PROTOCOL FOR A SYSTEMATIC REVIEW –SYPNOSIS

Title: Systematic review of the non-specific effects of selected routine childhood immunizations

Authors: Andrew Pollard and Karlijn De Nie, Department of Paediatrics, University of Oxford

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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 available studies and data addressing the possible "non-specific" or "heterologous" effects of BCG, measles, DPT, including studies with immunologic endpoints and, to critically appraise the evidence using the GRADE approach, as modified by WHO Strategic Advisory Group of Experts (SAGE).

1. The protocol	
1.1 Primary questions	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 DTP 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?
1.2 Secondary questions	e. Do the effects on immune response markers, if any, of any of the vaccines under review vary by sex of the child? f. Do the effects on immune response markers, if any, of any of the vaccines under review vary by age at which they are delivered? g. Do the effects on immune response markers, if any, of any of the vaccines under review vary by co-administration of Vitamin A? h. 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?
2. Methods	
2.1 Criteria for selecting studies for this review	Types of studies included • randomized controlled trials (RCTs), quasi-randomized control trials, clinical trials, • cohort studies, case-control studies, case series and case reports. .
Types of **P**articipants	Children up to five years of age
Types of **I**nterventions	Vaccinations with all BCG and standard titre measles containing vaccines, all diphtheria and tetanus toxoids, and Bordetella pertussis containing vaccines..
Types of **O**utcome measures	• All available immune response markers •
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 effect of vaccines on immunological markers

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	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.
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)	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).
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 heterologous effects.