EDITORIAL

THE BALANCE OF RISKS AND BENEFITS IN THE COVID-19 "VACCINE HESITANCY" LITERATURE: A CRITICAL UMBRELLA REVIEW.

AUTHORS :
_ Claudia Chaufan, MD, PhD. 4700 Keele St, Toronto, ON M3J 1P3. York University
cchaufan@yorku.ca / ORCID https://orcid.org/0000-0001-9208-7630
_ Camila Heredia, MD, MA, MSc. York University
cheredia@my.yorku.ca / ORCID ID 0000-0002-1356-0889
_ Jennifer McDonald, MA. York University
mcdljen@gmail.com / ORCID ID 0000-0002-6546-101
_ Natalie Hemsing, MA. York University
nhemsing@yorku.ca / ORCID ID https://orcid.org/0000-0003-1385-8279

https://doi.org/10.55634/1.2.9

ABSTRACT

Background: "Vaccine hesitancy" (VH) has been described as a "threat to global health", especially in the COVID-19 era. Research on VH indicates that the concerns of vaccine recipients with the balance of risks and benefits of COVID-19 vaccination, which involve safety and effectiveness considerations (hereafter "safety concerns"), are a leading driver of VH. However, what explains these concerns is underexplored.

Goal: We conducted a critical umbrella review following PRISMA guidelines and informed by critical perspectives in policy analysis to examine how the safety concerns of COVID-19 vaccine recipients are addressed in the VH literature.

Methods: We searched PubMed, the Epistemonikos COVID-19 platform (COVID-19 L. OVE), and the WHO Global Research on COVID-19 Database. We included 49 refereed reviews examining VH in any population involved with COVID-19 vaccination decisions for themselves or as caretakers, with no methodological, quality, temporal, or geographic restrictions, and were published in English, excluding those that authors did not identify as "systematic". Two reviewers completed article screening and data extraction and synthesis. Disagreements were resolved through full team discussion. Thematic synthesis was used to identify themes and frequencies were calculated to assess the strength of support for themes. The protocol was registered with PROSPERO (ID CRD42022351489) and partially funded by a SSHRC grant (# 435-2022-0959).

Findings: All reviews assumed that VH was a major barrier to ending the COVID-19 crisis. With vaccines assumed to be "safe and effective", recipients' safety concerns were downplayed or dismissed as "misinformation". Informed consent was either not discussed or presented as a potential threat to "vaccine confidence". We observed no differences regardless of study population, methodology, or other study characteristics. Limitations are discussed.

Conclusions: Neglecting or dismissing vaccine recipients' safety concerns contributes to the problem that research on COVID-19 VH purports to address. It also undermines the implementation of informed consent, a fundamental bioethical principle. The scant attention to bioethical considerations in current COVID-19 VH research is concerning and its implications for ethical medical and public health research, policy, and practice are discussed.

Key words: COVID vaccine hesitancy; risk-benefit analysis; informed consent; umbrella reviews; critical reviews; critical policy analysis

Vaccination has been shown to contribute to reducing deaths and severe illness from COVID-19 [...] to reduce the transmission of COVID-19. [and to] protect vulnerable people [...]. Failure to vaccinate widely also enables continued circulation of the virus and the generation of variants, including some that may pose a greater risk. Widespread vaccination will help prevent people from having to go to hospital and contribute to fewer people getting sick, ultimately alleviating the burden of COVID-19 on healthcare systems. It will also help [to] return to normal societal functioning, and the re-opening of economies.
World Health Organization, 2022

The Idols of the Tribe have their foundation in human nature itself [...]. For it is a false assertion that the sense of men is the measure of things.
On the contrary [...] the human understanding is like a false mirror, which [...] distorts and discolours the nature of things by mingling its own nature with it.
Francis Bacon, 1620

BACKGROUND

"Vaccine hesitancy" (VH) has been defined as the "delay in acceptance or refusal of vaccines despite availability of vaccination services [and as a] complex and context specific [phenomenon] varying across time, place and vaccines" (1). It has also been described as a major public health problem — "one of 10 threats to global health" — already in the pre-COVID-19 era (2), and especially since (3). While multiple factors have been identified as driving COVID-19 VH — including socioeconomic status, educational attainment, political ideology, and levels of trust in government (4,5) - the concerns of vaccine recipients (or of caretakers of vaccine recipients, such as parents) with the safety, side effects, and risk-benefit ratio (hereafter "safety concerns") of COVID-19 "vaccines" [2] are a major driver of VH (10–14). However, what explains these concerns themselves is underexplored.

Examining the expert literature on COVID-19 VH sheds light on why this may be so. For instance, in their systematic review Anakpo et al. (15) found that safety concerns leading to distrust drives VH in low-income populations. The authors recommended educating this population about vaccines to overcome their hesitancy but did not question whether these concerns themselves were warranted. Similarly, in their systematic review Abba-Aji et al. (16) 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 yet did not address the safety concerns of vaccine recipients. Batteux et al. (17)'s systematic review noted that concerns with the speed of COVID-19 vaccine development was a major cause of VH, and recommended personalizing communications on vaccination to promote greater acceptance, yet did not elaborate on whether recipients' concerns were justified given the dramatic contrast between the speed of development of COVID-19 vaccines and the usual 10 to 15 years required to test the safety profile of any pharmaceutical (18). In turn, van Mulukom et. al. (19) assessed "antecedents and consequences of COVID-19 conspiracy beliefs", which they argue may lead to VH, based on the authors' assumption that distrust in government authorities, as per the Conspiracy Mentality Questionnaire (20), indicates a "conspiratorial" personality. The authors did not discuss explanations for distrust alternative to perceived personality types, for instance, the decades-long history of regulatory capture of public institutions that may explain why individuals or communities may distrust the trustworthiness of authorities to evaluate the safety of pharmaceuticals (21). If good reasons exist to believe otherwise concerning COVID-19 vaccines, the authors did not elaborate on them.

If these observations indicate a trend, it appears that the expert literature on VH, as represented by systematic reviews, assumes that the safety concerns of recipients of COVID 19 vaccines are unjustified and solely explained by features of prospective vaccine recipients themselves - cognitive, emotional, behavioural, ideological. This finding in itself is revealing, because systematic reviews, which should "adhere to a strict scientific design based on explicit, pre-specified, and reproducible methods" (22) (p10), are generally considered at the top of the "evi-

2_ While our review does not engage the issue of whether the term "vaccine" should be applied to novel mRNA / DNA biologicals, we call attention to the term because it plays a role in the public's reaction, positive ("trust/confidence") or negative ("distrust/hesitancy"), towards these products. We propose that two factors are involved: first, by labelling these products "vaccines" drug companies producing them have been afforded full liability protection (6) that no other drug enjoys; second, these biologicals have also been afforded the social trust that they would likely not enjoy if they were identified as "gene therapy", as per the FDA definition (7). Our own research has revealed that much "hesitancy" has been generated by these factors. For an in-depth discussion on vaccine safety we refer readers to the work of Joy Garner and Brian Hooker (8,9).

dence-based medicine pyramid" (23). This consideration applies to many systematic review types, including those that, like ours, address "diverse information needs of healthcare professionals and policymakers [and] focus on analysing human experiences and cultural or social phenomenon" – "phenomena of interest" rather than "outcomes" (24) (p.2). Notably, however, safety concerns, as well as concerns with the lack of transparency in communicating potential harms (25–27), are increasingly being reported in the scientific literature, and multiple adverse events post administration of COVID-19 vaccines have been documented — from mild (28,29), to moderate (30,31), to severe or unusual for a given age group (e.g., myopericarditis in adolescents) (25,32–34). Importantly, transparency in communicating the risks, benefits, and alternatives to vaccination or any medical procedure are critical to obtaining informed consent, a fundamental bioethical principle, enshrined for over half a century in medical research and practice (35,36), and much longer if the Nuremberg Code, and even the Hippocratic Oath, are considered. What is true for any medical intervention is even truer for one that relies on novel technologies (37) and is intended for delivery on a global scale (38). In sum, there is substantial evidence to support the concerns underpinning reluctance or refusal to willingly accept COVID-19 vaccines, concerns that deserve engagement by VH researchers.

A preliminary search of PROSPERO, Epistemonikos, 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 type is analyzing how major scientific and ethical issues relevant to VH are addressed by scholars in the field. Therefore, our umbrella review broadens the scope of research on VH by examining how the expert literature explains the safety concerns of COVID-19 vaccine recipients, handles the potential evidence base of these concerns, and addresses the ethical tensions posed by the policy of vaccination.

METHODS

As noted by Aromataris et al, the most salient feature of umbrella reviews is that this type of evidence synthesis "only considers for inclusion the highest level of evidence syntheses, namely other systematic reviews and meta-analyses" (39) (p.132). Umbrella reviews also afford researchers the opportunity to raise questions about a given issue that have not been asked (40,41). This is especially the case for scholars working in the critical tradition, described as one that probes the assumptions underlying knowledge claims (42). Applied to reviews, Saunders and Rojon propose that these can be "critical" if they go beyond what is all too often a mere "listing or catalogues of previous research" to consider "if [authors'] conclusions can be justified by the evidence" (43) (p.159). Because one of our goals was to problematize the framing of VH, rather than assuming it, as the literature generally does, as a "problem", our analysis was informed by Carol Bacchi's critical approach to policy, "What is the problem represented to be?" (WPR). WPR helps precisely to engage the process whereby societal issues — in our case, VH — become framed as "problems" requiring intervention (44). As Bacchi argues, assuming "problems" as the "starting points for reflection" can limit the "critical potential" of policy analysis (45) (p.1). The critical policy tradition also includes Mary Dixon-Woods' "Critical Interpretive Synthesis" approach, that not only summarizes extant data but engages in a "more fundamental critique [of] taken-for-granted assumptions" (46)(p. 35), albeit in our case preserving the rigour and reproducibility of data selection methods of traditional umbrella reviews.

SEARCH STRATEGY

Our main research question was: "How does the expert literature on VH address the safety concerns of vaccine recipients?" An ancillary question was "How does the expert literature on VH engage ethical issues concerning vaccination policy?" To answer these questions, we conducted an umbrella review, limiting our data to systematic reviews retrieved from 1) PubMed, 2) the Epistemonikos 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. We used the search terms ["vaccine hesitancy" OR "vaccine uptake" OR "vaccine acceptance"]. In databases that are not COVID-19-specific (e.g., PubMed), these terms were combined with ["COVID-19" OR "SARS Cov2"] terms. The searches were conducted on July 31, 2022. Complementary searches on VH were performed and the documents retrieved were included when relevant (e.g., reports by leading public health agencies), for context, although not as data.

SELECTION CRITERIA AND SCREENING

To capture broad and diverse data and perspectives on our phenomenon of interest, we included quantitative, qualitative, and mixed-studies reviews (47) on VH, with no restrictions of time, place, or population type, regardless of whether they evaluated an intervention, and with a wide range of outcomes, such as 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), in English. We considered a review "systematic" when the authors labeled it as such, were explicit about the methodology, the methodology appeared to be reproducible, the search strategy was clearly described, and inclusion / exclusion criteria were predefined. We classified each systematic review as quantitative, qualitative, or mixed methods based on the research question, the presentation of the evidence, and the approach chosen to synthesize data. Only completed, peer reviewed systematic reviews in English were included [Graph 1 & Table 1]. We narrowed our selection to systematic reviews to ensure the data we analyzed on VH represented the highest level of evidence on the matter.

INCLUDED STUDIES

We identified a total of n=289 articles. After removing duplicates, n=182 articles remained for screening. Upon title and abstract screening, we excluded n=120 articles, which left n=62 for full text review. We subsequently excluded n=13 articles, leaving n=49 that met our inclusion criteria [Table 2]. Two researchers independently screened each abstract or article, and a third reviewer computed the inter-rater reliability. Screening disagreements were resolved by full team discussion and consensus. Our interrater reliability for the screening process was 89%.

DATA EXTRACTION AND OUTCOMES OF INTEREST

The data extraction form was prepared using Microsoft Excel and pre-tested and calibrated using a sample of studies [form available upon request]. It included details about study populations, study design / methods / outcomes, the phenomena of interest, and contextual factors (e.g., conflicts of interests). Data extraction was performed by two researchers. Outcomes of interest included authors' reporting on VH, their assessment of safety concerns of vaccine recipients as well as of other drivers of VH like trust, and their perspectives on and recommendations about how to manage these concerns and other drivers of VH. Other outcomes included the evidence cited to support claims about vaccine safety and effectiveness, clinical dimensions of COVID-19 (e.g., morbidity and mortality), and reports on special populations (e.g., health workers). Selected studies were subject to quality assessment, using a modified version of AMSTAR, a tool to assess the methodological quality of systematic reviews (48) [Table 3]. However, given our study goal, of appraising how the expert literature on VH engages safety concerns of vaccine recipients and bioethical issues around vaccination, no review was excluded based on methodological quality. Two researchers independently assessed each review, a third reviewer computed the rate of quality concordance, results were compared during full team meetings, and disagreements were resolved by full team discussion and consensus. Our inter-rater reliability for quality evaluation was 90%.

DATA SYNTHESIS

In convergent synthesis designs, data is transformed into either qualitative or quantitative findings. In convergent qualitative synthesis, our chosen approach, 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 (47). In this umbrella review, thematic synthesis was used to "transform the data" into themes (49,50) by applying a hybrid, deductive-inductive approach whereby researchers read and re-read the evidence to identify themes, compare them with the evidence as the analysis progresses, and meet regularly to resolve uncertainties or ambiguities. Finally, we performed subgroup analyses 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 was 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). In the next section, we report our qualitative thematic synthesis and frequency distributions - rounded up to the nearest highest or lower integer - if higher / equal or lower than 0.5%, respectively - to describe study characteristics and evaluate the strength of support for themes (51).

PROTOCOL REGISTRATION AND PUBLICATION

The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; https://www.crd.york.ac.uk/prospero, registration ID CRD42022351489), followed recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P), and was published in the peer-reviewed International Journal of Vaccine Theory, Practice and Research (IJVTPR) (52). The PRISMA

2020 statement was used to report the completed umbrella review (53).

RESULTS

Study Characteristics

Despite our search having no geographical or temporal restrictions, we only identified records published in 2021 and 2022, because one inclusion criterion was an exclusive focus on COVID-19. The 49 included reviews were methodologically diverse (quantitative 43/49, 88%; qualitative 5/49, 10%; and mixed 1/49, 2%) and were conducted by first authors from diverse locations (Italy and Ethiopia 7/49, 14%; United States of America [USA] 6/49, 12%; China 4/49, 8%; Pakistan, Indonesia and Iran 3/49, 6%, Malaysia and Greece 2/49, 4%, and Turkey, Poland, The Netherlands, Ghana, Taiwan, Czech Republic, United Kingdom [UK], Jordan, Peru, Bangladesh, Nigeria and Thailand 1/49, 2%). The first authors of the reviews were affiliated with institutions across 23 countries, with Ethiopia and Italy exhibiting the highest (7/49; 14%) number of author affiliations. Most reviews (46/49; 94%) provided a conflict-of-interest statement. Funding sources were declared in a minority (8/49; 16%) of reviews.

Most reviews (30/49; 61%) referred to distinct demographic groups. For example, reviews focused on pregnant women (63,75,83,85–89), healthcare workers (56,67,68,86,90), college students (52,56,67), racial/ethnic minorities and migrants (16,53,79), parents or guardians (48,73), older adults (61), LGBTQ+ individuals (51), and multiple sclerosis patients (91), and country-specific populations (including: Black Americans, Ethiopians, USA population, Italian healthcare workers, Africans, Latin Americans and Caribbean). A large minority of reviews (19/49; 39%) had no study population or country restrictions.

The most frequent review goals were to investigate intention to vaccinate (30/49; 61%) and to assess willingness and hesitancy associated factors (26/49; 53%). Less frequent goals were to analyze attitudes of specific populations towards vaccination (14/49; 29%), examine how rates of vaccine acceptance and hesitance differ across countries or continents (11/49; 22%), identify populations prone to VH (9/49; 18%), estimate the prevalence of vaccine uptake (7/49; 14%), characterize PubMed publications on VH depending on various attributes (e.g., article type, methodology) (1/49, 2%), appraise the potential of the Health Belief Model to inform VH (1/49; 2%), evaluate the effectiveness of interventions to increase vaccine uptake (1/49; 2%), gauge the role of social media in shaping vaccination attitudes (1/49; 2%), and document the acceptance of boosters in individuals who have completed the primary series, i.e., formerly "fully vaccinated" (1/49; 2%). Because some reviews stated more than one goal, the percentages add up to more than 100%. Outcomes were consistent with review goals and included rates of vaccination acceptance, willingness, and refusal, associated determinants of VH, variation across demographic groups, and drivers of acceptance or refusal in specific populations [Graph 2 & Table 4].

FRAMING, ASSESSING, AND REPORTING ON VACCINE HESITANCY

Close to half of the reviews defined "vaccine hesitancy" (22/49; 45%) – the rest did not – with most within this group (17/22; 77%) citing the WHO / SAGE definition mentioned earlier (16,54–69). The remaining reviews within this group (5/22; 23%) offered their own definitions, such as "an individual or group choice to either agree or decline when given the opportunity to be vaccinated" (70) (p.490), "reluctance … to receive safe and recommended available vaccines" (71) (p.2), "indecision, reluctance or concerns regarding vaccination" (72) (p.63), or "willingness to take the COVID-19 vaccine" (73) (p.2-3), with one author noting that in contrast to the concepts of "pro/anti" vaccine, "hesitancy" exists in a continuum in which individuals are amenable to persuasion – albeit implying persuasion always in the direction of accepting vaccination (69) (p.2).

Regardless of whether and how VH was defined, all reviews framed it as a problem to identify, research, and address through public or private policies promoting vaccine "confidence" and "uptake." As an example, one review author asserted that addressing vaccine hesitancy would be the "primary" key to "success" (74) (p.3884), implying that whatever interferes with vaccination stands in the way of controlling or ending the COVID-19 crisis. Over one third (19/49; 39%) of reviews elaborated on the idea that vaccination is essential for controlling the COVID-19 crisis (16,56,58,60,61,66,67,69,70,74–79,79–83), offering as explanations that broad vaccine uptake is required to support the recovery of an economy hit hard by public health countermeasures, prevent further viral mutations leading to new outbreaks, and achieving herd immunity. Achieving herd immunity was indeed the most frequently cited explanation for the urgency to overcome VH and was mentioned in one quarter of reviews (13/49; 27%) (63) with most reviews within this group (10/13; 77%) asserting that by undermining herd immunity VH would prolong the crisis (59,63,64,70–72,84–87). Five reviews (5/49; 10%) also perceived VH as a threat not only concerning COVID-19 but also other communicable diseases where vaccina-

tion is believed to be critical to slowing down viral mutation and preventing repeated outbreaks that increase the global burden of disease (59,64,65,69,73). Lastly, eight reviews (8/49; 16%) alerted about the economic impact of VH (55,71,74,75,86,88–90), with two specifically stating that COVID-19 would lead to a "major decline" in the workforce (90) (p.1) and VH would undermine efforts to overcome the "financial crisis from COVID-19" (74) (p. 3884).

While drivers of VH were presented as diverse as the populations expressing it, virtually all reviews (48/49; 98%) found that safety concerns were present in all populations, yet most authors attributed them to prospective recipients relying on the wrong type of information – "misinformation" or "conspiracy beliefs" (37/49; 76%) – or to conservative/right wing/support for Trump ideology (6/49; 12%) (17,54,69,77,85,91). A minority of authors (11/49; 22%) agreed that recipients' safety concerns had some legitimate medical grounds, albeit qualified. For instance, one review acknowledged that vaccines have historically been "connected to harmful effects" (90), yet this connection did not apply to COVID-19 vaccines that, according to the authors, had been proven safe (62,92). Two reviews acknowledged that there was not enough data to confirm that COVID-19 vaccines were not safe (70,93) and one review (1/49; 2%) observed the limited data in vaccine trials on some populations, such as pregnant women (93), albeit not elaborating on this observation. Nevertheless, most authors who identified some grounds for safety concerns ultimately dismissed them, for instance, asserting that they were grounded on a "perception" of side effects that was "far above the side effects that can actually occur" (57) (p.81), or that side effects were mostly minor, i.e., a fever (89,89,93), soreness or injection-site pain (93,94), or headaches (94). Overall, vaccine risks tended to be minimized, with most reviews (47/49; 96%) asserting that COVID-19 vaccination yielded benefits - preventing infection (16,55,57–59,61,63,71,73,76,77,79,81,85,89,90,92,95–97), achieving herd immunity (62,64,65,72,73,77,82,84,95), reducing severe health outcomes (16,69,74,81,95), controlling/ending the pandemic (16,58,64,65,70,75,78,84,87,92,95) , or reducing transmission, particularly to the vulnerable (16,17,55,77,80,81). Some authors stated that benefits existed but did not specify them (67,83,86,91,93,98).

Trust, or rather, distrust, followed safety concerns as a driver of VH (41/49; 84%), reported as distrust in science or in scientific or government institutions or authorities (56,59,63,64,66,69,75,77,77,83,85,87,88,94,96). Distrust was at times reported as grounded on a history of abuse - as noted in one review, "caused by historical misdeeds" such as the Tuskegee Syphilis Study (93) (p. 11) - experienced by certain ethnic and other minorities (16,60,69,85,93). Additional objects of distrust included the mainstream media (74,96), the process - typically the speed - of vaccine development (54,55,63,75,83,85,88), or the fact that vaccines were often presented as the main solution to health problems (54,57,68,71).

Recommendations to address VH followed from the framing of, explanations for, and perceived urgency to, address, VH, and included calls for "changing attitude[s]" (99) (p. 4092) or "convincing VH individuals through […] strategic campaigns" (72) (p. 63). Other frequent themes included tailoring pro-vaccine messaging to specific demographic groups (17,54,55,57–60,62,63,65,70,71,80,81,87,90,91,96,98), disseminating "reliable" information or "better control" of information (17,55,58,59,68,70,73,75,77–79,82,83,87–90,94,96), forming partnerships with trusted community leaders - religious, medical, celebrities (16,59,74,85,89,93), and implementing vaccine mandates as a "a winning strategy to deal with low uptake" (96) (p.2) and achieve universal vaccination (66,75,92,95,95,100).

Recommendations to address safety concerns of vaccine recipients also followed from author's assumptions about the safety of vaccination, and included to reduce "perceived" risk of vaccine side effects and "heighten the perceived benefits" through "communication efforts" (62) (p.10), to inform the community "about [vaccine] safety and potential benefits" (57) (p. 81), to prepare the public to expect side effects, as many of them such as "increased temperature [are] not unusual" in some demographic groups, for instance, pregnant women, "and can be successfully lowered with acetaminophen" (89)(p.2), to increase the representation of "segments of the population…in research about health treatments that can diminish health disparities" (85) (p 1156), to be mindful of the language used in public health communications - for instance, replacing phrases like "balance potential for benefit with risk" with less negative ones like "known benefit with no known risk of harm" (97) (p.11) - to operate through healthcare workers, especially nurses, "the most trusted professionals in the community [and] able to provide authoritative recommendations to the public" (72) (p. 84) – which required addressing VH among healthcare workers with "better messaging […] to eliminate" their concerns (91)(p.6) - and finally, to "ensure" that vaccines are safe as a matter of "ethical and humanistic responsibility" even when events post-vaccination are not being monitored (87) (p.2619).

ETHICAL CONSIDERATIONS

The ethical imperative to obtain informed consent was seldom (3/49; 6%) mentioned by review authors, and when it was mentioned, it was generally to call attention to the challenges of obtaining it. For example, Geng (59) suggested that obtaining informed consent would decrease "willingness" about vaccination and increase uptake, although failed to explain why. Yasmin (69) recommended maximum transparency in clinical trials and Garg (58) proposed using decision aids that described the benefits and harms of vaccination, implying that said aids would lead to greater acceptance. About one third of the reviews (15/49; 31%) mentioned implementing vaccine mandates to increase uptake, with most reviews within this group (13/15; 87%) citing mandates as solutions to VH (59,63,65,67,69,75,79,83,87,91,92,96,100), especially among healthcare workers (63,79,91,92,100). The remaining reviews (2/15; 13%) suggested that mandating vaccination would have "a negative impact" (17) (p.1) on VH, particularly in "individualistic societies" (77).

About one fifth of the articles (11/49; 22%) discussed other topics relevant to ethics. Restrepo (85), Garg (58), Abba-Aji (16) and Hussain (60) noted that historically discriminated against groups, such as black Americans, ethnic minorities, or the LGBTQ+ community, have been disproportionately, i.e., inequitably, affected by the pandemic and called for more "accessible" (58) (p.882) access to COVID-19 vaccinations. In a similar spirit, Bianchi (96) and Shamshirsaz (97) questioned the ethics of excluding pregnant women from vaccine trials, and Mekonnen (73), Roy (65) and Wang (91) discussed how vaccination could be "equitably" allocated. In turn, Restrepo argued that "hesitation" in Black communities may be due to "lack of "sound and scientifically developed information" leading to "mistrust […] toward health agencies", implying that mistrust was not grounded on science but rather on the experience of past wrongs (85) (p. 1154-1155). Only two articles by the same author acknowledged that the medical profession and public health authorities were responsible for ensuring the safety of vaccines, yet stopped short of elaborating about what ensuring that safety would require (86,87).

Recommendations on ethical matters included to inform the population that vaccination was needed to achieve herd immunity (62), to train communities about the safety and benefits of vaccination (16,57,60), to make vaccines more accessible through outreach campaigns (58,69,74), to encourage public health and other leaders to reach out and mend relationships with historically discriminated against communities to make them more open to accepting vaccination (60,85), and to implement mandated vaccination for healthcare workers to "guarantee the protection of operators and patients" (100) (p. 7). Notably, Galanis (80) suggested that providing information on vaccine safety and effectiveness could be "counterproductive" (p.15), yet did not elaborate on just how a counterproductive outcome would result from a prima facie good, such as properly informing recipients of a medical intervention about its safety and effectiveness.

CLINICAL AND EPIDEMIOLOGICAL CONSIDERATIONS

Most reviews (41/49; 84%) presented COVID-19 as "lethal", while a small minority (8/49; 16%) did not use that word, but still implied that reported death counts (e.g., by the WHO) were higher than deaths caused by other diseases, thus reason for concern (17,54,64,73,77,96,99,100). Five reviews among those referring to COVID-19 as "lethal" (5/41; 12%), asserted that vaccines were critical to decrease COVID specific mortality, especially among demographic groups deemed at high morbidity and mortality risk (57,59,66,72,94). Age as a risk factor for higher mortality and other poor health outcomes was mentioned in almost half of the reviews (22/49; 45%), with most reviews within this group (20/22; 91%) noting that older adults and long-term care residents experience higher infection, hospitalization, and mortality, one review (1/22; 5%) asserting that COVID-19 was rare but severe in children (55) and another review (1/22; 5%) warning about VH among youngsters due to their "perception of being at lower risk of viral harm" (77). Seven reviews (7/49; 14%) also listed pregnancy and ethnic minority status as risk factors of poor COVID-19 outcomes (57,58,66,69,72,85,94), with two of these (2/49; 4%) observing that black Americans experience higher morbidity and mortality compared to white Americans (69,85).

Prevention of poor health outcomes was mentioned in most reviews (42/49; 86%), with most within the group that mentioned prevention (27/42; 64%) presenting vaccines as the "most important prevention mechanisms known today" (57) (p.70), in addition to behavioural approaches (e.g., social distancing), and four reviews (4/49; 8%) (73,82,85,99), asserting that vaccines were the primary strategy to "stop the pandemic" (99) (p.1). A significant minority (20/42; 48%) within the reviews that mentioned prevention also stated that nonpharmaceutical measures, including social distancing, lockdowns, face masking, hand hygiene, mass testing, and border closures, had successfully reduced poor health outcomes, with one review identifying "testing and social restrictions [as] among the most powerful approaches" (87) (p.2610). Only

eight reviews mentioned natural immunity (8/49; 16%), with two among these (2/8; 25%) observing that the "belief in pre-existing [natural post-infection] immunity" led to VH (64,71) (p. 8, p. 1), one review (1/8; 13%) asserting that vaccinal immunity was significantly stronger than natural immunity (93), and another (1/8; 13%) that vaccinal immunity was short-lasting (67). Only one review (1/49; 2%) mentioned treatment of COVID-19, citing antivirals, antibiotics, anti-inflammatories, or immune modulators, albeit concluding that no "certain" therapy for COVID-19 existed, at least at the time of the review's acceptance for publication in March of 2022 (82) (p.843).

Concerning clinical considerations relevant to special populations, about one third of the reviews (17/49; 35%) discussed the potential reproductive health impact of COVID-19 or vaccines, albeit only on females. Over half among these reviews (9/17; 53%) asserted that pregnant women were at risk of severe COVID-19 outcomes, including COVID-19 complications specific to their pregnant state (e.g., preterm birth, stillbirth, and intubation), which the authors perceived as justifying a greater need for vaccinating this demographic group (70,76,82,84,89,93,96–98). One review identified "poor knowledge" (1/17; 6%) regarding fertility, pregnancy, and breastfeeding as a driver of VH in this population (80) (p.15), and another review (1/17; 6%) recommended that "safety information on COVID-19 vaccines must be clearly communicated to pregnant women to […] facilitate informed pregnancy vaccine decisions" (60) (p.3428), implying that properly informed pregnant women would willingly accept vaccination. Safety concerns of pregnant women were mentioned in only three reviews within this group (3/17; 18%), two of which dismissed them as "misinformation" (16,56) (p.7; p. 37) and one as "rumors" (64) (p.15).

OTHER CONSIDERATIONS

Virtually all reviews asserted that COVID-19 vaccines are safe, although only around half (25/49; 51%) referenced their assertions. When adverse effects post vaccination were mentioned, only "minor" ones like injection-site pain, soreness, fever, or chills were listed – see for instance (93). Within these reviews, three asserted that COVID-19 vaccination was safe during pregnancy, citing as evidence of safety a New England Journal of Medicine article that had reported a similar rate of spontaneous abortion by week 20 (12%) among vaccinated women pre- and post-COVID vaccination (101)– we elaborate further on this point in the discussion section - with one (1/25; 4%) noting that no study had enrolled pregnant women. As to risk factors for severe disease outcomes such as old age and presence of co-morbidities (87), these were mentioned in some reviews, suggesting that authors were aware of their role, even if their recommendations in favour of mass vaccination of all age groups, regardless of clinical background, appeared unaffected.

DISCUSSION

Our findings indicate that in systematic reviews of the literature on COVID-19 VH, researchers typically ignored, downplayed, or dismissed safety concerns of vaccine recipients, addressing them not by evaluating the medical evidence on vaccine risks and side effects, but by explaining them away as caused by the cognitions, emotions, intentions, or ideological biases of vaccine recipients, features that we argue are irrelevant to the safety of vaccination. Overall, reviews did not consider evidence that undermined the goal of universal vaccine uptake. These include: the role of natural immunity in preventing infection, serious illness, hospitalization, or death (102), of proper micronutrient supply in strengthening immunity (103), of stress in vulnerability to upper respiratory infections (104), of the social determinants of health in host resistance (105), or of repurposed drugs in early outpatient treatment (106–109).

The management of safety concerns was problematic and selective. For context, assessments of medical interventions are always performed relative to the risk/benefit ratio of said interventions. In other words, when the benefits to a person receiving an intervention outweigh the risks of not receiving it – for instance, when not receiving it is likely to lead to significant disability or death – it may be worth to that person to run the risk of being harmed by that intervention. From an ethical standpoint, this assessment requires that prospective recipients be fully informed about benefits, risks, and alternatives, including the alternative to do nothing. However, reviewers downplayed or did not mention the empirical basis of the concerns of vaccine recipients, despite extensive evidence of serious adverse effects, especially among children and young adults (32,110). Serious adverse effects were already identifiable in the original Pfizer trials, as indicated by re-analyses of publicly available data revealing concerning rates of adverse events, including death (25).

As mentioned earlier, claims about the safety of vaccines during pregnancy were supported by an article from the New England Journal of Medicine (101) that had reported no difference in the rate of spontaneous abortion by week 20 (12%) among vaccinated women post and pre-COVID vaccination. However, readers were not informed that among the 712 live births of 827 completed pregnancies, most occurred, as per the authors, "among participants

vaccinated in the third trimester", when vaccination is far less likely to have adverse effects (p. 2273). This was noted in a critique of the article in the same journal stating that "the risk of spontaneous abortion should be determined on the basis of the group of participants who received the vaccination before week 20", a recognition that would have led to much higher rates of the outcome of interest (111) (p.1535). Nor did any review that made assertions about the safety of COVID-19 vaccination for pregnant women cite competing evidence, such as UK government documents revealing the absence of animal studies data' on reproductive toxicity and acknowledging that "sufficient reassurance of the safe use of the vaccine in pregnant [or breast-feeding] women [cannot] be provided at the present time" (112). In sum, had authors considered the large body of available evidence on COVID-19 adverse effects they may have concluded that the "policy problem" of VH may instead reflect legitimate concerns about vaccination. Further, VH researchers who have stigmatized evidence contrary to official policy as "misinformation" may be participating in a concerning, long-standing practice of silencing dissent in scientific research (113), especially around vaccines (114,115). This can only undermine the transparency of, and further erode the public's trust in the health policy making process and institutions.

Importantly for determining the burden of disease and formulating appropriate public health policy, no review noted that a positive PCR test, a test incidentally reserved "for research [and not] diagnostic procedures" (116), is not equivalent to clinical illness, so discussions around increases in cases were unclear in terms of their clinical or public health significance. Nor did any review refer to a seminal study published in the summer of 2021, of 68 countries and 2,947 US counties, showing no correlation between COVID-19 vaccination rates and cases (117). This feature of COVID-19 vaccines was already apparent in the original trials, which did not include transmission, hospitalizations, or deaths as clinical endpoints (118). Nor did review authors consider risk-stratifying their recommendations, critical in any health condition (119,120), especially for interventions intended to be mass delivered, or mention the high survival rate – over 99% - for the global population under 60 years of age (121) recently updated to over 99.98% (122). The negligible danger of asymptomatic spread was not acknowledged by any review author. However, this point has been well documented by the largest study ever conducted, of close to 10,000,000 individuals in Wuhan, China, revealing no positive tests amongst 1,174 close contacts of asymptomatic cases (123). This finding raises doubts abouts about the wisdom to mass vaccinate healthy people to prevent the spread of infection, also calling into question whether the documented risks outweigh the potential benefits.

Importantly for our goal, our findings revealed not only a pattern of dismissal of evidence for the adverse effects of COVID-19 vaccination, but also a pattern of neglect of the multiple bioethical tensions - such as with the ethical imperative to obtain informed consent - built into the formulation of the policy of universal, often mandatory, vaccination to participate in social life (124). For context, the Oxford English Dictionary defines consent as "the voluntary agreement to, or acquiescence in, what another person proposes or desires; agreement as to a course of action" (125). In the medical context, informed consent is the right of all human beings, and the obligation of all health workers – or anyone delivering a medical intervention – to respectively be asked for, or obtain, consent. The right to be asked for consent, established in 1947 by the Nuremberg Code, a landmark document in medical and research ethics, was meant to be "informed", i.e., the recipient was to be made fully aware not only of the presumed benefits of an intervention, but also of its known or potential risks, and of existing alternatives, including the alternative to abstain from the intervention, free from explicit or implicit coercion (35). As per the Code, this right holds regardless of the demonstrated or assumed benefits of the medical intervention to the recipient or to humanity, the intentions of those administering it, or the motivations of those rejecting it (35). It follows from this definition that whoever delivers a medical intervention, including a diagnostic procedure that involves interference with persons, must obtain free, uncoerced, and informed consent from the recipient (126).

Nevertheless, the few reviews that discussed ethical issues assumed that COVID-19 vaccines were a basic human need – much like housing or drinkable water – and even a human right, and therefore lower vaccination rates among discriminated against groups indicated "inequities". This was the case even when their own findings revealed safety concerns among these groups as drivers of VH. As one notable exception, some authors identified VH as a legitimate response by ethnic and racial minority groups to experiences (current and historical) of discrimination and medical abuses – who are more likely to question or reject vaccination (127). Nevertheless, their proposed policy solution remained the same, namely, to decrease VH and increase vaccine uptake to address "inequities". Authors also consistently failed to discuss alternatives to vaccination or to acknowledge that, from a bioethical standpoint, doing nothing should always be an

alternative. None of the reviews listing or recommending mandated vaccination engaged the tension between it and the ethical imperative that consent must be voluntary and informed (35). Indeed, the conceptualization of COVID-19 VH as a "global health threat" independently of context, and worth overcoming at (almost) all costs regardless of relevant clinical factors, population studied, stage in the vaccination campaign, or study location, made a proper evaluation of the magnitude of this "threat" all but impossible, and the conclusion that without repeated vaccination "upgrades" no human community would survive all but inevitable.

Our approach to reviewing the literature on vaccination, not by assuming researchers' "findings" at face value but rather by critically examining the assumptions underlying research questions and aims, while investigating their empirical grounds, is rare, but not unique. Specifically applied to vaccination research, we identified at least one precedent, of a systematic review of qualitative research on vaccination against the 2009 swine flu that, like ours, engaged researchers' findings and interpretations concerning VH as objects of inquiry, concluding that the major weakness of reviewed studies was a "lack a reflexivity and [...] information about study content", meaning ignorance of actual facts about the swine flu and vaccination as a policy, as well as an inability to reflect on the implications of this ignorance for the internal validity of their own study findings. Authors also pointed out that "hesitation" to embrace vaccination – a policy strongly promoted at the time by governments and the media, and assumed, albeit not demonstrated, by study authors - was well justified, as predictions about morbidity and mortality had been overblown, and vaccine safety had been compromised by the speed of their development, a fact confirmed - long after the demise of the presumed pandemic - by the serious adverse effects experienced by those who accepted, or were coerced into, vaccination (128). This review shares with ours the strength of reaching "beyond mere description [to include] analysis and conceptual innovation [that may offer] a completely new interpretation of existing data", and in so doing inform "more effective ways of targeting [research] funds" towards more promising research objectives (129) (p. 104).

LIMITATIONS

A limitation of our study is the inclusion of only English language reviews. Due to limited time and resources, we were only able to include reviews published in English. This may have introduced a language bias to the results of our review, particularly since vaccine hesitancy has been identified as a global issue and it is possible that VH be framed differently in non-English speaking countries. However, as Graph 2 shows, our search captured reviews from a range of regions (based on the first author's reported location) including many non-English speaking countries, minimizing somewhat this potential language bias. Further, the website of the Pan-American Health Organization, an organization informing health policy in the Spanish- and Portuguese-speaking Americas, indicates that a major concern of regional governments and public health officials has also been VH, also assumed to be largely driven by "misinformation" (in Spanish, "desinformación") (130), which suggests that our findings obtain beyond our sample. Including grey literature may have also revealed greater diversity of perspectives on VH yet would have undermined our goal of assuring that our findings represent views vetted by the research community. Still, we partially offset this limitation by including non-peer reviewed documents from major public health agencies for comparison (for instance, SAGE).

As well, contacting systematic review authors may have broadened our understanding of the absence or neglect of thorough discussions around risk-benefit or informed consent. However, to the best of our knowledge this limitation is shared by most systematic reviews, certainly by all those included in our study. Finally, while we documented funding sources and conflicts of interests, we were unable to determine whether and how these played a role in shaping the dominant framing of VH or the dearth of discussion around bioethical matters. Nevertheless, our research confirms the overlap of official policy positions around VH and VH researchers' lack of engagement with key bioethical principles or with evidence that challenges official policy.

CONCLUSIONS

We suggest that insufficient attention to prospective vaccine recipients' safety concerns and dismissal of the evidence informing these concerns is contributing to the very problem that the literature on VH purports to address. It is also compounding the erosion of trust in public institutions that national governments and international organizations appear to be concerned about (131). We also question the "VH-as-a-problem" construct because the object of study is unverifiable (132), meaning that no amount of empirical evidence would persuade researchers that those who "hesitate" to embrace COVID-19 vaccination may have very good reasons to do so. Therefore, we argue that the "policy problem" of COVID-19 VH is not evidence-based, but rather a problem for those who believe in its existence. We are concerned as well about

the assumption that VH researchers and policy makers are justified in their attempts to "change" the "targets" of their actions – by correcting "misperceptions" and "educating" about the "right" decisions (133). This attitude ignores long-standing ethical principles, such as informed consent, violates the dignity of human beings by treating them as contingent means towards ostensibly higher societal goals, and neglects the long history of medical and public health interventions implemented "for [the recipient's] own good" and "in the name of health" (134) (p. 87) that all too often turned out to be morally repugnant.

We conclude that the policy of mass vaccination, implemented through "nudges", coercion, and mandates, will be remembered as one such intervention. Until it is fully dropped, we call for all research exploring the public's disposition to accept vaccination or any other medical procedure to openly discuss risks, benefits, and alternatives, including the alternative to do nothing, and to conscientiously engage the ethical tensions posed by the procedure.

Funding
This work has been partially funded by Social Sciences and Humanities Research Council (SSHRC) Grant # 435-2022-0959. The funders played no role in the study design, data collection and analysis, manuscript preparation, or decision to publish.

Ethics approval
Not applicable.

Authors' details
All authors are affiliated with York University, School of Health Policy and Management.

Author contributions
CCh conceptualized the project, designed the study, oversaw, and participated in every step of the research, and drafted the first version of the manuscript and subsequent ones as needed. CH participated in data selection, extraction, synthesis, and analysis, and completed the tables and charts. JM participated in data selection, extraction, synthesis, and analysis. NH assisted with the design of the study and led the initial article screening and selection process. All authors contributed substantive expertise, assisted with revisions, and approved the final version.

Competing interests
The authors have no relevant conflicts of interest to declare. All of them are members of several academic and professional organizations, none of which played a role in the study design, data collection and analysis, manuscript preparation, or decision to publish this research. Information about the first author's affiliations and past/present funding agencies is publicly available through the website of York University, Canada.

Appendices
1. Graph 1 - PRISMA flow chart
2. Graph 2 - Bar charts of key study characteristics
3. Table 1 - PRISMA item and abstract checklist
4. Table 2 – Included reviews
5. Table 3 - AMSTAR
6. Table 4 – Table of key study characteristics

References

1. WHO/SAGE. Report of the SAGE Working Group on Vaccine Hesitancy [Internet]. WHO; 2014 [cited 2022 Sep 1]. Available from: https://www.asset-scienceinsociety.eu/sites/default/files/sage_working_group_revised_report_vaccine_hesitancy.pdf

2. World Health Organization. Ten health issues WHO will tackle this year [Internet]. 2019 [cited 2022 Jul 31]. Available from: https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019

3. Sallam M. COVID-19 Vaccine Hesitancy Worldwide: A Concise Systematic Review of Vaccine Acceptance Rates. Vaccines (Basel). 2021 Feb 16;9(2):160.

4. Hudson A, Montelpare WJ. Predictors of Vaccine Hesitancy: Implications for COVID-19 Public Health Messaging. Int J Environ Res Public Health. 2021 Jul 29;18(15):8054.

5. Park HK, Ham JH, Jang DH, Lee JY, Jang WM. Political Ideologies, Government Trust, and COVID-19 Vaccine Hesitancy in South Korea: A Cross-Sectional Survey. International Journal of Environmental Research and Public Health. 2021 Jan;18(20):10655.

6. Health Resources & Services Administration. About the National Vaccine Injury Compensation Program | HRSA [Internet]. 2023 [cited 2023 Jan 15]. Available from: https://www.hrsa.gov/vaccine-compensation/about

7. FDA. What is Gene Therapy? FDA [Internet]. 2018 Jul 25 [cited 2023 Jan 13]; Available from: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy

8. Garner J. Health versus Disorder, Disease, and Death: Unvaccinated Persons Are Incommensurably Healthier than Vaccinated. International Journal of Vaccine Theory, Practice, and Research. 2022 Nov 15;2(2):670–86.

9. Hooker BS. Measles-mumps-rubella vaccination timing and autism among young african american boys: a reanalysis of CDC data. Translational Neurodegeneration. 2014 Aug 27;3(1):16.

10. Khairat S, Zou B, Adler-Milstein J. Factors and Reasons Associated with Low COVID-19 Vaccine Uptake among Highly Hesitant Communities in the US. American journal of infection control [Internet]. 2022; Available from: http://www.epistemonikos.org/documents/86600cb2b099e915060cedd843c1e04ad297d841

11. Ledford CJW, Cafferty LA, Moore JX, Roberts C, Whisenant EB, Garcia Rychtarikova A, et al. The dynamics of trust and communication in COVID-19 vaccine decision making: A qualitative inquiry. null. 2022 Feb 27;1–10.

12. Mills E, Jadad AR, Ross C, Wilson K. Systematic review of qualitative studies exploring parental beliefs and attitudes toward childhood vaccination identifies common barriers to vaccination. Journal of Clinical Epidemiology. 2005 Nov 1;58(11):1081–8.

13. Momplaisir F, Haynes N, Nkwihoreze H, Nelson M, Werner RM, Jemmott J. Understanding Drivers of COVID-19 Vaccine Hesitancy Among Blacks. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/4bd5ce22a1d6c6576e3c4bc6a7b7e191305bf072

14. Tram KH, Saeed S, Bradley C, Fox B, Eshun-Wilson I, Mody A, et al. Deliberation, Dissent, and Distrust: Understanding Distinct Drivers of Coronavirus Disease 2019 Vaccine Hesitancy in the United States. Clin Infect Dis. 2021 Jul 16;ciab633.

15. Anakpo G, Mishi S. Hesitancy of COVID-19 vaccines: Rapid systematic review of the measurement, predictors, and preventive strategies. Hum Vaccin Immunother. 2022 Jun 17;2074716.

16. Abba-Aji M, Stuckler D, Galea S, McKee M. Ethnic/racial minorities' and migrants' access to COVID-19 vaccines: A systematic review of barriers and facilitators. J Migr Health. 2022 Feb;5:100086–100086.

17. Batteux E, Mills F, Jones LF, Symons C, Weston D. The Effectiveness of Interventions for Increasing COVID-19 Vaccine Uptake: A Systematic Review. Vaccines (Basel). 2022 Mar 3;10(3).

18. New York State Department of Health. The Science Behind Vaccine Research and Testing [Internet]. 2014 [cited 2022 Oct 12]. Available from: https://www.health.ny.gov/prevention/immunization/vaccine_safety/science.htm

19. van Mulukom V, Pummerer LJ, Alper S, Bai H, Čavojová V, Farias J, et al. Antecedents and consequences of COVID-19 conspiracy beliefs: A systematic review. Soc Sci Med. 2022 May;301:114912.

20. Bruder M, Haffke P, Neave N, Nouripanah N, Imhoff R. Measuring Individual Differences in Generic Beliefs in Conspiracy Theories Across Cultures: Conspiracy Mentality Questionnaire. Front Psychol [Internet]. 2013 [cited 2022 Oct 12];4. Available from: http://journal.frontiersin.org/article/10.3389/fpsyg.2013.00225/abstract

21. Light DW, Lexchin J, Darrow JJ. Institutional Corruption of Pharmaceuticals and the Myth of Safe and Effective Drugs. J Law Med Ethics. 2013;41(3):590–600.

22. Gopalakrishnan S, Ganeshkumar P. Systematic Reviews and Meta-analysis: Understanding the Best Evidence in Primary Healthcare. J Family Med Prim Care. 2013;2(1):9–14.

23. Murad MH, Asi N, Alsawas M, Alahdab F. New evidence pyramid. BMJ Evidence-Based Medicine. 2016 Aug 1;21(4):125–7.

24. Munn Z, Stern C, Aromataris E, Lockwood C, Jordan Z. What kind of systematic review should I conduct? A proposed typology and guidance for systematic reviewers in the medical and health sciences. BMC Med Res Methodol. 2018 Jan 10;18:5.

25. Fraiman J, Erviti J, Jones M, Greenland S, Whelan P, Kaplan RM, et al. Serious adverse events of special interest following mRNA COVID-19 vaccination in randomized trials in adults. Vaccine [Internet]. 2022 Aug 31 [cited 2022 Sep 1]; Available from: https://www.sciencedirect.com/science/article/pii/S0264410X22010283

26. Malhotra A. Curing the pandemic of misinformation on COVID-19 mRNA vaccines through real evidence-based medicine - Part 1. Journal of Insulin Resistance. 2022 Sep 26;5(1):8.

27. Malhotra A. Curing the pandemic of misinformation on COVID-19 mRNA vaccines through real evidence-based medicine -

Part 2. Journal of Insulin Resistance. 2022 Sep 26;5(1):10.
28. Blumenthal KG, Robinson LB, Camargo CA Jr, Shenoy ES, Banerji A, Landman AB, et al. Acute Allergic Reactions to mRNA COVID-19 Vaccines. JAMA. 2021 Apr 20;325(15):1562–5.
29. Mevorach D, Anis E, Cedar N, Bromberg M, Haas EJ, Nadir E, et al. Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel. N Engl J Med. 2021 Dec 2;385(23):2140–9.
30. Català A, Muñoz-Santos C, Galván-Casas C, Roncero Riesco M, Revilla Nebreda D, Solá-Truyols A, et al. Cutaneous reactions after SARS-CoV-2 vaccination: a cross-sectional Spanish nationwide study of 405 cases*. British Journal of Dermatology. 2022;186(1):142–52.
31. Chow KW, Pham NV, Ibrahim BM, Hong K, Saab S. Autoimmune Hepatitis-Like Syndrome Following COVID-19 Vaccination: A Systematic Review of the Literature. Dig Dis Sci [Internet]. 2022 Apr 29 [cited 2022 May 8]; Available from: https://doi.org/10.1007/s10620-022-07504-w
32. Mansanguan S, Charunwatthana P, Piyaphanee W, Dechkhajorn W, Poolcharoen A, Mansanguan C. Cardiovascular Manifestation of the BNT162b2 mRNA COVID-19 Vaccine in Adolescents. Tropical Medicine and Infectious Disease. 2022 Aug;7(8):196.
33. Tiede A, Sachs UJ, Czwalinna A, Werwitzke S, Bikker R, Krauss JK, et al. Prothrombotic immune thrombocytopenia after COVID-19 vaccination. Blood. 2021 Jul 29;138(4):350–3.
34. Yamamoto K. Adverse effects of COVID-19 vaccines and measures to prevent them. Virol J. 2022 Dec;19(1):100.
35. Shuster E. Fifty Years Later: The Significance of the Nuremberg Code. N Engl J Med. 1997 Nov 13;337(20):1436–40.
36. World Medical Association. Declaration of Helsinki. New England Journal of Medicine. 1964;271(9):473–4.
37. MatiČZ, Šantak M. Current view on novel vaccine technologies to combat human infectious diseases. Appl Microbiol Biotechnol. 2022;106(1):25–56.
38. World Health Organization. Global COVID-19 Vaccination Strategy in a Changing World: July 2022 update [Internet]. 2022 Jul [cited 2022 Aug 12]. Available from: https://www.who.int/publications/m/item/global-covid-19-vaccination-strategy-in-a-changing-world--july-2022-update
39. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. Int J Evid Based Healthc. 2015 Sep;13(3):132–40.
40. Guyatt GH, Sackett DL, Sinclair JC, Hayward R, Cook DJ, Cook RJ, et al. Users' Guides to the Medical Literature: IX. A Method for Grading Health Care Recommendations. JAMA. 1995 Dec 13;274(22):1800–4.
41. Smith V, Devane D, Begley CM, Clarke M. Methodology in conducting a systematic review of systematic reviews of healthcare interventions. BMC Medical Research Methodology. 2011 Feb 3;11(1):15.
42. Mingers J. What is it to be Critical?: Teaching a Critical Approach to Management Undergraduates. Management Learning. 2000 Jun 1;31(2):219–37.
43. Saunders MNK, Rojon C. On the attributes of a critical literature review. Coaching: An International Journal of Theory, Research and Practice. 2011 Sep;4(2):156–62.
44. Bacchi C. Why Study Problematizations? Making Politics Visible. OJPS. 2012;02(01):1–8.
45. Bacchi C. Questioning How "Problems" Are Constituted in Policies. SAGE Open. 2016;6(2):2158244016653986.
46. Dixon-Woods M, Cavers D, Agarwal S, Annandale E, Arthur A, Harvey J, et al. Conducting a critical interpretive synthesis of the literature on access to healthcare by vulnerable groups. BMC Med Res Methodol. 2006 Dec;6(1):35.
47. Pluye P, Hong QN. Combining the Power of Stories and the Power of Numbers: Mixed Methods Research and Mixed Studies Reviews. Annu Rev Public Health. 2014 Mar 18;35(1):29–45.
48. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. Journal of Clinical Epidemiology. 2009 Oct 1;62(10):1013–20.
49. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology. 2006 Jan 1;3(2):77–101.
50. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. BMC Med Res Methodol. 2008 Dec;8(1):45.
51. Popay J. Moving beyond floccinaucinihilipilification: Enhancing the utility of systematic reviews. Journal of Clinical Epidemiology. 2005 Nov 1;58(11):1079–80.
52. Chaufan C, Hemsing N, McDonald J, Heredia C. The Risk-Benefit Balance in the COVID-19 "Vaccine Hesitancy" Literature: An Umbrella Review Protocol. International Journal of Vaccine Theory, Practice, and Research. 2022 Nov 9;2(2):652–69.
53. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;n71.
54. Cascini F, Pantovic A, Al-Ajlouni Y, Failla G, Puleo V, Melnyk A, et al. Social media and attitudes towards a COVID-19 vaccination: A systematic review of the literature. EClinicalMedicine. 2022;101454.
55. Chen F, He Y, Shi Y. Parents' and Guardians' Willingness to Vaccinate Their Children against COVID-19: A Systematic Review and Meta-Analysis. Vaccines (Basel). 2022 Jan 24;10(2).
56. Dhanani L, Franz B. A meta-analysis of COVID-19 vaccine attitudes and demographic characteristics in the United States. Public Health. 2022 Jun;207:31–8.
57. Ergün A, Bekar A, Aras B, Dere C, Tekneci D, Sariçiçek G, et al. Determination of Novel Coronavirus Disease (COVID-19) Vaccine Hesitancy Using a Systematic Review Approach Based on the Scientific Articles in PubMed Database. Turk Thorac J. 2022 Feb;23(1):70–84.
58. Garg I, Hanif H, Javed N, Abbas R, Mirza S, Javaid MA, et al. COVID-19 Vaccine Hesitancy in the LGBTQ+ Population: A Systematic Review. Infectious disease reports. 2021;13(4):872–87.

59. Geng H, Cao K, Zhang J, Wu K, Wang G, Liu C. Attitudes of COVID-19 vaccination among college students: A systematic review and meta-analysis of willingness, associated determinants, and reasons for hesitancy. Hum Vaccin Immunother. 2022 Nov 30;18(5):2054260.
60. Hussain B, Latif A, Timmons S, Nkhoma K, Nellums LB. Overcoming COVID-19 vaccine hesitancy among ethnic minorities: A systematic review of UK studies. Vaccine. 2022 May 31;40(25):3413–32.
61. Kazeminia M, Afshar ZM, Rajati M, Saeedi A, Rajati F. Evaluation of the Acceptance Rate of Covid-19 Vaccine and its Associated Factors: A Systematic Review and Meta-analysis. J Prev (2022). 2022 Aug;43(4):421–67.
62. Limbu Y, Gautam R, Pham L. The Health Belief Model Applied to COVID-19 Vaccine Hesitancy: A Systematic Review. Vaccines [Internet]. 2022;10(6). Available from: http://www.epistemonikos.org/documents/b67c1dc311d0f05c3d8c80dd1b8d4dd600f6733d
63. Lin GS, Lee HY, Leong JZ, Sulaiman MM, Loo WF, Tan WW. COVID-19 vaccination acceptance among dental students and dental practitioners: A systematic review and meta-analysis. PloS one. 2022;17(4):e0267354.
64. Nehal K, Steendam L, Campos Ponce M, Van Der Hoeven M, Smit GS. Worldwide Vaccination Willingness for COVID-19: A Systematic Review and Meta-Analysis. Vaccines [Internet]. 2021;9(10). Available from: http://www.epistemonikos.org/documents/a2cc44612ea7ce55e8327c630ac5e4b972a2a453
65. Roy DN, Biswas M, Islam E, Azam MS. Potential factors influencing COVID-19 vaccine acceptance and hesitancy: A systematic review. PLoS One. 2022;17(3):e0265496.
66. Salomoni MG, Di Valerio Z, Gabrielli E, Montalti M, Tedesco D, Guaraldi F, et al. Hesitant or Not Hesitant? A Systematic Review on Global COVID-19 Vaccine Acceptance in Different Populations. Vaccines [Internet]. 2021;9(8). Available from: http://www.epistemonikos.org/documents/15517bd36b0658d3acd90c0d680a310316b87e4e
67. Snehota M, Vlckova J, Cizkova K, Vachutka J, Kolarova H, Klaskova E, et al. Acceptance of a vaccine against COVID-19 - a systematic review of surveys conducted worldwide. Bratisl Lek Listy. 2021;122(8):538–47.
68. Veronese N, Saccaro C, Demurtas J, Smith L, Dominguez LJ, Maggi S, et al. Prevalence of unwillingness and uncertainty to vaccinate against COVID-19 in older people: A systematic review and meta-analysis. Ageing Res Rev. 2021;72:101489.
69. Yasmin F, Najeeb H, Moeed A, Naeem U, Asghar MS, Chughtai NU, et al. COVID-19 Vaccine Hesitancy in the United States: A Systematic Review. Front Public Health. 2021;9:770985–770985.
70. Pragitara CF, Rahmasena N, Ramadhani AT, Fauzia S, Erfadila R, Faraj DMW, et al. COVID-19 concerns, influenza vaccination history and pregnant women's COVID-19 vaccine acceptance: a systematic review. International Journal of Public Health Science. 2022;11(2):490–502.
71. Kukreti S, Rifai A, Padmalatha S, Lin CY, Yu T, Ko WC, et al. Willingness to obtain COVID-19 vaccination in general population: A systematic review and meta-analysis. Journal of Global Health. 2022;12:11–11.
72. Al-Amer R, Maneze D, Everett B, Montayre J, Villarosa AR, Dwekat E, et al. COVID-19 vaccination intention in the first year of the pandemic: A systematic review. J Clin Nurs. 2022 Jan;31(1–2):62–86.
73. Mekonnen BD, Mengistu BA. COVID-19 vaccine acceptance and its associated factors in Ethiopia: A systematic review and meta-analysis. Clin Epidemiol Glob Health. 2022 Apr;14:101001.
74. Hajure M, Tariku M, Bekele F, Abdu Z, Dule A, Mohammedhussein M, et al. Attitude Towards COVID-19 Vaccination Among Healthcare Workers: A Systematic Review. Infect Drug Resist. 2021 Sep;14:3883–97.
75. Ackah M, Ameyaw L, Gazali Salifu M, Afi Asubonteng DP, Osei Yeboah C, Narkotey Annor E, et al. COVID-19 vaccine acceptance among health care workers in Africa: A systematic review and meta-analysis. PLoS One. 2022;17(5):e0268711–e0268711.
76. Alarcón-Braga EA, Hernandez-Bustamante EA, Salazar-Valdivia FE, Valdez-Cornejo VA, Mosquera-Rojas MD, Ulloque-Badaracco JR, et al. Acceptance towards COVID-19 vaccination in Latin America and the Caribbean: A systematic review and meta-analysis. Travel Med Infect Dis. 2022 Jun 6;49:102369.
77. Cascini F, Pantovic A, Al-Ajlouni Y, Failla G, Ricciardi W. Attitudes, acceptance and hesitancy among the general population worldwide to receive the COVID-19 vaccines and their contributing factors: A systematic review. EClinicalMedicine. 2021;40:101113–101113.
78. Dadras O, SeyedAlinaghi S, Karimi A, Shamsabadi A, Mahdiabadi S, Mohammadi P, et al. Public acceptability of COVID-19 vaccines and its predictors in Middle ŒEastern/North African (MENA) countries: a systematic reviewČ. Hum Vaccin Immunother. 2022 Nov 30;18(5):2043719.
79. Galanis P, Vraka I, Katsiroumpa A, Siskou O, Konstantakopoulou O, Katsoulas T, et al. First COVID-19 Booster Dose in the General Population: A Systematic Review and Meta-Analysis of Willingness and Its Predictors. Vaccines (Basel). 2022;10(7).
80. Galanis P, Vraka I, Siskou O, Konstantakopoulou O, Katsiroumpa A, Kaitelidou D. Willingness, refusal and influential factors of parents to vaccinate their children against the COVID-19: A systematic review and meta-analysis. Prev Med. 2022;157:106994–106994.
81. Mose A, Wasie A, Shitu S, Haile K, Timerga A, Melis T, et al. Determinants of COVID-19 vaccine acceptance in Ethiopia: A systematic review and meta-analysis. PLoS One. 2022;17(6):e0269273–e0269273.
82. Nikpour M, Sepidarkish M, Omidvar S, Firouzbakht M. Global prevalence of acceptance of COVID-19 vaccines and associated factors in pregnant women: a systematic review and meta-analysis. Expert Rev Vaccines. 2022;21(6):843–51.
83. Shakeel CS, Mujeeb A, Mirza M, Chaudhry B, Khan SJ.

Global COVID-19 Vaccine Acceptance: A Systematic Review of Associated Social and Behavioral Factors. Vaccines [Internet]. 2022;10(1). Available from: http://www.epistemonikos.org/documents/a5802fc8c7ba211b8f932dc7ed103973b81c7bfc

84. Norhayati MN, Che Yusof R, Azman YM. Systematic Review and Meta-Analysis of COVID-19 Vaccination Acceptance. Front Med (Lausanne). 2021;8:783982.

85. Restrepo N, Krouse HJ. COVID-19 Disparities and Vaccine Hesitancy in Black Americans: What Ethical Lessons Can Be Learned? Otolaryngol Head Neck Surg. 2022;166(6):1147–60.

86. Wake AD. The Acceptance Rate Toward COVID-19 Vaccine in Africa: A Systematic Review and Meta-analysis. Glob Pediatr Health. 2021;8:2333794X211048738.

87. Wake AD. The Willingness to Receive COVID-19 Vaccine and Its Associated Factors: "Vaccination Refusal Could Prolong the War of This Pandemic" - A Systematic Review. Risk Manag Healthc Policy. 2021 Jun;14:2609–23.

88. Bayou FD, Amare SN. Acceptance of COVID-19 Vaccine and Its Associated Factors Among Ethiopian Population: A Systematic Review. Patient Prefer Adherence. 2022 May;16:1093–103.

89. Januszek SM, Faryniak-Zuzak A, BarnaČE, ŁoziČski T, Góra T, Siwiec N, et al. The Approach of Pregnant Women to Vaccination Based on a COVID-19 Systematic Review. Medicina (Kaunas). 2021 Sep 17;57(9).

90. Nindrea RD, Usman E, Katar Y, Sari NP. Acceptance of COVID-19 vaccination and correlated variables among global populations: A systematic review and meta-analysis. Clin Epidemiol Glob Health. 2021;12:100899.

91. Wang Q, Yang L, Jin H, Lin L. Vaccination against COVID-19: A systematic review and meta-analysis of acceptability and its predictors. Prev Med. 2021;150:106694.

92. Luo C, Yang Y, Liu Y, Zheng D, Shao L, Jin J, et al. Intention to COVID-19 vaccination and associated factors among health care workers: A systematic review and meta-analysis of cross-sectional studies. Am J Infect Control. 2021 Oct;49(10):1295–304.

93. Rawal S, Tackett RL, Stone RH, Young HN. COVID-19 vaccination among pregnant people in the United States: a systematic review. Am J Obstet Gynecol MFM. 2022;4(4):100616.

94. Fani T, Saptorini KK, Anggreani AD. The willingness of COVID-19 vaccination and associated factors: A systematic review. South Eastern European Journal of Public Health [Internet]. 2022;18. Available from: https://doi.org/10.11576/seejph-5454

95. Alemayehu A, Demissie A, Yusuf M, Gemechu Lencha A, Oljira L. Covid-19 Vaccine Acceptance and Determinant Factors among General Public in East Africa: A Systematic Review and Meta-Analysis. Health Serv Res Manag Epidemiol. 2022 Dec;9:23333928221106268.

96. Bianchi FP, Stefanizzi P, Di Gioia MC, Brescia N, Lattanzio S, Tafuri S. COVID-19 vaccination hesitancy in pregnant and breastfeeding women and strategies to increase vaccination compliance: a systematic review and meta-analysis. Expert Rev Vaccines. 2022 Jul 20;1–12.

97. Shamshirsaz AA, Hessami K, Morain S, Afshar Y, Nassr AA, Arian SE, et al. Intention to Receive COVID-19 Vaccine during Pregnancy: A Systematic Review and Meta-analysis. Am J Perinatol. 2022 Apr;39(5):492–500.

98. Carbone L, Di Girolamo R, Mappa I, Saccone G, Raffone A, Di Mascio D, et al. Worldwide beliefs among pregnant women on SARS-CoV-2 vaccine: a systematic review. Eur J Obstet Gynecol Reprod Biol. 2022 Jan;268:144–64.

99. Yazdani A, Mirmosayyeb O, Ghaffary EM, Hashemi MS, Ghajarzadeh M. COVID-19 vaccines and patients with multiple sclerosis: willingness, unwillingness and hesitancy: a systematic review and meta-analysis. Neurol Sci. 2022;43(7):4085–94.

100. Bianchi FP, Stefanizzi P, Brescia N, Lattanzio S, Martinelli A, Tafuri S. COVID-19 vaccination hesitancy in Italian healthcare workers: a systematic review and meta-analysis. Expert review of vaccines. 2022;1–12.

101. Shimabukuro TT, Kim SY, Myers TR, Moro PL, Oduyebo T, Panagiotakopoulos L, et al. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. N Engl J Med. 2021 Jun 17;384(24):2273–82.

102. Gazit S, Shlezinger R, Perez G, Lotan R, Peretz A, Ben-Tov A, et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Naturally Acquired Immunity versus Vaccine-induced Immunity, Reinfections versus Breakthrough Infections: A Retrospective Cohort Study. Clinical Infectious Diseases. 2022 Jul 1;75(1):e545–51.

103. Argano C, Mallaci Bocchio R, Natoli G, Scibetta S, Lo Monaco M, Corrao S. Protective Effect of Vitamin D Supplementation on COVID-19-Related Intensive Care Hospitalization and Mortality: Definitive Evidence from Meta-Analysis and Trial Sequential Analysis. Pharmaceuticals (Basel). 2023 Jan 16;16(1):130.

104. Cohen S. Psychological Stress, Immunity, and Upper Respiratory Infections. Current Directions in Psychological Science. 1996;5(3):86–90.

105. Cassell J. The contribution of the social environment to host resistance: The fourth Wade Hampton frost lecture. American Journal of Epidemiology. 1976;104(2):107–23.

106. Carvallo H, Hirsch R, Alkis P, Contreras V. Study of the Efficacy and Safety of Topical Ivermectin + Iota-Carrageenan in the Prophylaxis against COVID-19 in Health Personnel. J biomed res clin investig [Internet]. 2020 Nov 17 [cited 2022 Oct 24];2(1). Available from: https://www.medicalpressopenaccess.com/single_article.php?refid=82

107. Kory P, Meduri GU, Varon J, Iglesias J, Marik PE. Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19. American Journal of Therapeutics. 2021;20.

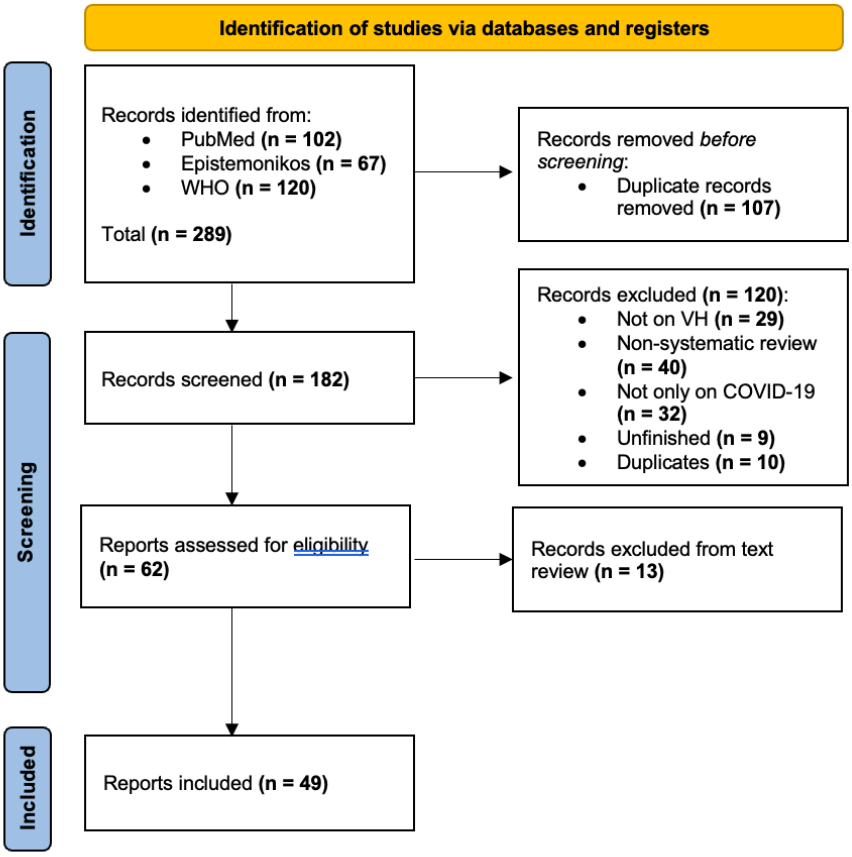
108. McCullough PA, Kelly RJ, Ruocco G, Lerma E, Tumlin J, Wheelan KR, et al. Pathophysiological Basis and Rationale for Early Outpatient Treatment of SARS-CoV-2 (COVID-19) Infection. The American Journal of Medicine. 2021 Jan;134(1):16–22.

109. Risch HA. Early Outpatient Treatment of Symptomatic, Hi-

gh-Risk COVID-19 Patients That Should Be Ramped Up Immediately as Key to the Pandemic Crisis. American Journal of Epidemiology. 2020 Nov 2;189(11):1218–26.
110. Muhaidat N, Alshrouf MA, Azzam MI, Karam AM, Al-Nazer MW, Al-Ani A. Menstrual Symptoms After COVID-19 Vaccine: A Cross-Sectional Investigation in the MENA Region. Int J Womens Health. 2022 Mar 28;14:395–404.
111. Sun H. On Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. N Engl J Med. 2021 Oct 14;385(16):1535–6.
112. UK.Gov. GOV.UK/MHRA. 2022 [cited 2022 Nov 22]. Summary of the Public Assessment Report for COVID-19 Vaccine Pfizer/BioNTech. Available from: https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/summary-public-assessment-report-for-pfizer-biontech-covid-19-vaccine
113. Moran G. Silencing Scientists and Scholars in Other Fields: Power, Paradigm Controls, Peer Review, and Scholarly Communication. Greenwood Publishing Group; 1998. 216 p.
114. Elisha E, Guetzkow J, Shir-Raz Y, Ronel N. Suppressing Scientific Discourse on Vaccines? Self-perceptions of researchers and practitioners. HEC Forum [Internet]. 2022 May 19 [cited 2023 Mar 17]; Available from: https://doi.org/10.1007/s10730-022-09479-7
115. Elisha E, Guetzkow J, Shir-Raz Y, Ronel N. Retraction of scientific papers: the case of vaccine research. Critical Public Health. 2022 Aug 8;32(4):533–42.
116. Braunstein GD, Schwartz L, Hymel P, Fielding J. False Positive Results With SARS-CoV-2 RT-PCR Tests and How to Evaluate a RT-PCR-Positive Test for the Possibility of a False Positive Result. Journal of Occupational and Environmental Medicine. 2021 Mar;63(3):e159.
117. Subramanian SV, Kumar A. Increases in COVID-19 are unrelated to levels of vaccination across 68 countries and 2947 counties in the United States. Eur J Epidemiol [Internet]. 2021 Sep 30 [cited 2021 Oct 10]; Available from: https://doi.org/10.1007/s10654-021-00808-7
118. Doshi P. Will covid-19 vaccines save lives? Current trials aren't designed to tell us. BMJ. 2020 Oct 21;371:m4037.
119. Kannel WB. Risk stratification in hypertension: new insights from the Framingham study*. American Journal of Hypertension. 2000 Jan 1;13(S1):3S-10S.
120. Roobol MJ, Carlsson SV. Risk stratification in prostate cancer screening. Nat Rev Urol. 2013 Jan;10(1):38–48.
121. COVID-19 Forecasting Team. Variation in the COVID-19 infection–fatality ratio by age, time, and geography during the pre-vaccine era: a systematic analysis. The Lancet. 2022 Apr;399(10334):1469–88.
122. Pezzullo AM, Axfors C, Contopoulos-Ioannidis DG, Apostolatos A, Ioannidis JPA. Age-stratified infection fatality rate of COVID-19 in the non-elderly population. Environmental Research. 2023 Jan 1;216:114655.
123. Cao S, Gan Y, Wang C, Bachmann M, Wei S, Gong J, et al. Post-lockdown SARS-CoV-2 nucleic acid screening in nearly ten million residents of Wuhan, China. Nat Commun. 2020 Nov 20;11(1):5917.
124. Bardosh K, De Figueiredo A, Gur-Arie R, Jamrozik E, Doidge J, Lemmens T, et al. The unintended consequences of COVID-19 vaccine policy: why mandates, passports and restrictions may cause more harm than good. BMJ Global Health. 2022;7(5):e008684.
125. Oxford English Dictionary. Consent. In 1989 [cited 2023 Feb 4]. Available from: https://www.oed.com/oed2/00047775
126. Canadian Medical Protective Association. CMPA. 2021 [cited 2021 Oct 1]. Consent: A guide for Canadian physicians. Available from: https://www.cmpa-acpm.ca/en/advice-publications/handbooks/consent-a-guide-for-canadian-physicians
127. Sayles R, Anim G, McGee E. Systematic review of vaccination hesitancy in the minority population in relation to the potential for COVID vaccine uptake. JACCP Journal of the American College of Clinical Pharmacy. 2020;3(8):1686–1686.
128. Carlsen B, Glenton C. The swine flu vaccine, public attitudes, and researcher interpretations: a systematic review of qualitative research. BMC Health Services Research. 2016 Jun 24;16(1):203.
129. Grant MJ, Booth A. A typology of reviews: an analysis of 14 review types and associated methodologies. Health Information & Libraries Journal. 2009;26(2):91–108.
130. Organizacion Panamericana de la Salud. La desinformación alimenta las dudas sobre las vacunas contra la COVID-19, según la Directora de la OPS - OPS/OMS | Organización Panamericana de la Salud [Internet]. 2021 [cited 2023 Mar 15]. Available from: https://www.paho.org/es/noticias/21-4-2021-desinformacion-alimenta-dudas-sobre-vacunas-contra-covid-19-segun-directora-ops
131. United Nations - Department of Economic and Social Affairs. Trust in public institutions: Trends and implications for economic security | DISD [Internet]. 2021 [cited 2023 Mar 17]. Available from: https://www.un.org/development/desa/dspd/2021/07/trust-public-institutions/
132. Popper K. The Logic of Scientific Discovery. 2 edition. London: Routledge; 2002. 544 p.
133. Kraaijeveld SR, Jamrozik E. Moralization and Mismoralization in Public Health. Med Health Care Philos. 2022 Dec;25(4):655–69.
134. Zola IK. In the name of health and illness: On some socio-political consequences of medical influence. Social Science & Medicine. 1975;9:83–7.

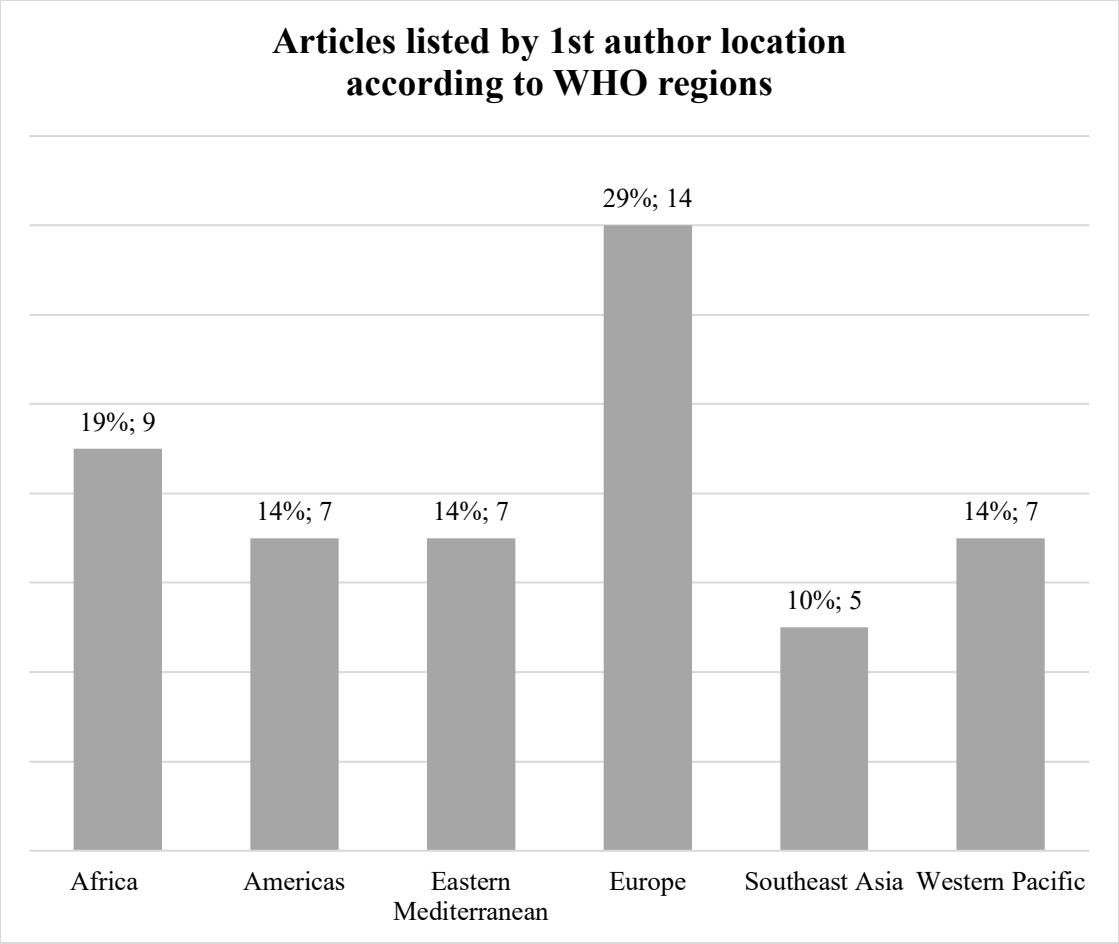
1. GRAPH 1 - PRISMA FLOW CHART

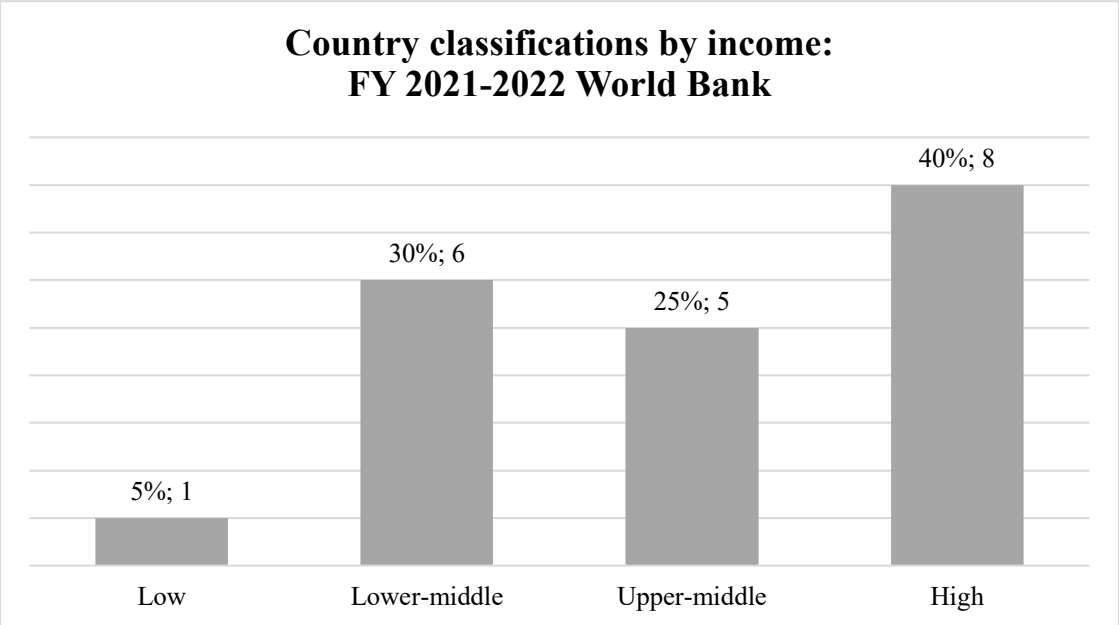
Graph 1 - PRISMA flow chart.



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

2. GRAPH 2 – BAR CHARTS OF KEY STUDY CHARACTERISTICS





3. TABLE 1 - PRISMA ITEM AND ABSTRACT CHECKLIST

Table 1 - PRISMA 2020 item checklist.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Section and topic	Item #	Checklist item	Location where item is reported
Title			
Title	1	Identify the report as a systematic review.[1]	1
Abstract			
Abstract	2	See the PRISMA 2020 for Abstracts checklist (table 2).	
Introduction			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question([1]s) the review addresses.	5
Methods			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6,7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study	7

[1]Umbrella reviews are reviews of systematic reviews, so the category of systematic reviews is included in the label by definition.

		were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6,7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	N/A
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
Results			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram (see fig 1).	7,8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	6,7

Study characteristics	17	Cite each included study and present its characteristics.	7,8, Table 4
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	N/A
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	7-13
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
Discussion			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	14
	23b	Discuss any limitations of the evidence included in the review.	15
	23c	Discuss any limitations of the review processes used.	15
	23d	Discuss implications of the results for practice, policy, and future research.	15,16
Other information			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	7
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	7
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	2
Competing interests	26	Declare any competing interests of review authors.	2

Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	6

PRISMA 2020 for Abstracts checklist*

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Section and topic	**Item #**	**Checklist item**	**Reported (Yes/No)**
Title			
Title	1	Identify the report as a systematic review.	Yes
Background			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
Methods			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	No
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	No
Synthesis of results	6	Specify the methods used to present and synthesize results.	Yes
Results			
Included studies	7	Give the total number of included studies and participants and summarize relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
Discussion			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
Other			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

4. TABLE 2 - INCLUDED REVIEWS.

1. Abba-Aji, M., Stuckler, D., Galea, S., & McKee, M. (2022). Ethnic/racial minorities' and migrants' access to COVID-19 vaccines: A systematic review of barriers and facilitators. *J Migr Health*, *5*, 100086–100086. MEDLINE. https://doi.org/10.1016/j.jmh.2022.100086

2. Ackah, M., Ameyaw, L., Gazali Salifu, M., Afi Asubonteng, D. P., Osei Yeboah, C., Narkotey Annor, E., Abena Kwartemaa Ankapong, E., & Boakye, H. (2022). COVID-19 vaccine acceptance among health care workers in Africa: A systematic review and meta-analysis. *PLoS One*, *17*(5), e0268711–e0268711.

3. Al-Amer, R., Maneze, D., Everett, B., Montayre, J., Villarosa, A. R., Dwekat, E., & Salamonson, Y. (2022). COVID-19 vaccination intention in the first year of the pandemic: A systematic review. *Journal of Clinical Nursing*, *31*(1–2), 62–86. https://doi.org/10.1111/jocn.15951

4. Alarcón-Braga, E. A., Hernandez-Bustamante, E. A., Salazar-Valdivia, F. E., Valdez-Cornejo, V. A., Mosquera-Rojas, M. D., Ulloque-Badaracco, J. R., Rondon-Saldaña, J. C., & Zafra-Tanaka,
J. H. (2022). Acceptance towards COVID-19 vaccination in Latin America and the Caribbean: A systematic review and meta-analysis. *Travel Medicine and Infectious Disease*, *49*, 102369. https://doi.org/10.1016/j.tmaid.2022.102369

5. Alemayehu, A., Demissie, A., Yusuf, M., Gemechu Lencha, A., & Oljira, L. (2022). Covid-19 Vaccine Acceptance and Determinant Factors among General Public in East Africa: A Systematic Review and Meta-Analysis. *Health Services Research and Managerial Epidemiology*, *9*, 23333928221106268. https://doi.org/10.1177/23333928221106269

6. Batteux, E., Mills, F., Jones, L. F., Symons, C., & Weston, D. (2022). The Effectiveness of Interventions for Increasing COVID-19 Vaccine Uptake: A Systematic Review. *Vaccines*, *10*(3). https://doi.org/10.3390/vaccines10030386

7. Bayou, F. D., & Amare, S. N. (2022). Acceptance of COVID-19 Vaccine and Its Associated Factors Among Ethiopian Population: A Systematic Review. *Patient Prefer Adherence*, *16*, 1093–1103. MEDLINE. https://doi.org/10.2147/PPA.S360174

8. Bianchi, F. P., Stefanizzi, P., Brescia, N., Lattanzio, S., Martinelli, A., & Tafuri, S. (2022). COVID-19 vaccination hesitancy in Italian healthcare workers: A systematic review and meta- analysis. *Expert Review of Vaccines*, 1–12. https://doi.org/10.1080/14760584.2022.2093723

9. Bianchi, F. P., Stefanizzi, P., Di Gioia, M. C., Brescia, N., Lattanzio, S., & Tafuri, S. (2022). COVID-19 vaccination hesitancy in pregnant and breastfeeding women and strategies to increase vaccination compliance: A systematic review and meta-analysis. *Expert Review of Vaccines*, 1– 12. https://doi.org/10.1080/14760584.2022.2100766

10. Carbone, L., Di Girolamo, R., Mappa, I., Saccone, G., Raffone, A., Di Mascio, D., De Vivo, V., D'Antonio, F., Guida, M., Rizzo, G., & Maria Maruotti, G. (2022). Worldwide beliefs among pregnant women on SARS-CoV-2 vaccine: A systematic review. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, *268*, 144–164. https://doi.org/10.1016/j.ejogrb.2021.12.003

11. Cascini, F., Pantovic, A., Al-Ajlouni, Y., Failla, G., Puleo, V., Melnyk, A., Lontano, A., & Ricciardi, W. (2022). Social media and attitudes towards a COVID-19 vaccination: A systematic review of the literature. *EClinicalMedicine*, 101454. https://doi.org/10.1016/j.eclinm.2022.101454

12. Cascini, F., Pantovic, A., Al-Ajlouni, Y., Failla, G., & Ricciardi, W. (2021). Attitudes, acceptance and hesitancy among the general population worldwide to receive the COVID-19 vaccines and their contributing factors: A systematic review. *EClinicalMedicine*, *40*, 101113– 101113.

13. Chen, F., He, Y., & Shi, Y. (2022). Parents' and Guardians' Willingness to Vaccinate Their Children against COVID-19: A Systematic Review and Meta-Analysis. *Vaccines*, *10*(2). https://doi.org/10.3390/vaccines10020179

14. Dadras, O., SeyedAlinaghi, S., Karimi, A., Shamsabadi, A., Mahdiabadi, S., Mohammadi, P., Amiri, A., Shojaei, A., Pashaei, Z., Mirzapour, P., Qaderi, K., MohsseniPour, M., Alilou, S., Mehraeen, E., & Jahanfar, S. (2022). Public acceptability of COVID-19 vaccines and its predictors in Middle Eastern/North African (MENA) countries: A systematic review. *Human Vaccines & Immunotherapeutics*, *18*(5), 2043719. https://doi.org/10.1080/21645515.2022.2043719

15. Dhanani, L., & Franz, B. (2022). A meta-analysis of COVID-19 vaccine attitudes and demographic characteristics in the United States. *Public Health*, *207*, 31–38. https://doi.org/10.1016/j.puhe.2022.03.012

16. Ergün, A., Bekar, A., Aras, B., Dere, C., Tekneci, D., Sariçiçek, G., Akdere, S. N., Telli, S., Pehlivanli, S. B., Özyurek Ucael, D., Özden, M. E., Altintas, E., & Aslan, D. (2022). Determination of Novel Coronavirus Disease (COVID-19) Vaccine Hesitancy Using a Systematic Review Approach Based on the Scientific Articles in PubMed Database. *Turk Thorac J*, *23*(1), 70–84. MEDLINE. https://doi.org/10.5152/TurkThoracJ.2022.21082

17. Fani, T., Saptorini, K. K., & Anggreani, A. D. (2022). The willingness of COVID-19 vaccination and associated factors: A systematic review. *South Eastern European Journal of Public Health*,
18. Scopus. https://doi.org/10.11576/seejph-5454

18. Galanis, P., Vraka, I., Katsiroumpa, A., Siskou, O., Konstantakopoulou, O., Katsoulas, T., Mariolis-Sapsakos, T., & Kaitelidou, D. (2022). First COVID-19 Booster Dose in the General Population: A Systematic Review and Meta-Analysis of Willingness and Its Predictors. *Vaccines*, *10*(7). https://doi.org/10.3390/vaccines10071097

19. Galanis, P., Vraka, I., Siskou, O., Konstantakopoulou, O., Katsiroumpa, A., & Kaitelidou, D. (2022). Willingness, refusal and influential factors of parents to vaccinate their children against the COVID-19: A systematic review and meta-analysis. *Prev Med*, *157*, 106994–106994. MEDLINE. https://doi.org/10.1016/j.ypmed.2022.106994

20. Garg, I., Hanif, H., Javed, N., Abbas, R., Mirza, S., Javaid, M. A., Pal, S., Shekhar, R., & Sheikh, A. B. (2021). COVID-19 Vaccine Hesitancy in the LGBTQ+ Population: A Systematic Review. *Infectious Disease Reports*, *13*(4), 872–887. https://doi.org/10.3390/idr13040079

21. Geng, H., Cao, K., Zhang, J., Wu, K., Wang, G., & Liu, C. (2022). Attitudes of COVID-19 vaccination among college students: A systematic review and meta-analysis of willingness, associated determinants, and reasons for hesitancy. *Human Vaccines & Immunotherapeutics*, *18*(5), 2054260. https://doi.org/10.1080/21645515.2022.2054260

22. Hajure, M., Tariku, M., Bekele, F., Abdu, Z., Dule, A., Mohammedhussein, M., & Tsegaye, T. (2021). Attitude Towards COVID-19 Vaccination Among Healthcare Workers: A Systematic Review. *Infect Drug Resist*, *14*, 3883–3897. MEDLINE. https://doi.org/10.2147/IDR.S332792

23. Hussain, B., Latif, A., Timmons, S., Nkhoma, K., & Nellums, L. B. (2022). Overcoming COVID-19 vaccine hesitancy among ethnic minorities: A systematic review of UK studies. *Vaccine*, *40*(25), 3413–3432. https://doi.org/10.1016/j.vaccine.2022.04.030

24. Januszek, S. M., Faryniak-Zuzak, A., Barnaś, E., Łoziński, T., Góra, T., Siwiec, N., Szczerba, P., Januszek, R., & Kluz, T. (2021). The Approach of Pregnant Women to Vaccination Based on a COVID-19 Systematic Review. *Medicina (Kaunas, Lithuania)*, *57*(9). https://doi.org/10.3390/medicina57090977

25. Kazeminia, M., Afshar, Z. M., Rajati, M., Saeedi, A., & Rajati, F. (2022). Evaluation of the Acceptance Rate of Covid-19 Vaccine and its Associated Factors: A Systematic Review and Meta-analysis. *Journal of Prevention (2022)*, *43*(4), 421–467. https://doi.org/10.1007/s10935- 022-00684-1

26. Kukreti, S., Rifai, A., Padmalatha, S., Lin, C.-Y., Yu, T., Ko, W.-C., Chen, P.-L., Strong, C., & Ko, N.-Y. (2022). Willingness to obtain COVID-19 vaccination in general population: A systematic review and meta-analysis. *Journal of Global Health*, *12*, 11–11. Web of Science. https://doi.org/10.7189/jogh.12.05006

27. Limbu, Y., Gautam, R., & Pham, L. (2022). The Health Belief Model Applied to COVID-19 Vaccine Hesitancy: A Systematic Review. *Vaccines*, *10*(6). https://doi.org/10.3390/vaccines10060973

28. Lin, G. S., Lee, H. Y., Leong, J. Z., Sulaiman, M. M., Loo, W. F., & Tan, W. W. (2022). COVID-19 vaccination acceptance among dental students and dental practitioners: A systematic review and meta-analysis. *PloS One*, *17*(4), e0267354. https://doi.org/10.1371/journal.pone.0267354

29. Luo, C., Yang, Y., Liu, Y., Zheng, D., Shao, L., Jin, J., & He, Q. (2021). Intention to COVID-19 vaccination and associated factors among health care workers: A systematic review and meta- analysis of cross-sectional studies. *American Journal of Infection Control*, *49*(10), 1295–1304. https://doi.org/10.1016/j.ajic.2021.06.020

30. Mekonnen, B. D., & Mengistu, B. A. (2022). COVID-19 vaccine acceptance and its associated factors in Ethiopia: A systematic review and meta-analysis. *Clinical Epidemiology and Global Health*, *14*, 101001. https://doi.org/10.1016/j.cegh.2022.101001

31. Mose, A., Wasie, A., Shitu, S., Haile, K., Timerga, A., Melis, T., Sahle, T., & Zewdie, A. (2022). Determinants of COVID-19 vaccine acceptance in Ethiopia: A systematic review and meta- analysis. *PLoS One*, *17*(6), e0269273–e0269273.

32. Nehal, K., Steendam, L., Campos Ponce, M., Van Der Hoeven, M., & Smit, G. S. (2021). Worldwide Vaccination Willingness for COVID-19: A Systematic Review and Meta-Analysis. *Vaccines*, *9*(10). http://www.epistemonikos.org/documents/a2cc44612ea7ce55e8327c630ac5e4b972a2a453

33. Nikpour, M., Sepidarkish, M., Omidvar, S., & Firouzbakht, M. (2022). Global prevalence of acceptance of COVID-19 vaccines and associated factors in pregnant women: A systematic review and meta-analysis. *Expert Review of Vaccines*, *21*(6), 843–851.

34. Nindrea, R. D., Usman, E., Katar, Y., & Sari, N. P. (2021). Acceptance of COVID-19 vaccination and correlated variables among global populations: A systematic review and meta- analysis. *Clinical Epidemiology and Global Health*, *12*, 100899.

35. Norhayati, M. N., Che Yusof, R., & Azman, Y. M. (2021). Systematic Review and Meta- Analysis of COVID-19 Vaccination Acceptance. *Frontiers in Medicine*, *8*, 783982.

36. Pragitara, C. F., Rahmasena, N., Ramadhani, A. T., Fauzia, S., Erfadila, R., Faraj, D. M. W., Ramadhanti, D. C. G., & Handayani, S. (2022). COVID-19 concerns, influenza vaccination history and pregnant women's COVID-19 vaccine acceptance: A systematic review. *International Journal of Public Health Science*, *11*(2), 490–502. Scopus. https://doi.org/10.11591/ijphs.v11i2.21187

37. Rawal, S., Tackett, R. L., Stone, R. H., & Young, H. N. (2022). COVID-19 vaccination among pregnant people in the United States: A systematic review. *American Journal of Obstetrics & Gynecology MFM*, *4*(4), 100616.

38. Restrepo, N., & Krouse, H. J. (2022). COVID-19 Disparities and Vaccine Hesitancy in Black Americans: What Ethical Lessons Can Be Learned? *Otolaryngol Head Neck Surg*, *166*(6), 1147– 1160.

39. Roy, D. N., Biswas, M., Islam, E., & Azam, M. S. (2022). Potential factors influencing COVID- 19 vaccine acceptance and hesitancy: A systematic review. *PloS One*, *17*(3), e0265496.

40. Salomoni, M. G., Di Valerio, Z., Gabrielli, E., Montalti, M., Tedesco, D., Guaraldi, F., & Gori, D. (2021). Hesitant or Not Hesitant? A Systematic Review on Global COVID-19 Vaccine Acceptance in Different Populations. *Vaccines*, *9*(8). http://www.epistemonikos.org/documents/15517bd36b0658d3acd90c0d680a310316b87e4e

41. Shakeel, C. S., Mujeeb, A., Mirza, M., Chaudhry, B., & Khan, S. J. (2022). Global COVID-19 Vaccine Acceptance: A Systematic Review of Associated Social and Behavioral Factors. *Vaccines*, *10*(1). http://www.epistemonikos.org/documents/a5802fc8c7ba211b8f932dc7ed103973b81c7bfc

42. Shamshirsaz, A. A., Hessami, K., Morain, S., Afshar, Y., Nassr, A. A., Arian, S. E., Asl, N. M., & Aagaard, K. (2022). Intention to Receive COVID-19 Vaccine during Pregnancy: A Systematic Review and Meta-analysis. *American Journal of Perinatology*, *39*(5), 492–500. https://doi.org/10.1055/a-1674-6120

43. Snehota, M., Vlckova, J., Cizkova, K., Vachutka, J., Kolarova, H., Klaskova, E., & Kollarova, H. (2021). Acceptance of a vaccine against COVID-19—A systematic review of surveys conducted worldwide. *Bratisl Lek Listy*, *122*(8), 538–547.

44. Veronese, N., Saccaro, C., Demurtas, J., Smith, L., Dominguez, L. J., Maggi, S., & Barbagallo, M. (2021). Prevalence of unwillingness and uncertainty to vaccinate against COVID-19 in older people: A systematic review and meta-analysis. *Ageing Research Reviews*, *72*, 101489.

45. Wake, A. D. (2021a). The Acceptance Rate Toward COVID-19 Vaccine in Africa: A Systematic Review and Meta-analysis. *Global Pediatric Health*, *8*, 2333794X211048738.

46. Wake, A. D. (2021b). The Willingness to Receive COVID-19 Vaccine and Its Associated Factors: "Vaccination Refusal Could Prolong the War of This Pandemic"—A Systematic Review. *Risk Manag Healthc Policy*, *14*, 2609–2623. MEDLINE. https://doi.org/10.2147/RMHP.S311074

47. Wang, Q., Yang, L., Jin, H., & Lin, L. (2021). Vaccination against COVID-19: A systematic review and meta-analysis of acceptability and its predictors. *Preventive Medicine*, *150*, 106694.

48. Yasmin, F., Najeeb, H., Moeed, A., Naeem, U., Asghar, M. S., Chughtai, N. U., Yousaf, Z., Seboka, B. T., Ullah, I., Lin, C.-Y., & Pakpour, A. H. (2021). COVID-19 Vaccine Hesitancy in the United States: A Systematic Review. *Front Public Health*, *9*, 770985–770985.

49. Yazdani, A., Mirmosayyeb, O., Ghaffary, E. M., Hashemi, M. S., & Ghajarzadeh, M. (2022). COVID-19 vaccines and patients with multiple sclerosis: Willingness, unwillingness and hesitancy: A systematic review and meta-analysis. *Neurological Sciences : Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *43*(7), 4085–4094

5. TABLE 3 - AMSTAR

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." [57] It is usually used when developing and conducting high-quality reviews. For this umbrella review, we have selected from AMSTAR 2 the questions that fit our research goals and modified domains considered critical to the quality of a given review accordingly, as follows:

1. (Former #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. *(Former #4). Did review authors use a comprehensive literature search strategy?*
3. (Former #5). Did review authors perform study selection in duplicate?
4. (Former #6). Did review authors perform data extraction in duplicate?
5. *(Former #10). Did review authors report on sources of funding in included studies?*
6. (Former #16). *Did review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?*

Three domains were considered critical to our review because they provide evidence that the authors of a given review made a good faith effort to capture the broadest range of perspectives on the phenomenon of interest and revealed their own and others' conflicts of interest or funding sources. Our phenomenon of interest, rather than the methodological quality of inquiries into vaccine hesitancy, was to capture how the risk-benefit ratio, safety, and side effects concerns of patients are addressed in the literature, thus our choice of critical domains:

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

We followed the original AMSTAR and did not rate individual items for an overall score but rather considered each domain 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 weakness

6. TABLE 4 – TABLE OF KEY STUDY CHARACTERISTICS

ID	1st Author	Year	1st Author Location	Study Location	Study Type	Population
1	Geng	2022	China	No restrictions	Quantitative	Students aged 18 and above
2	Ergün	2021	Turkey	No restrictions	Quantitative	No restrictions
3	Shakeel	2022	Pakistan	No restrictions	Quantitative	No restrictions
4	Limbu	2022	USA	No restrictions	Quantitative	No restrictions
5	Salomoni	2021	Italy	No restrictions	Quantitative	No restrictions
6	Dhanani	2022	USA	No restrictions	Quantitative	No restrictions
7	Cascini	2022	Italy	No restrictions	Qualitative	No restrictions
8	Lin	2022	Malaysia	No restrictions	Quantitative	Dental students
9	Januszek	2021	Poland	No restrictions	Quantitative	Pregnant women
10	Nehal	2021	Netherlands	No restrictions	Quantitative	No restrictions
11	Restrepo	2021	USA	USA	Qualitative	Black Americans
12	Cascini	2021	Italy	No restrictions	Quantitative	No restrictions
13	Wake	2021	Ethiopia	No restrictions	Quantitative	No restrictions
14	Ackah	2022	Ghana	Africa	Quantitative	HCWs and health science students from Africa
15	Mose	2022	Ethiopia	Ethiopia	Quantitative	Ethiopians
16	Fani	2022	Indonesia	No restrictions	Quantitative	No restrictions
17	Bayou	2022	Ethiopia	Ethiopia	Quantitative	Ethiopians
18	Pragitara	2022	Indonesia	No restrictions	Quantitative	Pregnant women
19	Kukreti	2022	Taiwan	No restrictions	Quantitative	No restrictions
20	Chen	2022	China	No restrictions	Quantitative	Parents and guardians
21	Yasmin	2021	Pakistan	USA	Quantitative	USA population
22	Hajure	2021	Ethiopia	No restrictions	Quantitative	HCWs
23	Snehota	2021	Czech Republic	No restrictions	Quantitative	No restrictions
24	Veronese	2021	Italy	No restrictions	Quantitative	Older adults
25	Bianchi	2022	Italy	Italy	Quantitative	Italian HCWs
26	Rawal	2022	USA	USA	Quantitative	USA pregnant women
27	Bianchi	2022	Italy	No restrictions	Quantitative	Pregnant women
28	Yazdani	2022	Iran	No restrictions	Quantitative	Multiple sclerosis patients
29	Shamshirsaz	2021	USA	No restrictions	Quantitative	Pregnant women
30	Batteux	2022	UK	No restrictions	Qualitative	No restrictions
31	Galanis	2022	Greece	No restrictions	Quantitative	Parents
32	Wang	2021	China	No restrictions	Quantitative	No restrictions
33	Al-Amer	2021	Jordan	No restrictions	Mixed	HCWs and general population
34	Luo	2021	China	No restrictions	Quantitative	HCWs
35	Nindrea	2021	Indonesia	No restrictions	Quantitative	No restrictions
36	Wake	2021	Ethiopia	Africa	Quantitative	African adults
37	Garg	2021	USA	No restrictions	Quantitative	LGBTQ+ communities

ID	1st Author	Year	1st Author Location	Study Location	Study Type	Population
38	Norhayati	2022	Malaysia	No restrictions	Quantitative	No restrictions
39	Alarcón-Braga	2022	Peru	Latin America and Caribbean	Quantitative	Latin America and Caribbean
40	Roy	2022	Bangladesh	No restrictions	Quantitative	No restrictions
41	Mekonnen	2022	Ethiopia	Ethiopia	Quantitative	Ethiopians
42	Nikpour	2022	Iran	No restrictions	Quantitative	Pregnant women
43	Alemayehu	2022	Ethiopia	East Africa	Quantitative	East Africans
44	Kazeminia	2022	Iran	No restrictions	Quantitative	No restrictions
45	Abba-Aji	2022	Nigeria	No restrictions	Qualitative	Ethnic minorities and migrants
46	Dadras	2022	Thailand	Middle East and North Africa	Quantitative	Middle East and North Africa
47	Hussain	2022	Pakistan	UK	Qualitative	Ethnic minorities in UK
48	Galanis	2022	Greece	No restrictions	Quantitative	No restrictions
49	Carbone	2021	Italy	No restrictions	Quantitative	Pregnant women