Commentary

Title: Safe in Pregnancy: A Global Living Systematic Review and Meta-Analysis of COVID-19 Vaccines in Pregnancy.

Authors: Pierre Buekens,[a] Mabel Berrueta,[b] Agustín Ciapponi[b,c] Ariel Bardach,[b,c] Agustina Mazzoni,[b] Federico Rodriguez-Cairoli,[b] Sami L. Gottlieb,[d] Beate Kampmann,[e,f] Edward P. K. Parker,[e] Xu Xiong,[a] Sabra Zaraa,[g] Andy Stergachis.[g,h]

Affiliations:

[a] Department of Epidemiology, Tulane School of Public Health and Tropical Medicine, New Orleans, Louisiana, USA

[b] Instituto de Efectividad Clínica y Sanitaria, Buenos Aires, Argentina

[c] Center for Research in Epidemiology and Public Health, CONICET, Buenos Aires, Argentina

[d] Department of Sexual and Reproductive Health, World Health Organization, Geneva, Switzerland

[e] Vaccine Centre, Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK

[f] Charite Centre for Global Health, Charité Universitätsmedizin, Berlin, Germany

[g] Comparative Health Outcomes, Policy, Economics (CHOICE) Institute, School of Pharmacy, University of Washington, Seattle, Washington, USA

[h] Department of Global Health, School of Public Health, University of Washington, Seattle, Washington, USA

Corresponding Author:

Pierre Buekens, MD
W. H. Watkins Professor of Epidemiology
School of Public Health and Tropical Medicine, Tulane University
1440 Canal St., Suite 2001, New Orleans, LA 70112, USA
Email: pbuekens@tulane.edu

Word Count: 619

Authors' Contributions: All authors participated equally in the conceptualization. PB and AS wrote the initial draft. All authors critically reviewed the manuscript. MB and AC accessed and verified the underlying data reported in the manuscript.

Funding Sources: Funded by the Bill & Melinda Gates Foundation (INV-008443). The funding source had no involvement in the study design, the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit for publication.

Acknowledgements: We thank Ros Hollingsworth for her support.

Pregnant persons are a high priority-use group for COVID-19 vaccination, given their higher risk of maternal and perinatal complications and death following COVID-19 infections in pregnancy.(1, 2) However, global coverage of COVID-19 vaccines in pregnancy remains low and several countries still do not recommend the vaccines in pregnancy.(3,4) One of the challenges for policymakers and clinicians is access to the rapidly growing literature on COVID-19 vaccines in a user-friendly, synthesized format from trustworthy sources. Living systematic reviews continuously update the relevant literature, incorporating new evidence as it becomes available and making the evidence more accessible to decision makers. We are conducting a living systematic review and meta-analysis of COVID-19 vaccines in pregnancy, which assesses vaccine safety, immunogenicity, efficacy and effectiveness in pregnant persons and their infants (PROSPERO ID=CRD42021281290) via an interactive online database (https://safeinpregnancy.org/lsr/).(5, 6) This project is supported by a diverse, expert Scientific and Technical Advisory Group (STAG).(6) We presently report data on more than half a million vaccinated pregnant persons across 26 countries. The database is updated every two weeks to provide rapid access to up-to-date information.

As of May 1, 2023, our living systematic review identified 6,748 potentially eligible published articles and pre-prints. Of these, 138 studies including 519,741 observations of vaccinated pregnant persons are included in the online database. All included studies to date are observational designs, of which 84 were comparative cohort studies. Most of the articles (N=123) reported data on mRNA vaccines. Only 19 (13.7%) studies included data from low- and middle-income countries (LMICs) (Figure 1). The web-based interface yields automated meta-analyses of outcomes of interest by user-selected subgroups. To obtain the best available

estimations for the meta-analyses only papers that reported adjusted effect measures comparing pregnant persons vaccinated against COVID-19 during pregnancy with never-vaccinated pregnant persons in the same setting are included. Among 138 studies, 32 studies with 244,683 pregnant persons vaccinated were eligible for meta-analysis through May 1, 2023.

We found that for vaccinated pregnant persons and their infants, there was no association between vaccination during pregnancy and increased risk of adverse events of special interest in pregnancy and infants (e.g., spontaneous abortion, cesarean section, instrumental delivery, hypertensive disorders, congenital malformations, preterm birth, low Apgar score, neonatal intensive care unit admission, stillbirth, and neonatal death). This confirms our earlier systematic review.(7) The vaccine effectiveness (VE) of the primary series complete schedule for maternal hospital admission due to COVID-19 was 89% (95% confidence interval (CI) 43-98%) for the pre-Omicron period, 98% (95% CI 96-99%) for Delta variant and 77% (95% CI 26-93%) for the Omicron variant. The VE of a booster dose for the same outcome was 97% (95% CI 81-100%) for Delta variant and 76% (95% CI 28-92%) for the Omicron variant.

Rapidly available, up-to-date information that can address critical ongoing issues is important for guiding policy decisions in the setting of an evolving pandemic. Our living systematic review includes only observational studies, as no randomized controlled trial assessing COVID-19 vaccines during pregnancy has been completed to date. The exclusion of pregnant and lactating persons from initial COVID-19 vaccine clinical trials resulted in delayed access of this population to the vaccines after emergency use authorization was granted and contributed to the variability in policy recommendations.(8) Although observational studies are beginning to fill this evidence gap, the vast majority of available data are on mRNA vaccines. Data from other

COVID-19 vaccine types and from LMICs are urgently required to overcome challenges for policymakers. Despite these limitations, data through our living systematic review are now available for more than half a million vaccinated pregnant persons and show that COVID-19 vaccines have a favorable safety and effectiveness profile in pregnancy. There is no time to lose to increase the global use of COVID-19 vaccines in pregnancy.

Caption

Figure 1: Countries participating in observational studies on COVID-19 vaccines and pregnancy.(6)

References

1. Ciapponi A, Bardach A, Comandé D, Berrueta M, Argento FJ, Rodriguez Cairoli F, et al. COVID-19 and pregnancy: An umbrella review of clinical presentation, vertical transmission, and maternal and perinatal outcomes. PLoS One. 2021;16(6):e0253974.

2. WHO. WHO SAGE Roadmap for prioritizing uses of COVID-19 vaccines Geneva, Switzerland: WHO; 2023 Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-Vaccines-SAGE-Roadmap. Accessed July 7, 2023.

3. Lara Lona E, Magos Vázquez FJ, Paternina-Caicedo A, Buekens P. Letter to the editor: COVID-19 vaccination uptake among pregnant individuals in a middle-income setting. Int J Gynaecol Obstet. 2023;160(1):351-2.

4. Covid-19 Maternal Immunization Tracker (COMIT). Available from: https://www.comitglobal.org/. Accessed July 7, 2023.

5. Ciapponi A, Berrueta M, Ballivian J, Bardach A, Mazzoni A, Anderson S, et al. Safety, immunogenicity, and effectiveness of COVID-19 vaccines for pregnant persons: A protocol for systematic review and meta analysis. Medicine (Baltimore). 2023;102(9):e32954.

6. COVID-19 Vaccines for Pregnant Persons: A Living Systematic Review and Meta-Analysis: Tulane University, IECS, London School of Hygiene and Tropical Medicine, University of Washington; 2023 Available from: https://www.safeinpregnancy.org/lsr/. Accessed July 7, 2023.

7. Ciapponi A, Berrueta M, P K Parker E, Bardach A, Mazzoni A, Anderson SA, et al. Safety of COVID-19 vaccines during pregnancy: A systematic review and meta-analysis. Vaccine. 2023;41(25):3688-3700.

8. Maykin MM, Heuser C, Feltovich H. Pregnant people deserve the protection offered by SARS-CoV-2 vaccines. Vaccine. 2021;39(2):171-2.