



Overview of DMID's Consultative Conferences on Enrolling Pregnant Women in Clinical Trials of Antimicrobials and Vaccines

Mirjana Nesin MD, FAAP
Senior Medical Officer
DMID/NIAID/NIH

NIAID





- **Background:** Studies sponsored by DMID identified a need for a ‘tool kit’ to facilitate protocol development and implementation of (mostly) vaccine trials during pregnancy.
- **Objectives:** Assemble a panel of experts and task them with reaching a consensus on issues related to studies of vaccines during pregnancy: definitions, normal values, outcomes, toxicity tables, etc.
- **Deliverables:** Public access resources for investigators, sponsors, safety oversight and regulatory committees engaged in clinical trials of vaccines during pregnancy.



First Consultative Conference (2011)

Subject Matter Experts (SMEs) reviewed and presented available resources:

physiological changes during pregnancy, normal range of laboratory tests and vital signs; toxicity grading tables including DMID, FDA-CBER, DAIDS, NCI etc, published literature on AE reporting, clinical trials design on clinical trials.gov, AEs reported on VAERS and other reporting systems, etc.

Conclusions:

- Inconsistent definitions of AEs during pregnancy
- Limited experience in grading and reporting adverse events (AEs) in pregnant women participating in clinical trials
- Absence of standardized toxicity tables for pregnant women

Recommendation:

- Organize series of working groups to address these issues



Overview of conferences to date:

- **Format:**

six consultative conferences:

- First May, 2011; next September 29-30, 2014

numerous teleconferences

- **Invited Participants** (~50/conference):

Shareholders and Subject Matter Experts (SME) over 300 invited participants from diverse areas of research during pregnancy

- **Seven Working Groups**

Tasks will be described later

- **Publications:**

- Two manuscripts and editorial (*Vaccine*, vol 31, 2013, 4261-79)
- Five manuscripts and editorial accepted for publication (Supplement to *Clinical Infectious Diseases*, December 2014)



Tasks for the working groups

1. Protocol design for maternal immunizations trials:
 - inclusion/exclusion criteria,
 - definitions and grading of adverse outcomes during pregnancy
 - halting rules
2. Toxicity grading tables during pregnancy
 - Reference values for vital signs and laboratory assessments
3. *Reporting and grading of adverse events in infants whose mothers participate in maternal immunization trials*
4. *Assessing and reporting congenital anomalies in maternal immunization trials*
5. Barriers and opportunities for research in maternal immunization
6. Strategies for recruitment and retention in maternal immunization trials
7. Protocol design for PK/PD studies of antimicrobials during pregnancy

Methodology applied by working groups to develop DMID toxicity tables:



- Identify AEs in pregnant women and their infants **commonly reported and relevant to studies of vaccines during pregnancy.**
- **Identify definitions, normal values, outcomes...** to be included in the toxicity tables.
- Reach a consensus on the format and content of the tables.
- Develop grading system for adverse events.
- **Harmonize with other resources**, whenever possible.
- Present draft tables to a larger group of experts and incorporate their comments, as appropriate.
- Publish DRAFT version of the tables in a peer reviewed journal (*Vaccine 2013 and Supplement to CID, December 2014*)
- *Evaluate impact of this 'tool' and revise it as needed*

Relevance of DMID effort



- **Improved protocol design**
 - inclusion/exclusion criteria, safety assessments

- **Improved protocol implementation**
 - clear guidance on risks and evaluations,
 - no unnecessary halting of the study for expected rate of events

- **Consistent reporting within and across studies**

- **Improved data analysis**
 - no overlaps and no ambiguities

- **Potentially easy revisions**

Sixth Conference:
Clinical research in pregnant women-knowledge, gaps and opportunities
Sponsored by NIH and BMGF
5601 Fischers Lane (September 29 & 30, 2014)



Objectives:

- Identify key knowledge gaps, opportunities and barriers to research during pregnancy in the context of global health, vaccines and antimicrobials.
- Develop research tools to assist designing and implementation on clinical trials of antimicrobials and vaccines during pregnancy with emphasis on research in low resource settings.
- **Organizational Committee:** Ajoke Sobanjo-ter Meulen (BMGF), Anne Zajicek (NICHD), Tonse Raju (NICHD), Marion Koso-Thomas (NICHD), Maggie Brewinski Isaacs (ORWH), Jennifer Read (DAID/NIAID), Olivia Sparer (NIAID/DMID) and Mirjana Nesin (NIAID/DMID).



Meeting Agenda

Day 1

- **Overview of issues related to enrollment of pregnant women in clinical trials**
- **Clinical Research During Pregnancy in Low Resource Settings**
- **Morbidities and pregnancy**
- **Roundtable discussion**

Day 2

- **Regulatory science and ethics**
- **Effect of maternal immunization and treatment on neonatal outcomes**
- Working groups:
 1. Training tool for investigators on reporting birth defects in maternal immunization trials
 2. Developing eCRFs in CDISC for studies during pregnancy
 3. Developing web-based resources for investigators implementing clinical research of antimicrobials and vaccines during pregnancy



Path Forward:

- *Publications?*
- *Evaluate impact of this 'tool' and revise it as needed*
- Trans-NIH effort to facilitate research during pregnancy: FY2015/16



National Institute of Allergy and Infectious Diseases

Thank you for your attention!

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National Institutes of Health

EXTRA SLIDES

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Selected adverse events in pregnant women participating in clinical trials of vaccines



- Pregnancy loss: spontaneous abortion (miscarriage) and stillbirth (fetal loss/death)
- Uterine bleeding: (first trimester, second trimester, abruption, placenta previa, postpartum hemorrhage)
- Premature rupture of membranes
- Premature uterine contractions and premature labor
- Premature delivery
- Pregnancy related hypertension (preeclampsia, eclampsia)
- Intrauterine growth restriction/poor fetal growth
- Gestational diabetes
- Infections: chorioamnionitis, endometritis

Selected adverse events in infants born to pregnant women participating in clinical trials of vaccines



- Prematurity
- Low birth weight
- Neonatal complications in term infants
- Congenital anomalies (birth defects)

Definitions and evaluations of selected adverse events in pregnant women participating in clinical trials

Vaccine, Munoz et al.



Adverse Event	Definition	Rates in the US; and Risk Factors	Evaluations	AE category	SUSAR	Halting Rules
Pregnancy loss	Spontaneous miscarriage or abortion in the first or second trimester <u>early</u> occurs 0 -14 weeks <u>late miscarriage</u> 14 1/7-19 6/7 weeks of gestation.	<u>Overall rates:</u> 10-15% of all pregnancies in first or second trimester. <u>early</u> Up to 20% of all pregnancies in the first trimester. <u>Late fetal death:</u> Up to 2% in second trimester.	Document circumstances physical exam/estimated gestational age. If feasible collect results of pathology of fetus and placenta, and genetic testing to establish a possible etiology, association/causality.	Maternal AE. All late fetal deaths are reported as SAE.	If a fetal death occurred within 7 days of receiving a study vaccine.	SUSAR or increased incidence in the trial above reported background rates or above control group rates.

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

FDA/CBER, September 2007 and DMID Toxicity Tables, 2006)



Parameter	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Erythema/Redness	2.5 - 5 cm	5.1 - 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Nausea/Vomiting	No interference with activity, or 1-2 episodes/24 hours	Some interference with activity, or >2episodes/24 hours	Prevents daily activity, requires outpatient hydration	Results in hypotension or requiring iv hydration and treatment in hospital

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

Vaccine, Sheffield et al



Parameter	Normal for non pregnant healthy woman	Normal for pregnancy in first trimester	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin g/dL	12-15.8	11.6-13.9	10-11-5	8-9.9	7-7.9 or Requires transfusion	<7 or life threatening acute blood loss
Change from baseline value		Drop ~1.5g/dL is expected	1.6-2	2.1-4.5	4.6-5	>5

DIVISION OF AIDS Table for grading the severity of adult and pediatric AEs
Appendix C: Female Genital Grading Table INDIVIDUAL
SIGNS/SYMPTOMS /Complications of Pregnancy



Parameter	Normal (do not report as AE)	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life threatening
Hypertensive disorder of pregnancy	none	Pregnancy induced hypertension	Mild preeclampsia	Severe preeclampsia	HELLP syndrome, eclampsia, or life threatening sequelae of preeclampsia

Maternal Adverse Events (Adverse events during pregnancy)



Parameter	Normal	Grade 1	Grade 2	Grade 3	Grade 4 ^a
Pregnancy loss (Pregnancy does not result in a live birth) Spontaneous abortion or miscarriage in the first or second trimester of gestation Early: 0 to <14 weeks of gestation Late: 14 to < 20 weeks of gestation Fetal death at or after 20 weeks of gestation (stillbirth)	None	N/A	N/A	Early spontaneous abortion or miscarriage not requiring hospitalization ^b	Late spontaneous abortion or miscarriage or fetal death at/or after 20 weeks of gestation (stillbirth), requires hospitalization

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

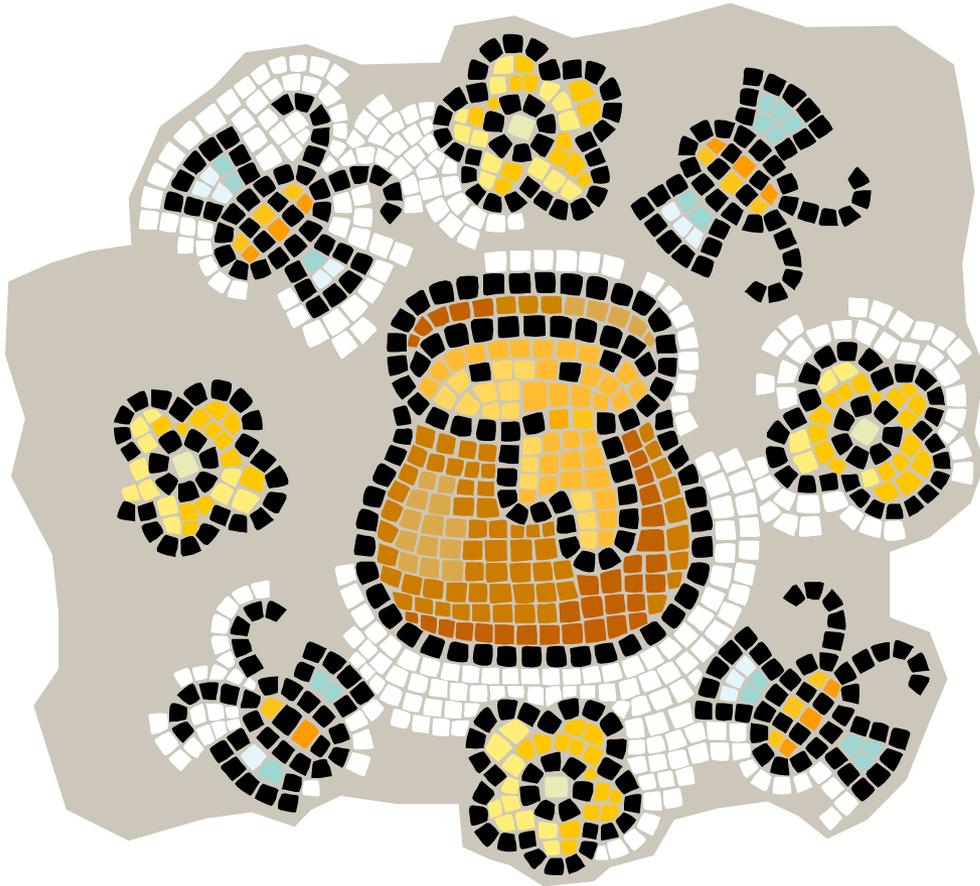


Event	Assessment of Severity				
Definition Normal range	Normal	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life Threatening)
Preterm birth based on gestational age assessed by PE and/or best available obstetric estimate, usually prenatal ultrasound or last menstrual period if ultrasound not available.	Born at or after 37 weeks gestation	Late preterm: 34 to < 37 weeks gestation	Preterm: 32 to < 34 weeks gestation	Very preterm: 28 to < 32 weeks gestation	Extreme preterm: < 28 weeks

GRADING THE SEVERITY OF ADVERSE EVENTS



Parameter	Grade 1 mild	Grade 2 moderate	Grade 3 severe	Grade 4 Potentially life threatening
Clinical AE NOT identified elsewhere in this AE Grading Table	<p>Symptoms causing no or minimal interference with usual social & functional activities</p> <p>Regarding study product: No immediate intervention, no follow-up</p>	<p>Symptoms causing greater than minimal interference with usual social & functional activities</p> <p>Regarding study product: Sufficiently abnormal to require evaluation as to causality and perhaps mild therapeutic intervention, but not of sufficient severity to warrant immediate change in study product</p>	<p>Symptoms causing inability to perform usual social & functional activities</p> <p>Regarding study product: Sufficiently severe to require evaluation and treatment, including at least temporary suspension of study product</p>	<p>Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death</p> <p>Regarding study product: Study product must be stopped immediately and must not be restarted until the alternate etiology of abnormality is clearly established.</p>



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