PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The use of supplementary immunisation activities to improve uptake of current and future vaccines in low-income and middle-income countries: a systematic review protocol
AUTHORS	Kagina, Benjamin; Wiysonge, Charles; Machingaidze, Shingai; Abdullahi, Leila; Adebayo, Esther; Uthman, Olalekan; Hussey, Gregory

VERSION 1 - REVIEW

REVIEWER	Angela Oyo-Ita Dept of Community Medicine University of Calabar Calabar Nigeria
REVIEW RETURNED	08-Dec-2013

GENERAL COMMENTS	ABSTRACT: should include how tge authors plan to manage the data. OBJECTIVES: routine immunisation coverage as secondary outcome fails to acknowledge the impact the SIA will create oin routine immunisatioin coverage. The outcome should be "immunisation coverage" This will address the general coverage for both routine and SIA. METHODS: the search term should include "mass campaign", "immunization campaign" Authors have not described how data will be synthesised considering the different study designs. What shall be the unit of analysis bearing in mind clustering effects from cluster randomised data? How will heterogeneity be explored? Missing data: will authors include studies that they cannot get outcome data? How will data be summarised if meta analysis is not feasible? The authors are inculding data from different study designs. They will need technical support to plan for the data analysis.

REVIEWER	Juliet Babirye Makerere University School of Public Health Uganda
REVIEW RETURNED	19-Dec-2013

GENERAL COMMENTS	This is a pertinent topic with the potential to improve immunization programs. However, since there are existing arguments for and against SIAs, it is therefore important to conduct this systematic review. I just have a few issues that need to be addressed: 1. The background was well written and an interesting read. It

	seems to focus quite a bit on TB, although the study questions are broad. Why the focus on only the single disease? 2. This protocol has three study questions: a. To determine whether SIAs increase vaccination coverage in LMICs b. To determine whether SIAs reduce disease outbreaks in LMICs c. To describe the lessons learnt during SIAs and how these may guide the introduction of future vaccines (TB, HIV, malaria) in LMICs. These questions make the systematic review very broad. A focus on one or two questions may help detailed study of the topic.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Angela Oyo-Ita

ABSTRACT: should include how the authors plan to manage the data

Authors' reply: This has now been included in the abstract section (Page 2 of the revised protocol: "Two authors will independently extract data from eligible studies and independently assess risk of bias by assessing the adequacy of study characteristics. The primary meta-analysis will use random effects models due to an expected inter-studies heterogeneity. Dichotomous data will be analysed using relative risk and continuous data using weighted mean differences (or standardised mean differences), both with 95% confidence intervals."

OBJECTIVES: routine immunisation coverage as secondary outcome fails to acknowledge the impact the SIA will create in routine immunisatioin coverage. The outcome should be "immunisation coverage" This will address the general coverage for both routine and SIA.

Authors' reply:
We agree with the reviewer's comment on addressing the general coverage for both SIAs and routine immunisation. We have revised this as suggested by the reviewer in the revised protocol (Page 8)

METHODS: the search term should include "mass campaign", "immunization campaign".

Authors' reply:
We agree with the reviewer's comment and have added the following terms in our revised protocol (page 20), in addition to the existing search terms: "mass campaigns OR immunisation campaigns OR vaccination campaigns OR immunization campaigns"

Authors have not described how data will be synthesized considering the different study designs. What shall be the unit of analysis bearing in mind clustering effects from cluster randomised data? How will heterogeneity be explored?

Authors' reply: We have now described how data will be synthesized on page 11 of the revised protocol "All eligible studies will be summarised and analysed using Stata version 12 for Windows. Two authors will extract the data, the first author will enter all data and second author recheck all entries. Disagreements will be resolved by discussion. If the studies are sufficiently similar, we will combine the data using random-effects model due to anticipated heterogeneity that may result from the difference in methodology and study settings. Where the rating scales used in the studies have a reasonably large number of categories (more than 10) the data will be treated as continuous variables arising from a normal distribution. We will use weighted mean difference (WMD) when the pooled studies use the same rating scale or test, and the standardised mean difference (SMD), the absolute mean difference divided by the standard deviation when the studies use different rating scales or tests. When the rating scales used are fewer than 10 and more than two, we will concatenate the data into two categories that best represent the contrasting states of interest, and treat the outcome measure as binary. Study results for dichotomous data will be expressed as relative risk (RR) and 95% confidence interval (CI). Time-to-event outcomes or generic inverse variance outcomes, such as

survival time and time to cure will be expressed as the log hazards ratio and 95% CI."

Similarly, the issues of unit of analysis has now been clarified on page 12 of the revised protocol: "All cluster randomised trials that meet the inclusion criteria will be included in the meta-analysis after adjusting for design effect using variation inflation method [34, 35]: design effect = 1 + (M - 1)ICC, where M is the average cluster size and ICC is the intra-cluster correlation coefficient. If the authors did not report the ICC, we will use ICC from a similar published trial. For estimated values of ICC, we will conduct sensitivity analyses using larger and smaller ICCs to determine if the results are robust."

Missing data: will authors include studies that they cannot get outcome data?
Authors' reply: We have now explained how we will deal with missing data on page 10 of the revised protocol: "The data will be analysed on an intention-to-treat basis as far as possible and attempts will be made to obtain missing data from the original corresponding author. Where missing data is unobtainable, imputation of individual values will be undertaken for the primary outcomes only. For other outcomes, only the available data will be analysed. Any imputation undertaken will be subjected to sensitivity analysis. If studies report sufficient detail to calculate mean differences but no information on associated standard deviation (SD), the outcome will be assumed to have standard deviation equal to the highest SD from other studies within the same analysis."
How will data be summarized if meta-analysis is not feasible?

Authors' reply: This has now been clarified on page 12 of the revised protocol: "When studies cannot be combined for meta-analysis due to diversity of interventions, narrative syntheses will be conducted and results of individual studies will be displayed graphically to enable more succinct summary of evidence."

The authors are including data from different study designs. They will need technical support to plan for the data analysis.

Authors' reply: The range of skills and knowledge embedded within proposed review team covers all the key areas required for conducting the systematic review including meta-analyses. Our group is ideally placed to conduct this type of meta-analysis. We have previously published extensively on the methods of meta-analysis for synthesis evidence from different sources, mixed treatment comparison meta-analysis and generalized evidence synthesis.

Reviewer Name Juliet Babirye
Institution and Country Makerere University School of Public Health Uganda

Please state any competing interests or state 'None declared':

Authors' reply: This statement has been added on page 1 of the revised manuscript. "None declared".

This is a pertinent topic with the potential to improve immunization programs. However, since there are existing arguments for and against SIAs, it is therefore important to conduct this systematic review. I just have a few issues that need to be addressed:
1. The background was well written and an interesting read. It seems to focus quite a bit on TB, although the study questions are broad. Why the focus on only the single disease?

Authors' reply: Our focus is on TB because current TB vaccination strategies show that new effective TB vaccines are likely to have the highest impact on adolescence population. Routine vaccination services do not target adolescence population and therefore, SIAs are possible strategies to roll out new and effective TB vaccines in the future.

2. This protocol has three study questions:
a. To determine whether SIAs increase vaccination coverage in LMICs
b. To determine whether SIAs reduce disease outbreaks in LMICs
c. To describe the lessons learnt during SIAs and how these may guide the introduction of future vaccines (TB, HIV, malaria) in LMICs.
These questions make the systematic review very broad. A focus on one or two questions may help detailed study of the topic.

Authors' reply: Thank you for pointing this out. Our main focus is on the first two objectives. The third objective is a descriptive of the lessons learnt from the first two objectives. Lessons learnt will help us identify any factors that may undermine or improve SIAs coverage. In no way will this third objective compromise a detailed redress of the first two objectives.