Protocol effectiveness of COVID-19 vaccines on variant of concern. A systematic review of observational studies

V2
31-8-2021

OBJECTIVES

To assess the effectiveness of COVID-19 vaccines against SARS CoV-2 variants of concern Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2) in addition to any other newly discovered variants of concerns as identified by WHO over time.
This is a protocol of a living systematic review. All results will be made available on the COVID-NMA platform (https://covid-nma.com/) and updated weekly.

METHODS

As this is an emerging topic and knowledge about this infection is evolving rapidly, we will set up regular meetings with content experts to update the protocol.

CRITERIA FOR CONSIDERING STUDIES FOR THIS SYSTEMATIC REVIEW

Types of studies

Inclusion criteria
We will include comparative non-randomized (observational) studies evaluating the effectiveness of COVID-19 vaccine in humans. Studies may have any design (including cohort studies, case control studies, test negative studies) but must present results in relation to one of the variants of concerns defined by WHO.
We will consider

- Direct evidence: the effectiveness on variant is determined by sequencing all cases
- Indirect evidence: The information is extrapolated from data on the prevalence of the variant in the population

We will have no restriction on language.

Exclusion criteria

- We will exclude observational studies that did not account for any confounders in the design or analysis (i.e. that present unadjusted results only).
- We will exclude observational studies that did not report at least one critical or important outcome defined for this review.

Types of participants

Participants will include:

- Children or adults with no restriction in age and comorbidities

Types of interventions

Eligible interventions will include any vaccination for preventing SARS-CoV-2. Several types of vaccines will be assessed, including the following:

- inactivated virus
- live attenuated virus
- protein subunit
- virus-like particle (vlp)
- non-replicating viral vector (e.g., recombinant adenovirus)
- replicating viral vector
- DNA based vaccine
- RNA based vaccine

The list of types of vaccine could expand over time, for any new type of vaccine candidate for COVID-19.

Type of comparator

- no vaccine
- other COVID-19 vaccine
- other COVID-19 vaccine schedule

Variants of concern (20/08/2021):

Source https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/

Label	Pango Lineages + additional mutation	GISAID clade	Nextstrain clade	Additional amino acid changes monitored*[1]	Spike mutations of interest	Earliest documented samples
Alpha	B.1.1.7	GRY	20I (V1)	+S:484K +S:452R	N501Y, D614G, P681H	United Kingdom, Dec-2020
Beta	B.1.351 ; B.1.351.2 ; B.1.351.3	GH/501Y.V2	20H (V2)	+S:L18F	K417N, E484K, N501Y, D614G, A701V	South Africa, May-2020
Gamma	P.1 ; P.1.1 ; P.1.2 ; P.1.4 ; P.1.6 ; P.1.7	GR/501Y.V3	20J (V3)	+S:681H	K417T, E484K, N501Y, D614G, H655Y	Brazil, Nov-2020
Delta	B.1.617.2 ; AY.1 ; AY.2 ; AY.3 ; AY.3.1	G/478K.V1	21A	+S:417N	L452R, T478K, D614G, P681R	India, Oct-2020

OUTCOMES

Critical outcomes

- Confirmed infection (symptomatic or asymptomatic) after **complete vaccination**
- Confirmed COVID-19 (symptomatic) after **complete vaccination**
- Severe or critical disease defined as follow
    - For severe or critical COVID-19, we will record the definition used and we will extract in preference 1) the WHO definition, 2) the definition used by investigators, 3) hospitalization or death, 4) admission in ICU or death.
- All-cause mortality
    - If only COVID-19 mortality is reported, it will be recorded for all-cause mortality. This information will be reported clearly.

For critical outcomes, we will consider different time points: short term (2-4 months), mid-term (6-8 months), long term (>12 months)

Important outcomes

- Confirmed infection (symptomatic or asymptomatic) **after first dose and before second dose**
- Confirmed COVID-19 (symptomatic) **after first dose and before second dose**
- Long COVID 19 diseases
    - We will record as reported in the study and extract the definition used.

Notes:

[1] *Notable spike (S) amino acid changes under monitoring, which are currently reported in a minority of sequenced samples.*

- As the start of follow-up (T0) may vary (e.g., follow-up starts “14 days after the last dose” or “21 days after the first dose”), we will systematically record the T0 considered.

- When, several T0 are considered in the study report, we will consider the T0 defined in the main phase 3 randomized trial for each vaccine when available (see table below) or rely on experts’ advices.

- When effect estimates are reported for specific time interval (e.g., 14-21 days), we will select the interval nearest the time zero considered. When feasible, we will extrapolate the effect estimates from the reported data per interval.

Vaccine-Developper	Reference	Start of follow up (T0)
Sinopharm - Inactivated virus WIV04 HBO2	Al Kaabi N, JAMA, 2021	□ 14 days after the second dose
ModernaTX - mRNA-1273	Baden LR, N Engl J Med, 2020	□ 14 days after the second dose □ 14 days after the first dose
Bharat Biotech Inactivated virus - BBV152	Ella R, medRxiv, 2021	Confirmed Symptomatic □ 14 days after the second dose
Gamaleya Research Institute of Epidemiology and Microbiology -GAM-COVID-VAC	Logunov D, Lancet, 2021 RESIST	Confirmed Symptomatic □ 21 days after the first dose
Sinovac - CoronaVac	Palacios R, SSRN, 2021 Tanriover M, Lancet , 2021	Confirmed Symptomatic □ 14 days after the second dose □ 14 days after the first dose
Pfizer/BioNTech + Fosun Pharma - BNT162b2	Polack F, N Engl J Med, 2020	□ 7 days after the second dose □ 11 days after the first dose
Janssen Pharmaceutical Companies - Ad26.COV2.S	Sadoff J, N Engl J Med, 2021	□ 14 days after the first dose
Novavax - NVX-CoV2373	Heath P, N Engl J Med, 2021	□ 7 days after the second dose □ 14 days after the first dose
AstraZeneca + University of Oxford - ChAdOx1	Voysey M, Lancet, 2021	□ 14 days after the second dose □ 22 days after the first dose

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

Electronic searches

Search Methods (February to August 27, 2021)

The search method was adopted from a paper on "Vaccines to prevent COVID-19: a protocol for a living systematic review", (see link): https://staticcontent.springer.com/esm/art%3A10.1186%2Fs13643-020-01516-1/MediaObjects/13643_2020_1516_MOESM2_ESM.pdf

Databases used to search for studies included PubMed, medRxiv, bioRxiv, L-OVE Platform.
The following keywords/filters were adopted using the advanced search facility:

1. COVID-19 OR COVID OR SARS-Cov-2 Or severe acute respiratory syndrome coronavirus 2 Or 2019 novel coronavirus
2. Vaccines OR Vaccination OR Immunization
3. Effectiveness OR real world
4. #1 AND #2 AND #3

Filtered was applied for only observational studies.

Search Methods (August 27, 2021)

Cochrane Response's information specialist has been searching every week since July 1, 2021 the following 2 resources for COVID-19 vaccine observational studies:

- Cochrane COVID-19 Study Register (https://covid-19.cochrane.org): using the Updated New References section from Last Week.

- L·OVE (https://iloveevidence.com): using the L·OVE Platform's COVID-19 Collection section with the Advanced Search BETA. Results were filtered by Primary Study>Non RCT and Epistemonikos date.

A single, truncated search term was used: **vaccin***

Duplicates from the downloaded records were removed in Endnote. Records for screening were uploaded to DistillerSR software and tagged with search date and databases labels.

The Cochrane COVID-19 Study Register includes the following data sources: PubMed, Embase.com (Elsevier), Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, WHO International Clinical Trials Registry Platform (ICTRP), medRxiv, and Retraction Watch. The L·OVE Platform is powered by Epistemonikos.

DATA COLLECTION AND ANALYSIS

Selection of studies

We will search and screen the citations retrieved on a weekly basis. Screening will be disseminated through an Excel spreadsheet to document search dates and numbers of hits identified. Screening of records and abstracts will be done in duplicate independently. A third reviewer will resolve disagreements.

Data extraction and management

All data will be extracted in duplicate. Two reviewers will independently read each preprint, publication, protocol, or other study reports, evaluate the completeness of the data availability, and extract all relevant study information.

We will use a specific structured online data extraction form to ensure consistency of extraction of information. All discrepancies automatically identified by the online tool are discussed by the two reviewers to find a consensus. When consensus is reached, data related to the characteristics of the study and risk of bias assessment are made available on the platform (covid-nma.com).

Information extracted will include study characteristics (such as first author, publication year and journal), number of participants, participants characteristics (age, gender), intervention details (developer, strain, route of administration, schedule).

We will record effect estimates accounting for confounding variables. When several analyses are reported, we will select the analysis accounting for the highest number of variables. We will record in priority: 1) vaccine effectiveness, 2) rate ratio, 3) risk ratio, 4) OR, 5) HR. For vaccine effectiveness, we will extract the way it was calculated (e.g., from rate ratio or risk ratio).

To explore the effectiveness of vaccine on variants, we will also record data related to the SARS-CoV-2 sequencing particularly the number of COVID-19 patients related to the wild-type SARS-CoV-2, and the different variants of concern such as Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2). This will be done only for critical outcomes of effectiveness.

Where reported, we will record outcome measures stratified by:

- age (children, adults, elderly; we will record the threshold used to define these age strata);
- immune status (competent or immunocompromised);
- pregnancy status.

Assessment of risk of bias in the included studies

Risk Of Bias In Non-randomized Studies - of Interventions

Each study will be assessed with a current version of the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool [iii]

We will assess the risk of bias for all outcomes of the review. Risk of bias will be assessed independently, in duplicate with consensus by researchers with epidemiological training (the number of people involved varies). All have been previously trained in clinical epidemiology and systematic reviews. All have participated in a training program where they performed assessment using the tool ROBINS-I and the assessment was discussed under the supervision of Prof Julian Higgins.

The Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool is structured into seven domains: 1) Bias due to confounding 2) Bias in selection of participants into the study 3) Bias in classification of interventions 4) Bias due to deviations from intended interventions 5) Bias due to missing data 6) Bias in measurement of the outcome 7) Bias in selection of the reported result.

Within each domain, a series of 'signalling questions' elicit information relevant to the risk of bias assessment. The response options to the signalling questions are: “Yes”; “Probably yes”; “Probably no”; “No”; and “No information”. Some questions are answered only if the response to a previous question is “Yes” or “Probably yes” (or “No” or “Probably no”). Responses of “Yes” are intended to have similar implications to responses of “Probably yes” (and similarly for “No” and “Probably no”), but allow for a distinction between something that is known and something that is likely to be the case.

Responses to signalling questions provide the basis for domain-level judgements about risk of bias. The categories for risk of bias judgements are “Low risk”, “Moderate risk”, “Serious risk” and “Critical risk” of bias.

Overall, risk of bias will be considered as “low risk of bias” if all domains are at ‘low risk’; “Moderate risk” if at least one domain is of ‘Moderate risk and no domains are at “Serious risk” or ‘Critical risk of bias’; “Serious risk” if at least one domain is of ‘Serious risk and no domains are at ‘Critical risk of bias’; and “Critical risk of bias” if there is at least one domain assessed as ‘Critical risk’, or several domains with ‘Serious risk”.

We will use a specific templates for cohort studies and for case control studies (including test negative studies).

We have prespecified the list of time fixed and time varying confounding factors that will be considered.
Time-fixed confounding factors

- Age
- Sex
- Socioeconomic status
- Ethnicity
- Geographic location
- Health-seeking behaviour

- Specific subpopulation (e.g. healthcare worker/elderly in institution/pregnancy)
- Comorbidities

Time-varying confounding factors
- Calendar time (to reflect changing incidence of virus)
- Symptoms at time of planned vaccination
- Hospitalization and need for health care

At the moment of writing this protocol, we have not identified on any co-intervention that could impact on outcomes once provided unevenly between intervention groups. Therefore, we do not prespecify any co-interventions, we will monitor studies for evidence of any such co-interventions.

Measures of treatment effect

We will record effect estimates accounting for confounding variables accompanied by the 95% confidence interval (CI). When several analyses are reported, we will select the analysis accounting for the highest number of confounding variables identified as relevant. We will record in priority: 1) vaccine effectiveness, 2) rate ratio, 3) risk ratio, 4) OR, 5) HR

Dealing with missing data

To assess the potential impact of missing outcome data on the results, we will conduct sensitivity analyses excluding studies with high missing data rate.

Assessment of heterogeneity

We will generate descriptive statistics for both the trial and population characteristics and examine the distribution of important clinical and methodological variables (e.g. age, pre-comorbidities, location, adjustment factors, risk of bias). Visual inspection of forest plots, the I^2 statistic and the magnitude of between-study variance (τ^2) will be used to estimate the level of heterogeneity. We will also produce prediction intervals to convey the heterogeneity and assess its potential impact on future results.

Assessment of reporting biases

We will assess the selective non-reporting or under-reporting of results in the studies identified according to the framework proposed in Chapter 13 of the Cochrane Handbook.(33) We will use funnel plots (in the presence of at least ten studies per meta-analysis) and statistical tests (such as the Egger's test) to assess the potential for small-study effects. If asymmetry is found, we will explore possible reasons for the apparent association between study size and study effect.

DATA SYNTHESIS

The primary analysis will be performed at the vaccine and variant level. All eligible studies will be included in the primary analysis, whatever the risk of bias assessment. For each direct comparison with at least two studies providing data, we will undertake meta-analyses and present effect estimates with 95% confidence intervals (CIs). We will use the random-effects model to incorporate the anticipated clinical and methodological heterogeneity across studies. Studies assessed as at critical risk of bias will be excluded from meta-analyses.

In the presence of excessive heterogeneity across studies, we will not synthesize them quantitatively but only qualitatively and no diamonds will be presented in the forest plots. This decision will be made by judgment, including considerations such as opposing directions of effect, substantially conflicting effect estimates and important differences in how the studies were done.

Presentation of results

Study and participant characteristics, risk of bias data as well as outcome data will be made publicly available on the COVID-NMA platform (https://covid-nma.com/vaccines/os_vaccines/) and updated weekly.

---

i Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JPT. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. BMJ 2016; 355; i4919; doi: 10.1136/bmj.i4919.

ii https://www.bmj.com/content/355/bmj.i4919