Reproductive Health

COMMENT

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A global living systematic review and meta-analysis hub of emerging vaccines in pregnancy and childhood

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Abstract

The COVID-19 pandemic accelerated vaccine development and generated a rapidly evolving body of evidence before and after the vaccine rollout. We developed a robust online platform to efficiently synthesize this emerging information for current and future challenges. Expanding upon our interactive living systematic review—initially focused on COVID-19— we now include chikungunya and Lassa fever (with protocols presented in this issue), Mpox, and Disease X (https://www.safeinpregnancy.org). We aim to continuously monitor and periodically update and disseminate high-quality data on vaccine safety, efficacy, effectiveness, and immunogenicity in pregnancy and childhood. This platform computes real-time meta-analyses and features a visualization tool to present findings in a clear and accessible manner, supporting decision-making, vaccine development pipelines, and implementation strategies worldwide. It is also designed to integrate data on a hub of emerging vaccines in pregnancy and childhood and reflects a collaborative effort among multiple organizations.

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Background

The COVID-19 pandemic led to an unprecedented acceleration in vaccine development, accompanied by a rapidly expanding body of evidence. Yet, pregnant individuals and children were frequently excluded from early trials, leaving crucial gaps in safety and effectiveness data for these at-risk groups [1]. This scenario highlighted the need for timely, high-quality evidence to guide vaccine development and equitable access [2–6]. Although the acute phase of the pandemic has passed, the lessons it taught remain vital—particularly the importance of generating robust benefit-risk assessments throughout the vaccine lifecycle. Early stages require insight from preclinical and indirect data (e.g., platform technologies or adjuvants). At the same time, subsequent phases must

synthesize evolving clinical trial results and real-world evidence to inform policy and public trust [7].

Living systematic reviews (LSRs) offer an effective framework for this process. LSRs support dynamic decision-making across research, regulation, and implementation by continuously updating literature searches and evidence synthesis. They are particularly useful in under-resourced settings where data gaps persist [8]. Our approach consolidates data from high-income and low- to middle-income countries, shedding light on critical gaps in under-resourced settings. By offering a user-friendly evidence map and real-time meta-analyses based on trusted sources, we aim to support decision-making across vaccine development pipelines and implementation strategies worldwide.

To facilitate the rapid synthesis of emerging evidence, we developed an integrated web platform for current and future infectious disease threats. Initially focused on COVID-19 vaccines in pregnancy, our LSR has expanded to include vaccines for chikungunya, Lassa fever, Mpox, and Disease X, particularly for pregnant individuals and children. This initiative is dedicated to continuously gathering and evaluating data on vaccine safety, efficacy/effectiveness, and immunogenicity.

We developed an integrated online platform initially focused on COVID-19 vaccines in pregnancy to address this need. This LSR has since expanded to include vaccines for chikungunya, Lassa fever, Mpox, and Disease X, focusing on pregnancy and childhood populations. This issue contains detailed protocols for two new LSRs, focusing on chikungunya (CRD42024514513, CRD42024516754) [9] and Lassa fever (CRD42024554330, CRD42024556977) [10], which will serve as foundational frameworks for synthesizing emerging evidence. These diseases, prioritized for their public health impact, exemplify the importance of real-time, context-specific evidence to inform future responses.

Chikungunya has recently surged in the Americas, with over 214,000 cases reported in early 2023 [11]. The virus presents a significant burden due to its potential for severe congenital infections and long-term neonatal complications [12]. In August 2023, the first Chikungunya vaccine IXCHIQ™ (VLA1553, Valneva live attenuated vaccine) was approved in the United States [13, 14], marking a pivotal step in addressing this disease. More recently, on February 14, 2025, the U.S. FDA approved VIMKUNYA™ (Bavarian Nordic Chikungunya Vaccine, Recombinant) for individuals aged 12 and older, presenting a major milestone in Chikungunya prevention [15]. This underscores the urgent need for further data on vaccine safety and efficacy, particularly in pregnant women and children, as the risk of chronic morbidity and adverse pregnancy outcomes remains a significant concern. Moreover, climate change is expanding the range of mosquito-borne diseases, increasing the urgency of targeted interventions, including vaccines.

Lassa fever, caused by the Lassa virus and transmitted through contact with rodents, is endemic in West Africa [16] and has been designated as a priority for research and development by the World Health Organization (WHO) [3]. The disease is associated with an estimated 5,000 deaths annually and high mortality rates, particularly in pregnant women (29% maternal mortality in the third trimester) [17, 18] and neonates (87% fetal/neonatal death) [19]. Despite the urgent need for immunization, no approved vaccine is currently available. However, clinical trials are underway, with phase 2 studies in progress to evaluate vaccine candidates [20]. Ensuring the collection of robust safety and efficacy data, especially in children and pregnant women, remains a critical priority.

Evidence synthesis approach

Drawing on our previous experience with a LSR of COVID-19 vaccines administered during pregnancy, we have broadened the project to encompass vaccines for pregnant persons and children against other emerging infectious diseases (https://www.safeinpregnancy.org/) [21, 22]. Our review expanded to include vaccines against pathogens such as chikungunya, Lassa fever, and mpox, which present significant risks in various regions and have the potential for broader transmission. To gather pertinent information, we examine data about vaccine platforms and develop flexible protocols and search strategies that can be swiftly adjusted to address emerging threats. It is important to note that COVID-19 remains a global public health concern and remains in our LSR platform, with immunization coverage during pregnancy still low in several regions [23]. Overcoming barriers to adopting new, effective vaccines poses an even more significant challenge.

Our methodological approach, fully described in the protocols published in this issue [9, 10], based on Cochrane methods for these LSRs and meta-analyses, follows several key steps outlined in our initial article [24]. First, we perform exhaustive searches of published and grey literature across multiple databases—including the Cochrane Library, MEDLINE, EMBASE, LILACS, and Chinese databases—ensuring that studies are captured without language restrictions over relevant periods. Second, after a title and abstract screening accelerated by Nested Knowledge, pairs of authors independently select articles by full text. This web-based software, powered by artificial intelligence, facilitated the dual independent screening by a reviewer and robot screener after training the model with 50 records. Disagreements between humans and the robot were resolved by consensus of the whole review team [25]. They then extract data and

assess the risk of bias of included studies, solving disagreements by consensus. We meticulously extract data using REDCap electronic data capture tools, focusing on key aspects such as study identification, participant characteristics, interventions, and outcomes. This approach ensures rigorous data quality control processes and enhances the reliability of our analyses.

Presentation of findings

The data is consolidated and visualized using PowerBI, which provides an interactive dashboard for exploration. It is available at https://www.safeinpregnancy.org/living-systematic-review/. This tool allows stakeholders—including policymakers, researchers, guideline developers, and clinicians—to explore the evidence interactively through filters (e.g., population, vaccine type, outcome) and to generate customized figures, tables, and maps. RShiny enables real-time, user-defined meta-analyses and generates forest plots with pooled estimates and confidence intervals [26]. Users can select the relevant outcomes based on the population of interest and apply filters or subgroups such as vaccine platform, vaccine doses, population, and comparators to show emerging vaccines' overall safety and efficacy. The certainty of evidence from comparative studies is presented in Summary of Finding tables using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. It evaluates five key domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Based on these domains, the certainty of evidence is rated as high, moderate, low, or very low, helping users interpret how much confidence they can place in the effect estimates [24, 27]. This thorough process is supported by meticulous quality control and validation measures to ensure the robustness and reliability of the findings.

Discussion

The most compelling example of our work is our analysis of COVID-19 vaccines in pregnant persons [24]. Our study revealed that vaccination during pregnancy does not increase the risk of adverse outcomes for either the mother or the infant. Specifically, there is no evidence of increased risks for spontaneous abortion, cesarean delivery, assisted births, hypertensive disorders in pregnancy, congenital anomalies, preterm births, low Apgar scores, neonatal intensive care unit admissions, stillbirths, or neonatal deaths. Our findings underscore the importance of gathering more data on non-mRNA COVID-19 vaccines and evidence from low- and middle-income countries to support context-specific policy decisions. The findings of our LSR were designed for use by SAGE WHO, for example, to inform the development of clinical practice guidelines applicable worldwide.

Besides chikungunya and Lassa fever, we are expanding our LSR hub on emerging infectious diseases to cover vaccines against mpox and disease X, also for children and adult populations, posing challenges when applying it to vaccines at different developmental stages. Mpox, transmitted through close contact and sexual activity, remains a concern due to recent outbreaks, including the global surge in 2022 and ongoing cases in Central and East Africa. The potential for vertical transmission and severe disease in newborns highlights its public health relevance. While vaccines like JYNNEOS ® (Modified Vaccinia Ankara-Bavarian Nordic, live attenuated vaccine) are available, critical gaps remain regarding their use in children and pregnant women, particularly in assessing potential side effects and immunogenicity [28, 29], which is especially relevant given the severity of the disease in at-risk populations. Disease X, a term the WHO established to denote an unidentified pathogen that could emerge and cause a serious international epidemic or pandemic [3], is a stark reminder of the urgent need for pandemic preparedness. It reinforces the importance of real-time data synthesis to support the rapid development and deployment of vaccines against emerging threats. We incorporated this placeholder concept to foster proactive consideration of pathogens with pandemic potential.

Immunization efforts throughout the 20th and 21st centuries have reduced illness and death among children and adults, lessened disparities in infectious disease rates, and delivered economic benefits by curtailing the demand for medical treatments related to vaccine-preventable diseases [30, 31]. The selection of these diseases is guided by their substantial public health impact and the critical need for data on at-risk populations. Recent outbreaks, such as chikungunya in the Americas and mpox in Africa, highlight the urgency of addressing these threats. Lassa fever, identified as a WHO priority, is also a priority for the Coalition for Epidemic Preparedness Innovations (CEPI) as it poses significant risks, particularly in vulnerable groups. At the same time, Disease X reinforces the necessity of preparedness for future emerging pathogens [3, 11, 13, 16, 28].

Access remains limited despite the urgent need for chikungunya vaccines in regions heavily burdened by the disease. Bavarian Nordic aims to provide commercial availability of VIMKUNYA™ in the U.S. in the first half of 2025, with plans to launch in key European markets within the same timeframe, pending the European Commission's final decision on marketing authorization [15]. Similarly, Valneva's IXCHIQ™, which received FDA approval in November 2023, is also being commercialized primarily in the U.S. and Europe [32, 33]. It is concerning that despite the high incidence of chikungunya in the Americas, particularly in low- and middle-income

countries, initial commercial distribution remains concentrated in high-income settings. This situation highlights persistent inequities in vaccine access and the urgent need for mechanisms to ensure vaccines reach the populations most affected by these diseases.

Access to timely and current data is essential for informed policy-making during emerging infectious disease outbreaks. By incorporating data on the safety and effectiveness of chikungunya, Lassa fever, and mpox vaccines in pregnant persons and children, we will provide up-to-date evidence enriching our understanding of vaccine responses in these groups. This information is crucial for shaping public health strategies and developing tailored vaccination guidelines to improve health outcomes.

Our LSRs also highlight the persistent disparities in country representation across vaccine studies, with data disproportionately concentrated in high-income settings. Addressing vaccine equity remains a central challenge in global health, particularly for emerging infectious diseases that disproportionately affect low- and middle-income countries (LMICs). Disparities in vaccine availability and data representation, highlight the need of concrete actions to close these gaps. Strategies to strengthen global vaccine equity include bolstering mechanisms such as COVAX, promoting advance market commitments, supporting regional manufacturing capacities, and investing in funding models that prioritize the inclusion of LMICs in vaccine research and trials [34]. These measures can improve timely access to vaccines where they are needed most and enhance local trust in immunization programs. Regulatory and logistical barriers—such as fragmented approval processes, lack of harmonized guidelines, and cold chain limitations—also hinder vaccine deployment in resource-constrained settings. Streamlined regulatory pathways, possibly through regional harmonization or reliance models (e.g., WHO prequalification), could accelerate vaccine rollout without compromising safety.

Beyond equitable access, bridging the gap between research and policy implementation is essential. Our real-time meta-analysis and interactive dashboards are designed to inform decision-making in dynamic public health contexts. We are actively collaborating with WHO, the Safety Platform for Emergency vACcines (SPEAC), and CEPI to explore the integration of this evidence platform into policy frameworks, enabling rapid uptake of emerging data by national and regional health authorities. Participation of our diverse Scientific and Technical Advisory Group was critical in overcoming these challenges, and maintaining an active and capable team remains essential for effectively addressing emerging vaccine-preventable diseases on time.

By enhancing the visibility and usability of robust evidence, especially during public health emergencies, our platform aims to strengthen preparedness and response efforts while promoting equitable, data-informed decision-making on a global scale.

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Authors' contributions
All authors contributed to the conception and design of this study. AC, MBe, AM, JB, JC, JMS, JPS, MBr, NC, KS, DC, EC, VO, FS, EPKP, AS, XX, FMM, and PMB contributed equally to the acquisition, analysis, and interpretation of data. MB, AB, AC, and JB wrote the main manuscript text. All authors reviewed and approved the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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