Maternal Influenza Vaccine Trial in Bamako, Mali

CVD-Mali/CNAM,
Ministry of Health, Bamako, Mali
ANISE, Kenya, February 04th 2012
The Mali Experience

- Capital = Bamako (1.1 million)
- Pop’n: ~12.5 million
- Economy: Among 10 poorest countries
- U5MR: 191/1000
- HIV prevalence ~2% (2006 DHS)
- Seasonal malaria
History of CVD-Mali

Created by a 2001 concordat between:

• The Ministry of Health, Mali
  (Dr. Fatoumata Nafo-Traore, Minister of Health)
• The Univ. of Maryland, Baltimore, MD, USA
  (CVD-Maryland)
  (Prof. Myron M. Levine, Director, CVD-Maryland)
• Administratively part of Ministry of Health
• Includes the National Influenza Center
• National Pharmacovigilance Center
The mission of CVD-Mali is to prevent, control and treat endemic and epidemic infectious diseases in Mali, in particular those that are currently (or that in the future may become) vaccine-preventable, and in the course of doing so to train (mainly in Mali) cadres of Malian specialists who will expand this work in the future.
Maternal Influenza Vaccination

- CDC recommends vaccination of pregnant women with inactivated influenza vaccine
- Developing countries have no routine influenza vaccination activities though they do routinely immunize with tetanus toxoid in pregnancy
- In 2008, study performed in Bangladesh found that influenza vaccination in pregnancy reduced influenza illness by 63% in infants < 6 months of age.
  - 1/3 reduction in all febrile respiratory illness in mothers and infants
Influenza in Mali

• In 2009, CVD-Mali was designated as the National Influenza Center and acquired the necessary equipment to perform influenza RT-PCR testing.
  – Pilot surveillance activities in prenatal clinics and at the pediatric hospital
  – Detected circulating pandemic H1N1 virus
• In 2010, began systematic surveillance of a cohort of pregnant women and their infants through weekly home visits.
Incidence density of laboratory confirmed influenza in infants < 6 months of age

April 2010 – May 2011

Number of episodes per 1000 person-months of observation

- April 2010
- May 2010
- June
- July
- August
- September
- October
- November
- December
- January
- February
- March
- April
- May

Number of episodes per 1000 person-months of observation
• **Influenza vaccine**
  – Sanofi Pasteur - Vaxigrip® Inactivated Influenza Vaccine Trivalent Types A and B (split virion). Each 0.5 ml dose contains 15 µg of hemagglutinin (HA) for each of three strains of influenza virus (A/California/7/2009 (H1N1) – like strain, A/Perth/16/2009 (H3N2) – like strain and B/Brisbane/60/2008)

• **Quadrivalent meningococcal conjugate**
  – Sanofi Pasteur - Meningococcal Polysaccharide-Diphtheria Toxoid Conjugate Vaccine (Menactra®): each 0.5 ml dose contains 4 µg each of meningococcal A, C, Y, & W-135 PS conjugated to diphtheria toxoid
Primary Objectives

• To compare the incidence of laboratory-confirmed influenza (LCI) among infants up to 6 months of age born to mothers immunized with trivalent influenza vaccine (TIV) during the 3rd trimester of pregnancy versus infants born to mothers who received meningococcal conjugate vaccine (MCV) during the 3rd trimester of pregnancy (intention-to-treat (ITT) comparison)

• To compare the incidence of LCI among infants up to 6 months of age born to mothers immunized with TIV during the 3rd trimester of pregnancy versus infants born to mothers who received MCV during the 3rd trimester of pregnancy, for infants born to women immunized ≥ 14 days prior to delivery.
Sample size calculation

- ITT analysis
  - Assume attack rates of 2.2% in infants born to MCV recipients and 0.99% in infants born to TIV recipients – i.e., 55% effectiveness of the immunization program in reducing the LCI attack rate. For 90% power to demonstrate that the immunization program is effective – i.e., to obtain a 95% confidence interval for VE with lower limit > 0, the number of LCI cases required is 77 and the total number of randomized subjects needed is ~4828.
  - Allowing for 10% loss of follow-up (death, w/d), the sample size ~5370 subjects.

- Per-protocol analysis (infants born to mothers immunized at least 14 days prior to delivery)
  - Assume attack rates of 2.2% in infants born to MCV recipients and 0.88% in infants born to TIV recipients – i.e., VE of 60%. For 90% power to obtain a 95% confidence interval for VE with lower limit > 5%, 67 LCI cases and approximately 4352 subjects are needed.
  - Allowing for 20% loss to follow-up (delivery < 14 days after immunization), the sample size requirement becomes ~5440 subjects.

- In order to have 90% power in the analysis for each objective, we plan to randomize and immunize 5440 women in the 3rd trimester of their pregnancies; ~2720 women will receive TIV and ~2720 will receive MCV.
<table>
<thead>
<tr>
<th>Study Day</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Weekly visits</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>Visit 5</th>
<th>Visit 6</th>
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<tbody>
<tr>
<td>D&lt;sub&gt;0&lt;/sub&gt;</td>
<td>D&lt;sub&gt;D+7&lt;/sub&gt;</td>
<td>Weekly visits</td>
<td>D&lt;sub&gt;D+28&lt;/sub&gt;</td>
<td>D&lt;sub&gt;Delivery&lt;/sub&gt;</td>
<td>D&lt;sub&gt;Delivery+91&lt;/sub&gt;</td>
<td>D&lt;sub&gt;Delivery+182&lt;/sub&gt;</td>
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<td>Interval (days)</td>
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<td>Medical and Obstetrical History</td>
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<td>Physical Examination</td>
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<tr>
<td>Review Eligibility Criteria / Informed Consent procedure</td>
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<tr>
<td>Blood Sample collection for immunogenicity</td>
<td>√ (woman)</td>
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<td>√ (woman)</td>
<td>√ (cord and woman)</td>
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<td>Randomization/ Vaccination</td>
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<td>Recording of local and systemic reactions</td>
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<td>Brief history regarding interval health (including ER visits) and measurement of temperature</td>
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<tr>
<td>Collection of nasal and oropharyngeal swab</td>
<td>√ (ILI)</td>
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<td>(1/3 of infants)</td>
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<td>Collection of blood for malaria smear**</td>
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<td>(1/3 of infants)</td>
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<tr>
<td>Serious Adverse Event Recording</td>
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Efficacy Assessment

- Active surveillance to detect cases of LCI in participating households will be conducted via weekly visits for the entire follow-up period. At each visit, all participants (women, infants and household contacts) will be assessed for ILI. All those who meet the case definition will have a nasopharyngeal swab performed and tested for influenza virus. Any case that yields a specimen positive for influenza will be considered a case of LCI.

- Active surveillance for pneumonia and serious acute respiratory tract infection will occur during weekly visits. At each visit, any person that meets the corresponding case definition will be identified.

- Surveillance for meningococcal disease will occur at the principal pediatric hospital in Bamako, Hôpital Gabriel Touré. All infants born to participating women and who present with an axillary temperature ≥ 39°C or suspicion of invasive bacterial infection such as meningitis will have a blood culture and culture of any other clinically relevant normally sterile body fluid.
Clinical Definition of ILI – Infants < 6 mos

Any one of the following conditions either reported by the caretaker or observed by a clinician:

• Fever without an apparent source, documented by a clinician’s measurement to be an axillary temperature $\geq38°C$ or maternal perception of fever and administration of antipyretic in previous 8 hours
  – “No source” means there is no apparent cause for the fever such as soft tissue infection, although generalized symptoms such as irritability, loss of appetite, and/or lethargy may be present; OR

• Fever (as defined below)* plus ARI
  – Acute respiratory infection is defined as ANY of the following on the same or consecutive days: runny nose (that is more than usual), nasal congestion, cough, difficulty breathing, pus draining from ear or wheezing;

• > 7 days after last reported fever
Clinical Definition of ILI – age 0-59 mos.

Any one of the following conditions either reported by the caretaker or observed by a clinician:

• Fever without an apparent source, documented by a clinician’s measurement to be an axillary temperature $\geq 38^\circ\text{C}$ or maternal perception of fever and administration of antipyretic in previous 8 hours
  – No source means that there is no apparent cause for the fever such as soft tissue infection, although generalized symptoms such as irritability, loss of appetite, and/or lethargy may be present;

• OR

• Fever (as defined in Glossary)* plus ARI
  – Acute respiratory infection is defined as ANY of the following on the same or consecutive days: runny nose (that is more than usual), nasal congestion, cough, difficulty breathing, wheezing, sore throat, headache, earache, or muscles aches;

• $> 7$ days after last reported fever
• Pneumonia: cough or difficulty breathing AND rapid breathing (per age)

• Severe/very severe pneumonia: cough or difficulty breathing plus any danger sign (unable to drink/nurse, vomits everything, convulsions, lethargy or unconsciousness) or lower chest indrawing or stridor in a calm child or O2 saturation < 90%.

• Fever:
  – Mother’s perception that child had a fever during the previous 24 hours
  – Mother measured the child’s temperature as ≥38°C during the previous 24 hrs
  – Clinician or study staff measure the child’s temperature to be ≥38°C
  – Maternal perception of fever and administration of antipyretic in previous 8 hours
Clinical Definitions - ILI - Women

• Pregnant women will meet ILI criteria if the following are observed by the examining physician or part of clinical history:
  – Onset of fever (oral temperature ≥38°C) < 7 days duration AND
  – Cough or sore throat AND
  – Absence of other diagnoses, OR

  – Onset of feverish feeling < 7 days duration AND
  – Cough or sore throat or chest pain on breathing in AND
  – Absence of other diagnoses, OR

  – Sudden onset of fever over 38°C or perception of fever and self-administration of antipyretic in the previous 8 hours AND
  – Cough or sore throat AND
  – Shortness of breath or difficulty breathing
  – Patient may or may not be hospitalized
  – N.B.: This is the definition of severe ARI
Safety assessment

• Immediate reactions: all subjects will be kept under medical observation at the vaccination clinic until 30 minutes after injection.
• Local and systemic reactogenicity will be assessed during a home visit 7 days following vaccination.
• All serious adverse events occurring among vaccinated women during the entire follow-up period will be reported.
• All obstetrical complications observed during the follow-up period, including but not limited to pre-term labor, chorioamnionitis, pre-eclampsia and eclampsia will be reported.
• All perinatal complications including but not limited to stillbirth, prematurity, and congenital malformations will be reported.
Immunogenicity assessment

• Influenza antibodies in sera will be measured by HI. This testing will be performed on all serum samples collected from pregnant women prior to and 4 weeks after vaccination (with either TIV or MCV) and at delivery and in infants on sera collected at birth (cord blood) and at 3 and 6 months of age.

• Serogroup-specific (A, C, Y and W-135) antibodies will be measured by serum bactericidal assay. This testing will be completed in samples collected from pregnant women prior to and 4 weeks after vaccination (with either TIV or MCV) and in infants at birth (cord blood) and at 3 and 6 months of age.
  – Analysis may be stratified as it is possible that women will have received the recently introduced MenAfriVac (meningococcal A conjugate vaccine) in campaigns.

• Proposed change: Add maternal blood draw when infants 3 and 6 months of age
Progress thus far

• Working in 6 health centers in Bamako
• We have vaccinated 766 women
• 722 women have completed Visit 2
• 573 women have completed Visit 3
• 381 women have delivered thus far
  – Includes 5 stillbirths and 380 live births (there were 4 twin births)
  – There have been 5 perinatal deaths and 3 deaths outside the at period
  – 372 infants < 6 months of age that are under ILI surveillance
• 5 mother-infant pairs have completed Visit 5
• None have completed Visit 6
Progress thus far

- **Serious Adverse Events**
  - 11 preterm birth
  - 5 fetal death / stillbirth
  - 1 severe pre-eclampsia
  - 1 eclampsia
  - 1 placental abruption
  - 1 hemorrhagic placenta previa
  - 1 ruptured uterus
  - 1 rule out preterm premature rupture of membranes

- **Perinatal complications**
  - 5 neonatal death
  - 12 neonatal infection

- **Influenza-like illness** – 688
  - 132 pregnant women – 0 of 46 are positive
  - 38 post-partum women – 0 of 9 are positive
  - 155 index infants – 0 of 104 are positive
  - 363 in household contacts – 1 of 52 was positive for flu B
Acknowledgments

- Ministry of Health, Mali
- Participants and their households
- Local health centers
- Local community leaders
- CVD-Mali, CNAM team
- CVD-Baltimore team, University of Maryland, USA
- Centers for Disease Control and Prevention
- WHO
- University of Rochester
- NAMRU3
- Bill and Melinda Gates Foundation