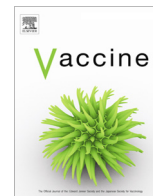




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Obstetrics risk Assessment: Evaluation of selection criteria for vaccine research studies in pregnant women



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ABSTRACT

Vaccines designed for use in pregnancy and vaccine trials specifically involving pregnant women are rapidly expanding. One of the key challenges in designing maternal immunization trials is that developing exclusion criteria requires understanding and quantifying the background risk for adverse pregnancy outcomes in the pregnancy being studied, which can occur independent of any intervention and be unrelated to vaccine administration.

The Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) project has developed and published case definitions and guidelines for data collection, analysis, and evaluation of maternal immunization safety in trials involving pregnant women. Complementing this work, we sought to understand how to best assess obstetric risk of adverse outcomes and differentiate it from the assessment of vaccine safety. Quantification of obstetric risk is based on prior and current obstetric, and maternal medical history. We developed a step-wise approach to evaluate and quantify obstetric and maternal risk factors in pregnancy based on review of published literature and guidelines, and critically assessed these factors in the context of designing inclusion and exclusion criteria for maternal vaccine studies. We anticipate this risk assessment evaluation may assist clinical trialists with study design decisions, including selection of exclusion criteria for vaccine trials involving pregnant women, consideration of sub-group classification, such as high or low risk subjects, or schedule considerations, such as preferred trimester of gestation for an intervention during pregnancy. Additionally, this tool may be utilized in data stratification at time of study analyses.

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1. Introduction

Immunization of pregnant women, or maternal immunization, is a practical, evidence-based strategy to prevent severe morbidity and reduce mortality in mothers, neonates and young infants [1]. Vaccine research requires careful assessment of safety and efficacy

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in all study participants. When administering a vaccine to pregnant women, safety evidence must encompass the mother, the developing fetus, and subsequently the neonate, infant, and the child. Accumulating this safety data with the ability to reliably measure potential adverse events of interest is improved by standardization of definitions of potential adverse events and data collection in a manner that is applicable across all resource settings.

With the goal towards broadening future maternal immunization trials, in 2014 the World Health Organization (WHO) convened a stakeholder meeting where key obstetric and neonatal terms were identified and prioritized for standardization of definitions [2]. The Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) project was established, and since 2014, GAIA [3], utilizing Brighton Collaboration methodology, has developed and published case definitions and guidelines for data collection, analysis, and presentation of maternal immunization safety data in trials involving pregnant women for twenty-one obstetric and neonatal terms [4]. These case definitions and tools have been adopted in recent maternal immunization studies to evaluate maternal and neonatal outcomes, including use in a recent Phase III maternal immunization trial [5,6].

Clinical trials in pregnant women are complex because, even in healthy pregnant women, adverse obstetric outcomes (such as fetal abnormalities, preterm birth, miscarriage, growth restriction and preeclampsia) occur and thus can also be anticipated to occur in the setting of a clinical trial, independent of the intervention. Many of the women who develop these problems do not have risk factors, making complications which occur in pregnancy difficult to predict. The risk of pregnancy complications can be, in part, informed by the background rates of these events in any given population. However, data on background rates of adverse pregnancy outcomes may not always be available [7].

Hence, it is challenging for clinical investigators to know which prior and current pregnancy risk factors are appropriate study exclusion criteria. The selection of criteria for inclusion or exclusion of subjects in the study is among the more critical study design decisions. In early phase clinical trials, it is common to enroll the healthiest populations to minimize risk. As the product profile is better defined in later stage studies, a broader group of individuals are generally enrolled. By Phase 3, study participants more closely mirror the target population for the vaccine and are enrolled in larger numbers, and it is typical to have fewer exclusion criteria.

Currently, standardized guidance is lacking that may inform the choice of inclusion and exclusion of pregnant participants for any of the vaccine trial development phases. Understanding the obstetric risk of common inclusion and exclusion criteria may facilitate not only a more informed choice of inclusion and exclusion criteria in these clinical studies of vaccines in pregnant women, but also a tailored use of these criteria based on the phase of development (I–IV) of the vaccine.

In an effort to assist clinical investigators in maternal immunization trials, a GAIA Working Group with broad geographic and specialty representation was formed to evaluate the selection criteria that have previously been used to select women for participation in clinical trials of vaccines in pregnancy and to develop a strategy to help assess obstetric risks for designing maternal immunization trials. The overriding aim is to develop a consolidated evaluation and quantification of risk factors in pregnancy that would be useful to investigators in designing vaccine trials involving pregnant women. While this assessment is designed specifically for vaccine trials, it may also offer applicability for other interventions being assessed in pregnant women.

2. Methods

We used several methods to identify the criteria previously used for inclusion and exclusion of study participants in studies of vaccines in pregnancy. We searched the National Institutes of Health U.S. National Library of Medicine ClinicalTrials.gov database to identify current, completed or withdrawn studies of vaccines in pregnant women. Studies were identified the search terms “pregnancy”, “pregnant women”, “maternal”, “mothers”, “immunization”, “vaccination”, “vaccine”, “vaccines”, and a combination of the term “pregnancy” or “maternal” with specific vaccines including “influenza”, “tetanus”, “Tdap”, “pertussis”, “respiratory syncytial virus”, “RSV”, “group B streptococcus”, “GBS”, “pneumococcal”, “pneumococcus”, “meningitis”, “meningococcal”, “hepatitis”, “pandemic”, “seasonal”. All relevant studies listed in the ClinTrials.gov through 07 October 2018 were included. We identified a total of 43 interventional and 21 observational studies of vaccines in pregnant women. We abstracted and reviewed the complete list of inclusion and exclusion criteria utilized in each of these studies. Appendix A delineates the list of included studies

We used similar search terms to conduct a literature search (2005–2018) in Medline, Embase, and leading textbooks to identify and catalogue published US and international guidelines used to classify pregnancies based on obstetric risk, and to identify guidelines for referral from a mid level provider to a high risk provider, or from a low risk facility to a high risk or tertiary facility. We chose to include guidelines for referral in our approach because high risk prenatal referral guidelines represent what pregnancy care providers utilize to judge increased obstetric risk, and could inform trial design. Lastly, we conducted a literature review searching for articles listing obstetric risk factors as they pertained to clinical trials and vaccine trials.

Based on these findings, we derived a comprehensive matrix of exclusion criteria and obstetric conditions used to determine the risk of adverse outcomes during pregnancy. We classified these into broad categories, including past obstetric and gynaecological history, family history, medical and obstetric conditions during the current pregnancy and fetal conditions. Individual tables were then derived from this matrix for interventional studies classified by development phase (phase I to IV), observational studies, and practice guidelines, detailing the number of studies or guidelines where each potential risk factor was cited. Based on this matrix, we created a heat map to indicate frequency of occurrence.

After creating this matrix, we identified the most commonly listed exclusion criteria in clinical studies conducted in pregnant women, and considered the most common factors that could increase the risk for adverse outcomes during pregnancy. In order to provide more detail about the risk of adverse events in the current pregnancy associated with these exclusion criteria, we looked for studies documenting risk of various adverse pregnancy outcomes when the identified condition listed as an exclusion criteria occurred during pregnancy.

3. Results

3.1. Exclusion factors matrix

Sixty three maternal immunization studies (25 Phase I/II, 7 Phase III, 11 post licensure, 21 observational) were identified from ClinicalTrials.gov (Appendix A) and six practice guidelines were identified by obstetric experts. Table 1 is an alphabetical and categorized line listing of the most common exclusion factors by study type with their respective frequency. Appendix B is a summation of all exclusion factors included in these studies and risk factors in practice guidelines. The exclusion and risk factors were grouped

Table 1
Enumeration of most frequent exclusion factors in study types and risk factors in antenatal clinical care guidelines.

Exclusion factors	Phase I/II studies (n = 25)	Phase III studies (n = 7)	Phase IV studies (n = 11)	Observational studies (n = 21)	Guidelines (n = 6)	Total (n = 70)
A) Current General risk factors						
Advanced maternal age	17	4	6	2	4	33
Current alcohol or drug misuse/dependency/ teratogenic drug	8	2	3	0	5	18
Young maternal age	19	4	8	16	4	51
B) Past Obstetric history						
Cesarean section	0	1	0	0	6	7
Congenital anomaly (genetic or structural)	3	2	4	0	5	14
Hypertensive disease (pre-eclampsia/ eclampsia)	5	1	4	0	6	16
Perinatal death/Stillbirth	6	2	2	0	6	16
Postpartum hemorrhage	2	0	0	0	5	7
Preterm birth	7	2	4	0	5	18
Spontaneous abortion	5	0	2	0	3	10
C) Current Maternal Medical Conditions during Pregnancy						
Anemia	2	1	1	1	5	10
Autoimmune/connective tissue disorder	8	2	4	2	5	21
Blood group antibodies (e.g. Kell, RH)	1	1	1	1	5	9
Cardiac disorders	12	1	3	3	4	23
Congenital or acquired clotting or bleeding disorders	8	1	4	1	4	18
Hepatitis B	8	1	4	1	4	18
HIV	15	1	8	5	5	34
Obesity	2	1	0	0	6	9
Psychiatric disorders	14	2	5	2	4	27
Renal disorders	7	1	3	3	4	18
Sickle cell disease	1	1	1	0	5	8
Systemic lupus erythematosus	3	1	0	1	4	9
Type 1 diabetes mellitus	9	1	4	1	5	20
Type 2 diabetes mellitus	5	1	4	0	5	15
D) Current pregnancy-related conditions and fetal conditions						
Fetal congenital anomaly (genetic or structural)	6	0	4	3	3	16
Gestational Diabetes	4	1	4	0	3	12
Gestational hypertension	5	3	2	1	5	16
Pre-eclampsia	9	4	3	1	4	21
Premature labor	7	3	3	3	5	21
	Phase I/II studies	Phase III studies	Post licensure studies	Observational studies	Guidelines	All studies and guidelines
Total exclusion factors and risk factors listed*	119	74	73	48	140	164

* Total number of exclusion or risks factors listed in each study type or clinical guideline.

by MedDRA criteria/organ system classification. Because the exclusion factors listed and referral risk factors were consistent, they were included in one matrix for ease of analysis.

3.2. Exclusion factors tabulation

When evaluating the matrix, for all phases of studies and for the practice guidelines investigated, a few obstetric risk factors were most commonly chosen as exclusion criteria. These included general risk factors present during the current pregnancy such as advanced (over 35) or young (10–19 years) maternal age, and current alcohol or drug use; past obstetric history of congenital anomalies, hypertensive disease during pregnancy, perinatal death or stillbirth, prior preterm birth, and spontaneous abortion; current maternal medical conditions varying from HIV or other immunodeficiency, to psychiatric disorders (see [Box 1](#)).

3.3. Exclusion criteria and study development Phase

More exclusion criteria were utilized in earlier phase clinical trials, as depicted in the overall heat map ([Appendix B](#)) of potential factors. In Phase I/II trials (n = 25), the number of exclusion criteria listed at least one time was 119. Thus far, the number of Phase 3 clinical trials in maternal immunization was limited (n = 7). While

the number of exclusion criteria (74) was less than in the Phase I/II trials, exclusion criteria were extensive. As expected, in observational studies (n = 21), we observed the least exclusion criteria (48) ([Table 1](#)).

3.4. Adverse outcomes for the most common exclusion criteria

While [Table 1](#) presents the frequencies that each of these factors were listed as exclusion criteria in different phases of clinical trials of vaccines in pregnancy and in relevant practice guidelines. [Table 2](#) summarizes the risks of adverse outcomes for some of the factors.

In addition to the [Table 2](#) summary of risk factors, we used our literature search to provide more detailed and highly referenced text discussions of these risk factors in [Appendix C](#). Due to the length of this discussion on these 15 most common exclusion criteria (listed in [Box 1](#)), this text discussion is presented in [Appendix C](#) as Supplemental Material.

4. Discussion

The purpose of this project was to provide clinical researchers with data that may be helpful in selecting appropriate exclusion criteria for maternal vaccine clinical trials. We created a compre-

Table 2
Elevation of Adverse Pregnancy, Maternal or Neonatal Outcomes Associated with Exclusion Criteria.

Factor	Outcome in current pregnancy, OR (95% CI)					
	SAB	Preterm labour	Preterm birth	Stillbirth	Adverse neonatal outcome	Adverse obstetric outcome
AMA [8,9]		1.2 (1.1–1.2)		1.5 (1.4–1.7)	ND 1.4 (1.3–1.5)	MM 1.7 (1.2–2.6)
Young Age [10–14]			1.6 (1.2–1.9)	1.3 (1.1–1.6)	1.6 (1.2–1.7)	Eclampsia Infections C/D rate
Drug and Alcohol use [15,16]	†IUFD 5.1 (3.3–7.2)	2.1 (2.0–2.3)	3.38 (2.7–4.2)	3.0 (1.4–6.4)	FGR 2.7 (2.4–2.9) 33–100%†	Cong Anom Plac ABR 2.4 (2.1–2.6)* Plac ABR 5.5 (4.9–6.3) ‡ Plac ABR 3.9 (2.8–5.5) §
Hypertension [17–22]			2.7 (1.9–3.6)		ND 4.2 (2.706.5) LBW 2.7 (1.9–3.8) NICU 3.2 (2.2–4.4)	Plac ABR 2-fold 29% pregnancies SIPE
Prior Stillbirth [23–29]			4.9 (1.5–15)	2–10 fold		
Prior Preterm Birth [30]			22% vs 9%	5.6 (1.8–17)		
Prior Pregnancy Loss [31]			1.4 (1.1–1.9)		LBW 1.4 (1.2–1.6)	
Bleeding Disorders [32–35]	FVL 1.7 (1.1–2.6) ACA 3.4 (1.3–8.7)				FGR, ACA 6.9 (2.7–17.7)	FVL, PIH 2.2 (1.5–3.3) Plac ABR, FVL 4.7 (1.1–19.6) PIH, ACA 2.7 (1.7–4.5)
Pre-gestational Diabetes Mellitus [36–42]			1.6 (1.2–2.2) iPTD 8.1 (6.0–10.9)	6.1 (4.4–8.4)	Cong Anom 2.4 (1.9–3.1)	C/D 1.6 (1.3–2.0) PIH 1.3 (1.2–1.4)
HIV Positive [43–46]	4.0 (2.8–6.0)		1.8 (1.6–2.1)	3.9 (2.7–5.8)	FGR 1.7 (1.4–2.0) ND 1.8 (1.1–2.8)	MM 1.8 (1.0–3.3)
Obesity (BMI > 30) [47,48]				1.4 (1.1–1.7)		GDM 3.6 (3.3–4.0) PIH 2.1 (1.9–2.5) IOL 1.8 (1.7–1.9) C/D 1.8 (1.7–1.9) PPH 1.4 (1.3–1.5) Wound infection 2.3 (1.9–2.6)

Abbreviations: ACA, anti-cardiolipin antibodies; AMA, advanced maternal age; C/D, cesarean delivery; FGR, fetal growth restriction; FVL, Factor V Leiden; GDM, Gestational Diabetes Mellitus; IOL, Induction of labour; iPTD, iatrogenic or medically indicated preterm birth; LBW, low birth weight; MM, maternal mortality; ND, neonatal death; NICU, neonatal intensive care admission; PIH, Pre-eclampsia / Pregnancy induced hypertension; Plac ABR, placental abruption; PPH, postpartum haemorrhage; SAB, spontaneous abortion.

* Opioid use.

† Alcohol.

‡ Methamphetamine use.

§ Cocaine use.

hensive matrix of exclusion and risk factors delineating the frequency of exclusion criteria and risk factors used across the spectrum of clinical studies of vaccines in pregnancy. The selection of subjects and the selection of the risk threshold that is acceptable will depend on the type of vaccine being used, the phase of the clinical study, and various other factors such as the perception of risk and potential real risks in a given population. We sought to catalogue and provide specific data on adverse pregnancy outcomes associated with the more commonly utilized exclusion criteria, to guide the use of obstetric risks for the selection of participants in clinical trials of maternal immunization. Adverse outcomes may occur in normal low risk pregnancies without interventions. These obstetric risks do not imply an increased risk of vaccination. Therefore, a better understanding of obstetric risks may facilitate not only a more informed choice of inclusion and exclusion criteria in these clinical studies of vaccines in pregnant women, but also a tailored use of obstetric risk criteria based on the phase of development of the vaccine.

The field of maternal immunization has continued to evolve and rapidly expanded after the 2009 influenza pandemic. Because of obstetric risks and the complexity of the maternal-fetal dyad, pregnant women have been considered a vulnerable population, excluded from participation in experimental trials of vaccines and drugs, particularly when these are not intended for the management of obstetric conditions. To facilitate inclusion of pregnant

women in studies and research on immunizations targeting pregnant women, bodies such as the Food and Drug Administration and the National Institutes of Health have addressed and published guidance on inclusion of pregnant women in clinical trials. Topics addressed have included ethical and consent consideration [49], and development of standards for laboratory and physiologic parameters in pregnant women to assist in evaluation of outcomes in pregnant women participating in clinical trials [50–54]. General guidance on the conduct of research in pregnancy has been developed by the National Institutes of Health after conducting clinical trials of licensed and experimental vaccines since the 1980's, and global experience has been growing as more studies funded by industry and other organizations like the Bill and Melinda Gates Foundation are being pursued in all resource settings in the last decade [1]. Consensus statements, such as PREVENT, advocating for inclusion of pregnant women in vaccine trials are now published [55]. The exclusion of pregnant women and their infants from the benefits of potentially life-saving drugs and vaccines through clinical trials is no longer considered acceptable [56,57]. At present, vaccines specifically for use in pregnant women against at least two pathogens: Respiratory Syncytial Virus (RSV) and Group B Streptococcus (GBS), are in clinical development. Active evaluation of these and other vaccines for women during or prior to pregnancy is ongoing (eg. Pertussis, Cytomegalovirus (CMV) and Hepatitis E).

Complications in pregnancy can occur even in normal low risk pregnancies, and all medicinal products including vaccines can have side effects – although not everyone has them. In clinical studies where there is a placebo or comparator group, similar frequency of obstetric adverse events is expected to occur in both groups. For Phase III trials, ideally the study population should mirror the target population. Exclusion criteria based on selection of women with low risk for obstetric complications can be too restrictive and limit the ability to assess safety of the vaccine in the populations who need it the most. Additionally, exclusion criteria may act indirectly to alter study results by excluding participants who would otherwise be at increased risk for a condition. For example, Group B Streptococcus (GBS) is considered an important cause of stillbirth and preterm labor globally. Eliminating pregnant women with a prior stillbirth or prior preterm labor from participation in clinical research on GBS may also impact efficacy results of an intervention and may add bias to the study [58,59]. In fact, inclusion of “higher risk” populations may better allow the ability to demonstrate differences between vaccine and control and potentially make a vaccine available to women sooner.

Researchers should determine what population they will evaluate (such as healthy and at risk), understand the potential risks (obstetric risks versus vaccine risks), and wherever possible, utilize the background rates of certain obstetric, maternal and neonatal events of interest in the general population for interpretation and assessment of these risks to determine if vaccination would potentially increase the occurrence of these events above such expected background rates. While the assessment of exclusion criteria presented in this article does not differentiate obstetric risks from vaccine risks, the quantitation of risk may facilitate trialists' ability to consider appropriate inclusion/exclusion criteria that reaches a balance between minimizing risk to participants and enabling inclusion of relevant populations. Its use may facilitate not only a more informed choice of inclusion and exclusion criteria in these clinical studies of vaccines in pregnant women, but also a tailored use of these criteria based on the phase of development of the vaccine. Having more granular information about the obstetric risks, as provided in Appendix C, may help trialists to anticipate the potential obstetric risks in each trimester. For instance, with spontaneous abortion risks mostly in the first trimester, or pre-eclampsia in the third trimester, a trialist could have a more accurate estimation of magnitude of adverse events, and consider these combined with the expected (background) risk in the studied population, the known or anticipated product safety profile, and the timing of the intervention (trimester of exposure) in pregnancy. Its use may facilitate not only a more informed choice of inclusion and exclusion criteria in these clinical studies of vaccines in pregnant women, but also a tailored use of these criteria based on the phase of development of the vaccine.

Using the information provided in this manuscript and its supplements may actually be most useful for the design of the studies that are currently being planned for some emerging infections. This is because there is a need to be more inclusive (with less restrictive criteria) which may be associated with the occurrence of adverse events linked to the population being evaluated. However, we cannot choose to leave pregnant women out of the opportunity to benefit from vaccines that are being given to or studied in the general population, such as Ebola or those to protect against coronavirus disease 2019 (COVID-19). In fact, the inclusion of pregnant and lactating women in studies of vaccines in epidemic or pandemic settings has been a topic of debate and publication even before the current COVID-19 pandemic [55,60–62].

This approach has several strengths. To our knowledge, this delineation and frequency mapping of exclusion criteria based on a comprehensive search of prior maternal immunization trials has not been done previously. Adding stratification by study phase

offers additional information for trialists. Including referral guidelines for high risk pregnancies in the matrix adds an obstetric provider perception of risk factors for adverse events. Another unique aspect of our approach and perhaps of the most useful to trialists may be to offer more quantitative information about these factors for the most commonly listed exclusion criteria.

This obstetrics risk assessment method we present here is not exhaustive nor is it meant to be prescriptive. This tool will not replace the need for detailed literature reviews about potential risk factors and exclusion criteria for specific products in pregnant populations, nor will it replace the need for using background rates of adverse events to assess safety. It is not designed to replace the clinical acumen and knowledge base that is offered by involving experienced obstetric providers and vaccine evaluators in trial design of vaccines in pregnancy. However, given that a standardized approach to the selection of participants in studies of vaccines in pregnancy is necessary, this information may serve to help clinical researchers reassess how conservative they need to be as a product progresses in development. The balance between deciding exclusion criteria and choosing a study population that mirrors the general population is complex. As clinical trials for vaccines specifically designed for an indication in pregnant women are novel, initial early phase trials may have more strict exclusion criteria. However, ongoing reassessment of criteria for inclusion in these and other protocols where pregnant women are study subjects will be imperative as data on background rates of expected obstetric events and safety information from epidemiologic studies and maternal immunization trials become more widely available.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Linda O Eckert: Site investigator: Novavax Trial. Received no personal funding for these activities.

Christine E Jones: Investigator for clinical trials done on behalf of her institutions, sponsored by vaccine manufacturers, but receives no personal funding for these activities. Alisa Kachikis: Site investigator: Novavax Trial but receives no personal funding for these activities. Advisory Boards on Maternal Immunization for GSK and Pfizer. Azucena Bardaji: None].

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2020.05.022>.

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