UPDATE

Since this protocol was first posted on the web after the April 2013 SAGE meeting the names of the investigators leading this review have changed.

The investigators are:

Co- Principal Investigators: Art Reingold (University of California at Berkeley), Julian Higgins (University of Bristol) and Karla Soares-Weiser (Enhanced Reviews).

All other researchers are no longer involved in this review.

Systematic Review of the Nonspecific Effects

of BCG, DTP and measles containing vaccines

on deaths from infections other than those conditions that

the given vaccine is designed to prevent and,

on all-cause mortality in children under five years of age

in children under 5 years of age

Protocol for a Systematic Review

version March 2, 2013

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Background

Over the past two decades, a number of publications have claimed that several vaccines routinely administered to infants may have "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, some authors have suggested that receipt of both BCG vaccine and measles vaccine is associated with a reduced risk of death (e.g. all cause mortality), while receipt of DTP vaccine is associated with an increased risk of death, at least among female infants. The vast majority of the evidence reporting these effects was generated using observational study designs (i.e. not randomized clinical trials) that are afflicted by the risk of bias, 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 possible implications of any such non-specific vaccine effects for the any adjustments to the infant immunization schedule remain unclear. Some authors have suggested that if such effects are document with robust evidence, the infant immunization schedule might need to be adjusted. However, prior WHO led reviews of this subject, including several assessments by WHO's Global Advisory Committee on Vaccine Safety, have concluded that the totality of evidence provided did not support a deleterious effect of DTP vaccination on child survival[1] and that conclusive evidence for or against non-specific effects of vaccines on mortality, including a potential deleterious effect of DTP vaccination on children's survival as has been reported in some studies, was unlikely to be obtained from observational studies[2].

As part of its continue appraisal of cross-cutting issues that could be relevant to inform global immunization policy, the WHO's Strategic Advisory Group of Experts (SAGE) has requested the WHO Secretariat to led a systematic review the evidence concerning the possible non-specific effects of vaccines included in the routine infant immunization schedule. This evidence will inform discussions on the topic during the SAGE meetings in 2013.

Preparatory to the discussions at the SAGE in 2013, it is necessary to systematically assemble, and to critical appraisal the available evidence.

[1] Weekly Epidemiological Report 2004; Vol79 N 29, p271.
[2] Weekly Epidemiological Report 2008; Vol83 N 32, p290.

Overall, our aim is to:

1. determine if the current evidence is sufficiently compelling to warrant further scientific investigation, and if so,
2. to define the path towards obtaining unequivocal evidence on these issues that would support future robust, evidence-based adjustments in immunization policies, if warranted.

1. Objectives

1.1. To systematically identify, assemble, and review all published and grey literature concerning epidemiological studies addressing "non-specific" effects of BCG, measles and, DTP-containing vaccines on: (i) survival/deaths from infections other than those conditions that the vaccine is designed to prevent and, (ii) on all-cause mortality in children under five years of age.

1.2. To critically appraise the evidence using existing guidelines[3] .

2. Methods

We will identify and critically appraise the available evidence that addresses the effect of BCG, DTP and measles-containing vaccines on: (i)survival/all-cause mortality/deaths from infections other than those conditions that the vaccine is designed to prevent and; (ii) on all-cause mortality/deaths by all causes/survival in children less than five years of age in all settings.
We will provide an evidence profile that summarizes the findings for each study question.

2.1. Study Questions

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

A. Is the administration of BCG in infancy associated with an effect on survival /deaths from infections other than those conditions that the vaccine is designed to prevent in children up to five years of age?

[3] Using the Cochrane Handbook guidelines for RCTs and we will develop a risk of bias assessment form for observational studies specifically for this review drawing on a new tool under development within the Cochrane Collaboration. We will also include any key elements reported in Fine P et al (2009) and Farringdon P et al (2009) and, WHO Strategic Advisory Group of Experts (SAGE) Guidance for the development of evidence-based vaccine related recommendations.
(http://www.who.int/entity/immunization/sage/Guidelines_development_recommendations.pdf)

B. Is the administration of DTP in infancy associated with an effect on survival/deaths from infections other than those conditions that the vaccine is designed to prevent in children up to five years of age?
C. Is the administration of Measles in infancy associated with an effect on survival/ deaths from 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 by this review are as follows:

A. Is administration or non-administration of BCG vaccine in infancy associated with an effect on all-cause mortality/deaths from all causes in children up to five years of age?
B. Is administration or non- administration of DTP-containing vaccine in infancy associated with an effect on all-cause mortality/deaths from all causes in children up to five years of age?
C. Is administration or non- administration of measles-containing vaccine in infancy associated with an effect on all-cause mortality/deaths from all causes 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.

STUDY QUESTIONS	VACCINES		
	BCG	Measles	DTP
PRIMARY QUESTION Is the administration of vaccine X in infancy associated with an effect on survival/deaths from infections other than those conditions that the vaccine is designed to prevent in children up to five years of age?	✚	✚	✚
SECONDARY QUESTION Is administration or non- administration of vaccine X given in infancy associated with an effect on all-cause mortality/deaths from all causes in children up to five years of age?	✚	✚	✚
Is there a difference of the effect:			
▪ between boys and girls	✚	✚	✚
▪ by number doses and age dose is received?	✚	✚	✚
▪ by sequence/order in which vaccines are given?	✚	✚	✚
• by prior, or co-administration of vitamin A and/ or other vaccines?	✚	✚	✚

2.2) Inclusion criteria

Studies done in any country and published in any language will be included

2.2.1) Types of studies

We plan to include the following study designs:

- RCT or quasi-randomized controlled trials
- Observational epidemiological studies
    - case-control studies and,
    - prospective, historical and ambi-directional cohort studies,
        - When two or more exposure cohorts are described by study investigators to be part of the same study, we will consider this to be a cohort study which could be considered for inclusion.

2.2.2) Types of participants

We will include studies containing data relating to the vaccination of children up to 5 years.

2.2.3) Types of interventions

We will include studies reporting on vaccination with BCG, DTP and measles-containing vaccine in children up to five years of age.

2.2.4) Types of outcomes measures

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.

P	**Population**	Children up to five years of age
I	**Intervention**	Vaccination with BCG, DTP or standard measles containing vaccines
C	**Comparator(s)**	No vaccination (BCG, DTP or measles) or simultaneous administration of other vaccine or order of vaccine administration
O	**Outcome(s)**	(i) survival /deaths from infections other than those conditions that the vaccine is designed to prevent (iii) death from all causes (e.g. all-cause mortality, child survival)

2.3) 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 vaccine on mortality. Additionally, we will exclude animal or laboratory studies,

2.4) Search Strategy

The search strategy will be developed jointly by two Reviewers (Ximena Riveros (XRL) and Ana Maria Henao-Restrepo (AMHR) and, a Senior Librarian (Tomas Allen (TA) with expertise in systematic searches. The Senior Librarian (TA) will conduct the systematic search using the agreed criteria.

Element	Description
Sampling strategy	Comprehensive strategy to identify all articles on: (i) effect of vaccines on survival/deaths from infections other than those conditions that the vaccine is designed to prevent and, (ii) effect of vaccines on or all-cause mortality
Type of studies	No restrictions, all study types included
Approaches	Electronic search in various databases plus: • Grey literature • Hand searches • Contact lead authors in the field
Range of years (start date and end date)	No restrictions From the beginning of each candidate database to December 15, 2012.
Limits	No limits
Inclusions and exclusions	No inclusions or exclusions applied
Terms used	See Annex 1

- **Electronic search in various databases**: We will search Embase (in Embase.com), PubMed, the Cochrane Library, African Index Medicus (AIM), the Indian Medlars Centre (IndMed), Latin American and Caribbean Health Sciences (LILACs), African Index Medicus, Eastern Mediterranean Index Medicus, South-East Asia IMSEAR, Western Pacific WPRIM, Current Controlled Trials metaRegister of Controlled Trials (mRCT, active and archived registers), UK Clinical Trials Gateway (UKCTG), US Food and Drug Administration (FDA), European Public Assessment Report (EPAR), listings of the European Medicines Agency (EMEA), WHO International Clinical Trials Registry Platform Search Portal (includes: ClinicalTrials.gov, International Standard Randomized Controlled Trial Number Register (ISRCTN), and clinical trial registries of Australia, China, Germany, India, Iran, The Netherlands, New Zealand, Sri Lanka), GSK Clinical Study Register, and Clinicalstudyresults.org (includes Wyeth trial listings).
- **Grey Literature**: unpublished study reports, articles submitted for publication, conference proceedings (e.g. EMBASE and Scopus) and posters, dissertations and theses.
- **Manual searches**: We will examine bibliographies of relevant previous reviews and the reference lists of all articles found to identify studies not identified through the databases listed above. We will hand search content pages of the INDEPTH network and the OPTIIMUNIZE Initiative together with list of publications mentioned in this websites.
- **Contact with lead authors**: We will also contact some authors (e.g. C S Benn and F Shann) to ask for copies of any reports (published or unpublished) that relate to the subject and that might fit our selection criteria.

There will be no restrictions on language, study design (except as noted above), length of follow-up, and report characteristics (e.g. date of publication or listing, publication status). Full text of all articles identified will be sought, using internet downloads, interlibrary loans, and contacting of authors. We will use terms relating to:

- BCG, standard titer measles vaccine DTP containing vaccines, or names of licensed BCG, DTP and measles containing vaccines AND vaccination, immunization or vaccine AND
- all-cause mortality, mortality, child mortality, infant mortality or death, cause of deaths, child deaths, infant deaths.

Search terms will be adapted as required for each database (See Annex 1 for details on full electronic search strategy example for EMBASE and Medline).

2.5) Selection of Eligible Studies

We will use DistillerSR, an online application designed specifically for the screening and data extraction phases of a systematic review. Paul Zhang (PZ), Michelle Beam (MB), Emily Han (EH)and Emma Smith (ES) will conduct the screening under the supervision of AR and KS.

For each step of the selection of potentially eligible articles we will develop and pilot test forms for screening using predefined data fields.

Steps	Procedure
1. Systematic search	After completing the systematic search we (KS, XRL and AMHR) will cross checked that all key articles were included in the search (e.g. hand search in reference lists of key articles, list on the web of INDEPTH's network, OPTIMUNIZE and, C S Benn and F Shann suggested publications)
2. Check for duplicates	We will compile all search results and identified any duplicates (KS, XRL and AMHR).
3. Title screening	Two Reviewers (XRL and AMHR) will conduct title screening with the aim to exclude studies that obviously do not include information on the outcome of interest. Disagreements between reviewers will be resolved by consensus after reviewing the abstracts for the given articles. The reviewers will have three response options for excluding records or promoting them to the next stage of the winnowing process: yes, no and, maybe.
4. Abstract screening	Abstract screening form will be pilot tested by applying it to 30 selected studies. The articles ID and outcome of the pilot will be documented and filed. The outcomes of the pilot will be discussed by all reviewers and, an adjusted final form will be developed. Each abstract of each potentially eligible article will be examined by two reviewers (e.g. PZ, MB, EH, ES organized in pairs of two) using predefined data fields and lists of studies considered eligible for inclusion will be compared. Studies identified by both reviewers as being potentially eligible for inclusion will be included in the next step of the review. Where there are discrepancies, the reasons for

Steps	Procedure
	these will be discussed by four Senior Reviewers (AR, KS, AMH, XRL) will adjudicate to make a final decision about eligibility after reviewing the full text of the articles.
5. Pdf screening	Pdf screening form will be pilot tested by applying it to 10 selected studies. The articles ID and outcome of the pilot will be documented and filed. The outcomes of the pilot will be discussed by all reviewers and, an adjusted final form will be developed. Each pdf file of each potentially eligible article will be examined by a pair of two reviewers (PZ, AM, EH, ES) using predefined data fields and lists of studies considered eligible for inclusion will be compared. Studies identified by both reviewers as being potentially eligible for inclusion will be included in the next step of the review. Where there are discrepancies, the reasons for these will be discussed and a decision about inclusion reached by consensus. If there is no agreement, the four Senior Reviewers (AR, KS, AMH, XRL) will adjudicate to make a final decision about eligibility. Both the reasons for the disagreements and the outcome will be documented.

2.6) Data Extraction Forms

We will develop a data extraction sheet using predefined data fields for extracting consistent data from eligible articles. The sheet will also include variables that will permit us to assess the risk of bias of each individual study[4] . We will pilot test the data extraction forms to ensure ease of use and capture all relevant data. The pilot test will include 10% randomly selected potentially eligible articles. It will be conducted by four selected independent epidemiologists not involved in the review that will use it independently.

We will develop the forms in an electronic format using web-based systematic review software called Distiller SR (http://systematic-review.net/).

2.7) Data Extraction

All relevant data will be extracted from articles meeting inclusion criteria and entered into a database. As stated above, we will extract the data for each study onto a structured electronic data extraction form. For all studies, data will be extracted by one reviewer. Data will be 100% checked for accuracy and completeness by one Senior Reviewer. Where there are discrepancies, the reasons for these will be discussed and a decision about inclusion reached by consensus among the Senior

[4] Using the Cochrane Handbook guidelines for RCTs and we will develop a risk of bias assessment form for observational studies specifically for this review drawing on a new tool under development within the Cochrane Collaboration. We will also include any key elements reported in Fine P et al (2009) and Farringdon P et al (2009) and, will use the SAGE Guidelines for review of evidence

reviewer (AR, XXX). If there is no agreement, a Senior Reviewer (A. Reingold) will adjudicate to make a final decision. All disagreements and the outcome will be documented.

Some of the included studies might be described in more than one publication because in some cases, additional analyses may have been conducted after completion of a study or re-analyses were reported. Where methods of study design are described in additional publications, we used all reports to inform our data extraction. Where additional analyses were conducted, we will choose to include the analysis that provided the most information and avoid duplication of results.

To ensure that all relevant data have been located from all studies, tables with eligible studies will be generated and shared with leading authors of eligible articles to ask if they can provide any missing information.

2.8) Assessment of risk of bias of included studies.

Controlled trials:

For each outcome in each controlled trial, we will classify results as at low, unclear or high risk of bias, based on domain-specific assessments of risk of bias done using the Cochrane Collaboration's "Risk of Bias" tool.

Observational studies:

We will develop a risk of bias assessment form for observational studies specifically for this review drawing on a new tool under development within the Cochrane Collaboration and informed by two articles on methodological issues in the design and analysis of observational studies of non-specific effects of vaccines (Fine P et al 2009 and Farrington P et al 2009). The form will include separate assessments for cohort studies and case-control studies.

In developing this risk of bias assessment for observational studies we will consider inclusion of items addressing issues of (i) confounding and selection bias (including confounders measured and addressed, use of matching, methods of adjustment and issues of timing of vaccination); (ii) performance bias (including any considerations of co-intervention); (iii) missing data (including missing vaccination status – leading to survival bias – and missing mortality data); detection bias (for cohort studies, including consideration of subjective assessment of causes of death) or recall bias (for case-control studies, including misclassification of vaccination status); and selective reporting bias. Most of these assessments are aided considerably by the specification of a 'target randomized trial', representing a hypothetical trial which would estimate the same parameter being targeted by the observational study. For each outcome in each observational study, we will classify results as at

low, unclear or high risk of bias. We will also document any inclusion and exclusion criteria, methods for ascertainment of vaccination status and measures to deal with missing data.

An *a priori* minimum set of confounders to designate a rate ratio as adjusted will be agreed based on consideration (blind to study results) of a tabulation of all the confounders used in each study, stratified by study design. Using existing literature we have identified potential confounding factors for a child being vaccinated. These include socioeconomic status, low parental education, orphan status, distance from a health center, child health status, low birth weight, nutritional status, previous/history of hospitalizations and consultations,

Two reviewers (XX and XX) will independently evaluate study quality and differences will be resolved by discussions with a third reviewer (XX). The overall results will be reported using a table designed for this review.

2.9) Data Analysis

Analysis of single studies

We will check the data for each study to identify possible data entry problems.

For each study, the rate ratio (RR) for vaccinated compared with unvaccinated individuals, with 95% confidence interval (CI) will be derived. If only hazard ratios are available for a study, we use these instead. If only 2×2 data (rather than person-years) are available we will estimate risk ratios. We will assume that these approximate to rate ratios provided that overall mortality risk is low.

For case-control studies we will derive odds ratios: we will assume that these approximate to rate ratios in the general population. Where possible, we will compare published estimates with those directly calculated from raw data. Where data are available for two or more time periods we will plot RRs and 95% CIs over time.

Descriptive tables - We will produce descriptive tables summarizing information about study design, risk of bias, and results of all included studies. Data will be presented by vaccine and by epidemiological or mortality setting, as appropriate.

Meta-analysis

Where studies are considered substantively similar enough for meta-analysis to be appropriate, both fixed- and random-effects analyses will be carried out using the **metan** command for Stata. Random-effects meta-analyses are based on the assumption that the true vaccine effects have a normal distribution across studies. All meta-analyses will be stratified according to study design (RCT or quasi-randomized controlled trials, cohort studies, case-control studies) and by type of vaccine. Meta-analyses of crude and adjusted rate ratios will be derived separately for each observational study design. Analysis will be on the log rate ratio scale, while results will be displayed both as rate ratios and as vaccine efficacy (=1-RR) if this is appropriate.

Fixed- and random-effects summary estimates will be displayed with estimates from the individual studies in forest plots. Differences between fixed- and random-effects estimates suggest that there are differences between RRs estimated from smaller and larger studies: such differences will be examined using funnel plots and Harbord's test for funnel plot asymmetry.

Variation in efficacy according to characteristics of individuals and studies

Heterogeneity (differences between the true vaccine effects in the different studies) will be quantified by estimating the between-study variance τ^2.. To illustrate the meaning of this quantity, the table below shows the ratio of the effect (for example, risk ratio or rate ratio) at the 90th centile of the distribution to the effect in a study at the 10th centile, based on the usual normal distribution assumption used in random-effects meta-analyses.

Variance τ^2	Standard deviation τ	Ratio of effect in study at 90th centile to study at 10th centile
0.02	0.141	1.44
0.05	0.224	1.77
0.1	0.316	2.25
0.2	0.447	3.15
0.4	0.632	5.06

Inconsistency in findings across studies will also be quantified using the I^2 statistic, which measures the percentage of observed variation that can be attributed to true differences between the studies[i]

In forest plots and meta-analyses, τ^2 will be estimated using the method-of-moments estimator proposed by DerSimonian and Laird. Within meta-regression analyses, τ^2 will be estimated by restricted maximum-likelihood, using the **metareg** command in Stata. We will conduct both

univariable and multivariable meta-regression analyses: results from multivariable analyses will be interpreted with caution because the number of studies is typically small compared with the number of study characteristics of interest.

When possible, differences in efficacy according to characteristics of individuals or of studies will be estimated by comparing efficacy (using ratios of RRs) between subgroups of studies. This can be done formally using meta-regression analyses. Specifically, variation in vaccine effects according to the following characteristics is of interest: (a) risk of bias in the different study designs, (b) time since vaccination, (c) gender, (d) age; (e) number of vaccine doses; (f) whether vaccines were administered alone or simultaneously with other vaccines, (g) prior or co-administration of Vitamin A; (h) different sequence of administration of vaccines.

Factors that may bias estimates from case-control studies will be examined by displaying the results in forest plots stratified by these factors and their effects will be estimated in meta-regression analyses. These factors include whether a matched design has been ignored in the analysis (giving "crude" estimates from studies that have a matched design), and whether the controls were sampled from the same population as the cases.As sensitivity analyses we will report analyses restricted to studies assessed as at low, and low or unclear, risk of bias if this is feasible.

Assessment of the strength of conclusions - We will use the GRADE approach, as modified by WHO Strategic Advisory Group of Experts (SAGE)[5], to assess the evidence in support of various hypothesized associations between various vaccines and (i)survival/all-cause mortality/deaths from infections other than those conditions that the vaccine is designed to prevent and/or; (ii) on all-cause mortality/deaths by all causes/survival in children less than five years of age in all settings. Results will be summarized in GRADE tables.

Report

A report summarizing the findings and conclusions will be written and provided to WHO's Department of Immunization Vaccines and Biologicals using the internationally accepted guidelines for systematic reviews (http://www.prisma-statement.org/).

Overall, the report will include:

- a summary of the evidence (tables, forest plots figures) as described above

[5] Guidance for the development of evidence-based vaccine related recommendations. (http://www.who.int/entity/immunization/sage/Guidelines_development_recommendations.pdf)

- critical appraisal of the evidence (methodological considerations, risk of bias and GRADE tables) as described above.

In addition, a verbal report of the findings will be presented at the 2013 meeting of SAGE in Geneva, Switzerland.

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Abbreviations Used in this Protocol

BCG: Bacille Calmette-Guerin Vaccine

DTP: Diphtheria-Tetanus-Pertussis Vaccine

RCT: Randomized controlled trial

Annex 1 – DRAFT

Basic search strategy – for Embase.

Search terms for other databases to be included.

#	Searches	Results
1	'child'/exp OR 'child' OR 'children'/exp OR 'children' OR 'youth'/exp OR 'youth' OR youth* OR newborn* OR 'newborn'/exp OR 'newborn' OR 'new born' OR 'childhood disease'/exp OR 'childhood disease' OR 'baby'/exp OR 'baby' OR babies OR 'infant'/exp OR 'infant' OR infant* OR childhood* OR toddler* OR kid OR kids OR 'young patient' OR boy* OR girl* OR 'young age' OR pediatr* OR paediatr* OR 'child death'/exp OR 'child death' OR 'child health'/exp OR 'child health' OR 'child care'/exp OR 'child care' OR 'childhood mortality'/exp OR 'childhood mortality' OR 'child hospitalization'/exp OR 'child hospitalization' OR 'pediatric hospital'/exp OR 'pediatric hospital' OR child*	3,751,199
2	'measles vaccine'/exp OR ‘anti measles vaccin’ OR ‘ attenuated live measles vaccine’ OR ‘ attenuated live rubeola virus vaccine’ OR ‘ attenuated measles vaccine’ OR ‘ attenuvax’ OR ‘ cam-kovac’ OR ‘ diplovax’ OR ‘ edmonston zagreb vaccine’ OR ‘ fibroblast grown measles vaccine’ OR ‘ formalin killed measles vaccine’ OR ‘ hyperimmune measles serum’ OR ‘ killed measles vaccine’ OR ‘ killed measles virus vaccine’ OR ‘ lirugen’ OR ‘ lirugen measles’ OR ‘ live attenuated measles vaccine’ OR ‘ live attenuated measles vaccine moraten strain’ OR ‘ live attenuated measles vaccine schwarz strain’ OR ‘ live attenuated measles virus vaccine’ OR ‘ live distemper vaccine’ OR ‘ live distemper virus vaccine’ OR ‘ live measles vaccine’ OR ‘ live rubeola virus vaccine’ OR ‘ m-vac’ OR ‘ measle vaccine’ OR ‘ measles killed vaccine’ OR ‘ measles killed virus vaccine’ OR ‘ measles live vaccine’ OR ‘ measles vaccine, chick embryo fibroblast grown’ OR ‘ measles vaccine, human diploid cell grown’ OR ‘ measles vaccine, tween ether’ OR ‘ measles virus vaccine’ OR ‘ measles virus vaccine live’ OR ‘ mevilin-l’ OR ‘ morbilli vaccine’ OR ‘ morbilvax’ OR ‘ rimevax’ OR ‘ rouvax’ OR ‘ rubeola vaccine’ OR ‘ rubeovax’ OR ‘ tween ether measles vaccine’ OR ‘ vaccine, measles’ OR ‘ vaccine, rubeola’ OR ’ jeryl lynn moraten vaccine’ OR ‘ mm vax’ OR ‘ mmvax’ OR ‘ mumps measles vaccine’ OR ‘ rimparix’ OR ‘ urabe am 9 rimparix’ OR ‘ urabe am 9 schwarz vaccine’ OR 'chickenpox measles mumps rubella vaccine'/exp OR ’measles mumps rubella varicella vaccine’ OR ‘ measles plus mumps plus rubella plus varicella vaccine live ’ OR ‘ proquad’	9,439
3	'BCG vaccine'/exp OR ‘antituberculosis vaccine’ OR ‘ b.c.g.’ OR ‘ b.c.g. vaccine’ OR ‘ bacillus Calmette Guerin’ OR ‘ bacillus calmette guerin vaccine’ OR ‘ BCG’ OR ‘ bcg cell wall vaccine’ OR ‘ bcg copenhagen 1331’ OR ‘ BCG live’ OR ‘ bcg test’ OR ‘ calgevax’ OR ‘ calmette guerin bacillus’ OR ‘ calmette vaccine’ OR ‘ calmette s vaccine’ OR ‘calmettes vaccine’ OR ‘ immucyst’ OR ‘ immun bcg pasteur’ OR ‘ monovax’ OR ‘ mva 85a’ OR ‘ mva85a’ OR ‘ mycobacterium bcg’ OR ‘ mycobax’ OR ‘ onco tice’ OR ‘ oncotice’ OR ‘ pacis’ OR ‘ pastimmun’ OR ‘ theracys intravesical’ OR ‘ tice bcg’ OR ‘ tice bcg vaccine’ OR ‘ ticebcg’ OR ‘ tubercle bacilli vaccine’ OR ‘ tuberculosis vaccine’ OR ‘ tuberculosis vaccines’	39,365
4	'diphtheria pertussis tetanus vaccine'/exp OR ‘absorbed pertussis diphtheria tetanus vaccine’ OR ‘ acel immune’ OR ‘ acel imune’ OR ‘ acelluvax dpt’ OR ‘ acelluvax DTP’ OR ‘ adacel’ OR ‘ adsorbed dt coq’ OR ‘ anatoxal di te per berna’ OR	11,728

	‘ boostrix’ OR ‘ certiva’ OR ‘ covaxis’ OR ‘ d.t. coq’ OR ‘ daptacel’ OR ‘ dif per tet all’ OR ‘ diphtheria-tetanus-acellular pertussis vaccines’ OR ‘ diphtheria-tetanus-pertussis vaccine’ OR ‘ diphtheria plus pertussis plus tetanus’ OR ‘ diphtheria tetanus acellular pertussis vaccines’ OR ‘ diphtheria tetanus pertussis trivaccine’ OR ‘ diphtheria tetanus pertussis vaccine’ OR ‘ diphtheria tetanus whooping cough vaccine’ OR ‘ diteper anatoxal berna vaccine’ OR ‘ dpt’ OR ‘ DPT vaccine’ OR ‘ DTAP vaccine’ OR ‘ DTP vaccine’ OR ‘ infanrix’ OR ‘ neodiftepertus’ OR ‘ p.d.t. vax purified’ OR ‘ pertugen’ OR ‘ pertussis diphtheria tetanus vaccine’ OR ‘ tetanus diphtheria pertussis vaccine’ OR ‘ tri immunol’ OR ‘ triacelluvax’ OR ‘ triaxis’ OR ‘ tripacel’ OR ‘ tripedia’ OR ‘ triplo vaccine’ OR ‘ tripvac’ OR ‘ tritanrix’ OR ‘ trivax’ OR ‘ vaccine, pertussis diphtheria tetanus’ OR ‘*DTP vaccine’ OR ‘Infanrix’*	
5	'sex difference'/exp OR ‘sex differences’ OR ‘ dimorphism, sex’ OR ‘ factor, sex’ OR ‘ gender difference’ OR ‘ gender differences’ ‘ sex dimorphism’ OR ‘ sex factor’ OR ‘ sex factors’ OR ‘ sexual difference’ OR ‘ sexual dimorphism’ OR ‘ sexual size dimorphism’ OR ‘evolution, sex’ OR ‘ sex characteristics’ OR ‘ sex development’ OR ‘ sex evolution’ OR ‘advanced puberty’ OR ‘ pseudopuberty’ OR ‘ pubescence’ OR ‘sex differentiation’/exp OR ‘sex related factors’ OR ‘sex related factor’ OR ‘sexual development’/exp OR 'male'/exp AND 'female'/exp AND 'gender'/exp OR 'boy'/exp AND 'girl'/exp AND 'gender'/exp	3,668
6	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	1,387,342

	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'	
7	'retinol'/exp OR '3, 7 dimethyl 9 (2, 6, 6 trimethyl 1 cyclohexen 1 yl) 2, 4, 6, 8 nonatetraen 1 ol' OR ' 3, 7 dimethyl 9 (2, 6, 6 trimethyl 1 cyclohexenyl) 2, 4, 6, 8 nonatetraen 1 ol' OR ' a 313' OR ' a fil' OR ' a mulsal' OR ' a mulsin' OR ' a mulsine' OR ' a sol' OR ' a vi pel' OR ' a vit' OR ' a vitadit' OR ' a vitamin' OR ' a vitan' OR ' a313' OR ' acon' OR ' acrisina' OR ' acrisine' OR ' actifral a' OR ' adatone' OR ' afaxin' OR ' afaxine' OR ' afilina' OR ' afiline' OR ' agiolan' OR ' alcovit a' OR ' alfa monovite' OR ' alfa sir' OR ' alfaergin' OR ' alfaergine' OR ' alfamin' OR ' alfamine' OR ' alfamonovit' OR ' alfasir' OR ' alfasole' OR ' alfasterolo' OR ' alfatar' OR ' alfavena' OR ' alfavene' OR ' alfavitina' OR ' alfavitine' OR ' alfene' OR ' all trans retinol' OR ' alphalin' OR ' alphaline' OR ' alphasterol' OR ' amulsal' OR ' amulsin' OR ' amulsine' OR ' amulvit' OR ' anatola' OR ' anatole' OR ' anavit' OR ' anti infective vitamin' OR ' antixerophthalmic vitamin' OR ' aoral' OR ' apexol' OR ' apostavit' OR ' aquasol a' OR ' arcavit A' OR ' asol' OR ' asteril' OR ' atav' OR ' aterapion' OR ' avibon' OR ' avibon theraplix' OR ' avimin' OR ' avimine' OR ' avipel' OR ' avipur' OR ' avit' OR ' avitabiol' OR ' avitadit' OR ' avital' OR ' avitaminum kolin' OR ' avitan' OR ' avitana' OR ' avitane' OR ' avite' OR ' avitil' OR ' avitina' OR ' avitol' OR ' avogina' OR ' avogine' OR ' avoleum' OR ' axerodina' OR ' axerodine' OR ' axerol' OR ' axerophthol' OR ' axerophthylium' OR ' bentavit a' OR ' bentavite a' OR ' bio tan' OR ' biosterol' OR ' biotan' OR ' chivibit a' OR ' cytobiase' OR ' dagravit a' OR ' davitamon a' OR ' difvitamin a' OR ' dohyfral a' OR ' elageno a' OR ' endo a' OR ' envit a' OR ' epiteliol' OR ' evitol zambeletti' OR ' fletase' OR ' gadeol' OR ' gadol' OR ' halivitan' OR ' halivitane' OR ' homagenets aoral' OR ' hydrosol' OR ' ido a' OR ' ido a 50' OR ' idratene' OR ' inovitan a' OR ' lord factor' OR ' meditalfa' OR ' mulsal a' OR ' multamine' OR ' nio a let' OR ' oleovit a' OR ' oleovitamin a' OR ' ophthalamin' OR ' panvita' OR ' plivit a' OR ' prepalin' OR ' prepaline' OR ' preparato a' OR ' primavit' OR ' quotivit' OR ' retinol alcohol' OR ' retinyl alcohol' OR ' ro-a-vit' OR ' ro a vit' OR ' super a' OR ' testavol' OR ' ucemine a' OR ' vaconex' OR ' vaflol' OR ' veroftal' OR ' vi alpha' OR ' vi dom a' OR ' viadenin' OR ' vialpha' OR ' viatate' OR ' vidoma' OR ' vitadone' OR ' vitadral' OR ' vitalen a' OR ' vitalfa' OR ' vitama' OR ' vitamin A' OR ' vitamin a alcohol' OR ' vitamin a1' OR ' vitaplex a' OR ' vitapur a' OR ' vitasan a' OR ' vitavel a' OR ' vitpex' OR ' vogan' OR ' vogan neu' OR ' wandervit a' OR ' xerophthol' OR 'vitamin A'	56,112
8	Death OR deaths OR died OR mortality OR 'mortality'/exp OR mortalities OR fatal OR dying OR deceased OR "life threatening" OR "severe reaction" OR ICU OR "intensive care" OR emergency OR urgent OR fatalities OR casualty OR casualties OR lethalness OR necrosis OR heterologous OR 'non specific' OR nonspecific OR 'non-specific'	3,369,761
9	'tetanus toxoid'/exp OR 'anatetall' OR ' anatoxal tetanica berna' OR ' anti tetanus toxoid' OR ' antitetanus toxoid' OR ' antitetanus vaccine' OR ' clostet' OR ' plain tetanus vaccine' OR ' tanrix' OR ' te anatoxal' OR ' te anatoxal berna' OR ' tet-tox' OR ' tetanol' OR ' tetanus anatoxin' OR ' tetanus toxoid fluid' OR ' tetanus toxoid vaccine' OR ' tetanus vaccine' OR ' tetatox' OR ' tetatoxoid' OR ' tetavax' OR	18,380

	'tetanus toxoid' OR '57425-69-1' OR ' 93384-51-1'	
10	'pertussis vaccine'/exp OR 'acellular pertussis vaccine' OR ' acelluvax' OR ' bordetella pertussis vaccin' OR ' Bordetella pertussis vaccine' OR ' jnih 6' OR ' pertussis acellular vaccine' OR ' pertussis vaccin' OR ' pertuvac' OR ' whooping cough vaccine'	7,746
11	Step 1 AND Step 3 AND Step 5	225
12	Step 1 AND Step 3 AND Step 8	
13	Step 1 AND Step 2 AND Step 7	100
14	Step 1 AND Step 4 AND Step 5	167
15	Step 1 AND Step 4 AND Step 8	896
16	Step 1 AND Step 4 AND Step 7	137
17	Step 1 AND Step 4 AND Step 6	2536
18	Step 1 AND Step 2 AND Step 5	210
19	Step 1 AND Step 2 AND Step 8	1751
20	Step 1 AND Step 4 AND Step 8	1823
21	Step 1 AND Step 4 AND Step 7	206
22	Step 4 AND Step 6	1268
23	Step 10 AND Step 6	95
24	Step 9 AND Step 6 NOT (Animal/exp NOT Human/exp)	2,811
25	Step 3 AND Step 6 NOT ((Animal/exp NOT Human/exp)) NOT neoplasm/exp	4,855

[i] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. BMJ 2003; 327: 557-560.