A systematic review and meta-analysis of fractional dose compared to standard dose inactivated polio vaccination in children.

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PREAMBLE

DECLARATION

I, **Thandiwe Mashunye,** hereby declare that the work on which this dissertation/thesis is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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THESIS ABSTRACT

The World Health Organisation (WHO) recommends the introduction of at least one single dose of inactivated polio vaccine (IPV) in routine immunisation schedules to mitigate the risk of a polio virus type 2 reintroduction or re-emergence. As a result, there has been an increased demand and concurrent supply shortages of IPV worldwide resulting in poor access to IPV. With the phasing out of the oral polio vaccine and the pursuit of global eradication of polio, ensuring an adequate supply of IPV is of paramount importance. One of the strategies to improve access is the use of the fractional dose because of its dose sparing and cost reduction properties. This mini-dissertation presents a research protocol (Section A), scoping review (Section B) and journal formatted manuscript (Section C) for a systematic review and meta-analysis of fractional dose compared to standard dose inactivated polio vaccination in children. Section A describes the rationale for the review, eligibility criteria, the search strategy and methods for data extraction and analysis. Section B is a scoping review that details the journey towards eradication of polio, the current state of IPV demand and supply and further explains the rationale for performing the systematic review. Section C is a manuscript that gives the results of the review after performing the methods outlined in Section A. The results showed that as the number of IPV doses increased the seroconversion rates for fractional dose and full dose IPV approximated each other such that at three doses the rates were similar. In conclusion, there is no difference in seroconversion between three doses of fractional dose IPV and three doses of full dose IPV. With the current IPV shortages, using fractional dose IPV instead of the full dose IPV can stretch supplies and possibly lower the cost of polio vaccination.

LIST OF ACROYNMS AND ABBREVIATIONS

ACPE	Advisory Committee on Poliomyelitis Eradication
aVDPV	Ambiguous vaccine derived poliovirus
AWI	Africa-Wide Information
bOPV	Bivalent oral poliovirus vaccine
CENTRAL	Cochrane Central Register of Controlled Trials
CDSR	Cochrane Database of Systematic Reviews
cVDPV	Circulating vaccine derived poliovirus
DARE	Database of Abstracts of Reviews of Effectiveness
EPI	Expanded programme on immunisation
f-IPV	Fractional-dose of inactivated poliovirus vaccine
GPEI	Global Polio Eradication Initiative
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
ICTRP	WHO International Clinical Trials Registry Platform
IPV	Inactivated poliovirus vaccine
ITT	Intention-to-treat analysis
iVDPV	Immunodeficiency vaccine derived poliovirus
MD	Mean difference
MeSH	Medical Subject Headings
OCLC	Online Computer Library Center
OPV	Oral poliovirus vaccine
PAHO	Pan American Health Organisation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
ROBINS-I	Risk of bias in non-randomized Studies - of Interventions
SAGE	Strategic Advisory Group of Experts on Immunization
tOPV	Trivalent oral poliovirus vaccine
UNICEF	United Nations International Children's Emergency Fund
VDPV	Vaccine derived poliovirus
VAPP	Vaccine associated paralytic poliomyelitis
WHA	World Health Assembly
WHO	World Health Organisation
WPV1	Wild poliovirus type 1
WPV2	Wild poliovirus type 2
WPV3	Wild poliovirus type 3

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SECTION A: RESEARCH PROTOCOL

1. INTRODUCTION

Poliomyelitis (or polio) is a communicable disease caused by one of three related wild polioviruses: poliovirus types 1, 2 and 3. Infection can occur at any age, but it mainly affects children under five.[1] The virus typically enters the body through the mouth and multiplies inside the gut. Initially it manifests as flu-like symptoms. Once established, it enters the bloodstream and attacks the central nervous system. As it proliferates, it destroys nerve cells which stimulate muscles. These nerve cells cannot be renewed, and affected muscles no longer function; causing paralysis. Up to 95% of infected individuals are asymptomatic and about 5% who develop minor flu-like symptoms fully recover.[2] Paralysis occurs in less than 1% of infected individuals.[2] Immunity against polio comes from either natural infection, which is when one recovers from polio or is immunised against contracting the disease through vaccination. There are two polio vaccines which are highly effective. The first is an injectable vaccine developed in the 1950s (the inactivated poliovirus vaccine) and the second an oral vaccine developed in the 1960s (the oral polio vaccine).[1]

In the early 1980s, more than 350 000 cases of paralytic polio were estimated to occur per year worldwide.[3] The widespread use of the oral poliovirus vaccine (OPV) resulted in substantial advances towards eradicating polio.[3-5] However, the vaccine has been associated with vaccine associated paralytic poliomyelitis (VAPP) and the generation of vaccine derived polioviruses (VDPVs).[6,7] These liabilities threaten the achievement of a polio free world. The Polio Eradication and Endgame Strategic Plan 2013-2018 outlines the necessary steps required to ensure that transmission of both wild polio viruses (WPV) and VDPVs is interrupted. One of its objectives is to prevent spread and re-emergence of VDPVs by gradually replacing OPV with the inactivated poliovirus vaccine (IPV).[8] The first stage in the phased removal of OPV was completed in April 2016.[9] It involved the cessation of the type 2 component of OPV through a global switch from trivalent OPV (tOPV) to bivalent OPV (bOPV).[8]

Prior to switching, in November 2012, the Strategic Advisory Group of Experts on Immunization (SAGE) recommended the introduction of at least one dose of IPV in national immunisation schedules to mitigate the risk of re-introduction or re-emergence of WPV type 2 or VDPV type 2.[10] This dose was meant to provide an immune base to improve immunological reactions and lower the risk of paralysis in the event of a type 2 polio outbreak.[3,11] In its 2016 polio vaccine position paper, the World Health

Organisation (WHO) endorsed the recommendation.[3] Globally, the demand for IPV increased globally from 80 million doses in 2013 to 200 million doses in 2016.[12] The global manufacturers that had assured the Global Polio Eradication Initiative (GPEI) and its partners about the feasibility of scaling up production to meet the demand, only managed to supply about half of the required doses for 2016 and 2017 and the supply is deteriorating.[12,13] With the limited supply and lack of competition in the market, the cost of IPV (up to US$ 2.8 per dose)[13,14] further restricts access in resource-constrained countries.

IPV shortages and high cost have given rise to delayed IPV introduction in some countries, while countries that already have IPV as part of their schedule are experiencing stock outs.[15,16] By September 2016, about 105 out of 126 countries that had OPV-only immunisation schedules had introduced IPV.[16] According to an update from UNICEF in March 2017, there were 18 countries that had introduced IPV which were only to receive IPV shipments in the first half of 2018.[18] Going forward, after the expected certification of global polio eradication in 2022, IPV will be the only vaccine being used.[19] This puts pressure on both the global community and individual countries to come up with strategies to ensure affordable and reliable long-term supply of IPV.

To address the current shortages and ensure availability of IPV, the GPEI and its partners are using a multipronged approach.[16] One of the recommended strategies is the use of dose sparing fractional doses instead of full doses of IPV.[3,16] One fractional dose (0.1ml) is one fifth of the full dose (0.5 ml) and it is usually delivered using an intradermal injection. Several randomised studies have assessed the immunogenicity of fractional-doses of IPV (f-IPV) compared to full dose(s) of IPV.[20-23] Randomised studies done in Cuba,[20,22] Oman[21] and Bangladesh[23] have shown that two fractional doses of IPV result in a better immunogenicity than one full dose of IPV.

Vaccination invokes a humoral immune response producing antibodies which, in most cases, offer long term protection against polio viruses.[3] Intradermal delivery of the polio vaccine is an efficient and effective mode of vaccination because it allows for the dose sparing approach.[24,25] Due to the abundance of immune cells in the dermis, when a vaccine is given via the dermis, a lower dose can be used compared to the intramuscular and subcutaneous routes.[25] In terms of cost, the price of one fifth of the dose is expected to be a fifth of the price of the full dose; hence reducing the cost.[4] According to an assessment

that was done by PATH, two f-IPV doses and the intradermal injection devices cost between US$1 to US$3 while a single intramuscular dose of IPV costs between US$ 1.1 and US$2.3.[25]

This dose sparing strategy might be the immediate solution to ensure that every child who is entitled to receive IPV is vaccinated. India and Sri Lanka have already introduced the f-IPV doses in their routine immunisation schedules with notable successes. In both countries, they have managed to vaccinate a larger number of eligible children while stretching their stocks; subsequently avoiding stock outs.[16] A mass vaccination campaign using a single f-IPV was successfully carried out in response to a VDPV type 2 outbreak in the Telangana State of India in May 2016.[26]

Countries are encouraged to consider the programmatic and logistic challenges that come with introducing f-IPV before rolling out the policy.[3] Intradermal administration involves purchasing of devices to administer, training health workers and other logistics which affect the feasibility of the programme.[17] Programmes in India and Sri Lanka have demonstrated that despite these challenges, a nationwide programme using f-IPV is possible even in an outbreak setting.[16,26]

The Sustainable Development Goal number 3 includes achieving access to affordable, safe and effective vaccines for all by 2030.[27] Replacing OPV with IPV is essential for the eradication of WPV and VAPP. As we progress towards the certification of the global eradication of polio, ensuring sustainable, reliable and affordable IPV supply is of paramount importance. The dose sparing, and cost reduction characteristics of fractionated doses can contribute to improved IPV access. This review will add to the evidence gathered by other reviews to inform decisions regarding the value of fractionated IPV dosages.

Grassly[28] performed a systematic review and meta-analysis to assess the immunogenicity and effectiveness of 1 or 2 doses of f-IPV in routine immunisation. The author found that two f-IPV doses administered after 10 weeks of age are likely to provide 80% protection against poliomyelitis. It is now 5-6 years since the literature search was conducted for this review, and new evidence has accumulated since then.[23,26] In addition, study selection and data extraction were not done in duplicate; increasing the risk of systematic errors in this timely review.[28] It is an indispensable practice in systematic reviews to conduct those steps in duplicate, and resolve discrepancies by discussion and consensus or arbitration.[29]

In another review, Anand et al.[11] focused on comparing immunogenicity of two f-IPV and one full dose of IPV. They concluded that two f-IPV doses are more immunogenic than a single dose. Of note, in both reviews,[11,28] there is absence of an extensive search of the literature. This evidenced by a limited number of databases searched by the authors. Grassly searched only the Web of Knowledge collection of databases and Anand and colleagues' search was restricted to the PubMed database only. Therefore, there might be other studies that were excluded from these reviews that may alter their findings. Vaccine safety and administration are important considerations when deciding on an immunisation schedule. The previous reviews did not evaluate adverse effects of different IPV dosages and the devices used to give the intradermal injections. In addition, none of the previous reviews used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method[30] to assess the certainty of the evidence on effects of f-IPV.

We aim to do a systematic review of studies comparing the effects of fractional compared to full dose IPV vaccination. We will evaluate the occurrence of adverse events and document the types of administration devices used for the intradermal delivery of f-IPV.

2. OBJECTIVES

The objective of this review is to assess the effects of fractional doses of inactivated polio vaccine, compared full doses of the vaccine.

3. METHODS

3.1 Criteria for considering studies for this review

3.1.1 Types of studies

We will include randomised trials, non-randomised trials, case-control studies and cohort studies.

3.1.2 Types of participants

The participants of interest will be children aged five years of age or younger.

3.1.3 Types of intervention

The eligible intervention will be the administration of fractional dose(s) of IPV, while the eligible comparison will be the administration of full dose(s) of the vaccine; irrespective of vaccination schedule or route of administration. Only studies comparing the same number of doses of fractional versus full doses of IPV will be compared.

3.1.4 Types of outcome measures

The primary outcome for this review is immunogenicity, measured using the proportion of participants who sero-converted (as defined by the authors of the included studies). As well as titres of poliovirus-neutralising antibodies for wild poliovirus serotypes 1, 2, and 3; assessed at least four weeks following vaccination. Our secondary outcomes include adverse events following polio vaccination; vaccine associated paralytic polio; and wild poliovirus associated paralytic polio and mucosal immunity (as defined by the authors). We will also describe the routes and devices used to administer the fractional doses of the vaccine.

3.2 Search methods for identification of studies

We will develop a comprehensive search strategy for peer-reviewed and grey literature. We will search the following databases from the inception to the date of the search; with no date or publication restrictions: Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE, Science Citation Index, Conference Proceedings Citation Index, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effectiveness (DARE), Scopus, EBSCO Host: AWI, CINAHL, Health Source: Nursing/Academic Edition, PDQ-Evidence, Network of Digital Library of and Theses and Dissertation, DART Europe E-theses Portal, ProQuest Dissertations & Theses A&I, PapersFirst (OCLC), Proceedings (OCLC), and the WHO International Clinical Trials Registry Platform (ICTRP). We will also search the reference lists of included studies, related reviews, and relevant WHO vaccine position papers. Table 1 below shows the proposed search strategy for the PubMed database, which will be adapted for the other databases.

Table 1. PubMed search strategy
#1: Poliovirus Vaccine, Inactivated [MeSH] OR inactivated polio vaccine OR inactivated poliovirus vaccine OR SALK OR IPV OR eIPV OR killed vaccine.

#2: Injections, Intradermal [MeSH] OR Injections, Intramuscular [MeSH] OR fractional dosing OR Fractionated dosing OR drug dose comparison OR intradermal OR intramuscular OR dose OR dosage.
#3: Dose-Response Relationship, Immunologic [MeSH] OR Antibody Formation [MeSH] OR Seroconversion [MeSH] OR Immunogenicity OR Immune response OR Seroconversion OR potency OR antibody formation OR antibody response.
#4: (#1 AND #2 AND #3).
#5: Animals NOT Human
#6: (#4 NOT #5)

3.3 Data extraction and management

For each included study, two authors will independently extract the information indicated in Table 2 using a pre-designed and piloted data extraction form. Extracted data will include study, participant, intervention, and outcome characteristics as well as study findings (Table 2). We will present this information in a table of the characteristics of included studies. Any differences will be resolved through discussion and consensus between the two authors. A third author will be consulted to arbitrate if disagreements persist between the two authors. If there are missing data, we will contact study investigators for the missing information**.**

Table 2. Information that will be extracted from each included study

Study design and methods	Citation information (authors, journal, year of publication, volume, issue, and page numbers); study design (randomised trial, non-randomised trial, case-control study, cohort study); study location (city, country), and period of study (start and end date i.e. month and year). Methods for generating randomisation sequence, concealing allocation of interventions, and blinding of outcome assessment; number of participants randomised and number with complete outcome data for each outcome; names of outcomes announced in study protocol but not reported in study publication, and other biases.
Participant characteristics	Age, sex, study location, study inclusion and exclusion criteria, flow of numbers of participants during the study (from participant enrolment to completion of data collection).
Intervention	Definition of fractional dose, manufacturer of vaccine, immunisation schedule (frequency, timing, interval between doses, etc), OPV co-administration, route of

	administration (intradermal, sub-cutaneous, etc), and types of devices used for administration of the fractional doses (name, manufacturing company, etc).
Comparison	Definition of full dose, manufacturer of vaccine, immunisation schedule (frequency, timing, interval between doses, etc), OPV co-administration, route of administration (intramuscular, sub-cutaneous, etc).
Outcome measures	Outcomes reported in the study (immunogenicity, adverse events following polio vaccination, vaccine associated paralytic polio, wild poliovirus associated paralytic polio, mucosal immunity), how they were defined, and how they were measured.
Outcome data	Seroconversion (number of participants randomised and number who seroconverted in each arm), antibody titres (geometric mean plus standard deviation or median and range in each arm), number of participants randomised and number who experienced the following events in each arm: adverse events following IPV vaccination, vaccine associated paralytic polio, wild poliovirus associated paralytic polio, mucosal immunity).

3.4 Assessment of risk and bias in included studies

Two authors will independently assess the risk of bias for each included study using the Cochrane Risk of Bias tool for trials[31] and the ROBINS-I tool non-randomised studies of interventions.[32] For trials, we will assess the risk of bias across seven domains: random sequence generation, allocation concealment, blinding of participants and study personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other potential source of bias. For each included study, whether trial or not, we will describe what the study authors reported that they did for each domain and then assign a judgement of low, high, or unclear risk of bias. Differences in judgement will be resolved by discussion and consensus, or arbitration by a third author. Based on these assessments, we will classify each included study as having a low, moderate, or high risk of bias. Each study that receives a judgement of high risk for allocation concealment, blinding of outcome assessment, or completeness of outcome data will be considered to have a high risk of bias. A study that is judged to have low risk of bias for all three domains will be considered to have a low risk of bias. All other studies will be considered to have a moderate risk of bias. We will use these risks of bias data in the GRADE assessments of certainty of evidence, as described below, by downgrading the certainty of the evidence of effects from trials with high risk of bias.

3.5 Dealing with missing data

For incomplete or missing data, we will contact corresponding authors to request additional information or clarification. Missing data and dropouts will be reported in the 'risk of bias' table and we will evaluate the impact of missing data on our results. Where possible we will conduct intention to treat analysis (ITT). We will conduct sensitivity analyses were by missing data is treated as successes or failures (worst-best and best-worst case scenario sensitivity analysis).

3.6 Data Synthesis

We will stratify the analyses by the type of study design, type of poliovirus, type of outcome measure, and number of IPV doses given. We will use the risk ratio (RR) and its corresponding 95% confidence interval to summarise data for the following binary outcome measures (seroconversion, adverse events following polio vaccination, vaccine associated paralytic polio, wild poliovirus associated paralytic polio and mucosal immunity). For geometric median titres (our only outcome measure with continuous data), we will calculate the mean difference (MD) and its 95% confidence interval when the outcome data is measured on the same scale. Alternatively, if the measurement scale differs, the standardised mean difference (SMD) and its 95% confidence interval will be used.

For each type of poliovirus, we will pool the outcome data from studies with the same design and amount of IPV doses administered using the random-effect method of meta-analysis. In studies where there are multiple interventions, we will include pair-wise comparisons that address the objectives of our review as outlined above. To avoid double counts when analysing correlated groups, we will pool the groups together to create a single pair-wise comparison

3.7 Assessment of heterogeneity

Initially we will assess for heterogeneity by visually inspecting the forest plots for overlapping confidence intervals. To further evaluate statistical heterogeneity, we use the χ^2 test of homogeneity; with significance defined at the alpha level of 0.10. We will also use the I^2 statistic to quantify the amount of heterogeneity.[33] We will investigate the causes of statistical heterogeneity using subgroup analyses.

We will define subgroups based on the timing of the first fractional dose, age of administration, number of fractional doses, interval between doses, poliovirus type (1, 2 and 3), type of intradermal injection device, immunisation schedules (OPV containing versus non-OPV schedules), and country income status.[34]

3.8 Assessment of reporting biases

We will reduce possible publication bias by using a comprehensive search strategy. Literature sources will include published, unpublished, and grey literature. To investigate possible publication bias, we will construct funnel plots if there are more than 10 studies included in the meta-analysis.[35]

3.9 Sensitivity analysis

We will perform sensitivity analyses to assess if the effect of f-IPV will be affected by of bias (by excluding studies with a high risk of bias), study designs (randomised versus non-randomised), and methods of meta-analysis (fixed versus random effects).

3.10 Reporting review findings

We have written this protocol, and we will report the outcome, following the recommendations of relevant PRISMA guidelines.[36-38] Additionally, forest plots and GRADE summary of findings tables will be used to report the outcome of our analysis. We will use the GRADE approach to evaluate the certainty of the evidence.

The GRADE approach assesses the certainty of a body of evidence as high, moderate, low, or very low; through evaluating the risk of bias, imprecision, inconsistency and indirectness of study results, and the risk of publication bias.[39,40] Regarding risk of bias, concerns that will limit our confidence in the evidence of effects are lack of allocation concealment, lack of blinding of outcome assessment, and differential losses to follow-up between intervention and comparison groups of more than 10%. Inconsistency of effects across included studies, for which we find no compelling explanations, will reduce our confidence in the evidence. Indirectness occurs when there are differences between the participants, interventions, comparisons, and outcomes of a

review, and those reported in included studies. We do not anticipate that this will be an issue in our planned review. For imprecision, if we obtain pooled estimates of effects with wide confidence intervals (a situation which occurs when included studies have small number of participants and experience few events), we will rate down the certainty of the evidence. Finally, we will downgrade the certainty of evidence of effects of f-IPV if our funnel plots show a high likelihood of publication bias.

4. ETHICS AND DISSEMMINATION

Collection of data for our review does not involve direct contact with human participants. Instead will use published and publicly accessed data. We obtained approval from the University of Cape Town Human Research Ethics Committee (HREC REF: 412/2018). We registered the review in the PROSPERO International Prospective Register of Systematic Reviews (CRD42018092647). The findings of this review will provide policy makers, health workers and donors with evidence for decision making with regards to IPV dosage. In the face of the current shortages, this might improve immediate and long-term access to the vaccine. The results of the review will be published in the University of Cape Town online library and published in a peer reviewed journal.

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SECTION B: SCOPING REVIEW

THE JOURNEY TOWARDS ERADICATING POLIO: IS THERE A ROLE FOR FRACTIONAL DOSAGE OF INACTIVATED POLIOVIRUS VACCINE?

1. INTRODUCTION

Walking the last mile towards polio eradication, requires interruption of wild poliovirus (WPV) transmission in the remaining endemic countries (Pakistan, Afghanistan and Nigeria) and cessation of oral poliovirus vaccine (OPV) use to interrupt transmission circulating vaccine derived polio virus (cVDPVs).[1,2] The stepwise removal of OPV has been affected by the increased demand and the short supply of inactivated poliovirus vaccine (IPV).[3] Currently a few countries have taken the initiative to introduce fractional-dose inactivated poliovirus (f-IPV) in their national immunisation schedules in place of the recommended full dose to ease the shortages.

This scoping review gives an account of the journey towards eradicating polio including an update on the current state of IPV supply and the rationale for performing a systematic review that compares f-IPV to the recommended standard dose.

To identify relevant literature for the scoping review, the search strategy outlined in table 1 of Section A (Research protocol) was used in PubMed and was adapted for the Cochrane Database of Systematic Reviews (CDSR), EBSCOhost and ProQuest Dissertations & Theses A&I databases. All literature that was related to reduced dose or intradermal delivery (ID) of IPV was included in the scoping review. The literature is explored in detail in Section 6 of the review which describes the study rationale.

Additional searches were performed to put this scoping review into context. Key phrases such as “history AND poliomyelitis”, “global eradication AND poliomyelitis”, “fractional IPV AND shortages” and “transition phase AND poliomyelitis” were used in PubMed, Google, Google scholar and World Health Organisation (WHO) and Global Polio Eradication Initiative (GPEI) web sites. References of included articles were also searched for relevant citations.

1.1 Background

1.1.1 What is Polio?

Poliomyelitis (polio) is an acute enteric viral infection that commonly affects children under the age of 5 years. [4,5] The disease is caused by any one of the three wild polioviruses (WPV) – WPV 1, WPV 2 and WPV 3.[5] These viruses can affect the nervous system leading to debilitating paralysis or even death.[4,6] Transmission of the virus is mainly through the faecal-oral route.

After the virus enters the host, it multiplies within the intestines and spreads to the blood stream causing viremia.[4] Clinical symptoms typically manifest after about 7 to 10 days.[6,7] Amongst infected individuals, 90-95% are asymptomatic and the 5% who develop minor flu-like symptoms fully recover.[8] Less than 1% of infected individuals develop an irreversible asymmetric paralysis in the lower limbs which continues to spread upwards as other parts of the nervous system are affected.[5,8] Diagnosis of paralytic polio can be either clinical or through laboratory techniques that isolate and identify the viruses. There is no cure for polio, treatment is focused on supportive management that limits disease progression and prevents skeletal deformities.[4,8]

1.1.2 Polio vaccines

Prevention through vaccination remains the key strategy in the fight against polio. There are two types of polio vaccines: the inactivated poliovirus vaccine (IPV) and the oral poliovirus vaccine (OPV). The key attributes of each vaccine are listed in table 1 below. OPV has contributed significantly to the eradication of polio. Compared to IPV, OPV has a lower cost, is easily administered orally and generates an enhanced mucosal immunity.[6,9] It is not surprising that it quickly became the vaccine of choice particularly in low-income countries. The association of OPV with a small risk of vaccine derived paralytic poliomyelitis (VAPP) caused by vaccine derived polioviruses (VDPVs)[10] has paved a way for IPV to be the vaccine of choice as the world pursues global eradication of polio.

Table 1. Key attributes of OPV and IPV

OPV	IPV
▪ Oral, live attenuated vaccine	▪ Injectable, inactivated vaccine
▪ Produced from attenuated Sabin strains*	▪ Produced using antigens from wild polioviruses[†] or from attenuated Sabin strains.
▪ Induces humoral immunity	▪ Induces humoral immunity
▪ Induces mucosal immunity	▪ Little or no direct effect on mucosal immunity but boosts immunity in those previously exposed to OPV.
▪ Induces life-long immunity	▪ Induces life-long immunity
▪ Promotes herd immunity	▪ Less likely to promote herd immunity
▪ Low risk of VAPP and VDPV	▪ Absent risk of VAPP and VDPV
▪ Low cost	▪ Expensive
▪ Easier to administer	▪ Requires skilled personnel to administer

OPV = oral poliovirus vaccine; IPV = inactivated poliovirus vaccine; VAPP = vaccine derived paralytic poliomyelitis; VDPV = vaccine derived poliovirus

*3 vaccine strains (Sabin1, 2 and 3) derived from attenuation of the parent wild poliovirus.

[†] Antigens for the vaccine are made from WPV strains – Mahoney or Brunhilde (type 1), MEF (type 2) and Saukett (type 3).

Data for the table extracted from the WHO position paper on Polio vaccines - March 2016.[6]

2. POLIO THEN – THE HISTORY OF POLIO

2.1 A time calamity

Polio has an intriguing history that has been well documented throughout the years. Suggestion of its existence dates to 1580-1350BC.[11] This evidence comes from an Egyptian stele which shows a priest with a withered leg that resembles the clinical presentation of polio.[11,12] The disease only became a public health concern in the 1890's and early part of the 20th century when North America, Europe and some Scandinavian countries experienced a significant increase in polio outbreaks.[11,13,14] Nathanson and Kew[12] suggest that the sudden surge in polio outbreaks was due to delayed infection secondary to improved hygiene and sanitation.

As the years progressed, the epidemics became more frequent and severe.[15] Surprisingly, compared to other diseases, the incidence of polio was relatively low.[12,15] Instead, it was the physical effects of polio that instilled a lot of fear, anxiety and panic among parents, communities and government officials. These effects included death, being confined to wheelchairs and the use of splinters, casts and iron lungs to counteract muscle paralysis (figure 1A and 1B below). Because of this calamity, the first half of the 20th century was filled with significant research on polio which contributed to finding a lasting solution to this crippling disease. [11,14,16]

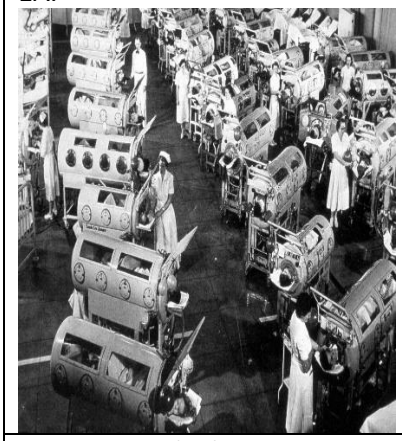
2.2 Success in the Americas

A breakthrough came in 1955 when Dr Jonas Salk, in one of the largest vaccine trials in history, proved that his formalin-inactivated polio vaccine resulted in 60-90% immunity against all three polio viruses.[17,18] In addition to its size, what made Salk's study unique was the magnitude of public participation and political willingness. The research was funded by the public through drives that were coordinated by the National Foundation of Infantile Paralysis which later became the March of Dimes.[14,18,19] The organisation was born out of United States of America (USA) President Franklin Roosevelt's quest to fight polio in 1938[19] (figure 1B below). History suggests he had suffered from polio which left him paralysed.[14,19] Following the publication of the trial results, IPV was licenced on the 12th of April 1955 and within two weeks it had been rolled out within the USA.[18]

The controversy between the use of a killed virus by Salk and the use of the tried and tested live attenuated virus resulted in Dr Albert Sabin and colleagues forming another polio vaccine.[8,18,20] Sabin's oral live attenuated vaccine trials were successfully done in the Soviet Union in the late 1950's.[8] In 1960, he published ground-breaking results that showed the safety and effectiveness of OPV in South America.[8,21] Sabin's OPV had an added advantage over Salk's IPV which included ease of administration, superior immunity and ability to induce mucosal immunity.[8,22] OPV was licenced in USA in 1961 and in the following 3 years it gradually replaced Salk's IPV.[8,13,20]

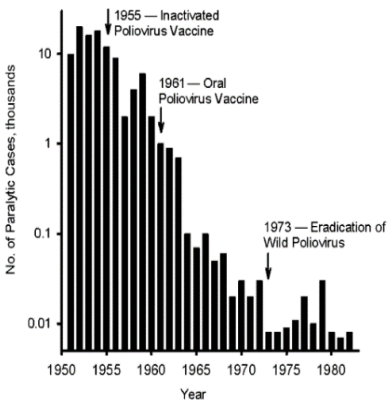
Figure 1. The effects of polio on children (1A and 1B) and the exponential decrease of cases after the introduction of IPV and OPV in USA (C)

1A.



1B.

1C.



IPV = Inactivated poliovirus vaccine; OPV = Oral poliovirus vaccine; USA = United States of America
1A- Children in a hospital using iron lungs to breathe. Picture accessed from GPEI website.[11]
1B- President Roosevelt dining with polio patients in Georgia. Picture from an article on polio by Leah Libresco.[23]
1C- Exponential decline in reported cases of poliomyelitis in the United States, 1951–1982 after IPV and OPV.[12]

Both IPV and OPV resulted in a 90% reduction in the incidence of polio[15] such that by 1973 polio had been eradicated in North America[11] (see figure 1C above). This exponential decline in the number of deaths and cases of paralysis in the USA motivated other countries experiencing outbreaks in the Americas to pursue eradication of polio. It was through the combined effort of organisations such as the Pan American Health Organisation (PAHO), Rotaract International, United Nations International Children's Emergency Fund (UNICEF) and WHO together with individuals like Dr Sabin, Ciro A. de Quadros and Rodolfo Rodriguez Cruz that led to the eradication of polio in the Americas.[15,24,25]

de Quadros, Cruz and colleagues used lessons learnt from small pox eradication as a guide to implementing polio eradication strategies in the Americas. The use of mass immunisation was instrumental in the eradication of polio in the Americas (figure 2A below). Cuba was the first country to use mass vaccination in 1962 and between 1962 and 1978 there were only 5 cases of polio and no deaths were reported.[11,15,24] After failing to interrupt polio transmission through routine immunisation, Brazil, in 1980, added national immunisation days which proved to be a great success.[15]

Encouraged by the success in Cuba, Brazil and Mexico, PAHO in 1985 resolved to interrupt the transmission of wild poliovirus in the Americas by the end of 1990.[8,15,25] From then on, other countries in the Western hemisphere started using similar strategies as those used by the 3 countries mentioned above. These strategies included mass vaccination, routine immunisation, polio surveillance and mop up strategies.[15,25] OPV, because of the advantages stated above, became the vaccine of choice for campaigns and routine immunisations. The last case of polio in the WHO region of the Americas was in 1991 and in 1994 the region was certified polio free.[11]

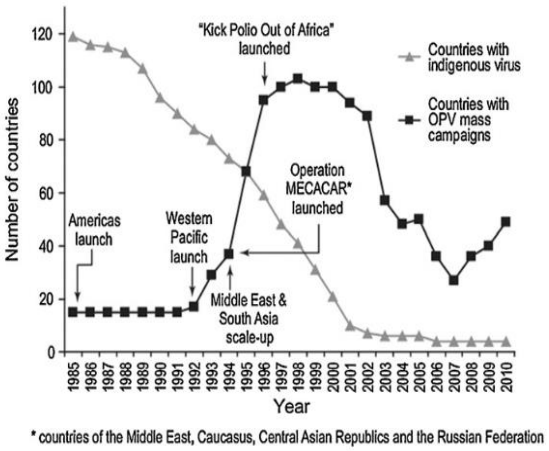
2.3 Polio Eradication becomes a global quest

From the beginning of the outbreaks in the Americas, it was perceived that the incidence of polio was low in developing countries.[26,27] The lameness surveys done in the 1970's proved otherwise.[26,27] The incidence of polio in some of the countries was found to be as high as USA's incidence during the pre-vaccine era.[26,27] In 1974, the WHO established the Expanded Programme on Immunisation (EPI).[28] This was the first step in taking polio eradication global. The EPI ensured

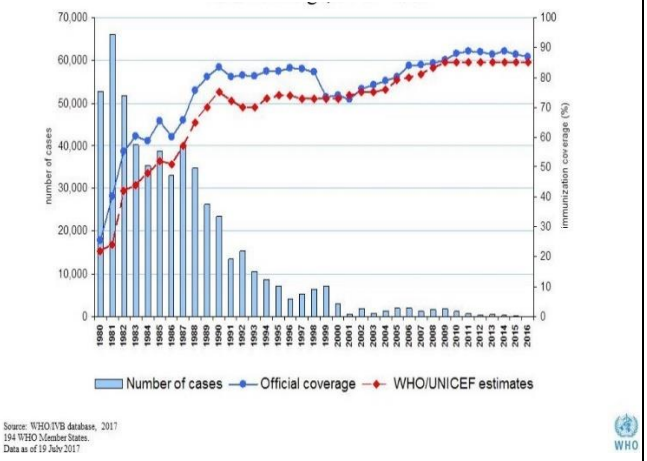
consistent vaccination against vaccine preventable diseases, including polio, worldwide.[28] Inspired by the success in the Americas and the eradication of small pox, in 1988 the World Health Assembly (WHA) committed to global eradication of polio by the year 2000.[29,30] The Global Polio Eradication Initiative (GPEI), a partnership between national governments and global partners, was then formed to facilitate the realisation of this goal.[11]

Figure 2. The effect of mass vaccination on the number of countries with indigenous virus (1985-2010) (2A) and global polio immunisation coverage and reported from 1990 to 2016 (2B).

2A.



2B.



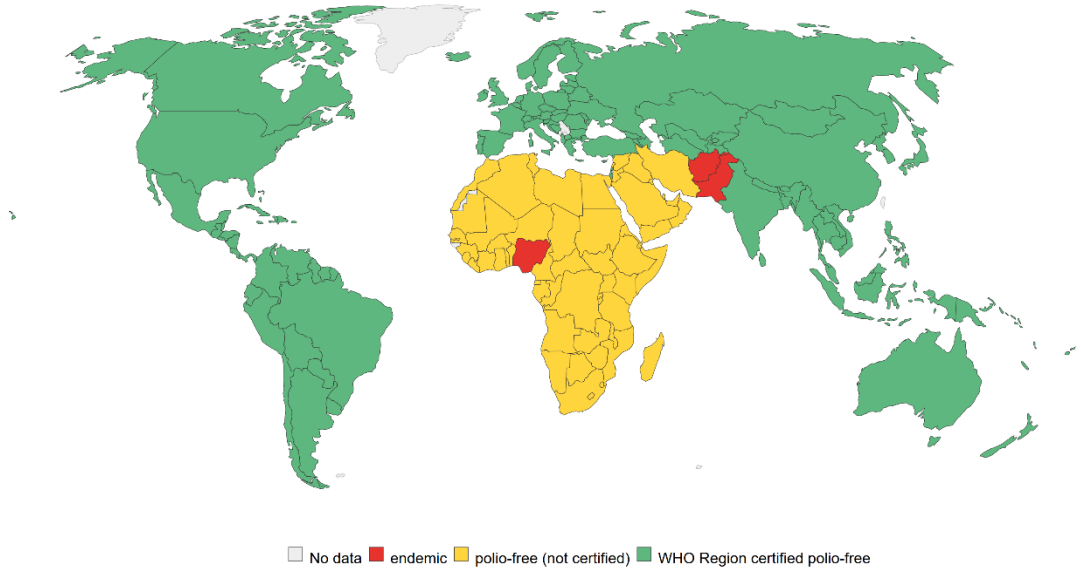
2A - Countries with wild poliovirus circulation deacreased as mass vaccination campaigns increased, 1985–2006. Graph accessed from a review by Aylward B. and Tangermann R. on the Global Polio Eradication Initiative.[31]
2B- A bar graph showing global decline of reported cases of polio and a line graph showing the increase in coverage of the third dose of polio vaccine from 1980 to 2016. The graph was accessed from WHO website.[32]

From the time the GPEI was formed up to now, there has been many successful efforts towards achieving global polio eradication. Global cases of polio have reduced from over 350 000 cases in 1988 to just 22 cases in 2017[5] (see figure 2B above). This 99.9% reduction in the global incidence of polio and the prevention of over 16 million cases of paralysis has resulted in the saving of up to US$27 billion globally.[6,33] In 1988, more than 125 countries reported cases of polio but now only three countries, Nigeria, Pakistan and Afghanistan, still have endemic polio[6] (figure 3 below).

The WHO Western Pacific region was certified polio free in 2000, followed by the WHO European region in 2002.[11] Eradicating polio in India and the declaration of the South East region as polio free in March 2014[34] further strengthened and reassured everyone that a world without polio is a possibility. Amongst the reported cases, WPV 1 remains the only cause of indigenous polio.[5] WPV

3 was last seen in November 2012 in Nigeria while WPV 2 was last detected in India in 1999.[5,6] WPV 2 eradication was eventually certified in September 2015.[35,36]

Figure 3. Achievements towards global eradication of polio: a map of endemic and polio free countries.



Only Nigeria, Pakistan and Afghanistan are the remaing endemic countries. The map was accessed from Our world in Data website.[37]

3. POLIO NOW

3.1 Polio fights back

The containment of WPV transmission over the years has forced the polioviruses to evolve in order to survive.[8] Continuous replication in the intestines or continuous circulation within a community of the attenuated Sabin strains in OPV results in genetic mutations which cause the strains to re-acquire their neurovirulence and transmissibility characteristics.[10,38,39] For this reason, OPV has been associated with VAPP and the generation of VDPVs.[8,38] It is estimated that there are 2-4 cases of VAPP per million birth cohort per year.[10] VAPP is indistinguishable to the paralytic poliomyelitis caused by WPV and the management is similar.[38,40]

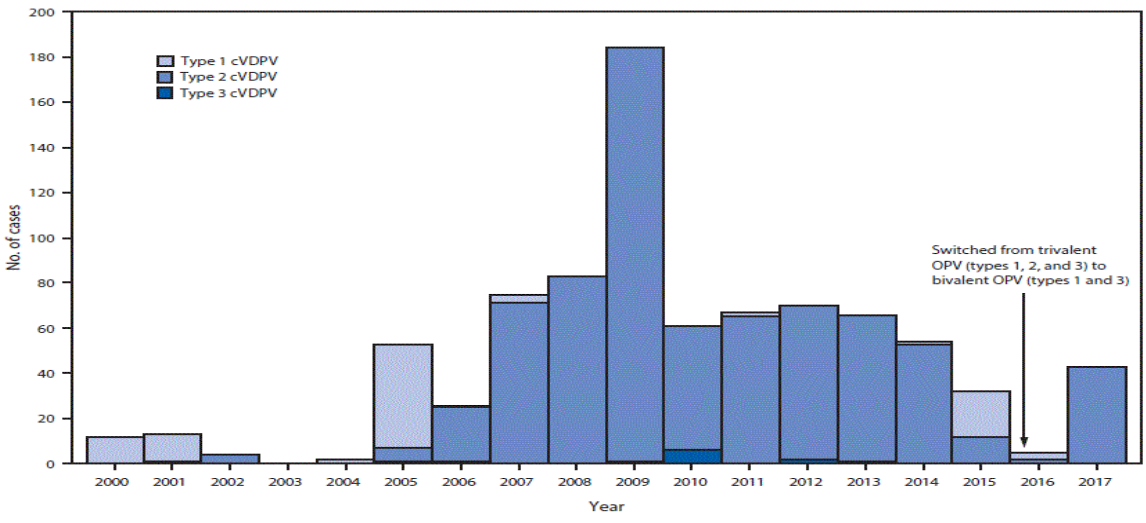
The existence of VDPVs is a major public health concern and affects current and future strategies for eradicating polio.[2,10,38] Of the three types of VDPVs that exist (table 2 below), cVDPVs have given rise to many polio outbreaks for the past 20 years.[39,41] From 2000 up to 2015, there were 24

cVDPV outbreaks in 21 countries resulting in about 760 cases of VAPP.[39,41] The largest outbreak spanned from 2005 to 2014 in Northern Nigeria with over 400 reported cases.[40,42,43]

Table 2. Types of vaccine derived polioviruses (VDPVs)
▪ **Circulating VDPVs (cVDPVs):** arises from sustained circulation of vaccine derived virus through transmission from one person to another. ▪ **Immunodeficiency VDPVs (iVDPVs):** arises from continuous replication of vaccine derived virus in a person with primary immune deficiency. ▪ **Ambiguous VDPVs (aVDPVs):** a virus that is vaccine derived that is not related to immunodeficiency and outbreaks or an environmental isolate whose source is unknown.
Data for the table adapted from review by Kew et al.[8] on VDPVs and polio eradication.

cVDPV from the type 2 Sabin strain is the main cause of outbreaks[44] (figure 4 below). By 2015, the type 2 cVDPV accounted for approximately 90% of cVDPVs[39,44] and 26-31% of VAPP cases.[10] Since the beginning of 2018, outbreaks have been reported in the Democratic Republic of Congo, Somalia and Nigeria.[42] The type 2 cVDPV isolated from the outbreak in Somalia is linked to an isolate that was detected in Kenya in March 2018; indicating the possibility of a regional spread in the Horn of Africa.[45] cVDPVs outbreaks are still occurring[46] therefore, cessation of OPV use is a key aspect in ensuring elimination of cVDPVs transmission.

Figure 4. Circulating vaccine-derived poliovirus cases detected, by serotype — worldwide, January 2000–June 2017

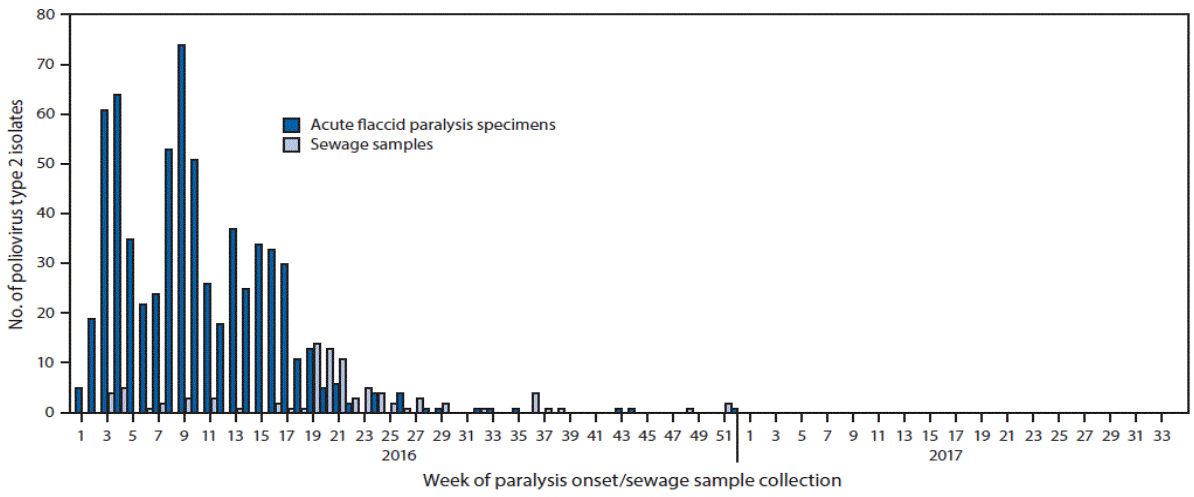


cVDPV = circulating vaccine-derived poliovirus; OPV = Oral polio vaccine. A bar graph showing that most of the detected case are cause by cVDPV type2. Graph assessed from an update on Vaccine-Derived Polioviruses by Jorba et al.[44] in 2017.

3.2 New strategy, renewed hope – The Polio Eradication & Endgame Strategy 2013-2018.

Considering that cVDPV from the type 2 Sabin strain is the main cause of VAPP and cVDPV outbreaks (figure 4 above), eradication of WPV type 2 in 1999 provided a platform for GPEI to simultaneously interrupt transmission of both WPVs and cVDPVs.[9,31,47,48] The Polio Eradication and Endgame Strategic plan 2013- 2018, outlined the necessary steps towards achieving this goal.[2] Objective 2 of the strategy was to gradually remove OPV and replace it with IPV.[2] The first step in the phased removal of OPV was the cessation of the type 2 component of OPV through a global switch from trivalent OPV (tOPV) to bivalent OPV (bOPV).[2,49] By April 2016, all the all OPV-using countries had successfully switched to bOPV. [50,51] Since then, the detection of type 2 isolates has been gradually decreasing[52] (see figure 5 below).

Figure 5. Number of poliovirus type 2 isolates from persons with acute flaccid paralysis or their contacts and from sewage samples in countries where mOPV2 was not used after the global synchronized switch from tOPV to bOPV — January 2016–March 2017



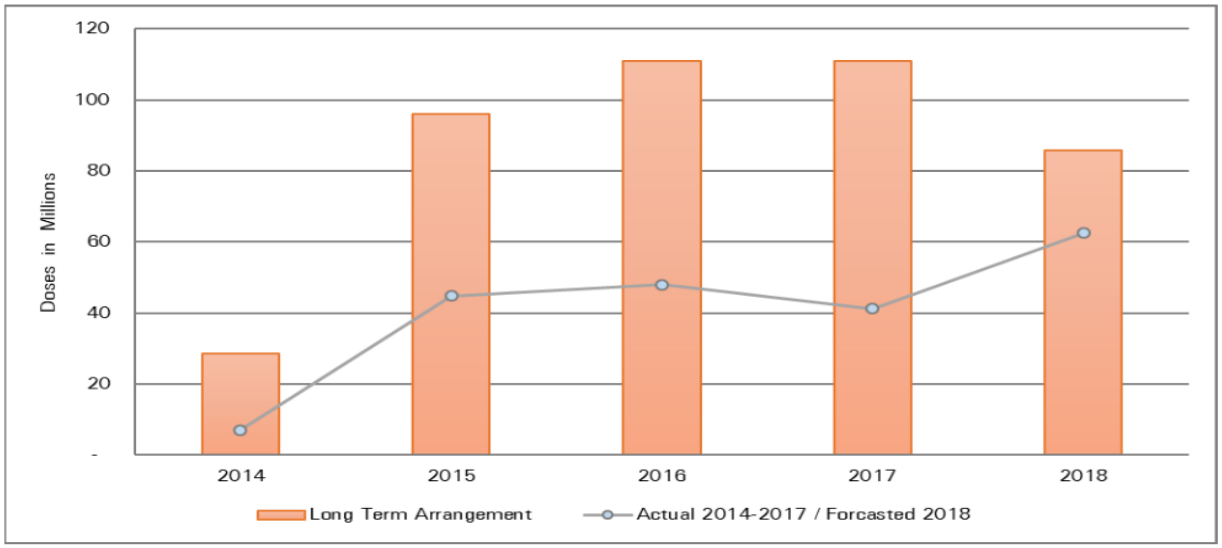
bOPV = bivalent oral poliovirus vaccine; mOPV2 = monovalent oral poliovirus vaccine type 2; tOPV = trivalent oral poliovirus vaccine. The histogram shows a gradual global decline in of type 2 isolates detected from samples collected for surveillance The graph was accessed from a report about the virologic monitoring of type 2 polio virus by Diop et al.[52]

3.3 One step forward, one step behind – The effects of IPV shortages.

To mitigate the risk of re-emergence and outbreaks of type 2 polio virus (wild or vaccine derived), in November 2012, Strategic Advisory Group of Experts on Immunization (SAGE) proposed the introduction of at least 1 dose of IPV in immunisation schedules.[53] The dose of IPV would prime individuals or create an immune base that would ensure a quick response to vaccination and

reduce the likelihood of developing paralysis following type 2 polio infection.[6] Though the recommendation was vital and in line with the phased replacement of OPV with IPV, implementation has been constrained by the global shortages of IPV that came after. As countries started making plans to introduce IPV into their schedules, the demand for IPV increased exponentially from 80 million doses in 2014 to 120 million doses in 2016.[51,54] On the supply end, manufactures who had assured UNICEF and other global partners of their ability to scale up production failed to meet their targets.[3] From 2014 to 2018, only 46% of the contracted quantities were supplied[3] (figure 6 below). Unanticipated procedural difficulties of scaling production and the unexpected increase in IPV use in outbreaks were the main reasons for the shortages.[3]

Figure 6. Long-term arrangements between UNICEF and suppliers versus actual and forecast supply 2014-2018

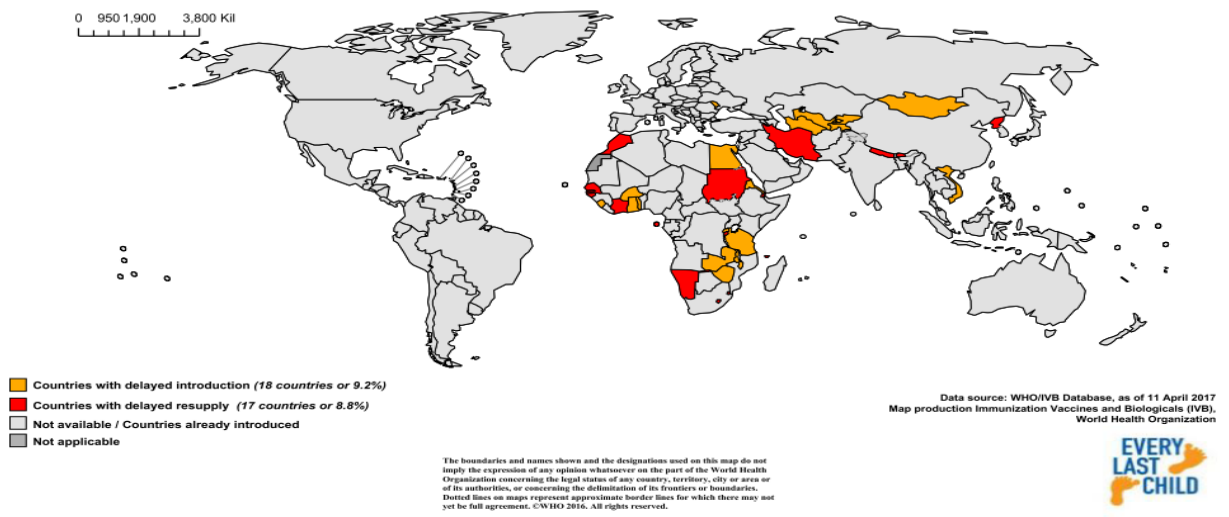


Source: UNICEF Supply Division

A bar graph showing the difference between the long-term supply arrangement between UNICEF and IPV suppliers and the actual supply that UNICEF received. The graph was accessed from an update on Inactivated Polio Vaccine supply by the UNICEF Supply Division (May 2018).[3]

The effects of these shortages included – a. delayed implementation of IPV introductions, b. drug stock outs in countries that have already introduced IPV in their schedules and c. depleted global reserves for outbreaks.[51,55,56] Amongst countries that secure IPV through UNICEF, 18 have delayed IPV introduction and 17 have delayed resupply[3,57] (figure 7 below). According to a report given by UNICEF in May 2018,[3] the supply for IPV in 2018 will be enough to allow for the introduction or resupply of IPV in these 35 countries whilst sustaining supply in the high-risk countries.

Figure 7. Countries with IPV supply disruptions



IPV= inactivated poliovirus vaccine, % = percent. The map was accessed from a presentation by Blanc D. C. and Ottosen A. about IPV supply.[57]

Though there is hope for improved supply from 2018 going forwards, the amount will not be enough to meet the demand. In October 2017, SAGE recommended that every child that missed IPV doses since the switch from tOPV to bOPV should receive their missed doses.[58] Therefore, in addition to sustaining supply for routine immunisation, the need for catch up immunisation campaigns is likely to increase demand. At the same time, a reserve for outbreaks should be in place to allow for quick response in affected areas. UNICEF estimates that the demand will be carried out beyond 2020.[3] Post-certification, IPV will be the only vaccine being used for immunisation against polio.[60] This impacts the current and future strategies for sustained IPV availability.

The earliest improvement in supply is expected in 2021 when new vaccines achieve WHO prequalification status.[3,59] From there on, excess capacity is expected to be in 2025.[3,59] With few suppliers, options are limited. This creates unfavourable market conditions for IPV price decrease.[3] The prices for the next UNICEF tender period are set to be higher than those for the period between 2014 and 2018.[3] A single full dose of IPV is expected to go for $3.50 in 2019 and will only

decrease to $2.80 in 2022.[3] Improvement in the market conditions that allow for price reduction are expected in 2021 as new manufactures enter the market creating some competition.[3,59]

4. THE FUTURE OF POLIO

4.1 Polio Eradication, Certification, and Integration Strategy 2019-2023

2018 marked the end of the Polio Eradication and Endgame Strategy 2013-2018 and yet again the goal to eradicate polio remains elusive. According to a joint statement released by the leaders of the GEPI committees in January 2019, the Polio Eradication & Endgame Strategy 2013-2018 is now being revised and will extend up to 2023.[61] The new strategy, the Polio eradication, certification and integration strategy 2019-2023, together with the Strategic action plan on polio transition[62] and the Polio post-certification strategy[63], will outline the necessary steps to eradicate polio, transition from eradication to certification and to maintain a polio-free world post certification.[62,63]

4.2 The future of IPV demand and supply

IPV demand and supply forecast has been described above. As the world progresses towards global certification, eradication of both wild and vaccine derived poliovirus remains the main goal. IPV will still play an important role in the realisation of this goal. During the eradication phase, the use of IPV instead of OPV will be instrumental in reducing the number of cVDPV outbreaks. Considering the transition phase, GPEI will gradually decreasing its involvement while countries are taking up ownership of their polio programmes.[62] Therefore, transitioning to independent country programmes will require adequate planning and availability of resources like IPV. To maintain a world-free of polio requires countries to use IPV only to mitigate the risk of cVDPV outbreaks.[63] Clearly, ensuring availability of IPV will continue to be part of the eradication, transition and post certification strategies.

In 2007, the Advisory Committee on Poliomyelitis Eradication (ACPE) expressed the need to come up with “strategies for making IPV use potentially affordable for low income settings” before the cessation of OPV use.[64] Since then, there has been research on schedule reduction,[65] IPV antigen dose reduction (the use of a fraction of an IPV dose),[66,67] adjuvant use[68,69] and production of IPV from Sabin strains.[68-71] The current shortages, bring us back to the same critical recommendation

that was made more than 10 years ago. These strategies need to be reconsidered in view of the current IPV shortages.

5. IS THERE A ROLE FOR FRACTIONAL-DOSE IPV?

5.1 What is fractional-dose IPV?

One fractional dose (0.1ml) is one fifth of the full dose (0.5 ml) and it is usually delivered using an intradermal injection.[72] Compared to the subcutaneous or intramuscular routes of vaccine delivery, the abundant immune cells in the dermis of the skin allows for a lower amount of the vaccine to be used to invoke an immunologic response.[56,73] Accordingly, using intradermal delivery of a fractional dose, it is possible to deliver 5 doses from the same volume of 1 full dose.

The price of IPV affects the ability of countries to introduce and sustain supplies of IPV. GPEI's target price for the universal use for IPV for a full dose is $0.50.[9] In 2022, the price for a single full dose of is expected to be $2.80[3], which is far from the desired target. The cost of f-IPV is expected to be a fifth of the full dose[9] therefore, as the market conditions become more favourable, reduced dosage might be quickest way to achieve the set target of $0.50. An assessment done by PATH showed that two f-IPV doses and the intradermal injection devices cost between US$1 to US$3 while a single intramuscular dose of IPV costs between US$ 1.1 and US$2.[3,56] As well, the assessment showed that the cost reduction from the reduced dosage can offset the cost of intradermal devices.[56]

The dose sparing and cost reduction characteristics of f-IPV provide a compelling argument for the substitution of a full dose. For countries experiencing shortages, SAGE has recommended the use of two f-IPV instead of a full IPV dose in routine immunisation[74,75] and the use of a single dose of f-IPV in outbreaks.[76] WHO endorsed this recommendation in its position paper on polio vaccines and advised that the two doses are to be given at 6 and 14 weeks.[6]

5.2 Considerations for adopting fractional-dose IPV in to national immunisation schedules.

5.2.1 Immunological considerations

Levels and duration of seroprotection against paralytic disease is of paramount importance when considering adopting a f-IPV schedule. Several studies have compared the immunogenicity and effectiveness of f-IPV to a full dose IPV[66,67,77,78] and a few reviews of literature have been done.[79-81] Adding to the knowledge about the effectiveness of reducing the dose of IPV, this study gives a systematic analysis of the evidence which will assist in making decisions about IPV dosage. A detailed comparison of the available literature is given in section 6 below under study rationale. In terms of duration of immunity induced by f-IPV, there is lack of data in this area[82,83] and more long-term research is required.

The effectiveness of IPV to induce an immune response has been shown to be affected by the level of maternal polio antibodies within the vaccinated child.[84,85] Interference of maternal antibodies has an impact on the age of administration of the IPV vaccine[86] therefore, it is a worthwhile consideration when deciding on a f-IPV vaccine schedule. Delaying immunisation to allow for maternal antibodies to decline results improves seroconversion.[66,67] The challenge in delaying immunisation is that most developing countries use the EPI schedule with vaccination occurring at 6 weeks, 10 weeks and 14 weeks of age.[86] At 6 weeks, maternal antibody are more likely to interfere but again this timing of administration is ideal because it allows for more children be vaccinated.[63] Weighing risks and benefits is essential for choosing an appropriate schedule. GPEI encourages countries to access the drop-out rates between 6 and 14 weeks to make sure every child receives at least 2 doses two doses.[86]

Induction of intestinal mucosal immunity by IPV has been subject to debate for a long time.[22,87] Having mucosal immunity during polio outbreaks is important because it prevents the replication of the polio virus within the intestines limiting person to person transmission.[88] Brickley et al.[89] suggests that without previous exposure to OPV, IPV does not improve intestinal mucosal immunity. This is consistent with other previous studies.[90-93] In keeping with these studies, Jafari et al.[94] and John et al.[95] provided evidence that in children who have been previously immunised with OPV, a full dose of IPV boosts mucosal immunity. Gamage et al.[96] compared the boosting of mucosal immunity by a single f-IPV versus a single

full dose of IPV in children aged 10-12 years who have been immunised with OPV. They showed that a f-IPV boosted mucosal immunity to a similar extent as a full dose IPV.[96] Based on these results, f-IPV can be effectively used in outbreak response. This supports the decision made by SAGE to use f-IPV in outbreaks instead of a full dose.[76]

5.2.2 Programmatic feasibility

Vaccine administration

A potential challenge in the use of f-IPV is the technical difficulty of intradermal vaccine delivery. The Mantoux technique, using a needle and syringe, requires technical expertise to ensure successful vaccine delivery whilst avoid vaccine wastage.[82,97] Especially in campaign settings, where many children must be vaccinated in a short period of time, poor technique might result in inefficiency and ineffectiveness. Various alternative intradermal injection devices have been developed and registered[56] (see table 3 below). Under trial and campaign conditions, some of these devices have been shown to give a similar or better immune response when compared to the standard needle and syringe.[97-100] In this review, we will describe the intradermal devices used by investigators and where possible compare the immunological responses. Indeed, new injection devices provide easier options for intradermal vaccine delivery, however the cost of buying and training health workers on how to use the devices must be considered.

Table 3. Devices for intradermal delivery of vaccines

Device (supplier)	**Description**	**Registered for use**
Tropis (PharmaJet)	Needle-free jet injector that uses a sterile single-dose syringe and pressurized liquid stream instead of needle	Yes
MicronJet 600 (NanoPass)	Hollow microneedle hub that can be attached to a luer syringe following filling with a separate needle	Yes
ID Adapter (West Pharmaceutical Services)	Plastic adapter that fits onto an autodisable intradermal needle and syringe that is provided with the device	Yes
Star ID Syringe (Star)	Needle/syringe with a short minineedle and 90-degree injection angle, filled with an integrated plastic spike	No

ID Pen (Bioject)	Needle-free jet injector developed as an alternative to Bioject's gas-powered Biojector2000 device that is optimized for intradermal administration in low-resource settings (manually powered, intradermal only)	No
Data in the table was extracted from table 1 in Okayasu et al.'s review on intradermal administration of fractional dose of IPV.[56]		

Another point to consider when looking at vaccine administration, is maintenance of the integrity of the vaccine vial stopper following repeated punctures. IPV is available in 1, 5 and 10 standard dose vials therefore, giving fractional doses increases the number of piercings on the vial stopper which may eventually lead to vaccine leakage or contamination.[101] Jarrahian et al.[101] examined vial stopper performance when using f-IPV. They concluded that after 50 punctures, less than 10% of the punctures resulted in particle formation and it was within the required target.[101] In terms of vaccine leakage, Jarrahain and colleagues showed that 100 punctures did not lead to any closure failures.[101] GPEI recommends the use of 1 and 5 standard dose which give up to 5 and 25 doses respectively.[86] The punctures required to withdraw f-IPV are way below the maximum punctures for contamination and leakage demonstrated by Jarrahain and colleagues.

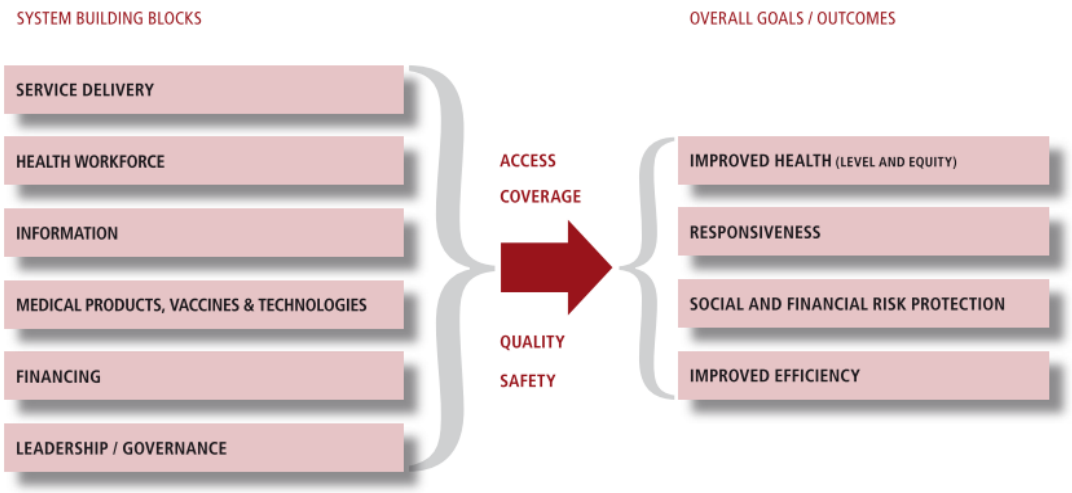
Health system considerations

The process of implementing any policy within the health system is complex and interactive.[101] It involves multiple actors at different levels of the health system, from the global level to the beneficiaries of the policy. Interactions between these people within the socio-political context of a country shapes the decision-making and implementation process[103] of the f-IPV schedules in different countries. The WHO framework for health system strengthening[104] is a tool that national steering committees can use as they consider the implementation of f-IPV schedules (see figure 8 below).

Factors within each system building block must be assessed prior, during and after implementation to improve access and coverage of high quality and safe polio vaccination.[104] National leaders should be proactive and approve the adoption of the policy whilst ensuring that there is enough funding to cater for costs like vaccines, training, device purchasing and other logistics. In addition, the national regulatory authorities, after considering available

evidence[86] and the use of fractional dosage in other vaccines,[79,105,106] must deliberate on the approval of off-the label use of f-IPV. In view of providing high quality and broad vaccine coverage, frontline health workers form an integral part in the process of adopting f-IPV. They must be involved in the early stages of policy formulation so that they can contribute and play an active role in the implementation process.

Figure 8. The WHO Health System Framework



The framework was assessed from report by the WHO in 2007 entitled Everybody's business: strengthening health systems to improve health outcomes: WHO's framework for action.[104]

The information building block highlights the importance of monitoring and evaluation in every step of the implementation process. Data collection for surveillance and information dissemination is the basis for evaluating the effects of the policy (including adverse effects). Hence, a plan on how to incorporate data on f-IPV into the national data registry is important. When considering service delivery, it is essential to look at how f-IPV will fit in with other vaccines in the national immunization schedule. This also includes cold chain management and availability of transportation and vaccinators.

Communication amongst global actors (WHO, UNICEF, GPEI and GAVI), national level actors (Presidents and health ministers) and provincial and frontline workers at different stages of policy development is of uttermost importance. This requires constant dialogue and feedback amongst all parties involved in an environment of mutual respect. Beneficiaries of

the policy (children, parents and community leaders) should be informed and educated about the benefits of f-IPV and immunisation in general. This cultivates an environment for the policy to be accepted by the community.

5.3 Experiences of fractional-dose IPV in other countries

5.3.1 Use of fractional-dose IPV in routine immunisation

This dose sparing strategy might be the immediate solution the world needs to ensure that every child who is entitled to get IPV gets vaccinated. From the WHO South-East Asia Region, India, Sri Lanka, Bangladesh and Nepal have decided to adopt f-IPV in their national routine immunisation schedules.[88,107] India has been the front runner amongst these countries. In April 2016, India introduced two f-IPV doses at 6 and 14 weeks in the routine immunisation schedule of 8 states then another 8 states were added in August 2016.[72] They managed to embark on a nationwide scale up in March 2017. Sri Lanka followed in July 2016, using the 2- and 4-months schedule.[72] In both countries, they have managed to immunise a larger number of eligible children, stretching their stocks and avoiding stock outs.[51,56] Bangladesh and Nepal were expected to shift to fractional dosage in the last quarter of 2017 and first quarter of 2018 respectively.[107]

Other WHO regions are now starting to discuss and setting up structures that enable the use of f-IPV. In the Americas, PAHO has recommended the use of f-IPV in 14 countries. Some of the countries are already conducting trainings in preparation for implementation.[107] WHO Eastern Mediterranean region and African region are also deliberating on the use of f-IPV.[107]

5.3.2 Use of fractional-dose IPV in campaigns

Supplementary immunisation activities using f-IPV have been successfully carried out in India and Pakistan. In response to a VDPV type 2 isolate that was found in Telangana State of India in May 2016, a mass vaccination campaign using a single f-IPV dose was successfully carried out.[108] The campaign was carried over 6 days and 311 064 children aged between 6 weeks and 3 months were vaccinated achieving a coverage of about 94 %.[107] In Pakistan, a mass vaccination campaign using a single dose of f-IPV was carried in the province of Hyderabad

and 3 other surrounding provinces in August 2016.[109] This was after a VDPV type 2 isolate was isolated from a sewage sample. Through the campaign a coverage of about 82% was achieved.[108] Challenges encountered in the campaign in Pakistan included the difficulty of intradermal delivery in an outbreak setting. However, Yousafzai et al.[97] and Saleem et al.[98] have shown the effectiveness of intradermal devices in door to door campaign and one-day campaign.

6. STUDY RATIONALE

As mentioned above, the immunogenicity and effectiveness of f-IPV are important considerations for countries that want to adopt f-IPV into their schedules. Advantages of evidence-based policy making have been elaborated.[110] Providing evidence about the effectiveness of f-IPV bridges the gap between research and policy adoption and implementation. This study adds to the body of knowledge that guides the use of f-IPV in the prevention of polio.

Recognizing the high cost of IPV and the imminent cessation of OPV use, Nelson et al.[79] performed a literature review in 2012 to describe available studies that used intradermal delivery of IPV. The authors concluded that intradermal delivery of IPV was a viable mechanism for cost reduction.[79] They also highlighted the need to consider the effect of maternal antibodies, duration of immunity and use of adjuvants.[79] In contrast to Nelson et al.'s[79] narrative description of included studies, Grassly[80] carried out a systematic review and metanalysis to assess the immunogenicity and effectiveness of 1 or 2 doses of IPV. Grassly[80] broadly outlined and compared the existing IPV dosage options. Concerning f-IPV, the author established that the immunogenicity of 2 doses of f-IPV is comparable to a single full dose, but the antibody titres were lower. This finding is similar to what Anand et al., [81] found in their literature review in 2017. Anand and colleagues (2017) only focused on studies that compared the immunogenicity of one full-dose of intramuscular IPV to two doses of intradermal f-IPV.[81] From their review, they established that two f-IPV doses are more immunogenic than a single full-dose.

All the authors used a narrow search strategy and they also searched for relevant studies in a limited number of sites. Nelson et al.[79] searched in PubMed and some chapters in Plotkin's Definitive Vaccine Textbook while Grassly[80] only searched the Web of Knowledge database. Anand et al.[81] performed their

search in PubMed only. Due to the absence of an extensive search for literature, there might be other studies that were excluded from these reviews that may alter their findings. In addition to a restricted search, Grassly's (2014) study selection and data extraction were not done in duplicate;[80] increasing the risk of systematic errors.[111] It is an indispensable practice in systematic reviews to conduct those steps in duplicate and resolve discrepancies by discussion and consensus or arbitration.[111]

In addition to effectiveness, vaccine safety and administration is of importance when deciding to adopt any vaccine. Showing that a vaccine is safe and effective promotes acceptability amongst health workers and the community at large. In the three reviews, there is dearth of information about the adverse effects and the devices used for intradermal injections.

None of the previous reviews used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method[112] to assess the certainty of the evidence on effects of f-IPV. This approach assesses the certainty of a body of evidence through evaluating the risk of bias, imprecision, inconsistency and indirectness of study results, and the risk of publication bias.[113,114] The level of certainty of evidence, is useful when providing evidence for policy making.

In view of the gaps identified in previous reviews, the purpose of this review is to do a systematic review of studies comparing the effects of fractional compared to full dose IPV vaccination. We will also, evaluate the occurrence of adverse events and types of administration devices used for the intradermal delivery of f-IPV. The review will have a broader search strategy and provide up to date evidence regarding the use of f-IPV. This will provide evidence to support the use of f-IPV in routine immunisation because of its dose sparing and cost reduction characteristics.

7. SUMMARY

It has been 31 years since the WHA decided to globally eradicate polio.[30] Learning from the successes of small pox eradication and eradication of polio in the Americas, GPEI and its partners, has successfully decreased the burden of polio worldwide. By so doing, they have averted polio deaths and saved the world millions of dollars. The Polio Eradication and Endgame Strategy 2013-2018 has brought us to the brink of eradication. Going forward, the Polio eradication, certification and integration strategy 2019-

2023, the Strategic action plan on polio transition and the Polio post-certification strategy will hopefully lead to the global certification of polio eradication.

In the remaining endemic countries, multiple social, political and economic factors affect polio eradication therefore, a multi-pronged approach is required to eradicate polio and tackle cVDPV outbreaks globally. One of the approaches is to replace OPV with IPV. Phased replacement of OPV by IPV has been initiated through the switch from tOPV to bOPV and the addition of at least 1 dose of IPV in all immunisation schedules. Progress in the phased removal has been affected by global shortages of IPV which resulted from increased demand and low supply. This delays the interruption of VDPVs and at an individual level, many children are being denied their right to access effective vaccines.

Fractional-dose IPV clearly has role to play in the journey towards eradicating polio. Administering reduced doses of IPV will stretch supplies of IPV whilst ensuring that every child receives their vaccine. Its dose sparing, and cost reduction properties can improve vaccine availability and affordability. Immunological and programmatic factors are important when deciding on national IPV immunisation schedules. The aim of this study is to provide immunological as well as vaccine safety and administration evidence to assist in decision making regarding IPV dosage.

8. RECOMMENDATIONS

8.1 Research

- More studies should focus on investigating the duration of immunity induced by f-IPV when compared to the full dose of IPV. This information will aid in determining an effective f-IPV schedule and whether booster immunisation is required.
- The importance of mucosal immunity has been highlighted above. Additional studies should be carried out to solidify the finding by Gamage et al.[92] (f-IPV boosts mucosal immunity to the same extent as a full dose of IPV).

8.2 Policy implementation

- Global partners and governments should engage manufactures of IPV to facilitate the mass production of IPV that will bridge the demand-supply gap

- Global partners and governments should engage manufactures of IPV to facilitate licensure of fractional-dose of IPV.
- National health committees in low-income regions should start discussing the possibility of taking up fractional-dose of IPV based on evidence from other regions like the WHO South-East Asia Region.
- Before the transition phase, financial and resource (including vaccine) availability should be considered. There is a risk of losing the eradication gains that have been achieved in the past 30 years if national governments fail to sustain their programmes.

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SECTION C: MANUSCRIPT

Title

A systematic review and meta-analysis of fractional dose compared to standard dose inactivated polio vaccination in children.

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Key words

Inactivated polio vaccine, IPV, fractional dosing, dose-sparing, polio eradication, vaccine shortage

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SUMMARY

Background

Following the recommendation by WHO to introduce at least a single dose of inactivated poliovirus vaccine (IPV) in routine immunisation schedules, there has been global IPV shortages. Fractional-dose IPV is one of the strategies to ensure IPV availability. We did a systematic review of studies comparing the effects of fractional compared to full dose IPV vaccination.

Method

For this systematic review and metanalysis, we searched for articles in 16 databases. The sites were searched from inception to the 11th of April 2018 with no date, language or publication restrictions. We included studies which compared fractional-dose to full-dose IPV in children aged 5 years or younger regardless of study design, number of doses and route of administration. Screening, selection of studies, data extraction and risk of bias assessment was done in duplicate. Differences in judgement between the two authors were resolved by discussion and consensus or arbitration by a third author. The main outcome of interest was immunogenicity which was assessed using seroconversion rates and geometric median titres. In studies with similar characteristics, estimates were pooled using a random-effects model. Heterogeneity was assessed using χ^2 test of homogeneity and quantified using the I^2 statistic. Analysis was stratified by type of outcome measure, type of poliovirus, and number of IPV doses given. Subgroup analysis and sensitivity analysis were carried out. Analysis was done using Rev Man 5.3. PROSPERO registration number: CRD42018092647.

Findings

We identified 858 non-duplicate records, of which 35 potentially eligible full-text articles were screened and 17 articles included. Of the 17 articles, 3 are records of on-going trials and the remaining 14 articles are publications of eight studies. For poliovirus type 2, seroconversion risk ratio (RR) at 3 doses was 0.95 (95% CI 0.91, 1.00; p=0.06) at 2 doses 0.87 (0.71, 1.05; p=0.14) and at 1 dose 0.61 (0.50, 0.73; p<0.00001). The standard mean difference (SMD) for poliovirus type 2 at 3 doses was -0.98 (95% CI -1.46, -0.51; p<0.0001), at 2 doses -0.55 (-0.80, -0.30; p<0.0001) and at 1 dose was -0.53 (-0.90, -0.15; p=0.006). The seroconversion meta-analysis for 3-dose comparison was homogenous (χ^2 p=0.45; I^2=0%) while

heterogeneity was observed in the 2-dose comparison (χ^2 p<0.00001; I^2=93%) and 1-dose comparison (χ^2 p=0.0002; I^2=77%). Immunisation schedules with a longer interval between birth and timing of first dose and between 2 doses were associated with increased immunogenicity. The certainty of the results for the 3-dose comparison was high.

Interpretation

There is no difference in seroconversion between 3 doses of f-IPV (0.1ml) and 3 doses of full dose IPV (0.5ml) even though the full dose gives higher anti-polio type 1, 2 and 3 titres. With the current IPV shortages, using f-IPV instead of the full dose IPV can stretch supplies.

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1. INTRODUCTION

The World Health Assembly (WHA) in 1988 committed to globally eradicate poliomyelitis (polio).[1] Since then, the incidence of polio has reduced to less than 1% globally; Nigeria, Afghanistan and Pakistan are the only countries that still have endemic polio; and of the 3 wild polioviruses, type 2 has been eradicated while type 3 was last seen in November 2012 in Nigeria.[2] Vaccination against polio using the oral poliovirus vaccine (OPV) has played a major role in achieving these successes. However, the association of OPV with vaccine derived polioviruses (VDPVs) and vaccine derived paralytic poliomyelitis (VAPP)[3] has paved a way for inactivated poliovirus vaccine (IPV) to be the vaccine of choice in this final phase of eradicating polio.

In April 2016, the global switch from trivalent OPV (tOPV) to bivalent OPV (bOPV) marked the first step towards the phased removal of OPV.[4] Prior to switching, the World Health Organisation (WHO) and the Strategic Advisory Group of Experts (SAGE) on immunisation recommended that countries should introduce at least 1 dose of IPV in their schedules.[5,6] Following the recommendation, the demand for IPV has increased while the supply has deteriorated.[7] This has led to delayed IPV introduction and resupply[7] while at the same time affecting global reserves for outbreaks.[8] The increase in demand is expected to stretch up to 2020 while supplies are expected to surpass demand by 2025.[7]

Fractional-dose IPV (f-IPV) is one of the strategies being used to address the IPV shortages.[8] The reduced dose which is usually given intradermally, is one fifth (0.1ml) of the full dose(0.5ml) and is expected to cost less than the full dose.[9] Due to its dose sparing and cost reduction characteristics, countries like India and Sri Lanka have opted to use f-IPV in their routine immunisation schedules instead of the full dose.[10] In addition, India and Pakistan have used f-IPV in outbreak situations.[10]

A few reviews have investigated the effects of f-IPV dose(s) compared to full dose(s) of IPV.[11-13] Of note, in these reviews there is an absence of extensive search for literature therefore, there might be other studies that were excluded that may alter their findings. Furthermore, none of these reviews investigated adverse events and vaccine administration which are important factors when deciding on a national vaccine schedule. In one of the systematic reviews the procedures were performed by one person.[12] This increases the risk of introducing bias in the process of reviewing literature.[14] After analysis, none of the authors used the Grading of Recommendations Assessment, Development and Evaluation

(GRADE) approach[15] to assess the certainty of their results. This approach guides evidence users in deciding on whether to adopt an intervention.

We performed a systematic review of studies comparing the effects of fractional to full dose(s) of IPV vaccination. We also evaluated the occurrence of adverse events and types of administration devices used for the intradermal delivery of f-IPV.

2. RESEARCH IN CONTEXT

2.1 Evidence before this study

To identify systematic or literature reviews that have compared f-IPV dose(s) to full dose(s) of IPV, we used the search strategy in appendix A table 1. From the search we found 2 literature reviews and 1 systematic review that were related to either reduced dose or intradermal delivery (ID) of IPV. Important gaps that were identified include: narrow search strategies, lack of assessment of certainty of results and absence of data concerning adverse events and vaccine administration. These factors reduce the reliability of results obtained from these reviews.

2.2 Added value of this study

In addition to looking at effectiveness of f-IPV dose(s) versus full-dose(s) IPV, in our systematic review, we compared the incidence of adverse events, wild poliovirus poliomyelitis and vaccine derived paralytic poliomyelitis in both arms. We also evaluated types of administration devices used for the intradermal delivery of f-IPV. To ensure that we capture all the relevant literature, we used a broad search strategy and searched for both peer-reviewed and grey literature in 16 databases. After data analysis, we used the GRADE approach to assess the certainty of our findings.

2.3 Implications of all the available evidence

Our review findings strengthened the existing evidence from previous reviews. We performed a same dose analysis including a comparison after 3 doses of either f-IPV or full dose IPV. In addition, we assessed the adverse events, the occurrence of wild poliovirus poliomyelitis and vaccine derived paralytic poliomyelitis (VAPP), mucosal immunity and intradermal devices used to deliver f-IPV. Together this evidence will advise immunisation policy makers and other key evidence users

on the f-IPV dosing and the adoption of f-IPV into national immunisation schedules. To further assist evidence users, we analysed the certainty of our results using the GRADE approach.

3. METHODS

3.1 Search strategy and selection criteria

In this systematic review and meta-analysis, using keywords and MeSH terms (appendix A table 1) developed in PubMed and adapted for other databases, we searched for peer-reviewed and grey literature from the 16 databases outlined in appendix A table 2. The databases were searched from inception to the 11th of April 2018 with no date, language or publication restrictions. 1 article[16] was translated before eligibility assessment. Trial registries (appendix A table 2) were searched for relevant completed and on-going studies. Additionally, we searched the WHO and Global Polio Eradication Initiative (GPEI) websites and reference lists of included studies, related reviews, and relevant WHO vaccine position papers.

We included studies which compared fractional-dose(s) to full-dose(s) IPV in children aged 5 years or younger regardless of study design, number of doses and route of administration. Studies were IPV was given in combination with OPV were also included. Summary estimates were extracted for comparison. Thandiwe Mashunye and Kopano Dube independently assessed eligibility and extracted data from included studies. Any disagreements between the two authors regarding study eligibility and data extraction were resolved by discussion and consensus. A third author, Duduzile Ndwandwe or Charles Wiysonge, adjudicated any unresolved disagreements. Were necessary, authors were contacted to obtain additional information or resolve disputes.

3.2 Data analysis

Study characteristics were extracted independently by Thandiwe Mashunye and Kopano Dube using a piloted data extraction form (appendix C). In studies with multiple study arms, only data from arms relevant to the review was extracted. Our main outcome of interest was immunogenicity. Specific measures for immunogenicity that were used were proportion of participants who seroconverted and changes in titres of anti-polio type 1, 2 and 3. Secondary outcomes analysed were the occurrence of adverse events; wild poliovirus poliomyelitis; vaccine

derived paralytic poliomyelitis and the development of mucosal immunity. We also described the routes and devices used for f-IPV vaccination.

To determine the quality of studies, the Cochrane Risk of Bias tool for trials[17] was used independently by Thandiwe Mashunye and Kopano Dube. 6 of the tool's 7 domains for assessing bias were used. Blinding of personnel and participants (performance bias) domain was excluded because of the challenge of blinding when different routes of vaccine administration, intradermal versus intramuscular, are used to vaccinate participants. Each study was classified into low, high and unclear risk and RevMan 5.3[18] was used to create a risk of bias table (table 4). Judgements for level of risk are outlined in appendix A table 5. Differences in judgements were resolved by discussion and consensus, or arbitration by a third author Duduzile Ndwandwe or Charles Wiysonge.

We used risk ratios (RR) and corresponding 95% confidence intervals to summarise seroconversion proportions, adverse events, mucosal immunity and the incidence of wild poliovirus poliomyelitis and vaccine derived paralytic poliomyelitis. The standardised mean difference (SMD) and its 95% confidence interval was used to summarise anti-polio 1, 2 and 3 titres. For studies with similar participants, interventions, outcomes, and study designs, we pooled the study data using the random-effect method of meta-analysis. Only studies comparing the same number of doses of fractional versus full doses of IPV were compared. Analysis was stratified by type of outcome measure, type of poliovirus, and number of IPV doses given. For all outcomes, the total number of participants that were randomised at the beginning of the study were used to analyse data. Drop outs were regarded as failures. To avoid double counts, multiple arms were combined. We assessed for statistical heterogeneity by visually inspecting forest plots and using the χ^2 test of homogeneity;[17] with significance defined at the alpha level of 0.10. The I^2 statistic[17] was used to quantify the amount of heterogeneity. To investigate heterogeneity, we performed subgroup analysis using the following classifications: timing of first dose, interval between doses, age of administration, number of fractional doses, poliovirus type (1, 2 and 3), type of intradermal injection device, immunisation schedules, and country income status. We performed sensitivity analysis based on level of bias, methods of metanalysis and by considering missing data as either successes or failures.

The GRADE approach[15] was used to evaluate the certainty of evidence and the results were summarised using a GRADE summary of findings table. Studies that were assigned a high risk for allocation concealment, blinding of outcome assessment, or completeness of outcome were considered to have a high risk of bias. Differential losses to follow-up of more than 10% between fractional and full dose groups was considered as high risk.

Statistical analysis was performed using RevMan 5.3.[18] This systematic review and metanalysis was reported in accordance to the PRISMA guidelines[19] (appendix C). The review was registered under PROSPERO International Prospective Register of Systematic Review (registration number: CRD42018092647).

4. ROLE OF FUNDING

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

5. RESULTS

1207 citations were identified through a systematic database search and 113 additional citations were identified from grey literature (figure 1, appendix A table 2). 482 duplicate citations were removed and the titles and abstracts of the remaining 858 citations were screened using the inclusion and exclusion criteria. 35 citations were eligible for full text review. From the 17 articles included after full-text review, 3 on-going trials were excluded, and 8 studies published in 14 articles were included in the meta-analysis.[20-33] We excluded 12 studies which assessed the effect of reduced antigen doses using Sabin derived IPV (table 3). 5 studies were participants were given f-IPV without the comparative full dose IPV were also excluded (table 3).

Of the 8 studies included in the meta-analysis (table 1), 3 studies took place in Cuba and the other studies were done in Oman, Philippines, India, Bangladesh and the Gambia. All 8 studies were randomised controlled trials published between 2010 and 2016. Studies done between 2010 and 2013 focused on comparing the immunogenicity of f-IPV and the full dose IPV[20-22,25,26] whilst the last 2 studies published

in 2015 and 2016[29,31] focused on assessing the quality and efficiency of using different intradermal devices for f-IPV administration. Study participants were below 12 months of age except in 1 study[29] were participants were aged between 12 to 20 months. In all studies, the intervention and control groups received an equal number of IPV doses. 3 studies had a 3-dose schedule,[20-22] 2 studies had a 2-dose schedule[26,27,] and in 3 studies[25,29,31] participants received a single dose. In all the single dose studies, participants were exposed to OPV before study vaccines as part of routine or supplementary immunisation. The outcome assessment for the studies were similar except for 1 study[28] which used the Salk based assay which is more sensitive than the Sabin based assay. Table 1 shows characteristics of studies included in the meta-analysis and table 2 shows characteristics of on-going trials.

For poliovirus type 2, the proportion of those who seroconverted after f-IPV vaccination increased as the number of IPV doses increased such that at 3 doses the proportion approximates the proportion that seroconverted after 3 full doses of IPV (figure 2). The risk ratio (RR) at 1 dose was 0.61 (95% confidence interval (CI) 0.50, 0.73; p<0.00001), at 2 doses 0.87 (0.71, 1.05; p=0.14) and at 3 doses 0.95 (0.91, 1.00; p=0.06). This result corresponds to what was observed for poliovirus type 1 and type 3 (appendix B figure 1 and 2) though some of the plots favour the full dose. For all dose schedules, participants vaccinated with full dose IPV had higher anti-polio 1, 2 and 3 titres than those vaccinated with f-IPV. The standardised mean difference (SMD) between the mean antibody titres increased as the number of IPV doses increased (figure 3). The SMD for poliovirus type 2 at 1 dose was -0.53 (95% CI -0.90, -0.15; p=0.006), 2 doses -0.55 (-0.80, -0.30; p<0.0001) and 3 doses -0.98 (-1.46, -0.51; p<0.0001). The trend was similar for poliovirus type 1 and type 3 (appendix B figure 3 and 4).

Severe adverse events were reported in 2 studies.[21,27] The events are described in appendix B table 1. Compared to the full dose arm, severe adverse events occurred less frequently in the f-IPV arm. The RR was 0.76 (95% CI 0.44, 1.32; p=0.32). Local injection site adverse events occurred more frequently in the f-IPV arm: pain/tenderness RR 1.20 (95% CI 0.95, 1.51; p=0.12), redness/erythema 4.10 (1.52, 11.11; p=0.005) and swelling/induration 4.96 (2.26, 9.74; p<0.0001). 7 systemic adverse events were analysed. 2 occurred more frequently in the full dose arm compared to the f-IPV arm: fever RR 0.71 (95% CI 0.58, 0.86; p=0.0006) and loss of appetite 0.81 (0.51, 1.27; p=0.36). 2 occurred more frequently in the f-IPV arm: vomiting RR 1.11 (95% CI 0.46, 2.71; p=0.81) and irritability 1.14 (0.86, 1.50; p=0.36). The occurrence of 3 systemic event was almost equal in both arms: drowsiness RR 1.07 (95% CI 0.76, 1.51;

p=0.68), excessive crying 0.93 (0.56, 1.55; p=0.78) and diarrhoea 1.03 (0.71, 1.74; p=0.88). Analysis of adverse events is shown in appendix B figure 5.

1 study[25] reported the occurrence of wild poliovirus type 3 infection in a single participant who had received a single full dose of IPV after receiving tOPV in routine immunisation and supplementary monovalent OPV type 1 (mOPV1). VAPP cases were not reported in any of the studies.

The intradermal vaccine delivery route was used for f-IPV vaccination in all included studies. 6 included studies[20-22,25-27] used a single intradermal device to vaccinate participants with f-IPV. Jet injection was used in 4 of the studies. 3 studies[20,21,26] used the Biojector 2000 (Bioject) whilst 1 study[25] used the Tropis (PharmaJet). 2 of the 6 studies that used a single intradermal device delivered f-IPV using microinjection and the Mantoux method.[22,27] The study that used microinjection used the Micronjet 600 (Nanopass)[27] and the one that used the Mantoux method used a needle and syringe.[22] 2 included studies used more than a single intradermal device to administer f-IPV.[29,31] In 1 study[29] 4 devices were used: BCG needle and syringe; Biojector 2000 (Bioject); Tropis (PharmaJet); and an intradermal pen injector (Bioject). The other study[31] used 2 devices: Tropis (PharmaJet) and a needle and syringe.

Mucosal immunity was investigated in 2 included studies[21,27] In 1 study[21] poliovirus shedding in stool was measured at 7 months, 1week after the participants were challenged with mOVP1 following 3 doses of either f-IPV or full dose IPV. VDPV type 2 shedding was detected in a single participant for each arm. 1 participant in the f-IPV arm had VDPV type 3 shedding while in the full dose IPV arm VDPV type 3 shedding was not detected. There was more VDPV type 1 shedding in the f-IPV compared to full dose IPV (RR 1.17; 95% CI 0.98, 1.41; p=0.09, appendix B figure 13). In the other study,[27] poliovirus shedding in stool was measured at 18weeks, 1week after the participants were challenged with tOPV following 2 doses of either f-IPV or full dose IPV. Amongst those who got f-IPV, one arm was given a single dose of bOPV at 10 weeks. Those who received the full dose had more VDPV type 1 and 2 shedding compared to the f-IPV/bOPV arm (VDPV type 1 RR 0.27; 95% CI 0.19, 0.40; p<0.00001 and VDPV type 3 RR 0.43; 95% CI 0.29, 0.66; p<0.0001, appendix B figure 14). In the f-IPV only arm there was more VDPV type 2 and 3 shedding compared to the full dose arm (VDPV type 2 RR 1.10; 95% CI 0.91, 1.32; p=0.32 and VDPV type 3 RR 1.26; 95% CI 0.94, 1.71; p=0.12, appendix B figure 13).

Visual inspection of the forest plots in figure 3 suggests heterogeneity in the plots for 2 and 1 dose comparisons of poliovirus type 2 seroconversion. In both plots, the I^2 statistic and chi-squared test for homogeneity confirmed the heterogeneity (2 dose comparison: χ^2 p<0.00001; I^2=93% and 1 dose comparison: χ^2 p=0.0002; I^2=77%, figure 3). The seroconversion meta-analysis for 3-dose comparison was homogenous (χ^2 p=0.45; I^2=0%). Subgroup analysis showed that poliovirus type 2 seroconversion was dependent on timing of first dose, interval between doses and immunisation schedule. Regardless of number of doses given, as the period between birth and timing of the first dose increased the RR moved much closer to the null (appendix B figure 6). For the 2-dose comparison, when the first dose was given at 6 weeks RR was 0.83 (95% CI 0.75, 0.92; p=0.004), at 2 months 0.82 (0.73, 0.92; p=0.78) and at 4 months 1.01 (0.96, 1.05; p=0.001). As the interval between 2 doses increased the RR moved closer to the null (appendix B figure 7). For the 2-dose comparison, a schedule with a 4-week interval had an RR of 0.77 (95% CI 0.64, 0.93; p=0.005), a 2-month interval 0.84 (0.78, 0.91; p<0.0001) and a 4-month interval 1.01 (0.96, 1.05; p=0.001). Immunisation schedules whose timing of the first dose was the furthest away from birth and whose 2-dose interval was the furthest apart, the RR was closer to the null (figure 4). For the 2-dose comparison, a 6wks and 10wks schedule had an RR of 0.77 (95% CI 0.64, 0.93; p=0.005), a 6wks and 14wks schedule 0.86 (0.77, 0.95; p=0.004), a 2 months and 4 months schedule 0.82 (0.73-0.92; p=0.001) and a 4 months and 8 months schedule 1.01 (0.96, 1.05; p=0.001).

Results after stratifying by country status and intradermal devices depended on the immunisation schedules used in the studies therefore, the results were not reliable (appendix B figure 8 and 9). Consequently, subgroup analysis for intradermal devices was done using 1-dose comparisons at the same age of administration. In the study that used the Tropis (PharmaJet) and a needle and syringe for f-IPV administration as a single dose at 10-12 months,[31] the RR when a needle and syringe was used was nearer to the null when compared to the RR when the Tropis (PharmaJet) was used (appendix B figure 11). For poliovirus type 1, the RR for the needle and syringe was 0.83 (95% CI 0.70, 0.99; p=0.04), and the RR for Tropis (PharmaJet) was 0.65 (95% CI 0.53, 0.79; p<0.0001. In the study that used 4 intradermal devices,[29] Tropis (PharmaJet) RR was nearest to the null followed by BCG needle and syringe and the Biojector 2000 (Bioject) (appendix B figure 12). The intradermal pen injector was the least successful device (appendix B figure 12). RR for Tropis (PharmaJet) was 0.60 (95% CI 0.46, 0.79; p=0.0002), Biojector

2000 (Bioject) 0.56 (0.48, 0.66; p<0.00001), BCG needle and syringe 0.55 (0.40, 0.75; p=0.0002) and intradermal pen injector (Bioject) 0.45 (0.32, 0.63; p<0.00001).

In general, all studies were low risk studies. Data for randomisation and allocation concealment in 5 studies[20-22,27,29] was either missing or not adequately described to make a judgement (table 4). Two studies had missing data amounting to 23%[20] and 13%[25] respectively. Since the differential loss to follow up between the review comparison groups was less than 10% (5%[20] and 7%[25]) both studies were assigned a low risk of attrition bias. All the studies had a low risk of detection bias, reporting bias and having any other biases (table 4).

We performed sensitivity analysis were missing data was regarded as success or failures. The difference in the results using either participants who completed the study or participates who were randomised at the beginning of the study was negligible (appendix B figure 15-18). Especially for poliovirus type 2 and type 3, effects obtained using the fixed effects model were nearer to the null when compared to effects obtained using the random effects model (appendix B figure 18-20).

Using the GRADE approach (table 5), the certainty of evidence for poliovirus type 2 seroconversion at 3 dose comparison (RR 0.95; 95% CI 0.91, 1.00; p=0.06) was high. For the 2-dose comparison (RR 0.87; 95% CI 0.71, 1.05; p=0.14) was low and for the 1 dose comparison (RR 0.61; 95% CI 0.50, 0.73; p<0.00001) it was moderate. The levels were similar for poliovirus 1 and 3.

All the analysis is available under appendix B

6. DISCUSSION

Our results suggest that there is no difference in seroconversion between 3 doses of f-IPV and 3 dose of full dose IPV even though the full dose gives higher anti-polio type 1, 2 and 3 titres. As the number of doses increases the seroconversion rates for f-IPV and full dose IPV approximate each other. An immunisation schedule which has a longer interval between birth and timing of first dose and between two successive doses is more likely to improve the seroconversion potential following 3 doses of f-IPV. Our results strengthen and adds to the evidence of previous reviews.[11-13] These reviews showed that two doses of f-IPV were more immunogenic than 1 full dose of IPV and delaying timing of first dose and increasing interval between doses increased the immunogenicity of f-IPV.[12,13] This review added to this

evidence by performing same dose comparisons at 1, 2 and 3 doses of IPV. 1 of our included studies[22] used a Salk based assay to measure antibody titres which is more sensitive than the Sabin based assay. This could have pulled our results of the 3-dose comparison nearer to the null.

IPV supply is falling behind the increasing demand for the vaccine.[7] Our result show that f-IPV is a viable alternative to using full dose IPV. From 1 full dose of IPV it is possible to administer 5 f-IPV doses. Accordingly, f-IPV can stretch supplies offsetting the demand-supply gap. In countries, using the bOPV and 1 full dose IPV schedule, that are facing IPV shortages, WHO recommends the use 2 f-IPV doses given at 6 and 14 weeks instead of the full dose.[6] Our results push this recommendation further by proposing the replacement of bOPV with f-IPV. This even applies to countries who use the full dose IPV only schedules. These countries can conserve resources by using f-IPV. One of the polio eradication strategies is the phased replacement of OPV by IPV.[34] Some of the considerations for replacing OPV with f-IPV are discussed below.

Immunological considerations include the effect of maternal antibodies, mucosal immunity and duration of immunity. Maternal antibodies against polio interfere with the successful immunisation of a vaccinated child,[35] therefore, delaying timing of the first dose gives enough time for the maternal antibodies to wane off.[12,13,26] This affects polio immunisation schedules. Two commonly used polio immunisation schedules are the 6-, 10-, and 14-week schedule and the 2-, 4- and 6-month schedule.[36] From our review findings, the 2-,4- and 6-month schedule is more ideal for f-IPV vaccination. This creates a challenge for many low-income countries which use the 6-, 10- and 14-week schedule with a low dropout rate.[36] In such countries, it is worthwhile to weigh the benefits of delaying and increasing the dose intervals for f-IPV vaccination and the cost of children missing vaccination opportunities. Mucosal immunity after IPV vaccination has been subject to debate.[38] It has been suggested that without prior exposure to OPV, IPV does not improve intestinal immunity.[39] A study that compared mucosal immunity after ether a single dose of f-IPV or a full dose IPV in 10 year olds who had been exposed to OPV showed no difference between using either of vaccines.[40] In one of our studies,[27] the arm were f-IPV was given sequentially with OPV had less virus shedding than the arm given f-IPV only. The study where mucosal immunity was measured after ether 3 doses of f-IPV or 3 full doses of IPV[21] suggested that more doses can potentially reduce polio virus shedding. OPV promotes mucosal immunity therefore the risk of reduced mucosal immunity must be weighed against the benefits of replacing OPV with f-IPV. Looking

at duration of f-IPV immunity, a study that compared the booster dose of f-IPV and full dose after a 3-dose primary schedule showed comparable immunogenicity.[22] As up take of f-IPV increases, research on duration of immunity and booster vaccination is required.

Providing evidence for vaccine safety increases uptake. f-IPV is safe to administer to children. The incidence of the adverse events that we investigated was low in both comparison groups. Most of the severe adverse events were all hospitalisations that occurred after study vaccination. It is possible that these hospitalisations were not related to the study vaccine since young infants are susceptible to infection because of a weak immune system. Local injection adverse events are to be expected following f-IPV vaccination because of method and devices used to deliver the vaccine. One of the reasons why IPV is an ideal replacement for OPV is that it is not associated with VDPVs. In our review, VAPP was not detected in any of the studies. This reinforces the need for scaling up the replacement of OPV with IPV.

Using a the Mantoux method to administer f-IPV intradermally, affects the effectiveness and efficiency of wide scale f-IPV vaccination. Alternative intradermal devices have been developed and registered.[9] The use of the Bioject 2000 (Bioject) is limited because it requires a cartridge to function. An alternative is the Tropis (PharmaJet) which is a hand-held device that uses pressurized liquid stream.[9] In our review, this device was as effective as the needle and syringe. This complements results of a study that was done in Pakistan.[41] An intradermal adapter (West Pharmaceutical Services) and intradermal syringe (Star Syringe) have also been shown to be as effective as the BCG needle and syringe.[42] Different studies have shown the programmatic feasibility of using these devices in door to door vaccination campaigns and one day vaccination campaigns.[41,42] The cost of the device and the need to train vaccinators on how to use the devices should be considered.

Before introducing f-IPV into vaccine schedules WHO encourages countries to consider programme feasibility.[6] National health committees must decide on off the label use of f-IPV. Considering that other vaccines like rabies and influenza vaccines have been carried using fractional dosage,[9.37] it is possible to use f-IPV on a national scale. Other operational needs required to integrate f-IPV in national immunisation schedules include policy formation and implementation, vaccine availability and cost, availability of human resources, adaptation of surveillance systems, training and dissemination of information, cold-chain management and maintenance of the integrity of the vaccine vial stopper.[9,37]

A joint statement released by the leaders of the GEPI committees stated that the Polio Eradication & Endgame Strategy 2013-2018 is now being revised and will extend up to 2023.[46] As we progress towards global certification of polio eradication, f-IPV does have a role to play in ensuring sustained and affordable IPV supply. Notwithstanding the above considerations, India and Sri Lanka have shown that it is possible to use f-IPV at a national scale.

The lack of data on randomisation and allocation concealment in half of the studies limited our assessment of selection bias. We complemented our confidence in the participant selection by looking at the characteristics of comparison groups. In all studies there were almost comparable. In extracting data for anti-polio 1, 2 and 3 titres, the standard deviation for the median antibody titre were not reported therefore, the 95% confidence interval were used to estimate the standard deviations. These figures enabled us to have approximated results that we could use. Our standard mean differences concurred with results from other studies. Different definitions of seroconversion were used by the authors. We tried our best to combine studies that had a similar definition.

This systematic review and meta-analysis provided an evidence base that could be used by policy makers on deciding on adopting f-IPV in their national immunisation schedules. This evidence supports the replacement of bOPV with f-IPV. In the future, duration of humoral immunity and mucosal immunity are important areas of f-IPV research.

7. DECLARATION OF INTERESTS

We declare no competing interests.

8. ACKNOWLEDGMENTS

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Table 1. Characteristics of studies included in the meta-analysis

Study	Country	Years	Design	Participants	Intervention	Comparator	Outcome assessment
Resik et al. (2010)[20]	Cuba	2006-07	Clinical RCT	Healthy male and female new-born infants from 3 maternity hospitals and 15 vaccination sites in Camagüey Province.	235 vaccinated with fractional-dose IPV (0.1mL, or 1/5 of a full dose of IPV). ID delivery at 6, 10 and 14wks using a needle-free jet injector (Biojector 2000, Bioject).	236 vaccinated with full dose of IPV. IM delivery at 6, 10 and 14wks using a pre-filled syringe and needle.	**Seroconversion:** modified neutralization assay for anti-polio 1, 2, and 3 antibody titers. Starting dilution = reciprocal titer of 8; seropositivity = reciprocal titer ≥ 8; maternal antibody half-life decay = 28 days. **Antibody GMT**: reported as the overall median polio antibody titre and median polio antibody titre for seroconverted individuals only.
Mohammed et al. (2010)[21]	Oman	2007	Clinical RCT	Healthy male and female infants, recruited at birth, with a median age of 62 days at first dose. From clinics in 5 sites in Oman.	200 vaccinated with fractional-dose IPV (0.1 ml, representing one fifth of a full dose). ID delivery at 2, 4 and 6M using a needle-free jet injector (Biojector 2000, Bioject).	200 vaccinated with full-dose IPV (0.5ml). IM delivery at 2, 4 and 6M using an auto-disable syringe and needle	**Seroconversion:** modified neutralization assays for anti-polio 1, 2, and 3 antibody titers. Starting dilution = reciprocal titer of 8; seropositivity = reciprocal titer ≥ 8; maternal antibody half-life decay = 28 days. **Antibody GMT**: reported as median reciprocal titre.
Cadorna-Carlos et al. (2012)[22-24]	Philippines	2008-09	Clinical RCT	**Primary series study:** healthy male and female infants aged 45.5days on average. **Booster study:** children, aged 15-18M, who completed the primary series study. *	**Primary series study:** 118 vaccinated with fractional IPV dose (1/5th of the IM volume). ID delivery using needle and syringe at 6, 10 and 14wks. **Booster study:** 113 vaccinated at 15-18M.	**Primary series study:** 118 vaccinated with full dose; 0.5ml**.** IM delivery using pre-filled syringes with a 16-mm 25-gauge needle**;** at 6, 10 and 14wks. **Booster study:** 112 vaccinated at 15-18M.	**Seroconversion:** seroneutralization assay for anti-polio 1, 2, and 3 antibody titers using wild-type Salk strains. Lower limit of quantification = 4 (1/dil); seroprotection = antibody titre ≥8 (1/dil); maternal antibody half-life decay = 28days. **Antibody GMT:** reported as geometric median titres for anti-polio 1, 2 and 3. .
Estivariz et al. (2012)[25]	India	2009	Community-based RCT	Healthy male and female infants in high risk areas of Moradabad, who had received tOPV in RI and supplementary doses of mOPV1. Aged 6-9M. †	202 vaccinated with GSK ID fractional-dose IPV 0.1 mL (20% of the full dose)**.** ID delivery of 1 dose at 5-9M using a needle-free jet injector (Tropis, PharmaJet).	204 vaccinated with GSK IM full dose 0.5ml**.** IM delivery of 1 dose at 5-9M using a needle and syringe.	**Seroconversion:** modified neutralization assays for anti-polio 1, 2, and 3 antibody titers. Titres less than the starting dilution = <8; titres more than the final dilution = ≥1448; maternal antibody half-life decay = 6M. **Antibody GMT:** reported as median reciprocal titres
Resik et al. (2013)[26]	Cuba	2009	Clinical RCT	Healthy male and female infants recruited from 2M of age. From 13 vaccination sites in 4 districts of Camagüey Province, Cuba.	160 vaccinated with fractional dose of IPV (0.1 ml, or one fifth of the full dose)**.** ID delivery at 4 and 8M using a needle-free jet injector (Biojector 2000, Bioject)	160 vaccinated with full dose of IPV. IM delivery at 4 and 8M using an auto-disable syringe and needle	**Seroconversion:** modified neutralization assay anti-polio 1, 2, and 3 antibody titer. Starting dilution = reciprocal titre of 8; seropositivity = reciprocal titer of ≥8; maternal antibody half-life decay = 30 days. **Antibody GMT:** reported as median reciprocal antibody titres

Anand et al. (2015)[27,28]	Bangladesh	2012-13	RCT	Healthy male and female infants with a median age of 44 days and a range of 41-53days from 5 different sections of Mirpur.ǂ	2 arms vaccinated with ID f-IPV (0.1 ml) using microneedle injection (Nanopass Micronjet 600). -164 vaccinated with f-IPV only at 6 and 14wks. -216 vaccinated with f-IPV/bOPV. ID f-IPV at 6 and 14wks and bOPV at 10wks.	162 vaccinated with IM IPV (0.5 ml) at 6 and 14wks using a standard needle and syringe	**Seroconversion**: microneutralization assays for anti-polio 1, 2, and 3 antibody titres. Seronegative = titers below a dilution of 1:8; highest measurable titer = 1:1448; maternal antibody half-life decay = 28 days. **Antibody GMT:** reported as reverse cumulative antibody titres presented using cumulative distribution graphs.
Resik et al. (2015)[29,30]	Cuba	2013	Clinical RCT	Healthy male and female children aged between 12-20M in Camagüey Province who had received 2 doses of OPV per Cuban immunisation policy	4 arms (583 participants) vaccinated with fractional dose IPV (1/5th of full dose). ID delivery 1 dose at 12-20M using 1 of 4 devices: BCG needle and syringe, Biojector 2000, Tropis ID jet injector and Bioject ID Pen injector.	146 vaccinated with full IPV dose (0.5 mL). IM delivery 1 dose at 12-20M using a needle and syringe.	**Seroconversion:** standard neutralization assays for anti-polio 1, 2, and 3 antibody titres. Seropositivity = reciprocal titers ≥8; the highest dilution of sera = 1:11,300; maternal antibody half-life decay not reported. **Antibody GMT:** reported as median titres
Clarke et al. (2016)[31-33]	Gambia	2013-14	Clinical RCT	**Stage 1:** healthy male and female infants with a mean age of 9.5M who had received at least 3 tOPV doses. **Stage 2:** participants who did not receive IPV in stage 1. §	**Stage 2** 378 vaccinated with ID fractional-dose (0.1 mL) IPV 1 dose at 10-12 M using either needle and syringe or Tropis ID jet injector.	**Stage 2** 376 vaccinated with IM full-dose (0.5 mL) IPV 1 dose at 10-12 M using either needle and syringe or Stratis jet injector	**Seroconversion:** neutralisation assays anti-polio 1, 2, and 3 antibody titres. Starting dilution = 1 in 8; seropositivity = reciprocal titre ≥8; maternal antibody half-life decay not reported. **Antibody GMT:** Estimated using the mean/median of $\log_2$-transformed titre data and reported as antibody titres.

RCT = randomised controlled trial, RI = routine immunisation, GSK = GlaxoSmithKline, IPV = inactivated polio vaccine, f-IPV = fractional dose IPV, mOPV1 = monovalent oral polio vaccine type 1, tOPV = trivalent oral polio vaccine, ID = intradermal, IM = intramuscular, GMT = geometric median antibody titres, dil = dilution, M = months, wks = weeks, mins = minutes, hrs = hours, ml = millilitre, CI = confidence interval. *The study was located at the University of the East Ramon Magsaysay Memorial Medical Center, Manila, Philippines. ǂ1002 participants were randomised to 5 arms, 2 arms which were relevant to the review are reported in table. Amongst these participants, a median of 7 mOPV1 doses and a median of 2 tOPV doses were administered before the trial vaccination. ǂ975 participants were randomised to 5 arms, 3 arms which were relevant to the review are reported in table. §Stage 1 assessed the interference associated with co-administering a full dose of IPV with measles-rubella vaccine and the yellow fever vaccine. Participants in stage 2 received single doses of measles-rubella vaccine and yellow fever vaccine alone or combined according to the group allocation in stage 1.

Table 2. Characteristics of on-going studies*

Study ID	Sponsors and collaborators	Country	Study design	Start date	Primary completion date†	Recruitment status	Population	Intervention	Comparator	Main Outcomes
NCT02847026	CDC and International Centre for Diarrheal Disease Research, Bangladesh	Bangladesh	RCT	Sept. 2016	May 2017	Completed	Healthy infants aged between 42-48 days	Fractional IPV (f-IPV; 0.1 mL, one-fifth the full-dose). f-IPV only; 3 doses at 6, 14 and 22wks. F-IPV/IPV; 2 arms: IPV at 6wks, f-IPV at 22wks and IPV at 14wks, f-IPV at 22wks.	0.5 mL, full-dose, IPV at 14 and 22wks	1. Seroconversion and priming after vaccination with f-IPV compared to IPV 2. Seroconversion after rotavirus vaccination (Each intervention has 2 arms comparing 2 rotavirus vaccines)
NCT03239496	FIDEC Corporation and Bill and Melinda Gates Foundation	Panama and the Dominican Republic	RCT	Oct. 2017	Nov. 2018	Completed	Healthy 6 weeks old Infants	Fractional-dose IPV ID delivery, 3 doses at 10, 14 and 16wks and 2 doses at 14 and 16wks	IM IPV, 3 doses at 10, 14 and 16wks and 2 doses at 14 and 16wks	Seroconversion after vaccination with f-IPV or IPV and comparison between 2 and 3 doses.
NCT03286803	Aga Khan University and World Health Organisation	Pakistan	RCT	Aug. 2017	Apr. 2019	Active, not recruiting	2 groups of healthy infants aged between 14wks and 10M	Fractional dose (0.1ml); 1 group will receive 1 dose at 14weeks and the other at 9M	Full dose (0.5ml); 1 group will receive 1 dose at 14weeks and the other at 9	Seroconversion and immune response across study arms and at different time points

*Trial status reported by investigators as of 28 January 2019 under the ClinicalTrials.gov trial registry. †Final data collection date for primary outcome measure. References for on-going trials are outlined in appendix A table 3.

Table 3: Excluded full text articles and reasons for exclusion	
Study ID	**Reason for exclusion**
Nirmal et al. (1998)	The study compared immune responses at different number and interval of f-IPV doses. There was no full dose arm.
Samuel et al. (1991)	The study had only one arm with fractional doses. There was no full dose arm.
Samuel et al. (1992)	The study had only one arm with fractional doses. There was no full dose arm
Guoyang et al. (2012)	The study compared immunogenicity of 3 different formulations of a Sabin derived IPV to the Salk based IPV.
Quiambao et al. (2012)	The study compared immunogenicity of a hexavalent vaccine with different formulations of the IPV component to co-administration with full dose IPV.
Okada et al. (2013)	Phase 2 and 3 clinical studies that assessed the immunogenicity of a new combined vaccine containing Sabin derived IPV derived at different reduced antigen doses.
Verdijk et al. (2014)	The study compared the immunogenicity of 3 different formulation of a new Sabin based IPV vaccine with or without aluminium adjuvant to Salk based IPV.
Saleem et al. (2017)	The study 3 comparison groups all given f-IPV using one of three intradermal devices. There was no full dose arm.
Sun et al. (2017)	Assesses the neutralising capacity of the Sabin derived IPV vaccine with 3 different formulations to OPV and Salk based IPV.
Rivera et al. (2017)	Compares the immunogenicity of aluminium adjuvanted IPV vaccine with reduced antigen doses given as 0.5ml injections versus the full dose IPV
Ye et al. (2018)	Compares the safety and immunogenicity of two different sequential schedules Sabin derived IPV and bOPV.
NCT01048190	Completed trial that assessed the safety and immunogenicity of 3 formulations of Sabin derived IPV compared to a placebo.
NCT02967783	A trial with 3 comparison groups all given f-IPV using one of three intradermal devices. There was no full dose arm.
NCT03032419.	Compares safety and immunogenicity of adjuvanted reduced doses of Sabin derived IPV to non-adjuvanted full dose Sabin derived IPV.
NCT03025750	Compares safety and immunogenicity of adjuvanted reduced doses of Sabin derived IPV to non-adjuvanted full dose Sabin derived IPV.
NCT03169725	Compares a reduced form of a new Sabin based IPV vaccine versus full dose Salk based IPV.
NCT03092791	Compares a reduced form of a new Sabin based vaccine versus full dose Salk based vaccine.
References for excluded full text articles are outlined in appendix A table 4	

Table 4. Summary of risk of bias in included studies

	Resik et al. (2010)[20]	Mohammed et al. (2010)[21]	Cadorna-Carlos et al. (2012)[22]	Estivariz et al. (2012)[25]	Resik et al. (2013)[26]	Anand et al. (2015)[27]	Resik et al. (2015)[29]	Clarke et al. (2016)[31]
Random sequence generation (selection bias)	?	?	?	+	+	+	?	+
Allocation concealment (selection bias)	?	?	?	+	+	?	?	+
Blinding of outcome assessment (detection bias)	+	+	+	+	+	+	+	+
Incomplete outcome data (attrition bias)	+	+	+	+	+	+	+	+
Selective reporting (reporting bias)	+	+	+	+	+	+	+	+
Other bias	+	+	+	+	+	+	+	+

+ **Low risk;** ? **Unclear risk;** − **High risk**

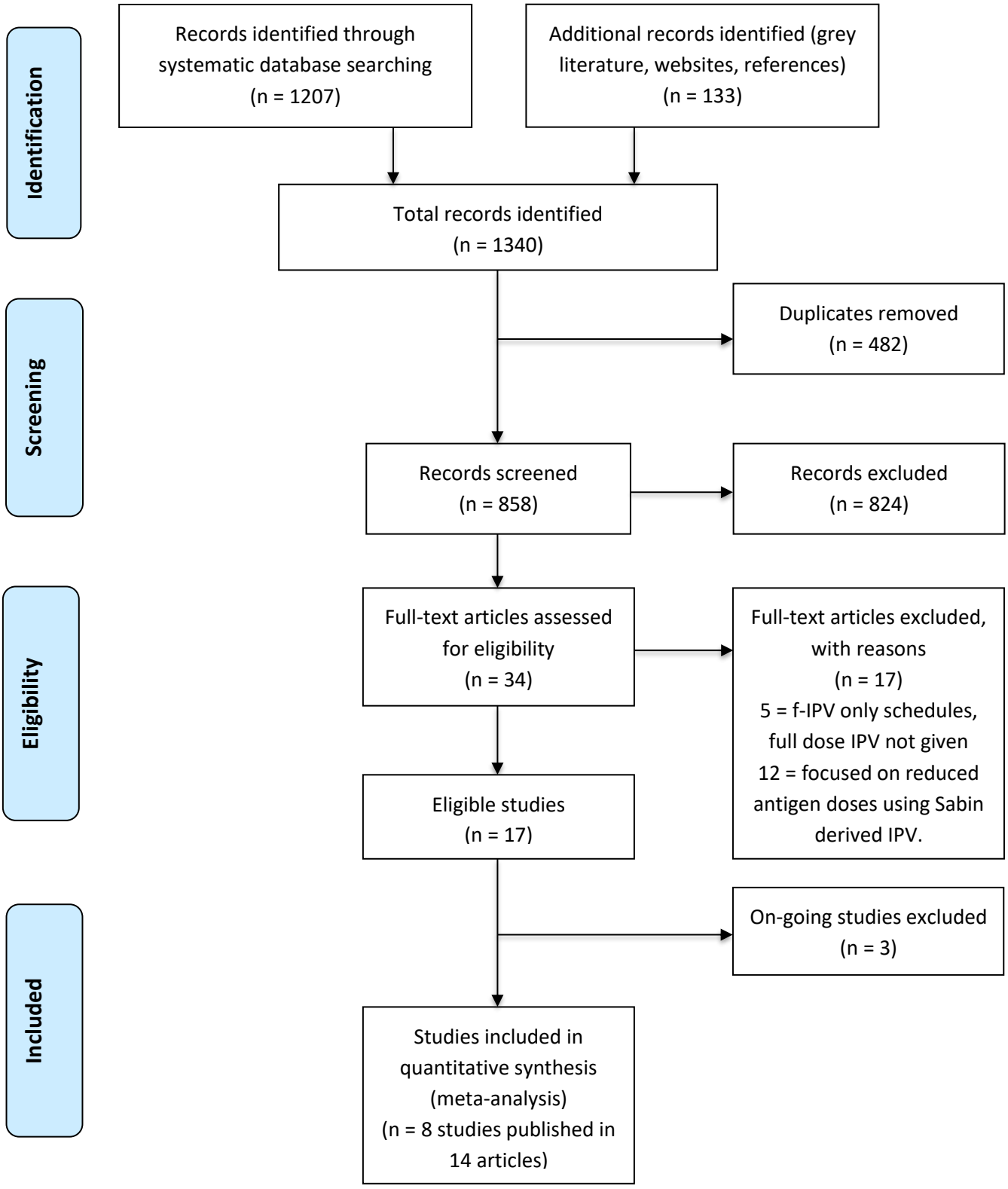
Table 5. GRADE summary of findings for the effects of fractional-dose inactivated poliovirus vaccine

Population: Healthy infants
Settings: Bangladesh, Cuba, The Gambia, India, Oman and Philippines
Intervention: Vaccination with fractional-dose inactivated poliovirus vaccine
Comparison: Vaccination with standard dose inactivated poliovirus vaccine

Outcomes	Illustrative comparative effects (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of evidence (GRADE)
	Standard dose	Fractional-dose			
Seroconversion rates; 3 standard doses vs 3 f-IPV doses	83 per 100 (71 to 95)	79 per 100 (76 to 83)	RR 0.95 (0.91 to 1.00)	1107 (3 RCTs)	⨁⨁⨁⨁ High
Seroconversion rates; 2 standard doses vs 2 f-IPV doses	78 per 100 (57 to 95)	68 per 100 (55 to 82)	RR 0.87 (0.71 to 1.05)	1517 (4 RCTs)	⨁⨁⨁⨀ Low *
Seroconversion rates; 1 standard doses vs 1 f-IPV doses	49 per 100 (26 to 87)	30 per 100 (25 to 36)	RR 0.61 (0.50 to 0.73)	2815 (7 RCTs)	⨁⨁⨁⨀ Moderate†

CI = confidence interval; GRADE: Grading of Recommendations Assessment, Development and Evaluation; f-IPV = fractional dose inactivated poliovirus vaccine; RR: Risk ratio; RCTs = Randomised controlled trials.
* Downgraded because of a high level of inconsistency (high level of heterogeneity (I^2 =93%))
† Downgraded because of a moderate level of inconsistency (moderate level of heterogeneity (I^2 =77%))

Figure 1. PRISMA flow chart for study selection*



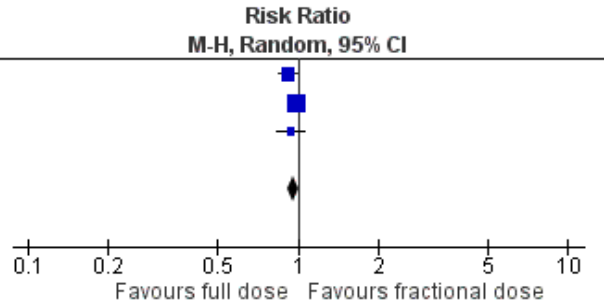
IPV = inactivated poliovirus vaccine, f-IPV = fractional-dose IPV. Study selection done in duplicate. *16 sites searched. Databases and sites searched, and the number of articles retrieved shown in appendix A table 2.

Figure 2. Meta-analysis of seroconversion proportions for poliovirus type 2 by number of doses

Three fractional doses compared to three full doses of IPV

Study or Subgroup	3 f-IPV Events	Total	3 IPV Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cadorna-Carlos 2012	103	118	112	118	35.0%	0.92 [0.85, 1.00]
Mohammed 2010	177	200	180	200	49.1%	0.98 [0.92, 1.05]
Resik 2010	159	235	169	236	15.9%	0.94 [0.84, 1.06]
Total (95% CI)		**553**		**554**	**100.0%**	**0.95 [0.91, 1.00]**
Total events	439		461			

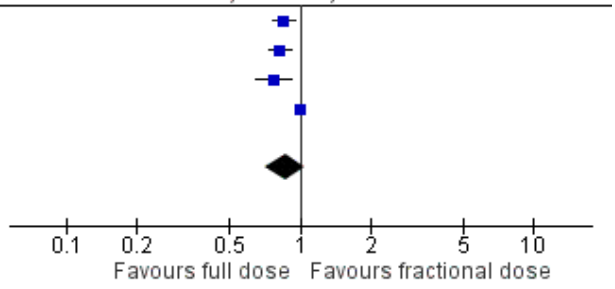
Heterogeneity: Tau² = 0.00; Chi² = 1.58, df = 2 (P = 0.45); I² = 0%
Test for overall effect: Z = 1.92 (P = 0.06)



Two fractional doses compared to Two full doses of IPV

Study or Subgroup	2 f-IPV Events	Total	2 IPV Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Anand 2015	123	164	142	162	25.5%	0.86 [0.77, 0.95]
Mohammed 2010	134	200	163	200	25.1%	0.82 [0.73, 0.92]
Resik 2010	103	235	134	236	22.2%	0.77 [0.64, 0.93]
Resik 2013	154	160	153	160	27.2%	1.01 [0.96, 1.05]
Total (95% CI)		**759**		**758**	**100.0%**	**0.87 [0.71, 1.05]**
Total events	514		592			

Heterogeneity: Tau² = 0.04; Chi² = 44.76, df = 3 (P < 0.00001); I² = 93%
Test for overall effect: Z = 1.47 (P = 0.14)



One fractional dose compared to one full dose of IPV

Study or Subgroup	1 f-IPV Events	Total	1 IPV Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Anand 2015	30	164	62	162	11.4%	0.48 [0.33, 0.70]
Clarke 2016	177	368	229	365	18.9%	0.77 [0.67, 0.88]
Estivariz 2012	21	49	35	50	11.6%	0.61 [0.42, 0.89]
Mohammed 2010	31	200	57	200	11.1%	0.54 [0.37, 0.80]
Resik 2010	35	235	63	236	11.6%	0.56 [0.38, 0.81]
Resik 2013	74	160	96	160	16.6%	0.77 [0.63, 0.95]
Resik 2015	164	375	80	91	18.8%	0.50 [0.43, 0.57]
Total (95% CI)		**1551**		**1264**	**100.0%**	**0.61 [0.50, 0.73]**
Total events	532		622			

Heterogeneity: Tau² = 0.05; Chi² = 26.65, df = 6 (P = 0.0002); I² = 77%
Test for overall effect: Z = 5.16 (P < 0.00001)

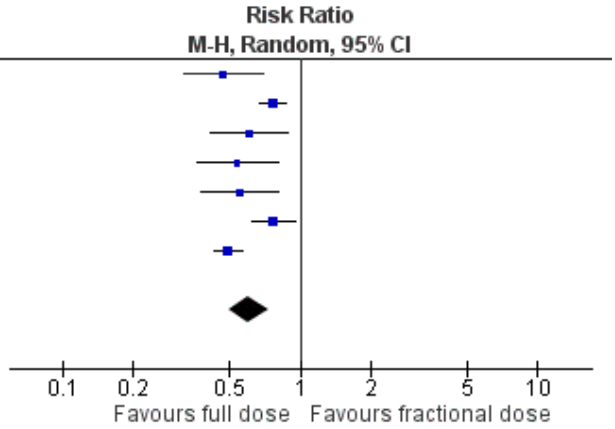
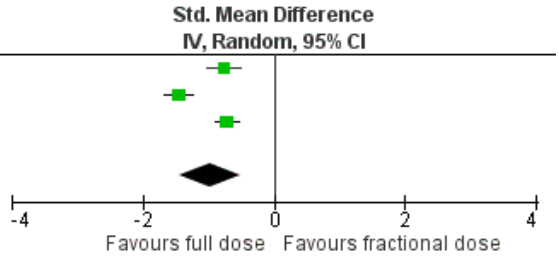


Figure 3. Meta-analysis of standard median antibody titres differences for poliovirus type 2 by number of doses

Three fractional doses compared to three full doses of IPV

Study or Subgroup	3 f-IPV Mean	3 f-IPV SD	3 f-IPV Total	3 IPV Mean	3 IPV SD	3 IPV Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cadorna-Carlos 2012	234	299.3	118	795	981	118	32.4%	-0.77 [-1.04, -0.51]
Mohammed 2010	8.1	1.8	200	10	0.4	200	33.4%	-1.45 [-1.68, -1.23]
Resik 2010	45	62.6	235	214	325.3	236	34.1%	-0.72 [-0.91, -0.53]
Total (95% CI)			**553**			**554**	**100.0%**	**-0.98 [-1.46, -0.51]**

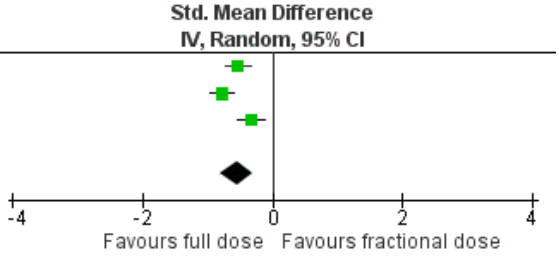
Heterogeneity: Tau² = 0.16; Chi² = 27.63, df = 2 (P < 0.00001); I² = 93%
Test for overall effect: Z = 4.04 (P < 0.0001)



Two fractional doses compared to two full doses of IPV

Study or Subgroup	2 f-IPV Mean	2 f-IPV SD	2 f-IPV Total	2 IPV Mean	2 IPV SD	2 IPV Total	Weight	Std. Mean Difference IV, Random, 95% CI
Mohammed 2010	6	4.3	200	8.1	3.6	200	33.6%	-0.53 [-0.73, -0.33]
Resik 2010	20	7.8	235	130	199.9	236	34.4%	-0.78 [-0.96, -0.59]
Resik 2013	898	2,371.7	160	1,448	0.3	160	32.1%	-0.33 [-0.55, -0.11]
Total (95% CI)			**595**			**596**	**100.0%**	**-0.55 [-0.80, -0.30]**

Heterogeneity: Tau² = 0.04; Chi² = 9.44, df = 2 (P = 0.009); I² = 79%
Test for overall effect: Z = 4.24 (P < 0.0001)



One fractional dose compared to one full dose of IPV

Study or Subgroup	1 f-IPV Mean	1 f-IPV SD	1 f-IPV Total	1 IPV Mean	1 IPV SD	1 IPV Total	Weight	Std. Mean Difference IV, Random, 95% CI
Estivariz 2012	724	1,649.7	202	1,448	0.4	204	25.1%	-0.62 [-0.82, -0.42]
Mohammed 2010	2.8	1.4	200	3.6	0.7	200	25.0%	-0.72 [-0.92, -0.52]
Resik 2010	8	3.9	235	8	3.9	236	25.4%	0.00 [-0.18, 0.18]
Resik 2013	9	9.7	160	58	87.1	160	24.5%	-0.79 [-1.02, -0.56]
Total (95% CI)			**797**			**800**	**100.0%**	**-0.53 [-0.90, -0.15]**

Heterogeneity: Tau² = 0.14; Chi² = 41.58, df = 3 (P < 0.00001); I² = 93%
Test for overall effect: Z = 2.77 (P = 0.006)

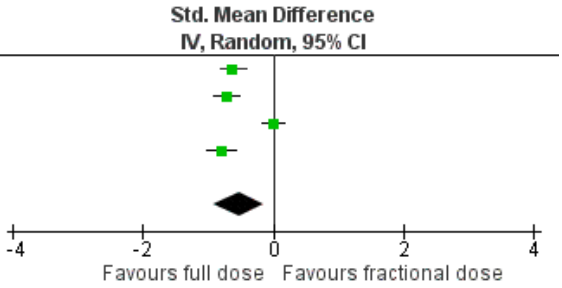
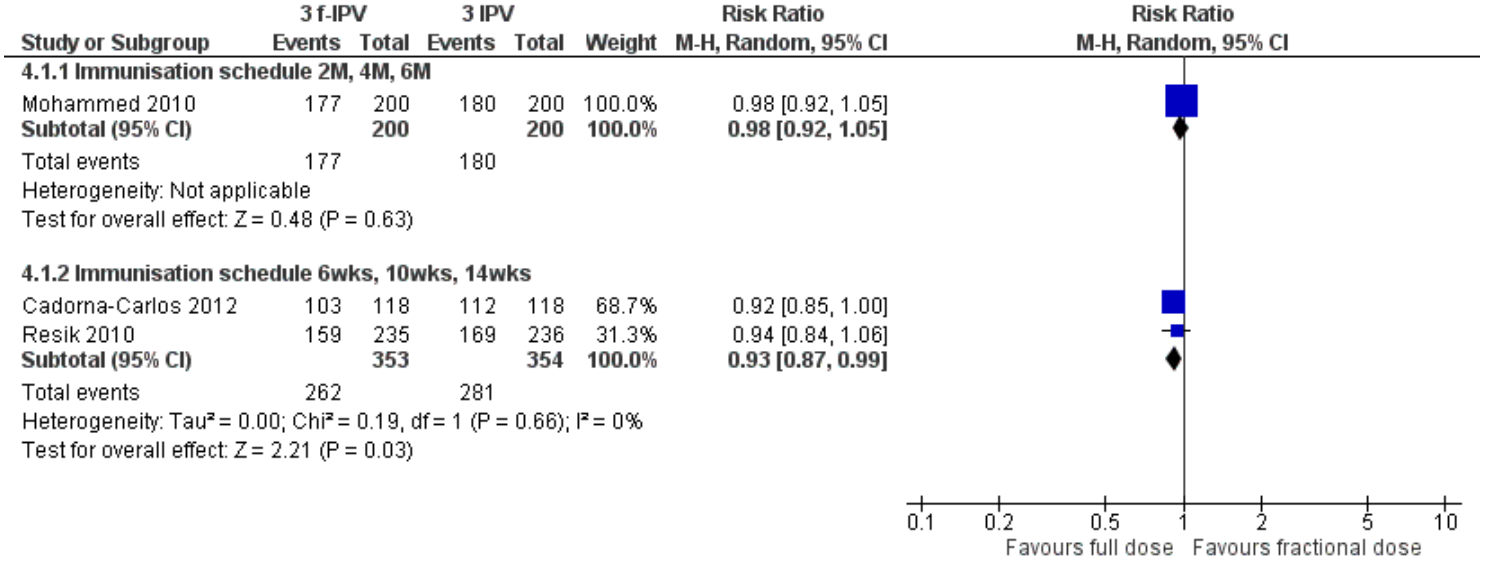
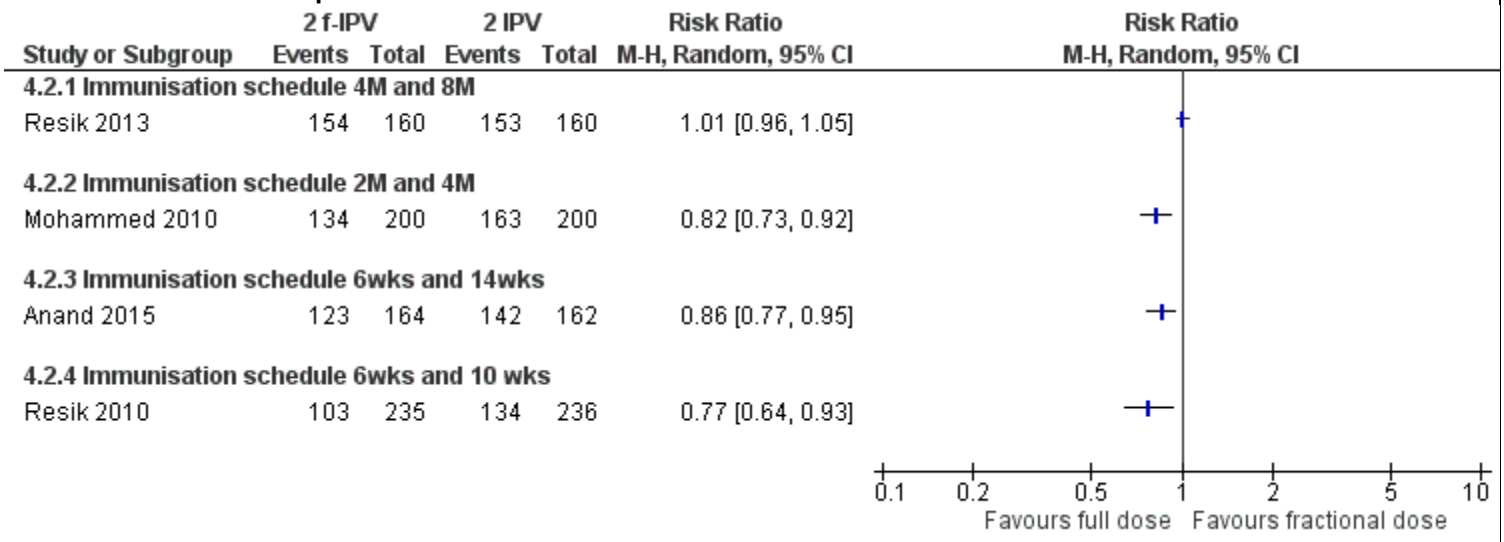


Figure 4. Subgroup analysis of seroconversion proportions for poliovirus type 2 by number of doses and immunisation schedules

Three fractional doses compared to three full doses of IPV by immunisation schedule



Two fractional doses compared to two full doses of IPV immunisation schedule



SECTION D: APPENDICES

APPENDIX A: RECORD SELECTION AND BIAS ASSESSMENT.

Table 1: Search strategy created using PubMed and adapted for other databases

#1: Poliovirus Vaccine, Inactivated [MeSH] OR inactivated polio vaccine OR inactivated poliovirus vaccine OR SALK OR IPV OR eIPV OR killed vaccine.
#2: Injections, Intradermal [MeSH] OR Injections, Intramuscular [MeSH] OR fractional dosing OR Fractionated dosing OR drug dose comparison OR intradermal OR intramuscular OR dose OR dosage.
#3: Dose-Response Relationship, Immunologic [MeSH] OR Antibody Formation [MeSH] OR Seroconversion [MeSH] OR Immunogenicity OR Immune response OR Seroconversion OR potency OR antibody formation OR antibody response.
#4: (#1 AND #2 AND #3).
#5: Animals NOT Human
#6: (#4 NOT #5)

Table 2: Number of records retrieved from databases and search for grey literature.

Database	Articles retrieved	Grey Literature	Articles retrieved
PubMed/Medline	609	ClinicalTrials.gov	42
Cochrane*	322	WHO International Clinical Trials Registry Platform	11
Scopus†	84	PapersFirst (OCLC)	8
SCI‡	53	Proceedings (OCLC)	52
AWI	54	PDQ-Evidence	1
CINAHL	38	ProQuest Dissertations & Theses A&I	10
Health Source: Nursing/Academic	47	DART-Europe E-theses Portal (DEEP)	5
		Networked Digital Library of Theses and Dissertations	4
Total articles	1207		133

SCI = Science Citation Index, AWI = Africa Wide Index, CINAHL = Cumulative Index of Nursing and Allied Health Literature, OCLC = Online Computer Library Center. *Cochrane = CENTRAL, CDSR and DARE. †Scopus searched for EMBASE records and 631 articles indexed by Medline excluded. ‡1057 records indexed by Medline and tagged zoological excluded. Databases were searched on the 10th of April 2018 and grey literature was searched for on the 11th of April 2018 with no date, language or publication restrictions. Records from WHO and GPEI websites and reference lists of included studies, related reviews, and relevant WHO vaccine position papers were already included in other searches. Conference Proceedings Citation Index is part of SCI.

Table 3. References for on-going trials	
Study ID	**References**
NCT02847026	CDC and International Centre for Diarrheal Disease Research, Bangladesh. Fractional Inactivated Poliovirus Vaccine Booster and Rotavirus Study. 2016. https://ClinicalTrials.gov/show/NCT02847026 (accessed Jan. 29, 2019).
NCT03239496	FIDEC Corporation and Bill and Melinda Gates Foundation. A Study to Evaluate Immunogenicity of Intramuscular Full-Dose and Intradermal Fractional Dose of IPV.2017. https://ClinicalTrials.gov/show/NCT03239496 (accessed Jan. 29, 2019).
NCT03286803	Aga Khan University and World Health Organisation. Comparison of Immunity Following IPV Versus fIPV: A Community Based Randomized Controlled Trial in Pakistan. 2017. https://ClinicalTrials.gov/show/NCT03286803 (accessed Jan. 29, 2019).

Table 4. References for excluded studies	
Study ID	**Reference**
Nirmal et al. (1998)	Nirmal S, Cherian T, Samuel BU, Rajasingh J, Raghupathy P, John TJ. Immune response of infants to fractional doses of intradermally administered inactivated poliovirus vaccine. *Vaccine* 1998; 16(9-10): 928-31.
Samuel et al. (1991)	Samuel BU, Cherian T. Immune response to intradermally injected inactivated poliovirus vaccine. Lancet 1991; 338(8763): 343.
Samuel et al. (1992)	Samuel BU, Cherian T, Rajasingh J, Raghupathy P, John TJ. Immune response of infants to inactivated poliovirus vaccine injected intradermally. *Vaccine* 1992; 10(2): 135.
Guoyang et al. (2012)	Guoyang L, Rongcheng L, Changgui L, et al. Safety and Immunogenicity of Inactivated Poliovirus Vaccine Made From Sabin Strains: A Phase II, Randomized, Positive-Controlled Trial. *J Infect Dis* 2012; 205(2): 237-43.
Quiambao et al. (2012)	Quiambao B, Van Der Meeren O, Kolhe D, Gatchalian S. A randomized, dose-ranging assessment of the immunogenicity and safety of a booster dose of a combined diphtheria-tetanus-whole cell pertussis-hepatitis B-inactivated poliovirus-Hemophilus influenzae type b (DTPw-HBV-IPV/Hib) vaccine vs. co-administration of DTPw-HBV/Hib and IPV vaccines in 12 to 24 months old Filipino toddlers. *Hum Vaccin Immunother* 2012; 8(3): 347-54.
Okada et al. (2013)	Okada K, Miyazaki C, Kino Y, Ozaki T, Hirose M, Ueda K. Phase II and III Clinical Studies of Diphtheria-Tetanus-Acellular Pertussis Vaccine Containing Inactivated Polio Vaccine Derived from Sabin Strains (DTaP-sIPV). J Infect Dis 2013; 208(2): 275-83.
Verdijk et al. (2014)	Verdijk P, Rots NY, van Oijen MG, et al. Safety and immunogenicity of a primary series of Sabin-IPV with and without aluminium hydroxide in infants. *Vaccine* 2014; 32(39): 4938-44.
Saleem et al. (2017)	Saleem AF, Mach O, Yousafzai MT, et al. Needle adapters for intradermal administration of fractional dose of inactivated poliovirus vaccine: Evaluation of immunogenicity and programmatic feasibility in Pakistan. *Vaccine* 2017; 35(24): 3209-14.

Sun et al. (2017)	Sun M, Li C, Xu W, et al. Immune Serum From Sabin Inactivated Poliovirus Vaccine Immunization Neutralizes Multiple Individual Wild and Vaccine-Derived Polioviruses. *Clin Infect Dis* 2017; 64(10): 1317-25.
Rivera et al. (2017)	Rivera L, Pedersen RS, Pena L, et al. Immunogenicity and safety of three aluminium hydroxide adjuvanted vaccines with reduced doses of inactivated polio vaccine (IPV-Al) compared with standard IPV in young infants in the Dominican Republic: a phase 2, non-inferiority, observer-blinded, randomised, and controlled dose investigation trial. *Lancet Infect Dis* 2017; 17(7): 745-53.
Ye et al. (2018)	Ye H, Huang T, Ying ZF, et al. [Comparing the immunogenicity and safety of sequential inoculation of sIPV followed by bOPV (+) in different dosage forms]. Zhonghua Yu Fang Yi Xue Za Zhi 2018; 52(1): 43-9.
NCT01048190	Chinese Academy 2008. The Clinical Trial Protocol for the Inactivated Poliomyelitis Vaccine Made from Sabin Strains., 2008. https://ClinicalTrials.gov/show/NCT01048190 (accessed Apr. 28, 2018).
NCT02967783	Medical Research Council Unit, The Gambia 2017. Prevention. A Campaign-based ID fIPV Administration Trial. 2017. https://ClinicalTrials.gov/show/NCT02967783 (accessed Apr. 29, 2018).
NCT03032419.	Statens Serum Institut 2017. Safety and Immunogenicity of Adjuvanted Reduced Dose Inactivated Polio Vaccine Given at 6, 10, 14 Weeks and 9 Months., 2017. https://ClinicalTrials.gov/show/NCT03032419 (accessed Apr. 28, 2018).
NCT03025750	. Statens Serum Institut 2017. Safety and Immunogenicity of Adjuvanted Reduced Dose Inactivated Polio Vaccine in 2, 4, 6 Months of Age., 2017. https://ClinicalTrials.gov/show/NCT03025750 (accessed Apr. 28, 2018).
NCT03169725	LG Chem 2017. A Clinical Study to Evaluate the Safety and Immunogenicity of Inactivated Poliomyelitis Vaccine in Healthy Infants. 2017. https://clinicaltrials.gov/show/NCT03169725 (accessed Apr. 28, 2018).
NCT03092791	Takeda 2017. IPV-102 Safety, Tolerability and Immunogenicity of TAK-195 in Healthy Infants, Toddlers and Adults., 2017. https://ClinicalTrials.gov/show/NCT03092791 (accessed Apr. 28, 2018).

Table 5. Bias judgements adapted from the Cochrane Handbook of Systematic Reviews		
Random sequence generation (selection bias): Random- every participant has an equal probability of being allocated to any of the treatment arms.		
Low risk: Methods of random sequence generation 1. computer generated system/block randomisation 2. random number table 3. drawing of lots 4. tossing of coin 5. shuffling of cards 6. throwing dice as	**High risk:** Methods of random sequence generation 1. Dates 2. Medical record numbers 3. Order of recruitment 4. Days of the week 5. Any Quasi-random allocation 6.Allocation based on individual's judgement (clinician, laboratory result, availability of treatment options)	**Unclear risk:** Method not described or described in insufficient detail to make a decision.
Allocation concealment (selection bias): Concealment- the person who is allocating treatment options is prevented from knowing the allocation of the next person who has been enrolled.		
Low risk: Methods of concealment 1. Controlled by central independent unit 2. Sealed opaque envelopes 3. On-site computer-generated computer secure and locked 4. Sequentially numbered drug packages with the same schedules, appearance and administration of treatment allocation 5. Block randomisation	**High Risk:** Methods of concealment 1. Alternation 2. Dates and registration numbers 3. Any method were allocation was not concealed, allocation was known to both investigator and participants	**Unclear risk:** Method not described or described in insufficient detail to make a decision.
Blinding of personnel and participants (performance bias): Systematic difference between comparison groups because of knowledge of the treatment allocation by personnel and participants.		
Remove this domain because blinding is impossible with the different routes of vaccine administration in the comparison arms (IM vs ID)		
Blinding of outcome assessment (measurement bias): Systematic difference between comparison groups because of a difference in the application of standards of measuring the outcome due to knowledge of treatment options by outcome assessors.		
Low risk: Methods of blinding 1. Adequate description of blinding of assessors and no chance of blinding being broken 2. If the lab analysis was done in another country, consider it low risk	**High risk:** Methods of blinding 1. No blinding or incomplete blinding of assessors 2. Assessors are blinded but blinding is broken	**Unclear risk:** Method not described or described in insufficient detail to make a decision
Incomplete outcome data (Attrition bias): Systematic differences between comparison groups in the amount, nature and handling of retention of study participants.		

Low risk: Amount, nature and methods of handing missing data. 1. there are no missing data 2. the reasons for the missing data are unrelated to the study outcome 3. The proportion and reasons for missing data are similar amongst all comparison groups. 4. Proportion of missing data is not enough to bias the effect size (</=10 % differential loss to follow up) 5. the study used appropriate methods that account for the missing data.	**High risk:** Amount, nature and methods of handing missing data. 1. The reasons for the missing data are related to the study outcome 2. The proportion and reasons for missing data are significantly different amongst the comparison groups. >10 % difference between comparison groups 3. ITT used when there is significant departure from treatment allocation after randomisation 4. The study used inappropriate methods to impute the data.	**Unclear risk:** Method not described or described in insufficient detail to make a decision.
Selective outcome reporting: Systematic differences between reported and findings not reported due to selective reporting.		
Low risk: 1. Study outcomes (primary and secondary) are reported as per pre-specifications	**High risk:** 1. Prespecified outcomes are not reported. 2. Use of methods of measurement and analysis of a primary outcome that was not prespecified. 3. Inclusion of a primary outcome that was not in the protocol without a valid reason.	**Unclear risk:** Method not described or described in insufficient detail to make a decision
Other Bias: Bias due to other reasons not stated in this table		
Low risk: Absence of bias in the study	**High risk:** Presence of a factor that could introduce bias	**Unclear risk:** Method not described or described in insufficient detail to make a decision

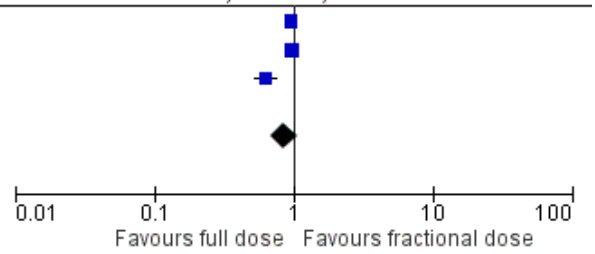
APPENDIX B: SUPPLEMENTARY ANALYSIS

Figure 1. Meta-analysis of seroconversion proportions for poliovirus type 1 by number of doses

Three fractional doses compared to three full doses of IPV

Study or Subgroup	3 f-IPV Events	3 f-IPV Total	3 IPV Events	3 IPV Total	Weight	Risk Ratio M-H, Random, 95% CI
Cadorna-Carlos 2012	108	118	112	118	35.0%	0.96 [0.90, 1.03]
Mohammed 2010	179	200	182	200	35.1%	0.98 [0.92, 1.05]
Resik 2010	99	235	158	236	29.9%	0.63 [0.53, 0.75]
Total (95% CI)		**553**		**554**	**100.0%**	**0.85 [0.68, 1.08]**
Total events	386		452			

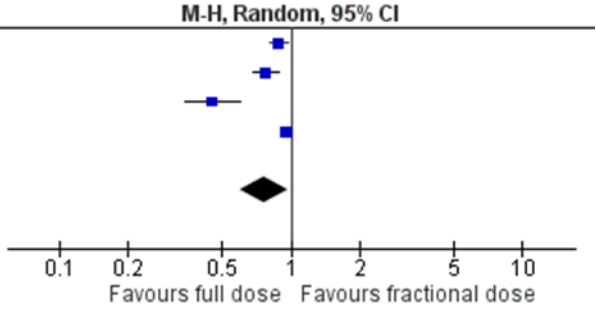
Heterogeneity: Tau² = 0.04; Chi² = 41.62, df = 2 (P < 0.00001); I² = 95%
Test for overall effect: Z = 1.34 (P = 0.18)



Two fractional doses compared to two full doses of IPV

Study or Subgroup	2 f-IPV Events	2 f-IPV Total	2 IPV Events	2 IPV Total	Weight	Risk Ratio M-H, Random, 95% CI
Anand 2015	133	164	148	162	26.7%	0.89 [0.81, 0.97]
Mohammed 2010	129	200	165	200	25.9%	0.78 [0.69, 0.88]
Resik 2010	51	235	112	236	20.2%	0.46 [0.35, 0.60]
Resik 2013	147	160	153	160	27.2%	0.96 [0.91, 1.02]
Total (95% CI)		**759**		**758**	**100.0%**	**0.77 [0.60, 0.98]**
Total events	460		578			

Heterogeneity: Tau² = 0.05; Chi² = 64.99, df = 3 (P < 0.00001); I² = 95%
Test for overall effect: Z = 2.15 (P = 0.03)



One fractional dose compared to One full dose of IPV

Study or Subgroup	1 f-IPV Events	1 f-IPV Total	1 IPV Events	1 IPV Total	Weight	Risk Ratio M-H, Random, 95% CI
Anand 2015	20	164	57	162	12.9%	0.35 [0.22, 0.55]
Clarke 2016	176	368	230	365	19.9%	0.76 [0.66, 0.87]
Estivariz 2012	9	16	19	22	12.9%	0.65 [0.41, 1.03]
Mohammed 2010	19	200	40	200	11.9%	0.47 [0.29, 0.79]
Resik 2010	9	235	34	236	8.4%	0.27 [0.13, 0.54]
Resik 2013	26	160	71	160	14.5%	0.37 [0.25, 0.54]
Resik 2015	104	206	51	57	19.5%	0.56 [0.48, 0.66]
Total (95% CI)		**1349**		**1202**	**100.0%**	**0.49 [0.38, 0.65]**
Total events	363		502			

Heterogeneity: Tau² = 0.09; Chi² = 31.86, df = 6 (P < 0.0001); I² = 81%
Test for overall effect: Z = 5.16 (P < 0.00001)

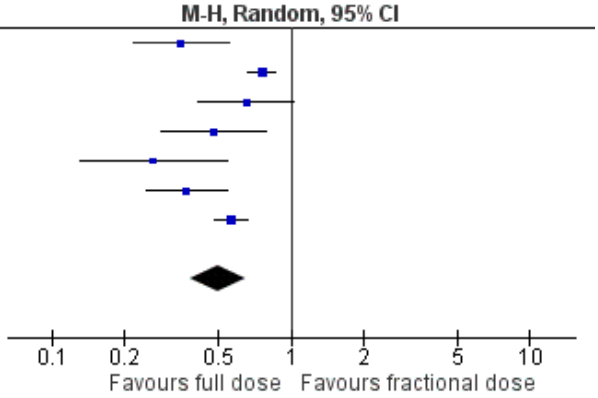
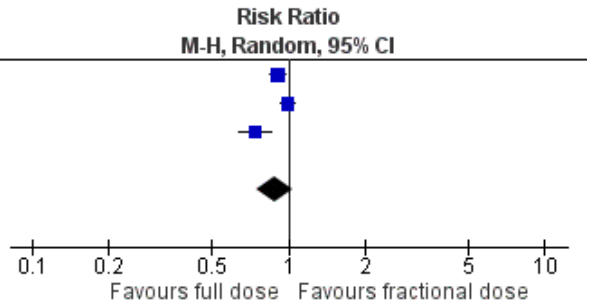


Figure 2. Meta-analysis of seroconversion proportions for poliovirus type 3 by number of doses

Three fractional doses compared to three full doses of IPV

Study or Subgroup	3 f-IPV Events	Total	3 IPV Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cadorna-Carlos 2012	104	118	114	118	34.8%	0.91 [0.85, 0.98]
Mohammed 2010	182	200	183	200	35.7%	0.99 [0.94, 1.06]
Resik 2010	129	235	175	236	29.5%	0.74 [0.64, 0.85]
Total (95% CI)		**553**		**554**	**100.0%**	**0.88 [0.75, 1.04]**
Total events	415		472			

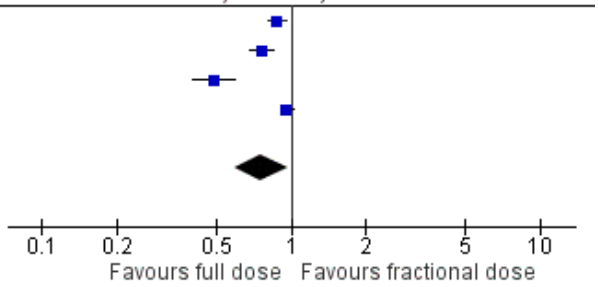
Heterogeneity: Tau² = 0.02; Chi² = 22.39, df = 2 (P < 0.0001); I² = 91%
Test for overall effect: Z = 1.48 (P = 0.14)



Two fractional doses compared to two full doses of IPV

Study or Subgroup	2 f-IPV Events	Total	2 IPV Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Anand 2015	135	164	152	162	25.8%	0.88 [0.81, 0.95]
Mohammed 2010	134	200	175	200	25.2%	0.77 [0.69, 0.86]
Resik 2010	81	235	165	236	22.9%	0.49 [0.41, 0.60]
Resik 2013	146	160	152	160	26.1%	0.96 [0.90, 1.02]
Total (95% CI)		**759**		**758**	**100.0%**	**0.76 [0.59, 0.98]**
Total events	496		644			

Heterogeneity: Tau² = 0.06; Chi² = 83.72, df = 3 (P < 0.00001); I² = 96%
Test for overall effect: Z = 2.13 (P = 0.03)



One fractional dose compared to one full dose of IPV

Study or Subgroup	1 f-IPV Events	Total	1 IPV Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Anand 2015	22	164	54	162	12.9%	0.40 [0.26, 0.63]
Clarke 2016	265	368	283	365	17.4%	0.93 [0.85, 1.01]
Estivariz 2012	23	34	35	39	15.7%	0.75 [0.58, 0.97]
Mohammed 2010	17	200	82	200	12.3%	0.21 [0.13, 0.34]
Resik 2010	14	235	75	236	11.4%	0.19 [0.11, 0.32]
Resik 2013	23	160	49	160	12.9%	0.47 [0.30, 0.73]
Resik 2015	348	496	120	124	17.5%	0.72 [0.68, 0.77]
Total (95% CI)		**1657**		**1286**	**100.0%**	**0.49 [0.36, 0.67]**
Total events	712		698			

Heterogeneity: Tau² = 0.14; Chi² = 125.25, df = 6 (P < 0.00001); I² = 95%
Test for overall effect: Z = 4.54 (P < 0.00001)

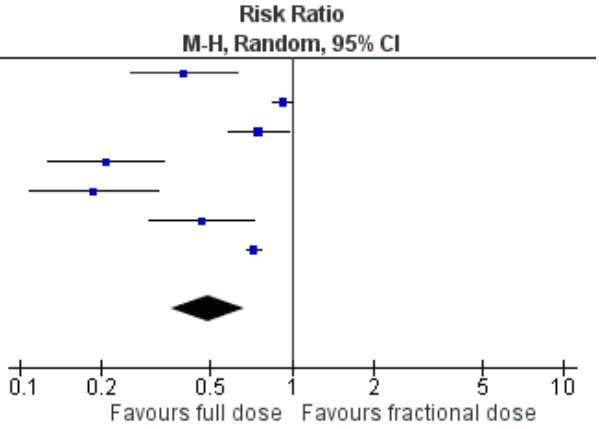
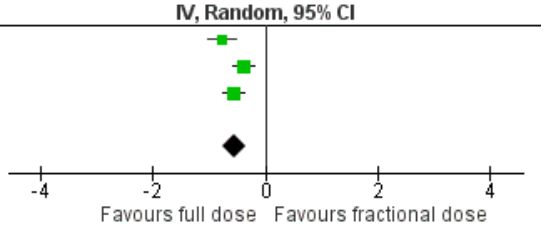


Figure 3. Meta-analysis of standard median antibody titres differences for poliovirus type 1 by number of doses

Three fractional doses compared to three full doses of IPV

Study or Subgroup	3 f-IPV Mean	SD	Total	3 IPV Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cadorna-Carlos 2012	221	196.7	118	585	631.8	118	28.0%	-0.78 [-1.04, -0.51]
Mohammed 2010	8	4.7	200	9.6	3.6	200	35.2%	-0.38 [-0.58, -0.18]
Resik 2010	11	7.8	235	74	156.8	236	36.8%	-0.57 [-0.75, -0.38]
Total (95% CI)			**553**			**554**	**100.0%**	**-0.56 [-0.77, -0.35]**

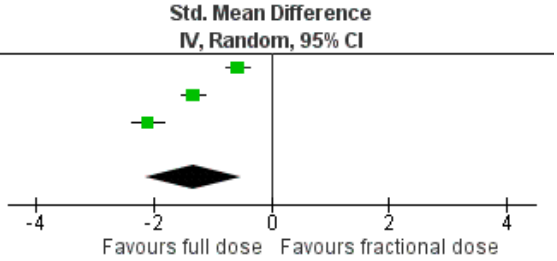
Heterogeneity: Tau² = 0.02; Chi² = 5.58, df = 2 (P = 0.06); I² = 64%
Test for overall effect: Z = 5.34 (P < 0.00001)



Two fractional doses compared two 2 full doses of IPV

Study or Subgroup	2 f-IPV Mean	SD	Total	2 IPV Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Mohammed 2010	5.1	6.5	200	8.1	3.6	200	33.5%	-0.57 [-0.77, -0.37]
Resik 2010	13	3.9	235	50	39.2	236	33.5%	-1.32 [-1.52, -1.13]
Resik 2013	450	674.4	160	1,448	0.3	160	32.9%	-2.09 [-2.36, -1.81]
Total (95% CI)			**595**			**596**	**100.0%**	**-1.32 [-2.13, -0.51]**

Heterogeneity: Tau² = 0.50; Chi² = 80.25, df = 2 (P < 0.00001); I² = 98%
Test for overall effect: Z = 3.21 (P = 0.001)



One fractional dose compared to one full dose of IPV

Study or Subgroup	1 f-IPV Mean	SD	Total	1 IPV Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Estivariz 2012	1,448	0.4	202	1,448	0.4	204	25.2%	0.00 [-0.19, 0.19]
Mohammed 2010	3	1.1	200	3.8	1.1	200	24.9%	-0.73 [-0.93, -0.52]
Resik 2010	8	3.9	235	11	7.8	236	25.4%	-0.49 [-0.67, -0.30]
Resik 2013	8	0.3	160	11	16.1	160	24.5%	-0.26 [-0.48, -0.04]
Total (95% CI)			**797**			**800**	**100.0%**	**-0.37 [-0.67, -0.06]**

Heterogeneity: Tau² = 0.09; Chi² = 28.20, df = 3 (P < 0.00001); I² = 89%
Test for overall effect: Z = 2.36 (P = 0.02)

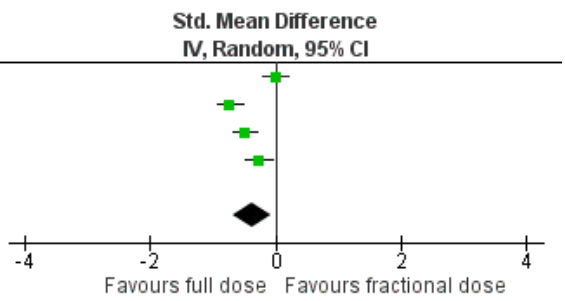
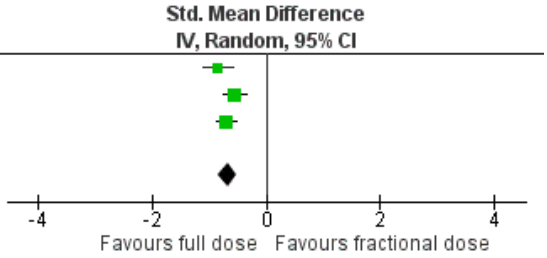


Figure 4. Meta-analysis of standard median antibody titres differences for poliovirus type 3 by number of doses

Three fractional doses compared to three full doses of IPV

Study or Subgroup	3 f-IPV Mean	3 f-IPV SD	3 f-IPV Total	3 IPV Mean	3 IPV SD	3 IPV Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cadorna-Carlos 2012	194	230	118	774	945	118	24.6%	-0.84 [-1.11, -0.57]
Mohammed 2010	8.6	3.6	200	10	0.4	200	36.1%	-0.55 [-0.75, -0.35]
Resik 2010	13	20	235	295	568.5	236	39.2%	-0.70 [-0.89, -0.51]
Total (95% CI)			**553**			**554**	**100.0%**	**-0.68 [-0.83, -0.52]**

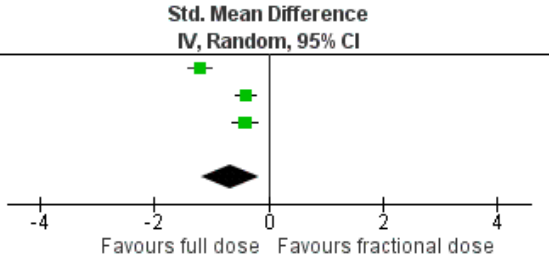
Heterogeneity: Tau² = 0.01; Chi² = 3.16, df = 2 (P = 0.21); I² = 37%
Test for overall effect: Z = 8.58 (P < 0.00001)



Three fractional doses compared to three full doses of IPV

Study or Subgroup	2 f-IPV Mean	2 f-IPV SD	2 f-IPV Total	2 IPV Mean	2 IPV SD	2 IPV Total	Weight	Std. Mean Difference IV, Random, 95% CI
Mohammed 2010	5	5.8	200	10	0.7	200	33.2%	-1.21 [-1.42, -0.99]
Resik 2010	13	3.9	235	140	450.7	236	33.7%	-0.40 [-0.58, -0.22]
Resik 2013	71	248.5	160	898	2,846	160	33.1%	-0.41 [-0.63, -0.19]
Total (95% CI)			**595**			**596**	**100.0%**	**-0.67 [-1.19, -0.15]**

Heterogeneity: Tau² = 0.20; Chi² = 38.23, df = 2 (P < 0.00001); I² = 95%
Test for overall effect: Z = 2.54 (P = 0.01)



Three fractional dose compared to three full dose of IPV

Study or Subgroup	1 f-IPV Mean	1 f-IPV SD	1 f-IPV Total	1 IPV Mean	1 IPV SD	1 IPV Total	Weight	Std. Mean Difference IV, Random, 95% CI
Estivariz 2012	202	2,523.5	202	455	2,656.2	204	25.1%	-0.10 [-0.29, 0.10]
Mohammed 2010	2.6	0.4	200	3.6	0.7	200	24.9%	-1.75 [-1.98, -1.52]
Resik 2010	8	3.9	235	9	3.9	236	25.1%	-0.26 [-0.44, -0.07]
Resik 2013	8	0.3	160	8	0.3	160	24.9%	0.00 [-0.22, 0.22]
Total (95% CI)			**797**			**800**	**100.0%**	**-0.52 [-1.26, 0.21]**

Heterogeneity: Tau² = 0.55; Chi² = 155.19, df = 3 (P < 0.00001); I² = 98%
Test for overall effect: Z = 1.39 (P = 0.16)

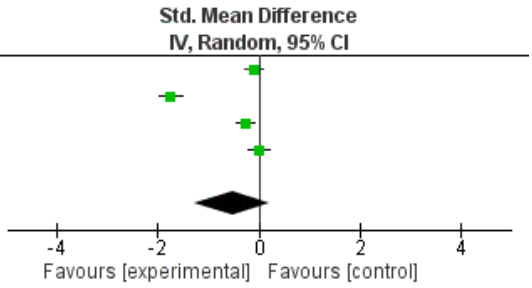


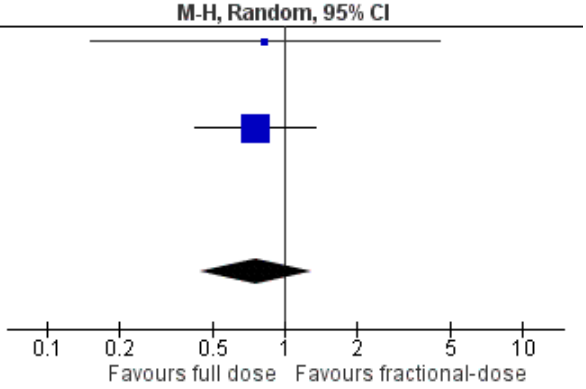
Figure 5. Analysis of adverse events

Serious adverse effects

5.1 Serious adverse effects

Study or Subgroup	f-IPV Events	f-IPV Total	IPV Events	IPV Total	Weight	Risk Ratio M-H, Random, 95% CI
Anand 2015	4	380	2	156	10.5%	0.82 [0.15, 4.44]
Cadorna-Carlos 2012	0	118	0	118		Not estimable
Clarke 2016	0	378	0	376		Not estimable
Mohammed 2010	18	200	24	200	89.5%	0.75 [0.42, 1.34]
Resik 2010	0	235	0	235		Not estimable
Resik 2013	0	160	0	160		Not estimable
Resik 2015	0	583	0	146		Not estimable
Total (95% CI)		**2054**		**1391**	**100.0%**	**0.76 [0.44, 1.31]**
Total events	22		26			

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 1.00 (P = 0.32)

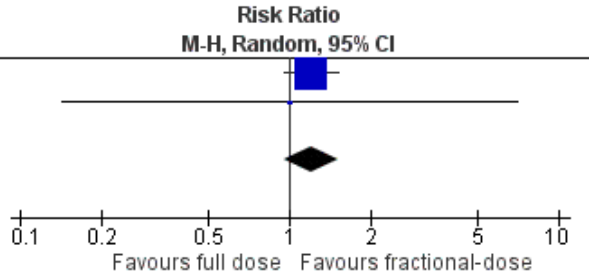


Local adverse events

5.2 Pain/tenderness

Study or Subgroup	f-IPV Events	f-IPV Total	IPV Events	IPV Total	Weight	Risk Ratio M-H, Random, 95% CI
Cadorna-Carlos 2012	71	118	59	118	98.6%	1.20 [0.95, 1.52]
Resik 2010	2	235	2	236	1.4%	1.00 [0.14, 7.07]
Total (95% CI)		**353**		**354**	**100.0%**	**1.20 [0.95, 1.51]**
Total events	73		61			

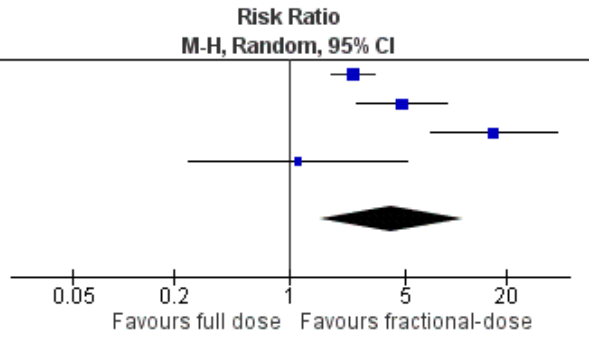
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%
Test for overall effect: Z = 1.55 (P = 0.12)



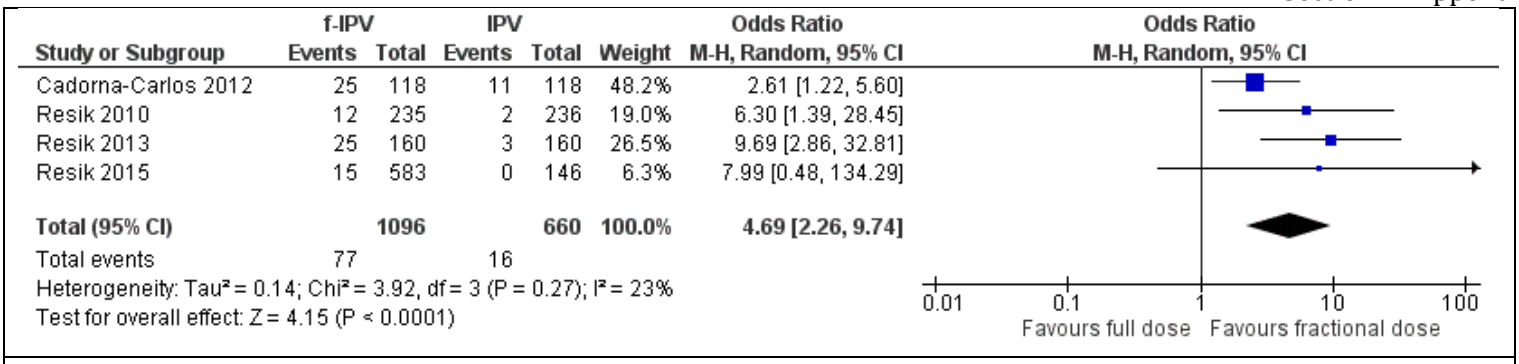
5.3 Redness/erythema

Study or Subgroup	f-IPV Events	f-IPV Total	IPV Events	IPV Total	Weight	Risk Ratio M-H, Random, 95% CI
Cadorna-Carlos 2012	82	118	34	118	29.9%	2.41 [1.77, 3.28]
Resik 2010	52	235	11	236	27.4%	4.75 [2.54, 8.87]
Resik 2013	84	160	5	160	24.8%	16.80 [7.00, 40.31]
Resik 2015	9	583	2	146	17.9%	1.13 [0.25, 5.16]
Total (95% CI)		**1096**		**660**	**100.0%**	**4.10 [1.52, 11.11]**
Total events	227		52			

Heterogeneity: Tau² = 0.84; Chi² = 24.90, df = 3 (P < 0.0001); I² = 88%
Test for overall effect: Z = 2.78 (P = 0.005)

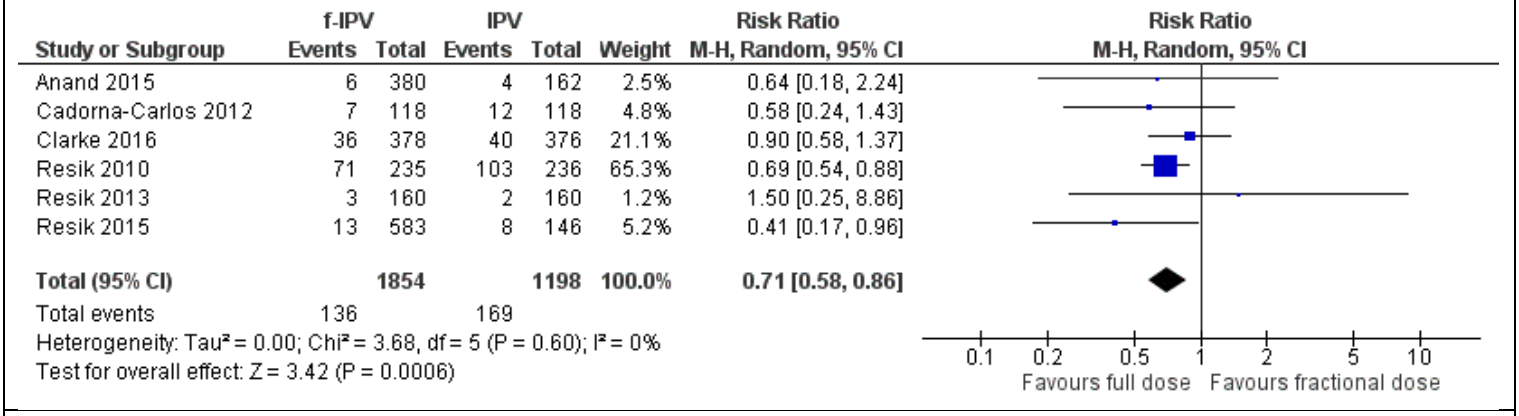


5.4 Swelling/induration

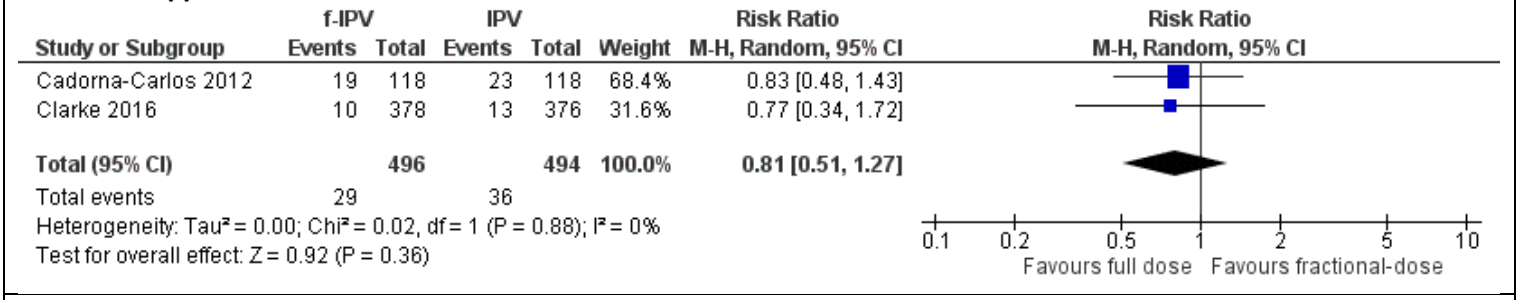


Systemic adverse events

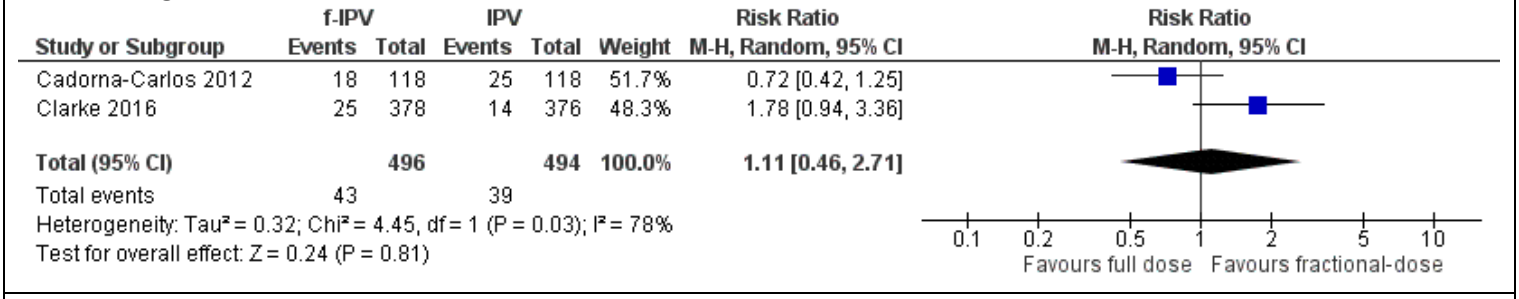
5.5 Fever



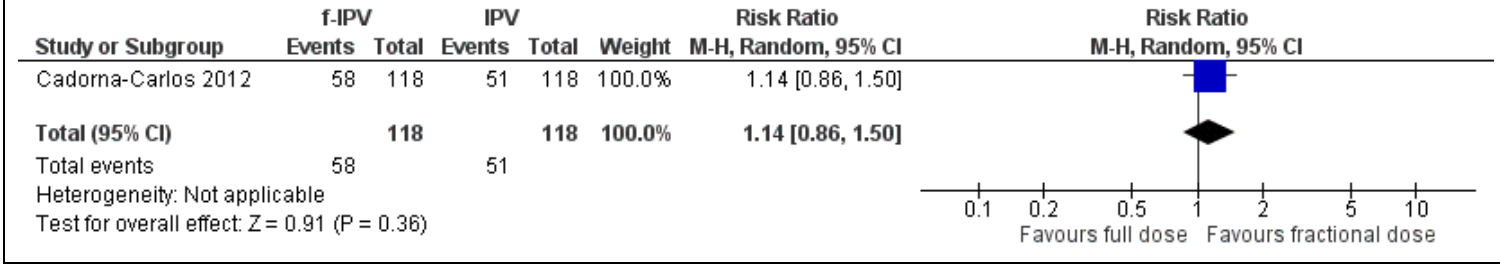
5.6 Loss of appetite



5.7 Vomiting



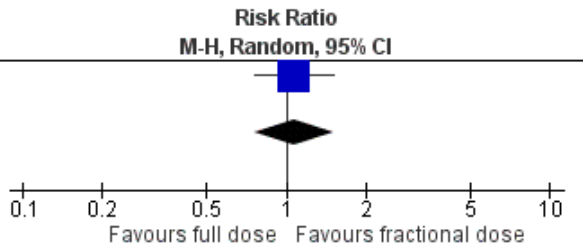
5.8 Irritability



5.9 Drowsiness

Study or Subgroup	f-IPV Events	f-IPV Total	IPV Events	IPV Total	Weight	Risk Ratio M-H, Random, 95% CI
Cadorna-Carlos 2012	44	118	41	118	100.0%	1.07 [0.76, 1.51]
Total (95% CI)		**118**		**118**	**100.0%**	**1.07 [0.76, 1.51]**
Total events	44		41			

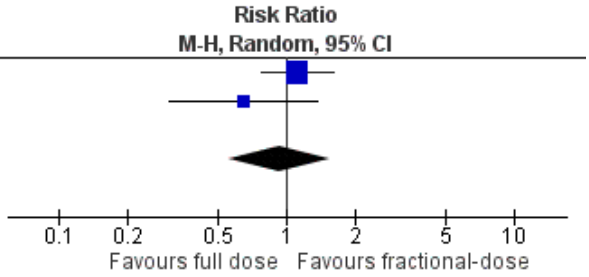
Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)



5.10 Excessive crying

Study or Subgroup	f-IPV Events	f-IPV Total	IPV Events	IPV Total	Weight	Risk Ratio M-H, Random, 95% CI
Cadorna-Carlos 2012	40	118	36	118	67.7%	1.11 [0.77, 1.61]
Clarke 2016	11	378	17	376	32.3%	0.64 [0.31, 1.36]
Total (95% CI)		**496**		**494**	**100.0%**	**0.93 [0.56, 1.55]**
Total events	51		53			

Heterogeneity: Tau² = 0.06; Chi² = 1.70, df = 1 (P = 0.19); I² = 41%
Test for overall effect: Z = 0.27 (P = 0.78)



5.11 Diarrhoea

Study or Subgroup	f-IPV Events	f-IPV Total	IPV Events	IPV Total	Weight	Risk Ratio M-H, Random, 95% CI
Anand 2015	4	380	2	162	4.9%	0.85 [0.16, 4.61]
Clarke 2016	47	378	45	376	95.1%	1.04 [0.71, 1.52]
Total (95% CI)		**758**		**538**	**100.0%**	**1.03 [0.71, 1.49]**
Total events	51		47			

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.15 (P = 0.88)

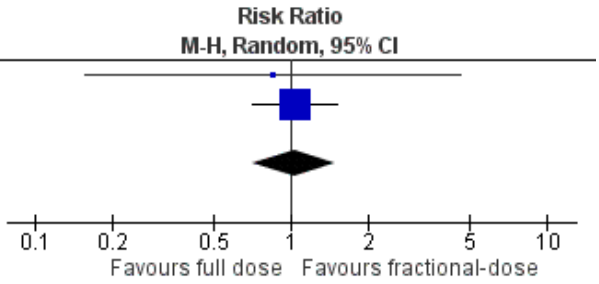
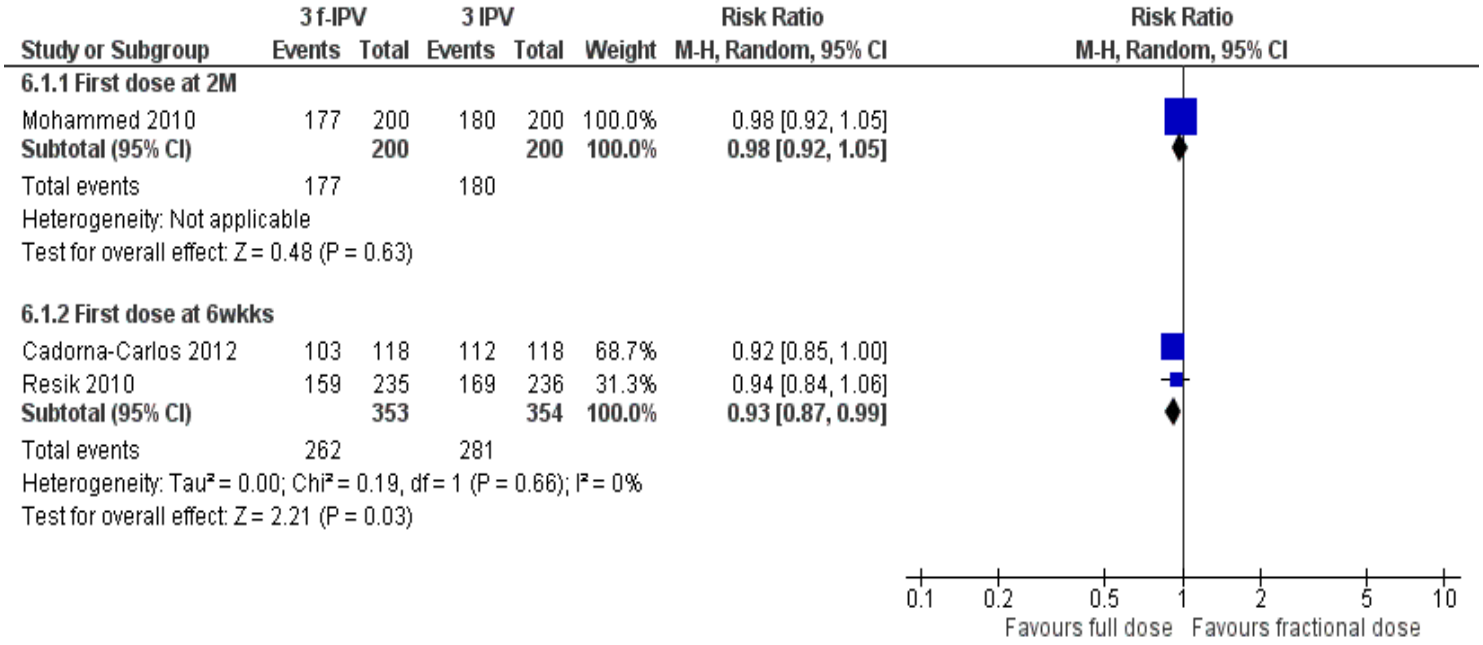


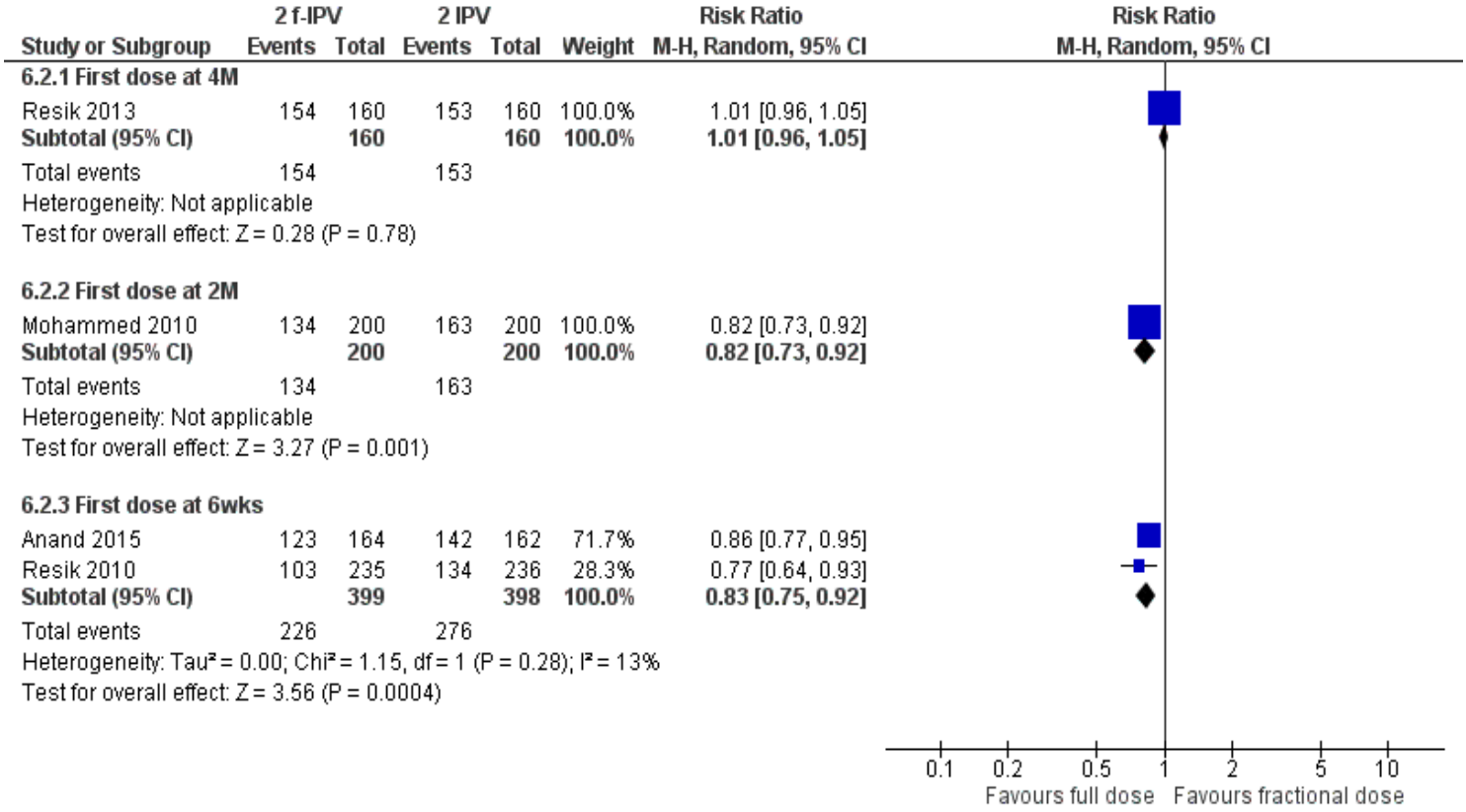
Table. 1 Description of severe adverse effects	
Mohammed et al. 2010[27]	Reported SAE we due to 42 hospitalisations: 18 were vaccinated with f-IPV and 24 were vaccinated with full dose IPV. 39 had diarrhoea and upper respiratory tract infections, 1 had anaemia, 2 were admitted after a fall and 5 of the 42 hospitalisations occurred before vaccination.
Anand et al. 2015[31]	3 infants died. 1 received f-IPV only and 2 received sequential f-IPV and bOPV. All deaths were investigated and were not related to IPV vaccination. The causes of death were Sudden infant death syndrome, pneumonia and infantile seizures. 1 infant who received sequential fractional-dose IPV only and bOPV had severe diarrhoea while the another 2 who received full dose IPV had severe meningitis and diarrhoea.
SAE= severe side effects, IPV = inactivated polio vaccine, f-IPV = fractional-dose, bOPV = bivalent OPV	

Figure 6. Subgroup analysis of seroconversion proportions for poliovirus type 2 by number of doses and timing of first dose

6.1. Three fractional doses compared to three full doses of IPV by timing of first dose



6.2. Two fractional doses compared to two full doses of IPV timing of first dose



6.3. One fractional dose compared to one full dose of IPV timing of first dose

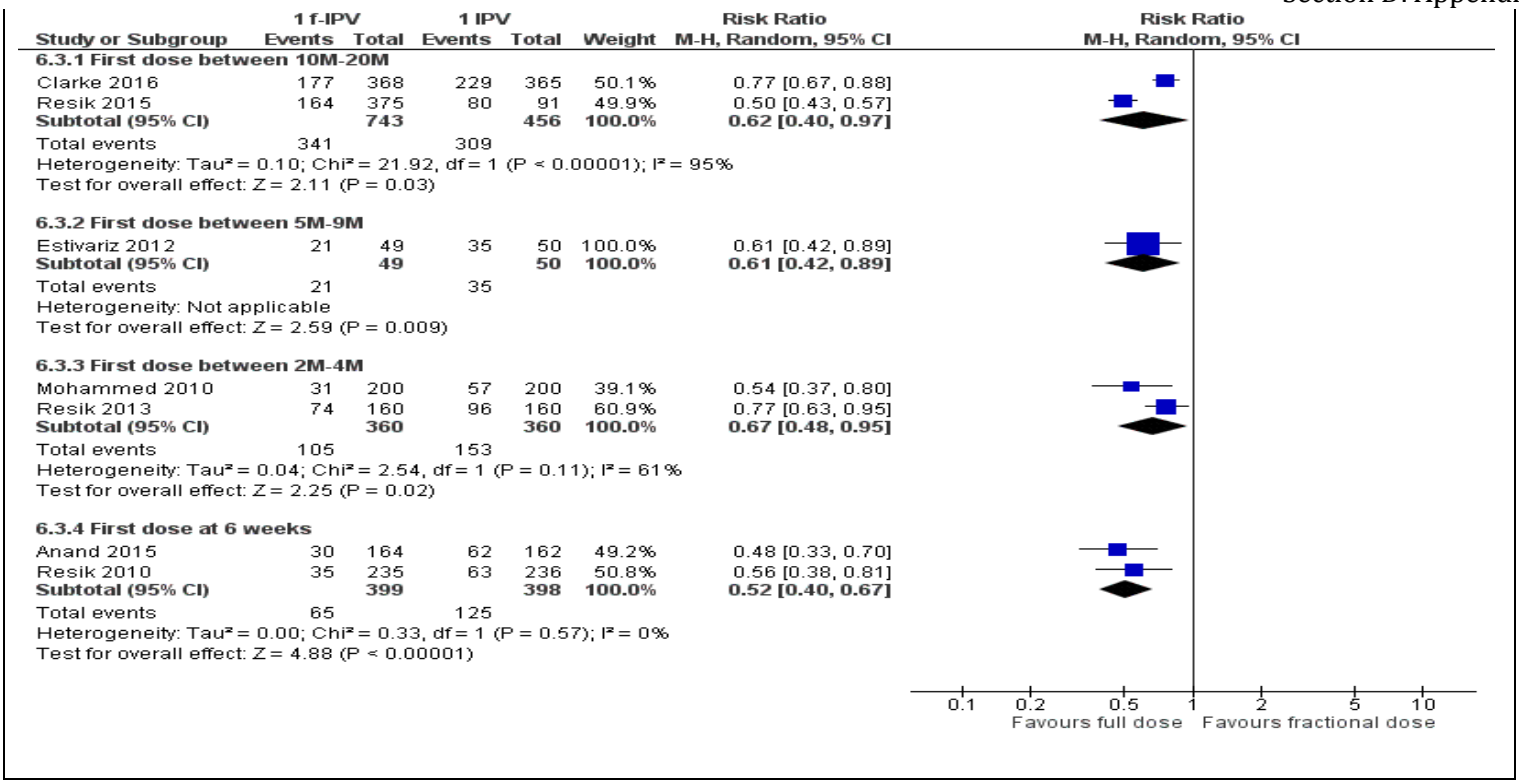
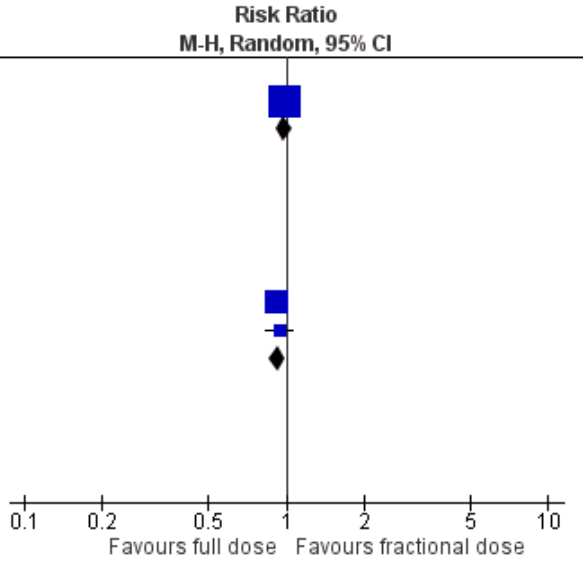

1 f-IPV
1 IPV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
6.3.1 First dose between 10M-20M
Clarke 2016 177 368 229 365 50.1% 0.77 [0.67, 0.88]
Resik 2015 164 375 80 91 49.9% 0.50 [0.43, 0.57]
Subtotal (95% CI) 743 456 100.0% 0.62 [0.40, 0.97]
Total events 341 309
Heterogeneity: Tau² = 0.10; Chi² = 21.92, df = 1 (P < 0.00001); I² = 95%
Test for overall effect: Z = 2.11 (P = 0.03)
6.3.2 First dose between 5M-9M
Estivariz 2012 21 49 35 50 100.0% 0.61 [0.42, 0.89]
Subtotal (95% CI) 49 50 100.0% 0.61 [0.42, 0.89]
Total events 21 35
Heterogeneity: Not applicable
Test for overall effect: Z = 2.59 (P = 0.009)
6.3.3 First dose between 2M-4M
Mohammed 2010 31 200 57 200 39.1% 0.54 [0.37, 0.80]
Resik 2013 74 160 96 160 60.9% 0.77 [0.63, 0.95]
Subtotal (95% CI) 360 360 100.0% 0.67 [0.48, 0.95]
Total events 105 153
Heterogeneity: Tau² = 0.04; Chi² = 2.54, df = 1 (P = 0.11); I² = 61%
Test for overall effect: Z = 2.25 (P = 0.02)
6.3.4 First dose at 6 weeks
Anand 2015 30 164 62 162 49.2% 0.48 [0.33, 0.70]
Resik 2010 35 235 63 236 50.8% 0.56 [0.38, 0.81]
Subtotal (95% CI) 399 398 100.0% 0.52 [0.40, 0.67]
Total events 65 125
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 4.88 (P < 0.00001)
0.1
0.2
0.5
1
2
5
10
Favours full dose
Favours fractional dose

Figure 7. Subgroup analysis of seroconversion proportions for poliovirus type 2 by number of doses and interval between 2 doses

Three fractional doses compared to three full doses of IPV by interval between 2 doses

Study or Subgroup	3 f-IPV Events	Total	3 IPV Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
7.1.1 Interval between 2 doses: 2M						
Mohammed 2010	177	200	180	200	100.0%	0.98 [0.92, 1.05]
Subtotal (95% CI)		**200**		**200**	**100.0%**	**0.98 [0.92, 1.05]**
Total events	177		180			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (P = 0.63)						
7.1.2 Interval between 2 doses: 4wks						
Cadorna-Carlos 2012	103	118	112	118	68.7%	0.92 [0.85, 1.00]
Resik 2010	159	235	169	236	31.3%	0.94 [0.84, 1.06]
Subtotal (95% CI)		**353**		**354**	**100.0%**	**0.93 [0.87, 0.99]**
Total events	262		281			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.19$, df = 1 (P = 0.66); $I^2 = 0\%$						
Test for overall effect: Z = 2.21 (P = 0.03)						



Two fractional doses compared to two full doses of IPV by interval between 2 doses

Study or Subgroup	2 f-IPV Events	Total	2 IPV Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
7.2.1 Interval between doses - 4M						
Resik 2013	154	160	153	160	100.0%	1.01 [0.96, 1.05]
Subtotal (95% CI)		**160**		**160**	**100.0%**	**1.01 [0.96, 1.05]**
Total events	154		153			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.28 (P = 0.78)						
7.2.2 Interval between doses - 2M						
Anand 2015	123	164	142	162	55.4%	0.86 [0.77, 0.95]
Mohammed 2010	134	200	163	200	44.6%	0.82 [0.73, 0.92]
Subtotal (95% CI)		**364**		**362**	**100.0%**	**0.84 [0.78, 0.91]**
Total events	257		305			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.25$, df = 1 (P = 0.62); $I^2 = 0\%$						
Test for overall effect: Z = 4.34 (P < 0.0001)						
7.2.3 Interval between doses - 4wks						
Resik 2010	103	235	134	236	100.0%	0.77 [0.64, 0.93]
Subtotal (95% CI)		**235**		**236**	**100.0%**	**0.77 [0.64, 0.93]**
Total events	103		134			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.78 (P = 0.005)						

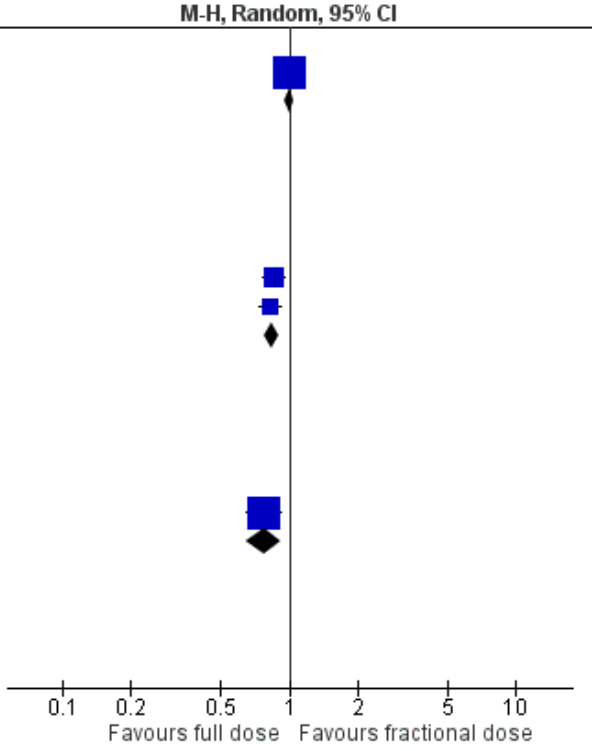
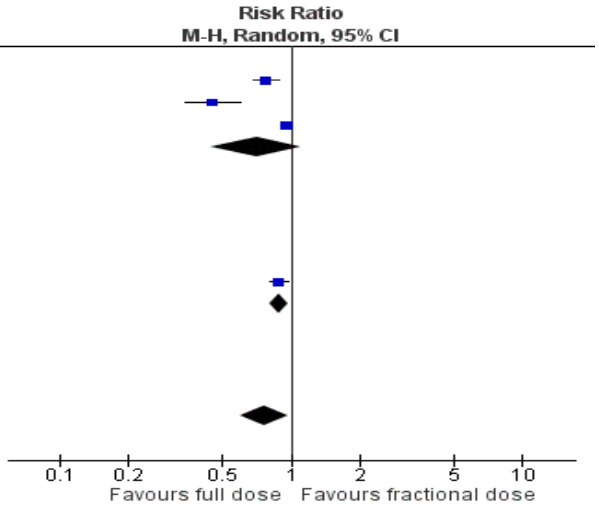


Figure 8. Subgroup analysis of seroconversion after 2 fractional doses compared to 2 full doses of IPV per poliovirus type by intradermal devices

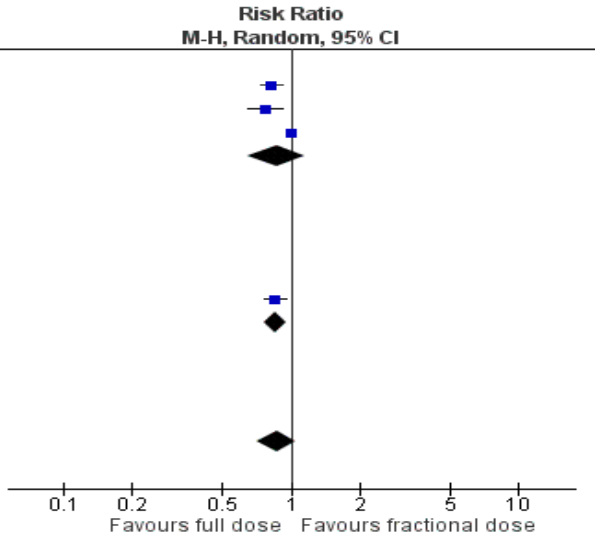
Poliovirus type 1 by intradermal device

Study or Subgroup	2 f-IPV Events	2 f-IPV Total	2 IPV Events	2 IPV Total	Weight	Risk Ratio M-H, Random, 95% CI
8.1.1 Biojector 2000						
Mohammed 2010	129	200	165	200	25.9%	0.78 [0.69, 0.88]
Resik 2010	51	235	112	236	20.2%	0.46 [0.35, 0.60]
Resik 2013	147	160	153	160	27.2%	0.96 [0.91, 1.02]
Subtotal (95% CI)		**595**		**596**	**73.3%**	**0.71 [0.46, 1.11]**
Total events	327		430			
Heterogeneity: Tau² = 0.15; Chi² = 77.84, df = 2 (P < 0.00001); I² = 97%						
Test for overall effect: Z = 1.49 (P = 0.14)						
8.1.2 Micronjet 600						
Anand 2015	133	164	148	162	26.7%	0.89 [0.81, 0.97]
Subtotal (95% CI)		**164**		**162**	**26.7%**	**0.89 [0.81, 0.97]**
Total events	133		148			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.66 (P = 0.008)						
Total (95% CI)		**759**		**758**	**100.0%**	**0.77 [0.60, 0.98]**
Total events	460		578			
Heterogeneity: Tau² = 0.05; Chi² = 64.99, df = 3 (P < 0.00001); I² = 95%						
Test for overall effect: Z = 2.15 (P = 0.03)						
Test for subgroup differences: Chi² = 0.90, df = 1 (P = 0.34), I² = 0%						



Poliovirus type 2 by intradermal device

Study or Subgroup	2 f-IPV Events	2 f-IPV Total	2 IPV Events	2 IPV Total	Weight	Risk Ratio M-H, Random, 95% CI
8.2.1 Biojector 2000						
Mohammed 2010	134	200	163	200	25.1%	0.82 [0.73, 0.92]
Resik 2010	103	235	134	236	22.2%	0.77 [0.64, 0.93]
Resik 2013	154	160	153	160	27.2%	1.01 [0.96, 1.05]
Subtotal (95% CI)		**595**		**596**	**74.5%**	**0.87 [0.65, 1.15]**
Total events	391		450			
Heterogeneity: Tau² = 0.06; Chi² = 42.72, df = 2 (P < 0.00001); I² = 95%						
Test for overall effect: Z = 0.99 (P = 0.32)						
8.2.2 Micronjet 600						
Anand 2015	123	164	142	162	25.5%	0.86 [0.77, 0.95]
Subtotal (95% CI)		**164**		**162**	**25.5%**	**0.86 [0.77, 0.95]**
Total events	123		142			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.89 (P = 0.004)						
Total (95% CI)		**759**		**758**	**100.0%**	**0.87 [0.71, 1.05]**
Total events	514		592			
Heterogeneity: Tau² = 0.04; Chi² = 44.76, df = 3 (P < 0.00001); I² = 93%						
Test for overall effect: Z = 1.47 (P = 0.14)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%						



Poliovirus type 3 by intradermal device

Study or Subgroup	2 f-IPV Events	2 f-IPV Total	2 IPV Events	2 IPV Total	Weight	Risk Ratio M-H, Random, 95% CI
8.3.1 Biojector 2000						
Mohammed 2010	134	200	175	200	25.2%	0.77 [0.69, 0.86]
Resik 2010	81	235	165	236	22.9%	0.49 [0.41, 0.60]
Resik 2013	146	160	152	160	26.1%	0.96 [0.90, 1.02]
Subtotal (95% CI)		**595**		**596**	**74.2%**	**0.72 [0.46, 1.11]**
Total events	361		492			
Heterogeneity: Tau² = 0.14; Chi² = 94.04, df = 2 (P < 0.00001); I² = 98%						
Test for overall effect: Z = 1.49 (P = 0.14)						
8.3.2 Micronjet 600						
Anand 2015	135	164	152	162	25.8%	0.88 [0.81, 0.95]
Subtotal (95% CI)		**164**		**162**	**25.8%**	**0.88 [0.81, 0.95]**
Total events	135		152			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.16 (P = 0.002)						
Total (95% CI)		**759**		**758**	**100.0%**	**0.76 [0.59, 0.98]**
Total events	496		644			
Heterogeneity: Tau² = 0.06; Chi² = 83.72, df = 3 (P < 0.00001); I² = 96%						
Test for overall effect: Z = 2.13 (P = 0.03)						
Test for subgroup differences: Chi² = 0.79, df = 1 (P = 0.38), I² = 0%						

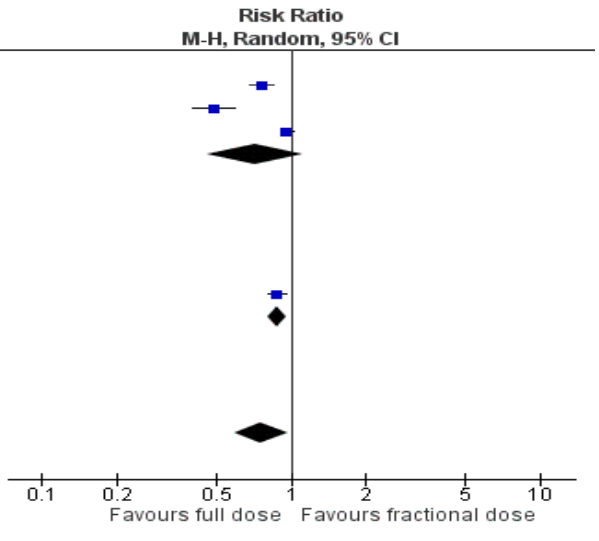
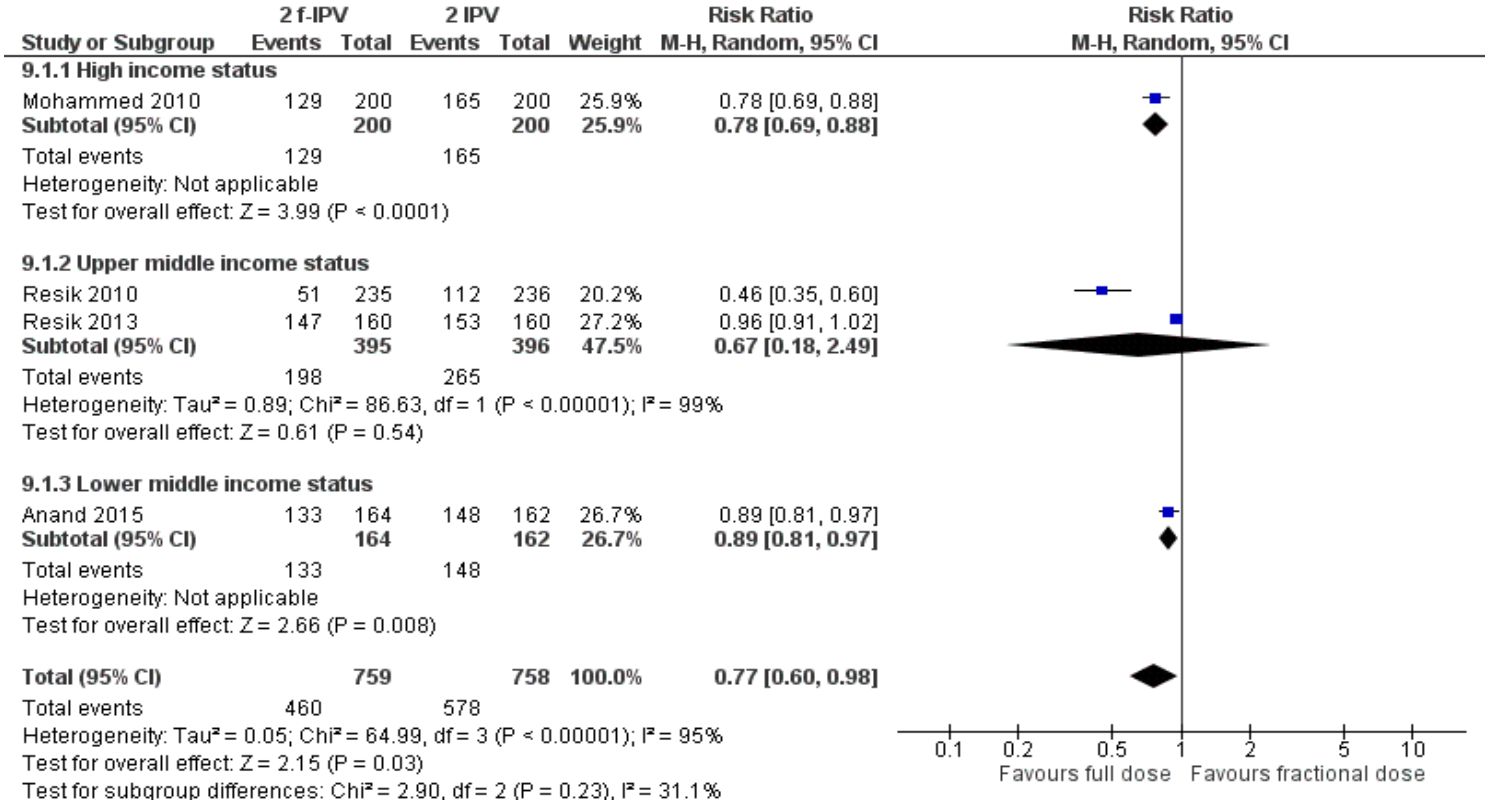
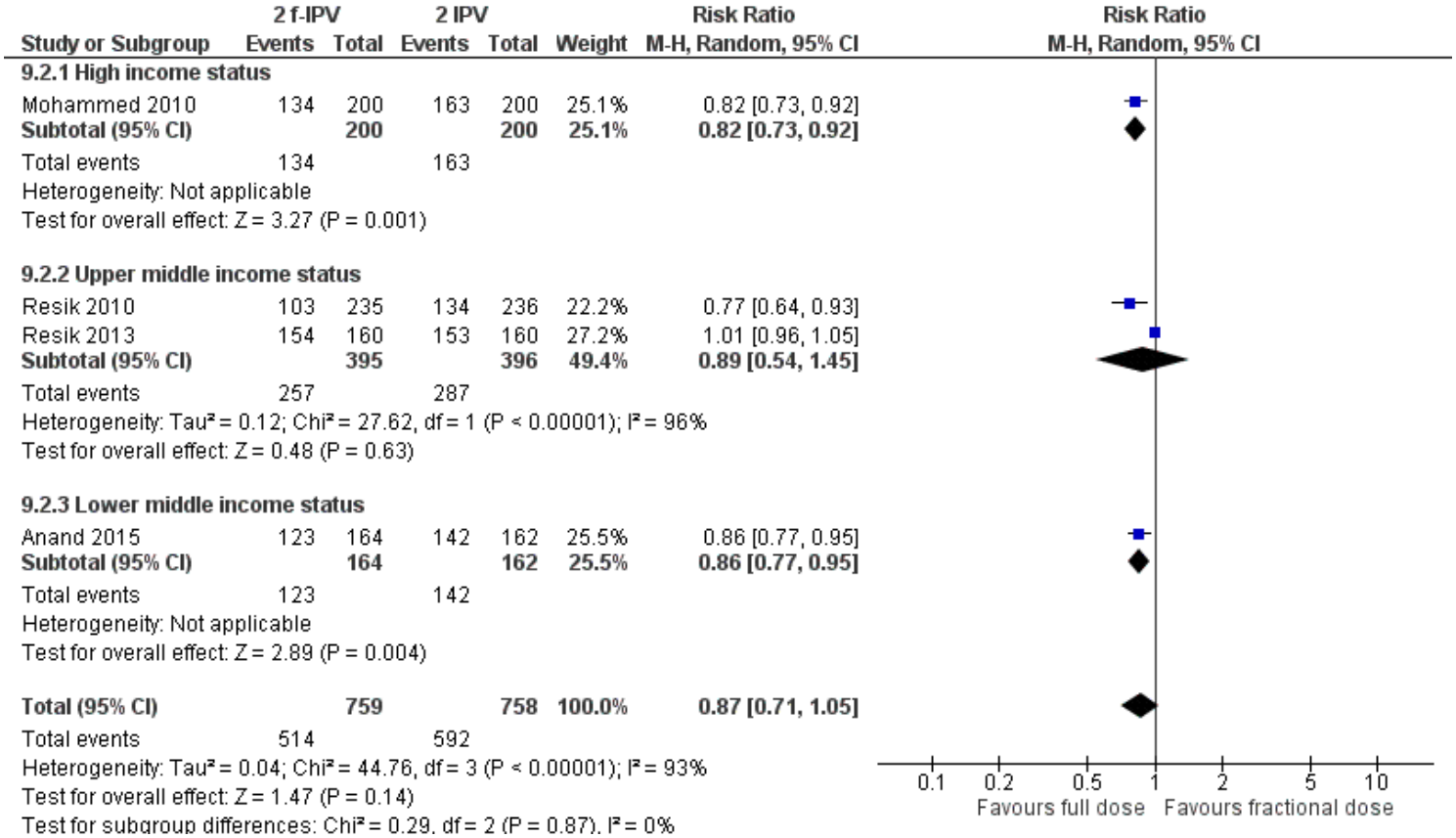


Figure 9. Subgroup analysis of seroconversion after 2 fractional doses compared to 2 full doses of IPV per poliovirus type by country income status

Poliovirus type 1 by country income status



Poliovirus type 2 by country income status



Poliovirus type 3 by country income status

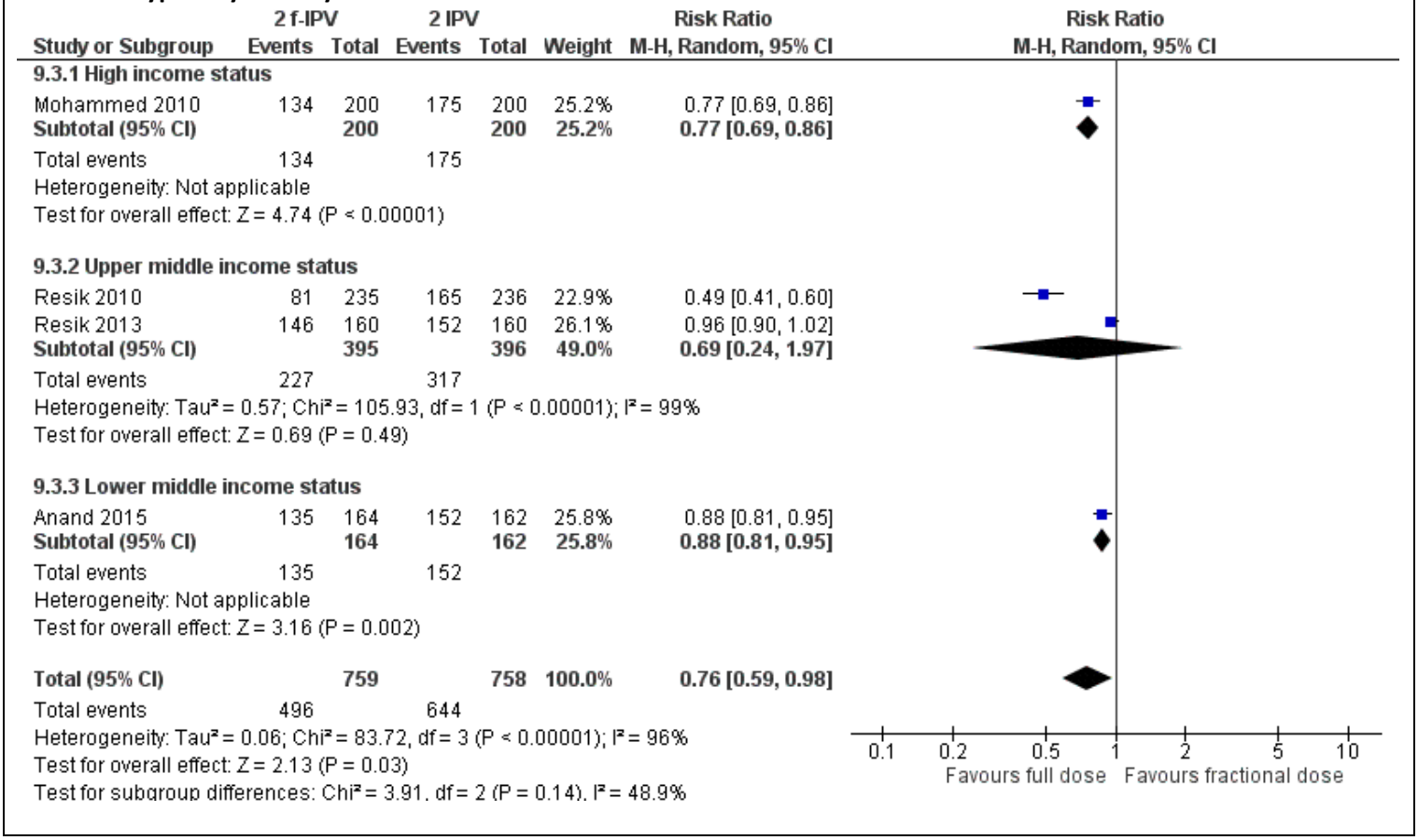
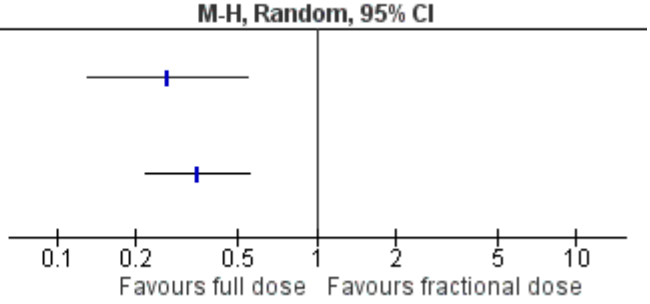


Figure 10. Subgroup analysis of seroconversion after 1 fractional dose compared to 1 full dose of IPV per poliovirus type by ID devices at 6 weeks

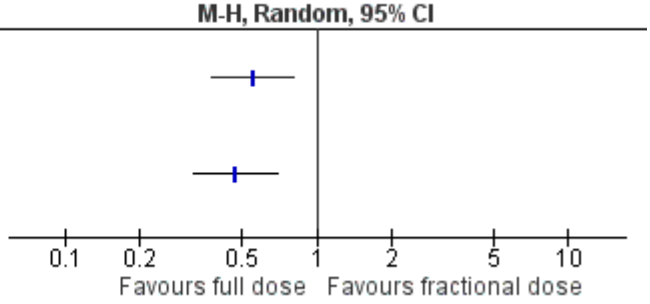
Poliovirus type 1 by ID device at 6 weeks

Study or Subgroup	1 f-IPV Events	Total	1 IPV Events	Total	Risk Ratio M-H, Random, 95% CI
10.1.1 Biojector					
Resik 2010	9	235	34	236	0.27 [0.13, 0.54]
10.1.2 Microinjection					
Anand 2015	20	164	57	162	0.35 [0.22, 0.55]



Poliovirus type 2 by ID device at 6 weeks

Study or Subgroup	1 f-IPV Events	Total	1 IPV Events	Total	Risk Ratio M-H, Random, 95% CI
10.2.1 Biojector					
Resik 2010	35	235	63	236	0.56 [0.38, 0.81]
10.2.2 Microinjection					
Anand 2015	30	164	62	162	0.48 [0.33, 0.70]



Poliovirus type 3 by ID device at 6 weeks

Study or Subgroup	1 f-IPV Events	Total	1 IPV Events	Total	Risk Ratio M-H, Random, 95% CI
10.3.1 Biojector					
Resik 2010	14	235	75	236	0.19 [0.11, 0.32]
10.3.2 Microinjection					
Anand 2015	22	164	54	162	0.40 [0.26, 0.63]

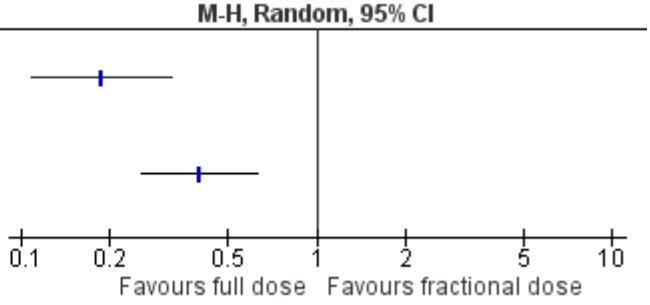
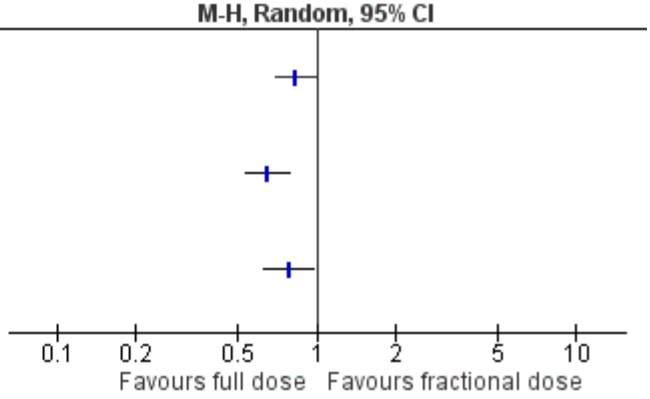


Figure 11. Sub group analysis of seroconversion after 1 fractional dose compared to 1 full dose of IPV per poliovirus type by ID devices at 10-12M

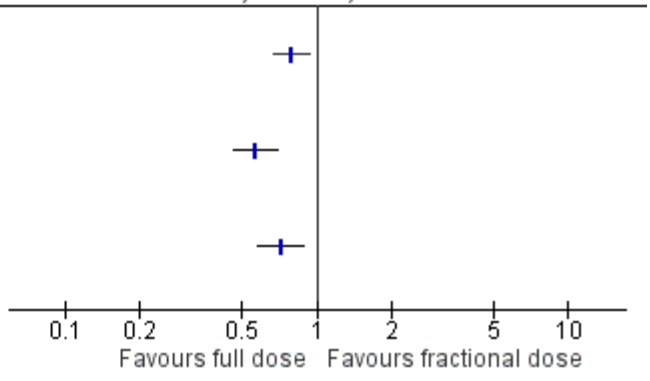
Poliovirus type 1 by ID device at 10-12M

Study or Subgroup	1 f-IPV Events	Total	1 IPV Events	Total	Risk Ratio M-H, Random, 95% CI
11.1.1 f-IPV needle and syringe vs full dose needle and syringe					
Clarke 2016	99	184	119	184	0.83 [0.70, 0.99]
11.1.2 f-IPV Tropis vs full dose needle and syringe					
Clarke 2016	77	184	119	184	0.65 [0.53, 0.79]
11.1.3 f-IPV Tropis vs f-IPV needle and syringe					
Clarke 2016	77	184	99	184	0.78 [0.63, 0.97]



Poliovirus type 2 by ID device at 10-12M

Study or Subgroup	1 f-IPV Events	Total	1 IPV Events	Total	Risk Ratio M-H, Random, 95% CI
11.2.1 f-IPV needle and syringe vs full dose needle and syringe					
Clarke 2016	103	184	129	184	0.80 [0.68, 0.94]
11.2.2 f-IPV Tropis vs full dose needle and syringe					
Clarke 2016	74	184	129	184	0.57 [0.47, 0.70]
11.2.3 f-IPV Tropis vs f-IPV needle and syringe					
Clarke 2016	74	184	103	184	0.72 [0.58, 0.89]



Poliovirus type 3 by ID device at 10-12M

Study or Subgroup	1 f-IPV Events	Total	1 IPV Events	Total	Risk Ratio M-H, Random, 95% CI
11.3.1 f-IPV needle and syringe vs full dose needle and syringe					
Clarke 2016	142	184	147	184	0.97 [0.87, 1.07]
11.3.2 f-IPV Tropis vs full dose needle and syringe					
Clarke 2016	123	184	147	178	0.81 [0.72, 0.91]
11.3.3 f-IPV Tropis vs f-IPV needle and syringe					
Clarke 2016	123	184	142	184	0.87 [0.76, 0.99]

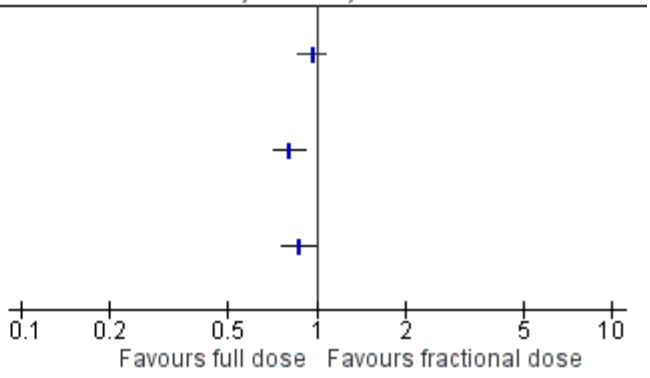
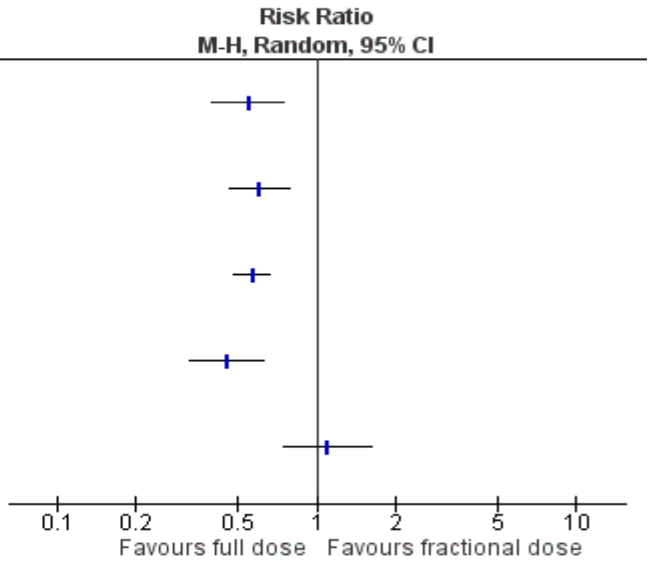


Figure 12. Sub group analysis of seroconversion after 1 fractional dose compared to 1 full dose of IPV per poliovirus type by ID devices at 12-20M

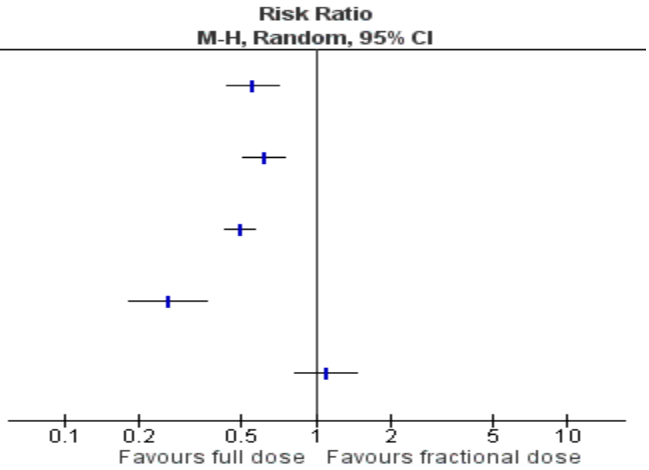
Poliovirus type 1 by ID device at 12-20M

Study or Subgroup	1 f-IPV Events	1 f-IPV Total	1 IPV Events	1 IPV Total	Risk Ratio M-H, Random, 95% CI
12.1.1 f-IPV needle and syringe vs full dose needle and syringe					
Resik 2015	21	43	51	57	0.55 [0.40, 0.75]
12.1.2 f-IPV Tropis vs full dose needle and syringe					
Resik 2015	28	52	51	57	0.60 [0.46, 0.79]
12.1.3 f-IPV Biojector 2000 vs full dose needle and syringe					
Resik 2015	104	206	51	57	0.56 [0.48, 0.66]
12.1.4 f-IPV ID Pen vs full dose needle and syringe					
Resik 2015	23	57	51	57	0.45 [0.32, 0.63]
12.1.5 f-IPV Tropis vs f-IPV NS					
Resik 2015	28	52	21	43	1.10 [0.74, 1.64]



Poliovirus type 2 by ID device at 12-20M

Study or Subgroup	1 f-IPV Events	1 f-IPV Total	1 IPV Events	1 IPV Total	Risk Ratio M-H, Random, 95% CI
12.2.1 f-IPV needle and syringe vs full dose needle and syringe					
Resik 2015	40	81	80	91	0.56 [0.44, 0.71]
12.2.2 f-IPV Tropis vs full dose needle and syringe					
Resik 2015	55	101	80	91	0.62 [0.51, 0.75]
12.2.3 f-IPV Biojector 2000 vs full dose needle and syringe					
Resik 2015	164	375	80	91	0.50 [0.43, 0.57]
12.2.4 f-IPV ID Pen vs full dose needle and syringe					
Resik 2015	24	106	80	91	0.26 [0.18, 0.37]
12.2.5 f-IPV Tropis vs f-IPV NS					
Resik 2015	55	101	40	81	1.10 [0.83, 1.46]



Poliovirus type 3 by ID device at 12-20M

Study or Subgroup	1 f-IPV Events	1 f-IPV Total	1 IPV Events	1 IPV Total	Risk Ratio M-H, Random, 95% CI
12.3.1 f-IPV needle and syringe vs full dose needle and syringe NS vs NS					
Resik 2015	93	118	120	124	0.81 [0.74, 0.90]
12.3.2 f-IPV Tropis vs full dose needle and syringeNS					
Resik 2015	98	132	120	124	0.77 [0.69, 0.85]
12.3.3 f-IPV Biojector 2000 vs full dose needle and syringe vs NS					
Resik 2015	348	496	120	124	0.72 [0.68, 0.77]
12.3.4 f-IPV ID Pen vs full dose needle and syringe vs NS					
Resik 2015	54	121	120	124	0.46 [0.38, 0.56]
12.3.5 f-IPV Tropis vs f-IPV NS					
Resik 2015	98	132	93	118	0.94 [0.82, 1.08]

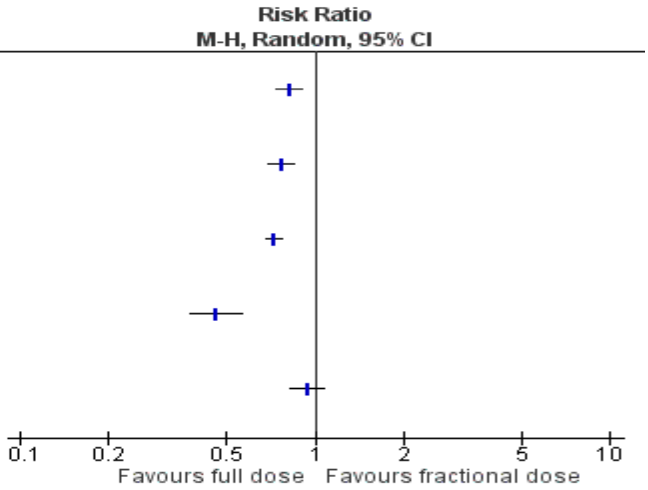
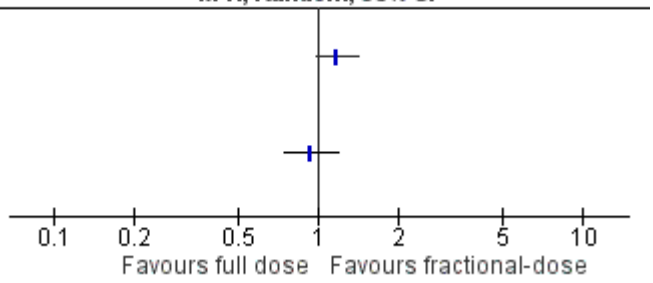


Figure 13. Meta-analysis of poliovirus shedding after OPV challenge by timing of outcome measurements f-IPV only

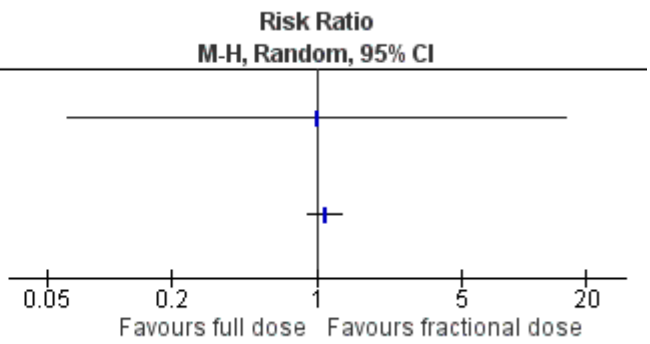
Poliovirus type 1

Study or Subgroup	f-IPV Events	f-IPV Total	IPV Events	IPV Total	Risk Ratio M-H, Random, 95% CI
13.1.1 At 7 months					
Mohammed 2010	116	200	99	200	1.17 [0.98, 1.41]
13.1.2 At 18 weeks					
Anand 2015	73	164	77	162	0.94 [0.74, 1.18]



Poliovirus type 2

Study or Subgroup	f-IPV Events	f-IPV Total	IPV Events	IPV Total	Risk Ratio M-H, Random, 95% CI
13.2.1 At 7 months					
Mohammed 2010	1	200	1	200	1.00 [0.06, 15.88]
13.2.2 At 18 weeks					
Anand 2015	99	164	89	162	1.10 [0.91, 1.32]



Poliovirus type 3

Study or Subgroup	f-IPV Events	f-IPV Total	IPV Events	IPV Total	Risk Ratio M-H, Random, 95% CI
13.3.1 At 7 months					
Mohammed 2010	1	200	0	200	3.00 [0.12, 73.20]
13.3.2 At 18 weeks					
Anand 2015	64	164	50	162	1.26 [0.94, 1.71]

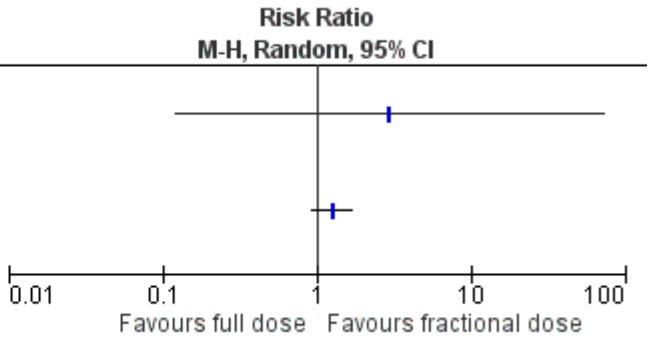
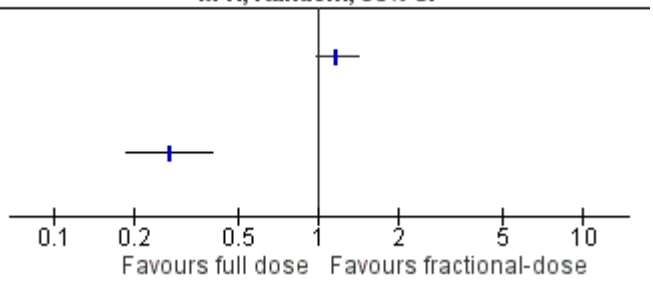


Figure 14. Meta-analysis of poliovirus shedding after OPV challenge by timing of outcome measurements f-IPV/bOPV

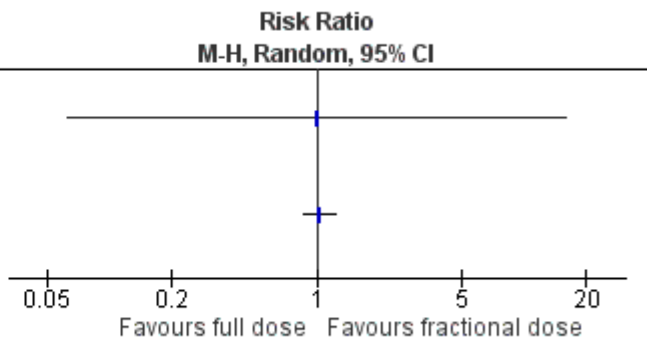
Poliovirus type 1

Study or Subgroup	f-IPV Events	f-IPV Total	IPV Events	IPV Total	Risk Ratio M-H, Random, 95% CI
14.1.1 At 7 months					
Mohammed 2010	116	200	99	200	1.17 [0.98, 1.41]
14.1.2 At 18 weeks					
Anand 2015	28	216	77	162	0.27 [0.19, 0.40]



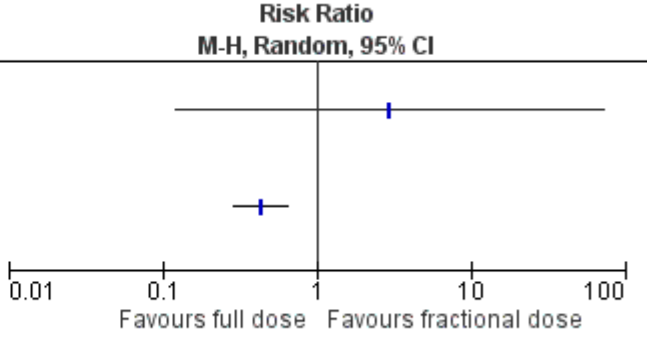
Poliovirus type 2

Study or Subgroup	f-IPV Events	f-IPV Total	IPV Events	IPV Total	Risk Ratio M-H, Random, 95% CI
14.2.1 At 7 months					
Mohammed 2010	1	200	1	200	1.00 [0.06, 15.88]
14.2.2 At 18 weeks					
Anand 2015	122	216	89	162	1.03 [0.86, 1.23]



Poliovirus type 3

Study or Subgroup	f-IPV Events	f-IPV Total	IPV Events	IPV Total	Risk Ratio M-H, Random, 95% CI
14.3.1 At 7 months					
Mohammed 2010	1	200	0	200	3.00 [0.12, 73.20]
14.3.2 At 18 weeks					
Anand 2015	29	216	50	162	0.43 [0.29, 0.66]



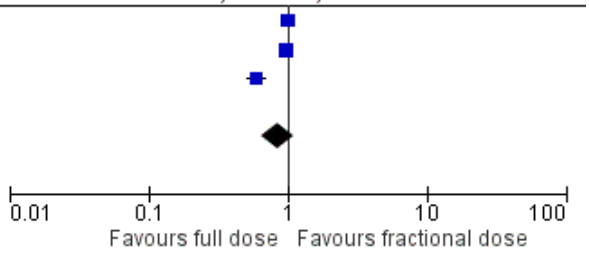
Missing data excluded in the analysis/ according to author's analysis

Figure 15. Meta-analysis of seroconversion after 3 fractional doses compared to 3 full doses of IPV per poliovirus type

Poliovirus type 1

Study or Subgroup	3 f-IPV Events	3 f-IPV Total	3 IPV Events	3 IPV Total	Weight	Risk Ratio M-H, Random, 95% CI
Cadorna-Carlos 2012	108	109	112	114	34.4%	1.01 [0.98, 1.04]
Mohammed 2010	179	184	182	182	34.4%	0.97 [0.95, 1.00]
Resik 2010	99	187	158	177	31.2%	0.59 [0.51, 0.69]
Total (95% CI)		**480**		**473**	**100.0%**	**0.84 [0.65, 1.10]**
Total events	386		452			

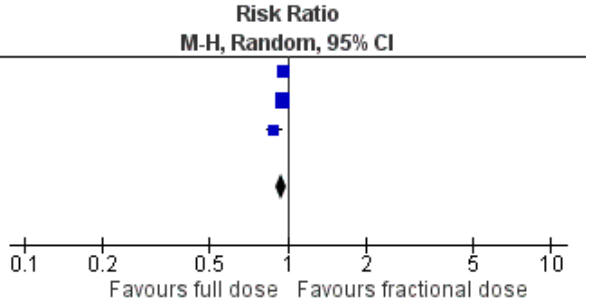
Heterogeneity: Tau² = 0.05; Chi² = 259.06, df = 2 (P < 0.00001); I² = 99%
Test for overall effect: Z = 1.27 (P = 0.20)



Poliovirus type 2

Study or Subgroup	3 f-IPV Events	3 f-IPV Total	3 IPV Events	3 IPV Total	Weight	Risk Ratio M-H, Random, 95% CI
Cadorna-Carlos 2012	103	109	112	114	32.4%	0.96 [0.91, 1.01]
Mohammed 2010	177	185	180	180	42.6%	0.96 [0.93, 0.99]
Resik 2010	159	187	169	177	25.0%	0.89 [0.83, 0.95]
Total (95% CI)		**481**		**471**	**100.0%**	**0.94 [0.90, 0.99]**
Total events	439		461			

Heterogeneity: Tau² = 0.00; Chi² = 5.42, df = 2 (P = 0.07); I² = 63%
Test for overall effect: Z = 2.53 (P = 0.01)



Poliovirus type 3

Study or Subgroup	3 f-IPV Events	3 f-IPV Total	3 IPV Events	3 IPV Total	Weight	Risk Ratio M-H, Random, 95% CI
Cadorna-Carlos 2012	104	109	114	114	33.8%	0.95 [0.91, 1.00]
Mohammed 2010	182	186	183	183	34.1%	0.98 [0.96, 1.00]
Resik 2010	129	187	175	177	32.1%	0.70 [0.63, 0.77]
Total (95% CI)		**482**		**474**	**100.0%**	**0.87 [0.70, 1.09]**
Total events	415		472			

Heterogeneity: Tau² = 0.04; Chi² = 137.00, df = 2 (P < 0.00001); I² = 99%
Test for overall effect: Z = 1.23 (P = 0.22)

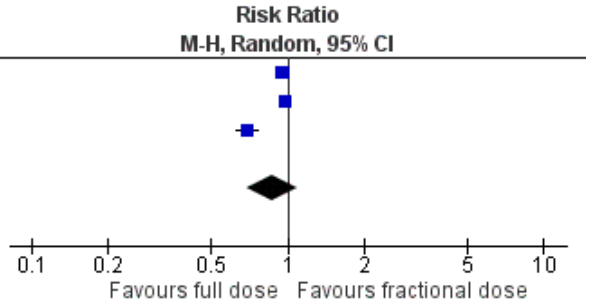
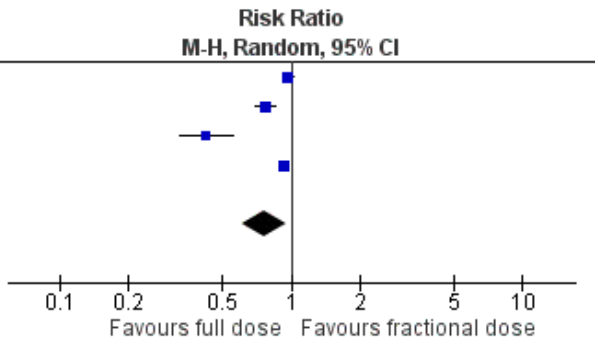


Figure 16. Meta-analysis of seroconversion after 2 fractional doses compared to 2 full doses of IPV per poliovirus type

Poliovirus type 1

Study or Subgroup	2 f-IPV Events	2 f-IPV Total	2 IPV Events	2 IPV Total	Weight	Risk Ratio M-H, Random, 95% CI
Anand 2015	335	363	148	156	27.1%	0.97 [0.93, 1.02]
Mohammed 2010	129	184	165	182	25.8%	0.77 [0.70, 0.86]
Resik 2010	51	187	112	177	19.9%	0.43 [0.33, 0.56]
Resik 2013	147	157	153	153	27.1%	0.94 [0.90, 0.98]
Total (95% CI)		**891**		**668**	**100.0%**	**0.77 [0.62, 0.96]**
Total events	662		578			

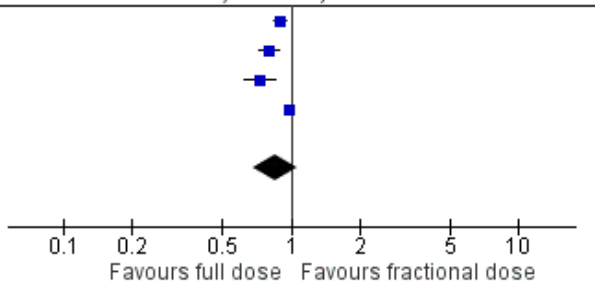
Heterogeneity: Tau² = 0.05; Chi² = 118.42, df = 3 (P < 0.00001); I² = 97%
Test for overall effect: Z = 2.29 (P = 0.02)



Poliovirus type 2

Study or Subgroup	2 f-IPV Events	2 f-IPV Total	2 IPV Events	2 IPV Total	Weight	Risk Ratio M-H, Random, 95% CI
Anand 2015	295	363	142	156	25.6%	0.89 [0.83, 0.96]
Mohammed 2010	134	185	163	180	24.9%	0.80 [0.72, 0.88]
Resik 2010	103	187	134	177	23.4%	0.73 [0.62, 0.85]
Resik 2013	154	157	153	153	26.1%	0.98 [0.96, 1.01]
Total (95% CI)		**892**		**666**	**100.0%**	**0.85 [0.68, 1.06]**
Total events	686		592			

Heterogeneity: Tau² = 0.05; Chi² = 121.01, df = 3 (P < 0.00001); I² = 98%
Test for overall effect: Z = 1.42 (P = 0.16)



Poliovirus type 3

Study or Subgroup	2 f-IPV Events	2 f-IPV Total	2 IPV Events	2 IPV Total	Weight	Risk Ratio M-H, Random, 95% CI
Anand 2015	333	363	152	156	25.8%	0.94 [0.90, 0.98]
Mohammed 2010	134	186	175	183	25.1%	0.75 [0.69, 0.83]
Resik 2010	81	187	165	177	23.3%	0.46 [0.39, 0.55]
Resik 2013	146	157	152	153	25.8%	0.94 [0.90, 0.98]
Total (95% CI)		**893**		**669**	**100.0%**	**0.75 [0.59, 0.97]**
Total events	694		644			

Heterogeneity: Tau² = 0.06; Chi² = 184.76, df = 3 (P < 0.00001); I² = 98%
Test for overall effect: Z = 2.21 (P = 0.03)

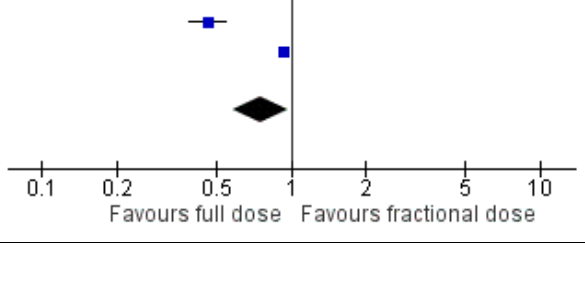
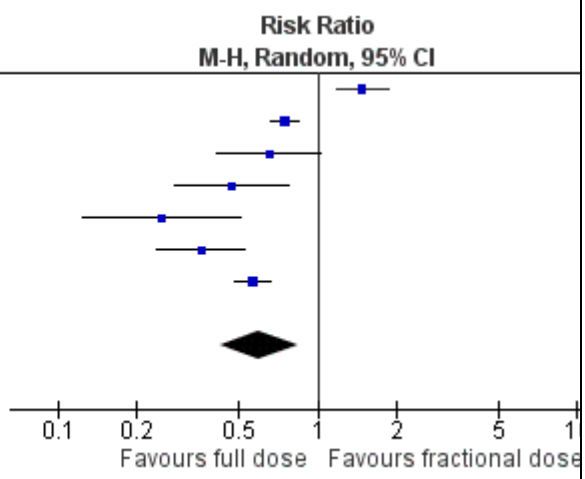


Figure 17. Meta-analysis of seroconversion after 1 fractional dose compared to 1 full doses of IPV per poliovirus type

Poliovirus type 1

Study or Subgroup	1 f-IPV Events	1 f-IPV Total	1 IPV Events	1 IPV Total	Weight	Risk Ratio M-H, Random, 95% CI
Anand 2015	193	366	57	161	16.1%	1.49 [1.18, 1.87]
Clarke 2016	176	354	230	346	16.9%	0.75 [0.66, 0.85]
Estivariz 2012	9	16	19	22	13.3%	0.65 [0.41, 1.03]
Mohammed 2010	19	184	40	182	12.7%	0.47 [0.28, 0.78]
Resik 2010	9	187	34	177	10.1%	0.25 [0.12, 0.51]
Resik 2013	26	157	71	153	14.2%	0.36 [0.24, 0.53]
Resik 2015	104	206	51	57	16.7%	0.56 [0.48, 0.66]
Total (95% CI)		**1470**		**1098**	**100.0%**	**0.59 [0.42, 0.84]**
Total events	536		502			

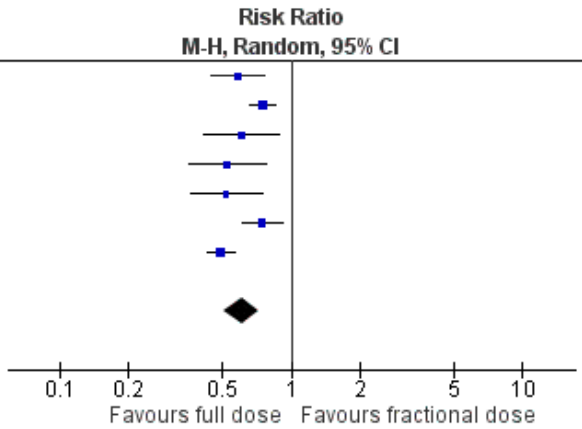
Heterogeneity: Tau² = 0.18; Chi² = 71.38, df = 6 (P < 0.00001); I² = 92%
Test for overall effect: Z = 2.93 (P = 0.003)



Poliovirus type 2

Study or Subgroup	1 f-IPV Events	1 f-IPV Total	1 IPV Events	1 IPV Total	Weight	Risk Ratio M-H, Random, 95% CI
Anand 2015	83	366	62	161	13.9%	0.59 [0.45, 0.77]
Clarke 2016	177	354	229	346	19.0%	0.76 [0.66, 0.86]
Estivariz 2012	21	49	35	50	10.7%	0.61 [0.42, 0.89]
Mohammed 2010	31	185	57	180	10.3%	0.53 [0.36, 0.78]
Resik 2010	35	187	63	177	11.1%	0.53 [0.37, 0.75]
Resik 2013	74	157	96	153	16.3%	0.75 [0.61, 0.92]
Resik 2015	164	375	80	91	18.7%	0.50 [0.43, 0.57]
Total (95% CI)		**1673**		**1158**	**100.0%**	**0.61 [0.51, 0.73]**
Total events	585		622			

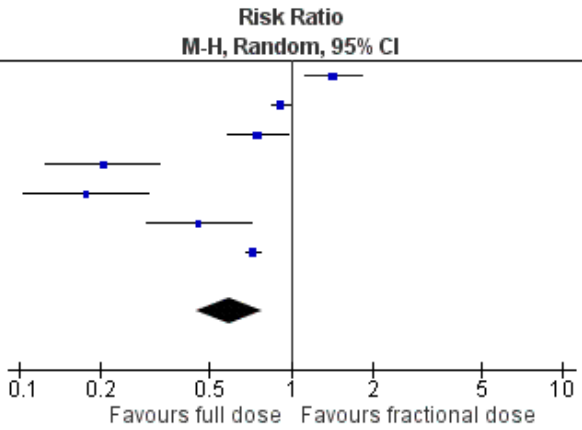
Heterogeneity: Tau² = 0.04; Chi² = 24.07, df = 6 (P = 0.0005); I² = 75%
Test for overall effect: Z = 5.61 (P < 0.00001)



Poliovirus type 3

Study or Subgroup	1 f-IPV Events	1 f-IPV Total	1 IPV Events	1 IPV Total	Weight	Risk Ratio M-H, Random, 95% CI
Anand 2015	175	366	54	161	15.5%	1.43 [1.12, 1.82]
Clarke 2016	265	354	283	346	17.4%	0.92 [0.85, 0.99]
Estivariz 2012	23	34	35	39	15.3%	0.75 [0.58, 0.97]
Mohammed 2010	17	186	82	183	11.5%	0.20 [0.13, 0.33]
Resik 2010	14	187	75	177	10.7%	0.18 [0.10, 0.30]
Resik 2013	23	157	49	153	12.2%	0.46 [0.29, 0.71]
Resik 2015	348	496	120	124	17.4%	0.72 [0.68, 0.77]
Total (95% CI)		**1780**		**1183**	**100.0%**	**0.59 [0.45, 0.78]**
Total events	865		698			

Heterogeneity: Tau² = 0.11; Chi² = 117.82, df = 6 (P < 0.00001); I² = 95%
Test for overall effect: Z = 3.70 (P = 0.0002)



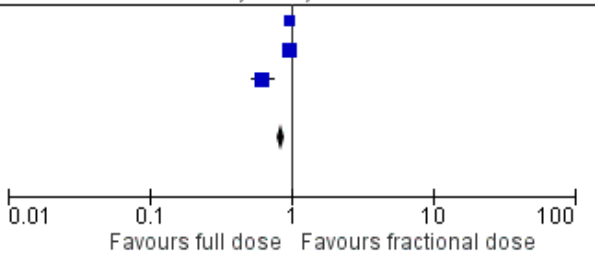
Fixed effects model

Figure 18. Meta-analysis of seroconversion after 3 fractional doses compared to 3 full doses of IPV per poliovirus type

Poliovirus type 1

Study or Subgroup	3 f-IPV Events	3 f-IPV Total	3 IPV Events	3 IPV Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cadorna-Carlos 2012	108	118	112	118	24.8%	0.96 [0.90, 1.03]
Mohammed 2010	179	200	182	200	40.3%	0.98 [0.92, 1.05]
Resik 2010	99	235	158	236	34.9%	0.63 [0.53, 0.75]
Total (95% CI)		**553**		**554**	**100.0%**	**0.86 [0.80, 0.91]**
Total events	386		452			

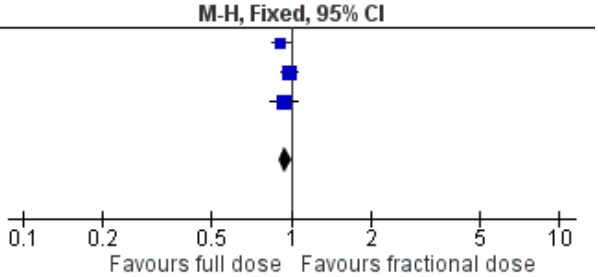
Heterogeneity: Chi² = 41.62, df = 2 (P < 0.00001); I² = 95%
Test for overall effect: Z = 4.95 (P < 0.00001)



Poliovirus type 2

Study or Subgroup	3 f-IPV Events	3 f-IPV Total	3 IPV Events	3 IPV Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cadorna-Carlos 2012	103	118	112	118	24.3%	0.92 [0.85, 1.00]
Mohammed 2010	177	200	180	200	39.1%	0.98 [0.92, 1.05]
Resik 2010	159	235	169	236	36.6%	0.94 [0.84, 1.06]
Total (95% CI)		**553**		**554**	**100.0%**	**0.95 [0.90, 1.01]**
Total events	439		461			

Heterogeneity: Chi² = 1.58, df = 2 (P = 0.45); I² = 0%
Test for overall effect: Z = 1.70 (P = 0.09)



Poliovirus type 3

Study or Subgroup	3 f-IPV Events	3 f-IPV Total	3 IPV Events	3 IPV Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cadorna-Carlos 2012	104	118	114	118	24.2%	0.91 [0.85, 0.98]
Mohammed 2010	182	200	183	200	38.8%	0.99 [0.94, 1.06]
Resik 2010	129	235	175	236	37.0%	0.74 [0.64, 0.85]
Total (95% CI)		**553**		**554**	**100.0%**	**0.88 [0.83, 0.93]**
Total events	415		472			

Heterogeneity: Chi² = 22.39, df = 2 (P < 0.0001); I² = 91%
Test for overall effect: Z = 4.43 (P < 0.00001)

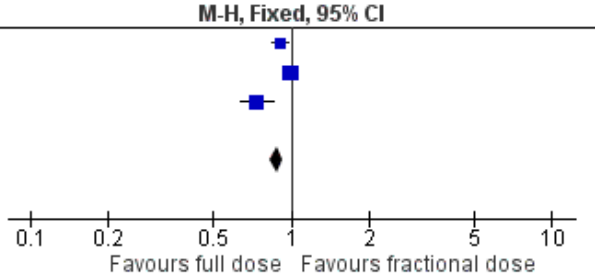
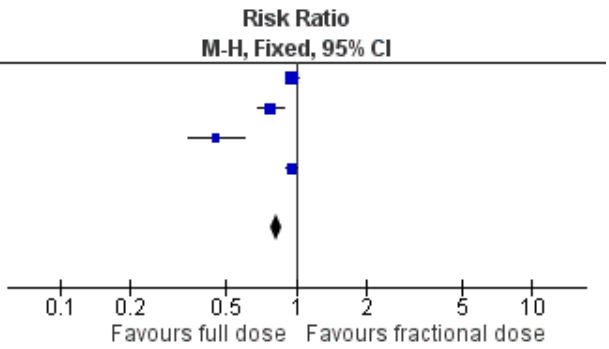


Figure 19. Meta-analysis of seroconversion after 2 fractional doses compared to 2 full doses of IPV per poliovirus type

Poliovirus type 1

Study or Subgroup	2 f-IPV Events	2 f-IPV Total	2 IPV Events	2 IPV Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anand 2015	335	380	148	162	32.6%	0.96 [0.91, 1.02]
Mohammed 2010	129	200	165	200	25.9%	0.78 [0.69, 0.88]
Resik 2010	51	235	112	236	17.5%	0.46 [0.35, 0.60]
Resik 2013	147	160	153	160	24.0%	0.96 [0.91, 1.02]
Total (95% CI)		**975**		**758**	**100.0%**	**0.83 [0.78, 0.87]**
Total events	662		578			

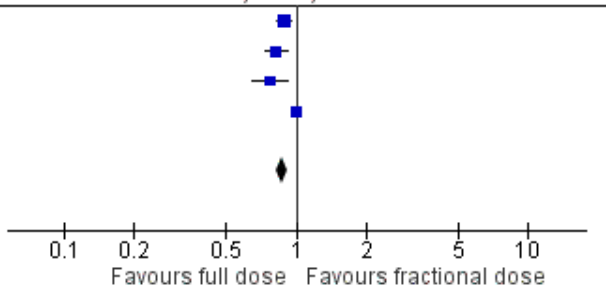
Heterogeneity: Chi² = 70.17, df = 3 (P < 0.00001); I² = 96%
Test for overall effect: Z = 6.89 (P < 0.00001)



Poliovirus type 2

Study or Subgroup	2 f-IPV Events	2 f-IPV Total	2 IPV Events	2 IPV Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anand 2015	295	380	142	162	30.7%	0.89 [0.82, 0.96]
Mohammed 2010	134	200	163	200	25.1%	0.82 [0.73, 0.92]
Resik 2010	103	235	134	236	20.6%	0.77 [0.64, 0.93]
Resik 2013	154	160	153	160	23.6%	1.01 [0.96, 1.05]
Total (95% CI)		**975**		**758**	**100.0%**	**0.87 [0.83, 0.92]**
Total events	686		592			

Heterogeneity: Chi² = 40.16, df = 3 (P < 0.00001); I² = 93%
Test for overall effect: Z = 4.96 (P < 0.00001)



Poliovirus type 3

Study or Subgroup	2 f-IPV Events	2 f-IPV Total	2 IPV Events	2 IPV Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anand 2015	333	380	152	162	30.2%	0.93 [0.88, 0.99]
Mohammed 2010	134	200	175	200	24.8%	0.77 [0.69, 0.86]
Resik 2010	81	235	165	236	23.4%	0.49 [0.41, 0.60]
Resik 2013	146	160	152	160	21.6%	0.96 [0.90, 1.02]
Total (95% CI)		**975**		**758**	**100.0%**	**0.79 [0.76, 0.84]**
Total events	694		644			

Heterogeneity: Chi² = 95.48, df = 3 (P < 0.00001); I² = 97%
Test for overall effect: Z = 8.94 (P < 0.00001)

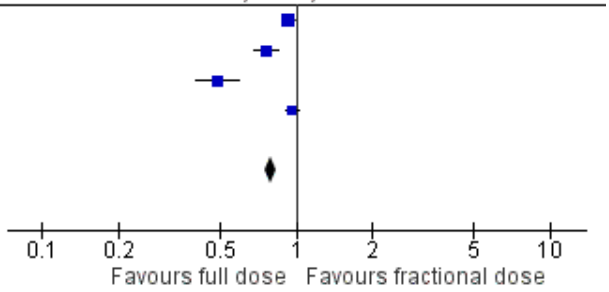
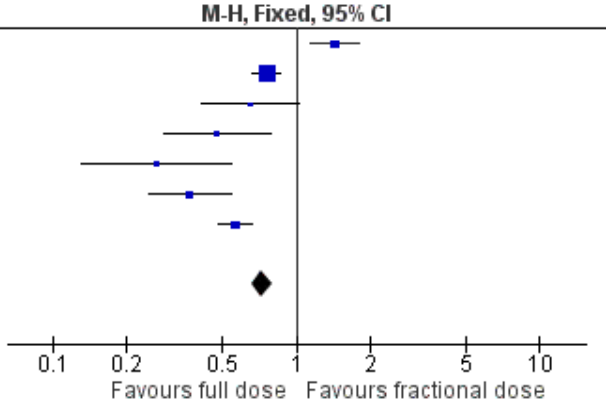


Figure 20. Meta-analysis of seroconversion after 1 fractional dose compared to 1 full dose of IPV per poliovirus type

Poliovirus type 1

Study or Subgroup	1 f-IPV Events	1 f-IPV Total	1 IPV Events	1 IPV Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anand 2015	193	380	57	162	14.5%	1.44 [1.15, 1.82]
Clarke 2016	176	368	230	365	41.9%	0.76 [0.66, 0.87]
Estivariz 2012	9	16	19	22	2.9%	0.65 [0.41, 1.03]
Mohammed 2010	19	200	40	200	7.3%	0.47 [0.29, 0.79]
Resik 2010	9	235	34	236	6.1%	0.27 [0.13, 0.54]
Resik 2013	26	160	71	160	12.9%	0.37 [0.25, 0.54]
Resik 2015	104	206	51	57	14.5%	0.56 [0.48, 0.66]
Total (95% CI)		**1565**		**1202**	**100.0%**	**0.73 [0.66, 0.80]**
Total events	536		502			

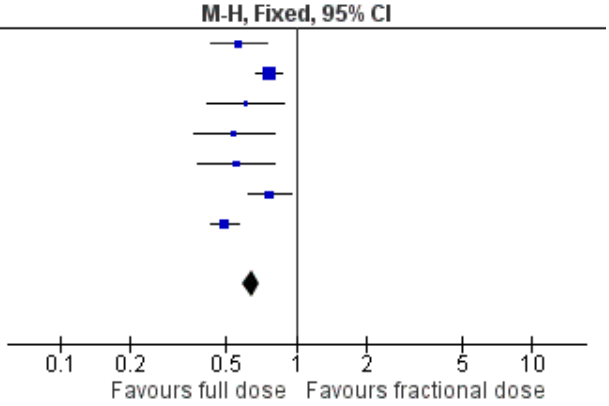
Heterogeneity: Chi² = 65.87, df = 6 (P < 0.00001); I² = 91%
Test for overall effect: Z = 6.66 (P < 0.00001)



Poliovirus type 2

Study or Subgroup	1 f-IPV Events	1 f-IPV Total	1 IPV Events	1 IPV Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anand 2015	83	380	62	162	12.5%	0.57 [0.43, 0.75]
Clarke 2016	177	368	229	365	33.0%	0.77 [0.67, 0.88]
Estivariz 2012	21	49	35	50	5.0%	0.61 [0.42, 0.89]
Mohammed 2010	31	200	57	200	8.2%	0.54 [0.37, 0.80]
Resik 2010	35	235	63	236	9.0%	0.56 [0.38, 0.81]
Resik 2013	74	160	96	160	13.8%	0.77 [0.63, 0.95]
Resik 2015	164	375	80	91	18.5%	0.50 [0.43, 0.57]
Total (95% CI)		**1767**		**1264**	**100.0%**	**0.65 [0.60, 0.70]**
Total events	585		622			

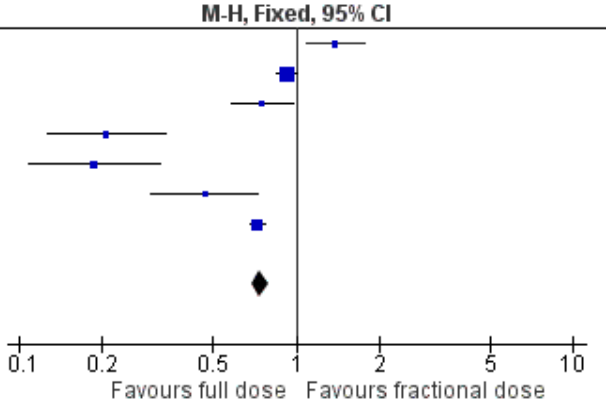
Heterogeneity: Chi² = 25.30, df = 6 (P = 0.0003); I² = 76%
Test for overall effect: Z = 10.21 (P < 0.00001)



Poliovirus type 3

Study or Subgroup	1 f-IPV Events	1 f-IPV Total	1 IPV Events	1 IPV Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anand 2015	175	380	54	162	9.6%	1.38 [1.08, 1.76]
Clarke 2016	265	368	283	365	36.0%	0.93 [0.85, 1.01]
Estivariz 2012	23	34	35	39	4.1%	0.75 [0.58, 0.97]
Mohammed 2010	17	200	82	200	10.4%	0.21 [0.13, 0.34]
Resik 2010	14	235	75	236	9.5%	0.19 [0.11, 0.32]
Resik 2013	23	160	49	160	6.2%	0.47 [0.30, 0.73]
Resik 2015	348	496	120	124	24.3%	0.72 [0.68, 0.77]
Total (95% CI)		**1873**		**1286**	**100.0%**	**0.74 [0.69, 0.79]**
Total events	865		698			

Heterogeneity: Chi² = 108.35, df = 6 (P < 0.00001); I² = 94%
Test for overall effect: Z = 8.85 (P < 0.00001)



APPENDIX C: PRISMA CHECKLIST AND DATA EXTRACTION FORM

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	47
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	48
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	50,51
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	51,52
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	54
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	52
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Appendix A table 2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	52
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	52
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Appendix C
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	53
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	53
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	53
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	54
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	53
RESULTS			

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	54
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	54,55
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	58, 70
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	72-74, Appendix B
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	55-57
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	70
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	57, 58 Appendix B
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	58,59
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	61
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	61
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	54, 61

Data Extraction Form Version 3

Review Title: A systematic review and meta-analysis of fractional dose compared to standard dose inactivated polio vaccination in children.

Study ID			
Person extracting data		Data of extraction	
Person cross checking		Date of data cross checking	

Section A: Source
Section B: Study eligibility
Section C: Full text data extraction eligibility
Section D: Methods of the study
Section E: Study characteristics - Setting of the study and Participant characteristics
Section F: Study characteristics - Interventions
Section G: Study characteristics - Outcomes and comparison groups
Section H: Data and results
Section I: Bias assessment
Section J: Additional information required
Section K: Bibliography search

A. Source

Title	
Published	Yes: ☐ No: ☐
Year of publication	
First Author	
Contact details	
Full citation	
Notes	

	Eligibility criteria	Evaluation Yes	No	Unclear	Not reported	Location in text or source
Study design						
	Randomised Control Trial	☐	☐	☐	☐	
	Quasi-Randomised Control Trial	☐	☐	☐	☐	
	Cohort	☐	☐	☐	☐	
	Case Control	☐	☐	☐	☐	
	Other Specify:	☐	☐	☐	☐	
Participants						
	≤ 5years	☐	☐	☐	☐	
Intervention						
	Administration of one or more fractional doses of inactivated polio vaccine	☐	☐	☐	☐	
Comparison						
	Administration of a full dose of inactivated polio vaccine	☐	☐	☐	☐	
Outcome						
Primary						
	Assess for polio type 1, type 2 and type 3 seroconversion rates	☐	☐	☐	☐	
	Assess for polio type 1, type 2 and type 3 geometric titres	☐	☐	☐	☐	
Secondary						
	Assess for adverse events	☐	☐	☐	☐	
	Assess for vaccine associated paralytic poliomyelitis	☐	☐	☐	☐	

	Assess for wild virus paralytic poliomyelitis	☐	☐	☐	☐	
	Specified device used to deliver fractional doses	☐	☐	☐	☐	

B. Study Eligibility

C: Final set of articles to be included in the review

Overall decision	Include: ☐ Exclude: ☐ Not sure: ☐
Reason for exclusion	
Notes	

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

D: Methods of the study

		Location in the text or source or Notes
Aim/s of the study stated And objectives	Yes: ☐ No: ☐ Unclear: ☐ Not reported: ☐	
Aim/s		
Primary objectives		
Secondary objectives		
Duration of study		
Study design		
Number of study arms		
Sample size (Enrolled and Randomised)		
Power calculation Sample size achieved	Yes: ☐ No: ☐ Unclear: ☐ Not reported: ☐ Yes: ☐ No: ☐ Unclear: ☐ Not reported: ☐	
Notes about Power calculation and or/ sample size		
Data Analysis	Intention to treat: ☐ Per protocol: ☐ Unclear: ☐	
Consumer involvement	Yes: ☐ No: ☐ Unclear: ☐ Not reported: ☐	
If yes, which part of study		
Funding source stated or Donations	Yes: ☐ No: ☐ Unclear: ☐ Not reported: ☐	
If yes, specify		
Possible conflict of interest	Yes: ☐ No: ☐ Unclear: ☐ Not reported: ☐	
Note		
Ethics approval obtained	Yes: ☐ No: ☐ Unclear: ☐ Not reported: ☐	p. 1346
Informed consent obtained	Yes: ☐ No: ☐ Unclear: ☐ Not reported: ☐	p. 1346
Summary of study design		
Notes		

E: Setting of the study and Participant characteristics

		Location in the text or source
Country where the study took place		
Country's income status (as defined by the World Bank)	Low: ☐ Lower middle: ☐ Upper Middle: ☐ High: ☐	
Setting (hospital, clinic, community)		
Description of participants		
Inclusion criteria		
Exclusion criteria		

Age median range in characteristics		
Summary of participant characteristics		
Notes		

Flow of participants in the study

Before randomisation			
	Number of Participants		Location in the text or source
Screened (Recruited)			
Enrolled and Randomized			
Excluded			
Excluded-did not meet exclusion criteria			
Excluded-Refused to take part			
Reasons for exclusion other than those above			
After randomisation			
If multiple intervention, focus on comparison of interest	Intervention	Control	Location in the text or source
Number after randomisation			
Excluded post randomisation			
Reasons for exclusion			
Withdrawn			
Reasons for withdrawing			
Loss to protocol Violation			
Loss to follow up			
Reasons for loss to follow up			
Reasons for exclusion other than those stated above			
Number of participants who completed the study			
Excluded			
Reasons for exclusion from analysis			
Included in the analysis			
Summary of participant flow			
Notes			

F: Study Characteristics- Interventions

Intervention characteristics

	Intervention	Location in the text	Control	Location in the text
Definition of Intervention				
Intervention				
Manufacturer of the vaccine				
Vaccine Formulation				
Route of vaccine delivery	intradermal: ☐ subcutaneous: ☐ intramuscular:☐ other:		intradermal: ☐ subcutaneous: ☐ intramuscular: ☐ other:	
Who delivered the vaccine?				
Method and device (supplier) used to deliver the vaccine (First choose method of delivery in bold then device specified below. If option not available specify under other)	Needle and syringe: ☐ BCG delivery method: ☐ Mantoux delivery method: ☐ Other: Microneedle injection: ☐ MicronJet 600 (NanoPass): ☐ Other:			

	Jet injection: ☐ Tropis (PharmaJet): ☐ ID Pen (Bioject): ☐ Other: Needle-free Biojector 2000, Bioject Microneedle arrays: ☐ ID Adapter (West Pharmaceutical Services): ☐ Other: Other:			
Number of doses given				
Age at time of administration				
Interval between doses				
Notes				

Description and Schedules of Co-administered vaccine and drugs

	Intervention	Location in text	Control	Location In text
Is the intervention co-administered with OPV or it is an IPV only schedule?	OPV: ☐ IPV only schedule: ☐ Unclear: ☐ Other:		OPV: ☐ IPV only schedule: ☐ Unclear: ☐ Other:	
If yes to OPV co-administration,				
Relation with the delivery of the intervention	Administered same time: ☐ Sequential: ☐ Other:		Administered same time: ☐ Sequential: ☐ Other:	
Type of OPV used	bOPV: ☐ tOPV: ☐ other:		bOPV: ☐ tOPV: ☐ other:	
Number of OPV doses				
Timing of OPV doses	Dose 1: Dose 2: Dose 3:		Dose 1: Dose 2: Dose 3:	
Is the schedule	6, 10, 14 weeks: ☐ 2, 4, 6 months: ☐ Other:		6, 10, 14 weeks: ☐ 2, 4, 6 months: ☐ Other:	
Fully describe the schedule				
If yes to inactivated polio vaccine only schedule,			THE CONTROL ARM IS ALREADY A FULL DOSE IPV ONLY SCHEDULE	
Relation of the full dose IPV with the delivery of the intervention	Administered same time: ☐ Sequential: ☐ Other:			
IPV dosage given at a single delivery				
Route of vaccine delivery				
Number of IPV doses				
Timing of IPV doses				
Is the schedule	6, 10, 14 weeks: ☐ 2, 4, 6 months: ☐ Other:			
Fully describe the schedule				
Other vaccines or drugs given In both arms				
Name				
Relation with the delivery of the intervention				
dose				
Number of doses				
Timing of doses				

Summary of intervention	
Notes	

G: Study characteristics – outcomes and comparison groups

Outcome:			
Definition of outcome:		Is it the same for the all the comparison groups?	Location in the text
		Yes: ☐ No: ☐ Unclear: ☐	
Method of assessment		Yes: ☐ No: ☐ Unclear: ☐	
Timing of assessment		Yes: ☐ No: ☐ Unclear: ☐	
Statistic used		Yes: ☐ No: ☐ Unclear: ☐	
Length of follow up		Yes: ☐ No: ☐ Unclear: ☐	
Measures of following up non-responders		Yes: ☐ No: ☐ Unclear: ☐	
Notes			

Summary of outcomes	

H: Data and results

Seroconversion

Polio type	**Intervention**			**Control**		
	Number of participants who seroconverted (n)	Total participants (N)		Number of participants who seroconverted (n)	Total participants (N)	
		Analysed	Randomised		Analysed	Randomised
Polio type 1						
Polio type 2						
Polio type 3						
Notes						

Median polio antibody titres

Antibody titres	**Intervention**				**Control**			
	Median titres	95%CI interval	Total participants (N)		Median titres	95% CI interval	Total participants (N)	
			analysed	Randm			analysis	Randm
Polio type 1								
Polio type 2								
Polio type 3								
Notes								

Adverse events

Adverse events	**Intervention**			**Control**		
	Number of adverse events (n)	Total Participants (N)		Number of adverse events (n)	Total participants (N)	
		Analysed	Randomised		Analysed	Randomised
Local injection site reactions						
Pain/tenderness						
Redness/erythema						
Swelling/induration						

General systemic reactions						
Fever						
Irritability						
Drowsiness						
Loss of appetite						
Vomiting						
Diarrhoea						
Other specify						
Severe adverse events						
Death						
Any other reactions above regarded as serious by author						
Notes						

I: Bias assessment

Domain	Risk of bias Low High Unclear	Support for judgement	Location in text of source
Random sequence generation	☐ ☐ ☐		
Allocation concealment	☐ ☐ ☐		
Blinding of personnel and participants	☐ ☐ ☐		
Blinding of outcome assessment	☐ ☐ ☐		
Incomplete outcome data	☐ ☐ ☐		
Selective outcome reporting?	☐ ☐ ☐		
Other bias	☐ ☐ ☐		
Overall validity judgement	Low risk of bias ☐ Moderate risk of bias ☐ High risk of bias ☐		Comment:

J: Additional information required

Author contact details	
Further information required	Yes: ☐ No: ☐
Information required	
Correspondence successful	Yes: ☐ No: ☐
Information received	
Date received	
Inclusion of additional unpublished data in the review	
Notes	

K: Bibliography search

Citations that may be relevant to the study
1.
2.
3.