Vaccine regulation should require and enforce the inclusion of pregnant and breastfeeding women in prelicensure clinical trials

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ABSTRACT

Exclusion of pregnant and breastfeeding women from the pivotal randomized controlled trials for COVID-19 vaccines that led to emergency regulatory approval created gaps in data needed for vaccine policy, healthcare provider recommendations, and women’s decisions about vaccination. We argue that such knowledge gaps increase potential for vaccine hesitancy and misinformation relating to the health of women and infants, and that these gaps in evidence are avoidable. Over several decades, ethical and scientific guidance, scholarship, and advocacy in favor of pregnant and breastfeeding women’s participation in clinical development of vaccines has accumulated. Guidance on how to include pregnant and breastfeeding women in vaccine trials ethically and safely predates the COVID-19 pandemic but has yet to be routinely incorporated in vaccine development. We highlight the important role regulatory authorities could play in requiring that pregnant and breastfeeding women be eligible as volunteer participants in prelicensure vaccine trials for products that are expected to be used in this population. Inclusion of pregnant and breastfeeding populations in clinical trials leading to market approval or emergency use authorization should be undertaken early or concurrently at the time of trials in the general population.

Exclusion from trials creates gaps in data

At the start of vaccine rollout in December 2020, many, but not all in the general population had access to information about the safety and efficacy of recommended COVID-19 vaccines with the reassurance that populations representing them participated in the pivotal prelicensure randomized controlled trials (RCTs) that served as evidence for vaccine efficacy and safety. Although public funds accelerated COVID-19 vaccine development and manufacturing (e.g., in the United Kingdom, in the United States through Operation Warp Speed), several authors, it was not known all populations that could be at increased risk from COVID-19 were considered in the vaccine development process. Prelicensure COVID-19 RCTs were criticized for systematically excluding pregnant and breastfeeding women; even though guidance were available on how to include pregnant and breastfeeding women in COVID-19 vaccine trials ethically and safely.

This systematic exclusion creates uncertainties about vaccine safety and efficacy in pregnant and breastfeeding populations as well as space for hesitancy, distrust, and misinformation. Exclusion is particularly concerning because populations prioritized for early access to vaccination (e.g., healthcare workers) included women who were pregnant or breastfeeding. Exclusion of a population from trials also threatens the integrity of public health supported mass vaccination programs, since the first safety and effectiveness data in that population arises in observational studies without control data. Encouragement for the inclusion of pregnancy and breastfeeding women in clinical trials dates back two decades and has been summarized elsewhere. Notably, the Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT) and COVID-19 Vaccine Global Access (COVAX) published guidance on how to include these populations, with a COVAX Maternal Immunization Working Group (MI-COVAX) specifically addressing pregnant and breastfeeding women in the pandemic context of COVID-19.

Ultimately, regulatory authorities establish the criteria for measuring pharmaceutical safety and efficacy prior to market approval and emergency use authorization. Although governments, funders, and other civil actors influence study design, vaccine developers seek regulatory input to trial design. Therefore, we argue that regulators are uniquely positioned to lead existing momentum toward ensuring pregnant and breastfeeding women are included when appropriate and at the necessarily early timeframe in future RCTs, especially during infectious disease emergencies.

Guidance on inclusion is not enough

In 2019, the PREVENT Working Group published 22 recommendations for including pregnant women in vaccine research and deployment, including a shift to the “presumptive inclusion of pregnant women” in medical research.
COVAX subsequently developed guidelines outlining how to include pregnant and breastfeeding women in COVID-19 vaccine development and deployment. Although this discussion about inclusion early in COVID-19 vaccine development marked a change in approach from the past, systematic exclusion persisted. Two reviews of hundreds of trials of therapeutic COVID-19 interventions in early to mid 2020 found that most excluded pregnant women. One review included ten COVID-19 vaccine RCTs, all of which explicitly excluded pregnant women. When COVID-19 vaccines received initial emergency regulatory authorization in many countries, the only available data about COVID-19 vaccination safety in pregnancy were from ongoing preclinical (animal) trials and from women who inadvertently became pregnant during the RCTs. These data provided reassuring results. COVID-19 vaccine RCTs for pregnant women were not initiated until February 2021, after the rollout started for the general population in many countries. Many pregnant women gained access to COVID-19 vaccination via public health programs before and while these trials were enrolling, and as a result, RCTs involving pregnant women were unable to meet recruitment targets and were halted by August 2021.

Evidence that pregnant women are at higher risk of severe COVID-19 than age-matched non-pregnant females began emerging in mid-2020. Pregnant women with COVID-19 are more likely to be admitted to an intensive care unit than non-pregnant females and to experience adverse pregnancy events (e.g., preeclampsia, preterm birth, stillbirth) compared to uninfected pregnant women. Pressure mounted to permit, and in many countries recommend that, pregnant women be vaccinated. Women and professional organizations advocated for pregnant and breastfeeding women in priority groups to be given access to COVID-19 vaccination prior to initiating clinical trials in these populations as part of shared decision-making. For these reasons, many countries permitted COVID-19 vaccination in pregnancy, although they did not initially recommend pregnant women to get vaccinated. Recommendations and messaging about vaccination were inconsistent between and within countries. Globally, hundreds of thousands of pregnant women received COVID-19 vaccines based on limited data, but many more hesitated, delayed, or in some countries, were initially restricted from accessing vaccines.

The COVID-19 pandemic drew unprecedented attention to gaps in data about vaccine and pharmaceutical use while pregnant or breastfeeding. In early 2021, the International Coalition of Medicines Regulatory Authorities (ICMRA) held a workshop outlining gaps in data about COVID-19 vaccination and treatment for pregnant and breastfeeding women. ICMRA emphasized, “There is an absolute and pressing need to change the way we approach medicines in pregnancy and breastfeeding” and regulators should “request pre-authorization data from clinical trials in pregnant and breastfeeding women.” In 2021, leading regulatory bodies from high-income countries including the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the UK Medicines and Healthcare products Regulatory Agency (MHRA) called for changes to the status quo of systematically excluding pregnant and breastfeeding women from pre-licensure clinical trials for vaccines and therapeutics. Vaccine manufacturers would be motivated to include pregnant and breastfeeding women in RCTs if that inclusion was required to gain access to markets in the US, Europe, and UK. Furthermore, manufacturers were not required to provide evidence to regulators describing COVID-19 vaccine efficacy and safety in pregnancy to update product monographs or to move from emergency to full market authorization. COVID-19 vaccine product labels updated in March 2022 still include statements, such as, “The safety and efficacy of [product name] in pregnant women have not yet been established.”

The pandemic provides a unique opportunity for all stakeholders funding and leading vaccine development and manufacturing to implement the paradigm shift that was already occurring in discourses about the inclusion of pregnant women in vaccine trials.

**Why exclusion persists**

Systematic exclusion persists in regular and pandemic vaccine development despite increasing support and attention to the importance of including pregnant and breastfeeding women in vaccine RCTs due to many challenges (real and perceived). Perceptions of vulnerability and anxieties about potential harm to fetal and infant bodies from pharmaceutical use in pregnancy likely shape the practices of excluding pregnant and breastfeeding women from RCTs. One systematic review shows “potential harm to the fetus” was the most cited reason for exclusion. Other reasons researchers gave for exclusion from trials for pharmaceutical products include interpretations of research ethics committee requirements, the increased level of complexity in trial design with attendant increased costs, lack of financial incentive, and assumptions about pregnant women’s willingness and ability to consent to participation on behalf of their fetus. In another systematic review, over 86% of 376 RCTs for the prevention, treatment, diagnosis, and screening of infectious diseases, including 48 vaccine studies, did not provide a rationale for excluding pregnant or breastfeeding women. Legal liability for adverse events following vaccination to the woman, pregnancy, or child, whether or not there is evidence of causality, is a challenging but insurmountable barrier to inclusion.

There are few real challenges to including breastfeeding women. A potential challenge most relevant to inclusion of breastfeeding women may be related to unequal inclusion of females and women in medical research broadly speaking, and assumptions that pregnant and breastfeeding women are vulnerable, and therefore, incapable of consent on behalf of their fetus or infant. Indeed, unequal inclusion of women was observed in observational and interventional studies on COVID-19.

The speed and urgency of pandemic vaccine development created additional challenges to inclusion. For example, manufacturers would have needed to complete developmental and reproductive toxicology (DART) studies, which generally take several months, and develop study protocols for pregnant women earlier in vaccine development than they have for other routine vaccines.
Regulatory approaches to ensure inclusion

It is ultimately regulatory authorities that establish the criteria for measuring pharmaceutical safety and efficacy that lead to market approval and emergency use authorization. Regulatory discussions and development of non-binding guidance about participant eligibility and trial design show a path forward, but they must be required, supported, and enforced to facilitate a new standard practice of including pregnant and breastfeeding women in vaccine development. Vaccine research should include pregnant and breastfeeding women when the product is reasonably expected to be safe, effective, and used by these populations. Manufacturers must be required to scientifically and ethically justify the exclusion of pregnant and breastfeeding women from RCTs when they cannot be appropriately included, with the default pathway to be inclusion of these populations if other adult populations are included. Regulatory bodies should require pre-clinical studies, such as DART studies to be initiated as early as possible in the vaccine development pathway (e.g., coincident with early Phase 1 trials, or Phase 2 when less feasible in Phase 1) to facilitate inclusion in later phases without slowing development for the wider adult population. As part of pandemic preparedness, regulators could require manufacturers to conduct DART studies during development of vaccine platforms that may be used for pandemic vaccines and/or accept DART data from other vaccines using the same platforms. With non-live vaccines (e.g., mRNA, viral vector COVID-19 vaccines), it would have been reasonable to begin trials with pregnant women after safety was confirmed in DART studies and safety and immunogenicity were demonstrated in Phase 1 and 2 trials in the non-pregnant adult population.

Regulators could require the inclusion of breastfeeding women in most RCTs because there are few real risks to including breastfeeding women. There are no theoretical or real risks to infants from vaccinating breastfeeding women with inactivated vaccines nor from any routinely offered live vaccines. The only vaccines that have raised safety concerns and require special consideration when used during breastfeeding are first- and second-generation smallpox vaccines and yellow fever vaccines. Without regulatory requirements and enforcement, substantial disincentives remain for manufacturers interested in including pregnant and breastfeeding women in RCTs. For example, trial design in pregnancy is complex and costly because of the need to monitor safety for pregnant participants, the course of the pregnancy, and their fetuses throughout the trial, and the resulting increase in data collection on adverse pregnancy and neonatal outcomes. Innovative mechanisms to share liability with partners (e.g., government) for adverse events during pregnancy should be explored. For example, trial insurance and compensation programs, such as global no-fault vaccine compensation systems could be established to mitigate liability concerns, while supporting individuals who suffer serious adverse events following vaccination, including women who are pregnant and/or breastfeeding and their offspring. There are also concerns that public trust in vaccines could decrease following any negative outcome in a vaccinated woman’s pregnancy, even when it is not attributable to the vaccine. Anticipatory risk and communication planning with public health actors, comprehensive safety planning, and rapid data review of accumulating data could mitigate this risk. Trials in pregnancy are delayed in part because of the perceived challenges of recruiting and including pregnant women, especially given the speed and urgency of COVID-19 vaccine development. Research into women’s views of RCTs and successfully completed trials with pregnant participants suggest that these challenges are surmountable.

A stronger regulatory framework to include pregnant and breastfeeding women in RCTs would prompt developers, funders, and other research institutions to adapt and incorporate PREVENT and MI-COVAX recommendations into existing supports and guidelines. Funders would need to provide adequate resources to cover the additional costs associated with monitoring pregnant and breastfeeding women and their infants in RCTs. Guidelines for considering sex and gender in RCTs and other medical research could be updated to include reproductive health. Existing post-market surveillance programs could be expanded to include active surveillance for adverse events following immunization in pregnant and breastfeeding populations. Enforced requirements and support to meet those requirements, should motivate and better enable manufacturers to include pregnant and breastfeeding women in pre-licensure RCTs.

Required inclusion could improve confidence in vaccination

Gaps in data about vaccination while pregnant or breastfeeding create space for vaccine hesitancy and misinformation to take hold, especially when those gaps pertain to novel vaccines. Despite being at higher risk of severe disease and complications from COVID-19, pregnant women have lower vaccine uptake than their non-pregnant peers. Hesitancy to receive vaccines is relatively high among pregnant women and many healthcare providers hesitate to recommend COVID-19 vaccination in pregnancy. Pregnant women report wanting better quality data to inform their decisions, concerns about vaccine safety for their offspring, and difficulty deciding whether to receive a COVID-19 vaccine. Prioritizing inclusion in prelicensure RCTs should generate high-quality evidence to inform women’s decisions about vaccination while pregnant or breastfeeding, and to support healthcare provider recommendations. The systematic exclusion of women who are pregnant or breastfeeding from medical research has yet to be adequately addressed, despite decades of scholarship and advocacy. Regulators are uniquely positioned to lead the shift toward ensuring that pregnant and breastfeeding women are included in vaccine research, development, and
implementation by enforcing requirements for inclusion in prelicensure vaccine research.

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Contributor's statement

Dr. Manca conceived of the idea, drafted, and revised the manuscript in response to feedback from the coauthors, Drs. Sadarangani, Langley, Halperin, McClymont, MacDonald, and Top; contributed to critically revising the intellectual content of the manuscript.

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