The Effects of Pneumococcal and Haemophilus Vaccines in Children Under 5 Years of Age on Severity of Illness and Deaths From Infections Other Than Those Conditions That the Vaccine is Designed to Prevent, and on All-cause Mortality and All-cause Hospitalisation: A Systematic Review Protocol

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Protocol

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Abstract

Background

Vaccination in children has reduced morbidity and mortality worldwide from infectious diseases. It has been suggested that vaccines have beneficial effects beyond the diseases they are designed to prevent. These are known as “non-specific effects” and include reductions in severity of illness and hospitalisation for illnesses other than those the vaccine is designed to prevent. This protocol will focus specifically on the non-specific effects of pneumococcal and haemophilus influenza vaccines in children under 5 years of age.

Methods

We will systematically search Medline, Embase, Cochrane Central Register of Controlled Trials, the European Union Clinical Trials Register and the clinicaltrials.gov databases using a broad range of search terms pertaining to pneumonia, morbidity, mortality and children to identify potentially relevant studies. These will be limited to randomised controlled trials, quasi randomised controlled trials and cohort studies in English. Two independent reviewers will conduct all levels of screening, data abstraction, and quality appraisal (using the Cochrane risk of bias tool).

Discussion

Our results can be used by researchers and policy-makers to identify if there are non-specific effects of pneumococcal and haemophilus vaccines which should be explored further. The review will be also be of interest to patients and clinicians to determine if vaccines have beneficial effects beyond the illnesses they are designed to prevent.

Systematic review registration

The systematic review protocol is registered with the PROSPERO database, Registration number: CRD42020146640.

Background

The beneficial effects of vaccination in reducing morbidity and mortality from the illnesses they are designed to prevent is widely reported with estimates that vaccines prevent approximately 6 million deaths worldwide annually.[i],[ii] Vaccination has attempted to reduce morbidity and mortality from major diseases such as diphtheria, tetanus, yellow fever, pertussis, haemophilus influenza type b disease, measles, mumps, rubella, typhoid and rabies, with the successful eradication of smallpox and near-complete eradication of poliomyelitis.[iii]

Pneumonia remains a major cause of morbidity and mortality worldwide, the World Health Organisation (WHO) estimates there to be 156 million cases of pneumonia each year in children younger than five

years, with as many as 20 million requiring hospital admission, accounting for an estimated 0.935 million deaths every year.[iv],[v] However the number of pneumonia deaths in young children has almost halved between 2000 and 2015.[vi] This is likely attributable to improved provision of primary care through the Integrated Management of Childhood Illness programme, and increasing use of universal vaccination, including haemophilus influenza type B (Hib) and pneumococcal vaccines.[vii]

Vaccination with the Hib and pneumococcal conjugate vaccines protects children from invasive disease caused by these organisms. Routine vaccination has been shown to dramatically decrease the incidence of invasive Hib disease in children leading to a reduction in the number of hospital admissions.[viii],[ix] A study by Cowgill et al. reported a reduction of the incidence of invasive Hib disease to 12% of its baseline level three years after the vaccine was introduced. The 7-valent pneumococcal conjugate vaccine (PCV7) has been shown to reduce incidence rates of invasive pneumococcal disease by as much as 75%.[x] The introduction of the 13-valent pneumococcal conjugate vaccine (PCV13), replacing PCV7 in 2010, is likely to further reduce the incidence of pneumonia due to enhanced coverage of serotypes responsible for the majority of pneumococcal pneumonia cases in children worldwide.[xi] GAVI the Vaccine Alliance (previously the Global Alliance for Vaccines and Immunization) has been pivotal in the introduction of vaccination protocols enabling an estimated reduction of between 6 to 7.5 million cases of pneumonia and the avoidance of between 230,000 to 290,000 deaths since its introduction of its pneumococcal vaccine programme in 2007.[xii]

There is evidence also that vaccines have effects not just limited to the illnesses they are designed to prevent. These effects are commonly termed “non-specific” effects. Vaccination with measles-containing vaccines, Bacille Calmette-Guérin (BCG), and oral polio vaccine (OPV) have all been shown to reduce both hospitalisation rates and mortality in children with further research required to better understand the impact on mortality.[xiii],[xiv],[xv] Non-specific beneficial effects of vaccination in pneumonia may be due to bacteria and viruses acting as co-pathogens in the aetiology of pneumonia.[16] Evidence also indicates that respiratory viruses contribute to bacterial infections, often leading to bacterial superinfections.[xvi] Non-specific beneficial effects of vaccination may be due to the results of altered immune system memory, leading to a reduction in all-cause mortality.[xvii],[xviii] However there is contradictory evidence with one systematic review demonstrating that receipt of the diphtheria pertussis tetanus (DPT) vaccine was shown to be associated with an increase in all-cause mortality. This should be interpreted with caution as all ten studies within the analysis were observational and classed as having a “high risk of bias.”[xix],[xx] Further work is required to determine the presence or absence of non-specific effects of newer vaccines such as pneumococcus and haemophilus influenza which were more recently added to schedules internationally.

The objective of this protocol is to describe a systematic review strategy which will determine the evidence for “non-specific” effects of pneumococcal and Hib vaccines on:

- deaths from infections other than those conditions that the vaccine is designed to prevent in children under five years of age.

- hospitalisations from infections other than those conditions that the vaccine is designed to prevent in children under five years of age.
- severity of all infectious illnesses as defined by the authors in children under 5 years of age.
- all-cause mortality in children under five years of age.
- all-cause hospitalization in children under five years of age.

We will provide an evidence profile that summarizes the findings for each study question.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement will be used to guide the reporting and conduct of this review.[i] The systematic review protocol was registered with the PROSPERO database (registration number

CRD42020146640)

Study Questions

The primary questions to be addressed by this review are as follows:

1. Is the administration of pneumococcal and/or Hib vaccines in infancy associated with an effect on survival from infections other than those conditions that the vaccine is designed to prevent in children up to five years of age?
2. Is the administration of pneumococcal and/or Hib vaccines in infancy associated with an effect on severity of the illness as defined by the authors or hospitalisations for infections other than those conditions that the vaccine is designed to prevent in children up to five years of age?

The secondary questions to be addressed are:

1. Is the administration of pneumococcal and/or Hib vaccines in infancy associated with an effect on all-cause mortality in children up to five years of age?
2. Is the administration of pneumococcal and/or Hib vaccines in infancy associated with an effect on all-cause hospitalisation in children up to five years of age?

For each question we will also assess if the effect is modified by gender, number of doses, age at vaccination, sequence/order in which vaccines are given and/or prior, or co-administration of vitamin A or zinc if reported.

Eligibility criteria

Children under the age of five will be our population of interest. Pneumococcal vaccines of all formulations, encompassing PCV7, PCV13 and PCV23, will be included along with Hib vaccines. Studies reporting survival/all-cause mortality/deaths from infections other than those conditions that the vaccine

is designed to prevent and studies reporting death from all causes (e.g. all-cause mortality, child survival) will be eligible for inclusion. Inclusion of studies will not be limited by publication status or year of dissemination. Only randomized controlled trials (RCT's), quasi-RCTs or cohort studies written in English will be included. The draft eligibility form can be found in Additional file 1: Appendix 1.

Exclusion criteria

We will exclude ecological studies, uncontrolled studies (i.e. case reports and case series studies), studies including only individuals with the outcome of interest in the analyses ("case only" studies) and, self-controlled case series studies because these studies provide less reliable data for assessing non-specific effects of vaccines on mortality. Additionally, we will exclude animal or laboratory studies. Studies involving adults or children older than five years of age or where children under five years of age are not reported separately will be excluded.

Data Management

The results from the literature search will be imported into Rayyan (http://rayyan.qcri.org/) for review.[ii] This software will be used for screening the citations from the electronic database, as well as all full-text articles indicated via the search. Two reviewers will independently screen the literature search results for inclusion. They will then independently review the full text of potentially relevant articles and screen them to determine inclusion using the same inclusion and exclusion criteria. Conflicts will be resolved by discussion or the involvement of a third reviewer.

Information sources and search strategy

Literature search strategies using medical subject headings (MeSH) and text words related to children, pneumococcal and Hib vaccination will be used (Appendix). We will search MEDLINE (OVID interface, 1948 onwards)[iii], EMBASE (OVID interface, 1980 onwards)[iv], the Cochrane Central Register of Controlled Trials (Wiley interface, current issue)[v]. The electronic database search will be supplemented by searching for trial protocols through the European Union Clinical Trials Register (EURACT)[vi] and the clinicaltrials.gov website.[vii] To ensure literature saturation, we will review the reference lists of included studies or relevant reviews identified through the search. We will also search the author's personal files to make sure that all relevant material has been identified. Finally, we will circulate a bibliography of the included articles to experts in the field to obtain a comprehensive study list.

Data collection process

A draft data abstraction form has been developed (appendix) according to the Cochrane EPOC format and will be piloted and modified as necessary. For each included study, the following information will be extracted if reported: Year published, location of study, type of study, vaccines studied, number of doses, age at vaccination, sequence in which vaccines are given, inclusion criteria, age group, gender, co-administration of Vitamin A or Zinc, pre-specified outcomes and results.

To ensure data accuracy, two reviewers will independently abstract the data using the standardised data abstraction form. Discrepancies will be resolved by discussion amongst the review team with final adjudication by the study group chair.

Risk of Bias assessment

We will use Cochrane tools for assessing risk of bias in clinical trials (RoB2)[viii] and for non-randomised studies we will use the Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I).[ix] We will also consider potential confounders and determine if reported in the studies. These will be age and gender distribution, health status of the children (including nutritional status and birth weight), and socioeconomic status (including location of the study, poverty, education, and hygiene conditions). We will also assess if any other interventions were undertaken as part of the study including malaria interventions, de-worming, co-administration of vitamin A or zinc or other micronutrient supplements, breast feeding, hygiene programmes, water programmes and other vaccinations that may be reported in the studies.

Discussion

Vaccination remains a topical and controversial subject area, particularly in the media. The beneficial effects, particularly regarding well established vaccines such as BCG, OPV and DTP vaccines, are well documented and accepted. As pneumococcal and Hib vaccines are introduced to vaccination schedules worldwide it is anticipated that they will have similar success rates. Since their introduction there has been impressive reductions in morbidity and mortality, as reported by GAVI. Non-specific beneficial effects are less widely reported and if found to be significant may enable increased uptake rates of these vaccines, further reducing the disease burden in childhood worldwide. This systematic review will comprehensively examine the extent to which pneumococcal and Hib vaccines influence survival, severity of illness, all-cause mortality and all-cause hospitalisation due to illnesses not caused by the organism the vaccine is designed to prevent. The results can be used by researchers and policy-makers for implementation of vaccination protocols, particularly in the context of low income countries. This work will also facilitate the development of improved vaccines in the future.

Limitations of the review include that the search strategy may not identify every vaccination protocol due to the use of diverse terminology and by restricting the studies to those written in English we may miss evidence in other languages.

This is the first systematic review, to our knowledge, that will investigate the non-specific effects of pneumococcal and Hib vaccines on survival, severity of disease, all-cause mortality and all-cause hospitalisation.

List Of Abbreviations

PCV7=7-valent pneumococcal conjugate vaccine.

PCV13=13-valent pneumococcal conjugate vaccine.

BCG=Bacille Calmette-Guérin.

DPT=Diphtheria pertussis tetanus.

Hib=Haemophilus influenza type B.

OPV=Oral polio vaccine.

PRISMA=Preferred reporting items for systematic reviews and meta-analyses.

WHO=World Health Organisation.

Declarations

- Ethics approval and consent to participate: Not applicable.
- Consent for publication: Not applicable.
- Availability of data and materials: All data generated or analysed during this study are included in this published article and its supplementary information files.
- Competing interests: The authors declare that they have no competing interests.
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- Authors contributions: DR and JG composed the search strategy. All authors read and approved the final manuscript composed by DR. JG is the guarantor of the manuscript
- Acknowledgements: Not applicable.

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Appendix

Appendix 1 Search Strategy

Medline

((((((child/exp OR child OR children/exp OR children OR newborn* OR newborn/exp OR newborn OR new born))) AND (((((((Pneumococcal Vaccines[MeSH] OR (Pneumococc*[tiab] AND (vaccin* OR immuniz* [tiab] OR immunis*[tiab]))) OR (PPV23[tiab] OR "PPV 23"[tiab] OR Pneumovax[tiab] OR PCV13[tiab] OR "PCV 13"[tiab] OR PCV7[tiab] OR "PCV 7"[tiab] OR Prevnar[tiab] OR Prevenar[tiab] OR "Pneumo 23"[tiab] OR Pneumo23[tiab])))))) OR ((((("haemophilus vaccines"[MeSH] OR "haemophilus conjugate vaccine [All

Fields] OR " "haemophilus conjugate vaccines"[All Fields] OR "hemophilus conjugate vaccine"[All Fields] OR "haemophilus conjugate vaccine"[All Fields] OR "haemophilus vaccine"[All Fields] OR "hemophilus vaccine"[All Fields] OR "haemophilus vaccines"[All Fields] OR "hemophilus vaccines"[All Fields] OR "H. influenzae vaccine"[All Fields] OR "H. influenzae vaccines" OR "haemophilus influenzae vaccine"[All Fields] OR "hemophilus influenzae vaccine" OR "haemophilus influenzae vaccines"[All Fields] OR "hemophilus influenzae vaccines" OR "ActHib"[All Fields] OR "PedVaxHib"[All Fields] OR "Comvax"[All Fields] OR "DTaP/Hib"[All Fields] OR "TriHIBit"[All Fields] OR "DTPw-HB/Hib"[All Fields])))))))) AND ((((death OR deaths OR died OR mortality OR mortality/exp OR mortalities OR fatal OR dying OR decreased OR "life threatening" OR "severe reaction" OR ICU OR "intensive care" OR emergency OR urgent OR fatalities OR casualty OR casualties OR lethalness OR “hospitalisation" or “hospitalization” OR “heterologous” OR non specific OR nonspecific OR “non specific”)))))

Embase

('child'/exp OR 'child' OR 'children') AND ('pneumococcal vaccines'/exp OR 'pneumococcal vaccines' OR (pneumococcal AND ('vaccines'/exp OR vaccines)) OR pneumococc) AND ('vaccine'/exp OR vaccine OR immuniz OR immunis OR ppv23 OR 'ppv 23'/exp OR 'ppv 23' OR (ppv AND 23) OR 'pneumovax'/exp OR pneumovax OR 'pcv13'/exp OR pcv13 OR 'pcv 13'/exp OR 'pcv 13' OR (pcv AND 13) OR pcv7 OR 'pcv 7'/exp OR 'pcv 7' OR (pcv AND 7) OR 'prevnar'/exp OR prevnar OR 'prevenar'/exp OR prevenar OR 'pneumo 23'/exp OR 'pneumo 23' OR (pneumo AND 23) OR 'pneumo23'/exp OR pneumo23 OR 'haemophilus conjugate vaccines' OR (('haemophilus'/exp OR haemophilus) AND ('conjugate'/exp OR conjugate) AND ('vaccines'/exp OR vaccines)) OR 'hemophilus conjugate vaccine' OR (('hemophilus'/exp OR hemophilus) AND ('conjugate'/exp OR conjugate) AND ('vaccine'/exp OR vaccine)) OR 'haemophilus conjugate vaccine' OR (('haemophilus'/exp OR haemophilus) AND ('conjugate'/exp OR conjugate) AND ('vaccine'/exp OR vaccine)) OR 'haemophilus vaccine'/exp OR 'haemophilus vaccine' OR (('haemophilus'/exp OR haemophilus) AND ('vaccine'/exp OR vaccine)) OR 'hemophilus vaccine'/exp OR 'hemophilus vaccine' OR (('hemophilus'/exp OR hemophilus) AND ('vaccine'/exp OR vaccine)) OR 'haemophilus vaccines'/exp OR 'haemophilus vaccines' OR (('haemophilus'/exp OR haemophilus) AND ('vaccines'/exp OR vaccines)) OR 'hemophilus vaccines' OR (('hemophilus'/exp OR hemophilus) AND ('vaccines'/exp OR vaccines)) OR 'h. influenzae vaccine' OR (h. AND influenzae AND ('vaccine'/exp OR vaccine)) OR 'h. influenzae vaccines' OR (h. AND influenzae AND ('vaccines'/exp OR vaccines)) OR 'haemophilus influenzae vaccine'/exp OR 'haemophilus influenzae vaccine' OR (('haemophilus'/exp OR haemophilus) AND influenzae AND ('vaccine'/exp OR vaccine)) OR 'hemophilus influenzae vaccine'/exp OR 'hemophilus influenzae vaccine' OR (('hemophilus'/exp OR hemophilus) AND influenzae AND ('vaccine'/exp OR vaccine)) OR 'haemophilus influenzae vaccines' OR (('haemophilus'/exp OR haemophilus) AND influenzae AND ('vaccines'/exp OR vaccines)) OR 'hemophilus influenzae vaccines' OR (('hemophilus'/exp OR hemophilus) AND influenzae AND ('vaccines'/exp OR vaccines)) OR 'acthib'/exp OR acthib OR 'pedvaxhib'/exp OR pedvaxhib OR 'comvax'/exp OR comvax) AND (((((death OR deaths OR died OR mortality OR 'mortality'/exp OR mortalities OR fatal OR dying OR decreased OR life) AND threatening OR severe) AND reaction OR icu OR intensive) AND care OR emergency OR urgent OR

fatalities OR casualty OR casualties OR lethalness OR hospitalisation OR hospitalization OR heterologous OR non) AND specific OR nonspecific OR non) AND specific.