BMJ Open

COVID-19 vaccine hesitancy in periconceptional and lactating women: a systematic review and meta-analysis protocol

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To cite: Su X, Lu H, Li X, *et al*. COVID-19 vaccine hesitancy in periconceptional and lactating women: a systematic review and meta-analysis protocol. *BMJ Open* 2022;**12**:e059514. doi:10.1136/bmjopen-2021-059514

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-059514).

Received 23 November 2021
Accepted 30 September 2022

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ABSTRACT

Introduction The pandemic of COVID-19 disease has caused severe impact globally. Governments consider vaccination as an effective measure to control pandemic. However, many people have been hesitant to receive COVID-19 vaccine, particularly periconceptional and lactating women. Although research has indicated that pregnant women with COVID-19 are at a higher risk of adverse pregnancy and birth outcomes, as well as severe illness. There appears to be a lack of systematic and comprehensive evidence of the prevalence and determinants of COVID-19 vaccine hesitancy among periconceptional and lactating women. As a result, it has been essential to investigate periconceptional and lactating women's vaccination views and behaviours. This study will review articles on vaccine hesitancy among periconceptional and lactating women to assess the impact of the COVID-19 vaccine hesitancy during the pandemic.

Methods and analysis We will systematically search observational studies from 1 November 2019 to 30 October 2021 in the following databases: Web of Science, PubMed, EMBASE, MEDLINE, Cochrane Library, EBSCO, WHO COVID-19 Database, CNKI and WanFang Database. The following medical subject headings and free-text terms will be used: "COVID-19 vaccines" AND "female" AND "vaccine hesitancy". Eligibility criteria are as follows: population (women of reproductive age); exposure (currently pregnant, lactational or trying to get pregnant); comparison (general women who are not in preconception, gestation or lactation) and outcome (the rate of COVID-19 vaccine hesitancy). Article screening and data extraction will be undertaken independently by two reviewers, and any discrepancy will be resolved through discussion. We will use I^2 statistics to assess heterogeneity and perform a meta-analysis when sufficiently homogeneous studies are provided. We will explore the potential sources of heterogeneity using subgroup and meta-regression analysis.

Ethics and dissemination This study will use published data, so ethical approval is not required. The findings will be disseminated by publication in peer-reviewed journal(s).

PROSPERO registration number CRD42021257511.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The systematic review will be guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.
⇒ This review will synthesise evidence of COVID-19 vaccine hesitancy among periconceptional and lactating women.
⇒ This review will glean out evidence from all WHO regions.
⇒ To our knowledge, this will be the first systematic review to assess the impact of periconception and lactation on the COVID-19 vaccine hesitancy in women during COVID-19 pandemic.
⇒ One limitation of this study may be the potentially misleading of potential biases from the original studies in observational studies.

INTRODUCTION

According to WHO, the COVID-19, caused by the SARS-CoV-2, resulted in 255 324 963 confirmed cases of COVID-19 and 5 127 696 deaths worldwide.[1] Because of the severity of pandemic, governments believe that vaccination is an effective measure to control pandemic. So far, eight COVID-19 vaccines have been added to the emergency use listing, and 7 370 902 499 vaccine doses have been administered.[2] Historically, immunisation has been a public health success method due to its ability to prevent infectious diseases.[3] However, for various reasons, many people have recently declined immunisation.[4–6] This evolving problem of vaccine hesitancy and the challenge it could pose to global health has been declared as one of the top 10 global health threats by WHO.[7] The WHO defines vaccine hesitancy as 'a delay in acceptance or refusal of vaccines despite the availability of vaccine services'. Vaccine hesitancy is a major hurdle for stopping the COVID-19 pandemic, particularly among the periconceptional and lactating women.

Epidemiological and experimental studies have shown that periconception (the period prior to and during conception)[8] and lactation are particularly vulnerable periods for infection.[9 10] Pregnant women with COVID-19 are at a higher risk of morbidity and mortality from COVID-19, as well as adverse pregnancy and birth outcomes compared with age-matched non-pregnant women.[11–15] Physiological changes during pregnancy may have a positive or negative effect on the progression of COVID-19 disease.[16] Although there is some disagreement about the vertical transmission of COVID-19, studies show that it is possible.[10] Surveillance and research have demonstrated vaccine efficacy among pregnant and breastfeeding women, as well as placental and breast milk antibody transfer to offspring.[17] As a consequence, it is recommended by the Centers for Disease Control and Prevention and several professional medical organisations that any female who is pregnant, planning to become pregnant, or is currently breastfeeding get vaccinated against COVID-19 as soon as possible.[18] Nevertheless, many periconceptional and lactating women are hesitant to accept COVID-19 vaccine due to vaccine-specific safety concerns and adverse effects on the fetus and breast feeding.[19] Vaccine hesitancy studies have revealed that on account of rumours circulating widely on diverse social media platforms regarding the vaccines adversely affecting fertility and pregnancy, higher hesitancy rates have been associated with the female gender.[20] It is worth noting that periconceptional and lactating women exhibited higher vaccine hesitancy than the general population.[21–24] However, these claims are anecdotal, with unavailable scientific evidence to support them.

Systematic reviews and meta-analysis are comprehensive reviews of existing survey work and fundamental to evidence-based healthcare because they provide the highest evidence to inform decision making.[25 26] There has been no systematic review of the potential role of COVID-19 vaccine hesitancy among periconceptional and lactating women. One of the most critical questions that remain to be answered is whether periconceptional women exhibit a higher hesitancy rate for COVID-19 vaccines or what causes vaccine hesitancy. As a result, we decided to conduct a systematic review and meta-analysis to understand better the magnitude and nature of COVID-19 vaccine hesitancy in periconceptional and lactating women and facilitate the development of vaccination strategies at the individual and population levels.

Objective

To assess the impact of periconception and lactation on the COVID-19 vaccine hesitancy in women during COVID-19 pandemic.

METHODS AND ANALYSIS

Study design

This study will be reported based on the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) statement[27] and Meta-analysis of Observational Studies in Epidemiology.[28] The protocol for this review was registered to the International Prospective Register of Systematic Reviews (ID: CRD42021257511).

Types of eligible studies

All observational studies (cohort studies, cross-sectional studies and case–control studies) will be considered for this review. The clinical trials were excluded because the participant's original ideas determined vaccine hesitancy without human intervention. These studies should also report the hesitancy rate of COVID-19 vaccine trial among periconceptional or lactating women. There will be no language restriction for study eligibility. In addition, the most up-to-date and comprehensive version will be selected for studies. Articles with no access to the full text or studies with insufficient or incomplete data will be excluded from this study.

Participants

Inclusion criteria included the following: women who are currently pregnant, are currently in lactation period, are currently trying to get pregnant or are planning to get pregnant within the next 6 months.

Exclusion criteria included the following: women who are not pregnant, recently or are not planning it for the next 6 months.

Comparators

The comparator group will be the internal study controls or general women who are not in preconception, gestation and lactation.

Primary outcome

The rate of COVID-19 vaccine hesitancy in periconceptional and lactating women. Vaccine hesitancy was defined as vaccine refusal despite availability of vaccination services, vaccination delay until the end of periconceptional or lactational period, and incomplete vaccination including incomplete primary series and booster vaccination.

Secondary outcomes

Secondary outcomes which will be considered include: (1) race and country/region of periconceptional and lactation women; (2) literacy and career of periconceptional and lactation women; (3) age, obstetrical history and time to pregnancy (TTP) of periconceptional and lactation women.

Information sources and search strategy

The following databases will be searched by two independent reviewers: Web of Science, PubMed, EMBASE, MEDLINE, Cochrane Library, EBSCO, WHO COVID-19 Database, China National Knowledge Infrastructure (CNKI) and WanFang Database. As we aim to examine both the scientific and grey literature, we will also search Google and Google Scholar in addition to the mainstream and regional databases listed earlier. We will search for

Table 1 Search strategy for the PubMed

No	Search terms
#1	Vaccin*
#2	Hesita* OR Refus* OR reluctan* OR Attitude* OR Accept* OR Behaviour OR Non-vaccin* OR Uptake
#3	#1 and #2
#4	Immuni*
#5	#3 OR #4
#6	Novel Coronavirus OR SARS-CoV-2 OR COVID-19 OR COVID-19 disease
#7	COVID-19 Vaccines [MeSH Terms]
#8	#6 OR #7
#9	Female [MeSH Terms] OR Women [MeSH Terms]
#10	Perinatology [MeSH Terms] OR Peripartum Period [MeSH Terms] OR Postpartum Period [MeSH Terms] OR Perinat* OR Lactat* OR Suck*
#11	Pregnancy [MeSH Terms] OR Pregnant Women [MeSH Terms] OR Pregnan*
#12	Preconception* OR Prepregnan*
#13	#9 OR #10 OR #11
#14	Observational study
#15	Cohort study
#16	Cross-sectional study
#17	Case–control study
#18	#14 OR #15 OR #16 OR #17
#19	#5 and #8 and #13 and #18

relevant articles in the reference lists of selected studies and relevant reviews and identify additional papers that are not indexed in the databases included. A systematic search strategy will be employed to identify articles from the start of the pandemic in 1 November 2019 to 30 October 2021, with no language restrictions; the non-English articles will be translated. Before submitting the manuscript, new searches will be conducted to represent more target populations. The search term will combine Medical Subject Headings with accessible text to look for terms like “COVID-19 vaccines” and “vaccine hesitancy”. A detailed search strategy for PubMed is described in table 1, and it will be adapted for other databases as appropriate and then double-checked by another reviewer. We will also request and screen unpublished manuscripts and thesis, as well as make contact with researchers.

Study selection

As described in detail previously,[29] all the citations retrieved from the database searches will be imported into EndNote V.X9.1 software, and duplicate records will be removed. Two reviewers will independently screen titles and abstracts for the first level of filtering and remove non-conforming studies based on the study eligibility criteria. Full text of eligible articles passing the first level of filtering will be independently screened. A third reviewer will cross-check the studies according to the predetermined inclusion and exclusion criteria to determine their final inclusion. We will examine the included and excluded studies, and verify the reasons for each decision. Consensus meetings will be held at each stage, and the third reviewer will take part in the solution if discrepancies arise. As figure 1 shows, the selection of studies is summarised in a PRISMA flow diagram.

Data extraction

Once studies included, two independent reviewers will use a standard extraction form to extract data. Extracted data will include: first author, year of publication, study location (country/region), policies regarding vaccination (mandatory or not within the research context and manufacturers of available vaccines), research design, aim(s), population characteristics (age, race, literacy, career and obstetrical history), sample type and size, comparator characteristics, the rate of vaccine refusal and delay, follow-up and primary and secondary results, source(s) of funding and reported conflicts of interest, and other information relevant to the review questions. All data will be synthesised in narrative and tabular formats.

Quality and bias assessment

Two reviewers will independently assess the methodological quality of included studies using appropriate tools. The Newcastle-Ottawa Scale (NOS) will be used to evaluate the quality of cohort and case–control studies.[30] A study is evaluated on NOS using three broad criteria: the selection of study groups; the comparability of groups and the ascertainment of either the exposure or outcome of interest for case–control or cohort studies respectively. In NOS, a ‘star system’ has been developed with a maximum score of 9 stars. The Agency for Healthcare Research and Quality (AHRQ) methodology checklist will be applied to assess the quality of cross-sectional studies.[31] In total, 11 questions on AHRQ checklist will be answered with ‘yes’, ‘no’ or ‘unclear’ A table containing those risks will be created. The certainty of evidence will be rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, and findings will be presented in GRADE evidence profiles and summary of findings tables using standardised terms.[32] GRADE tool categorises the studies as low, moderate or high quality. This evaluation will be completed independently by two authors, and any disagreements will be resolved through discussion or consultation with a third reviewer.[33]

Data analysis

We will use Review Manager software (V.5.3) to perform statistical analyses. The D’Agostino & Pearson omnibus normality test will be used to validate the normal distribution of data. Dichotomous data will be analysed by using the risk ratio or ORs.[34] As described in detail previously,[35] continuous outcomes data measured on the same scale will be expressed as a mean value and SD and be analysed by using weighted mean differences. The study-specific

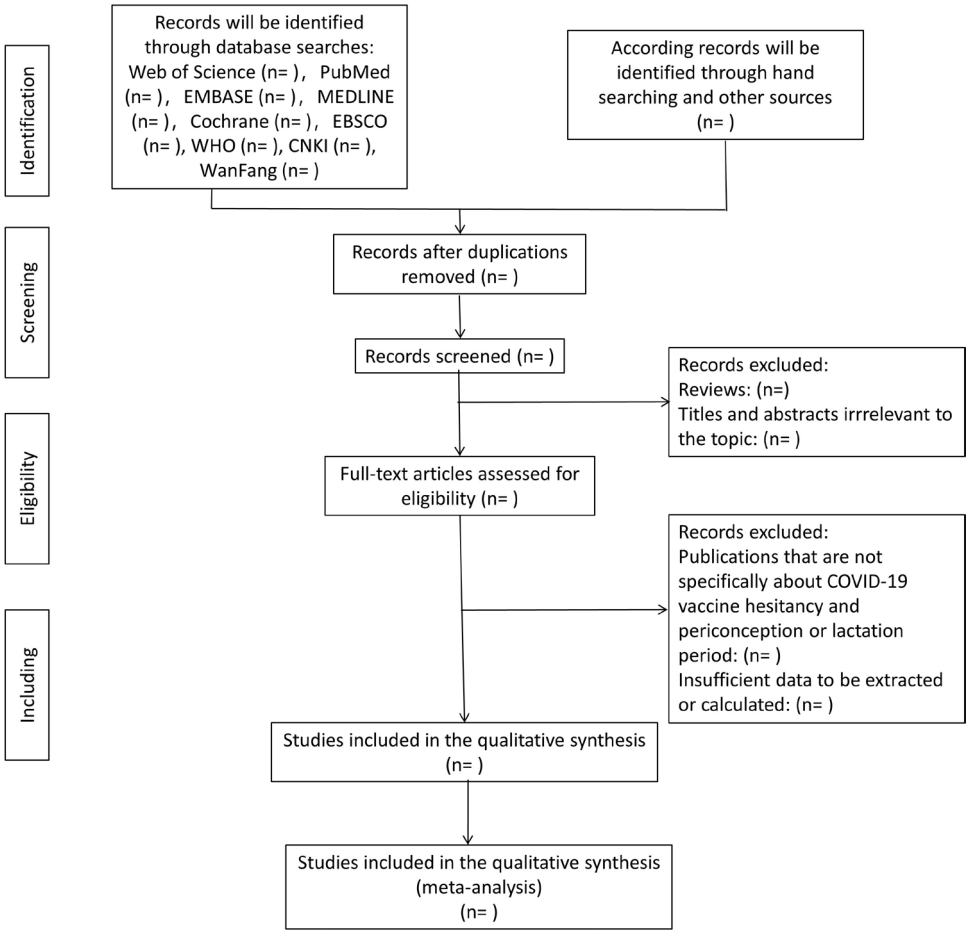

Figure 1 PRISMA flow chart of the study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

estimates with 95% CI will be pooled to produce an overall hesitancy rate across the chosen studies. All statistical tests will be two tailed, and a $p<0.05$ will be considered statistically significant. The heterogeneity of estimates will be then evaluated by using the χ^2 test (Q) and I^2 statistics. Q statistic will be conducted to find the presence of heterogeneity, and I^2 test will be conducted to calculated percentage of variation of heterogeneity. The outcome variable is considered statistically significant when the Q value is >0.05. The I^2 value of <50% indicates a non-significant level of heterogeneity, and a fixed-effect model will be used to the meta-analysis. The I^2 value of >50% indicates a significant level of heterogeneity, and a random-effects model will be chosen. When substantial heterogeneity is detected, we will use subgroup analysis and meta-regression analysis to investigate sources of heterogeneity. For the hesitancy rate of COVID-19 vaccine trial among periconceptional and lactating women, forest plots will be built. Subgroup and sensitivity analyses will be performed where there are sufficient data to do so. Where studies allow, we will descriptively compare COVID-19 vaccine hesitancy rate by the following subgroups: age, country/region, obstetrical history, time to TTP and education. Funnel plots, Egger's regression and will be used to investigate publication bias.

Patient and public involvement

There was no patient and public involved.

Ethics and dissemination

Ethical approval is not required as this study will use published data rather than any involvement of participants. Results will be disseminated via the publication of the manuscript in peer-reviewed journal(s) and presentations at scientific conferences. If there is new evidence that may cause any changes in the conclusions of the review, we will conduct an update.

DISCUSSION

Some reports have speculated that COVID-19 may become another common cold coronavirus much like the influenza.[36] In continuous outbreaks of COVID-19, vaccination is an effective measure to interrupt transmission. Nevertheless, vaccine hesitancy against COVID-19 is estimated to be nearly one-third.[37] 'Vaccine hesitancy' is one barrier against full population inoculation.[38] It has been reported that special period such as periconception and lactation negatively affect female COVID-19 vaccine acceptance. However, there is an urgent need for further secondary analysis to confirm the impact, and

effective interventions to eliminate COVID-19 vaccine hesitancy in periconceptional and lactating women must be implemented.

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Contributors XS and HL conceptualised and designed this study. The manuscript of the protocol was drafted by XS and critically revised by HL and XL. The search strategy was developed by XS and XL. ML and FL will conduct the study selection. QZ and ML will be in charge of data extraction, and statistical analysis will be performed by XS, FL and ML. HL will be the third party and host consensus meetings at each stage in case of disagreement. All authors read, revised and approved the final manuscript.

Funding This study was supported by the Ministry of Science and Technology of the People's Republic of China (Grant number: 2018YFC1704305) and Sichuan Provincial Administration of Traditional Chinese Medicine (Grant number: 2022C003).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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