Interventions to Improve Oral Vaccine Performance in developing countries: A Systematic Review and Meta-analysis

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Protocol Information

Review title

Interventions to improve oral vaccine performance in developing countries: systematic review and meta-analysis

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Risk of bias (quality) assessment	No	No
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Background & Rationale

Oral vaccines significantly underperform when given to children in developing compared to developed countries[1]. This was first observed in early field trials of oral poliovirus vaccine in the 1950's[2] and has since been described for oral vaccines against several viral and bacterial pathogens in multiple countries. The results of large rotavirus vaccine efficacy trials in South Asia[3] and sub-Saharan Africa[4] are the most recent to highlight this "efficacy gap". Rotavirus vaccine efficacy against severe rotavirus gastroenteritis was as low as 39.3% (95%CI 19.1-54.7) in Ghana, Kenya and Mali[4] compared to 85-98% in Europe and the USA[5,6].

Our understanding of the mechanisms of oral vaccine underperformance remains incomplete[7]. Multiple factors have been proposed, including genetic determinants, concurrent enteric infections[8,9], environmental enteric dysfunction[10,11], interference from breast milk antibodies[12,13], and deficiency of micronutrients such as zinc[14] and Vitamin A[15,16]. Their relative contribution may vary depending on the specific oral vaccine and setting; however, it is likely that these factors overlap and interact.

Without a clear understanding of the causal relationships underpinning poor vaccine response, developing interventions to improve oral vaccine efficacy has proven difficult. A series of studies report interventions designed to address one or more of the above factors to overcome oral vaccine failure, including micronutrient supplementation, antibiotics, anthelminthics, probiotics, timing of breastfeeding and vaccine dose adjustments. However, whilst several reviews have stressed the challenge of oral vaccine failure in developing countries, there are no articles to date that have systematically reviewed the literature on interventions and oral vaccine performance*.

An up-to-date review and evaluation of this topic would be a timely contribution to the field. In light of the burden of diarrhoeal disease globally (childhood deaths from diarrhoea amount to 700,000 per year – second only to pneumonia), an effective intervention capable of closing the vaccine "efficacy gap" would avert substantial morbidity and mortality. The publication of several trials in recent years exploring interventions to improve oral vaccine immunogenicity attests to the interest and urgency in this field of research. The results of other trials will soon become available. Synthesising these findings will therefore strengthen

our understanding of oral vaccine failure as well as highlighting the gaps in our knowledge. Moreover, a better grasp of existing trials, their design and outcomes will help to focus research priorities and guide policy.

*Search of *DARE* (Database of Abstracts of Reviews of Effects) and *Cochrane Database* revealed no existing reviews on interventions to improve oral vaccine efficacy. The closest match was a review titled "Interventions that will increase and sustain the uptake of vaccines in low- and middle-income countries" which relates to interventions designed to improve vaccine coverage rather than vaccine performance itself. Several articles from the *Discussion meeting issue* 'Biological challenges to effective vaccines in the developing world' (Phil. Trans. R. Soc. B 2015 370) review different interventions (especially *Praharaj et al*[17]). In addition a recent article published in November 2016 discusses options for improving oral rotavirus vaccine effectiveness in developing countries[18]. However, neither of these articles used systematic review methodology and their findings do not cover all interventions and relevant vaccines.

Plain Language Summary

Vaccines given by mouth protect against infections that cause diarrhoea and other diseases. These vaccines work very well in developed countries; however, the same vaccines are considerably less effective when given to infants in developing countries, where the need for protection is greatest. The reasons for this remain unclear but are thought to include differences in genetics, immune function and environment.

A number of studies have explored ways of improving the performance of oral vaccines, including giving micronutrients, antibiotics and deworming medications with or before the vaccine, or changing the timing of vaccine doses. To date there has been no comprehensive review of all these studies. We will therefore conduct a systematic review and, if possible, a meta-analysis to evaluate the scope and quality of evidence for a defined set of interventions. We hope this will not only improve our understanding of why oral vaccines fail in these children but also highlight areas for future research.

Review methods

Review question/main objective

The primary objective is to evaluate the impact of interventions aimed at increasing either oral vaccine efficacy or immunogenicity among children under 5 years of age in developing countries.

Secondary objectives

1) To evaluate the impact of interventions aimed at increasing either oral vaccine efficacy or immunogenicity in older age groups (over 5 years) and in developed countries, to provide supportive evidence for the primary objective.
2) To conduct a meta-analysis of studies exploring interventions to improve oral vaccine immunogenicity.
3) To apply the GRADE approach (see Appendix 1) to evaluate the quality of evidence presented in studies exploring interventions aimed at improving oral vaccine immunogenicity.
4) To assess the impact of interventions to improve oral vaccine performance on intermediary outcomes, including markers of gut health as well as intervention safety, acceptability and adherence data if available. This will help to identify any factors associated with the success or failure of interventions.

All available evidence will be reviewed, summarised and where possible synthesised. Ongoing trials will also be described. The review will be undertaken and reported in accordance with the PRISMA statement (Liberati 2009).

Searches

The search process will be summarized in a PRISMA flow diagram (see Appendix 2).

Electronic searches

- Cochrane Infectious Disease Group Specialized Register
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Ovid (Epub ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946 to Present)

- EMBASE

MeSH headings will be used in addition to keywords in Medline and EMTREE terms in Embase. The initial search will be restricted by language to English literature only. To find protocols for planned trials or trials in progress, the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) will be searched, which is a central database for a number of trials registries including Clinical Trials.gov, controlledtrials.gov, the EU Clinical Trials Register and Pan African Clinical Trials Registry. The reference lists and citations of key studies and review articles will also be examined to pick up additional relevant studies.

Searching other resources

The following experts in the field of oral vaccines and enteric infections will be consulted to identify any potential studies missed by the above search strategy.

- Joe Brown (Georgia Tech);
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- Roma Chilengi (Centre for Infectious Disease Research in Zambia)
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We will also search the Grey Literature report in public health www.greylit.org, African index Medicus (www.indexmedicus.afro.int) and resources specific to South East Asia (www.imsear.hellis.org) and Western Pacific (www.wprim.org), plus the WHO virtual health sciences library www.emro.who.int/information-resources/vhsl, and websites from actors in the field of enteric disease and vaccines including WHO, UNICEF, Gavi – The Vaccine Alliance, USAID, SHARE, WSUP, ICDDR,B, CDC and the Bill & Melinda Gates Foundation.

Additional data

Where possible, study authors will be contacted to obtain original data and any further unpublished results which are relevant.

URL to search strategy

Our detailed search strategy is available on Ovid-Medline (see appendix 3)

Condition or domain being studied

Immunogenicity or induced immune response following vaccination with any one or more of the following oral vaccines:

- Oral poliovirus vaccine (Orimune®, monovalent, bivalent or trivalent OPV)
- Oral rotavirus vaccine (Rotarix®, Rotateq®, Rotavac®, Rotavin-M1®)
- Oral cholera vaccine (Dukoral®, Shanchol®, Orachol®, Mutachol®, Orc-Vax®)

- Oral typhoid Ty21a vaccine (Vivotif®)
- Oral shigella vaccine (*Shigella flexneri* 2a SC602)

Participants/population

Humans of any age and in any setting[1] receiving the above mentioned oral vaccines.

Intervention(s), exposure(s)[2]

A. Micronutrients (especially Vitamin A and Zinc)
B. Antibiotics
C. Anthelminthics
D. Probiotics or prebiotics or synbiotics
E. Withholding breastfeeding
F. Dosing or formulation changes (dose timing, dose number, dose titre, OPV valency, concomitant use of RVV and OPV or buffer)
G. WASH (water, sanitation & hygiene)
H. Other plausible interventions e.g. macronutrients, maternal interventions (e.g. antihelminthics) during pregnancy

The above list of interventions was compiled based on background literature and discussion between the authors. However, we will include other plausible interventions (H) that have been tested with the aim of increasing vaccine immunogenicity, identified through our systematic review.

Comparator(s)/control

The comparator or control group will vary depending on the intervention being examined. The following are possible controls to the interventions listed above

- Study participants receiving a placebo, or no active intervention (A, B, C, D)
- Study participants who are breastfed during or around the time of vaccine administration (E)

[1] See **Context** for clarification of population parameters (p12)
[2] See **Description and rationale for interventions** (p20)

- Study participants given a vaccine at time and dose in accordance with the existing schedule at the time of the study (F).
- Study participants with unimproved sanitation and/or no hand-washing promotion and/or no water quality or quantity intervention; i.e. a continuation with usual WASH practices (G).

Types of study to be included

Both published studies and protocols of planned/on-going studies will be considered. Only studies with a clearly described intervention and concurrently enrolled control group will be eligible for review. Eligible study designs include: meta analyses, randomised trials, cluster-randomised trials and case-control studies. We will include controlled before-after (CBA) studies, where observations are made before and after the implementation of an intervention, where there is a control group that does not receive it. We will also include interrupted time series (ITS) studies, which use observations at multiple points before and after an intervention. ITS studies are designed to detect whether the intervention has had an effect significantly different from the general trend.

Exclusion criteria

The following criteria will form the basis of exclusion of studies from the review

1) Study type: cross-sectional studies, case series (i.e. <10 subjects), outbreak investigations and animal studies.
2) Study design:
    a. Studies that do not have an intervention (listed above). This includes studies of epidemiological exposures such as infants fed formula rather than breast milk.
    b. Studies that do not have an appropriate control group (listed above). This includes vaccine studies where the control group is not in receipt of an established regimen or pre-licensure dose finding studies.

c. Studies that do not measure vaccine efficacy or immunogenicity (detailed in outcomes below).

3) Other:

a. Studies that include strategies to improve oral vaccine performance by using alternative routes of immunization e.g. parenteral.

Criteria will be sequentially applied according to the data collection spreadsheet (see appendix 4).

We aim to conduct a meta-analysis for any of the interventions and vaccines, provided there are sufficient studies and data. In this case, additional exclusion criteria will be applied in order to limit heterogeneity and establish generalisability of findings. Exclusion criteria will reflect the gold-standard timing of vaccine administration and immunogenicity measurement and optimum dose and formulation for a given vaccine.

Context

In order to clarify our research question and choice of exclusion criteria for this review, two characteristics of the problem of oral vaccine failure, setting and participants, warrant closer consideration.

Firstly, oral vaccine failure occurs predominantly in developing countries. For example, the licensed oral live cholera vaccine (Orochol) and several other live oral cholera vaccines, provide good levels of protection against challenge in vaccinated US volunteers[19]; however, they fail to be sufficiently immunogenic or to protect South Asian vaccinees (both children and adults)[20,21]. More recently, evidence from large rotavirus vaccine efficacy trials has illustrated the gap in vaccine efficacy between North America/Europe[5,6] and South Asia[3] and sub-Saharan Africa[4]. This gap is more pronounced the poorer the country. A sub-analysis of multiple trials illustrates a trend towards reducing vaccine efficacy with declining country GDP[22].

Secondly, the burden of oral vaccine failure is predominantly among infants. Not only are

infants most vulnerable to the consequences of oral vaccine failure (rotavirus diarrhoea is most common in infancy and carries high risk of mortality in many countries[23]) but oral vaccines (rotavirus and OPV) are key components of national childhood immunization schedules and among the vaccines promoted by *Gavi, the Vaccine Alliance*. Conversely, among adult subjects, oral vaccines are often immunogenic (despite failing in infants) and oral vaccination is less commonly required.

In conclusion, it is intervention studies among infants in developing countries that are most relevant to our main research question, whilst studies from developed countries, in older children and in adults are less directly relevant. We therefore considered narrowing the inclusion criteria to include only studies of infants in developing countries. However, this would exclude some trials conducted in adults or among children in high- and middle-income countries which may provide valuable insights into the underlying biology of oral vaccine failure. We have therefore chosen broad inclusion criteria, and will not include age or setting in our exclusion criteria. Instead, we will stratify by age and setting where possible and explore interventions to improve vaccine performance in older subjects and or in developed countries as secondary objectives. In the overall analyses, studies including older subjects or developed countries will be downgraded in the GRADE process due to indirectness to the primary research question.

Primary outcome(s)

Oral vaccine efficacy or immunogenicity

The gold-standard method for assessing a preventive vaccine is a randomized, double-blind, placebo-controlled trial, with a clear outcome case definition and assessment of efficacy in a per-protocol analysis. Vaccine efficacy, measured as the percentage reduction of disease in a vaccinated compared to a non-vaccinated group, represents the optimum correlate of protection for most vaccines. However, trials of this rigor and scale have been seldom possible to test interventions aimed at improving oral vaccine response, either due to insufficient cases of disease (e.g. poliomyelitis) or due to constraints of scale and cost.

To our knowledge, the only trials measuring vaccine efficacy as a primary outcome of an intervention have been studies exploring adjustments to rotavirus and typhoid vaccine preparations (dose or buffer) [24,25]. Instead, measures of immunogenicity are accepted as surrogate endpoints for vaccine evaluation studies and therefore will often be the primary outcome reported in studies. Even where efficacy is listed as the primary outcome, immunogenicity is often described as a secondary outcome.

Therefore, in order to maximize our pool of analysis, we will use immunogenicity as the primary outcome where vaccine efficacy is not reported. We acknowledge that the use of immunogenicity as a primary outcome carries a few caveats. Firstly, immunogenicity is a broad term comprising a range of outcome measures with the potential to introduce heterogeneity. Based on author consensus and the most widely used endpoints for immunogenicity, we outline in Table 1 our preferred measures of immunogenicity for each oral vaccine including constraints such as titre cut-off and timing for each measure. Timing of assays post-vaccination is likely to influence immunogenicity results, and we will report data with this in mind, particularly when comparing studies using different time-points. This will allow for consistency in our measure of effect and generalisability of our findings. For studies where seroconversion is not specified we will consider alternative measures of immunogenicity or vaccine 'take' as an endpoint. Secondly, measures of immunogenicity do not always correspond to vaccine efficacy, because correlates of protection have not been established for all vaccines. However, measures of increased immunogenicity tend to broadly reflect improved oral vaccine performance and would provide an important proof of concept that interventions have biological plausibility to improve oral vaccine efficacy.

Table 1: Measures of immunogenicity in order of preference by oral vaccine type

VACCINE	**Measures of Immunogenicity**		
	Preferred measure	*Timing of measure*	**Alternative measure**

Oral poliovirus vaccine	Seroconversion (serum neutralizing antibody titres ≥ 1:8)	*21-28 days post last dose*	Neutralisation titre post vaccine Polio virus shedding ('take') [3] Anti-polio specific IgA or IgG (serum or stool)
Oral rotavirus vaccine[26]	Seroconversion (≥3 fold rise) or seroresponse (≥20U/ml) measured by serum RV-specific IgA antibody titres	*14-28 days post last dose*	RV-sIgA or Copro Ig A (and total IgA) Serum NAs[4] to different serotypes
Oral cholera vaccine	Seroconversion (≥4 fold rise) serum vibriocidal (IgM) antibody titres	*7-14 days post dose*	Vibriocidal sIgA LPS IgA or IgG CTB IgA or IgG
Oral typhoid vaccine	Serum IgG O antibody titres Gut derived IgA O antibody secreting cells	*7-14 days post dose*	Intestinal sIgA Anti-S.typhi LPS
Oral shigella vaccine	*Not defined* Gut /serum LPS O specific IgA	*7-14 days post dose*	

[3] OPV shedding must be measured between 1 and 4 weeks after vaccination

[4] NA = neutralising antibody, sIgA = secretory IgA, LPS = lipopolysaccharide, CTB = cholera toxin subunit B

Secondary outcome(s)

In some studies, in addition to a measure of immunogenicity or induced immune response, other markers of immune function or factors relating to an intervention's plausible mechanism of action may be described e.g. biomarkers of gut health, growth parameters, enteropathogen carriage. These outcomes will not be included in the primary analysis or meta-analysis; however, where relevant they will be described in the main text to provide insights into the biological mechanisms of oral vaccine underperformance and additional effects of the interventions.

Data extraction (selection and coding)

Articles identified from the systematic search will be downloaded and assembled in an Endnote library. First we will undertake screening of titles and abstracts to identify suitable articles and to exclude articles that do not fulfil inclusion and exclusion criteria. We will then obtain full-text articles of relevant studies, downloaded electronically or retrieved from library archives, and each will be independently evaluated by two researchers (JAC and EP) to identify the final list of articles suitable for inclusion in the review. Data will then be extracted from these articles independently by JAC and EP using the data extraction form (Appendix 4). Authors will be contacted to supply missing data where possible. Our data extraction tool is based on the Cochrane Public Health Group and EPOC Group "Good practice data extraction form", modified for this study. The data extraction form will be piloted to ensure comparable results are retrieved between reviewers. Any discrepancies will be resolved with the assistance of a third author (AJP). Data will be entered into a spreadsheet. Below is a brief description of the categories of data that will be collected:

1. Publication details: 1st author, title, publication date, journal, volume, issue, page numbers
2. Population characteristics: country, setting, number, gender percentage, ages at recruitment, intervention and measurement, length of follow up
3. Intervention characteristics: details of intervention type, dose and duration; type of randomisation, control group details.
4. Outcome: measure of vaccine efficacy or immunogenicity, [effect size, confidence intervals and standard errors of effect if available, p values], additional results on

other outcomes if available: e.g. morbidity, mortality, immune markers, gut markers, safety/toxicity.

5. Assessment of methodological quality: study type & size, confounding variables & attempts to correct for them, blinding and allocation concealment
6. Implementation factors, cost, acceptability and sustainability data, if available.
7. Source of funding of study

Where a single study provides data at multiple points in time or on multiple similar outcomes, we will extract data as close as possible to the preferred outcomes detailed in Table 1. For tOPV, where seroconversion to serotypes 1,2 and 3 is often detailed, we will present data for OPV3 only. However, we will consider effect varying across serotypes in a separate within polio meta-analysis. If multiple eligible reports of the same trial are encountered, the most comprehensive report will be used for data extraction. A standard approach will be used for comparisons of multiple reports and publications of the same study will be checked to ensure data are only used once. Authors of primary studies will be contacted where information is needed. A shared Dropbox folder will be used to manage data storage and analysis.

Risk of bias (quality) assessment

Two authors (JC and EP) will independently assess the risk of bias of included studies. This will be using the EPOC *'risk of bias'* tool for studies with a separate control group. This tool includes assessment of allocation, baseline characteristics, baseline outcome, incomplete outcome data, blinding, selective outcome reporting and contamination of the treatment groups. It also contains additional items to assess the risk of incomplete data, selection bias, attrition bias and subsequent confounding. For non-randomised studies, there are also items that assess the risk of selection bias and subsequent confounding. Where information is not detailed, this will be recorded in the spreadsheet as *not specified (NS).*

A GRADE score will be assigned to each study based on study quality, consistency, directness and effect size. Study quality encapsulates the selection, allocation and blinding

of the study population; consistency refers to agreement or even dose response across studies, directness indicates the generalisability of either the population or the outcome; and effect size refers to the magnitude of effect measured if at all. Each category is assigned a minimum and maximum number of points and the points from each category totaled to give a final GRADE score. Any discrepancies in scoring will be resolved with the assistance of a third author (AJP). Risk of bias will also be summarised at the outcome level for each study with an overall risk of bias level of 'low', 'unclear' or 'high' derived from the risks noted in the spreadsheet. Finally, we will check for the existence of publication bias using a funnel plot and test for asymmetry using Egger's test.

Strategy for data synthesis

We will report all statistically significant and non-significant outcomes according to type of study design. If meta-analysis is possible, data synthesis of study outcomes by group (intervention and control) will be performed and a random-effects model meta-analysis will be carried out. A forest plot with appropriate effect sizes and 95% confidence intervals will be provided for each analysis along with a measure of heterogeneity (I^2).

Efficacy data, when available, will not be included in the meta-analyses however it will be detailed separately in a narrative synthesis. Similarly, ratios of intervention versus control post-vaccine titres will be presented in a qualitative analysis and significant effects highlighted. Where possible, studies will be compared that have similar subgroups of age and low, middle or high income country status. If there are sufficient studies, they will also be grouped by vaccine and by the type of intervention.

For either narrative or quantitative analysis, the review findings will be summarised using the GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias – see appendix 1) to assess the quality of the evidence for each outcome. All assessments will be documented, together with a 'Summary of Findings' (Table 2), which will include the evidence for each type of intervention and the effect on vaccine response depending on the vaccine.

The GRADE scoring will take into account study quality and relevance of the study population to the primary objective of the review. For example, viral vaccines (OPV and rotavirus) will be more pertinent to younger children whereas bacterial vaccines (cholera) will be more pertinent to older children.

Table 2: Summary of findings (with effect size graded as strong, moderate, weak or insufficient data).

	Vitamin A	Zinc	Antibiotics	Anthelminthic	Probiotic	Dosing	Breastfeeding	WASH	Other
Rotavirus									
OPV									
Cholera									
Typhoid									

Strong	
Moderate	
Weak	
No data	

Analysis of subgroups or subsets

We will carry out a number of subgroup analyses.

1) A subgroup analysis by vaccine. Oral vaccines and the enteric pathogens that they mimic, behave differently and interact at different places along the mucosal barrier[29]. *Vibrio cholerae* for example colonises the intestinal mucosa without invasion or damage whereas rotavirus locally invades mature enterocytes at the villus tip destroying the mucosa. It is feasible therefore that an intervention that improves immune response to oral cholera vaccine does not have the same beneficial effect when tested with rotavirus vaccine. We will perform a meta-regression in order to evaluate whether heterogeneity is driven by different vaccines i.e. is there an effect for type of vaccine? If we demonstrate an effect, then this will have to be factored into subsequent analyses.

2) A subgroup analysis by age, with subgroups of <1 year (infants), 1-<5 years (pre-school), 5-<16 years (school age) and >16 years (adults). This is to separate infants from older children and adults. Infants are more likely to receive oral vaccines and have a different set of environmental exposures including breastfeeding as well as important differences in immune function.
3) A subgroup analysis by country type, with subgroups of low-income, middle-income and high-income countries. Oral vaccine failure is more common in developing countries; however the relative effectiveness of an intervention may vary depending on the country and setting. We will separate countries based on their World Bank definition[27,28], for which data are available from 1987. For any historical studies found prior to 1987, we will apply the classification as recorded in 1987.

Sensitivity analysis

We plan to conduct a sensitivity analysis by restricting the analysis to trials classified as having low risk of bias overall.

Description and rationale for interventions

A. Micronutrients

Vitamin A encompasses a group of retinoid compounds (biological activity all-*trans*-retinol) which play an essential role in a number of physiological functions including immunity. Vitamin A is essential for healthy immune responses at mucosal surfaces and deficiency results in increased mortality and morbidity from measles, diarrhoea, blindness and anaemia. Vitamin A deficiency is prevalent in regions where oral vaccines underperform and Vitamin A supplementation (VAS) is widely accepted and considered to be among the most important tools to reduce childhood mortality in children aged 6-59 months[30]. Animal studies have shown that Vitamin A deficiency impairs vaccine-elicited gastrointestinal immunity and that replacement with Vitamin A or its metabolite retinoic acid fully restores the mucosal immune response[15,31]. Vitamin A derivatives have also shown adjuvant potential in humans when given alongside vaccines[32,33].

Zinc is an essential mineral involved in multiple aspects of cellular metabolism. Deficiency in zinc leads to growth retardation, loss of appetite and impaired immune function and is strongly correlated to increased diarrhoeal morbidity and mortality[34]. Several studies describe clear benefits of both supplemental and therapeutic zinc in protecting children from diarrhoeal disease[35]. Like Vitamin A, zinc deficiency is more prevalent in regions where oral vaccines underperform. Given its integral role in gut health both through intestinal epithelial repair and regulation of mucosal immune responses, it is plausible that deficiency may attenuate seroconversion to oral vaccines and conversely supplementation may improve immune responses to oral vaccines.

B. Antibiotics

Many children in developing countries have frequent and recurrent exposure to enteric pathogens from early life[36]. This adverse exposure could impair the efficacy of an oral vaccine in several ways. Firstly, enteropathogen exposure can cause diarrhoea, which may either reduce intestinal transit time, thereby lessening vaccine exposure, or accentuate

mucosal innate immune responses, thereby impairing vaccine replication. For example, in children infected with non-polio enteroviruses or having diarrhoea at the time of vaccination, immunogenicity to oral poliovirus vaccine is significantly reduced[37]. Secondly, induction of innate and adaptive immune responses at the intestinal mucosa can cause perturbations to the gut microbiota[38], which can in turn interfere with oral vaccine responses (see *Probiotics* below). Thirdly, pathogens scavenge and compete for energy sources which may interfere with the action and replication of live vaccine virus. Finally, repeated exposure to intestinal pathogens can contribute to chronic alterations in gut structure and function, characterised by increased permeability, reduced absorptive capacity and chronic inflammation, which together have been termed environmental enteric dysfunction (EED)[39]. Biomarkers of EED have been associated with reduced immune responses to oral poliovirus and rotavirus vaccines in some studies[40] (Becker-Dreps 2017). Given the potentially deleterious effect of enteric infection or colonisation on the mucosal immune response, a course of antibiotic therapy given around the time of vaccine administration may reduce enteropathogen carriage and improve oral vaccine performance.

C. Anthelminthics

Helminth infestation is prevalent among children in developing countries[41] and their geographical distribution has extensive overlap with areas in which oral vaccines underperform. Intestinal helminth infection is associated with substantial childhood morbidity including anaemia, malabsorption and stunting[42]. As well as contributing to gut malabsorption, geohelminths inhabiting the small intestine may also interfere with the uptake of oral vaccines in the intestinal lumen. Anthelminthics, a group of antiparasitic drugs, are recommended by the WHO for periodic deworming to reduce morbidity among children living in endemic areas[43]. Treating helminth infections may additionally enhance immune responses to oral vaccines. Following two doses of albendazole prior to vaccination, Cooper *et al* observed increased responses to oral cholera vaccine among Ecuadorian school-age children[44]. However, helminth infestation is rare in early infancy when routine oral vaccines are administered.

D. Probiotics or prebiotics

The role of the intestinal microbiota on health and immunity is garnering increasing interest. Experiments in germ-free animal models have helped explain mechanisms by which the microbiota influences early immune development and responses[45]. In humans, a recent study described differences in the microbiota composition of Ghanaian infants who responded and failed to respond to oral rotavirus vaccine[46]. Moreover, the microbiota of the Ghanaian infants who responded to oral rotavirus vaccine was more similar than non-responders to that of rotavirus unvaccinated Dutch infants of matched age. Although these findings are yet to be replicated elsewhere, it seems plausible that alterations to the intestinal flora can modulate response to oral vaccines. Probiotics are live microorganisms intended to have health benefits, which have been linked to actions that may directly or indirectly influence immune action. In principle, they have the capacity to alter the composition of the gut microbiota and communicate with many cell types, thereby enhancing barrier function, increasing mucin production and promoting IgA secretion. The same is true to a lesser extent with prebiotics, which are non-digestible fibre compounds designed to stimulate the growth and activity of advantageous commensal bacteria in the gut. As a result, well-chosen probiotics or prebiotics, or synbiotics (a combination of prebiotics and probiotics) may modify the intestinal environment in favour of robust mucosal responses to oral vaccines.

E. Withholding breastfeeding

It has been postulated that breastfeeding may attenuate immune responses to oral vaccines[26]. Breast milk contains secretory IgA antibodies as well as innate immune factors such as lactoferrin which can inhibit the replication of live viruses[47]. There are also geographical differences in the composition of breast milk. Rotavirus neutralizing titres in breast milk are higher in Indian mothers compared to mothers from the U.S.A, mirroring the geographical patterns of oral vaccine underperformance. It is therefore possible that withholding breastfeeding around the time of administration of an oral vaccine may enhance the mucosal immune response. However, the evidence for an inhibitory effect of breast milk is heterogeneous. An older study examining the timing of breast feeding on oral

polio vaccine responses showed that withholding breast milk around the time of vaccine administration had no significant effect on vaccine response[13]. In addition, a recent study of children in Bangladesh showed that added months spent exclusively breast-fed was associated with increased serum neutralising responses to oral polio vaccine[8].

F. Dosing or schedule changes

The endgame to eradicate poliomyelitis has been challenged by oral vaccine underperformance and exemplifies strategies used to close immunity gaps. In some areas, despite high coverage and intensive use of OPV, polio eradication has remained challenging. There are probably several contributing factors (listed above) including a high force of infection. One approach to addressing these polio 'hotspots' has been to resort to higher potency vaccines and supplemental doses. In Uttar Pradesh, India, high potency mOPV1 and supplemental IPV has been shown to enhance OPV-induced mucosal immunity[48].

Research tackling the underperformance of rotavirus vaccines has also explored dose adjustments (delayed dosing and or increased number of doses)[14,24,25]. Rotavirus vaccine is currently recommended at 6 and 10 weeks of age; however, in developing countries, doses at younger ages generally yield lower rotavirus vaccine responses. A post-hoc exploratory analysis of vaccine trial data showed that African children receiving the first dose of pentavalent rotavirus vaccine at <8 weeks had lower efficacy (23.7%; 95% CI: -8.2%-46.3%) than those vaccinated at >8 weeks (59.1%; 95% CI: 34.0%-74.6%)[49]. Reasons for this may include the interference of concomitantly administered OPV and maternally acquired antibodies. IgA seroconversion was reduced among participants with higher levels of pre-vaccination maternally-derived IgG[24,50]. A delayed or additional dose of rotavirus vaccine, given after 10 weeks, may limit interference from circulating maternal antibodies and live oral polio vaccine virus as well as benefiting from a more mature infant immune system. Additional rotavirus vaccine doses however must be weighed up against the increased risk of intussusception when rotavirus vaccine is given later in childhood.

Within dosing or schedule changes, we will not include strategies which bypass the oral route; for example, the use of IPV as a booster to immunisation with OPV. The strengths of

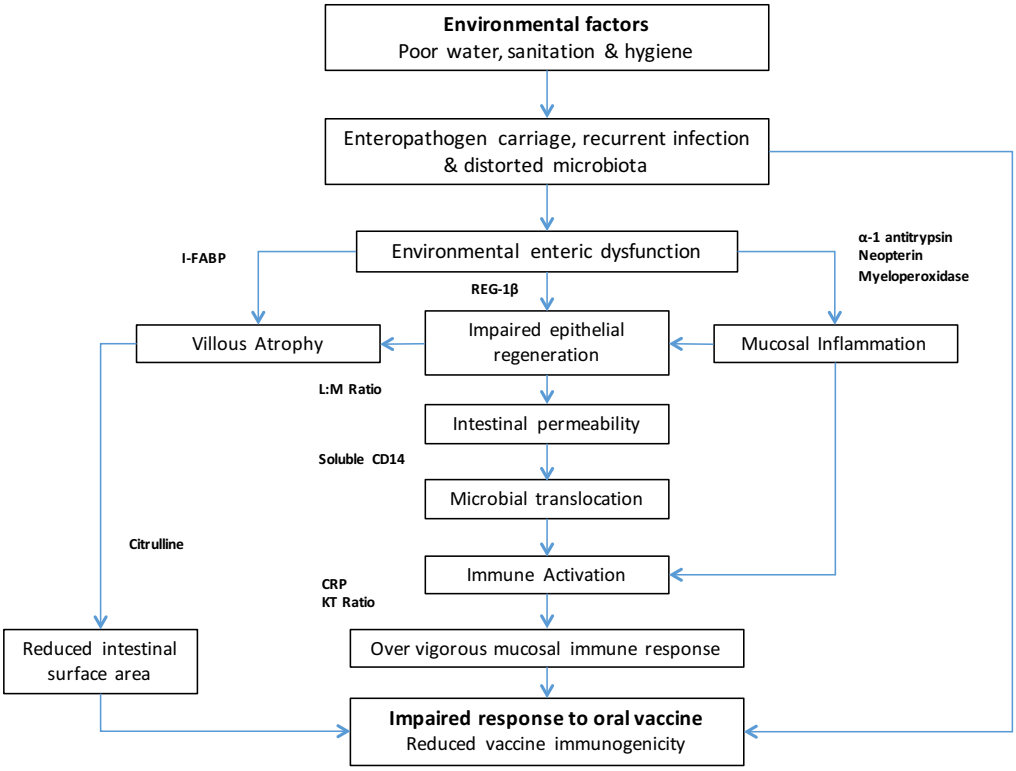
oral vaccination lie in its relative inexpensiveness, ease of administration and avoidance of needles as well as its direct action at the site of infection. Alternative routes of administration, which may be a highly plausible way of overcoming the barriers to oral vaccines, are therefore not the subject of this review and studies exploring this angle will be excluded (as detailed above).

G. WASH (water, sanitation & hygiene) interventions

Safe drinking water, access to sanitation and hygiene have long been viewed as key determinants of population health. Indeed, it was following the pioneering work of Chadwick, Farr and Snow in the 19th century that 'sanitary conditions' became integral to the transmission of disease, giving rise to the field of public health. The term WASH captures several interventions, which can be designed and implemented in a variety of ways and affect a broad range of outcomes, beyond just health. *Water* is usually subdivided into two different interventions: one to improve water quantity, the other to improve water quality. *Sanitation* refers to technologies to safely contain excreta and limit human contact. Finally, *hygiene* usually refers to hand hygiene and washing with soap at critical times (e.g. after defecation and before meal preparation and consumption)[51]. Together these interventions create an interconnected set of barriers, limiting exposure to and transmission of infectious pathogens between human subjects via five predominant transmission pathways (fluids, flies, food, fields and fingers) – commonly referred to as the F-diagram (Wagner & Lanoix 1958).

In many developing countries, children grow up in conditions of poor WASH. It is possible that this leads to increased subclinical carriage of enteric pathogens, diarrhoea and EED, altering the intestinal environment and reducing immunogenicity of oral vaccines *(see schematic in Figure 1 below)*. If this hypothesis is correct, it is logical that interventions to improve WASH may prevent pathogen carriage, diarrhoea and EED and thereby enhance responses to oral vaccines.

Figure 1: Proposed biological pathway demonstrating the link between conditions of poor WASH and the underperformance of oral vaccines, mediated by adverse conditions with the intestine.



H. Other plausible interventions

Given the numerous factors that have been linked to the underperformance of oral vaccines, it is possible that other interventions have been tested outside of those listed above. One example would be nutritional interventions beyond zinc and Vitamin A supplementation. Malnutrition underlies 45% of deaths in children under 5 years in developing countries and there is high degree of overlap between regions affected by malnutrition and oral vaccine failure. Responses to parenteral vaccines are largely unaffected by malnutrition[52], and the monovalent rotavirus vaccine *Rotarix* remains efficacious regardless of nutritional status (Perez-Schael RIX 4414 JID 2007). However seroconversion rates to oral polio vaccination have been reported to be significantly lower in stunted versus non-stunted infants[53]. It is therefore possible that other interventions to improve nutritional status in undernourished children may also improve responses to oral

vaccines. For this reason, macronutrients as well as micronutrients have been included in our list of interventions to evaluate.

Another potential window of opportunity is prenatal interventions. The first 1000 days (from conception to a child's birthday) is increasingly recognized as a critical period of child growth and development, including dynamic intestinal adaptation and immune ontogeny. Environmental factors and maternal health from early pregnancy can also shape epigenetic changes in the developing fetus[54] and impact on later health and immunity. There is evidence, for example, that prenatal exposure to maternal helminth infections may modulate infant responses to vaccination and infectious pathogens[55,56]. It is therefore conceivable that a maternal anthelminthic intervention could boost immune responses to infant oral vaccines. Results of a large randomised controlled trial have shown that neither albendazole nor praziquantel given during pregnancy affect infant immune responses to BCG, tetanus and measles immunisations[57]. In this trial, oral vaccine responses were not examined; however, another study in Ecuador evaluated oral vaccine responses in the context of maternal helminth infection in pregnancy and paradoxically showed a protective effect, with maternal infection associated with higher infant IgA titres to oral polio and rotavirus vaccine antigens[58].

Review general information

Type and method of review

Systematic review and meta-analysis (if possible)

Language

English

Country

England, UK

Other registration details

None

Reference and/or URL for published protocol

Dissemination plans

The results of this review will hopefully help define the scope and quality of existing evidence for interventions to improve vaccine performance as well as highlighting research priorities moving forwards. These findings and messages will be disseminated to key stakeholders in the field of oral vaccines from research groups to policy makers through conference proceedings and academic publications.

Keywords

Oral, vaccine, intervention, immunogenicity, efficacy, developing, infants

Details of any existing review of the same topic by the same authors

Any additional information

Members of our group of authors have also been invited to submit a review paper exploring the factors which influence the performance of oral vaccines in developing countries. In spite of the considerable effort that has been devoted towards explaining this "gap" in performance, the biological mechanisms responsible for the impaired performance of oral vaccines in impoverished settings remain uncertain. This commissioned review exploring biological mechanisms will provide a timely background to our systematic review.

Results

Discussion

Acknowledgements

Francis Delwiche, Health Sciences Librarian and Associate Professor at the Dana Medical Libarary, University of Vermont, for her early guidance in designing and later refining the systematic search strategy.

Contributions of authors

Appendix 1 – GRADE Scoring

The GRADE scoring system used for *Clinical Evidence* reviews

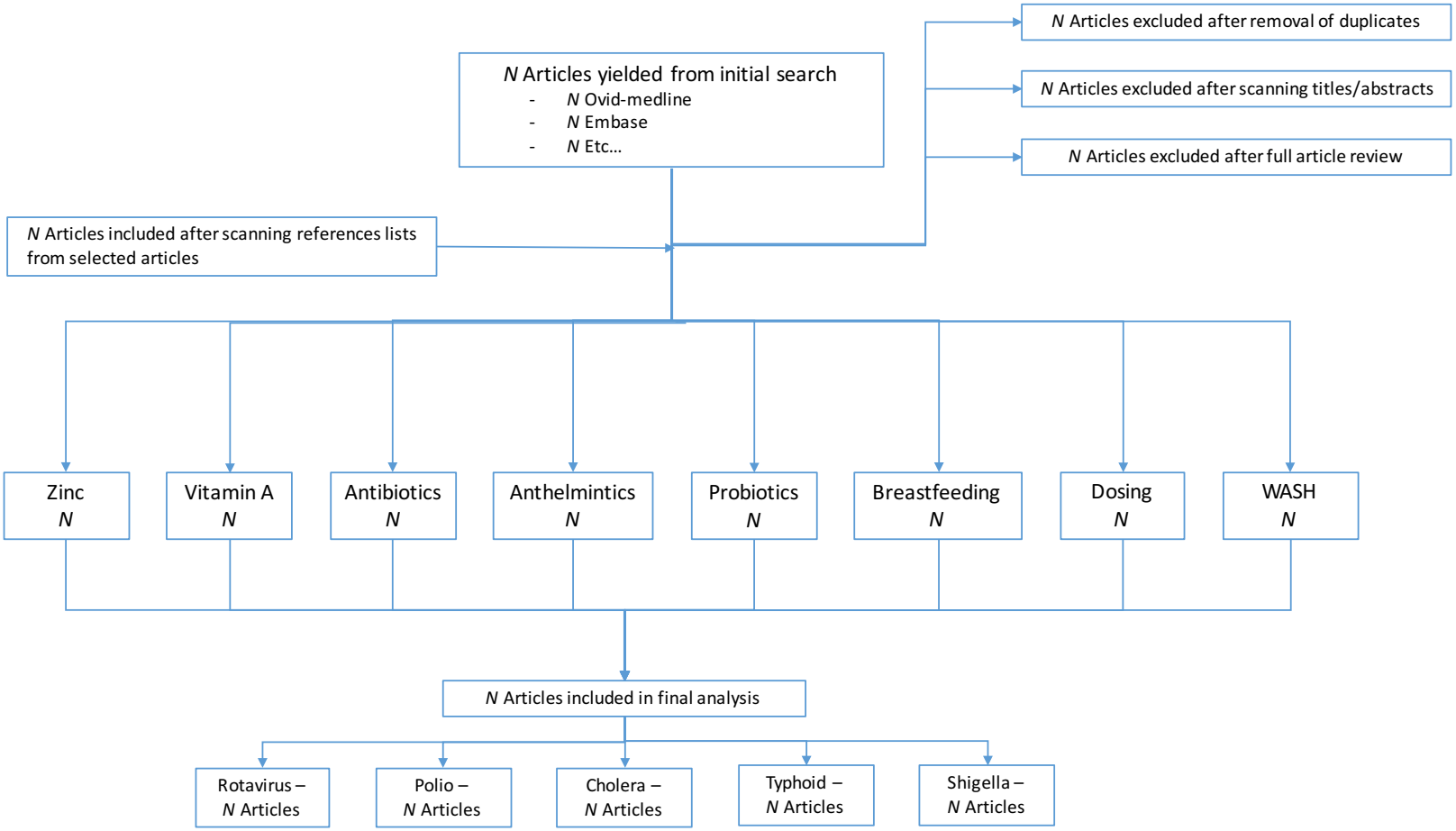
Type of evidence		
Initial score based on type of evidence	+4	RCTs/ SR of RCTs, +/– other types of evidence
	+2	Observational evidence (e.g., cohort, case-control)
Quality		
Based on	Blinding and allocation process	
	Follow-up and withdrawals	
	Sparse data	
	Other methodological concerns (e.g., incomplete reporting, subjective outcomes)	
Score	0	No problems
	–1	Problem with 1 element
	–2	Problem with 2 elements
	–3	Problem with 3 or more elements
Consistency		
Based on	Degree of consistency of effect between or within studies	
Score	+1	Evidence of dose response across or within studies (or inconsistency across studies is explained by a dose response); also 1 point added if adjustment for confounders would have increased the effect size
	0	All/most studies show similar results
	–1	Lack of agreement between studies (e.g., statistical heterogeneity between RCTs, conflicting results)
Directness		
Based on	The generalisability of population and outcomes from each study to our population of interest	
Score	0	Population and outcomes broadly generalisable
	–1	Problem with 1 element
	–2	Problem with 2 or more elements

Type of evidence		
Effect size		
Based on	The reported OR/RR/HR for comparison	
Score	0	Not all effect sizes >2 or <0.5 and significant; or if OR/RR/HR not significant
	+1	Effect size >2 or <0.5 for all studies/meta-analyses included in comparison and significant
	+2	Effect size >5 or <0.2 for all studies/meta-analyses included in comparison and significant

The final GRADE score: we use 4 categories of evidence quality based on the overall GRADE scores for each comparison: high (at least 4 points overall), moderate (3 points), low (2 points), and very low (one or less).

Appendix 2 – PRISMA Flow diagram

PRISMA Flow diagram outlining systematic search process

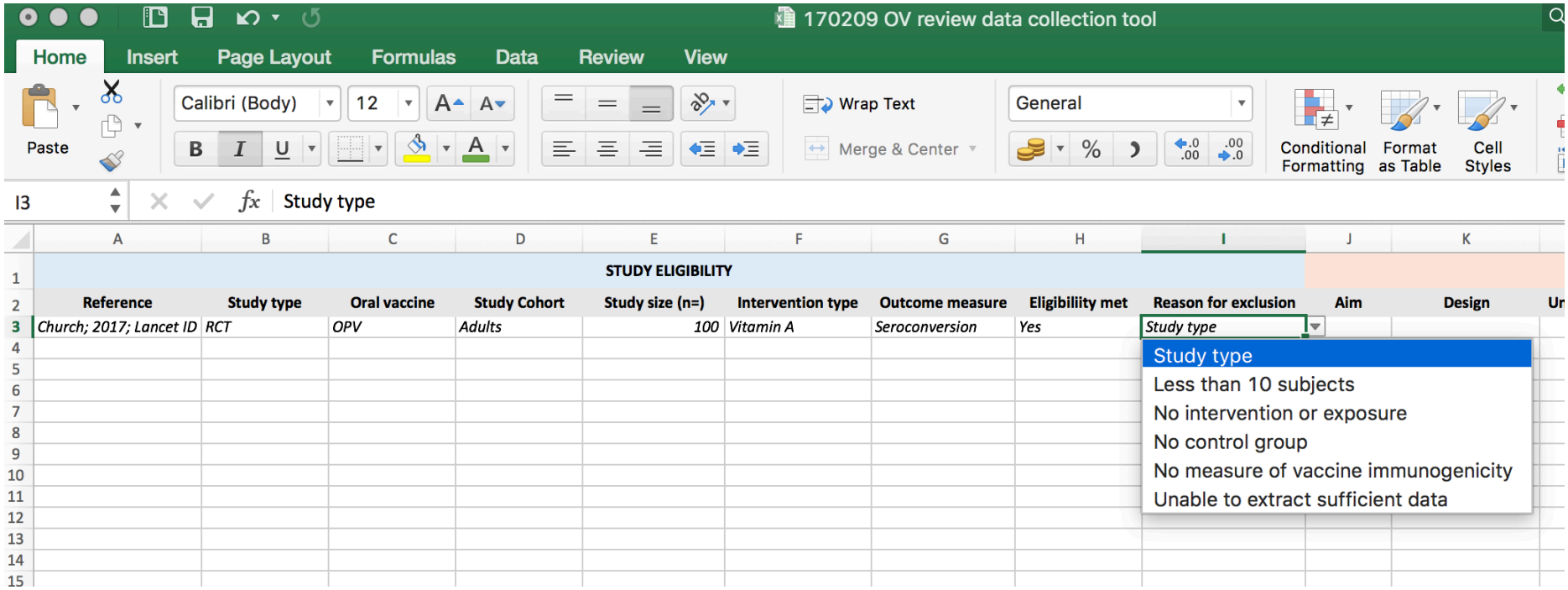


Appendix 3 – Search strategy

Using **Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present)

Interventions	Outcomes
43. Zinc.mp.	1. exp Vaccination/
44. 42 and 43	2. Vaccin*.mp.
45. Vitamin A.mp.	3. 1 or 2
46. 42 and 45	4. Poliovirus/
47. Micronutrient.mp	5. Poliovirus:.mp.
48. Micronutrients/	6. Polio.mp.
49. 47 or 48	7. Rotavirus/
50. 42 and 49	8. Rotavirus:.mp.
51. Macronutrient.mp	9. Cholera/
52. 42 and 51	10. Cholera:.mp.
53. Anti-bacterial agents.sh.	11. Typhoid Fever/
54. Antibiotic.mp.	12. Typhoid:.mp.
55. 53 or 54	13. Salmonella typhi/
56. 42 and 55	14. Salmonella typhi:.mp.
57. Anthelmintics.sh.	15. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
58. Anthelmintic.mp.	16. 3 and 15
59. Albendazole.mp.	17. Poliovirus Vaccines/
60. Praziquantel.mp.	18. exp Administration, Oral/
61. 57 or 58 or 59 or 60	19. 17 and 18
62. 42 and 61	20. Poliovirus Vaccine, Oral/
63. Prebiotic.mp.	21. Rotavirus Vaccines/
64. Probiotics.sh.	22. Cholera Vaccines/
65. Probiotic.mp.	23. Typhoid-Paratyphoid Vaccines/
66. Synbiotic.mp.	24. Shigella Vaccines/
67. LGG.mp.	25. 19 or 20 or 21 or 22 or 23 or 24
68. 63 or 64 or 65 or 66 or 67	26. 16 or 25
69. 42 and 68	27. Immunogenicity.mp.
70. Breast Feeding.sh.	28. Immunogenicity, Vaccine/
71. Breastfeed:.mp.	29. Response.mp.
72. 70 or 71	30. Seroresponse.mp
73. 42 and 72	31. Seroconversion.mp
74. Dosing.mp.	32. Shedding.mp.
75. Schedule.mp.	33. Virus shedding/
76. Ad.fs.	34. Efficacy.mp
77. 74 or 75 or 76	35. Titre.mp.
78. 42 or 77	36. Antibodies, Viral/
79. (hand*1 adj3 (wash* or clean* or disinfect*)).mp.	37. Antibodies, Bacterial/
80. (hand*1 adj3 hygien*).mp.	38. Performance.mp
81. Hand washing.sh.	39. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
82. (handwashing or hand washing).mp.	40. 28 and 39
83. Hygiene/	
84. (hygiene adj2 educat*).mp.	
85. Sanita*.mp.	
86. (faeces or human faeces).sh.	
87. Water Supply/	
88. Water Purification/	41. limit X to (clinical trial, all or meta analysis or multicenter study or observational study or systematic reviews)
89. (Soaps/ or soap.mp.) adj3 (water* or hygien* or educat* or wash*).mp.	
90. Sanitation/	
91. (latrine*1 or toilet*1 or water closet*1 or privy).mp.	
92. 79 or 80…. Or 90	
93. 40 and 92	

Appendix 4 – Data collection tool



Appendix 5 – Examples of published studies

1. **Micronutrient supplementation**
    a. Vitamin A (see Benn 2012 review)
    b. Zinc (Albert, JID, 2003 – Cholera; Ahmed, Vaccine, 2009 – Cholera; Habib, Vaccine, 2015 – Polio)
2. **Antibiotics** (Grassly, Lancet ID 2016 – OPV)
3. **Anthelminthic** (Cooper, JID, 2000 – Cholera; Bruckner, Vaccine, 2016 – Cholera & PLoS Negl, 2016 - Influenza; Webb Lancet, 2011 – BCG, Tetanus, Measles after maternal antenatal Rx)
4. **Probiotic** (Isolauri, Vaccine, 1995; Zhang, Vaccine, 2008 pigs – RV; Matsuda, Vaccine, 2011 – Cholera, de Vrese, Eu Jn Nutr 2005 – Polio)
5. **Timing of breastfeeding** (Ahmed, Vaccine, 2009 – Cholera; Ali, PLoS one, 2015 – RV; Rongsen-Chandola, Vaccine, 2015 – RV; Groome, Bull WHO, 2014 – RV)
6. **Dosing**
    a. Dose timing (PROVIDE Colgate, CID, 2016)
    b. Dose increases and additional doses (Ali JID 2014; Armah JID 2016 – RV; Moriniere, Lancet, 1993; Sutter, NEJM, 2000 – Polio)
    c. EPI changes and administration with other vaccines (Mychalekyj, Vaccine 2016; Ramani, PIDJ, 2016 – RV)
7. **WASH interventions** (SHINE trial, Mal-ED, SaniVac (MapSan) – Brown 2015)

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