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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

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ABSTRACT

Introduction: Immunisation coverage data in low-income and middle-income countries (LMICs) suggest that more strategies need to be implemented to achieve and sustain optimal vaccine uptake. Among possible strategies to improve immunisation coverage are supplementary immunisation activities (SIAs). We are therefore interested in conducting a systematic review to assess whether SIAs complement routine immunisation programmes to improve vaccination coverage and prevent disease outbreaks.

Methods: Our systematic review will focus on studies conducted in LMICs. With the help of an information specialist, we will search for eligible studies in PubMed, Web of Science, Scopus, Africa-Wide, Cochrane Library, WHOLIS, CINAHL, PDQ-Evidence as well as reference lists of relevant publications. Additionally, we will contact relevant organisations such as WHO and GAVI. 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 expected interstudies heterogeneity. Dichotomous data will be analysed using relative risk and continuous data using weighted mean differences (or standardised mean differences), both with 95% CIs.

Discussion: The findings from this systematic review will be discussed in the context of strengthening routine childhood immunisation services, routine adolescent immunisation services and introduction of future vaccines against tuberculosis and HIV/AIDS.

Study strengths: Unbiased selection of many studies conducted in different settings. This will strengthen the validity of the review results.

Study limitations: Heterogeneity of the study settings of the low-income, lower-middle-income and upper-middle-income countries as well as heterogeneity in study designs.

BACKGROUND

Infectious diseases are prevalent in low-income and middle-income countries (LMICs). For example, tuberculosis (TB) is a pandemic of great public health concern. In 2011, the WHO estimated that 1.4 million people died worldwide from TB.[1] To control the TB pandemic, stakeholders have proposed multipronged approaches, including development of new and more effective vaccines, novel and better drug regimens, faster and more accurate diagnostic tools as well as strengthening of public health systems. Among these approaches, more effective TB vaccines are likely to have the greatest impact.[2] Research and development of new and better TB vaccines has been accelerated. There were 12 candidates with new TB vaccines in human clinical trials in the year 2012.[3 4] For the effective TB vaccines to achieve the desired impact, vaccination coverage must be optimal.

Uptake of vaccines delivered through routine immunisation programmes remains variable, and often poor in many LMICs,[5 6] suggesting that routine immunisation services alone are insufficient to achieve optimal immunisation coverage in LMICs. Taking into account that TB burden is highest in LMICs,[7] it is likely that future effective TB vaccines will not reach desirable vaccination coverage in these settings if delivered only through the routine immunisation services. Therefore, additional strategies will need to be adopted to improve immunisation coverage, including supplementary immunisation activities (SIAs).[8 9]

SIAs have been successfully used in different disease conditions, including typhoid, measles,[10–12] polio,[13] human papillomavirus[14]

and cholera.[15] The major reported benefits of SIAs are increased immunisation coverage, reduced disease spread and cost effectiveness.[16] Abu-Raddad *et al*[2] have used a mathematical model to show a significant additive public health benefit in the reduction of TB incidence by incorporating SIAs to other key interventions of neonatal vaccination and better TB treatment and diagnostic tools.

However, the use of SIAs to improve immunisation coverage and prevent disease outbreaks in LMICs relative to routine immunisation services remains controversial.[8 17] To utilise SIAs successfully in the control of TB with future effective vaccines, it is worthwhile to synthesise the current best evidence on the effectiveness of this strategy. A study conducted in South Africa, a middle-income country with a high burden of TB, showed that TB incidence peaks in adolescence and that adolescents are the greatest force of *Mycobacterium tuberculosis* infection within a population.[18] This study suggests that a new effective TB vaccine would have the greatest impact in the control of TB when targeted at the adolescent population. We propose to conduct a systematic review to assess whether, at present, there exists evidence that SIAs improve immunisation coverage and reduce disease burden in LMICs.

To the best of our knowledge, the most recent comprehensive systematic review on SIAs was conducted by Dietz and Cutts[16] in 1997 and involved studies published up to 1992. Since then, there have been many changes, among them population increase,[19] change in disease epidemiology,[20] emergence of antivaccine groups[21] as well as expanded healthcare infrastructure. These changes may negatively affect the performance of immunisation services in obtaining optimal vaccination coverage. Furthermore, new vaccines continue to be incorporated in the existing Expanded Programme on Immunisation,[22 23] adding more logistical and financial pressure to the routine immunisation services.

In the context of these changes that may affect the vaccination coverage, it is rational to hypothesise that at present the effects of SIAs in complementing routine immunisation services may be different from those reported in the past by Dietz and Cutts in 1997. In support of this hypothesis, some authors reported that SIAs negatively affect the routine immunisation services,[24 25] whereas some studies report the opposite: SIAs increase immunisation coverage and reduce disease outbreaks.[26–29] Therefore, an up to date systematic review is critical to provide evidence on the relevance of SIAs in the current health systems environment. This evidence will be useful, particularly for LMICs, because these settings are the epicentre of vaccine-preventable diseases and (by definition) have limited resources.

OBJECTIVES

1. To determine whether SIAs increase vaccination coverage and reduce disease outbreaks in LMICs.
2. To describe the lessons learnt during SIAs and how these may guide the introduction of future vaccines (TB, HIV, malaria) in LMICs.

METHODS

Types of studies

We will consider primary studies with the following designs:

- Intervention studies: individually randomised controlled trials (RCTs), cluster-RCTs, non-RCTs, interrupted time series and controlled before-and-after studies.
- Observational studies: cohort studies, case–control studies and cross-sectional studies.

Review articles will be excluded.

Study settings

Studies conducted in LMICs as defined by the World Bank gross domestic product ranking in July 2013.

Types of interventions

This study will focus on SIAs, also referred to as mass vaccination campaigns. SIAs are defined as immunisation activities whereby a vaccine is taken simultaneously to many residents of a community within a defined short space of time. We will exclude studies of routine immunisation services, that is, immunisation services rendered (at fixed, outreach or mobile sites) regularly throughout the year. In addition, mass campaigns conducted for purposes other than immunisation, for example, mass information campaigns to educate communities about general health issues will not be included.

Types of outcome measures

Primary outcomes

- Vaccination coverage achieved during SIAs
- Disease outbreaks
- Disease incidence

Secondary outcome

- Immunisation coverage

Search methods for identification of studies

A comprehensive search strategy will be developed, including various terms relating to SIAs and LIMCs, for identification of published and unpublished articles with no language restriction. We will search academic peer-reviewed journals, grey literature (non-published or non-reviewed papers, reports) and reference lists of relevant publications. The detailed electronic search strategy is provided in online supplementary appendix 1 while the summary of the search outputs retrieved from different databases is in online supplementary appendix 2.

Electronic searches

We will search the following electronic databases for primary studies: PubMed, Web of Science, Cochrane

Central Register of Controlled trials (CENTRAL), Scopus, Africa Wide, PDQ-Evidence, WHOLIS and CINAHL.

Data collection and analysis

Selection of studies

Two authors will independently screen the search outputs for potentially eligible studies, compare their results and resolve disagreements by discussion and consensus. The two authors will then independently go through the full text of all potentially eligible studies to assess whether the studies meet the inclusion criteria defined by the study design, setting, intervention and outcomes. Discrepancies in the list of eligible studies between the two authors will be resolved through discussion and consensus.

Data extraction

A structured and standardised data collection form has been developed for extracting data from the selected studies. The form will capture key study characteristics, including methods, participants and outcomes (see online supplementary appendix 3). Prior to use, the extraction form will be piloted on at least four included studies identified randomly from the list of included studies.

Assessment of risk of bias in included studies

The quality of studies will be assessed using the Cochrane Collaboration's tool for assessing risk of bias[30] for experimental studies and the Scottish Intercollegiate Guidelines Network (SIGN) checklist for other study designs.[31]

Measures of treatment effect

We will express the result of each study as a risk ratio with its corresponding 95% CIs for dichotomous data, or mean difference with its SD for continuous data. We will conduct a meta-analysis for the same type of participants, interventions, study designs and outcome measures where homogeneity of data allows. Heterogeneity will be assessed using the χ^2 test of homogeneity, and quantified using the I^2 statistic.[32 33]

Dealing with missing data

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 are 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 SD, the outcome will be assumed to have SD equal to the highest SD from other studies within the same analysis.

Data synthesis

All eligible studies will be summarised and analysed using Stata V.12 for Windows. Two authors will extract the data; the first author will enter all data and the second author will recheck all entries. Disagreements will be resolved by discussion. If the studies are sufficiently similar, we will combine the data using the random effects model due to the 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 the weighted mean difference when the pooled studies use the same rating scale or test, and the standardised mean difference, the absolute mean difference divided by the SD, when the studies use different rating scales or tests. When the rating scales used are fewer than 10 and more than 2, 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 and 95% CI. Time-to-event outcomes or generic inverse variance outcomes, such as survival time and time to cure, will be expressed as the log HR and 95% CI.

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 a more succinct summary of evidence.

Unit of analysis

All cluster randomised trials that meet the inclusion criteria will be included in the meta-analysis after adjusting for design effect using the variation inflation method:[34 35] design effect=1+(M−1) ICC, where M is the average cluster size and ICC is the intracluster 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.

Assessment of heterogeneity

We anticipate substantial variation in study results due to differences in the study design, cointerventions, study settings (low-income vs lower-middle-income vs upper-middle-income countries) and risk of bias. We will examine statistical heterogeneity between study results using the χ^2 test of homogeneity (with significance defined at the α-level of 10%), and quantify any statistical heterogeneity between study results using the I^2 statistic.[30]

Assessment of reporting biases

A funnel plot will be used to investigate the risk of publication bias by intervention type, provided 10 or more

studies are included in the analysis for each intervention type.[36 37] The funnel plot will be critically examined for asymmetry.

Sensitivity analysis

We will conduct sensitivity analysis to establish if the meta-analysis results are influenced by: the effect of study designs; publication type (peer-reviewed vs grey literature); the geographical settings (low-income vs lower-middle-income vs upper-middle-income countries); and study period (published before 2000 vs published after 2000).

DISCUSSION

This systematic review will establish whether SIAs improve immunisation coverage, prevent disease outbreaks and have a negative impact on routine immunisation services in LMICs. The review will provide an up-to-date evidence base of the benefits and harms of the use of SIAs in the control of vaccine-preventable disease. Additionally, we will discuss how the findings of this review may be applicable in the context of future vaccines against TB, HIV and malaria.

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Contributors BMK, CSW, SM and GDH conceived the study. BMK, SM, LHA and EA wrote the protocol with supervision from CSW and GDH. OAU wrote the statistical analysis plan for the study and provided comments on the manuscript. GDH sourced the funds for the study.

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Competing interests None.

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