

Assessment of Safety in Newborns of Mothers Participating in Clinical Trials of Vaccines Administered During Pregnancy

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A panel of experts convened by the Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, developed proposed guidelines for the evaluation of adverse events in newborns of women participating in clinical trials of maternal immunization in the United States.

Keywords. maternal immunization; safety; pregnancy; vaccines; clinical trials.

There is growing interest in the development and use of vaccines for administration during pregnancy to protect mothers and young infants against infectious diseases. Vaccination of women during pregnancy against tetanus, influenza, and pertussis is currently recommended in the United States [1–3]. These vaccines, available and licensed for nonpregnant adolescents and adults, are also recommended for pregnant women. These recommendations are based on the increased risk these infections pose to the mother and/or the infant, the known safety profile of these vaccines in nonpregnant populations, and the recognition that immunization during pregnancy is the best approach to protect infants when infections occur early in life, before effective infant vaccination is possible and when boosting the concentrations of maternal

antibodies transferred transplacentally offers the most direct and efficient protection to the newborn [4, 5].

Worldwide, other approved vaccines are given to pregnant women in special circumstances, such as during outbreaks or when the risk of exposure to a serious vaccine-preventable infection is high. This is the case with meningococcal A vaccine in the African “meningitis belt” and yellow fever vaccine in endemic regions or during outbreaks, where women who are pregnant are not excluded from receiving these life-saving vaccines [6, 7]. The potential applicability of this approach to prevent other serious infections in young infants is obvious, and vaccines are currently in development for administration during pregnancy to protect infants against group B *Streptococcus* (GBS) and respiratory syncytial virus (RSV) [8]. Globally, pregnant women are currently participating in clinical trials of pertussis, influenza, and pneumococcal vaccines, and safety is being assessed in women who have become pregnant after receiving recommended or experimental vaccines for the prevention of hepatitis B virus, human papillomavirus, Japanese encephalitis virus, human immunodeficiency virus, and malaria [9, 10].

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The assessment of the safety of maternal immunization involves the evaluation of adverse events (AEs) following immunization of the mother to ascertain any immediate injection site and systemic reactogenicity events, as well as any potential vaccine-associated adverse effects on the pregnancy, on the outcomes of pregnancy, and in the postpartum period. The potential for maternal vaccination to result in AEs in the offspring underscores the importance and need to assess AEs in the infants of mothers vaccinated during pregnancy. However, the methodology and definitions to assess the safety of vaccination during pregnancy in mothers and infants have not been standardized.

BACKGROUND

It is not feasible to evaluate the safety of vaccines already in use and recommended for pregnant women in the same manner as new vaccines that are in development or under consideration for administration during pregnancy. Vaccines currently recommended for pregnant women were first licensed and approved for use in nonpregnant populations based on their demonstrated safety and immunogenicity, and recommended for pregnant women based on their perceived benefit and minimal risk for the mother and infant [1–3]. Given that placebo-controlled clinical trials are not ethical for vaccines that all pregnant women are recommended to receive, assessment of their safety in mothers and their infants is limited to retrospective data reviews, passive and active reporting systems, and observational studies [11, 12]. Salient outcomes documented in these reports include maternal, fetal, and infant mortality and morbidity, including obstetric complications such as pregnancy-induced hypertension or gestational diabetes; pregnancy outcomes such as preterm labor, preterm delivery, and cesarean delivery; and infant outcomes such as preterm birth, low birth weight, and congenital anomalies. The frequencies of these events are compared to their expected background rates or to rates in the control group of studies (cohort or case-control studies) to assess a potential association with the maternal receipt of vaccines. This assessment of safety is limited by the retrospective nature of these studies, the variability in definitions and ascertainment of specific outcomes, the degree to which background rates are applicable to the group under study, and the role of potential unmeasured confounders. Whereas clinical trials to evaluate new vaccines in pregnancy can use randomized, placebo-controlled study designs to overcome some of these limitations, there is still a need for standardized methods and definitions for the prospective assessment of AEs in infants born to mothers who receive investigational vaccines.

The Division of Microbiology and Infectious Diseases (DMID) of the National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), has been an active

participant in maternal immunization research in the United States. In 2013, DMID convened a group of experts in areas related to maternal immunization clinical research and tasked this working group with following objectives:

1. To develop a document with definitions and grading of AEs for infants born to mothers participating in clinical trials of vaccines administered during pregnancy. The focus is to provide guidance for studies conducted in the United States or industrialized countries, given the availability of resources to capture AEs in these settings, with the potential to adapt and expand their use in other regions.
2. To identify knowledge gaps and barriers for implementation of the use of these guidelines and the assessment of safety in maternal immunization trials.

Methodology

The working group participated in several teleconferences and 2 meetings sponsored by DMID to develop this report. We searched and identified published and unpublished guidelines and procedures available to date for safety assessment of infants exposed in utero to vaccines. No guidelines were available for this specific purpose, but procedures used in previous clinical trials of vaccines in pregnant women were reviewed [13, 14]. We also searched and identified existing guidelines for the assessment of infant AE outcomes from infant studies (interventional or not) in the United States. Available resources included DMID Pediatric Toxicity Tables (draft November 2007) [15], Division of AIDS Tables for Adult and Pediatric Adverse Events (version 2.0, May 2013) [16], the Baylor College of Medicine Neonatal Toxicity Tables [17, 18], and the Brighton Collaboration reports on safety of vaccines [19].

We then compared definitions of outcomes and determined where there was consensus or disagreement. The outcomes were organized in a table indicating definitions, supporting diagnostic tools, and grading of severity based on DMID criteria (Table 1) [15]. For outcomes without a consensus definition, a “best definition” was suggested and the rationale for this recommendation was documented.

The working group evaluated the options and practicality of this document and decided that this guidance should focus on the assessment of AEs in term infants. Preterm birth and its associated morbidities should be considered independent AEs. Events were selected and prioritized based on frequency of occurrence and significance, and organized by organ system. We included both clinical events and laboratory definitions with a “normal” reference range for each laboratory parameter. Standard definitions and values were used when available. We used “x-fold times above the upper limit of the reference range” or “x-fold times below the lower limit of the reference range” to indicate severity associated with clinically relevant

Table 1. Recommended Core Data Set of Adverse Event Definitions and Severity Grading to Be Collected for Safety Monitoring of Term Infants in Studies of Vaccines Administered During Pregnancy, National Institute of Allergy and Infectious Diseases/Division of Microbiology and Infectious Diseases

Event Definition Normal Range	Assessment of Severity				
	Normal	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life Threatening)
Assessment of neonatal and infant adverse events					
Preterm birth ^a Based on gestational age assessed by best available obstetric estimate, usually prenatal ultrasound or last menstrual period if ultrasound not available	Born at or after 37 wk gestation	Late preterm: 34 to <37 wk gestation	Preterm: 32 to <34 wk gestation	Very preterm: 28 to <32 wk gestation	Extreme preterm: <28 wk gestation
BW, g	BW >2500–3999 Varies with gestational age, sex, race, ethnicity, maternal BMI, and other maternal health factors	NA	Low BW: 1501–2500 High BW : ≥4000 g associated with infant morbidity requiring medical intervention	Very low BW: 1001–1500 High BW: ≥4000 g associated with infant morbidity resulting in prolonged hospitalization	Extremely low BW: ≤1000
Birth weight in relation to gestational age (based on best obstetric estimate, usually prenatal ultrasound or last menstrual period if ultrasound not available)	Based on population specific curves	NA	SGA: BW <10% for infants of same gestational age in same population LGA: >90% for infants of same gestational age in same population	SGA associated with morbidity resulting in prolonged hospitalization LGA associated with infant morbidity resulting in prolonged hospitalization	NA
Birth length	Varies with gestational age, sex, race, ethnicity, and parental height	NA	<10% for gestational age	<1% for gestational age	NA
Birth FOC Microcephaly, low FOC Macrocephaly, high FOC	Varies with gestational age, sex, race and ethnicity	NA	Low FOC: >2–3 SD below mean for gestational age and sex High FOC: >2–3 SD above mean for gestational age and sex	Low FOC: >3 SD below mean for gestational age and sex High FOC: >3 SD above mean for gestational age and sex	NA
General assessment					
Neonatal complications in a term infant, including congenital anomalies ^b , clinical or laboratory abnormalities, and events not listed in this table	Normal term infant discharged home with mother after uncomplicated delivery and nursery course	Transient or minimal signs, symptoms, or findings requiring no intervention, symptomatic treatment, or only monitoring, and resolved at the time of discharge	Signs, symptoms or findings requiring intervention or specific therapy resulting in prompt clinical response or resolution and infant discharged home within a week of initiation of therapy	Signs, symptoms, or findings requiring therapy and/or interventions (including surgery) leading to prolonged hospitalization	Life-threatening laboratory or/and clinical signs and symptoms
Systemic conditions					
Fever Elevated body temperature assessed by axillary temperature	Normal newborn temperature: 36.5°C–37.6°C (97.7°F–99.7°F)	37.7°C–38.6°C (99.8°F–101.4°F) resolving spontaneously or with environmental measures (eg, removal of clothing, blankets or heat source)	38.7°C–39.3°C (101.5°F–102.7°F) transient, with or without symptoms, or requiring medical treatment	39.4°C–40.5°C (102.8°F–104.9°F) with associated clinical symptoms, or requiring medical treatment	>40.5°C (>104.9°F), and/or shock ^c , convulsions, coma

Table 1 continued.

Event Definition Normal Range	Assessment of Severity				
	Normal	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life Threatening)
Hypothermia ^d : Low body temperature, assessed by axillary temperature Preterm and low-BW infants are at risk Symptoms may include: Decreased activity, weak cry, decreased feeding ability, cool skin	Normal newborn temperature: 36.5°C–37.6°C (97.7°F–99.7°F) Affected by gestational age, environment at delivery and postnatally, and neonatal conditions.	36.0°C to <36.5°C (96.8°F to <97.7°F), resolving with routine measures to maintain normal temperature after birth ^d	<36.0°C–35.0°C (<96.8°F–95.0°F) requiring and responding to intervention needed in addition to routine measures to maintain normal temperature	<36.0°C–35.0°C (<98.9°F–95.0°F) persistent despite intervention	<35.0°C (<95.0°F)
Infection (congenital or acquired)	None	Localized, superficial, self-limited, or requiring only topical or oral therapy	Localized or systemic, requiring evaluation and systemic treatment with adequate response	Systemic, single or multiorgan involvement, requiring prolonged therapy. May result in long term sequelae	Sepsis, shock Life-threatening congenital infection
Bleeding Symptoms may include tachycardia, hypotension, diaphoresis, lethargy, pallor, cyanosis, shock	None	Transient, low volume, not associated with symptoms and not requiring intervention	Symptomatic, responsive to volume replacement	Symptomatic, resulting in anemia, requiring transfusion	Shock, anemia, bleeding requiring multiple transfusions
Failure to thrive or growth deficiency Failure to grow and develop normally compared to infants of the same gestational and postnatal age; or inability to maintain expected growth rate over time, evaluated by plotting individual weight gain and growth on standard growth charts for the population	Normal newborn weight gain includes weight loss of up to 10% of birth weight in the first 1–2 weeks of life, with steady, predictable weight gain thereafter. Progress varies by gestational and postnatal age, genetic, and environmental factors	Growth is slow or stopped progressing Requires dietary supplementation to maintain weight gain	Weight for age below the 5th percentile for age, or <80% ideal body weight for age, and/or requires alternative methods of enteral nutrition (nasogastric or nasoduodenal or gastric tube feedings) to maintain weight gain	Weight for age below the 5th percentile for age, or <80% ideal body weight for age, and/or requires parenteral nutrition or surgical interventions to maintain weight gain	NA
Respiratory Respiratory distress Assessed by evaluation of RR, nasal flaring, grunting, retractions, pallor, and cyanosis or hypoxemia.	Unlabored breathing and RR, no oxygen requirement RR varies with gestational age and decreases with postnatal age. A term newborn normal RR is usually 30–60 breaths/min	Transient tachypnea and/or hypoxemia (oxygen saturation <95%) requiring brief period of oxygen supplementation with <70% FiO ₂	Persistent tachypnea and/or hypoxemia requiring high (70%–100%) FiO ₂ supplementation or CPAP. Associated with other clinical symptoms (nasal flaring, grunting, retractions, pallor, or cyanosis)	Respiratory failure requiring mechanical ventilation and/or inhaled nitric oxide	Respiratory failure requiring high frequency oscillatory ventilation or extracorporeal membrane oxygenation

Table 1 continued.

Event Definition Normal Range	Assessment of Severity				
	Normal	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life Threatening)
Apnea ^e Cessation of breathing for 15 s or more, or a shorter respiratory pause associated with bradycardia, cyanosis, pallor, and/or hypotonia	None	Transient, requires no intervention except stimulation and/or airway clearing	Frequent, recurring, prolonged, and/or requiring oxygen supplementation or medication	Frequent, recurring, prolonged and/or requiring CPAP and/or medication	Requires intubation for ventilatory support Acute life-threatening event: combination of apnea, color change (cyanosis, pallor, or plethora), marked limpness, and choking or gagging
Cardiovascular					
Hypotension	Blood pressure varies by gestational age and sex	Transient asymptomatic decrease in systolic or mean arterial blood pressure at least 10 mm Hg below normal for age and sex	Symptomatic and persistent decrease in systolic or mean arterial blood pressure at least 15 mm Hg below normal for age and sex	Symptomatic and persistent decrease in systolic or mean arterial blood pressure ≥ 20 mm Hg below normal for age and sex	Shock, end organ failure (particularly renal), ischemic injury as a result of hypotension
Hypertension	Blood pressure varies by gestational age and sex, and length/height	Transient asymptomatic increase in systolic or mean arterial blood pressure at least 25 mm Hg above normal for age and sex	Symptomatic increase in systolic or mean arterial blood pressure at least 25 mm Hg above normal for age and sex OR in the 91st–94th percentile for age, length, and sex (systolic and/or diastolic)	Symptomatic increase in systolic or mean arterial blood pressure at least 30 mm Hg above normal for age and sex OR >95 th percentile for age, length, and gender (systolic and/or diastolic)	Shock, end organ failure (particularly heart and renal), intracranial or retinal hemorrhage, other hypertension related sequelae
Tachycardia: Heart rate above normal range for gestational age and postnatal age Bradycardia: Heart rate below normal range for gestational age and postnatal age	Heart rate within normal ranges for gestational and postnatal age	Transient, asymptomatic increase or decrease in heart rate, not requiring intervention	Asymptomatic or symptomatic increase or decrease in heart rate, responsive to medical therapy	Symptomatic increase or decrease in heart rate, requiring urgent and/or prolonged medical therapy	Persistent increase or decrease in heart rate despite medical therapy, cardiogenic shock
Heart failure	None	Cardiac dysfunction documented by ECG and/or echocardiography, not requiring intervention	Cardiac dysfunction requiring nonurgent medical therapy	Symptomatic, non-life-threatening cardiac dysfunction requiring medical therapy	Symptomatic, life-threatening cardiac dysfunction requiring medical therapy and mechanical ventilation support
Neurologic					
Mental status	Varies with infant gestational age and postnatal age	Transient lethargy or irritability	Persistent lethargy or irritability requiring intervention	Unresponsiveness, lethargy or irritability associated with event that could result in long-term sequelae	Non-medically induced coma that results in failure of spontaneous respirations

Table 1 continued.

Event Definition Normal Range	Assessment of Severity				
	Normal	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life Threatening)
Seizures	None observed or suspected	Brief (<5 min), nonfocal, resolved spontaneously or upon correction of precipitating factor, not requiring anticonvulsant therapy	Focal or generalized, recurrent or persistent, lasting 5–20 min with <24 h. postictal state, receiving anticonvulsant therapy	Focal or generalized, recurrent or persistent, lasting >20 min, prolonged postictal period, receiving anticonvulsant therapy	Status epilepticus. Refractory seizures not responding to treatment
Muscle tone and reflexes	Normal for gestational and postnatal age	Transiently decreased or increased, not requiring specific therapy	Persistently decreased or increased requiring evaluation and specific therapy	Persistently decreased or increased, requiring additional testing and specific therapy, not improving	Neuromuscular disease that is incompatible with life
Developmental delay	Normal development for gestational and postnatal age based on history, physical examination, and standard assessment tools	Mild delay in motor or cognitive skills as determined by developmental screening tool appropriate for age and setting	Moderate delay in motor or cognitive skills as determined by developmental screening tool appropriate for age and setting	Severe delay or regression in motor or cognitive skills as determined by developmental screening tool appropriate for age and setting	NA
Musculoskeletal					
Arthritis: stiffness or joint swelling, with or without erythema, usually associated with pain Myositis: muscle swelling or induration, with or without erythema, usually associated with pain and limited mobility		Transient and mild arthritis or myositis <24 h in duration	Transient arthritis or myositis 24–72 h duration	Persistent, disabling myositis or arthritis, with or without systemic signs	NA
Gastrointestinal					
Difficulty feeding	None	Transient difficulty feeding not resulting in additional intervention	Difficulty feeding resulting in need for supplemental or alternative methods of feeding, resolves with specific therapy	Difficulty feeding requiring intervention, including medications, parenteral nutrition, and/or surgery and affecting infant growth	Difficulty feeding requiring intervention, including medications, parenteral nutrition, and/or surgery and affecting infant growth, does not resolve or not expected to resolve over time
Vomiting	None	Postfeeding, small volume, occasional, not altering feeds, no dehydration	May or may not be associated with feeds, frequent, requiring evaluation and/or treatment, but not affecting growth or hydration status	Persistent vomiting, requiring treatment and intravenous fluids; only transiently affects growth or hydration status	Vomiting associated with hypotension and/or shock, or poor growth despite intervention

Table 1 continued.

Event Definition Normal Range	Assessment of Severity				
	Normal	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life Threatening)
Diarrhea	Newborn stools vary depending on type of feeding, formula vs breast milk	Transient change in consistency (liquid stools) but not frequency of stools, normal feeding, no dehydration, no intervention	Change in consistency (liquid stools) and/or frequency of stools, requiring intervention to prevent or treat dehydration with prompt resolution	Persistent diarrhea requiring treatment for dehydration and/or specific etiologic treatment	Diarrhea associated with hypotension and shock, requiring aggressive rehydration
Liver dysfunction evaluated by measurement of liver enzymes (AST, ALT, GGT, alkaline phosphatase) Each value graded independently	Values vary by gestational and postnatal age	1.25 to <2.5 × ULN	2.5 to <5 × ULN	5 × to <10 × ULN	≥10 × ULN requiring surgical intervention or liver transplant
Hyperbilirubinemia ^f : total bilirubin (mg/dL) ^g (not cholestasis related)	Normal levels vary by gestational and postnatal age and change in the first days and weeks of life, also affected by breastfeeding status	<1.5 × ULN for age and gestational age	1.6–2.0 × ULN	2.1–5.0 × ULN or reach cutoff for indication of phototherapy	>5.1 × ULN or reach cutoff for indication of exchange transfusion
Hyperbilirubinemia ^f : direct bilirubin (mg/dL) ^g (cholestasis)	Normal levels vary by gestational and postnatal age and change in the first days and weeks of life, also affected by breastfeeding status	1.0–1.5 mg/dL	1.6–2.0 mg/dL	2.1–2.5 mg/dL OR >ULN and >10% of total bilirubin	>2.6 mg/dL OR >ULN with signs and symptoms of liver failure
Hematologic					
Anemia ^g (hemoglobin in mg/dL)	Hemoglobin and hematocrit levels vary by gestational age, sex, and race/ethnicity	<7 d 13.0–14.0 7–60 d 8.5–9.4	<7 d 12.0–12.9 7–60 d 7.0–8.4	<7 d <12.0 7–60 d <7.0 OR any value requiring transfusion	Congestive heart failure due to anemia
Leukopenia ^g : WBC (cells/mm ³) decreased	Varies by gestational age, sex, and race/ethnicity	2000 to <2500	1500 to <2000	1000 to <1500	<1000
Neutropenia ^g ANC (cells/mm ³) decreased	Varies by gestational age, sex, and race/ethnicity	≤1 d: 4000 to <5000 2–7 d: ANC 1250 to <1500 7–60 d: ANC 1000 to <1300	≤1 d: 3000 to <4000 2–7 d: ANC 1000 to <1250 7–60 d: ANC 750 to <1000	≤1 d 1500 to <3000 2–7 d: ANC 750 to <1000 7–60 d: ANC 500 to <750	≤1 d <1500 2–7 d: ANC <750 7–60 d: ANC <500
Thrombocytopenia ^h : Platelet count (platelets/mm ³) decreased	Normal varies with gestational and postnatal age, usually ≥150 000	100 000–149 000	50 000 to <100 000	25 000 to <50 000	<25 000 OR any value associated with bleeding

Table 1 continued.

Event Definition Normal Range	Assessment of Severity				
	Normal	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life Threatening)
Coagulopathy ^h : INR of prothrombin time	Normal range varies with gestational and postnatal age, usually 0.9–1.1	<1.5 × ULN	1.5 to <2.0 × ULN	2.0 to <3.0 × ULN	≥3.0 × ULN
Bruising, petechiae, or ecchymosis	None	Localized, self-limited	Localized or widespread covering <50% of body surface	Covering ≥50% of body surface	NA
Metabolic/endocrine					
Hypoglycemia ⁱ : Low serum glucose (mg/dL) Represents failure to adapt from fetal continuous transplacental source of glucose to postnatal nutrient supply, or a nonspecific sign of illness	Normal range not defined. Values vary with birth weight, gestational and postnatal age, and feeding method. Preterm and SGA infants are at risk.	Transiently low <50 resolving with feeds	Transiently or persistently low, <50 not responding to oral feeds and requiring intravenous bolus of dextrose	Persistently low, <50 or symptomatic (apnea, cyanosis, jitteriness), unresponsive to bolus therapy and/or requiring continuous intravenous dextrose infusion and/or steroids	Hypoglycemia <50 associated with seizures, respiratory failure or cardiac arrhythmia
Calcium ^g (mg/dL) Hypocalcemia (low serum calcium): <8 hypercalcemia (high serum calcium): >11.0	Values vary in first days of life and with gestational and postnatal age	<7 d: Low: 6.5 to <7.5 High: 11.5 to <12.5 7–60 d: Low: 7.8 to <8.4 High: 10.6 to <11.5	<7 d: Low: 6.0 to <6.5 High: 12.5 to <13.0 7–60 d: Low: 7.0 to <7.8 High: 11.5 to <12.5	<7 d: Low: 5.5 to <6.0 High: 13.0 to <13.5 7–60 d: Low: 6.1 to <7.0 High: 12.5 to <13.5	<7 d: Low: <5.5 High: ≥13.5 7–6 d: Low: <6.1 High: ≥13.5
Ionized calcium ^g (mmol/L)		Low: ≤LLN to >1.0 High: ≥ULN to <1.5	Low: ≤1.0 to >0.9 and symptomatic; High: ≥1.5 to <1.6 and symptomatic	Low: ≤0.9 to >0.8 symptomatic, treatment indicated High: ≥1.6 to <1.8 symptomatic, treatment indicated	Low: ≤0.8 with life-threatening consequences High: ≥1.8 with life-threatening consequences
Magnesium ^g (meq/L)	Values vary in first days of life	Low: 1.2 to <1.4	0.9 to <1.2	0.6 to <0.9	<0.6
Renal					
Renal insufficiency: CrCl (mL/min/1.73 m ²) decreased	CrCl varies with gestational age and postnatal age	Normal urinary output and mild elevation of serum creatinine	CrCl <LLN to 60	CrCl <60 to ≥30 or requiring renal replacement therapy	CrCl <30 requiring any form of renal replacement therapy
Creatinine ^g (mg/dL) elevation may be associated with renal insufficiency	Values vary in first days of life and with gestational age; might reflect maternal creatinine	<7 d: 1.0–1.7 7–60 d: 0.5–0.9 OR 1.1–1.2 × ULN	<7 d: 1.8–2.4 7–60 d: 1.0–1.4 OR 1.3–1.7 × ULN	<7 d: 2.5–3.0 7–60 d: 1.5–2.0 OR 1.8–3.3 × ULN	<7 d: >3.0 7–60 d: >2.0 OR >3.4 × ULN
Sodium (meq/L)	Normal values vary with gestational and postnatal age	Low: 126–131 High: 145–149	Low: 121–125 High: 150–154	Low: 116–120 High: 155–164	Low: ≤115 High: ≥165
Potassium (meq/L)	Normal values vary with gestational and postnatal age	Low: 2.8–3.1 High: 5.6–6.1	Low: 2.4–2.7 High: 6.2–6.8	Low: 2.0–2.3 High: 6.9–7.5	Low: <2.0 High: >7.5

Table 1 continued.

Event	Assessment of Severity					
	Normal Range	Normal	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life Threatening)
Dermatologic						
Rash			Localized, superficial, resolves promptly with topical treatment	Localized or disseminated, requires evaluation and specific topical and /or systemic treatment	Disseminated, persistent despite specific and/or systemic treatment	Anaphylactic reaction, Stevens-Johnson syndrome, other congenital dermatologic disorders

Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BMI, body mass index; BW, birth weight; CPAP, continuous positive airway pressure; CrCl, creatinine clearance; ECG, electrocardiography; FiO₂, inspired fraction of oxygen; FOC, fronto-occipital head circumference; GGT, γ -glutamyltransferase; INR, international normalized ratio; LGA, large for gestational age; LLN, lower limit of normal; meq/L, milliequivalents per liter; NA, not applicable; RR, respiratory rate; SD, standard deviation; SGA, small for gestational age; ULN, upper limit of normal; WBC, white blood cell.

^a Preterm birth and low birth weight carry different risks and should be reported separately (or twice if an infant is both preterm and low birth weight). If gestational age is not known, birth weight should be reported. Infants should be plotted in appropriate growth scales for the population being studied and reported as appropriate, large, or small for gestational age [20–22].

^b Congenital anomalies can be classified as major or minor; severity depends on type of anomaly [23].

^c Shock is defined as failure of the circulatory system to maintain adequate perfusion of vital organs.

^d Routine measures include immediate drying, stimulation, appropriate clothing and bedding, skin-to-skin contact with mother, environmental thermal support [24].

^e Source data can be found in Ref. [25].

^f Hyperbilirubinemia is measured by total and direct bilirubin levels, which vary substantially according to gestational age at birth and in the first few days of life and the early postnatal period due to physiologic anemia, and is affected by breastfeeding and the function of the gastrointestinal tract. In general, severe hyperbilirubinemia should be consistent with cutoffs for indication for phototherapy, and grade 4 or life-threatening hyperbilirubinemia, with cutoffs for exchange transfusion [26].

^g Reference and values for age subgroups (<7 days, 7–60 days, 61–90 days) in term and preterm infants, and in infants >3 months of age are available for some parameters at in Refs. [15] and [16].

^h Source data can be found in Ref. [27–29].

ⁱ Source data can be found in Ref. [30].

laboratory data (ie, usually requiring intervention), when applicable, given the known variability of reference values across different laboratories. Of note, congenital anomalies were not included in this table, as a detailed description of congenital anomalies and their classification is discussed in previous studies [23], as well as in the accompanying publication by Rasmussen et al [31]. Regarding the assessment of severity of AEs, a 4-grade severity scale conformed to DMID requirements when this document was developed, and the working group considered these helpful to guide investigators in the assessment of more severe outcomes, while ensuring uniformity in the assessment of AEs. Recently, 3-point severity grading scales (mild, moderate, or severe) have been adopted by DMID to be in accordance with the Clinical Data Interchange Standards Consortium (CDISC) standards [32]. As CDISC standards become more frequently used, 4-point scale tables may need to be modified.

This guidance document should be adapted for use according to the specific needs of each trial, taking into consideration the type of vaccine being evaluated in pregnant women (eg, viral vs bacterial, adjuvanted vs nonadjuvanted), its phase of clinical development, existing preclinical and clinical safety information, the timing of administration during gestation (first, second, or third trimester), the research population, the setting of the study, and reporting requirements from the sponsor and regulatory agencies. These definitions are not all inclusive; events that are particularly relevant to a specific vaccine or clinical trial (ie, AEs of special interest) can be added using a similar framework. Categories of AEs can be added or expanded based on types of vaccines and population for study. The working group agreed on practicality and flexibility over detailed, all-encompassing definitions to improve usability. When applying these definitions, it is important to use local or regional data for background rates of adverse outcomes whenever available, and/or data from closely matched control groups in randomized controlled studies, for interpretation and assessment of risk.

RESULTS

Clinical studies of vaccines in pregnant women are designed to minimize the risk to the mother and to the infant. In clinical trials, live vaccines are avoided during pregnancy, as is the administration of most vaccines in the first trimester of gestation, the period of organogenesis. Therefore, these design strategies eliminate the possibility of infection of the fetus by a vaccine strain, and reduce the risk of vaccine-related congenital anomalies. Normal placental function minimizes the possibility of exposure of the fetus to the vaccine antigen following maternal vaccination. Immunoglobulin G (IgG) antibodies, but not other antibody types, pass from the mother to the fetus through an active transplacental transfer process. There are 2 main factors that determine the amount of antibody transferred to the

infant: gestational age and maternal antibody levels. Antibody transfer increases with gestational age and with maternal antibody levels, which can be enhanced by maternal immunization. The concentration of maternally derived IgG in the infant is dependent on the amount of antibody transferred by the time of delivery and its half-life; peak antibody concentrations measured at birth gradually wane over the infant's first 6–18 months of life, until all maternally derived antibody is depleted.

The basic information that must be collected for all infants born to mothers participating in clinical trials of vaccines include the mode of delivery (eg, cesarean vs vaginal); gestational age at birth; growth parameters, including birth weight, length, and fronto-occipital head circumference; and assessment of birth weight in relation to gestational age (small, appropriate, or large for gestational age) [13, 20].

Circumstances of delivery and obstetric complications should also be captured, including the presence of intrauterine growth retardation, the duration of rupture of membranes at the time of delivery, the appearance of the amniotic fluid with documentation of the presence of meconium or blood, and maternal fever. Similarly, the occurrence of complications of delivery and resulting interventions should be reported, such as live birth or fetal demise, nonvertex fetal presentation, failure to progress, prolonged labor, induced or assisted delivery, bleeding, the results of fetal monitoring indicating fetal distress (eg, fetal heart rate <120 or >160 beats per minute or abnormal tracing), and any other events that might result in neonatal complications, such as the presence of a tight nuchal cord, the integrity of the umbilical cord, and trauma to the infant at the time of birth. It is important to note that these obstetric events occur at a certain expected background frequency, and are likely to be independent of maternal vaccination, but documentation is helpful in the attribution of relatedness to maternal vaccine.

The physical examination at birth is the first assessment of the newborn and must be documented, along with infant Apgar scores, and results of routine laboratory testing and additional testing performed based on the newborn's status and evaluation. Findings and results outside acceptable normal reference ranges are considered AEs and graded. When pertinent and available, results of prenatal studies (eg, obstetric ultrasound, genetic screening, etc.) should be included to support the diagnosis of conditions detected before birth and assist with attribution assessments of events identified after birth. Table 1 [20–22, 24–30] provides definitions and grading of infant events recommended for evaluation of infants in clinical trials of maternal vaccines.

The working group identified areas with gaps in knowledge or guidance when assessing AEs in infants potentially exposed in utero to vaccines and to vaccine-induced maternal antibodies after delivery. One important question relates to the duration of follow-up of infants after birth. Although this might be

determined by regulatory agencies and the study sponsors, the duration of follow-up can be different depending on the specific study vaccine, the design of the study, specific outcome measures of interest selected based on available preclinical and clinical research data, and the epidemiology of the disease in infants. For example, a study of a vaccine for the prevention of a neonatal infection with a limited period of risk and for which no infant vaccine is available, such as GBS, will probably require a relatively short period of follow-up after delivery [33]; a study of a maternal vaccine that could provide protection to the infant in the first months of life but also potentially interfere with the infant's responses to active immunization with similar antigens in the first year of life will likely require at least 12–18 months of follow-up (eg, pertussis or influenza vaccine) [34, 35], whereas studies of vaccines that prevent infections early in life, but which can recur in early childhood, would require follow-up for several periods of exposure to evaluate the infant's response to natural infection (eg, RSV) [36].

Another prevailing question is the importance of, and how to best assess, growth and development, particularly neurological and behavioral development in infants whose mothers received a study vaccine during pregnancy. Growth measures are objective and should be collected for all infants from birth until the end of the safety assessment period, in accordance with routine growth assessments by the pediatrician (usually at 2, 4, 6, 9, 12, 15, 18, and 24 months of age) or at each study visit. Growth standards applicable to the study population should be used to document normal growth and identify variations from normal. The assessment of neurocognitive development is more difficult due to the variability in each individual, the complexity and time required for the evaluation depending on the specific function of interest, the limitations of available developmental assessment tools in identifying specific deficits vs variations from normal at a single time point, and the need for serial assessments to identify persistent abnormalities. Although subtle variations of normal or transient variability may be difficult to ascertain, major neurodevelopmental abnormalities should be detectable by the infant's primary care provider and the study physician by routine history and physical examination. Most maternal immunization studies include a method of developmental assessment. Normal development and variations from normal must be determined based on the specific assessment tool used.

Assessment of causality should take into consideration all the expected conditions of pregnancy and delivery previously described, as well as other postnatal exposures. The complexity of this assessment is compounded by the fact that the etiology of several neurodevelopmental and behavioral deficits is unknown or multifactorial. This is also true for other conditions such as immune and autoimmune disorders, certain endocrine and hematologic disorders, malignancy, and other major

medical conditions that first present in childhood. The decision regarding the duration of assessment of infant development and the incidence of medical conditions should be informed by the study design and each individual product being evaluated. These conditions are typically considered serious AEs and are captured in all clinical studies for the duration of study participation.

Ongoing surveillance for AEs after a vaccine is recommended for use in pregnancy is essential in the assessment of safety. A number of existing surveillance networks or special studies collect data on AEs of newborns exposed in utero to vaccines and other agents on an ongoing basis and can provide key data to inform investigators on the frequency of these events (background rates) and its evaluation. These networks include the Vaccine Adverse Event Reporting System [11]; the Vaccine Safety Datalink project [37]; and the Clinical Immunization Safety Assessment project of the Centers for Disease Control and Prevention [38]; the Vaccines and Medications in Pregnancy Surveillance System [39]; the Pregnancy Risk Assessment Monitoring System [40]; the Consortium on Safe Labor [41]; the Maternal-Fetal Medicine Unit Network [42]; and the Neonatal Research Network [43] of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, as well as study reports in the NIH website (www.clinicaltrials.gov) [9], pregnancy registries, and publications of numerous private and public organizations involved in the study of vaccines and maternal and child health (eg, the GAVI Alliance, the Global Alliance to Prevent Prematurity and Stillbirth, United Nations Children's Fund, and the World Health Organization) [44–47]. Although it is often difficult to predict which events would require special reporting, investigators can review events reported in these databases, as well as in published preclinical and clinical studies of vaccines in pregnancy and, whenever possible, develop a risk management plan to identify potential safety signals of interest and establish halting rules a priori during the development phase of study protocols.

CONCLUSIONS

There is a need to develop more uniform methods to assess the safety of maternal immunization in infants of mothers who participate in clinical trials of vaccines. When assessing safety, it is important to take into consideration multiple factors including the epidemiology of the vaccine-preventable disease in infants, preclinical and clinical data on the study vaccine, the clinical phase of vaccine development, the time of administration during gestation, the study design, and outcomes of special interest in infants after delivery. In addition to safety assessments tailored to the specific study vaccine, other important areas to consider include the effect of maternal antibodies on the infant's response to active immunization and/or natural infection, as

well as the overall effect on the occurrence of medical and neurodevelopmental conditions. Experience with currently recommended vaccines administered during pregnancy demonstrates the safety of maternal immunization in mothers and infants. This document provides guidance for the assessment of infant AEs for investigators performing maternal immunization trials in the United States and similar industrialized countries, with potential adaptability and expansion for use in other regions of the world.

Notes

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