Protocol for systematic review, meta-analysis and meta-regression of differential vaccine efficacy across high income, lower-middle income and low-income settings

# Overview

Most vaccine efficacy trials are conducted in higher income settings rather than in lower income settings. Lower income settings may differ from high-income settings in health service resources, the prevalence of comorbid diseases, and genetic characteristics of the infectious agent. This presents a challenge to policymakers in low-income settings, who must make some assumption about the applicability of trial data from high-income settings, or else seek to conduct trials locally. The latter is challenging as resources are scarce, while the former is difficult because there are few quantitative estimates as to how vaccine efficacy differs between high and low-income settings. Since 1990, at least 700 RCTs of vaccines have been conducted and 171 of these have had one or more site within a low or lower-middle income country. These data provide an opportunity to address this evidence gap.

We will therefore conduct a systematic review to identify all trials for vaccines of interest where at least one trial wholly or partly conducted in a low or lower-middle income country can be identified. Effect estimates and trial-level characteristics will be extracted for each trial, and where appropriate sub-group effect estimates for each site. Using these data, we will perform Bayesian hierarchical generalized linear modelling. We will include terms to estimate the difference in efficacy across settings, with additional terms to identify factors which modify the difference in efficacy. Vaccines will be grouped into clinically/biologically meaningful categories for rational information sharing within and between groups.

# Objectives

Conduct a systematic review and hierarchical meta-regression to determine, for selected vaccines: -

1. Estimate the frequency and magnitude with which vaccine efficacy differs across high/low income settings.

2. Estimate which trial-level characteristics (e.g. vaccine, agent, host, etc) are associated with 1.

# Outputs

New knowledge on the frequency and magnitude of differential vaccine efficacy between low and high-income settings and an improved understanding of which factors cause such differences. We will also use the modelling to produce a set of distributions concerning the probable difference in efficacy (with plausible ranges) for a given vaccine in a given setting, compared to the high income setting in which it was originally studied. Such priors may then be used directly in health economic modelling studies, or as informative priors for clinical trials. Following this systematic review and meta-analysis we will conduct simulation studies to determine how the use of our informative priors would affect the power (and hence required sample size) for clinical trials of vaccine efficacy in low income countries.

# Pre-registration

The systematic review protocol will be pre-registered on PROSPERO before data extraction, as per the latest PROSPERO rules (<https://www.crd.york.ac.uk/prospero/>). We may conduct the search and screening prior to registration.

# Protocol

## Defining vaccines of interest

Informed by a review of the vaccine trials identified in our recent scoping study (Appendix) we will define a set of vaccines which are of clinical interest, and where there are likely to be at least some vaccine trials performed in both high and low-income/lower-middle income settings. The vaccines will be drawn from the list of vaccines provided by the WHO Anatomic Therapeutic Classification (WHO ATC) dictionary (Table 1). We will confine the systematic review to this agreed set of vaccines for all subsequent analyses.

### Table 1 List of vaccine classes from WHO ATC drug dictionary

|  |  |
| --- | --- |
| J07A BACTERIAL VACCINES | J07B VIRAL VACCINES |
| J07AC Anthrax vaccines | J07BA Encephalitis vaccines |
| J07AD Brucellosis vaccines | J07BB Influenza vaccines |
| J07AE Cholera vaccines | J07BC Hepatitis vaccines |
| J07AF Diphtheria vaccines | J07BD Measles vaccines |
| J07AG Hemophilus influenzae B vaccines | J07BE Mumps vaccines |
| J07AH Meningococcal vaccines | J07BF Poliomyelitis vaccines |
| J07AJ Pertussis vaccines | J07BG Rabies vaccines |
| J07AK Plague vaccines | J07BH Rota virus diarrhea vaccines |
| J07AL Pneumococcal vaccines | J07BJ Rubella vaccines |
| J07AM Tetanus vaccines | J07BK Varicella zoster vaccines |
| J07AN Tuberculosis vaccines | J07BL Yellow fever vaccines |
| J07AP Typhoid vaccines | J07BM Papillomavirus vaccines |
| J07AR Typhus (exanthematicus) vaccines |  |

For all trials, the vaccines investigated will be described according to the full 7-digit ATC code (e.g. J07AL02 - pneumococcus, purified polysaccharides antigen conjugated). This will allow us to group the trials according to the 5-character WHO ATC code (Table 1).

With a view to the subsequent hierarchical modelling, the vaccines will subsequently be categorised according to: -

* Bacterial versus viral
* the dominant organ system (e.g. gastrointestinal, respiratory) – defined via expert consensus at KEMRI
* the vaccine type (live-attenuated; inactivated; subunit, recombinant, polysaccharide, and conjugate; and toxoid) vaccines
* OTHER CATEGORIES to help group vaccines more like each other than others within the above classes

Separate models will be fit for bacterial and viral vaccines and for different dominant organ systems. Within these stratified models, we will share information across the other classifications. The model will employ cross-classification rather than nesting. The final structure of the models will be pre-specified after the number of participants at each site for each trial within each vaccine have been obtained, but before any outcome data are extracted.

## Trial eligibility

The following describes eligible trials in the standard PICO format.

### Population

Trial including adults and/or children.

### Intervention

Any vaccine as identified in the “Defining vaccines of interest” section

### Comparator

No vaccination (regardless of whether or not a dummy-intervention is used), i.e. not an active comparator

### Outcomes

* Incidence of infection, hospitalisation for infection and/or mortality from infection
* Markers of immunological response – these will be pre-specified for each vaccine
* Adverse events

### Other eligibility criteria

We will include trials where randomisation was performed at either the level of the individual patient, or at a group-level (i.e. cluster randomisation).

We will exclude any trial without a report in English. We will exclude trials for any vaccine where at least one trial did not have at least one site in a low or middle-income country, where the vaccine has never been marketed or where it has been withdrawn in more than one country due to safety concerns. We will also exclude trials in special populations (e.g. people with HIV, premature babies etc).

# Search strategy

We will search the following sources for randomised clinical trials of vaccines; Medline, Cochrane Register of Controlled Trials (CENTRAL), EMBASE, clinicaltrials.gov (<https://clinicaltrials.gov/>) and the World Health Organisation International Clinical Trials Registry Platform (ICTRP - <http://apps.who.int/trialsearch/>).

We will use the following search terms for each database (example below for Medline): -

### Medline

|  |  |
| --- | --- |
|  | Terms |
| 1 | Vaccine[mh]exp |
| 2 | Vaccination[mh]exp |
| 3 | Synonyms for each of the vaccines in scope |
| 4 | Randomised controlled trial filter |
| 5 | (#1 OR #2 OR #3) AND #4 |

# Data sources and extraction

Data will be obtained from published reports of individual trials, published systematic reviews and meta-analyses, clinical study reports (CSRs) (e.g. as submitted to the European Medicines Agency), and where necessary by contacting authors. For those industry sponsors who require an application to access CSRs (some sponsors such as GSK make trials available immediately for download), we will apply for access. We do not anticipate applying for individual-level participant data from any trial due to resource constraints.

For each trial, we will obtain estimates of the vaccine efficacy for each outcome for each trial site. Where site level data is not available, we will obtain estimates for each income setting. Where settings outcome data are not available, we will obtain overall estimates as well as the proportion of participants in each site/setting. We will also obtain baseline characteristics data for each trial such as the mean age, sex etc. For all trials we will obtain the intention to treat population estimates where these are available. Where they are not, we will obtain the per protocol analysis estimates, but will note that these are the ones which have been presented.

# Overall comparison

For each vaccine, we will first compare the overall treatment efficacy for each outcome; treating high-income settings as the reference level, we will estimate interactions for upper middle, lower middle and low-income settings. We will increase robustness to outlying values and improve precision by “borrowing” information across related trials in the hierarchical model described above. We will use these to report the mean difference in vaccine efficacy across low, lower-middle and high-income settings.

## Covariate data for examining differences in site-specific efficacy

For any vaccine, where the mean difference in efficacy between low income and high-income settings was not close to null, we will subsequently perform a meta-regression of which site-specific factors are associated with differences in efficacy. Null will be defined for categorical outcomes as -0.1 <= log(difference) <= 0.1 and for continuous outcomes (standardised by dividing by the standard deviation) as -0.05 <= difference <= 0.05.

For the meta-regression, for each trial site we will obtain the following explanatory variables: -

* Climatic
  + Average temperature/peak temperatures
* Economic [World Bank]
  + Quality of transport infrastructure
  + GDP
* Health-related variables
  + Prevalence of relevant pre-specified comorbid diseases (e.g. other gastrointestinal infections)
  + Prevalence of incomplete immunisation
  + Vaccine program
* Agent-related
  + The extent of antigenic variation within and between countries
  + etc
* Trial design variables
  + For individual-level randomisation, the number of protocol violations
  + For cluster trials, the level of coverage

We will obtain these estimates from the websites of national and international agencies, and from the published literature. Where these are likely to be time-varying (e.g. incomplete immunisation), we will obtain data for the year closest to the mid-point between the trial end and start dates.

We will model the effect of these variables on treatment efficacy in hierarchical generalised linear models.

# Software

We will conduct the review using Covidence software (<https://support.covidence.org/help>) , for which DM has purchased a small group licence. Briefly, Covidence provides facilities to help with screening, data extraction, harmonisation and data management. It also provides online videos. AS has extensive experience in using Covidence to produce systematic reviews.