SAFETY OF VACCINATION DURING PREGNANCY: SCIENTIFIC CONTEXT AND SCOPE

IABS SCIENTIFIC WORKSHOP – ASSESSING POTENTIAL CONSEQUENCES OF MATERNAL IMMUNIZATION ON INFANT OUTCOMES, 13 AUGUST 2025

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DISCLOSURES

- **Research Funding**
  - NIH / VTEU (PI Observational study vaccines in pregnancy – Momi-Vax; AFM)
  - CDC / NVSN (Influenza and SARS CoV-2 burden in pregnancy; respiratory virus surveillance)
  - Pfizer (COVID vaccines children)

- **Special Groups**
  - AAP-COID Outbreaks Committee (2023-)
  - SOID (Chair elect)
  - ACIP IDSA Liaison, Flu and Mpox working groups
  - ACOG Immunization Expert Group
  - CEPI – SPEAC – Brighton Collaboration
  - GVDN – vaccine safety in pregnancy
  - NFID – Board Member
  - WHO – Vaccines in pregnancy/safety
  - FDA VBRPAC

- **Data Safety Monitoring Board**
  - NIH (Malaria, azythromycin)
  - Pfizer (RSV-GBS)
  - Moderna (various vaccines)
  - Dynavax (plague)

- **Advisory/Consulting**

  Astra-Zeneca

  GSK

  Sanofi

  Moderna

  Merck/MSD

PREGNANT WOMEN - SPECIAL POPULATIONS

Other Vulnerabilities:

Racial/Ethnic minorities
Socio-economic status
Educational status
Geography
Displacement
Conflict

REPRESENTATION

Evidence-based decision making

- Additional protections required in research
- Specific biologic and physiologic needs/considerations – (e.g. changes in immune response)
- Additional safety considerations (e.g. pregnancy – DART) and efforts
- **Exclusion from early clinical trials resulting in limited information on safety and efficacy of vaccines, delay in vaccination, increased risk !**
- Evolving guidance on participation in vaccine clinical trials and regulatory pathways

Maternal immunization began with the development of vaccines

1879 - MI with **Vaccinia** protected **mothers and infants** against **smallpox**

1940's - MI studies with **DTPw** vaccine in US to protect **infants** against **pertussis**

1960s – Influenza vaccine recommended for **pregnant women** (at risk) since the 1957 pandemic

1961- MI with **Tetanus Toxoid** to prevent **neonatal tetanus** added to WHO Expanded Program on Immunization (EPI) in 1970's; MNT elimination goal set in 1980's

Source: google images

Vaccines in Pregnancy Research:

1970's Oral polio, Yellow Fever
1980's **Group B Strep** (ongoing)
1990's Pneumococcal, Hib, seasonal influenza vaccines
1990's **RSV**
2000's Tdap
2000's Meningitis A
2009 Pandemic Influenza
2015 Monovalent aP
2018 Ebola vaccine
2020 Hepatitis E
2021 COVID-19
2024 Malaria
2025 mpox, (Chikungunya)

Vaccines Recommended in Pregnancy

WHO: Pregnancy should not deter a woman from receiving vaccines that are safe and will protect both her health and that of her unborn child.

Generally *recommended*	Recommended for disease prevention in specific situations	Contraindicated
Tetanus (Td, TT)	Cholera	BCG
Influenza Inactivated (IIV) *	Yellow Fever	Measles
Pertussis (Tdap) (*aP*) in areas of burden*	Meningitis A (meningococcal)	Mumps
SARS-CoV-2	Hepatitis A, B, E	Rubella
RSV	Japanese Encephalitis	Varicella
	Polio (OPV, IPV)	Live Typhoid T21a
	Rabies	Live influenza
	Mpox, Chikungunya	
	Recommended vaccines are NOT contraindicated in pregnancy!	Theoretical risk of fetal infection

* SAGE-WHO in 2012 made Influenza vaccination of pregnant women a global priority for all countries where influenza vaccination is administered, incorporating it into ANC services and recommended Tdap since 2015 in areas of high disease burden.

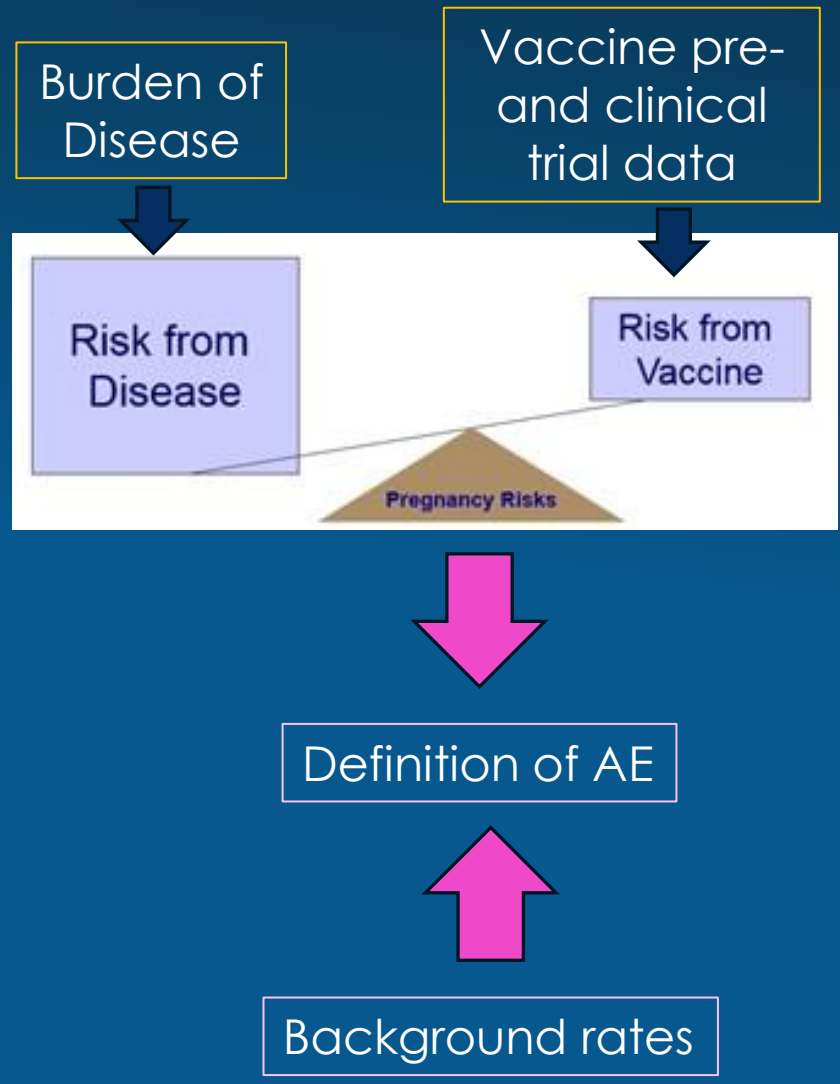
IIV, Tdap, SARS-CoV2 - Post-partum vaccination recommended if unable to vaccinate in pregnancy

MMR - Also given post-partum in non-immune mothers (rubella); most vaccines can be given post-partum w/lactation

WHO's specific vaccine position papers: http://www.who.int/immunization/documents/positionpapers_intro/en/.
https://www.cdc.gov/vaccines/pregnancy/hcp-toolkit/guidelines.html

KEY ISSUES ON MATERNAL IMMUNIZATION

- 2 vaccines are licensed specifically for pregnant women (RSV, aP)
- **Most licensed vaccines initially recommended for pregnancy based on risk:benefit assessment** (Influenza, Tdap, COVID-19) (vaccines given in special circumstances)
- **Potential impact** of maternal immunization as **public health strategy** for disease prevention in mothers and infants – is underutiized
- **New vaccines** that could benefit pregnant women and infants (**GBS**, Chikungunya, mpox, Ebola, Lassa Fever, Hepatitis E, malaria)
- **Pregnant women as research subjects**:
  - Assessment of ***disease burden*** and ***safety*** are critical
  - Definition of AE – **pregnancy vs. vaccine-related** ?
  - **Background risks inherent to pregnancy** challenge assessment of safety
  - Importance of **background rates / controlled studies**
  - **Benefit and efficacy/effectiveness** demonstrated **in mother, infant or both**
  - **Knowledge gaps** remain in basic maternal, fetal, early life immunology, etc
  - Evolving **ethics and regulatory environment, variable implementation of guidelines**



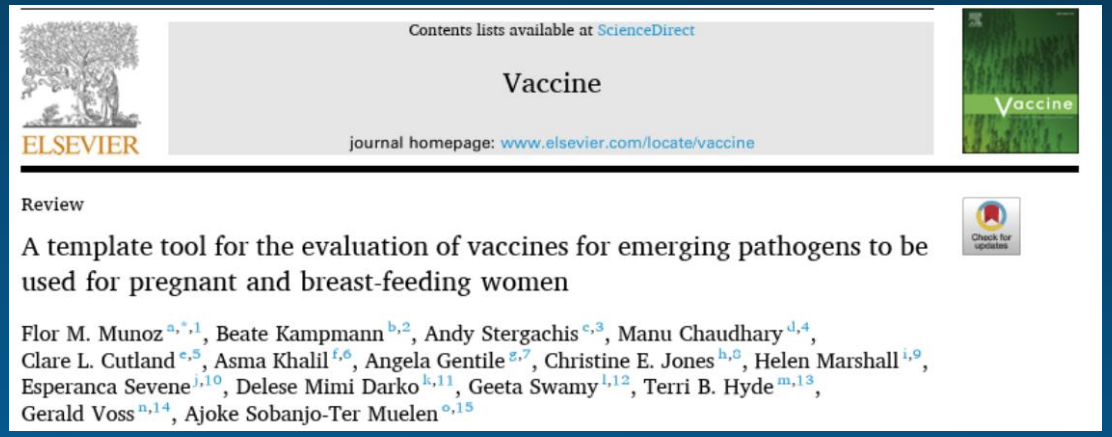
SPECIAL REQUIREMENTS FOR MATERNAL IMMUNIZATION STUDIES

- **Pre-clinical studies**
  - Reproductive toxicology (DART)
- **Clinical studies (phase I-II/III) in healthy adults**
  - Safety in adults and women of childbearing age
  - Data on Dosage/Immunogenicity
- **Clinical studies in Pregnant Women**
  - Phase Ia (first in pregnant women: primary endpoint = safety)
  - Phase II (primary endpoint = immunogenicity)
  - Phase III (primary endpoint = efficacy/immunogenicity)
- **Safety**
  - Pre-set definitions for AE/SAE, monitoring and documentation, halting/stopping rules
  - Background rates, control group, DSMB, post-authorization safety surveillance plan
- **Effectiveness** in mothers and infant protection
- **Ethics** (Informed consent, control/placebo group, acceptance

TEMPLATE TOOL TO ASSESS SUITABILITY OF VACCINES DURING PREGNANCY

CEPI-SPEAC
BRIGHTON COLLABORATION

Munoz FM et al. Vaccine
Volume 62, 30 August 2025, 127513



Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

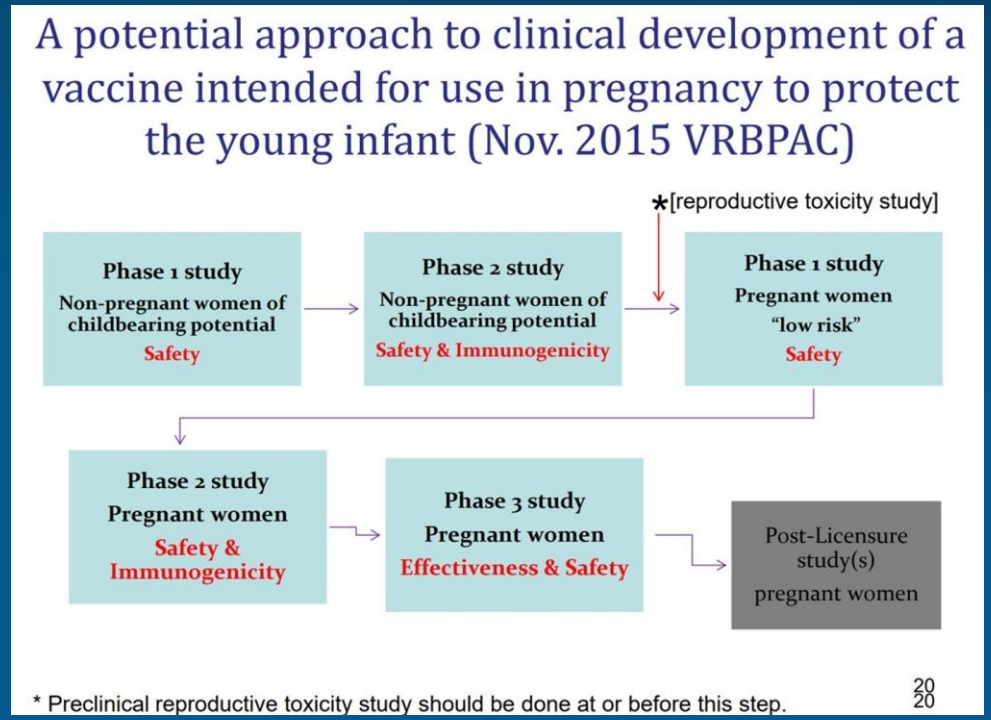
A template tool for the evaluation of vaccines for emerging pathogens to be used for pregnant and breast-feeding women

Flor M. Munoz [a,*,1], Beate Kampmann [b,2], Andy Stergachis [c,3], Manu Chaudhary [d,4], Clare L. Cutland [e,5], Asma Khalil [f,6], Angela Gentile [g,7], Christine E. Jones [h,8], Helen Marshall [i,9], Esperanca Sevene [j,10], Delese Mimi Darko [k,11], Geeta Swamy [l,12], Terri B. Hyde [m,13], Gerald Voss [n,14], Ajoke Sobanjo-Ter Muelen [o,15]

- The purpose of this tool is to provide a template for researchers and decision makers to consider the relevant aspects necessary to support the use of a vaccine in pregnancy or post-partum, with all elements considered important, and therefore not prioritized or mandated.
- The use of this tool should not hinder the development of clinical trials in emergency situations, including in LMIC, where the availability of some data might be limited.
- Input from pertinent regulatory agencies should be sought throughout the process of evaluation and implementation of vaccines for pregnant and breast-feeding women.

OPTIMIZING RESEARCH IN PREGNANCY: CLINICAL TRIALS

- Early inclusion: Minimum necessary safety and immunogenicity data from healthy adults clinical trials to include special populations
- Immunobridging studies
- Inclusion of pregnant women in phase 2/3 clinical trials
- DART studies for vaccines to be implemented during pregnancy
- Unexpected pregnancies protocols
- Plan for post-authorization safety assessment



GOALS OF SAFETY SURVEILLANCE OF VACCINES:

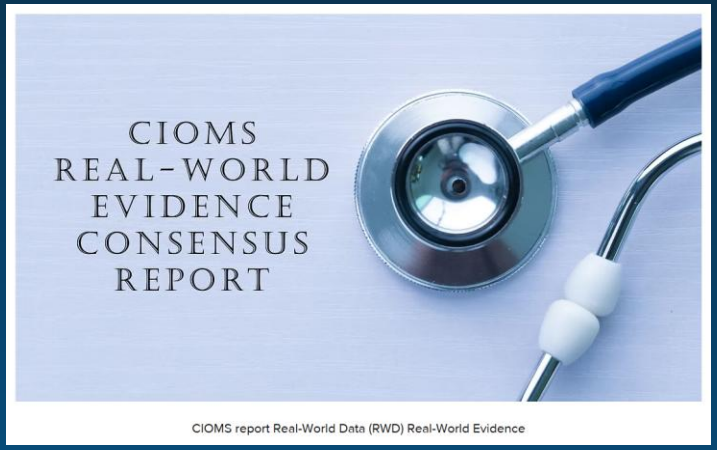
- **Detect and identify problems with vaccines** which could be due to the **product**, its **quality** or an **immunization error** in the program
- Evaluate the **rate of vaccine reactions observed** and compare them to the **expected** vaccine reaction rates reported
- Detection of **common (> 1/10,000 vaccinees) and rare events (< 1/100,000 vaccinees)**
- To ensure that **coincidental events** are not mistaken for vaccine reactions and affect the confidence in the immunization program
- To facilitate the **investigation and causality assessment** of AEFI reports that are collected when implementing the program
- To identify events that may indicate a **previously unknown or unexpected vaccine reaction** that can be investigated in more depth
- To **create awareness of immunization safety** in the community and share this information

POST-AUTHORIZATION SAFETY SURVEILLANCE

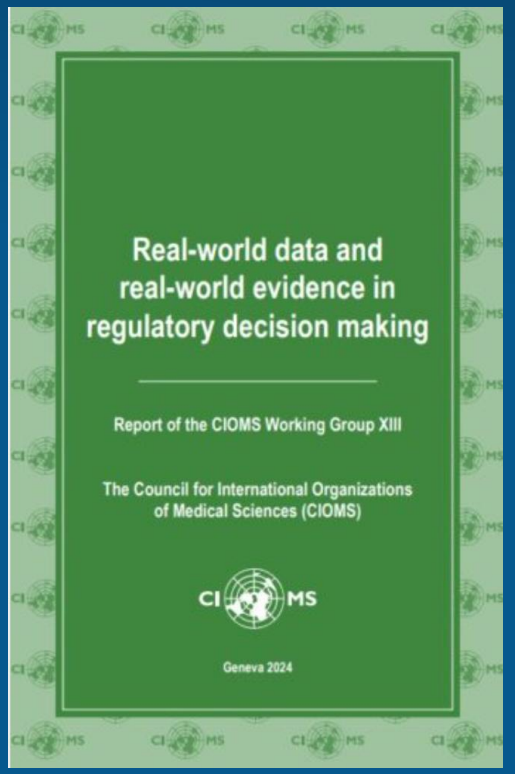
Active Surveillance	Requires regular contact with health care providers to actively search for AE and analysis of the incidence of specific AE in vaccinated and unvaccinated populations	Existing or adapted National Immunization Program surveillance systems UK: UKOSS US: VAMPSS, VSD, VAERS, PRISM, CISA – V-SAFE Registries (manufacturer or other; product/population/ or event specific) Cohort event monitoring EHR and large database Post-authorization studies
Passive Surveillance	Spontaneous adverse event reporting by health care providers, patients and vaccine manufacturers	
Enhanced Passive Surveillance	Passive surveillance with surveillance of targeted events and active outreach to investigate AESI 	
"REAL WORLD EVIDENCE" – analyzing REAL WORLD DATA		

REAL WORLD EVIDENCE

- Clinical evidence derived from real world data (RWD)
- RWD is collected from various sources outside RCT (e.g. EHR, claims, registries, patient generated data)
- COMPLEMENTS evidence obtained by RCT
- Assessment of PERFORMANCE of vaccines in populations and settings not often represented in RCTs
- Can support clinical guidelines and regulatory decision making
- Requires design and methods to ensure VALIDITY and RELIABILITY
  - Minimizing bias (e.g. selection, confounding)
  - Emulating conditions of RCT as much as possible (e.g.propensity score matching)



CIOMS report Real-World Data (RWD) Real-World Evidence



https://cioms.ch/publications/product/real-world-data-and-real-world-evidence-in-regulatory-decision-making/

PREGNANCY EXPOSURE REGISTRIES

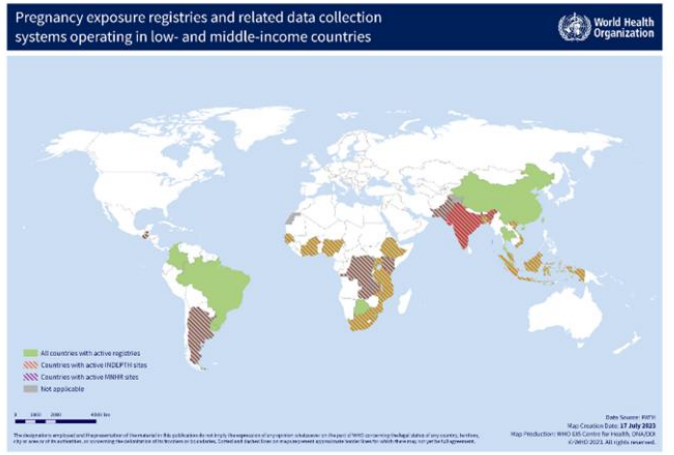
- **Actively and Systematically** collect information on exposures of interest during pregnancy and associated pregnancy and infant outcomes.
- **Prospective** - avoids recall bias and reporting bias.
- Could enable calculation of rates (if population based).
- Most commonly used in high-income countries; can be used in LMICs.
- Leverage existing surveillance systems, databases, and other infrastructure.
- Can be implemented in representative sentinel sites

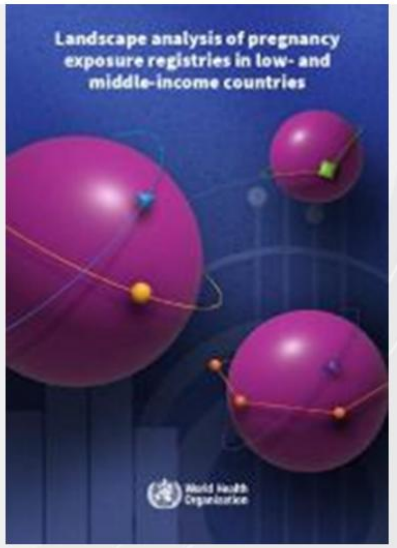
Stergachis A, Sevene E. Maternal and Neonatal Safety Surveillance Systems, in The Continuous Textbook of Medicine, Maternal Immunization


Open access Protocol

BMJ Open **Pregnancy exposure registries for drugs and vaccines in low-income and middle-income countries: scoping review protocol**

Rahmeh AbuShweimeh,[1] Sophie Knudson,[2] Sonia Chaabane,[3] Shanthi Narayan Pal,[3] Becky Skidmore,[4] Andy Stergachis ,[1,5] Niranjan Bhat[2]





https://www.who.int/publications/i/item/9789240087941

INTERNATIONAL REGISTRIES AND SOCIAL MEDIA TOOLS

To estimate the risk of the following outcomes:

Obstetric*	Neonatal*	Infant
Abortion	Congenital anomalies	Delayed developmental milestones
Antenatal bleeding	Failure to thrive	
Dysfunctional labor	Low birth weight	
Gestational diabetes	Neonatal death	
Hypertensive disorders of pregnancy	Neonatal encephalopathy	
Intrauterine growth retardation	Neonatal infections	
Maternal death	Preterm birth	
Non-reassuring fetal status	Respiratory distress in the newborn	
Pathways to premature birth	Small for gestational age	
Postpartum hemorrhage	Stillbirth	

among the offspring of women exposed to a COVID-19 vaccine during pregnancy relative to a matched unexposed reference group.

*Based on case definitions developed by the GAIA Network (Bonhoeffer J, et al. Vaccine. 2016)

- **International** study where COVID-19 vaccines available
- Participants enroll at any time during gestation via **web or mobile app**
- Information obtained directly from the mother
- Follow-up: monthly contacts throughout the pregnancy and through the infant's first year of life
- The C-VIPER collects data on
  - Baseline characteristics (such as maternal sociodemographic categories, behaviors, reproductive history, chronic conditions, use of medications, and measures of healthcare utilization),
  - Vaccination (brand, dose, timing, lot)
  - Obstetric, perinatal, and postnatal outcomes until one year after birth and
  - Health care access (tele-medicine), wellbeing, mental health
  - **De-identified medical records**

BECOME

MEETING REPORT

Check for updates

Multi-Stakeholder Call to Action for the Future of Vaccine Post-Marketing Monitoring: Proceedings from the First Beyond COVID-19 Monitoring Excellence (BeCOME) Conference

Vincent Bauchau[1] · Kaatje Bollaerts[2] · Phil Bryan[3] · Jim Buttery[4] · Kourtney Davis[5] · Robert T. Chen[6] · Daniel R. Feikin[7] · Antonella Fretta[8] · Sarah Frise[9] · Sonja Gandhi-Banga[10] · Hector S. Izurieta[11] · Corinne Jouquelet-Royer[12] · Alena Khromava[10] · Lin Li[13] · Raj Long[14] · Sarah MacDonald[8] · Lydie Marcelon[15] · Robert Massouh[3] · Wilhelmine Meeraus[16] · Flor M. Munoz[17] · Karen Naim[8] · Dale Nordenberg[18] · Hanna Nohynek[19] · Heather Rubino[8] · Daniel A. Salmon[20] · Sarah Sellers[21] · Laurence Serradell[15] · Laurence Torcel-Pagnon[22] · Jamie Wilkins[8]

The multi-stakeholder collaboration session highlighted proposals for formalizing continued collaboration, expanding to a broader set of public and private stakeholders, and thus to advance the BeCOME mission to "**Foster collaborations where experts in pharmacovigilance and pharmacoepidemiology from key stakeholders (public health, regulators, academics, industry) can openly discuss and collectively align to sustain relevant systems, improve processes, and develop innovations for the post-marketing monitoring of benefits and risks of vaccines, leveraging the learnings and keeping the momentum of the COVID-19 emergency.**"

OBSERVATIONAL COHORT / LARGE DATABASE STUDIES

Adverse events following COVID-19 vaccination or diagnosis among pregnant and non-pregnant women, United States, 2021-2022.
> 1 million participants, private / public

COVID-19 Vaccination During Pregnancy and Major Structural Birth Defects

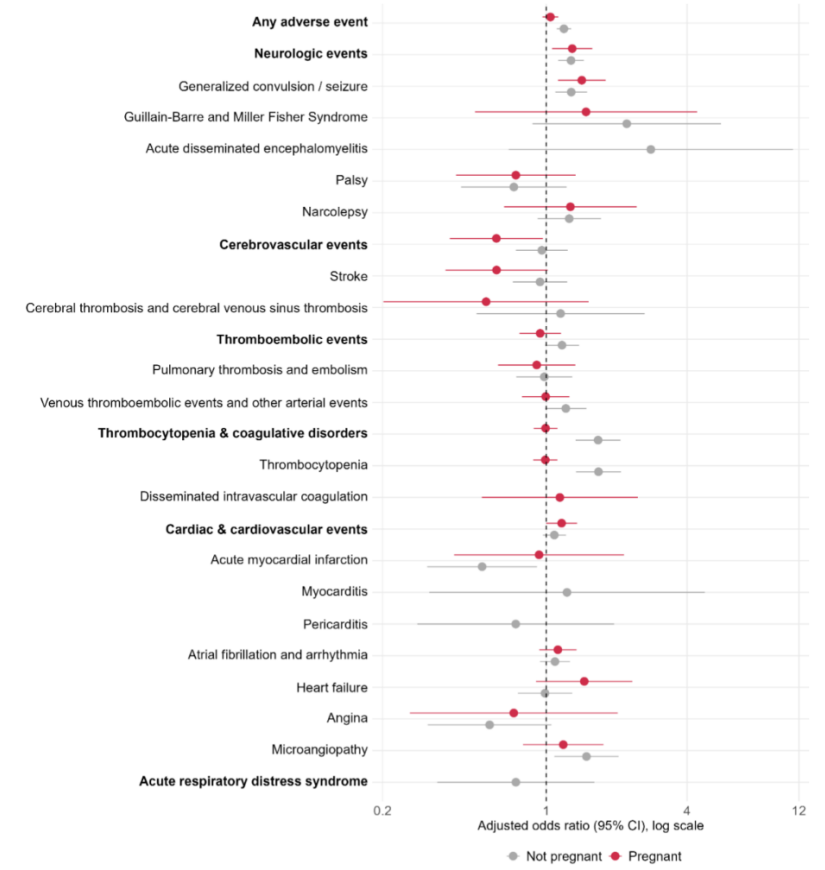
Stacey L. Rowe, PhD, MPH, BSc(Hons),[1,2,3,4] Sheena G. Sullivan, PhD, MPH, MSc, BSc(Hons),[5,6] Flor M. Muñoz, MD, MSc,[7] Matthew M. Coates, MPH,[3,4] Brianna Agnew, MPH,[1] Onyebuchi A. Arah, MD, DSc, PhD, MPH, MSc,[3,4,8,9] Annette K. Regan, PhD, MPH[1,3,4,10]

Among 78052 pregnancies, we identified 1248 major structural birth defects (1049 [159.9 per 10000 live births] among unvaccinated people and 199 [160.6 per 10000 live births] among vaccinated people)

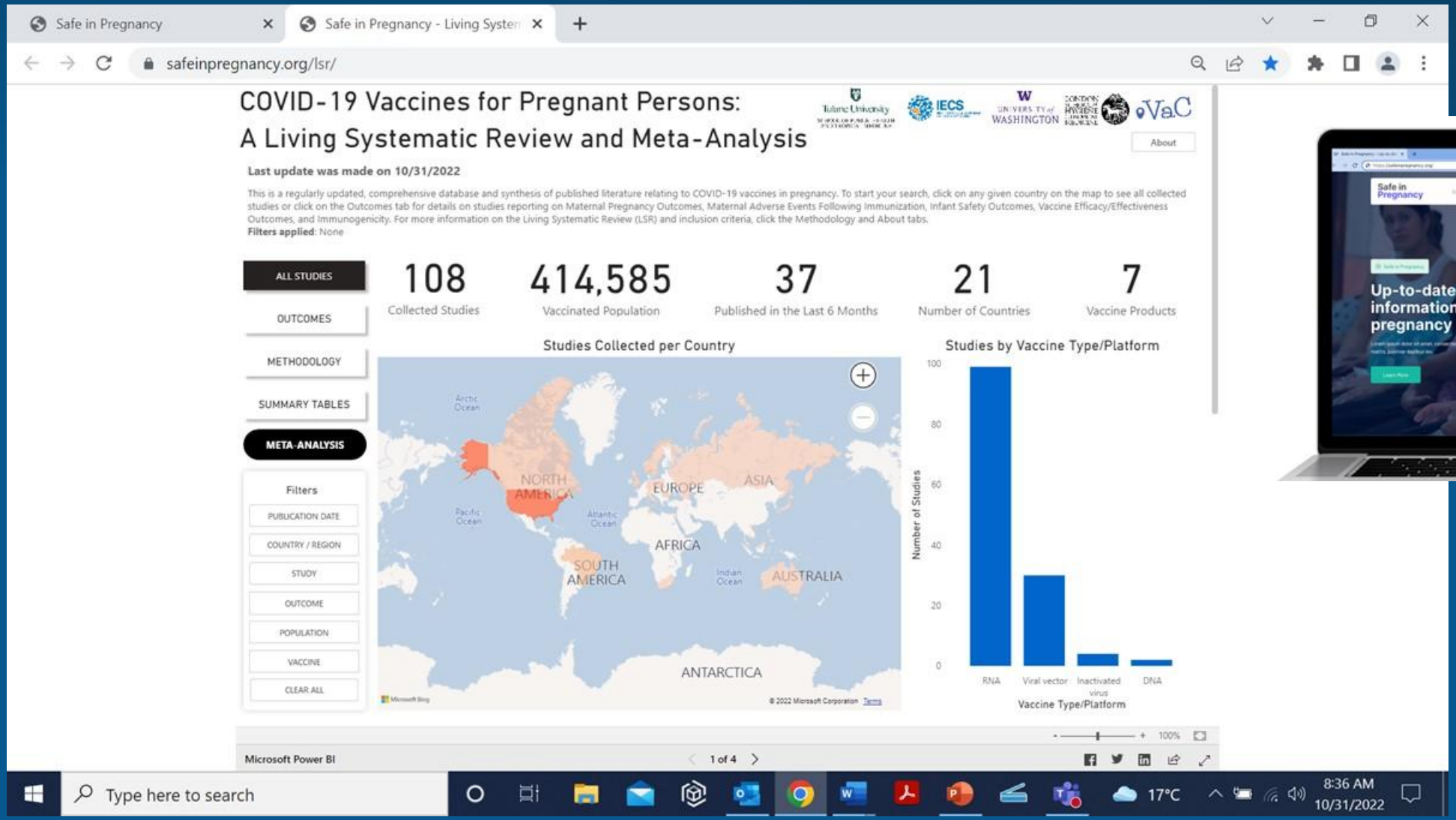
WHAT THIS STUDY ADDS: Major structural birth defects are not elevated among infants born to people vaccinated in the first 20 weeks of pregnancy. Moreover, the prevalence of birth defects is not modified by maternal SARS-CoV-2 infection nor concomitant administration of other maternal vaccines.

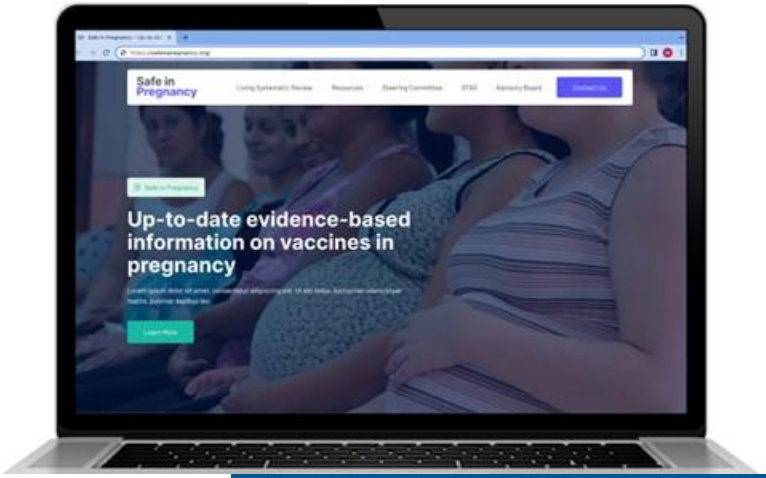
To cite: Rowe SL, Sullivan SG, Muñoz FM, et al. COVID-19 Vaccination During Pregnancy and Major Structural Birth Defects. *Pediatrics*. 2025;155(4):e2024069778

Figure 2: Odds of adverse events given COVID-19 vaccination (reference = unvaccinated) and 95% confidence intervals, by pregnancy.



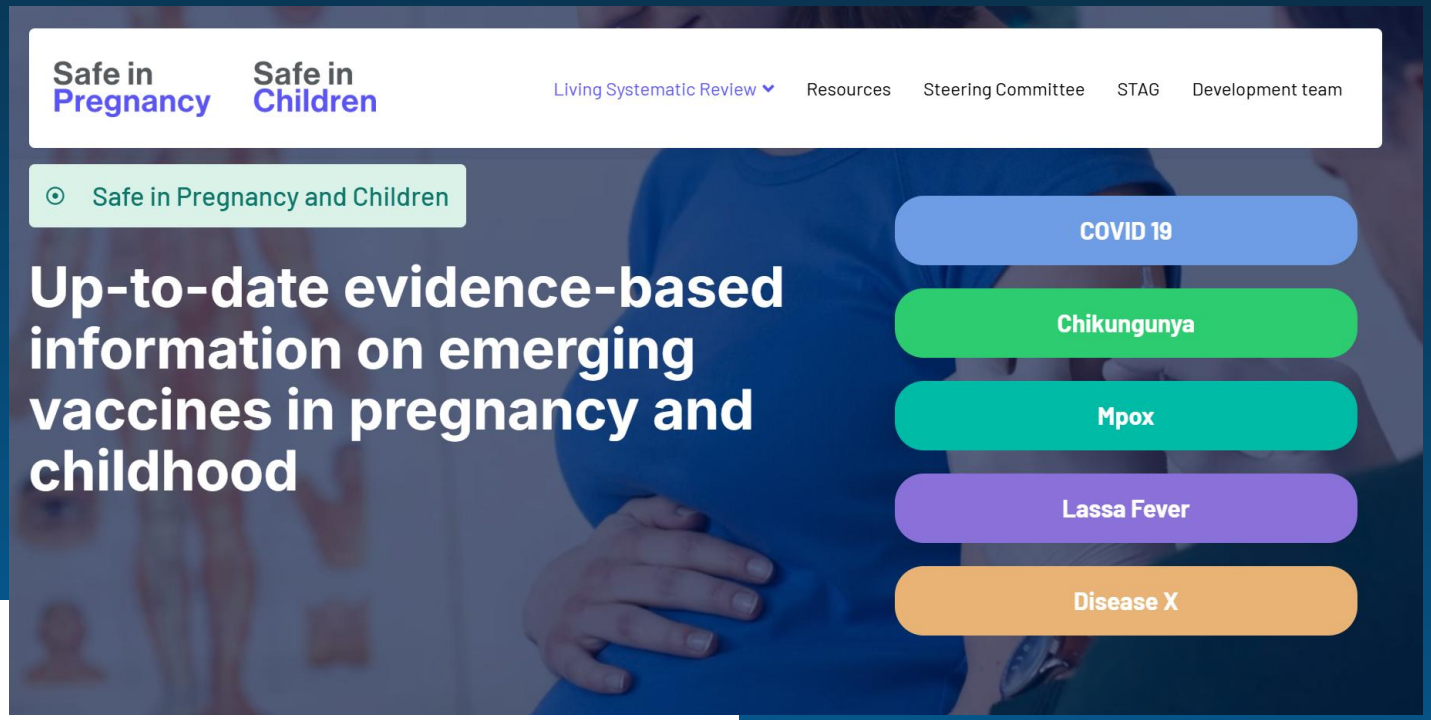
LIVING SYSTEMATIC REVIEWS





SAFEINPREGNANCY.ORG

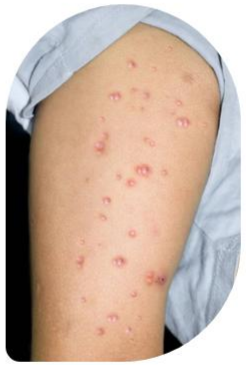
LIVING SYSTEMATIC REVIEWS FOR SPECIAL POPULATIONS AND EMERGING PATHOGENS

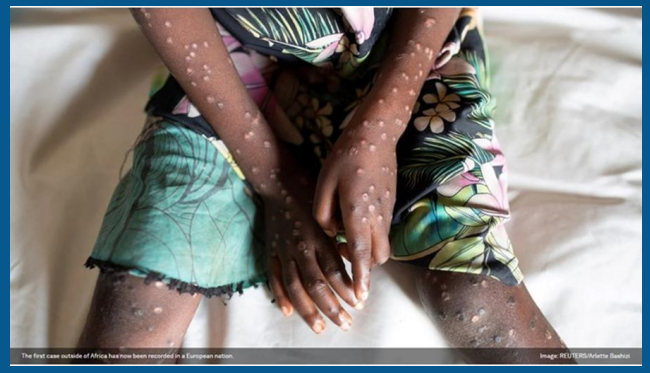


MPOX Vaccines for Pregnant Persons and Children

An ongoing, comprehensive review and analysis of published literature on safety, efficacy, effectiveness and immunogenicity of Mpox vaccines during pregnancy and childhood, utilizing a living systematic review and meta-analysis approach.

- **Mpox Vaccine Dashboard**
- **PROSPERO Protocols**
  - Pregnant persons
  - Children and adolescents
- **Pairwise and Proportional Meta Analyses**
- **PRISMA Flow Diagram**
- **Summary of Findings**
- **Quality Assessment**





HEALTH AND HEALTHCARE SYSTEMS

WHO says mpox outbreak is a global health emergency, and other top health stories

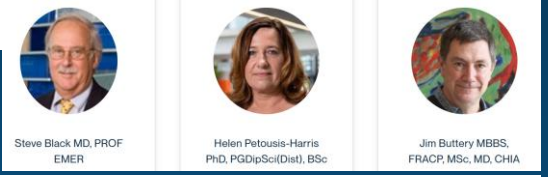
Published Aug 19, 2024 · Updated Aug 19, 2024

Supported by the Safety Platform for Emergency vACcines (SPEAC), Task Force for Global Health, Inc. – The Coalition for Epidemic Preparedness Innovations (CEPI).

MATERNAL AND NEONATAL SAFETY POST-COVID-19 VACCINATION

- **Design: Multi-center retrospective cohort**
  - Diverse settings – **16 sites** with varying cohort sizes (6,000 to >600,000) –**hospital and population-based surveillance**
  - **Standardized data elements** to ensure compatibility
  - **Meta-analysis** to generate pooled estimates
- Exposure: COVID-19 vaccination during pregnancy
- Outcomes: Maternal, neonatal, and adverse events
- Statistical analysis: Extended Cox models to account for time-varying exposures; Matched cohort analysis of AESI during pregnancy

Global Vaccine Data Network



Total study population > 3.2 million births

RSV IMPACT trial

Courtesy: Clare Cutland

- Phase IV, multicenter, randomized, double-blinded, placebo-controlled trial
- 13,000 pregnant women will be enrolled and their live-births will be included.
- The Gambia, Kenya (2 sites), Ghana (2 sites), South Africa (5 sites).
- Gestational age at enrolment: ≥28$^{0 days}$ weeks and <36$^{0 days}$ weeks (GAIA)
- Enrolment over 2 years- all year round
- Infant follow up for at least 365 days, up to 730 days.
- Enrolment to be initiated in South Africa in Q2-2025

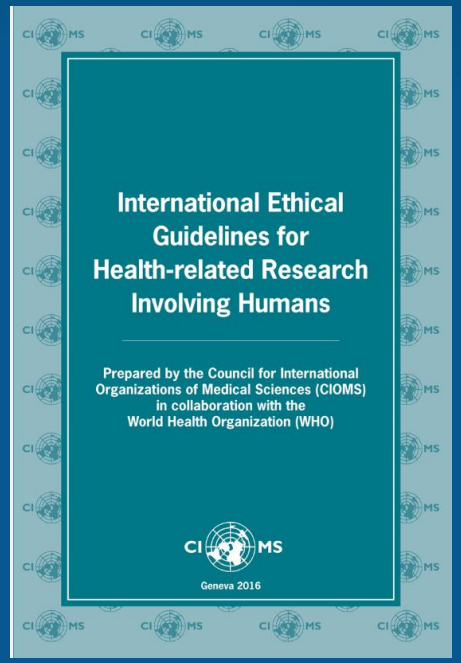
Funded by BMGF

PI: Shabir A. Madhi

- **Co-primary objectives:**
  - i. Evaluate the efficacy of RSVA/B-preF against RSV-A or RSV-B subtype confirmed severe LRTI through to 180 days of age.
  - ii. Evaluate the safety of RSVA/B-preF in relation to preterm births (born at <37 weeks GA) in women with gestational age (GA) staging Level of Certainty [LOC] 1 to 2B at time of enrolment.

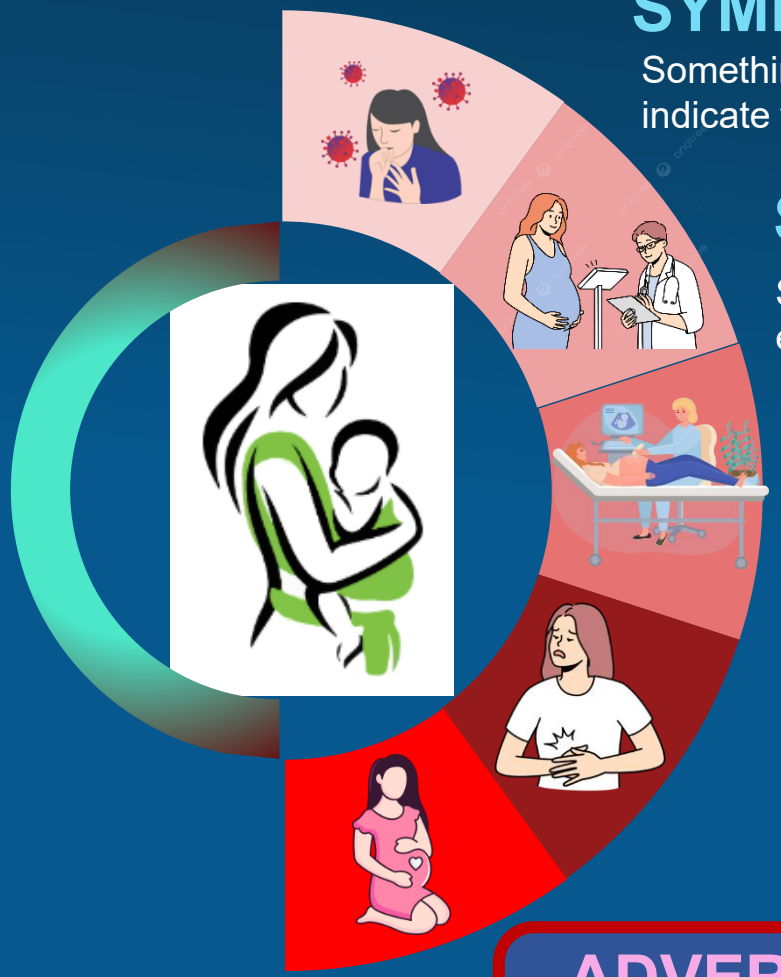
PROGRESS IN MATERNAL IMMUNIZATION RESEARCH

- NIH Research protocols (post-2009 influenza pandemic)
- GAIA Case Definitions (WHO/BC) 2014 - 2019
- Pregnancy and Lactation Labeling Rule 2014
- 2015 VRBAC Meeting
- NVAC 2015-16 MI group
- Common Rule Update 2016
- 21 Century Cures Act 2017
- **CIOMS 2016**
- WHO IVR – MI
- **PREVENT Guidance 2019**
- ACOG-ACIP access of COVID-19 vaccine for pregnant and lactating women – 2020



AEFMI CAUSALITY ASSESSMENT TOOL

An adverse event following maternal immunization (AEFMI) is any untoward medical occurrence (sign, symptom, lab finding or disease) or pregnancy outcome in a woman (or foetus) or the neonate that occurs following vaccination during pregnancy that may or may not be causally related to the use of the vaccine *



SYMPTOM

Something that a person feels or experiences that may indicate that they have a disease or condition

SIGN

Something found during a physical or clinical examination by the health care provider

LAB FINDING

Physiological or anatomic findings in medically acceptable and validaded laboratory diagnostic methods

DISEASE

A disorder of structure or function that can cause a distinctive group of symptoms, signs, physiological or psychological changes.

ADVERSE PREGNANCY OUTCOME

An outcome of the pregnancy involving the mother, fetus, or newborn.

* Adapted from
Definition and Application of Terms for Vaccine Pharmacovigilance; Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance

New WHO Statement: TB Vaccines and Pregnancy

Optimal and early inclusion of pregnant and lactating women in tuberculosis research

Consensus statement

World Health Organization

TB: tuberculosis.

World Health Organization

Accelerating research to end tuberculosis in pregnant and lactating women — **A call to action**

Introduction

Of the estimated 10.8 million people who fall ill with tuberculosis (TB) every year, over 1.7 million are women of reproductive age (15–45 years) *(1)*. An estimated 200 000 pregnant or postpartum women[1] develop TB annually (151 000 during pregnancy and 49 000 in the postpartum period) *(2)*. Pregnant and postpartum women have an increased risk of developing TB compared with the general population. TB disease during pregnancy is associated with an increased risk of maternal and infant complications, leading to perinatal and maternal morbidity and mortality. Considering the severe implications of TB for both the mother and her infant, it is critical that pregnant and lactating women can access the latest innovations and interventions to prevent, detect and treat TB *(3, 4)*.

Despite these risks, pregnant and lactating women (including adolescent girls) have been excluded from trials on the prevention and treatment of TB, and from vaccine trials. As a result, there are many unanswered questions about optimal TB regimens, optimal dosing of new or existing TB drugs, and their safety *(5)*. Hence, for most newer TB therapeutic regimens, there is limited evidence to support their use during pregnancy, which in turn limits the practical use of these medicines or regimens among pregnant women.

The consensus-building process

To address these challenges, the World Health Organization (WHO) coordinated a consensus-building process to develop approaches for the earlier and optimal inclusion of pregnant and lactating women in TB research. The process included the establishment of five thematic working groups, covering the areas of preclinical TB research, TB therapeutics research, TB vaccine research, maternal TB surveillance systems and advocacy. The working groups developed key approaches on the most impactful measures that need to be taken to advance the earlier inclusion of pregnant and lactating women in TB trials. The final consensus meeting took place in February 2025 and led to the publication of a consensus statement (https://iris.who.int/handle/10665/381875).

QR code to Optimal and early inclusion of pregnant and lactating women in tuberculosis research: consensus statement

[1] Note about language: Although the terms "women" and "mother" are used in this document, WHO recognizes that some people who become pregnant do not identify as a woman or mother. This call to action is intended to be inclusive of all who experience pregnancy, regardless of their gender identity. The terms "pregnant and lactating women" and "postpartum women" are also inclusive of adolescent girls who are pregnant, lactating or postpartum. "Postpartum period" refers to the period up to 6 months after giving birth.

News

New study to assess mpox vaccine in pregnant women and infants

CEPI • 6th November 2024

- First-of-its kind trial will assess the safety and immunogenicity of the **MVA-BN® vaccine** in **pregnant and breastfeeding women, and infants under two years of age.**
- Research data could help to expand vaccine access to these priority populations, known to be at risk of severe complications from mpox but not currently eligible for vaccination.
- Around **350 pregnant women and 250 children** aged two or under are due to take part in the study which will assess the safety and immunogenicity of the MVA-BN® vaccine in these populations for the first time.
- The trial will take place in **Boende, DRC, beginning in early 2025.**
- The project includes the University of Antwerp (Belgium) as Trial Sponsor, the University of Kinshasa (DRC) as Scientific Project Leader, and academic and research organisations Penta (Italy) and ACE Research (Kenya) as trial partners. Bavarian Nordic will supply the MVA-BN vaccine doses.

HEALTH

Ebola vaccine will be provided to women who are pregnant, marking reversal in policy

By HELEN BRANSWELL @HelenBranswell / FEBRUARY 20, 2019

A health worker carries a 4-day-old baby suspected of having Ebola into a treatment center in Butembo, Democratic Republic of the Congo.
JOHN WESSELS/AFP/GETTY IMAGES

https://www.nih.gov/news-events/news-releases/candidate-malaria-vaccine-provides-lasting-protection-nih-sponsored-trials

Media Advisory Wednesday, August 14, 2024

Candidate malaria vaccine provides lasting protection in NIH-sponsored trials

NIH National Institutes of Health
Turning Discovery Into Health

Approach could have role in preventing malaria in pregnancy.

What

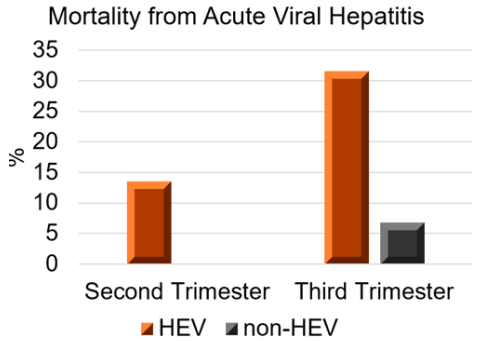
Two National Institutes of Health (NIH)-supported trials of an experimental malaria vaccine in healthy Malian adults found that all three tested regimens were safe. One of the trials enrolled 300 healthy women ages 18 to 38 years who anticipated becoming pregnant soon after immunization. That trial began with drug treatment to remove malaria parasites, followed by three injections spaced over a month of either saline placebo or the investigational vaccine at one of two dosages. Both dosages of the vaccine candidate conferred a significant degree of protection from parasite infection and clinical malaria that was sustained over a span of two years without the need for a booster dose—a first for any malaria vaccine. In an exploratory analysis of women who conceived during the study, the vaccine significantly protected them from malaria in pregnancy. If confirmed through additional clinical trials, the approach modeled in this study could open improved ways to prevent malaria in pregnancy.

NIAID

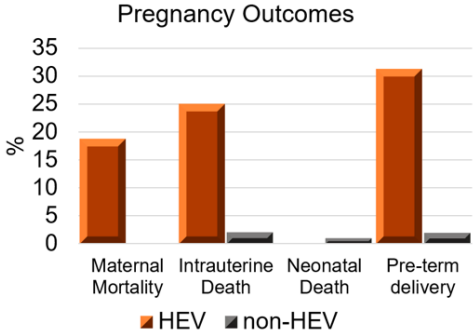
The investigational vaccine used in both trials was **PfSPZ Vaccine**, a radiation-attenuated vaccine based on Pf sporozoites (Sanaria Inc., Rockville, Maryland.)

Vaccine efficacy against parasitemia (whether before or during pregnancy) was **65%** in those who received the lower dose vaccine and **86%** in those who received the higher dose.

The researchers speculate that the **PfSPZ Vaccine might avert malaria-related early pregnancy losses** since **parasitemia risk during the periconception period was reduced by 65 to 86%.**



Patra et. al., Ann Int Med 2007.



Scott et. al., AJTMH 2021

2015 SAGE position paper suggests additional areas of study: Vaccination in pregnancy

1ST MAY 2015, 90th YEAR No. 18, 2015, 90, 185–200 http://www.who.int/wer

Name of Investigational Product: Hecolin®	
Name of Active Ingredients: HEV recombinant protein (rHEV) vaccine [Escherichia coli]	
Title of Study: A Phase II, Randomized, Observer-blinded, Placebo Controlled Trial to Evaluate the Safety and Immunogenicity of Hecolin® in Healthy Pregnant Women between Gestational Age 14-34 weeks and Non-Pregnant Women of 16 years of age and above	
Study Centers: The Aga Khan University	
Site Principal Investigators: Dr. Imran Nisar	
Study Period (years/months) Estimated date first participant enrolled: Jan 2023	**Phase of development:** II

Credits: Julia Lynch and Katherina Song, IVI

SUMMARY AND SCOPE OF DISCUSSIONS

- Substantial progress in maternal immunization research has occurred
- Safety assessment of maternal, obstetric and perinatal outcomes is essential in maternal immunization RCT and RWE studies
- Different analytic approaches could impact results – as exemplified by the outcome of interest : Preterm birth
- **The goal of this meeting is to discuss how differences in analytic approaches in clinical trials and in RWE analyses can impact assessment of safety outcomes (…and could even lead to a false rejection of a safe vaccine).**
- Consensus on methods would facilitate regulatory review of vaccines for use in pregnancy, safety evaluation in RCT and post-authorization studies, and public health recommendations for their use.

THANK YOU

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Texas Children's Hospital

OPPORTUNITIES FOR INCLUSION OF PREGNANT WOMEN IN RESEARCH

Emergent and re-emerging pathogens of importance to pregnant women and infants

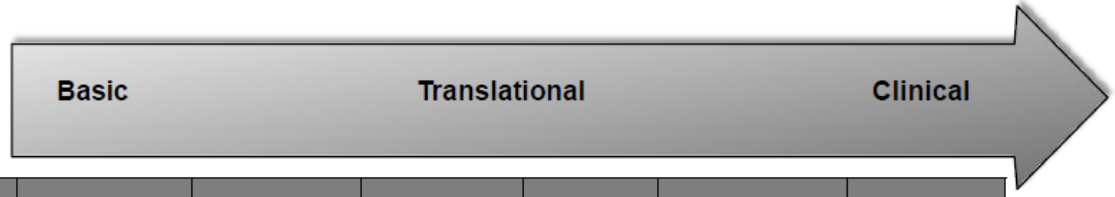
- 2009 Influenza pandemic
- 2014; 2018 Ebola outbreaks DRC
- 2015-16 Zika outbreaks Americas
- 2019 SARS-CoV-2 Pandemic
- 2023 Sudan Hepatitis E outbreak
- 2023-24 mpox outbreak globally
- 2024-25 Chikungunya outbreaks Americas and abroad
- 2024-25 Oropuche vertical transmission

Diseases that pose a risk to mothers and infants

- Malaria
- Hepatitis
- Yellow Fever
- Dengue
- Group B Streptococcus
- Meningitis B
- HSV
- Pertussis, CMV
- Respiratory Syncytial Virus

NIH MATERNAL IMMUNIZATION PROGRAM US 1980 TO PRESENT

DMID Maternal Immunization Research Pathway



Pathogens	Natural history studies including epidemiology	Vaccine antigen identification	Laboratory assays and reference materials	Animal models	IND-enabling studies; developmental toxicity	Phase I/II clinical trials
Group B streptococcus	X	X	X	X	X	X
Haemophilus influenza type B		X	X		X	X
Streptococcus pneumoniae			X		X	X
Pertussis			X	X		X
Respiratory Syncytial Virus	X		X	X	X	X
Influenza Virus			X			X

Rubin et al, Vaccine, 2015

Protocol design, safety monitoring, assessment and reporting tools for studies of vaccines in pregnancy

Vaccine 31 (2013) 4274–4279

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Research on vaccines during pregnancy: Protocol design and assessment of safety☆,☆☆

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Vaccine 31 (2013) 4264–4273

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Research on vaccines during pregnancy: Reference values for vital signs and laboratory assessments

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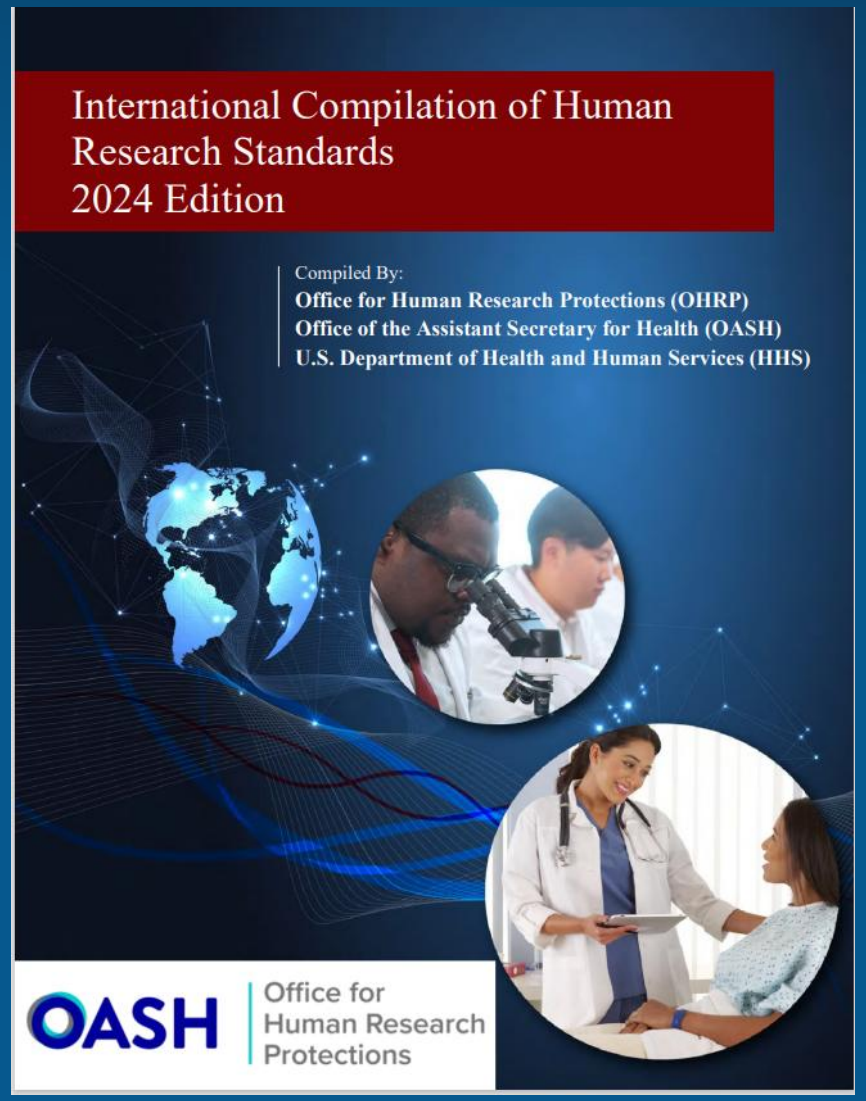
Activity	Year	Region and agency
Content and Format of Labeling for Human Prescription Drug and Biological Products: Requirements for Pregnancy and Lactation Labeling[1]	2014	US, US Food and Drug Administration
Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)[2]	2016	US, US Department of Health and Human Services
Report of the Commission on Human Medicines' Expert Working Group on Hormone Pregnancy Tests[3]	2017	UK, Commission on Human Medicines
PRGLAC Report to Congress[4]	2018	US, Department of Health and Human Services
Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials: Draft Guidance for Industry[5]	2018	US, US Food and Drug Administration
Drug Safety in Pregnancy in a Large, Multisite Database: Mother-Infant Linkage in Sentinel[6]	2018	US, US Food and Drug Administration
ConcePTION – Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology and Breastfeeding to Improve Outcomes Now[7]	2019	Europe, Innovative Medicines Initiative
Guideline on Good Pharmacovigilance Practices: Pregnant and Breastfeeding Women[8]	2019	Europe, European Medicines Agency
Postapproval Pregnancy Safety Studies: Guidance for Industry[9]	2019	US, US Food and Drug Administration
Clinical Lactation Studies, Considerations for Study Design: Guidance for Industry[10]	2019	US, US Food and Drug Administration
Programme of Work: Research to Support the Safer Use of Medicine during Pregnancy[11]	2019	UK, Medicines and Healthcare products Regulatory Agency
Strategic Reflection: EMA Regulatory Science to 2025[12]	2020	Europe, European Medicines Agency

Nooney, Clin Pharm and Therapeutics 2021

RESEARCH STANDARDS



The International Compilation of Human Research Standards enumerates **over 1,000 laws, regulations, and guidelines** (collectively referred to as "standards") **that govern the protection of research participants in more than 130 countries**, as well as standards from various international and regional organizations.

First published in 2005, the Compilation is intended for use by researchers, IRBs/Research Ethics Committees, sponsors, and others who are involved in the conduct or oversight of research involving human participants around the world.

International Compilation of Human Research Standards, 2024 Edition

TEMPLATE TOOL TO ASSESS SUITABILITY OF VACCINES DURING PREGNANCY

Key questions for the evaluation of candidate vaccines for emergent pathogen for pregnant and breast-feeding women
Section A. Key questions about the pathogen, disease, and pregnancy
Section B. Key questions about specific vaccine platforms and components
Section C. Key questions about the development and planning for all candidate vaccines (regardless of construct or platform) for pregnant and breast-feeding women and their exposed offspring
Section D. Key questions for post-licensure safety evaluation of vaccine use during pregnancy
Section E. Summary of the evaluation of the candidate vaccine for use in pregnant and breast-feeding women

Munoz FM et al. Vaccine Volume 62, 30 August 2025, 127513

TEMPLATE TOOL TO ASSESS SUITABILITY OF VACCINES DURING PREGNANCY

Section A
A1 What is known about the risk in pregnant and non-pregnant women of child-bearing age
A3. What is known about the effect of the pathogen on pregnancy and obstetric outcomes
A4. Is there any evidence for vertical transmission of the pathogen and natural immunity?
A5. Effects of maternal infection on the fetus, neonate and infant
A7 Post-partum and breast-feeding women

Section B
B1. What safety data are available to show that use of the vaccine in pregnancy and breast-feeding is safe?
B3 .Vaccine construct or platform (BRAVATO tables non-pregnancy)
B4. General and pre-clinical toxicology studies on vaccine construct and components

Section C
C1 Pre-clinical pregnancy data (DART)
C2 Clinical development status and plans for the vaccine in non-pregnant populations – Plan to include pregnant/lactatingwomen?
C… Immunogenicity, safety, efficacy data in non-pregnant and pregnant populations)
C.. Pregnancy specific – timing of vaccination, duration of follow up

Summary

E1 Key criteria to suggest vaccine for:

E1.1 Pregnant women

E1.2 Breast-feeding women

E2 Key criteria to reject vaccine for:

E2.1 Pregnant women

E2.2 Breast-feeding women

E3 Key considerations for proceeding with evaluation of a vaccine for:

E3.1 Pregnant women

E3.2 Breast-feeding women

E4 What safety data are needed for inclusion of pregnant women in clinical studies?

E5 What efficacy data are needed for inclusion of pregnant women in clinical studies?

E6 What are the identified data gaps?

E7 In which vaccine development phase should pregnant women be included?

E8 What is the optimal timing for vaccination during pregnancy?

E9 Has the communication plan been finalized and accepted by all stakeholders?

E9.1 Has the communication plan been implemented?

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