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.

PROTOCOL FOR A SYSTEMATIC REVIEW –EPIDEMIOLOGY OUTCOMES

Title: Systematic review of the nonspecific effects of BCG, DTP and standard titre 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.

Authors: Reingold A, Higgins J, Sterne J, Low N, Soares-Weiser K, Riveros X and Henao-Restrepo AM

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Overall aim

- To determine if the current evidence is sufficiently compelling 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.

Review Objectives: 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 and ; to critically appraise the evidence using existing guidelines.

1. The protocol	
1.1 Primary questions	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? 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?
1.2 Secondary questions	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.
2. Methods	
2.1 Criteria for selecting studies for this review	Types of studies included • RCT or quasi-randomized controlled trials • Observational epidemiological studies: case-control studies and, prospective, historical and ambi-directional cohort studies.
Types of Participants	Children up to five years of age
Types of Interventions	Vaccination with BCG, DTP and measles-containing vaccines
Types of Outcome measures	• survival/all-cause mortality/deaths from infections other than those conditions that the vaccine is designed to prevent and, • death from all causes (e.g. all-cause mortality, child survival)

2.2 Search methods for identification of studies	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). We will search in electronic databases, grey literature, conduct manual searches, and contact lead authors and search on specialized websites.
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 Full version of protocol
Electronic sources	See Full version of protocol
3.Data Collection and Analysis	
Data extraction	Data extraction sheet using predefined data fields for extracting consistent data from eligible articles. The sheet will also include variables that will permit assessment of the risk of bias of each individual study informed by key elements from two methods papers on nonspecific effects of vaccines (Fine et al 2009 and Farrindon P et al 2009)
Assessment of risk of bias of included studies	RCTs: COCHRANE-Risk of bias tool Observational studies: a new tool will be developed specifically for this review drawing on a new tool under development within the Cochrane Collaboration
Data analysis (summary)	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. Where studies are considered substantively similar enough for meta-analysis to be appropriate, both fixed- and random-effects analyses will be carried out. Heterogeneity (differences between the true vaccine effects in the different studies) will be quantified by estimating the between-study variance $\tau 2$. 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
4.Assessment of the strength of conclusions	We will use the GRADE approach, as modified by WHO Strategic Advisory Group of Experts (SAGE), 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.