 state (E), which is used here to represent the likely time that the outbreak starts.

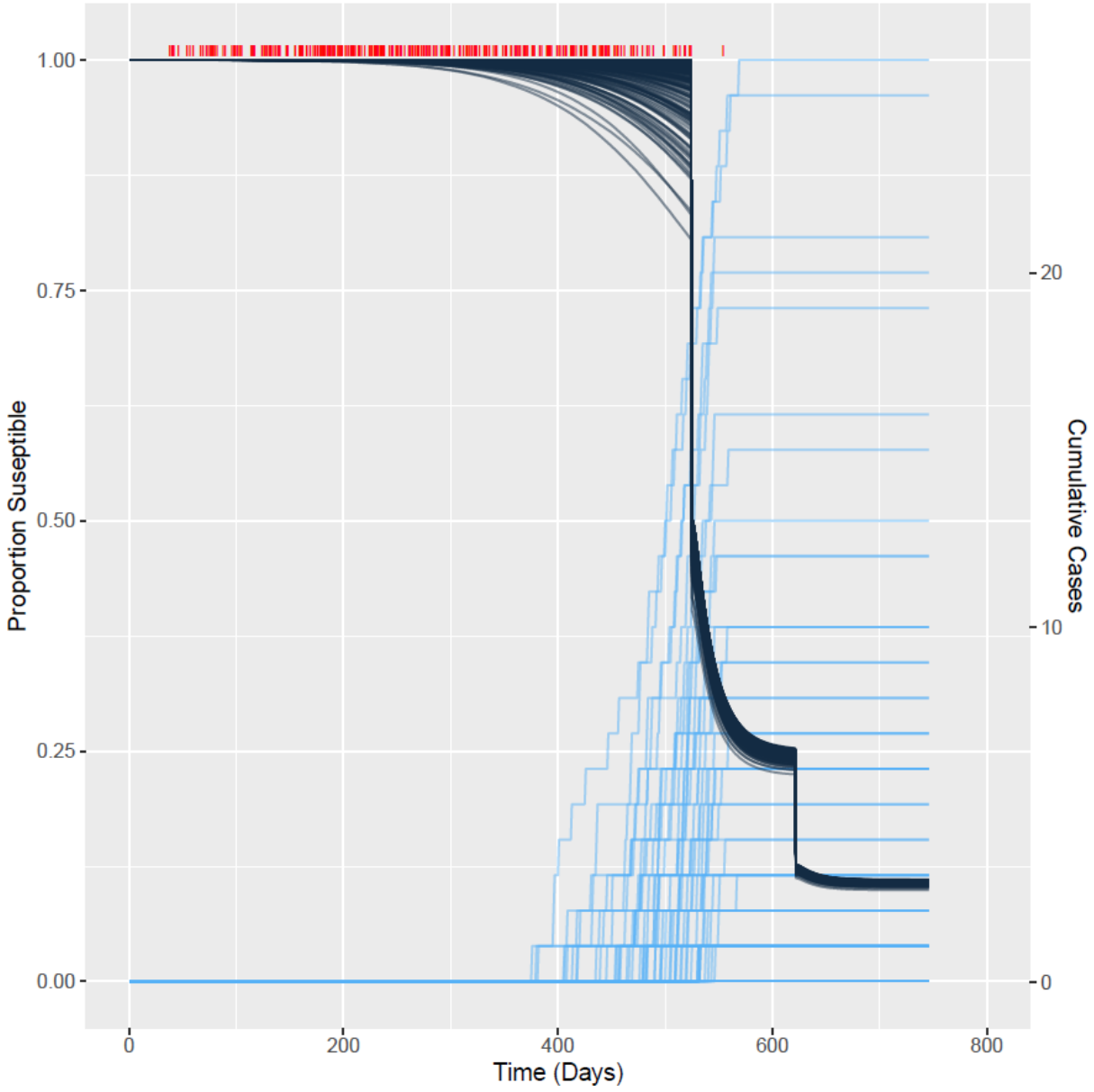


Fig. S11: Plot of 500 random simulations (out 5000) for the unit-pomp model for Guinea, Kankan (Unit 4). Description as in Figure S10.

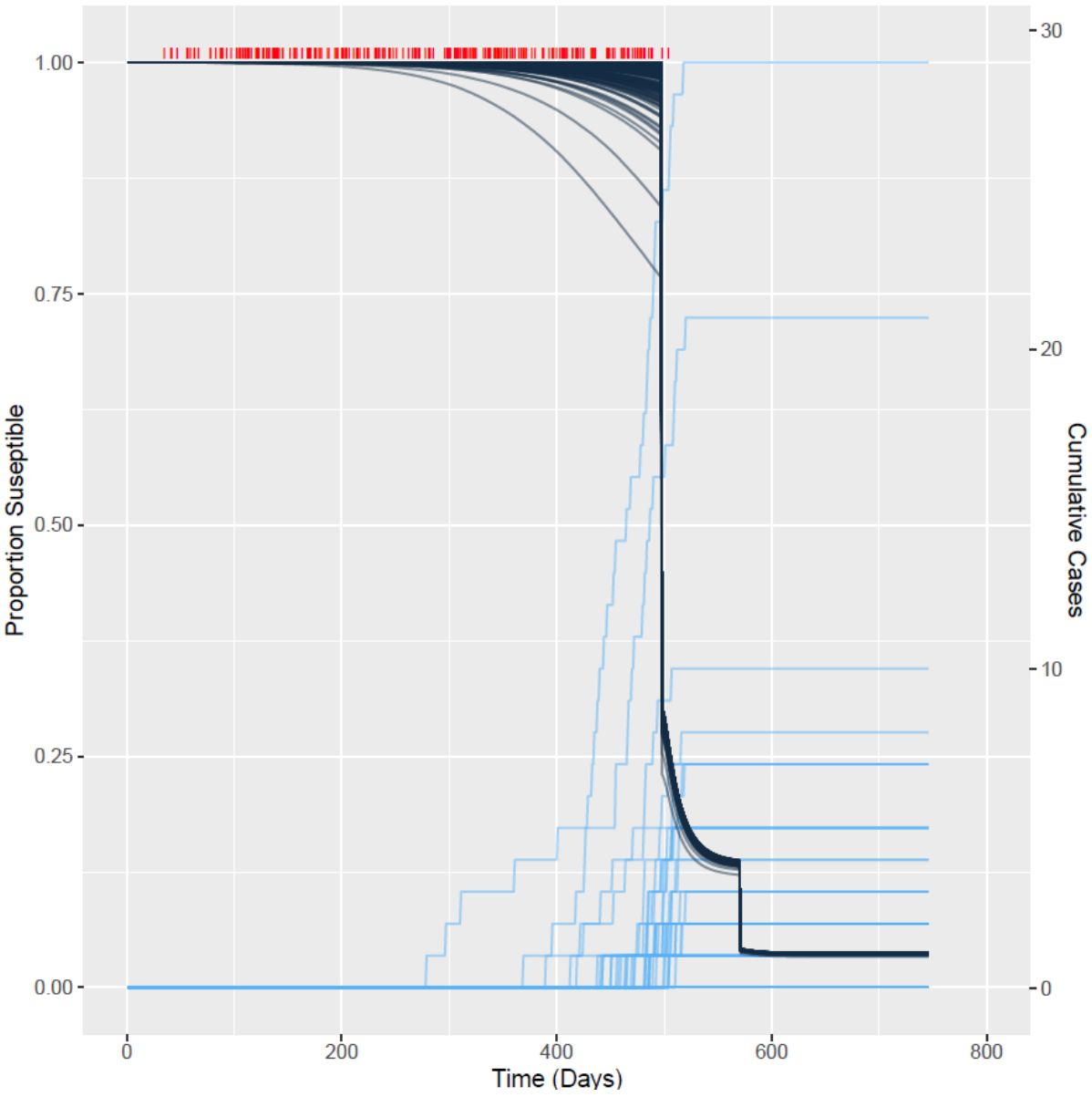


Fig. S12: Plot of 500 random simulations (out 5000) for the unit-pomp model for South Sudan, Central Equatoria (Unit 1). Description as in Figure S10.

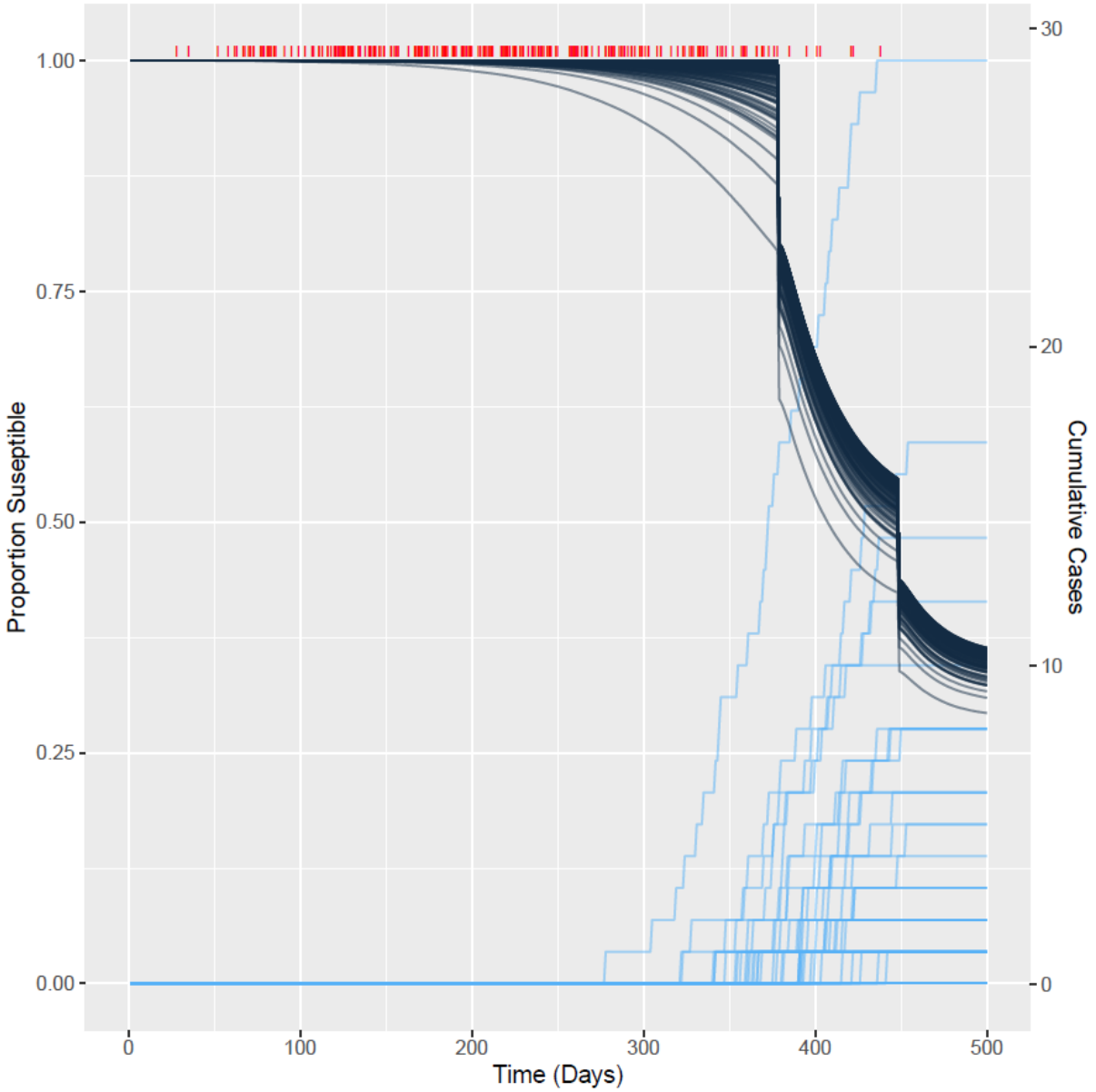


Fig. S13: Plot of 500 random simulations (out 5000) for the unit-pomp model for Tajikistan, Districts of Republican Subordination. Description as in Figure S10.

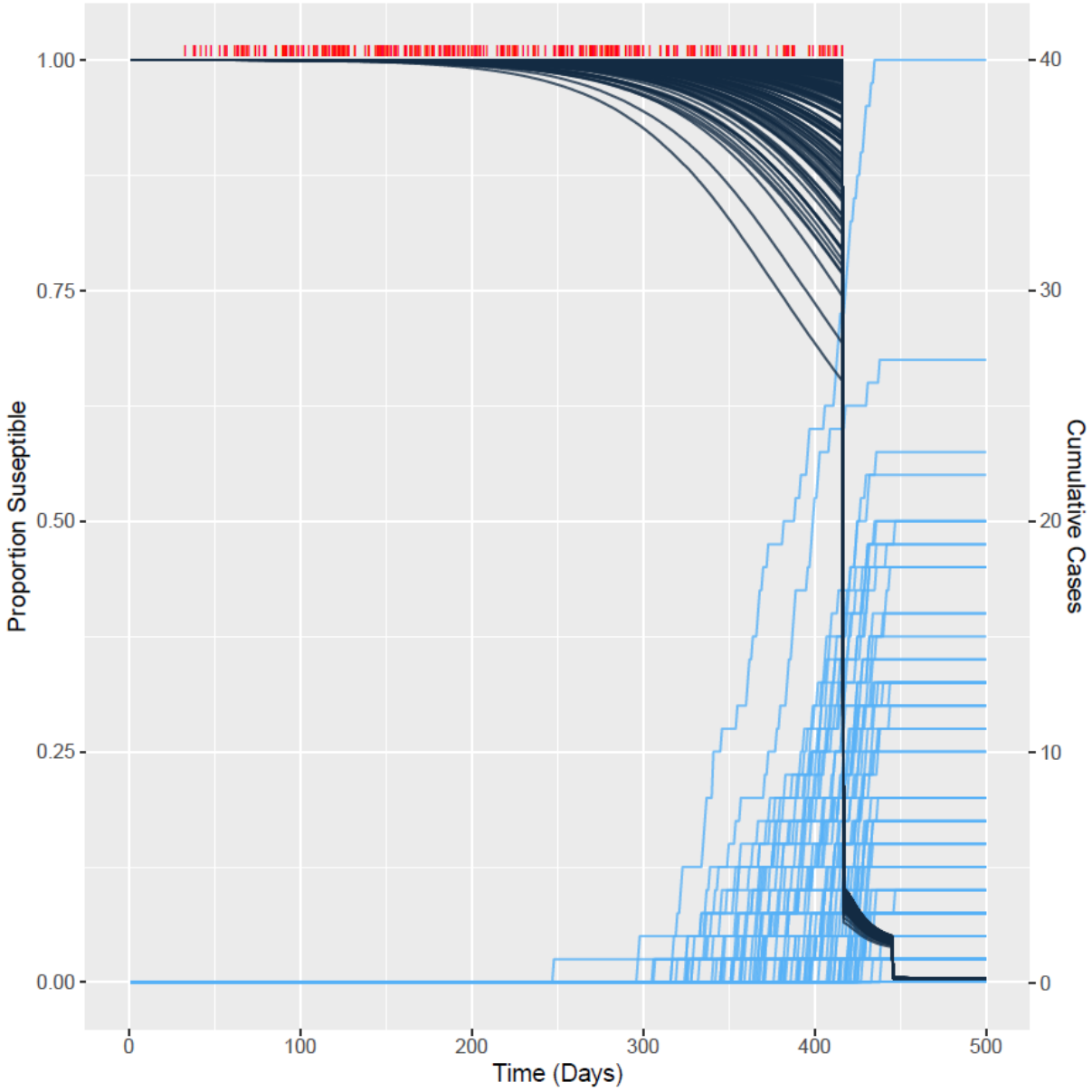
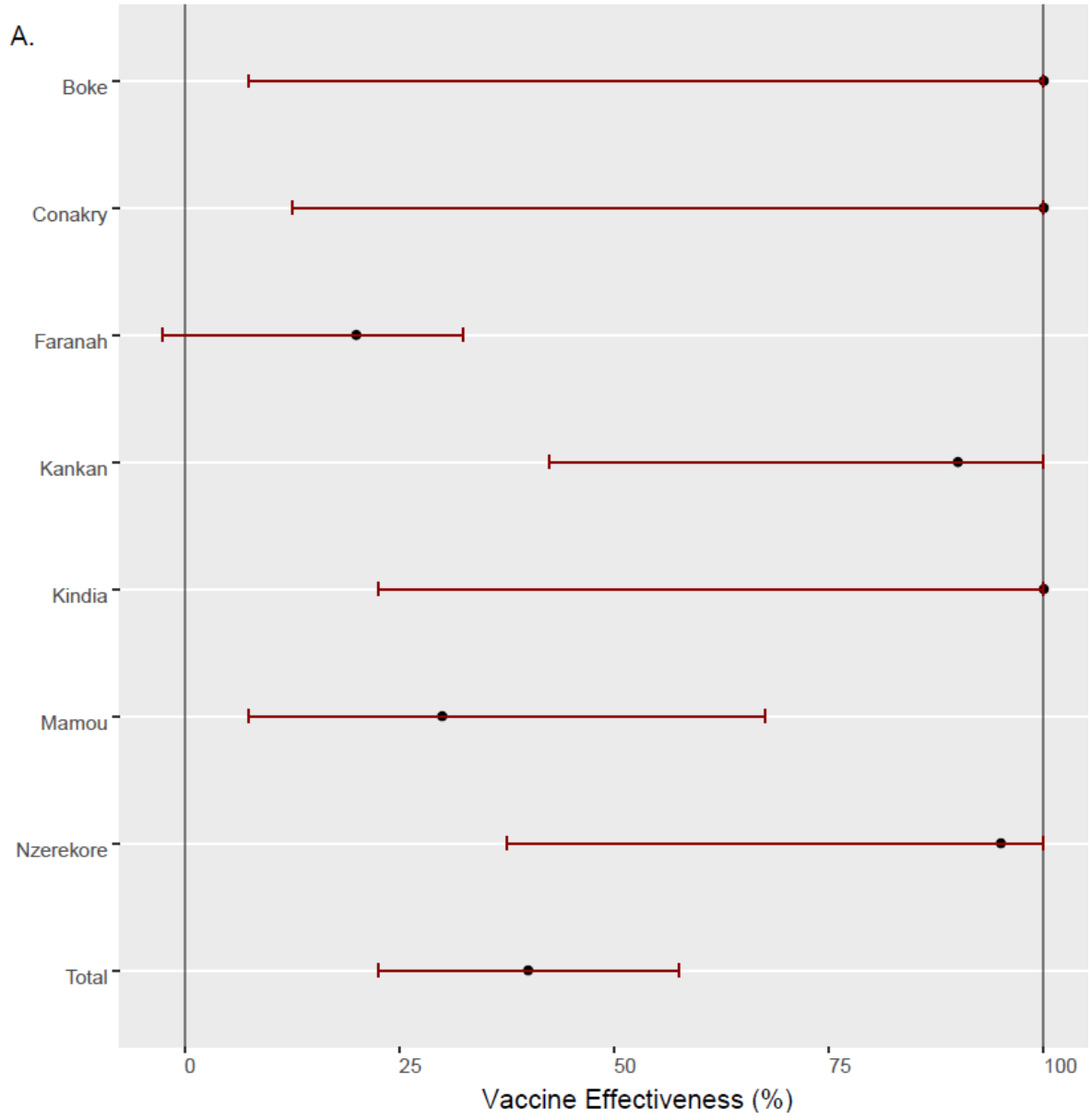
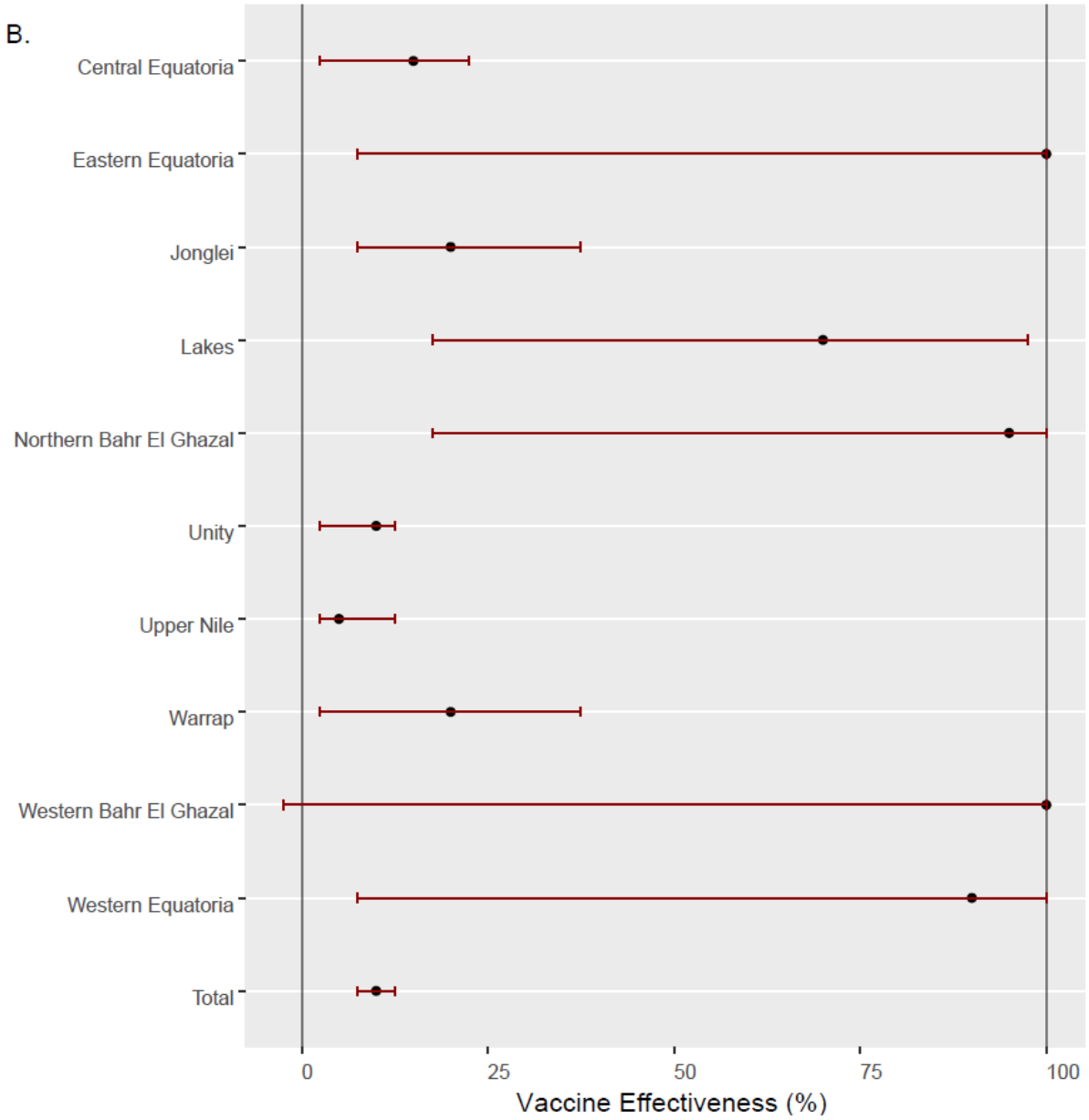
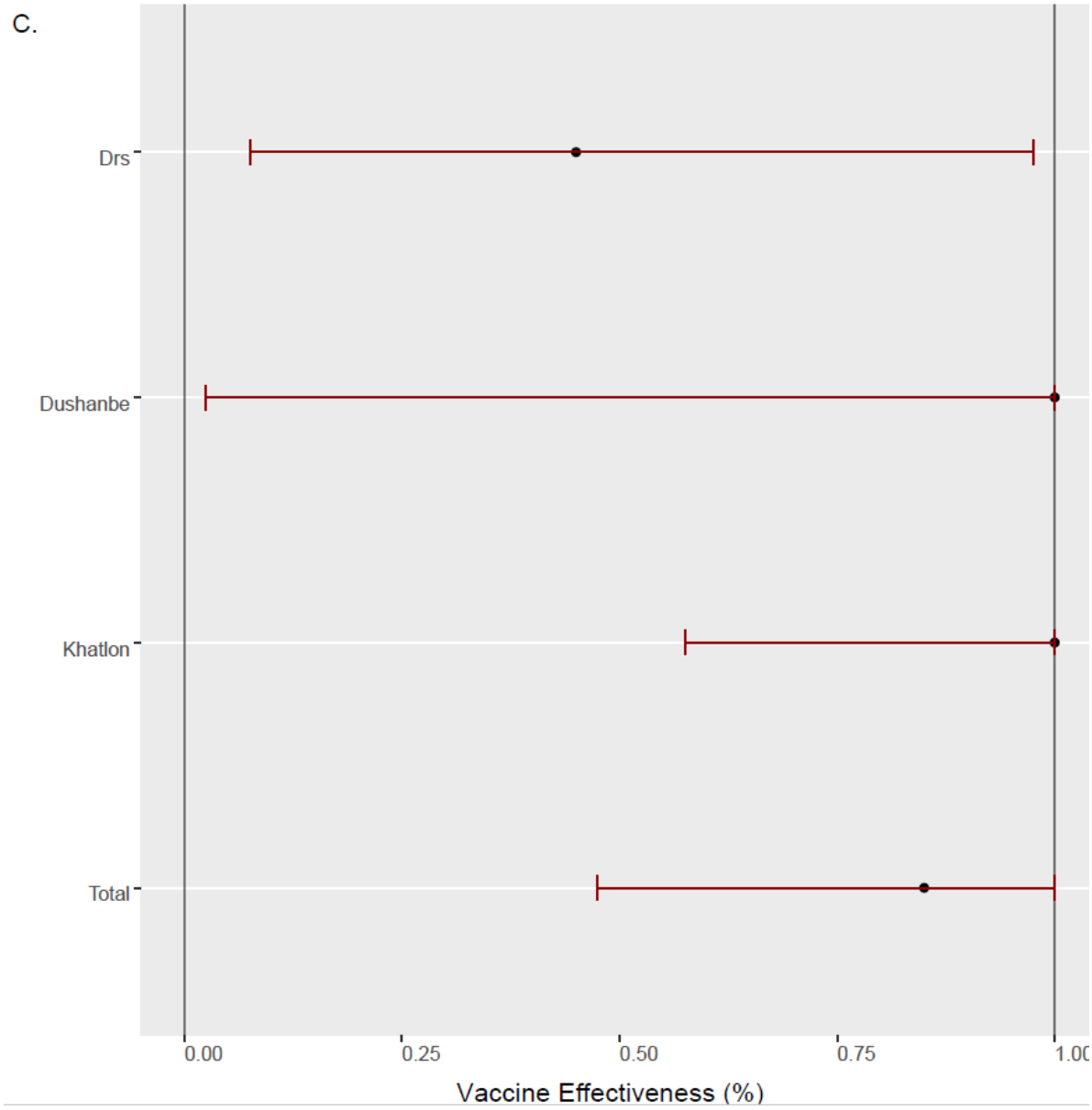


Figure S14: Sensitivity analysis of estimates of vaccine effectiveness with initial conditions starting 400 days before the first case, instead of 300 days as in main manuscript. Maximum likelihood estimates and 95% confidence intervals are given for each unit (province) and total panel (country), A. Guinea B. South Sudan and C. Tajikistan**.** Lines indicate the 95% confidence intervals, and circle indicates the maximum likelihood estimate.




B.
Central Equatoria
Eastern Equatoria
Jonglei
Lakes
Northern Bahr El Ghazal
Unity
Upper Nile
Warrap
Western Bahr El Ghazal
Western Equatoria
Total
0
25
50
75
100
Vaccine Effectiveness (%)


C.
Drs
Dushanbe
Khatlon
Total
0.00
0.25
0.50
0.75
1.00
Vaccine Effectiveness (%)

Supplementary Table 1: Parameter and States description in stochastic model of transmission

Parameters	Description
$\boldsymbol{\lambda}$	Force of infection for cVDPV2
$\boldsymbol{\lambda_V}$	Force of infection for OPV vaccine
γ	Recovery rate
ν	Latency period
z	Erlang distributed incubation period
ρ	Reporting rate
$\boldsymbol{\iota}$	Risk of importation
ε	Vaccination effectiveness (product of coverage and per-dose immunogenicity)
States	**Description**
S	Susceptible
V	Vaccinated with IPV
E	Exposed to VDPV2
I	Infected with VDPV2
R	Recovered
E_v	Exposed to OPV
I_v	Infected with OPV

Supplementary Table 2A: Stochastic Equations for the mathematical model of transmission. The stochastic model equations are given as follows, where Z^{XY} corresponds to the integer transitions from compartment X to compartment Y at time t. The transitions are evaluated by drawing random numbers from the binomial distribution, where dt is a small time-step, equal to one day in our simulations.

Movement between states	
Time ≠ vaccination time	$S_t = S_{t-1} - Z_t^{SE} - Z_t^{SE_V}$ $V_t = V_{t-1} - V_t^{VE} - Z_t^{VE_V}$ $E_t = E_{t-1} + Z_t^{SE} - Z_t^{EI}$ $I_t = E_{t-1} + Z_t^{EI} - Z_t^{IR}$ $E_{V,t} = E_{V,t-1} + Z_t^{SE_V} + Z_t^{VE_V} - Z_t^{E_V I_V}$ $I_{V,t} = I_{V,t-1} + Z_t^{E_V I_V} + Z_t^{VE_V} - Z_t^{I_V R}$ $R_t = R_{t-1} + Z_t^{IR} - Z_t^{I_V R}$
Time = vaccination time	$S_t = S_{t-1} - Z_t^{SE} - Z_t^{SE_V} - Z_t^{SE_V 1}$ $V_t = V_{t-1} - V_t^{VE} - Z_t^{VE_V} - Z_t^{VE_V 1}$ $E_{V,t} = E_{V,t-1} + Z_t^{SE_V} + Z_t^{VE_V} - Z_t^{E_V I_V} + Z_t^{SE_V 1} + - Z_t^{VE_V 1}$
Transitions	

$$Z_t^{SE} \sim Bin(S_{t-1}, \lambda\, dt)$$
$$Z_t^{VE} \sim Bin(V_{t-1}, \lambda\, dt)$$
$$Z_t^{EI} \sim Bin(E_{t-1}, \nu\, dt)$$
$$Z_t^{IR} \sim Bin(E_{t-1}, \gamma\, dt)$$
$$Z_t^{SE_V} \sim Bin(S_{t-1},\ \lambda_V\, dt)$$
$$Z_t^{VE_V} \sim Bin(V_{t-1},\ \lambda_V\, dt)$$
$$Z_t^{E_V I_V} \sim Bin(E_{t-1}, \nu\, dt)$$
$$Z_t^{SE_V 1} \sim Bin(S_{t-1}, \varepsilon\, dt)$$
$$Z_t^{VE_V 1} \sim Bin(V_{t-1}, \varepsilon\, dt)$$

Supplementary Table 2B: Force of infection equations

Force of infection for VDPV	$\boldsymbol{\lambda} = \frac{\beta}{N}\ (\boldsymbol{I(t)} + \boldsymbol{J(t)})$
where	$\beta = R_0\ \gamma$ $J(t) \sim Bin(\iota, dt)$
Force of infection for OPV	$\lambda_v = \frac{\beta_V(t)}{N}\ I_V(t)$
where	$\beta_V = R_{0V}\ \gamma$

Supplementary Table 3: Fixed parameter estimates in and data model with source

Parameters		**Estimate**	**Source**
Recovery rate, γ		1/14	(1)
Latency period, v		4 days	(2)
Reproductive ratio for OPV, R_{0V}		0.9	(3)
Erlang distributed incubation period, z		Rate = 0.329 Shape = 6	(3)
Reporting rate, ρ		1/2000	(4)
Efficacy of IPV		0.6	(5)
Coverage of IPV		**0.5**	(6)
Under-five population size by administrative 1 Region			
Guinea	Boke	223224	(7)
	Conakry	346430	
	Faranah	203130	
	Kankan	412408	
	Kindia	345694	
	Mamou	148118	
	Nzerekore	315828	
South Sudan	Central Equatoria	255002	(8)
	Eastern Equatoria	248783	
	Jonglei	422957	

	Lakes	187735	
	Northern Bahr El Ghazal	182856	
	Unity	218733	
	Upper Nile	265636	
	Warrap	201727	
	Western Bahr El Ghazal	147921	
	Western Equatoria	174871	
Tajikistan	Districts of Republican Subordination	267600	(9)
	Dushanbe	71600	
	Khatlon	451100	

Supplementary Table 4: Official estimates of coverage for vaccination campaigns that were modelled in the analysis, using methods of Administrative Estimate (AE), independent monitoring (IM) and Lot-quality assurance sampling (LQAS). All data exported as of March 2022.

Country	Start Date	End Date	Age Group (Years)	Vaccine Type	Campaign Quality Evaluation Estimates				
					AE Coverage	IM, % Missed Children, (House to House)	IM, % Missed Children (Out of House)	IM, Missed Children Out of House by Province	LQAS (% of lots passed)
Guinea	03/10/2020	06/10/2020	0 to 5	mOPV2	100.18%	9.4%	59.1%	Faranah -100% Kankan - 64.9 Nzerekore - 57.2%	NA
Guinea	15/12/2020	18/12/2020	0 to 5	mOPV2	105.75%	6.2%	59.1%	Faranah -100% Kankan - 64.9 % Nzerekore - 57.2%	NA
Guinea	26/02/2021	01/03/2021	0 to 5	mOPV2	94.98%	14.9%	21.1%	Boke - 12.4%, Conakry - 24.2%, Kindia - 23.0%, Mamou - 23.6%	25%
Guinea	03/06/2021	06/06/2021	0 to 5	mOPV2	105.00%	9.9%	10.8%	Boke - 1.9%, Conakry - 12.3%, Kindia - 11.6%, Mamou - 11.7%	80%
South Sudan	10/11/2020	11/12/2020	0 to 5	mOPV2	20.10%	10.2%	11.3%	NA	NA
South Sudan	08/12/2020	11/12/2020	0 to 5	mOPV2	86.58%	7.8%	4.4%	NA	NA
South Sudan	16/02/2021	19/02/2021	0 to 5	mOPV2	88.31%	NA	NA	NA	80%
Tajikistan	31/05/2021	05/06/2021	0 to 5	nOPV2	99.20%	NA	NA	NA	NA
Tajikistan	29/06/2021	05/07/2021	0 to 5	nOPV2	99.10%	NA	NA	NA	91.67%

Supplementary Table 5: The number of cases from 1000 simulations per unit of the best-fit-model with shared parameters of ι and R_0 and unit-specific vaccination effectiveness. Simulations are run under conditions with the vaccination campaigns as were conducted, and under hypothetical situation conducted one month earlier. The number of are presented as median and 95% confidence intervals (CI) after 5000 simulations for each unit, taking all units that result in at least one case. Where no simulations result in a case, the number of cases is 0. The total number of cases is taken as the median and 95% intervals after 1000 random sample draws of each unit (province) with replacement.

Country	**Unit**	**Observed cases**	**Vaccination campaigns unadjusted**			**Vaccination campaigns one month earlier**		
			Cases 2.5% CI	Cases, Median	Cases 97.5% CI	Cases 2.5% CI	Cases, Median	Cases 97.5% CI
Tajikistan	**Total**	**33**	**4**	**25**	**74**	**3**	**17**	**63**
	Districts of Republican Subordination	3	1	5	27	1	3	17
	Dushanbe	5	1	1	3	1	1	2
	Khatlon	27	1	15	65	1	10	52
Guinea	**Total**	50	**11**	**27**	**57**	**8**	**20**	**43**
	Boke	4	1	3	16	1	2	12
	Conakry	3	1	4	22	1	3	17
	Faranah	5	1	3	14	1	2	11
	Kankan	20	1	3	21	1	2	14
	Kindia	3	1	4	25	1	3	18
	Mamou	3	1	1	1	0	0	0
	Nzerekore	12	1	1	9	1	1	5
South Sudan	**Total**	**58**	**21**	**40**	**70**	**16**	**29**	**53**
	Central Equatoria	6	1	3	19	1	2	12
	Eastern Equatoria	1	1	3	15	1	2	11
	Jonglei	6	1	3	21	1	3	16
	Lakes	5	1	2	8	1	1	4

	Northern Bahr El Ghazal	4	1	2	9	1	2	7
	Unity	7	1	2	12	1	1	6
	Upper Nile	3	1	2	14	1	2	9
	Warrap	18	1	5	22	1	3	17
	Western Bahr El Ghazal	7	1	4	17	1	3	14
	Western Equatoria	1	1	1	3	1	1	3

Supplementary Table 6: Sensitivity analysis of parameter estimates with initial conditions starting 400 days before the first case, instead of 300 days as in main manuscript. Unit-specific and total panel maximum likelihood estimates (MLE) and 95% confidence intervals (CI), for the average basic reproductive ratio, R_0, per-day probability of importation, ι, and vaccination campaign effectiveness, ε.

Country	**Unit**	**Vaccination Campaign Effectiveness**			**R0**			**Probability of Importation**		
		Lower CI	Upper CI	MLE	Lower CI	Upper CI	MLE	Lower CI	Upper CI	MLE
Tajikistan	Districts of Republican Subordination	7.5%	97.5%	45.0%	1.175	1.325	1.25	0.005	0.1	0.1
	Dushanbe	2.5%	100.0%	100.0%	1.275	1.925	1.4	0.005	0.1	0.1
	Khatlon	57.5%	100.0%	100.0%	1.225	1.375	1.3	0.005	0.1	0.1
	Total	**47.5%**	**100.0%**	**85.0%**	1.275	1.375	1.3	0.045	0.1	0.1
South Sudan	Central Equatoria	2.5%	22.5%	15.0%	1.18	1.33	1.25	0.015	0.1	0.09
	Eastern Equatoria	7.5%	100.0%	100.0%	1.13	1.38	1.25	0.005	0.1	0.1
	Jonglei	7.5%	37.5%	20.0%	1.18	1.38	1.25	0.015	0.1	0.08
	Lakes	17.5%	97.5%	70.0%	1.23	1.43	1.35	0.015	0.1	0.08
	Northern Bahr El Ghazal	17.5%	100.0%	95.0%	1.23	1.43	1.30	0.015	0.1	0.1
	Unity	2.5%	12.5%	10.0%	1.23	1.48	1.35	0.015	0.1	0.1
	Upper Nile	2.5%	12.5%	5.0%	1.23	1.48	1.25	0.015	0.1	0.09
	Warrap	2.5%	37.5%	20.0%	1.23	1.38	1.30	0.005	0.1	0.1
	Western Bahr El Ghazal	0.0%	100.0%	100.0%	1.18	1.38	1.30	0.005	0.1	0.08
	Western Equatoria	7.5%	100.0%	90.0%	1.23	1.88	1.40	0.005	0.1	0.1
	Total	**7.5%**	**12.5%**	**10.0%**	1.23	1.28	1.25	0.085	0.095	0.09
Guinea	Boke	7.5%	100.0%	100.0%	1.13	1.23	1.15	0.025	0.1	0.1
	Conakry	12.5%	100.0%	100.0%	1.13	1.23	1.15	0.015	0.1	0.1
	Faranah	0.0%	32.5%	20.0%	1.13	1.23	1.20	0.015	0.1	0.1
	Kankan	42.5%	100.0%	90.0%	1.18	1.28	1.25	0.025	0.1	0.1
	Kindia	22.5%	100.0%	100.0%	1.13	1.18	1.15	0.005	0.1	0.09
	Mamou	7.5%	67.5%	30.0%	1.23	1.58	1.35	0.005	0.1	0.1
	Nzerekore	37.5%	100.0%	95.0%	1.18	1.33	1.25	0.005	0.1	0.08

	Total	**22.5%**	**57.5%**	**40.0%**	1.18	1.23	1.20	0.005	0.1	0.08

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