Systematic Review of the Nonspecific Effects of Selected Routine Childhood Immunizations

Review Protocol

Andrew Pollard, Karlijn de Nie, Arthur Reingold, Paul Zhang, Ana Maria Henao Restrepo, and Ximena Riveros de Laurie

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1) Background

Over the past 10-15 years, a number of published reports have claimed that several vaccines routinely administered to infants around the world may have "heterologous" or "non-specific" effects on mortality unrelated to prevention of illness and deaths caused by the specific diseases against which the vaccines have been formulated. For example, studies have suggested that receipt of both BCG vaccine and measles vaccine is associated with a reduced risk of death (i.e. all cause mortality), while receipt of DPT vaccine is associated with an increased risk of death, at least among female infants. The vast majority of the studies demonstrating these effects have been observational in nature (i.e. not randomized clinical trials), and as a result, poorly-controlled or uncontrolled confounding and various types of selection and information bias have been suggested as alternative explanations for these findings.

The biological plausibility of one or more vaccines having heterologous effects, either detrimental or beneficial, is supported by a number of studies in animals (e.g. mice) and observations in people. Nevertheless, the biological mechanisms and immune pathway components that would underlie and explain such effects remain largely unspecified and open to question. At the same time, the possible implications of any such heterologous vaccine effects for the formulation or re-formulation of the infant immunization schedule remain unclear, but it has been suggested that if such effects can be established beyond a reasonable doubt, the infant immunization schedule might need to be re-configured. However, prior reviews of this subject, including periodic assessments by WHO's Global Advisory Committee on Vaccine Safety, have concluded that any such effects remain unproven and therefore not a justification for altering the current schedule.

WHO's Strategic Advisory Group of Experts (SAGE) has requested the WHO Secretariat to review the evidence concerning the possible non-specific/heterologous effects of vaccines included in the routine infant immunization schedule. Overall, our aim is to determine if the current evidence is sufficiently sound to warrant further scientific investigation; and if so, to define the path towards obtaining unequivocal evidence on these issues that would support future robust, evidence-based adjustments in immunization policies, if warranted. Preparatory to such a review of the evidence by SAGE at its April, 2013 meeting, it is necessary to assemble the available evidence, both published and, if possible, unpublished, and subject that evidence to WHO's required GRADE-based systematic approach to review of evidence.

2) Objective

To systematically identify, assemble, and review all available studies and data addressing the possible "non-specific" or "heterologous" effects of BCG, measles, DPT, including studies with epidemiologic and immunologic endpoints and, to critically appraise the evidence using the modified GRADE approach developed and described by WHO's Strategic Advisory Group of Experts (SAGE).

3) Study Questions

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

A. What is the effect of BCG vaccine given before 5 years of age on all available immune response markers in a non-specific way?

B. What is the effect of measles vaccine given before 5 years of age on all available immune response markers in a non-specific way?

C. What is the effect of DPT vaccine given before 5 years of age on all available immune response markers in a non-specific way?

D. If, in infancy, one of the three vaccines under review is given first, does that effect the antibody response to a second different vaccine?

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

A. Do the effects on immune response markers, if any, of any of the vaccines under review vary by sex of the child?

B. Do the effects on immune response markers, if any, of any of the vaccines under review vary by age at which they are delivered?

C. Do the effects on immune response markers, if any, of any of the vaccines under review vary by co-administration of Vitamin A?

D. Do the effects on immune response markers, if any, of any of the vaccines under review vary by co-administration of a second different vaccine? .

4) Methods

A. Overall Approach

We will identify and critically appraise all available evidence (published and unpublished) that addresses the possible "non-specific" effects of vaccines when given before the age of 5 years, focusing primarily on the effects of vaccines on the child's immune system and the development of this immune system. Included in the review will be any randomized controlled trials (RCTs), quasi-randomized control trials, clinical trials, cohort studies, case-control studies, case series and case reports. . Vaccines to be examined will include live attenuated vaccines (all BCG and measles containing vaccines), inactivated vaccines and toxoids (all diphtheria and tetanus toxoids, and *Bordetella pertussis* containing vaccines). The target population is infants under five years of age. Gender, age at vaccination, order of vaccines given, and co-administration of vitamin A will be examined as possible effect measure modifiers.

B. Exclusion Criteria

Ecological studies, animal studies and in vitro studies will be excluded.

C. Search Strategy

Embase.com, which includes all records from MEDLINE, will be searched from 1947 onwards, through to 2012. A complementary, less extensive search of the pubmed library, the Cochrane library, and the trip database, will be performed in order to detect any articles missed by the search on Embase.com. A list of search entries going to be used is displayed in appendix A.

In addition, the reference lists of all included articles found and all relevant review articles will be manually searched to identify studies not included in the previously described search. Experts in the field will also be asked if they are aware of any unpublished reports of studies possibly meeting the inclusion criteria. Full text of all articles identified will be sought, using internet downloads, interlibrary loans, and contacting of authors. Articles in any language will be sought.

D. Selection of Eligible Studies

Each full text article will be examined by two independent reviewers and a list of studies considered eligible for inclusion will be made. Studies identified by both reviewers as being eligible for inclusion and having adequate data for extraction will be included in the review. Where there are discrepancies, the reasons for these will be discussed. A decision about inclusion will be reached by consensus. If there is no agreement, a further independent reviewer will adjudicate to make a final decision about eligibility.

E. Data Extraction Forms

We will develop forms for extracting consistent data about:

- exposures and outcomes (including methods or criteria for diagnosis);
- tests used to assess outcomes, any cut-off points used in the assessment of immunogenicity and the time between last vaccination and outcome assessment;
- presence of disease that might affect immunogenicity outcomes;
- co-administration of other vaccines or vitamin A;
- potential confounders if relevant;
- background data (e.g. geographic and demographic information);
- methodological and reporting quality (specific for each type of study design and based on published checklists of items likely to cause bias); and
- other potentially relevant information such as funding source.

We will pilot test the forms to ensure ease of use and capture all relevant data. The forms will be developed using DistillerSR software.

F. Data Extraction

All relevant data will be extracted from articles meeting inclusion criteria and entered into a database.

G. Data Analysis

We will produce descriptive tables summarizing information about study design, study quality, and results of all included studies. If there is more than one study reporting an exposure-outcome relationship, or the frequency of an outcome, we will present the results using forest plots and consider combining the data statistically in a meta-analysis. We will

examine heterogeneity of the results first using X2 test and I2 test (Higgins JP and Thompson SG, quantifying heterogeneity in a meta-analysis Stat Med 2002.21 (11):p. 1539-58). If a meta-analysis is appropriate we will calculate summary weighted effects measures and 95% CI using random effects models (Der Simmonian R Laird N Meta-analysis in clinical trials. Control Clin Trials, 1986. 7 (3): p177-88). If sufficient data are available, results will also be examined for apparent bias in a reporting/publication of studies using funnel plots and Egger's test (Egger M Davies-Smith G and Altman H. Systematic Review in health care, Meta-analysis in context (2001, London: BMJ books). We will use the GRADE approach, as modified by WHO's SAGE committee, to assess the evidence in support of various hypothesized associations between various vaccines and various "non-specific" health outcomes. Results will be summarized in GRADE tables.

H. Report

A report summarizing the findings will be written and provided to WHO using the internationally accepted guidelines for systematic reviews (http://www.prisma-statement.org/). In addition, a verbal report of the findings will be presented at the April, 2013 meeting of SAGE in Geneva, Switzerland.

References

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Abbreviations Used in this Proposal
BCG: Bacille Calmette-Guerin
DPT: Diphtheria-Pertussis-Tetanus
HBV: Hepatitis B virus
RCT: Randomized controlled trial
GRADE: Grading of Recommendations Assessment, Development and Evaluation
SAGE: Strategic Advisory Group of Experts
WHO: World Health Organization

Apendix A: search strategy

1. Embase search

Activins OR 'cytokine'/exp OR activin OR 'adipocytokines' OR ' adipokine' OR ' adipokines' OR ' adipose tissue derived cytokine' OR 'Acrp 30' OR ' Acrp30' OR ' adipocyte complement related protein 30' OR ' adipocyte most abundant protein 1' OR ' adipoq' OR ' APM 1' OR ' APM1' OR ' GBP 28' OR ' GBP28' OR ' gelatin binding protein 28' OR 'AIF 1' OR ' AIF1' OR ' cytokine AIF 1' OR ' cytokine AIF1' OR ' daintain' OR 'a proliferation inducing ligand' OR ' a proliferation inducing ligand protein' OR ' antigen CD256' OR ' CD256 antigen' OR ' protein APRIL' OR ' protein TALL2' OR ' protein TNFSF 13' OR ' protein TNFSF13' OR ' TALL 2 protein' OR ' TALL2 protein' OR ' TNF and ApoL related leukocyte expressed ligand 2' OR ' TNF related death ligand 1' OR ' TNFSF 13 protein' OR ' TNFSF13 protein' OR ' tumor necrosis factor and apolipoprotein related leukocyte expressed ligand 2' OR ' tumor necrosis factor ligand superfamily member 13' OR ' tumor necrosis factor related death ligand 1' OR ' tumor necrosis factor SF13' OR ' tumor necrosis factor superfamily member 13' OR 'B lymphocyte activating factor [134-285]' OR ' B lymphocyte stimulator [134-285]' OR 'ATX protein' OR ' ectonucleotide pyrophosphatase phosphodiesterase 2' OR ' ENPP2 protein' OR ' PDNP2 protein' OR ' protein ATX' OR ' protein ENPP2' OR ' protein PDNP2' OR 'antigen CD257' OR ' B-cell activating factor' OR ' B cell activation factor' OR ' B lymphocyte activating factor' OR ' B lymphocyte stimulator' OR ' B lymphocyte stimulator protein' OR ' BAFF' OR ' BLyS protein' OR ' CD257 antigen' OR ' protein BLyS' OR ' protein TALL 1' OR ' protein TALL1' OR ' protein TNFSF13B' OR ' TALL 1 protein' OR ' TALL1 protein' OR ' TNF and ApoL related leukocyte expressed ligand 1' OR ' TNFSF13B protein' OR ' tumor necrosis factor and apolipoprotein related leukocyte expressed ligand 1' OR ' tumor necrosis factor ligand superfamily member 13B' OR 'B cell differentiation factor' OR ' bcdf' OR 'B cell growth factor' OR ' bcgf' OR ' growth factor, b cell' OR 'bone morphogenetic proteins' OR ' bone morphogenic protein' OR 'BMP 12' OR ' BMP12' OR ' cartilage derived morphogenetic protein 3' OR ' CDMP 3' OR ' CDMP3' OR ' GDF 7' OR ' GDF7' OR ' growth and differentiation factor 7' OR ' growth differentiation factor 7' OR 'BMP 15' OR ' BMP15' OR ' GDF 9B' OR ' GDF9B' OR ' growth and differentiation factor 9B' OR ' growth differentiation factor 9B' OR 'BMP 2' OR ' BMP2' OR 'BMP 4' OR ' BMP4' OR 'BMP 5' OR ' BMP5' OR 'BMP 6' OR ' BMP6' OR 'BMP 9' OR ' BMP9' OR ' GDF 2' OR ' GDF2' OR ' growth and differentiation factor 2' OR ' growth differentiation factor 2' OR '4-1BB ligand' OR ' 4 1BB ligand' OR ' 4 1BBL protein' OR ' CD137L' OR ' ligand 4 1BB' OR ' protein 4 1BBL' OR 'antigen CD153' OR ' CD153 antigen' OR ' CD153 antigens' OR ' CD30L' OR ' protein TNFSF 8' OR ' protein TNFSF8' OR ' TNFSF 8 protein' OR ' TNFSF8 protein' OR ' tumor necrosis factor ligand superfamily member 8' OR ' tumor necrosis factor superfamily member 8' OR 'antigen CD154' OR ' CD154 antigen' OR ' CD40L' OR ' CD40L antigen' OR ' protein TNFSF 5' OR ' protein TNFSF5' OR ' TNFSF 5 protein' OR ' TNFSF5 protein' OR ' tumor necrosis factor ligand superfamily member 5' OR ' tumor necrosis factor superfamily member 5' OR 'antigen cd70' OR ' antigens, CD70' OR ' CD27 ligand' OR ' CD27L' OR ' CD70 antigens' OR 'colony-stimulating factors' OR ' colony stimulating activity' OR ' colony stimulating factors' OR 'fibroblast derived differentiation inducing factor' OR 'ectodermal dysplasia protein' OR ' ectodysplasin 1' OR ' ectodysplasins' OR ' EDA A protein' OR ' EDA protein' OR ' protein EDA' OR ' protein EDA A' OR 'am 424' OR ' am424' OR ' recombinant human leukemia inhibitory factor' OR ' recombinant leukemia inhibitory factor' OR 'EMAP II' OR ' endothelial monocyte activating polypeptide

2’ OR ‘antigen CD178’ OR ‘ CD178 antigen’ OR ‘ CD95 ligand’ OR ‘ CD95L’ OR ‘ CD95L protein’ OR ‘ Fas antigen ligand’ OR ‘ Fas ligand protein’ OR ‘ FasL protein’ OR ‘ protein CD95L’ OR ‘ protein FasL’ OR ‘ protein TNFSF 6’ OR ‘ protein TNFSF6’ OR ‘ TNF superfamily member 6’ OR ‘ TNFSF 6 protein’ OR ‘ TNFSF6 protein’ OR ‘ tumor necrosis factor ligand superfamily member 6’ OR ‘fibroblast growth factors’ OR ‘ fibroblast stimulating factor’ OR ‘ heparin binding growth factor’ OR ‘fgf 1’ OR ‘ FGF1’ OR ‘fgf 10’ OR ‘ FGF10’ OR ‘ fgf 14’ OR ‘ FGF14’ OR ‘ fgf 16’ OR ‘ FGF16’ OR ‘ fgf 18’ OR ‘ FGF18’ OR ‘ fgf 19’ OR ‘ FGF19’ OR ‘ fgf2’ OR ‘ FGF 2’ OR ‘ fgf21’ OR ‘ FGF 21’ OR ‘ fgf23’ OR ‘ FGF 23’ OR ‘ fgf3’ OR ‘ FGF 3’ OR ‘ fgf4’ OR ‘ FGF 4’ OR ‘ fgf5’ OR ‘ FGF 5’ OR ‘ fgf6’ OR ‘ FGF 6’ OR ‘ fgf8’ OR ‘ FGF 8’ OR ‘ fgf9’ OR ‘ FGF 9’ OR ‘interleukin’ OR ‘interleukins’ OR ‘il 1’ OR ‘il 2’ OR ‘il 4’ OR ‘il 5’ OR ‘il 6’ OR ‘il 9’ OR ‘il 10’ OR ‘il 12’ OR ‘il 13’ OR ‘il 17’ OR ‘il 23’ OR ‘interferon’ OR ‘helper cell type 1’ OR ‘ T helper 1’ OR ‘ T helper type 1’ OR ‘ Th1 cells’ OR ‘helper cell type 2’ OR ‘ T helper 2’ OR ‘ T helper type 2’ OR ‘ Th2 cells’ OR 'helper cell'/exp OR 't helper' OR 'B lymphocyte'/exp OR ‘B-lymphocyte subsets’ OR ‘ B-lymphocytes’ OR ‘ b-lymphocytes, regulatory’ OR ‘ B cell’ OR ‘ bone marrow derived lymphocyte’ OR ‘ bone marrow lymphocyte’ OR ‘ bursa derived lymphocyte’ OR ‘ lymphocyte, b’ OR ‘ lymphocyte, bone marrow derived’ OR ‘ lymphocyte, bursa derived’ OR ‘ regulatory B lymphocyte’ OR ‘antibody-producing cells’ OR ‘ antibody forming cell’ OR ‘ antibody producing cell’ OR ‘ immunoglobulin forming cell’ OR ‘B memory cell’ OR ‘ B memory cells’ OR ‘ B memory lymphocyte’ OR ‘ B memory lymphocytes’ OR ‘ memory B cell’ OR ‘ memory B cells’ OR ‘ memory B lymphocyte’ OR ‘ memory B lymphocytes’ OR ‘cell, plasma’ OR ‘ flamed plasma cell’ OR ‘ flamed plasmacell’ OR ‘ plasma cells’ OR ‘ plasmacyte’ OR ‘ plasmatocyte’ OR ‘ plasmocyte’ OR ‘ plasmocyte, flamed’ OR ‘B cell precursor’ OR ‘ B cell precursors’ OR ‘ B cell progenitor’ OR ‘ B cell progenitors’ OR ‘ B lineage precursor’ OR ‘ B lineage precursors’ OR ‘ B lineage progenitor’ OR ‘ B lineage progenitors’ OR ‘ B lymphocyte precursor’ OR ‘ B lymphocyte progenitor’ OR ‘ B lymphocyte progenitors’ OR ‘ B lymphoid precursor cell’ OR ‘ B lymphoid precursor cells’ OR ‘ B lymphoid progenitor’ OR ‘ B lymphoid progenitors’ OR ‘ B precursor’ OR ‘ B precursors’ OR ‘ B progenitor’ OR ‘ B progenitors’ OR ‘ cell, pre B’ OR ‘ immature B cell’ OR ‘ immature B cells’ OR ‘ pre B cell’ OR ‘ pre B cells’ OR ‘ precursor B cell’ OR ‘ precursor B cells’ OR ‘ precursor B lymphocyte’ OR ‘ precursor B lymphocytes’ OR ‘ precursor cells, B-lymphoid’ OR ‘ precursor cells, B lymphoid’ OR ‘ pro-B cell’ OR ‘ pro-B cells’ OR ‘ progenitor B cell’ OR ‘ progenitor B cells’ OR ‘ transitional B cell’ OR ‘ transitional B cells’ OR " tumor necrosis factor receptor 1"/exp OR " tumor necrosis factor receptor 1 " OR " CD120a antigen" OR " receptors, tumor necrosis factor, type I" OR " tumor necrosis factor receptor type 1" OR " tumor necrosis factor receptor type I" OR 'dendritic cell'/exp OR ‘dendritic cells’ OR ‘dendritic cell’ OR ‘langerhans cell' OR 'langerhans cells' OR 'T lymphocyte'/exp OR ‘amplifier t lymphocyte’ OR ‘ lymphocyte, thymus’ OR ‘ T-lymphocytes’ OR ‘ t-lymphocytes, suppressor-inducer’ OR ‘ T cell’ OR ‘ T cells’ OR ‘ thymic lymphocyte’ OR ‘ thymus dependant lymphocyte’ OR ‘ thymus dependent cell’ OR ‘ thymus dependent lymphocyte’ OR ‘ thymus derived cell’ OR ‘ thymus derived lymphocyte’ OR ‘ thymus lymphocyte’

This in combination with

- Any Bacillus Calmette Guerin containing vaccine
- Any Diphtheria toxoid containing vaccine
- Any Tetanus toxoid containing vaccine
- Any *Bordetella pertussis* containing vaccine
- Any measles containing vaccine

2. Pubmed search

((((("T-Lymphocytes, Helper-Inducer"[Mesh]) OR "T-Lymphocytes, Regulatory"[Mesh]) OR "Cytokines"[Mesh]) OR "Antigen-Presenting Cells"[Mesh]) AND
((("BCG Vaccine"[Mesh]) OR "Measles Vaccine"[Mesh]) OR "DTP Vaccine"[Mesh])

3. Cochrane search

((((("T-Lymphocytes, Helper-Inducer"[Mesh]) OR "T-Lymphocytes, Regulatory"[Mesh]) OR "Cytokines"[Mesh]) OR "Antigen-Presenting Cells"[Mesh]) AND
((("BCG Vaccine"[Mesh]) OR "Measles Vaccine"[Mesh]) OR "DTP Vaccine"[Mesh])

From this search only trials are going to be included.

4. Trip search

BCG vaccine OR Measles vaccine OR DTP vaccine

Apendix B: screening forms

Text in red means the article under review will be excluded at this point. Once an article is excluded at a certain point the rest of the form will not be completed after this point.

1. Title screening form
    a. Is this question relevant for answering the research questions?
        i. Yes
        ii. No
        iii. Unclear

2. Abstract screening form
    a. Is an abstract available?
        i. Yes
        ii. No (continue to pdf screening)
    b. What is the study type?
        i. RCT
        ii. Controlled trial
        iii. Retrospective cohort
        iv. Prospective cohort
        v. Case control study
        vi. Case series
        vii. case report
        viii. Ecological study
        ix. Meta-analysis
        x. Review
        xi. In vitro study
        xii. Letter to editor/comment
        xiii. Other, describe:
        xiv. Unclear
    c. Who are the study subjects?
        i. Humans
        ii. Partially humans
        iii. Mice
        iv. Other animals
        v. Unclear
    d. In this study do they use a DTP, measles or BCG vaccine, or a vaccine containing diphtheria, tetanus, pertussis or measles toxoids or antigens?
        i. Yes
        ii. No
        iii. Unclear
    e. Are immunological endpoints reported as part of the results?
        i. Yes

ii. No
iii. Unclear

f. Are there any other reasons for excluding this study?
i. Yes, explain:
ii. No

3. Pdf screening form
a. What is the study type?
i. RCT
ii. Controlled trial
iii. Retrospective cohort
iv. Prospective cohort
v. Case control study
vi. Case series
vii. case report
viii. Ecological study
ix. Meta-analysis
x. Review
xi. In vitro study
xii. Letter to editor/comment
xiii. Other, describe:
xiv. Unclear
b. Are the study subjects human?
i. Yes
ii. Partially
iii. No
iv. Unclear
c. If subjects are human, are the participants under 5 years of age?
i. Yes
ii. No
iii. Unclear
d. Which vaccine(s) is/are used in the study?
i. DTP vaccine
ii. Any diphtheria toxoid containing vaccine
iii. Any tetanus toxoid containing vaccine
iv. Any pertussis antigen containing vaccine
v. Measles vaccine
vi. Any measles containing vaccine
vii. BCG vaccine
viii. Any BCG containing vaccine
ix. Recombinant BCG vaccine
x. Recombinant DTP vaccine

xi. Recombinant Measles vaccine
xii. Other vaccine, describe:
xiii. No vaccine
xiv. Unclear

e. Are immunological endpoints reported as part of the results?
   i. Yes
   ii. Yes, but only specific antibody response
   iii. Yes, but only specific cytokine response
   iv. No
   v. Unclear

f. Are there any other reasons for excluding this study?
   i. Yes, explain
   ii. No