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Comparative effectiveness of mRNA-1273 and BNT162b2 COVID-19 vaccines following primary series and additional doses in adult patients with medical conditions: A systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

Support - Funded by Moderna, Inc.

Review Stage at time of this submission - Data analysis.

Conflicts of interest - Xuan Wang, Ankit Pahwa, Pawana Sharma, Anushri Chitkara, Mia Malmenäs, Sonam Vats and Michael Gordon Whitfield are employees of ICON plc, a clinical research organization paid by Moderna, Inc., to conduct the study. Nathan Green is an independent researcher based at University College London and paid by ICON plc to conduct a part of analysis for this study. Mary T. Bausch-Jurken, Nicholas Van de Velde and Ekkehard Beck are employees of Moderna, Inc. and hold stock/stock options in the company.

INPLASY registration number: INPLASY202460065

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 June 2024 and was last updated on 17 June 2024.

INTRODUCTION

Review question / Objective What is the comparative efficacy/effectiveness of mRNA COVID-19 vaccines (mRNA-1273, BNT162b2) following primary series and additional doses in adult patients with medical conditions? A systematic review and meta-analysis.

Condition being studied COVID-19 vaccine efficacy/effectiveness in adults with medical conditions.

METHODS

Search strategy The search for published literature was conducted in Embase (OVID SP®), Medline and MEDLINE In-Process, e-pubs ahead of print (OVID SP®), and Cochrane databases including CCRCT and CDSR (OVID SP®) on 9 February 2024.

Searches were restricted to English language only.

Participant or population Adults (≥18 years old) with following medical conditions will be included:
• Autoimmune disease
• Solid tumor
• Solid organ transplant
• Hematologic malignancy
• Chronic kidney disease (incl. CKD with/without hemodialysis)
• Diabetes (incl. type 1 and type 2)
• Cardiovascular disease (e.g., hypertension, heart failure, coronary artery disease, or cardiomyopathies)
• Cerebrovascular disease
• Chronic liver disease (e.g., cirrhosis, non-alcoholic fatty liver disease, alcoholic liver disease, autoimmune hepatitis)
• Neurological condition (i.e., dementia, Alzheimer's disease, amyotrophic lateral sclerosis [ALS], Parkinson's disease)

• Chronic respiratory conditions (e.g., asthma, bronchiectasis, COPD, interstitial lung disease, pulmonary embolism, pulmonary hypertension)
• Obesity (BMI≥30kg/m2)
Studies on general population should have >90% population with at least one comorbidity to be included in this review.

Intervention Any mRNA vaccines with at least two dose series will be considered,
– Moderna vaccine Spikevax®, elasomeran, mRNA-1273
– PfizerBioNTech vaccine Comirnaty®, tozinameran, BNT162b2

Only homologous two dose series will be considered.
For three or more than three dose series, both homologous and heterologous series with mRNA as a last dose will be considered.

Comparator mRNA vaccines including mRNA-1273 (Spikevax, Elasomeran), or BNT162b2 (COMIRNATY, Tozinameran).

Study designs to be included Randomised controlled trial (RCT) and non-randomised controlled trials, observational studies, and any kind of real-world evidence will be eligible for inclusion in this systematic review.

Eligibility criteria Exclusion criteria
– Studies on children and pregnant women will be excluded.
– Studies on general population with more than 90% comorbidity will be excluded.
– Two doses heterologous primary series will not be considered.
– Case reports and review articles will be excluded.

Any setting will be considered.

Information sources The search for published literature was conducted in Embase (OVID SP®), Medline and MEDLINE In-Process, e-pubs ahead of print (OVID SP®), and Cochrane databases including CCRCT and CDSR (OVID SP®) on 9 February 2024. To complement the database searches relevant and recent systematic reviews were cross-checked for additional references.
Authors were contacted for clarification and for the additional information from the study.

Main outcome(s)
-Vaccine efficacy/effectiveness against Covid-19 infection
– Vaccine efficacy/effectiveness against symptomatic Covid-19 infection
– Vaccine efficacy/effectiveness against severe Covid-19 infection
– Vaccine efficacy/effectiveness against hospitalization
– Vaccine efficacy/effectiveness against death
– SARS-CoV2 positivity (symptomatic or asymptomatic)
– Symptomatic laboratory-confirmed COVID-19 infection
– Severe COVID-19 infection (hospitalization or death)
– Breakthrough infection
– COVID-19 re-infection
– Hospitalization due to COVID-19 (ICU, ER, or ventilation etc.)
– Death due to COVID-19
Proportion of patients with infection/death/hospitalization, incidence risk ratio, risk ratio, hazard ratio etc. at any time was considered.

Additional outcome(s) None.

Data management Two independent reviewers will independently screen all identified items at two levels. Level I screening will be based on titles and/or abstracts, as available. The full text of all items passing Level I screening will be retrieved for Level II screening: an ascertainment of final eligibility for the review. Discrepancies will be resolved by consensus or by involving a third team member.
As stated above, all data will be extracted by two independent reviewers. Discrepancies will be resolved by consensus or by involving a third team member. Data extractors will not be blinded to any study information. Before data extraction begin, a standardized data extraction form/database and data extraction guidelines will be used following its review by the study statistician and upon achieving consensus by the study team on all included data fields.
The following information will be extracted from publications:
• Study design: study names, number of patients enrolled, study design, study duration (planned follow-up), mean/median follow-up duration, testing method, etc.
• Baseline patient and disease characteristics: age, sex, BMI, weight, race, region of origin, primary outcome, etc.
• Intervention characteristics: Description of dose, first dose (vaccine and dosage), time interval between 1st and 2nd dose, second dose (vaccine and dosage), third dose (vaccine and dosage), fourth dose (vaccine and dosage), proportion of individuals with one dose only, variant, etc.
• Efficacy endpoints: vaccine efficacy, COVID-19 infection (positive test and/or symptoms), severe

COVID-19 infection, hospitalization, COVID-19 related death, etc.

Quality assessment / Risk of bias analysis Formal risk of bias assessment will be performed by one reviewer and checked by second reviewer. Any disagreements will be resolved by discussion. Any lack of consensus will be resolved by third researcher.
For randomized controlled trials (RCTs), the risk of bias for each included RCT will be assessed using the methods proposed by the Cochrane Handbook.
For observational studies, the New-Castle Ottawa tool will be used for each study included in the review.

Strategy of data synthesis Published evidence comparing mRNA vaccines with any other mRNA vaccine will be identified to find direct evidence and to generate evidence.
A feasibility analysis will consider the similarity of the studies and patient characteristics, as well as outcome definitions and the risk of bias, to assess the relevance of identified studies to the decision problem. Studies identified by the systematic review and excluded from the meta-analysis will be recorded, and a rationale for that exclusion will be provided.
Random-effects meta-analysis models will be used to pool risk ratios (RR) and calculate absolute effects as risk difference (RD) per 100,000 individuals across studies. Inverse variance weights will be calculated for individual studies with the DerSimonian-Laird method. Heterogeneity across studies will be evaluated using Chi-square testing. The I2 statistic will be estimated (0–100%, 0% meaning no evidence of heterogeneity).
Presentation of findings
• The results of the pairwise meta-analysis will be presented in forest plots, including point estimates and 95% credible intervals of each intervention in comparison to the reference. These are VE, RR and corresponding 95% credible intervals.
Statistical packages
• The analyses will be conducted in R software.

Subgroup analysis Heterogeneity will be assessed through subgroup analyses. If data allow, following subgroup analysis will be performed by
1) each medical condition as stated above,
2) study participants age group, for example, aged ≤ 65 years and > 65 years,
3) dose regimens (two doses regimen, three doses regimen, more than three doses regimen etc.),
4) variants of concern (Delta and Omicron).

Sensitivity analysis Sensitivity analysis will be conducted for studies reporting severe infection by excluding studies with derived severe outcomes.

Language restriction English only.

Country(ies) involved UK, USA, Sweden, India, Germany.

Keywords Systematic Review; meta-analysis; severe acute respiratory syndrome coronavirus 2, SARS-CoV-2, COVID-19, mRNA vaccine, mRNA-1273, BNT162b2, adults, medical condition, effectiveness.

Dissemination plans The meta-analysis will be summarised in a manuscript which will provide an overview of the results of the SLR, as well as the methods, results, conclusions, and limitations of the meta-analysis. Additional disclosures may occur as agreed upon by the study team.

Contributions of each author
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