

BMJ Open Equity in vaccine trials for higher weight people? Protocol for a rapid review of inclusion and exclusion criteria for higher weight people in clinical trials for COVID-19

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ABSTRACT

Introduction Vaccination is a public health strategy that aims to reduce the burden of viral illness, especially important for populations known or likely to be at increased risk for inequitable outcomes due to the disease itself or disparities in care accessed and received. The role of weight status in COVID-19 susceptibility and disease burden remains unclear. Despite this, higher weight is frequently described as a definitive risk factor for both susceptibility and disease severity. Therefore, COVID-19 vaccine trials should recruit a study group representative of the full weight spectrum, and undertake appropriate subgroup analysis by weight status to evaluate response and titrate dose regimes where indicated to ensure equitable outcomes for higher weight people.

Methods and analysis We aim to review inclusion and exclusion criteria of clinical trial protocols registered with ClinicalTrials.gov, ISRCTN Register, the WHO official vaccine trial register, and 'The COVID-19 Vaccine Tracker'. To determine the number of trials including higher weight (body mass index >30 kg/m²) individuals and the number of trials conducting efficacy subgroup analyses by weight status. Screening, data extraction and quality appraisal of trial protocols will be completed independently by a minimum of two reviewers. Clinical trials will be assessed for risk of bias using the Risk of Bias-2 tool. We will conduct a descriptive analysis of extracted data. The following subsets are proposed: participation of higher weight people in COVID-19 vaccine trials by trial phase, country and vaccine platform.

Ethics and dissemination Ethical approval was not required for this review. The results of this rapid review will be presented at appropriate conferences and published in a suitable peer reviewed journal.

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INTRODUCTION

The clinical presentation of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection ranges from asymptomatic infection to organ dysfunction presenting as shock, acute respiratory distress

Strengths and limitations of this study

- To date, no review has been conducted for the inclusion rates of higher weight people in COVID-19 vaccine trials.
- These findings will help inform potential limitations in the evidence currently available in formulating advice on COVID-19 vaccinations for higher weight people.
- The review method is based on the recent interim guidance from the Cochrane Rapid Reviews Methods Group.
- A minimum of two reviewers will independently screen registered protocols, extract data, appraise quality and conduct the analysis.
- The inclusion of studies published only in English may mean that important additional findings are missed.

syndrome, acute cardiac or kidney injury and death.^{1,2} A major clinical risk factor for COVID-19 is older age and other risk factors reported include male sex and chronic health conditions such as hypertension and cardiovascular disease.^{3,4} Groups reported with higher risk for severe COVID-19 include people with high body mass.⁵ There remains uncertainty about the role weight plays in COVID-19 susceptibility and disease burden.

Research and development of safe and effective SARS-CoV-2 vaccines began early in 2020 and there has been rapid movement from feasibility studies through to human clinical trials and administration of vaccines in several countries.⁶ The rapid rate of development has been credited to the large body of preclinical trial work previously undertaken in vaccine development for other similar coronaviruses such as Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-CoV-1)

and Middle Eastern Respiratory Syndrome Coronavirus 7 (MERS-CoV-7).

Vaccination is a public health strategy that aims to reduce the incidence and severity of viral illness and may also reduce community transmission. The new COVID-19 vaccines that have been approved for use in many countries have demonstrated high levels of efficacy in reducing the establishment of severe viral illness. The extent to which COVID-19 vaccines interrupt viral transmission is yet to be fully established,⁷ although reviews by national agencies such as the US Food and Drug Administration show high levels of short term safety and efficacy in protecting against symptomatic COVID-19 for a number of vaccines now approved for use in many countries.⁸ Many of the current trials in the development of an SARS-CoV-2 vaccine seek to induce neutralising antibodies (nAbs) to the spike protein on the surface of the virus.⁹ Induction of nAbs is associated with protection in previous viral vaccine development.⁹ Further to traditional inactivated viral vaccine candidates, a range of modern—as yet unlicensed technologies—are being evaluated against SARS-CoV-2.¹⁰

Historically, population groups such as elderly people, young children and pregnant women have been excluded from clinical trials based on their designation as vulnerable groups.^{11 12} Higher weight people have also historically been excluded from clinical trials based on perceptions of vulnerability or in an attempt to reduce confounding. Such exclusions raise ethical and efficacy concerns. Exclusions of particular groups from clinical research can harm individuals by limiting their autonomy and denying them access to experimental interventions, and can harm groups by limiting the evidence available to inform their clinical care.¹³ Lack of diverse representation reduces the generalisability of the research findings to the whole population and specific application to the population groups excluded. This can result in poorer quality care, higher rates of adverse events and worse health outcomes for groups excluded from clinical research.¹⁴ For example, WHO has indicated that the exclusion of pregnant women from COVID-19 vaccine research is a significant concern.¹⁵

There is some evidence of the impact of body weight on drug efficacy. Clinical trials of cancer therapeutics have come under scrutiny in recent years for the exclusion of higher weight participants.¹³ Vaccine efficacy (VE) across the weight spectrum has been unclear in prior vaccines.^{16 17} An inverse relationship is reported between body mass index (BMI) and antibody response to a standard dose of HepA and HepB vaccination, with reduced antibody titres associated with higher weight status.¹⁶ Conversely in the administration of the trivalent inactivated influenza vaccine weight status was associated with higher initial antibody titres in participants of higher weight status, however by 12 months a greater decline in antibodies was noted.^{16 17} Early evidence from three trials (Pfizer, Moderna and Johnson & Johnson) shows that vaccine safety and efficacy is comparable in recipients across the weight spectrum.^{18 19}

Ideally, COVID-19 vaccine trials should recruit a representative study group and undertake appropriate subgroup analysis by weight status, to evaluate safety, efficacy and titrate dose regimes where indicated to ensure equitable outcomes for higher weight people.^{17 18} To date, no review has been conducted for the inclusion rates of higher weight people in COVID-19 vaccine trials.

OVERALL OBJECTIVE

The primary objective of this rapid review is to quantify the number of protocols that include higher weight people (defined as BMI of 30kg/m² and above) as participants in clinical trials of novel vaccines for COVID-19. Secondary objectives are to quantify the number of higher weight people participating in these trials and quantify the number of phase 3 efficacy trials conducting analysis of VE across the weight spectrum.

Specific review questions

To conduct a rapid review of clinical trial protocols of COVID-19 novel vaccines in order to quantify:

1. The proportion of trials that include higher weight people, as determined by BMI >30 kg/m², as participants.
2. The proportion of higher weight individuals (BMI >30 kg/m²) participating in novel COVID-19 vaccine trials.
3. The proportion of phase 3 trials conducting analysis of VE by weight status.

METHODS

Study design

A rapid review of registered vaccine trial protocols will be conducted with the aim of the review to be complete by 30 May 2021. The review method is based on the recent interim guidance from the Cochrane Rapid Reviews Methods Group.²⁰ Rapid reviews have emerged as an efficient tool to get evidence to decision makers more quickly and are now considered part of the knowledge synthesis family.²¹

Review constraints include:

1. A minimum of two reviewers will independently screen registered protocols, extract data, appraise quality and conduct the analysis.
2. Registered protocols in any stage prior to recruitment will be included in the primary objective analysis.

Protocol registration

Any revisions will be identified on the registered document. Post hoc changes will be reported with the published results. This protocol was drafted and written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols statement.^{22 23}

Eligibility criteria

Protocols will be included in the review if they meet the following criteria.

Types of studies

Inclusion criteria: trials of a novel COVID-19 vaccine in any clinical phase with registered protocols evaluating efficacy, safety and/or immunogenicity of the vaccine.

Exclusion criteria: clinical trials evaluating therapies that do not generate active immunity; trials including people infected by COVID-19; trials evaluating the efficacy of vaccines designed to protect against other pathogens eg, Bacille Calmette-Guerin (BCG) vaccine in the prevention or treatment of COVID-19; protocols written in a language other than English.

Participants

Any participant in the included studies with a negative test for COVID-19 infection at the time of recruitment. Participants will be adults, aged ≥ 18 years, and included irrespective of sex, gender and ethnicity.

Interventions(s) and exposure(s)

Clinical trials in any phase for any novel COVID-19 vaccine, and participation in those trials with a focus on the participation of higher weight individuals.

Comparator(s)/control

Not applicable.

Context/setting

There are no restrictions on the setting, location or the country in which the trials may be registered and conducted.

Outcome(s)

The proportion of vaccine trials including higher weight individuals as participants as a proportion of total included COVID-19 vaccine trials.

The proportion of higher weight individuals participating in trials (where recruitment is complete) as a proportion of total included COVID-19 vaccine trial participants.

Of trials where recruitment is complete, the proportion of trials planning to stratify their VE estimates by weight status.

Measures

Total numbers and percentages.

Time

All periods of time and duration of follow-up.

Search strategy

A search will be performed of ClinicalTrials.gov, ISRCTN Register, the WHO official website for vaccine trials, 'The COVID-19 Vaccine Tracker' developed by the Vaccine Centre at the London School of Hygiene & Tropical Medicine, and the Australia and New Zealand Clinical Trial Register to identify clinical trials for vaccines in different countries irrespective of publication status, publication year, and language.^{24 25} Further details of the search strategy are included in separate online supplemental table S1.

Data collection and appraisal

Data extraction (selection and coding)

Selection of trial protocols and data extraction will be performed by two reviewers (JC and LG) independently. Studies will be screened for relevance, and eligibility criteria as detailed above to be included in the review. Rayyan, a systematic review web-based application, will be used for selection and appraisal of protocols for eligibility with reviewer settings set to 'Blind ON'.^{26 27} To reduce the risk of missing eligible protocols a low threshold for inclusion will be applied to screening decisions by two reviewers with a third reviewer checking excluded protocols (MH). Disagreements will be resolved in consultation and by consensus (JC, LG and MH). A pilot review exercise will then be conducted independently by the review team on 10 selected trial protocols using a standardised data extraction form. Reviewers will examine any differences and calibrate the review form.

Each study will be reviewed using the calibrated data extraction form, collecting the following information. General study data: first author, year and language of publication, year and place(s) of study performance, trial number, trial status—recruiting, current, complete. Trial design: study phase, level of blinding, purpose—dose finding/dose confirmation. Participant characteristics: numbers, age range and mean (or median), health status. Vaccines: vaccine and placebo administered, antigen type/dose, adjuvant type/dose, vector type, dose regime. Risk of Bias (ROB): using the ROB-2 Tool, as described below (see online supplemental figure S1).

As outcomes, we will extract data on trials and review inclusion and exclusion criteria to determine participation of higher weight individuals, the number of higher weight individuals participating and whether the trial has, or will, conduct analysis of VE by weight status.

Where there is missing data or insufficient reporting in the protocol we will contact the protocol trial authors via email. Where communication is not received by 20th May, these will be reported as 'undefined'.

Risk of Bias

The risk of bias (ROB) in included studies will be independently evaluated by two reviewers (JC and LG). Any disagreements over ROB will be resolved in consultation with a third reviewer (MH). To assess the risk of bias in controlled trials we will use the ROB-2 Cochrane risk of bias assessment tool.^{28 29}

Strategy for data synthesis

We will conduct a descriptive analysis of extracted data to determine the total number of trials that include higher weight participants, the total number of higher weight people participating in trials and as a proportion of total participants across all trials. We will describe the number of trials evaluating the efficacy of the vaccine by weight status. We will present narrative and tabulated information for results.

Analysis of subgroups or subsets

The following subsets are proposed: participation of higher weight people in COVID-19 vaccine trials by trial phase, country and vaccine platform.

Ethics

Ethical approval was not required for this review.

DISSEMINATION

Due to the urgency of disseminating evidence-based information, particularly as countries move rapidly to roll out vaccination programmes, we seek to undertake this review with similar urgency. Dissemination may include the use of medRxiv.org, for example, as 'preprints' of review findings prior to formal peer review. The results of this rapid review will be presented at appropriate conferences and will be published in a suitable peer-reviewed journal.

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Contributors LG conceived the initial idea. A meeting was held via zoom with LG, JC, MH, LO, AB and AH to substantially contribute to the design and scope of the review, to agree registration of the review protocol and roles in the review to be undertaken. LG and JC prepared the initial outline draft manuscript. LG, JC, MH, LO, AB and AH contributed equally to drafting, critically revising the detailed protocol manuscript, approving all versions of the submitted protocol manuscript and are accountable for all aspects of the work.

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