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The Risk-Benefit Balance in the COVID-19 "Vaccine Hesitancy" Literature: An Umbrella Review Protocol

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Abstract

Background: "Vaccine hesitancy" has been described as a major public health problem, especially in the COVID-19 era. Identified factors driving "hesitancy" include the concerns of recipients with the safety, side effects, and risk-benefit ratio of COVID-19 vaccines[1] — a proper assessment and disclosure of which are critical to the requisite process of informed consent. However, the expert literature has given little attention to the evidence informing these concerns, focusing instead on features of the recipients themselves to explain the phenomenon of so-called "hesitancy".

Goal: This umbrella review will expand the scope of research on "vaccine hesitancy" by examining how the safety, side effects, and risk-benefit ratio concerns of recipients of COVID-19 vaccines are addressed in the expert literature.

Inclusion criteria: We will include systematic reviews on COVID-19 "vaccine hesitancy" that examine hesitancy in any population involved with COVID-19 vaccination decisions for themselves or as caretakers (e.g., decisions about "vaccinating" their children) to capture the broadest possible range of perspectives on the phenomenon of interest. Only completed, published, and refereed systematic reviews in English will be included.

Methods: We will search PubMed, the Epistemonokos COVID-19 platform (COVID-19 L·OVE), and the WHO Global Research on COVID-19 Database to locate quantitative, qualitative, and mixed methods studies reviews. Reviews that meet the inclusion criteria will undergo quality assessment (AMSTAR) and data extraction. Two reviewers will independently conduct title and abstract screening and extract and synthesize the data. Disagreements will be resolved through full team discussion. Subgroup analyses will be performed to compare findings according to social indicators of target populations, country location of the first author, and other contextual factors. Thematic analysis and synthesis will be used to "transform the data" into themes by applying a deductive-inductive approach. Frequency distributions will be calculated to assess the strength of support for each theme. Findings will be presented in tabular and narrative forms to facilitate their interpretation.

Significance: Informed consent is a fundamental bioethical principle in medical research and practice. Insufficient attention to the concerns of vaccine recipients about these matters, compounded by a neglect to discuss the evidence-base informing these concerns, may contribute to the very problem that the COVID-19 "vaccine hesitancy" expert literature purports to address. This is especially true of an intervention based on novel technologies and intended to be delivered on a global scale. Identifying if and how the expert literature engages with these concerns is critical.

Systematic review registration: *PROSPERO CRD42022351489.*

Keywords: *adverse effects, COVID-19 vaccine, critical policy analysis, risk-benefit ratio, informed consent, side effects of COVID vaccines, umbrella reviews of COVID vaccines, COVID vaccine hesitancy, COVID vaccine safety*

1 Background

[1] Although we use the phrase "COVID-19 vaccines" throughout, we believe they should more appropriately be referred to as "COVID-19 genetic vaccines", "COVID-19 injections", or "mRNA biologicals". However, we have chosen "vaccine" with no quotation marks for better readability. For an in-depth discussion of this issue, see Rose (2021).

1.1 The problem, condition, or issue

"Vaccine hesitancy" (VH) has been defined as a "complex and context specific phenomenon, varying across time and vaccines"(SAGE, 2014), and described as a major public health problem — "one of 10 threats to global health" — already in the pre-COVID era (World Health Organization, 2019), and especially since (Sallam, 2021). While multiple factors have been identified as driving COVID-19 VH — including socioeconomic status, educational attainment, political ideology, and levels of trust in government — (Hudson & Montelpare, 2021; Park et al., 2021) the concerns of vaccine recipients (or of caretakers of vaccine recipients, such as parents) with the safety, side effects, and risk-benefit ratio of COVID-19 vaccines are a major driver of VH (Khairat et al., 2022; Ledford et al., 2022; Mills et al., 2005; Momplaisir et al., 2021; Tram et al., 2021). However, the COVID-19 VH expert literature has given these concerns short shrift, addressing them not by evaluating their evidence-base, but by focusing instead on features of the populations expressing VH that may explain why they do so. This umbrella review will appraise how the expert literature on VH engages the concerns of prospective recipients with the safety, side effects, and risk-benefit ratio of COVID-19 vaccines.

A cursory exploration of this literature is revealing. For instance, in their systematic review of COVID-19 VH, Anakpo et al. (2022) found that fear of side effects, leading to distrust, drives VH in low-income populations, and recommended educating this population about vaccines to overcome their hesitancy, side-stepping the question of whether these fears were warranted. In their systematic review, Abba-Aji et al. (2022) also identified low trust and safety concerns as major reasons for VH among ethnic minorities, and recommended building greater trust to improve vaccine uptake in these communities, offering no recommendations on how to deal with safety concerns *per se*. Batteux et al. (2022) pointed out concerns with the speed with which COVID-19 vaccines were developed as a major cause of VH, and recommended personalizing communications on vaccination to promote greater acceptance, especially during the worldwide rollout of booster campaigns. The authors did not elaborate on whether concerns with the speed of development of COVID-19 vaccines may have justified VH among prospective recipients, even when this speed has contrasted dramatically with the usual 10 to 15 years required to test the safety profile, especially in the long term, of any pharmaceutical (New York State Department of Health, 2014.).

In a similar spirit, van Mulukom et. al.'s systematic review (2022) assessed "antecedents and consequences of COVID-19 conspiracy beliefs", which they argue may negatively impact vaccination decisions, based on the authors' assumption that distrust in government authorities, as per the Conspiracy Mentality Questionnaire (Bruder et al., 2013), indicates a "conspiratorial" personality. van Mulukom and collaborators seemed unaware of the well-documented, decades-long history of regulatory capture of public institutions that has severely compromised the evaluation of the safety of pharmaceuticals (Light et al., 2013). This history, it may be argued, provides very good reason for distrusting government authorities. If good reasons exist to believe otherwise concerning COVID 19 vaccines, the authors did not provide them. Therefore, their dismissal of patients' concerns may reveal more about the authors' beliefs, impressions, and ideological preferences than about empirically verifiable facts that may inform such medical decisions.

1.2 Description of the intervention

This qualitative umbrella review will not be examining an intervention. In the absence of an intervention or experiment, the data on the phenomenon of interest become the outcome.

1.3 Why it is important to do this review

If the considerations presented earlier indicate a trend, it appears that the expert literature on VH generally

assumes that concerns with the safety, side effects, or risk-benefit ratio of COVID 19 vaccines cannot be based on empirically verifiable evidence. However, this assumption is incorrect. We have hinted at a few reasons, and now proceed to expand on them: concerns with the lack of safety of COVID 19 vaccines (Fraiman et al., 2022), and with the lack of transparency in communicating potential harms (Malhotra, 2022a, 2022b), are being increasingly reported in the medical literature, and multiple and diverse adverse events post administration of COVID-19 vaccines have been documented — from mild (Blumenthal et al., 2021; Mevorach et al., 2021), to moderate (Català et al., 2022; Chow et al., 2022), to severe or unusual for a given age group (e.g., myopericarditis in adolescents) (Fraiman et al., 2022; Mansanguan et al., 2022; Tiede et al., 2021; Yamamoto, 2022).

While it may be argued that these adverse events post vaccination could not be known during the testing phase of COVID 19 vaccines, leading researchers, including Peter Doshi, editor of the *British Medical Journal*, and a team of international scholars have contended that they were. Their reanalysis of data from the placebo-controlled (first two months), phase III randomized clinical trials of Pfizer and Moderna mRNA COVID-19 vaccines published in the *New England Journal of Medicine* in December of 2020 (Polack et al., 2020) — the full data are yet to be made available to the public (Doshi et al., 2022) — indicate a combined, 16% higher risk of serious adverse events in mRNA vaccine recipients, with little clinically significant benefits (Fraiman et al., 2022). On the other hand, it cannot be assumed that for any given individual vaccine benefits, whatever those may be, outweigh the already documented, and as yet unknown, risks. The Infection Fatality Rate (IFR) of COVID-19 varies dramatically with age — less than 0.5% for individuals under 50 years old and as low as 0.0023% for 8 year old children — (Ioannidis, 2022; Thornley et al., 2022), co-morbidities such as obesity — with death rates 10 times higher in countries where over 50% of adults are obese or overweight — (Wise, 2021), and socioeconomic (SES) status — with an IFR 3 times higher in lowest as compared with highest SES groups (Mena et al., 2021), and over 80% of the global population already has natural or vaccine-acquired immunity (Ioannidis, 2022).

Nor can it be assumed, contrary to what was claimed in a recent refereed article in a leading Canadian medical journal, that unvaccinated individuals represent a threat to the public's health such that it is scientifically justified to discriminate against them, for instance, by isolating them, limiting their access to public spaces, or coercing them to accept a medical procedure against their best judgment (Fisman et al., 2022). Indeed, already with the Delta variant there appeared to be no difference in the viral load among the vaccinated and unvaccinated, meaning that both had a similar ability to transmit the infection (mean cycle threshold values for vaccinated 23.1, unvaccinated 23.4; $p = .54$) (Acharya et al., 2022), and at least one major study across 68 countries and 2947 counties in the United States showed that case increases were unrelated to levels of vaccination (Subramanian & Kumar, 2021). Especially since Omicron, COVID-19 vaccines have been less than successful in either stopping transmission (Hoffmann et al., 2022), or preventing disease, hospitalization, and death, with studies showing either no discernible difference between fully cooperating recipients and partial or fully non-participating persons / populations (Ridgway et al., 2022; Singanayagam et al., 2022), or, showing the ratio going in favor of the non-participating groups (Seneff & Nigh, 2021; Classen, 2021; Santiago, 2022). Also since Omicron, symptomatic infections have become milder and shorter (Wise, 2022), especially in the young (Say et al., 2021), and for high risk individuals, officially approved treatments in the outpatient setting are becoming increasingly available (Hammond et al., 2022).

This is to show that the science around COVID 19 vaccines is anything but settled. A full and transparent discussion of all the available and relevant evidence involved in deciding in favor of vaccination is critical if public health researchers, policy makers, and practitioners wish to support prospective vaccine recipients in

overcoming hesitancy, including hesitancy about committing, as recommended by leading global health agencies, to a lifetime of periodic inoculations for themselves and their children (World Health Organization, 2022). Transparency in communicating the risks, benefits, and alternatives to, any medical procedure is also critical for upholding informed consent, a fundamental bioethical principle, enshrined for over half a century in medical research and practice (Shuster, 1997; World Medical Association, 1964), and much longer if we look back to the Nuremberg Code, not to mention the Hippocratic Oath. What is true for any medical intervention is even more so for one that relies on novel technologies (Matić & Šantak, 2022) and especially for one intended for delivery on a global scale (World Health Organization, 2022).

A preliminary search of PROSPERO, Epistemonokos, and JBI Evidence Synthesis identified no umbrella review, completed or in progress, with the search term VH combined with phrases such as "vaccine safety", "side/adverse effects", or "risk-benefit ratio", indicating that at the time of this writing no such review is analyzing how major factors leading to VH are addressed by scholars in the field. We hypothesize that insufficient attention to prospective vaccine recipients' concerns with the safety, side effects, and risk-benefit ratio of COVID-19 vaccines, compounded by a neglect to discuss the evidence informing these concerns, may, however inadvertently, contribute to the very problem that the literature on VH purports to address. Therefore, our umbrella review broadens the scope of research on VH by examining how the concerns of prospective COVID-19 vaccine recipients are addressed in the expert literature.

We expect practical challenges: for instance, it may be challenging to appraise how researchers think about the risk-benefit ratio of vaccination if no information on this issue is forthcoming. However, this absence could be valuable, indicating an important gap in the literature and in medical and policy practice. We also expect our investigation to be important to decision-makers in government, health institutions, and other venues (e.g., academia) likely to formulate, influence, or support the implementation of, COVID-19 vaccination policy. If VH presents a major public health problem that must be addressed, it behooves researchers to engage its leading drivers by not only encouraging prospective vaccine recipients to assume and trust the benefits of COVID 19 vaccines — whatever these are and however well-intentioned this encouragement might be — but also by engaging in transparent discussion, and properly informing the public about, the safety, side effects, and the risks-benefit ratio of COVID-19 vaccination.

We have chosen to conduct an umbrella review because these reviews summarize the highest level of evidence to support medical policy and practice while affording the opportunity to raise questions about a given issue that have not been asked (Guyatt et al., 1995; Smith et al., 2011). We have also chosen to include all review types — quantitative, qualitative, and mixed-studies reviews — to capture the broadest variety of data and perspectives on the issue at hand (Pluye & Hong, 2014). Our decision to include only refereed systematic reviews is intended to guarantee that only articles that have been fully vetted by the community of researchers will be assumed to represent the official voice of this community.

As an additional contribution, our analysis will be informed by the critical tradition of policy studies, as exemplified by Carol Bacchi's approach, "What is the problem represented to be?" (WPR). This tradition examines the process whereby societal issues amenable to policy interventions — in this case, VH — become framed as problems in the first place (Bacchi, 2012). Mainstream approaches to policy analysis envision it as a technical task, take at face value dominant representations of policy problems, and seek solutions within the boundaries of these representations. In contrast, for researchers applying the WPR approach, problem framing and definition are interpretive endeavors, influenced by power relations. Applied to our case, we will examine if and how perspectives on VH vary with the social location of target populations (e.g., socioeconomic status, gender, or race/ethnicity), the presence of class tensions (e.g.,

employer / union-supported versus rank-and-file workers' opposition to mandated vaccination), the differential perception of the duties of occupational groups (e.g., frontline health workers versus other occupations), and geopolitical factors (e.g., country of study location and country of authors' location). We will also examine the discursive representation of diverse perspectives on VH (e.g., potential stigmatization of non-conforming positions; see Goffman, 2009; Broudy, 2021).

2 Objectives

To appraise how the expert literature on COVID-19 VH addresses the safety, side effects, and risk-benefit ratio concerns of prospective vaccine recipients.

3 Methods

3.1 Protocol registration and reporting

This protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; https://www.crd.york.ac.uk/prospero, registration ID CRD42022351489). We followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) [see *Additional File #1*]. The PRISMA 2020 statement will be used to report the final review, which will document amendments to the protocol (Page et al., 2021).

3.2 Criteria for considering studies for this review

3.2.1 Types of studies

This umbrella review will include qualitative, quantitative, and mixed method systematic reviews that focus on VH, with no temporal or geographic restrictions and in populations of any age, sex / gender, race / ethnicity, socioeconomic class, or national origin experiencing VH or going through the process of deciding whether to accept COVID-19 vaccination (for themselves or dependents). Outcomes of selected-in reviews may include prevalence and determinants of VH (and related concepts such as acceptance / uptake / concerns / refusal); attitudes and beliefs regarding vaccination; reasons for VH; vaccination behaviors; parental attitudes about childhood vaccination; attitudes and behaviors vis-à-vis vaccine mandates / vaccination policies; and changes in perceptions / attitudinal change (e.g., changes in intention to get vaccinated). We will consider a review "systematic" when the authors label it as such, are explicit about the methodology, the methodology is reproducible, the search strategy is clearly described, and inclusion / exclusion criteria are predefined. Only completed, refereed systematic reviews in English will be included.

3.2.2 Types of participants

To capture the broadest range of perspectives on the phenomenon of interest, selected reviews will include populations of any age, gender, socioeconomic status, race / ethnicity, and other social indicators, involved with COVID-19 vaccination decisions for themselves or as caretakers (e.g., decisions about vaccinating their children), regardless of whether they explicitly allude to recipients' concerns with the safety, side effects, and ratio of risk and benefits of vaccines.

3.2.3 Types of interventions

To capture the broadest range of perspectives on VH, all systematic reviews that meet the inclusion criteria will be included, regardless of whether they evaluate an intervention.

3.2.4 Types of outcome measures

Outcomes will be tailored to capture the phenomenon of interest. They will include the safety, side effects, and risk-benefit ratio concerns of vaccine recipients, and related factors driving VH (e.g., trust), as well as researchers' perspectives and recommendations on how to address these concerns and factors.

3.3 Search methods for identification of studies

3.3.1 Electronic searches

We will retrieve data from 1) PubMed, 2) the Epistemonokos Foundation Living Overview of Evidence (L*OVE) COVID-19 evidence repository, and 3) the WHO Global Research on COVID Database. COVID-specific evidence sources are updated regularly from multiple academic databases and use a COVID-19 Boolean strategy adapted to the sources searched. The Epistemonokos database can be found at https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d?population=5e7fce7e3d05156b5f5e032a&intervention_variable=603b9fe03d05151f35cf13dc&section=methods&classification=all. A description of the WHO Global Research on COVID-19 database is available at https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/. We will use the search terms ["vaccine hesitancy" OR "vaccine uptake" OR "vaccine acceptance"]. In databases that are not COVID-19-specific (e.g., PubMed), these terms will be combined with ["COVID-19" OR "SARS Cov2"] terms [see *Additional file #2*].

3.3.2 Searching other resources

Complementary searches on VH will be performed and the documents retrieved included when relevant (e.g., reports published by leading public health agencies), for context, although not as data, unless they meet inclusion criteria.

3.4 Data collection and analysis

3.4.1 Description of methods of the selected-in reviews.

This umbrella review will include qualitative, quantitative, and mixed method systematic reviews that focus on VH, informed by conventional and critical (e.g., interpretive) paradigms, to capture the broadest range of perspectives on the phenomenon of interest.

3.4.2 Selection of studies

Before including articles for assessment, we will conduct a preliminary screening of the literature search to discard irrelevant material. One reviewer will initially scan titles and remove the most irrelevant studies. Next, two reviewers will independently scrutinize the remaining abstracts in relation to the research question and eliminate those that do not meet the inclusion criteria. Where there is uncertainty in the abstract about the relevance of a research report, a third reviewer will break the tie, and if needed, the full text will be retrieved. Once the abstract review process is complete, we will retrieve full copies of the selected studies for assessment. Two reviewers will independently determine if the articles meet the inclusion criteria for the review and will screen them independently. Disagreements will be resolved by full team discussion.
We will monitor inter-rater reliability on a regular basis (after about one third of retrieved papers are screened) throughout the screening stage, and act if the reliability falls below 80% (Shea et al., 2009). We will report these scores in the final review, maintain a clear record of the articles included and excluded at each stage of the process, and note the reasons for excluding specific articles. Articles that do not meet the inclusion criteria but include relevant contextual material (e.g., policy papers) may be retained (although not rated / assessed) and narratively summarized in the background section of the final manuscript. Throughout the screening process, we will use the Rayyan literature review management software

(https://www.rayyan.ai/) to 1) facilitate double-blind screening, 2) record inclusion and exclusion decisions, and 3) identify any disagreements between reviewers.

3.4.3 Data extraction

The data extraction form will be prepared using Microsoft Excel. Extracted data will include details about study populations, study designs / methods / outcomes, the phenomena of interest relevant to our review objective, and contextual factors (e.g., geographical scope of the review; declared conflicts of interests). We will also extract synthesized findings from included reviews when appropriate. Data extraction will be performed by two researchers. Before beginning full extraction, two reviewers will independently extract data from a common sample of studies and the team will meet to calibrate the approach and discuss results. Tables for all included systematic reviews will be created and included as appendices in the final review.

3.4.4 Assessment of risk of bias in included studies

Studies that meet the inclusion criteria will be subjected to quality assessment and data extraction. For quality analysis, we will use a modified version of AMSTAR, a tool to assess the methodological quality of systematic reviews (Shea et al., 2009) [see *Additional file #3*]. Two researchers will independently assess each review, the results will be compared, and if disagreements occur, they will be resolved by consulting an additional reviewer, and if necessary, by full team discussion.

3.4.5 Data synthesis

In convergent synthesis designs, data is transformed into either qualitative or quantitative findings. In convergent *qualitative* synthesis, the approach chosen for our study, results from qualitative, quantitative, and mixed methods studies (in our case, mixed studies systematic reviews) are transformed into qualitative findings such as themes, concepts, and patterns. This design is recommended for research asking what, how, and why questions (Pluye & Hong, 2014). In this umbrella review, qualitative thematic synthesis will be used to "transform the data" into themes (Braun & Clarke, 2006; Thomas & Harden, 2008) by applying a hybrid, deductive-inductive approach. The research team will read and re-read the evidence to identify themes, compare these themes with the evidence as the analysis progresses, and meet regularly to resolve uncertainties or ambiguities. While we have identified themes through preliminary analysis and have transformed them into guiding questions/data extraction categories, as we assign data from the included studies to these themes, we will also appraise whether themes are supported by the data or require revision or addition of new themes, based on the emerging data (Pluye & Hong, 2014). In addition to qualitative thematic synthesis, we will also report frequency distributions to describe study characteristics (e.g., country of study, study design) and evaluate the strength of support for themes (Popay et al., 2006).

3.4.6 Subgroup analysis

Subgroup analyses of primary outcomes will be performed to compare findings according to 1) the target population's social indicators (e.g., age, gender, race/ethnicity, occupation); 2) level of income of countries included in the review (e.g., high versus middle versus low income); 3) whether the population studied is the target of vaccination or caretaker of the targets of vaccination (e.g., vaccine recipients versus parents); 4) stage in the vaccination campaign (e.g., first series versus boosters); and 5) relevant medical factors (e.g., presence of comorbidities among populations experiencing VH).

Author contributions

CCH designed the review, has written the current protocol, and will oversee, and participate in, every step of the project until completion and publication of the umbrella review. NH assisted with the study design, conducted the initial article search, contributed to drafting the protocol, and will assist with thematic synthesis, analysis, and final

review drafting. JM is participating in the data selection, extraction, synthesis, and analysis, and has contributed to drafting the protocol manuscript. CH is participating in the data selection, extraction, synthesis, and analysis, and has contributed to drafting the protocol manuscript. All the authors have read and approved the final version of this protocol manuscript.

Preliminary timeframe

Upon registration of the protocol, a six-month timeframe will be dedicated to the search, selection, data extraction and writing up of the umbrella review. This will result in a tentative completion date of the manuscript by April 2023.

Plans for updating this review

The first author, Dr. Claudia Chaufan, will have primary responsibility for updating the review within the proposed timeframe.

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Declarations

- Ethics approval and consent to participate — not applicable
- Consent for publication — not applicable

Competing interests

The authors have competing interests to declare. CCH is affiliated with the Canadian Academics for COVID Ethics and the Canadian COVID Care Alliance (Scientific and Medical Advisory Committee). She is also an Editorial Board member of IJVTPR. None of these entities have played any role in the conception, conduct, or decision to submit this research for publication.

Supplementary information

Additional file 1 — Prisma-P checklist
Additional file 2 — Search terms
Additional file 3 — AMSTAR

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Legal Disclaimer

Additional File # 1

PRISMA-P 2015 Checklist — We applied the checklist for use with systematic review protocol submissions from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported	
			Yes	No
ADMINISTRATIVE INFORMATION				
Title				
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐
Authors				
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐ NA	☐
Support				
Sources	5a	Indicate sources of financial or other support for the review	☒	☐
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐

INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐
METHODS				
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐
Study records				
• Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐
• Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐
• Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐

Data				
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐ NA	☐
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐ NA	☐
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐

Additional File #2: PubMed Search Terms

COVID-19

COVID-19

(("covid 19"[MeSH Terms] OR "covid 19"[All Fields] OR "covid19"[All Fields] OR ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) OR "covid 19"[All Fields] OR "2019ncov"[All Fields] OR ("sars cov 2"[MeSH Terms] OR "sars cov 2"[All Fields] OR "2019 ncov"[All Fields]) OR "2019 ncov"[All Fields] OR "2019 Novel Coronavirus"[All Fields] OR "2019 novel cov"[All Fields] OR ("wuhan"[All Fields] AND ("sars cov 2"[MeSH Terms] OR "sars cov 2"[All Fields] OR "ncov"[All Fields] OR ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronaviruses"[All Fields]))) OR "novel coronavirus pneumonia"[All Fields])

[AND]

Vaccination Hesitancy or Vaccination Uptake/Acceptance

Vaccination Hesitancy

("vaccination hesitancy"[MeSH Terms] OR ("vaccination"[All Fields] AND "hesitancy"[All Fields]) OR "vaccination hesitancy"[All Fields] OR

Vaccination Uptake or Vaccination Acceptance

(("vaccin"[Supplementary Concept] OR "vaccin"[All Fields] OR "vaccination"[MeSH Terms] OR "vaccination"[All Fields] OR "vaccinable"[All Fields] OR "vaccinal"[All Fields] OR "vaccinate"[All Fields] OR "vaccinated"[All Fields] OR "vaccinates"[All Fields] OR "vaccinating"[All Fields] OR "vaccinations"[All Fields] OR "vaccination s"[All Fields] OR "vaccinator"[All Fields] OR "vaccinators"[All Fields] OR "vaccine s"[All Fields] OR "vaccined"[All Fields] OR "vaccines"[MeSH Terms] OR "vaccines"[All Fields] OR "vaccine"[All Fields] OR "vaccins"[All Fields]) AND ("uptake"[All Fields] OR "uptakes"[All Fields] OR "uptaking"[All Fields])) OR (("vaccin"[Supplementary Concept] OR "vaccin"[All Fields] OR "vaccination"[MeSH Terms] OR "vaccination"[All Fields] OR "vaccinable"[All Fields] OR "vaccinal"[All Fields] OR "vaccinate"[All Fields] OR "vaccinated"[All Fields] OR "vaccinates"[All Fields] OR "vaccinating"[All Fields] OR "vaccinations"[All Fields] OR "vaccination s"[All Fields] OR "vaccinator"[All Fields] OR "vaccinators"[All Fields] OR "vaccine s"[All Fields] OR "vaccined"[All Fields] OR "vaccines"[MeSH Terms] OR "vaccines"[All Fields] OR "vaccine"[All Fields] OR "vaccins"[All Fields]) AND ("accept"[All Fields] OR "acceptabilities"[All Fields] OR "acceptability"[All Fields] OR "acceptable"[All Fields] OR "acceptably"[All Fields] OR "acceptance"[All Fields] OR "acceptances"[All Fields] OR "acceptation"[All Fields] OR "accepted"[All Fields] OR "accepter"[All Fields] OR "accepters"[All Fields] OR "accepting"[All Fields] OR "accepts"[All Fields])))

[AND]

Systematic Review

Systematic Review [Filter])

Additional File # 3

AMSTAR (A Measurement Tool to Assess systematic Reviews) is an appraisal tool designed to "create valid, reliable and useable instruments [to help] users differentiate between systematic reviews, focusing on their methodological quality and expert consensus" (AMSTAR, n.d.). It is usually used when developing and conducting high-quality reviews. The most recent version of the instrument, AMSTAR 2, includes categories for randomised and non-randomised studies that are simpler than earlier versions (Shea et al., 2009). For this umbrella review, we have selected from AMSTAR 2 the questions that suite our research goals and have accordingly modified the domains we shall consider critical to the quality of a review accordingly, as follows:

1. (*AMSTAR* #2). Did the report of the review contain *an explicit statement that the review methods were established prior to the conduct of the review* and did the report justify any significant deviations from the protocol?
2. *(AMSTAR #4).* Did review authors use a *comprehensive literature search strategy?*
3. (*AMSTAR* #5). Did review authors perform *study selection in duplicate*?
4. (*AMSTAR* #6). Did review authors perform *data extraction in duplicate*?
5. *(AMSTAR #10).* Did review authors report on *sources of funding in included studies*?
6. (*AMSTAR* #16). Did review authors report any potential *sources of conflict of interest, including any funding they received for conducting the review*?

Following AMSTAR 2, we have chosen domains critical to our review because they provide evidence that the authors have made a good faith effort to capture the broadest range of perspectives on the phenomenon of interest and have revealed their own and others' conflicts of interest, in addition to performing a methodologically adequate systematic review (e.g., data extraction in duplicate). Our selected critical domains are:

1. (*AMSTAR #4*). Did review authors use a comprehensive literature search strategy?
2. (*AMSTAR #10*). Did review authors report on funding sources of funding in included studies?
3. (*AMSTAR* #16). Did review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Following the original AMSTAR, we do not rate individual items for an overall score but rather consider them separately, according to the following scheme:

- **High confidence —** No or one non-critical weakness
- **Moderate confidence —** More than one non-critical weakness
- **Low confidence —** One critical flaw with or without non-critical weaknesses
- **Critically low confidence —** More than one critical flaw with or without non-critical weaknesses