Oral polio vaccine plus inactivated polio vaccine versus oral polio vaccine alone for reducing polio in children under two years of age (Protocol)

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*Oral polio vaccine plus inactivated polio vaccine versus oral polio vaccine alone for reducing polio in children under two years of age (Protocol)*

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Oral polio vaccine plus inactivated polio vaccine versus oral polio vaccine alone for reducing polio in children under two years of age

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

- To determine the effects of combined immunisation with OPV and IPV on intestinal mucosal immunity
- To determine any variation in effect with type of vaccine, number of doses, age at first dose, by human immunodeficiency virus (HIV) status or in high and low income countries
- To determine any serious adverse outcomes

BACKGROUND

Description of the condition
Poliomyelitis is an infectious disease caused by any of the three poliovirus serotypes (P1, P2 and P3). Exposure to and subsequent infection with each serotype results in serotype-specific lifelong immunity. Polio can strike at any age but is most prevalent in children under five years of age. Transmission is primarily via the gastrointestinal tract. Ingestion of food and water contaminated with poliovirus invades the gastrointestinal lymphoid tissue and is disseminated via the bloodstream.

The symptoms of poliovirus infection vary greatly across individuals. Up to 95% of those infected with poliovirus are asymptomatic. Others display a range of symptoms (symptomatic polio) depending on the severity of the disease (CDC 2012).

1. A mild, non-specific illness resembling respiratory tract infections, gastrointestinal infections or influenza, known as abortive poliomyelitis, occurs in 4% to 8% of all infections. Infected individuals fully recover within one week.
2. Stiffness of the trunk or legs following a viral prodrome due to aseptic meningitis occurs in 1% to 2% of infections. Recovery is complete within 10 days of contracting the illness.
3. An acute flaccid paralysis, known as paralytic poliomyelitis,
occurs in less than 1% of infections. Although muscle function returns for many people, for others, the residual debilitating weakness causes loss of disability-adjusted life years (DALYS). In 1988, the World Health Assembly adopted the Global Polio Eradication Initiative. Through its efforts, it successfully eliminated the wild-type P2 virus with no new cases attributed to this strain since 1999 (CDC 2001). It has also curtailed the number of outbreaks due to P1 and P3 in most countries; there are still frequent epidemics in Afghanistan, Nigeria and Pakistan (WHO 2012).

**Description of the intervention**

There are two types of vaccines available for polio prevention: a live oral polio vaccine (OPV) and an injectable inactivated polio vaccine (IPV). Mass immunisations with OPV have been the cornerstone of eradication efforts in endemic countries. OPV, also known as Sabin vaccine, is a live attenuated oral vaccine that produces local intestinal mucosal immunity against infection and shedding of poliovirus, largely through production of secretory gut antibodies (immunoglobulin A, IgA). There are three forms of OPV available for use depending on the serotype involved.

1. **OPV or trivalent OPV (tOPV):** OPV produces immunity to all three serotypes of polio virus (Sabin 1959). It is considered to be a superior vaccine due to its ease of administration (volunteers or minimally trained health workers distribute vials of OPV thereby circumventing the need for sterile injection equipment), lower cost (a single dose in a developing country cost between USD$0.11 to USD$0.14 in 2011) and its contribution to long-lasting community immunity by herd protection (the vaccine virus replicates in the intestine, is excreted in the faeces and can be spread to others in close contact for many weeks after immunisation) (Ghendon 1994). This means that in areas where hygiene and sanitation are poor, inoculation with OPV can result in the “passive” immunisation of people who have not been directly vaccinated.

2. **Monovalent OPV (mOPV):** mOPV is available as P1 or P3. The major advantages of mOPV, when compared with the same number of doses of OPV, are a more robust immune response and decreased transmission after subsequent infection of type-specific wild poliovirus.

3. **Bivalent OPV (bOPV):** bOPV contains the live attenuated strains of P1 and P3. Its efficiency rests between that of OPV and mOPV. It is employed in areas where both types of viruses circulate (Sutter 2010).

In contrast to OPV, IPV provides serologic immunity by inducing serum antibodies (IgM and IgG) against all three types of polioviruses. Transudation of IgG in the intestines may contribute to virus neutralisation after exposure to wild polio virus (Herremans 1999). Mucosal immunity after polio vaccination is mainly assessed in stool samples, by detecting the presence and/or quantity of vaccine poliovirus following administration of a challenge dose of mOPV. The excretion of the vaccine virus is inversely related to the degree of immunity (Ogra 1968; Valtanen 2000). Until better methods of measuring immunity become available, the OPV challenge test remains the gold standard surrogate for immunity to infection with wild-type polioviruses, after natural exposure.

Currently each country has its own programme of immunisation. There is variability with respect to age at first immunisation (six weeks versus one month), number of doses, the length of time between doses, and types of vaccine offered. These factors are known to impact the immunogenicity of vaccines, reflected in the degree of seroconversion after vaccine use (WHO 2010). The primary aim of immunisation against polio is to: 1) eradicate indigenous wild-type poliovirus transmission in endemic countries; and 2) prevent re-emergence of wild-type transmission as well as reduce the risk of vaccine-associated and vaccine-derived poliomyelitis in countries declared free of poliomyelitis. Therefore, in endemic countries, OPV remains the vaccine of choice for both routine and supplementary immunisation activities (WHO 1997). IPV is the preferred choice in countries where polio has been eradicated (GPEI 2013).

**How the intervention might work**

Immunity following inoculation with live attenuated OPV imitates that of natural infection, manifested as a local secretory IgA response, which results in decreased fecal shedding of poliovirus (Ogra 1968). IPV alone produces insufficient IgA responses. However, in mucosa previously primed to live virus (wild type or OPV), subsequent IPV can result in strong mucosal IgA responses (Herremans 1999). It can also result in increased effector memory responses through the production of gut homing lymphocytes that confer added immunity to subsequent infections (Krieg 2004). This added immunity from a combination/sequential schedule could potentially result in increased efficacy, mucosal immunity and herd protection compared with the use of OPV alone.

**Why it is important to do this review**

This review is important for several reasons.

- The impact of boosting immunity to infection with IPV is unknown, especially in countries where wild type transmission has continued unabated in spite of eradication initiatives with OPV. These are the populations where, for unknown reasons, even multiple doses of OPV have not resulted in seroconversion indicating decreased vaccine effectiveness. Therefore there is a need to evaluate combination immunisation with IPV (Ehrenfeld 2008).

- Once the transmission of wild polio virus has been interrupted, countries will need to move away from an OPV only program to an intermediate era of OPV plus IPV before
eventually switching to IPV alone. During this transitional period, it is imperative to evaluate the combined role of IPV and OPV in maintaining immunity to wild-type poliovirus infection (WHO 2006).

- The results of this review may be used to seek further evidence 'for' or 'against' a combined immunisation programme and may eventually have implications for vaccine policy.

**OBJECTIVES**

- To determine the effects of combined immunisation with OPV and IPV on intestinal mucosal immunity

- To determine any variation in effect with type of vaccine, number of doses, age at first dose, by human immunodeficiency virus (HIV) status or in high and low income countries

- To determine any serious adverse outcomes

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

All randomised controlled trials (RCTs) or quasi-RCTs that have used at least one dose of OPV compared with a combination of OPV and IPV as the comparison arm. All schedules with assessment of at least prevalence and/or quantity of shedding of vaccine poliovirus following a challenge dose will be eligible.

**Types of participants**

Healthy children under two years of age irrespective of HIV status.

**Types of interventions**

OPV compared with a combination of OPV and IPV.

**Types of outcome measures**

**Primary outcomes**

- Incidence of paralytic poliomyelitis

  - Since this outcome is extremely rare (< 1%) and would require long population-based surveillance of children to at least five years of age, we presume that we will be unable to find studies having this as a primary outcome

**Secondary outcomes**

- Prevalence of vaccine poliovirus shed in the stool after four days and within one month of receiving a challenge dose
  - This time period is selected because virus shedding up to four days may be due to direct, transient passage of the challenge vaccine. Moreover, vaccine virus excretion after challenge dose seldom lasts longer than three weeks

- Quantity of vaccine poliovirus shed in the stool after four days and within one month of receiving a challenge dose

- Any vaccine-related adverse effects

**Search methods for identification of studies**

**Electronic searches**

We will search the following databases.

1. Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library)
2. Ovid MEDLINE
3. Ovid MEDLINE In-Process and other Non-indexed Citations
4. EMBASE
5. CINAHL Plus
6. Science Citation Index (SCI)
7. Conference Proceedings Citation Index - Science (CPCI-S)
8. LILACS (Latin American and Caribbean Health Sciences)
9. IndMED (Indexing of Indian Medical Journals)
10. WHOLIS (World Health Organisation Library Information System)
11. PAHO (Pan American Health Organisation)
12. Cochrane Database of Systematic Reviews (CDSR)
13. Database of Abstracts of Reviews of Effects (DARE)
14. ClinicalTrials.gov (clinicaltrials.gov/)
15. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (apps.who.int/trialsearch/)
16. metaRegister of Controlled Trials (mRCT) (controlled-trials.com/mrct/)

We will use the following MEDLINE search strategy, which uses the Cochrane highly sensitive search strategy for RCTs (Lefebvre 2011), and adapt it for use in other databases. We will not limit our searches by date or language.

1. Poliomyelitis/
2. polio$.tw.
3. 1 or 2
4. Vaccines/
5. Vaccination/ or Mass Vaccination/ or Immunization/ or Immunization Schedule/ or Immunization Programs/
6. $or/4-7
9. 3 and 8
10. (polio$ adj3 (vaccin$ or immunis$ or immuniz$)).tw.
11. (polio$ adj3 (inactiv$ or in-activ$)).tw.
13. exp Poliovirus Vaccines/
14. Poliovirus Vaccine, Oral/
15. Poliovirus Vaccine, Inactivated/
16. (IPV or SALK or OPV or bOPV or mOPV or SABIN).tw.
17. or/10-16
18. 9 or 17
19. exp Infant/
20. exp child/
21. (baby or babies or infant$ or newborn$ or neonat$ or child$ or toddler$ or preschool$ or pre-school$ or p?ediatric$).tw.
22. or/19-21
23. 18 and 22
24. randomised controlled trial.pt.
25. controlled clinical trial.pt.
26. randomi#ed.ab.
27. placebo$.ab.
28. drug therapy.fs.
29. randomly.ab.
30. trial.ab.
31. groups.ab.
32. or/24-31
33. exp animals/ not humans.sh.
34. 32 not 33
35. 23 and 34

Searching other resources
We will scan the bibliographies of key studies and locate any additional published and unpublished trials which the electronic searches fail to capture. We will also search the websites of relevant organisations, including the Global Polio Eradication Initiative (polioeradication.org/)

Data collection and analysis

Selection of studies
Two review authors (FJ, MN) will independently screen each reference identified by the searches to decide if they meet inclusion criteria. Disagreements between authors will be resolved by discussion.

Data extraction and management
Two review authors (FJ, MN) will independently extract data using a pre-piloted data extraction form. Disagreements will be resolved by discussion. We will extract the following data from each study: type of vaccine, number of vaccine doses, target age at first vaccination, HIV status, country in which the trial was conducted, data on pre-specified outcomes listed above, and serious adverse effects. When required information is missing, we will attempt to contact the trial authors for clarification.

Assessment of risk of bias in included studies
Two review authors (MN, FJ) will independently assess the risk of bias in each trial. We will use the domain-based evaluation approach as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will compare the assessments and any discrepancies between the two review authors. We will assess the following domains as low, unclear or high risk of bias.

Randomisation/generation of allocation sequence
- Low risk of bias: if allocation sequence was generated by a computer or random number table. Drawing of lots, tossing of coin, shuffling of cards or throwing dice will be considered as adequate if a person who was not otherwise involved in the recruitment of participants performed the procedure
- Unclear (uncertain) risk of bias: if the trial was described as randomised, but the method used for the allocation sequence generation was not described
- High risk of bias: if a system involving dates, names or admittance numbers was used for the allocation of participants. These studies are known as quasi-randomised and their results will be reported separately from randomised trials

Allocation concealment
- Low risk of bias: if the allocation of participants involved a central independent unit, on-site locked computer, identically numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed envelopes
- Unclear risk of bias: if the trial was described as randomised, but the method used to conceal the allocation was not described
- High risk of bias: if the allocation sequence was known to the investigators who assigned participants

Blinding of participants and personnel
We will describe all measures used, if any, to blind study participants/parents and personnel from knowledge of which intervention a participant received.
- Low risk of bias: if blinding of participants and key study personnel has been ensured and it is unlikely that it could have been broken or if the outcome is not likely to have been influenced by a lack of blinding
- Unclear risk of bias: if the term "blinding" was mentioned but no details are given with regards to who was blinded and how the blinding was ensured
- High risk of bias: if blinding of participants and key study personnel was not done or was broken and if the outcome is likely to be influenced by lack of blinding

**Blinding of outcome assessment (checking for possible detection bias)**

We will describe all measures used, if any, to blind outcome assessors from knowing which intervention was allocated to the participant.

- Low risk of bias: if the outcome assessors were blinded to the intervention received by the participants or if the outcome was unlikely to be influenced by lack of blinding
- Unclear risk of bias: if it was only mentioned that the trial was double-blinded but not explicitly explained how the outcome assessors were blinded to the intervention received by the participants
- High risk of bias: if no blinding of outcome assessment was mentioned but measurement was likely to be influenced by lack of blinding, or where blinding could have been broken

**Incomplete outcome data**

- Low risk of bias: if the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals
- Unclear risk of bias: if the report gave the impression that there were no dropouts or withdrawals but this was not specifically stated
- High risk of bias: if the number or reasons for dropouts and withdrawals were not described

We will further examine the percentages of dropouts overall in each trial and per randomisation arm and we will evaluate whether intention-to-treat (ITT) analysis was performed or could be performed from the published information.

**Selective outcome reporting**

- Low risk of bias: if it is clear that all of the study’s prespecified outcomes and all expected outcomes of interest to the review were reported
- Unclear risk of bias: if there is inadequate information to classify reporting bias as low or high
- High risk of bias: if not all of the study’s pre specified outcomes were reported; one or more reported primary outcomes were not pre specified; outcomes of interest were reported incompletely and so cannot be used; study failed to include results of a key outcome that ought to have been reported

**Other sources of bias**

- Low risk of bias: the trial appears to be free of other components that could put it at risk of bias
- Unclear risk of bias: the trial may or may not be free of other components that could put it at risk of bias
- High risk of bias: there are other factors in the trial that could put it at risk of bias, for example, no sample size calculation made, early stopping, industry involvement or an extreme baseline imbalance

We will consider trials that have adequate generation of allocation sequence, adequate allocation concealment, adequate blinding, adequate handling of incomplete outcome data, no selective outcome reporting and are without other bias risks, as low risk of bias. Trials at moderate risk of bias will be between the low risk and high risk trials. Trials at high risk of bias are either 'No' or 'Unclear' in the majority of domains.

**Measures of treatment effect**

For dichotomous outcomes, we will calculate the risk ratios (RRs); continuous data will be presented as the mean difference (MD) of the scores, or the standardised mean difference (SMD) when the outcome is measured on different scales, for example, duration of shedding, which may be recorded in days or weeks. In this circumstance we will standardise the MDs to a uniform scale before combining.

**Unit of analysis issues**

Cluster-randomised trials will also be reported along with individually-randomised trials. To account for the design effect, sample sizes will be adjusted using the methods described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). If possible, an estimate of the intraclass correlation coefficient (ICC), derived either from the trial or another source, will be used. If ICs from other sources are used, this will be reported and sensitivity analyses will be done to examine the impact of variation in the ICC. If both cluster- and individually-randomised trials are identified, the relevant information will be used provided there is little heterogeneity between study designs, and interaction between the effect of intervention and choice of randomisation unit is unlikely (Higgins 2011).

For cross-over trials, only the first period of the trial prior to the washout period or to a change in the sequence of treatments will be used. This will be treated similar to a randomised trial with parallel arms.

**Dealing with missing data**

For each included trial, the overall percentages of dropouts in each randomisation arm will be determined. The method of analysis (per-protocol versus ITT) will be determined. If ITT analysis was
not performed, we will check if it can be performed with the available published information. For studies that report outcomes for participants completing the trial only or for participants who followed the protocol, the authors will be contacted to obtain additional information to permit analyses according to intention-to-treat principles. If this is not possible, an available case analysis will be performed and a discussion included on the extent to which the missing data could alter the conclusions of the review.

**Assessment of heterogeneity**

We will explore clinical heterogeneity across studies by comparing the distribution of important participant factors among trials (for example age, clinical setting) and trial factors (allocation concealment, blinding of outcome assessment, loss to follow-up, treatment type and co-interventions). We will perform the Chi squared test for statistical heterogeneity to assess the likelihood of heterogeneity (significance set at P < 0.10). If the P value is > 0.10, we will perform a meta analysis using a fixed-effect model. If P value is < 0.10 we will try to explore heterogeneity by performing subgroup analysis and excluding outlying studies. For unexplained heterogeneity, we will perform a random-effects meta-analysis.

**Assessment of reporting biases**

Attempts will be made to look for evidence regarding a few key outcomes that may have been planned but for which data has not been reported. This may include looking up trial registries or reading methods papers and protocols where available. We will also search trial registries to identify unpublished trials and will include them where possible. After examining the reasons why such outcomes may be missing from the study, a sensitivity analysis will be performed by excluding these studies to see the effect on the results of the meta-analysis. Furthermore we will draw funnel plots to investigate reporting biases when there are more than ten studies for an outcome. We will use the test proposed by Egger 1997 to test for funnel plot asymmetry.

**Data synthesis**

Statistical analysis will be carried out using the Cochrane Collaboration’s statistical software, Review Manager 2013. We will use the fixed-effect inverse variance meta-analysis for combining data where trials are examining the same intervention and the trials’ populations and methods are judged sufficiently similar. Where the clinical or methodological heterogeneity between studies is sufficient to suggest that treatment effects may differ between trials, we will use the random-effects meta-analysis by the Mantel-Haenszel method. Primary analysis will include all trials which meet the inclusion criteria. For trials with a total attrition of more than 20%, or where differences between the groups exceed 10%, or both, we will perform a sensitivity analysis. Based on the results, these will be included in the review but excluded from meta-analysis.

**Subgroup analysis and investigation of heterogeneity**

Subgroup analysis will be used to compare the outcome according to:
- type of vaccine used;
- number of prior doses given;
- age at first immunisation;
- HIV infection status;
- high-income versus low-income countries;
- tropical versus subtropical countries.

**Sensitivity analysis**

If sufficient trials are identified, we will conduct the following sensitivity analyses to compare the results of all trials:
1. effects of removing studies at high risk of bias (studies with poor or unclear allocation concealment and either or high/imbalance loss to follow-up) from the analysis;
2. effects of different ICC values for cluster studies (if these are included);
3. effects of including studies with mixed populations in which marginal decisions were made.

**ACKNOWLEDGEMENTS**

Elaine McKay for registering the title.
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CDC 2012

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Ehrenfeld 2008

Ghendon 1994

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Herremans 1999
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Higgins 2011

Higgins 2011

Krieg 2004

Lefebvre 2011

Ogra 1968

Review Manager 2013 [Computer program]

Sabin 1959

Sutter 2010

Valtanen 2000

WHO 1997

WHO 2006

WHO 2010

WHO 2012

* Indicates the major publication for the study
CONTRIBUTIONS OF AUTHORS

Fyezah Jehan - protocol writing
Muhammad I Nisar - protocol writing
Zohra S Lassi - protocol writing and methodological support
Saad B Omer - methodological support
Anita KM Zaidi - methodological support

DECLARATIONS OF INTEREST

Fyezah Jehan - none known.
Zohra S Lassi - none known.
Muhammad I Nisar - none known.
Saad B Omer - has been involved in the design, conduct and publication of a potentially eligible study for this Cochrane review.
Anita KM Zaidi - I received a research fund from the World Health Organisation to conduct two polio vaccine related trials.

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- No sources of support supplied