Shabir A. Madhi

Possibilities for reducing neonatal and young infant mortality through Maternal immunization

National Institute for Communicable Diseases & University of Witwatersrand, South Africa
Respiratory and Meningeal Pathogens Research Unit, & DST/NRF: Vaccine Preventable Diseases
Overview

- Why target neonates (<28 days) and young infants (<6 months age).
- Maternal vaccination success in reducing neonatal deaths.
- Prospects for new vaccines for pregnant women to protect mothers, improve birth outcomes and protect their children.
• Pneumonia causes 799,000 deaths annually in children 1-59 mnt (45% in 1-6 mnt agegroup)#

• 44% (2.76 mil) of under-5 deaths occur in first month of life, 20% (412,000) of which is due to pneumonia/sepsis.
Success of Maternal Tetanus Vaccination in Preventing Neonatal Tetanus Deaths
Neonatal Tetanus Global Annual Reported Cases and TT2plus coverage, 1980-2013

Reported TT2+ coverage & estimated NT deaths 1980-2013
Pertussis (Whooping cough)

Source: Public Health Image Library (PHIL)
The true incidence of pertussis is likely to be higher as a result of under-reporting\(^1\)\(^-\)\(^3\).

In 2008, 148,000 pertussis cases were reported, yet 16 million cases and **195,000 deaths** due to pertussis among children were estimated\(^4\).

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Pertussis (Whooping cough) epidemiology

- Pertussis, caused by *Bordetella pertussis*, is highly contagious, with a reproductive number of 5.5 (number of people infected per original index case)\(^1\)

- Pertussis affects people of all ages, but is of particular concern in young children\(^2\)
  - Worldwide, pertussis is among the top ten leading causes of childhood mortality\(^3,4\)
  - Young infants (aged <2 months) are most at risk for pertussis-associated complications and death, having the highest rates of:\(^5\)
    - hospitalisation (>90%), pneumonia (15–25%), seizures (2–4%), encephalopathy (0.5–1%)
    - death (0.5–1%)
  - During 2004–2008 in the USA, 83% of all pertussis-related deaths were in infants aged ≤3 months\(^6\)
    - In the 2010 California outbreak, 72% of hospitalised cases were infants <6 months of age; all deaths occurred in infants ≤2 months of age\(^7,8\)
Estimated Maternal Vaccine Coverage by Week of Birth (England and Wales).

Amirthalingam G et al. Lancet; 16 July 2014 (on line)
Annual Incidence of laboratory-confirmed Cases of Pertussis by Age-group (England and Whales).

Amirthalingam G et al. Lancet; 16 July 2014 (on line)
Effectiveness of Maternal Pertussis Vaccine by Infant Age at Onset and Timing of Vaccination, UK

Vaccine effectiveness calculated using the screening method:

\[ VE = \frac{1}{\text{(Odds of maternal vaccination in cases)}} - \frac{1}{\text{(Odds of vaccination in population)}} \]

<table>
<thead>
<tr>
<th>Infants &lt;3 months of age</th>
<th>Percentage of cases vaccinated</th>
<th>Average matched coverage* †</th>
<th>Vaccine effectiveness‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccination at least 7 days before birth</td>
<td>15% (12/82) §</td>
<td>62%</td>
<td>91% (84 to 95)</td>
</tr>
<tr>
<td>Vaccination at least 7 days before birth with coverage reduced by a relative 20%</td>
<td>15% (12/82) §</td>
<td>49%</td>
<td>84% (71 to 93)</td>
</tr>
<tr>
<td>Infants &lt;3 months of age by timing of maternal immunisation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccination at least 28 days before birth</td>
<td>14% (10/69) ¶</td>
<td>63%</td>
<td>91% (83 to 95)</td>
</tr>
<tr>
<td>Vaccination 7–27 days before birth</td>
<td>3% (2/72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccination 0–6 days before or 1–13 days after birth</td>
<td>3% (2/68) **</td>
<td>5%</td>
<td>38% (–95 to 80)</td>
</tr>
<tr>
<td>Infants &lt;2 months of age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccination at least 7 days before birth</td>
<td>15% (11/71)</td>
<td>61%</td>
<td>90% (82 to 95)</td>
</tr>
<tr>
<td>Vaccination at least 7 days before birth with coverage reduced by a relative 20%</td>
<td>15% (11/71)</td>
<td>49%</td>
<td>82% (67 to 90)</td>
</tr>
</tbody>
</table>

Amirthalingam G et al. Lancet; 16 July 2014 (on line)
Group B Streptococcus
Regional Meta-analysis of Incidence of Invasive GBS Disease, 2000-2011

CFR: 7%(4-10)  11%(6-16)  22%(12-32)  9% (6-13)

Pathogenesis of Early Onset GBS Disease

Maternal risks factors for EOD:
1. GBS bacteriuria during pregnancy.
2. Intrapartum maternal fever.
3. Prolonged rupture of membranes (>18 Hours).
4. Premterm labor and birth.
5. Previous sibling with invasive GBS disease.

Intrapartum Antibiotic Prophylaxis (IAP) for the Prevention of Perinatal Invasive Group B Streptococcal Disease; USA.

Risk-Based and Screening-based IAP Strategy

Cases per 1000 live births

Year

1st ACOG and AAP Statement
Consensus guidelines
Universal screening

Schrag, S. J. and Verani, J. R. Vaccine: 2013; 31S: D20-D26
Invasive Group B Streptococcal Disease in USA and South Africa.

Maternal **Serotype-Specific GBS Capsular Antibody** Protects Against Invasive Disease in Newborns of Colonized Women.

<table>
<thead>
<tr>
<th></th>
<th>Median CPS-specific IgG Concentration (ug/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type Ia</td>
</tr>
<tr>
<td>Mothers of Invasive GBS Cases</td>
<td>0.20 (IQ: 0.06-1.68)</td>
</tr>
<tr>
<td>Mothers of Healthy newborns</td>
<td>1.83 (0.20-5.54)</td>
</tr>
</tbody>
</table>

Ph II Dose-ranging in Pregnant Women of Trivalent GBS Conjugate Vaccine.

In mothers and infants with 0.5, 2.5 & 5.0 µg doses of vaccine or placebo

Madhi SA et al. 32nd ESPID; Dublin, Ireland; May 2013

First study globally of a trivalent GBS conjugate vaccine among pregnant women Undertaken in South Africa.
Influenza Virus
Influenza Vaccination of Pregnant Women and Protection of Their Infants

Shabir A. Madhi, M.D., Ph.D., Clare L. Cutland, M.D., Locadiah Kuvandra, M.Sc., Adriana Weinberg, M.D., Andrea Hugo, M.D., Stephanie Jones, M.D., Peter V. Adrian, Ph.D., Nadia van Niekerk, B.Tech., Floreote Tseumich, Ph.D., Justin R. Ortiz, M.D., Marietjie Yenter, Ph.D., Ayu Violari, M.D., Kathleen M. Neuzil, M.D., Eric A. F. Simões, M.D., Keith P. Klugman, M.D., Ph.D., and Marta C. Nunes, Ph.D., for the Maternal Flu Trial (MAtFlu) Team*

ABSTRACT

BACKGROUND

There are limited data on the efficacy of vaccination against confirmed influenza in pregnant women with and those without human immunodeficiency virus (HIV) infection and protection of their infants.

METHODS

We conducted two double-blind, randomized, placebo-controlled trials of trivalent inactivated influenza vaccine (IV3) in South Africa during 2011 in pregnant women infected with HIV and during 2011 and 2012 in pregnant women who were not infected. The immunogenicity, safety, and efficacy of IV3 in pregnant women and their infants were evaluated until 24 weeks after birth. Immune responses were measured with a hemagglutination inhibition (HAI) assay, and influenza was diagnosed by means of reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assays of respiratory samples.

RESULTS

The study cohorts included 2116 pregnant women who were not infected with HIV and 194 pregnant women who were infected with HIV. At 1 month after vaccination, seroconversion rates and the proportion of participants with HAI titters of 1:40 or more were higher among IV3 recipients than among placebo recipients in both cohorts. Newborns of IV3 recipients also had higher HAI titters than newborns of placebo recipients. The attack rate for RT-PCR–confirmed influenza among HIV-uninfected placebo recipients and their infants was 3.6%. The attack rates among HIV-uninfected IV3 recipients and their infants were 1.8% and 1.9%, respectively, and the respective vaccine-efficacy rates were 50.4% (95% confidence interval [CI], 14.5 to 71.2) and 48.8% (95% CI, 11.0 to 70.4). Among HIV-infected women, the attack rate for placebo recipients was 17.8% and the rate for IV3 recipients was 7.0%; the vaccine-efficacy rate for these IV3 recipients was 57.2% (95% CI, 0.2 to 82.1).

CONCLUSIONS

Influenza vaccine was immunogenic in HIV-uninfected and HIV-infected pregnant women and provided partial protection against confirmed influenza in both groups of women and in infants who were not exposed to HIV. (Funded by the Bill and Melinda Gates Foundation and others; ClinicalTrials.gov numbers, NCT0106669 and NCT01306682.)
Incidence of **Laboratory-confirmed Influenza Associated Hospitalization** in Soweto, South Africa

Cohen C et al. Emerg Infect Dis; 2013; 19; 1766-1774
Respiratory Syncytial Virus: Clinical Features

Nasal flaring

Chest wall retractions

Hypoxemia and cyanosis

Croupy cough

Expiratory wheezing, prolonged expiration, rales and rhonchi

Tachypnea with apneic episodes

## Estimated Burden of RSV associated Severe ALRI in Children: 2005 Estimates (Active Surveillance)

<table>
<thead>
<tr>
<th></th>
<th>&lt;1 year</th>
<th>&lt;5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low-income countries (Six studies, active surveillance)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence per 1,000 py. (95%CI)</td>
<td>16 (14-39)</td>
<td>7 (4-14)</td>
</tr>
<tr>
<td>Number new cases</td>
<td></td>
<td>3,080,700</td>
</tr>
<tr>
<td>Case fatality % (range)</td>
<td>2.1% (1.6-2.2)</td>
<td>2.1% (1.3%-3.4%)</td>
</tr>
<tr>
<td><strong>High-income countries (Single study, passive surveillance)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence per 1,000 py. (95%CI)</td>
<td>19 (15-25)</td>
<td>6 (4-7)</td>
</tr>
<tr>
<td>Number new cases</td>
<td></td>
<td>298,300</td>
</tr>
<tr>
<td>Case fatality % (range)</td>
<td>0.7% (0.3-4.8)</td>
<td>0.3% (0.2-0.4)</td>
</tr>
</tbody>
</table>

- Estimated: 66,000-199,000 deaths attributable to RSV in 2005.
- Proportion of deaths occurring in 1st six months of life needs detailing.

Nair H et al. Lancet; 2010; 375: 1455-1465
Positivity and Incidence of RSV Associated Hospitalization by Age-group in South African Infants, 2009-2012

SARI Unpublished data
## Titre of RSV-Mabs in Cord Blood and Incidence Rate Ratio of RSV Hospitalization Among Children Below 1.5 Years of Age.

<table>
<thead>
<tr>
<th>RSV-Mabs titre</th>
<th>0-5 months</th>
<th>6-11 months</th>
<th>12-18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>IRR (95% CI)</td>
<td>N</td>
</tr>
<tr>
<td>0-6</td>
<td>48</td>
<td>reference</td>
<td>10</td>
</tr>
<tr>
<td>6.5</td>
<td>25</td>
<td>0.40 (0.18-0.92)</td>
<td>2</td>
</tr>
<tr>
<td>7.0-7.5</td>
<td>57</td>
<td>0.57 (0.29-1.10)</td>
<td>25</td>
</tr>
<tr>
<td>8-8.5</td>
<td>35</td>
<td>0.41 (0.20-0.85)</td>
<td>31</td>
</tr>
<tr>
<td>9+</td>
<td>32</td>
<td>0.27 (0.13-0.57)</td>
<td>22</td>
</tr>
<tr>
<td>All</td>
<td>197</td>
<td>0.74 (0.62-0.87)</td>
<td>90</td>
</tr>
</tbody>
</table>

When the titer doubled, the risk of RSV hospitalization decreased by 26% (13–38%) in infants <6 months.

### Pipeline RSV: Vaccines Overview

<table>
<thead>
<tr>
<th>Discovery phase</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zeta Biologicals LLC</td>
<td><em>Agivax</em></td>
<td><em>Novavax</em></td>
<td><em>GlaxoSmithKline</em></td>
</tr>
<tr>
<td>RSV vaccine</td>
<td>GV-2311</td>
<td>RSV vaccine</td>
<td>GSK-3003891A</td>
</tr>
<tr>
<td>AMVAC</td>
<td><em>iBio</em></td>
<td>RSV vaccine</td>
<td>GSK-3003891A</td>
</tr>
<tr>
<td>RSV vaccine</td>
<td>RSV Vaccine</td>
<td>RSV vaccine</td>
<td>GSK-3003891A</td>
</tr>
<tr>
<td>LlAid</td>
<td><em>GlaxoSmithKline</em></td>
<td>RSV vaccine</td>
<td>GSK-3003891A</td>
</tr>
<tr>
<td>Bordetella pertussis vaccine [BP2E1]</td>
<td><em>Vacarex</em></td>
<td>RSV vaccine</td>
<td>GSK-3003891A</td>
</tr>
<tr>
<td>RSV vaccine</td>
<td><em>TechnoVax</em></td>
<td>RSV vaccine</td>
<td>GSK-3003891A</td>
</tr>
<tr>
<td>MVA-BN-RSV</td>
<td><em>Intravacc</em></td>
<td>RSV vaccine</td>
<td>GSK-3003891A</td>
</tr>
<tr>
<td>RSV vaccine</td>
<td><em>TechnoVax</em></td>
<td>RSV vaccine</td>
<td>GSK-3003891A</td>
</tr>
<tr>
<td><em>PEDAgenX</em> Inc.</td>
<td><em>Mucosys</em></td>
<td>RSV vaccine</td>
<td>GSK-3003891A</td>
</tr>
<tr>
<td>RSV vaccine</td>
<td><em>NanoBio</em></td>
<td>RSV vaccine</td>
<td>GSK-3003891A</td>
</tr>
<tr>
<td><em>Emergent</em> Bioresearch</td>
<td><em>Crucell</em></td>
<td>RSV vaccine</td>
<td>GSK-3003891A</td>
</tr>
<tr>
<td>RSV recombinant vaccine</td>
<td><em>SynGEM</em></td>
<td>RSV vaccine</td>
<td>GSK-3003891A</td>
</tr>
<tr>
<td></td>
<td><em>MedImmune</em></td>
<td>RSV vaccine</td>
<td>GSK-3003891A</td>
</tr>
</tbody>
</table>

**Phases:**
- **Discovery phase:** Early stage research focusing on identifying potential vaccine candidates.
- **Preclinical:** Evaluation of vaccine candidates in animal models to assess safety and efficacy.
- **Phase I:** Clinical trials in a small number of human volunteers to test safety and immune response.
- **Phase II:** Expanded clinical trials to further test safety and explore efficacy.
- **Phase III:** Large-scale clinical trials to confirm efficacy and safety.
- **Market:** The vaccine is approved for commercial distribution.

**Companies:**
- Agivax
- GenVec
- Novavax
- GlaxoSmithKline
- Adultis
- iBio
- AMVAC
- LlAid
- GlaxoSmithKline
- Vacarex
- TechnoVax
- Intravacc
- Mucosys
- NanoBio
- Emergent Bioresearch
- Crucell
- SynGEM
- MedImmune
Conclusion

- Addressing death during neonatal and early infancy period, key to further reduction in under-5 mortality.

- Maternal immunization during pregnancy been tremendously successful in prevention of control of neonatal tetanus.

- Evidence that pertussis and influenza during neonatal and early infant period can be controlled through maternal vaccination during pregnancy.

- Neonates and young infants born to HIV-infected women are at increased risk of hospitalization for influenza, RSV and GBS.

- GBS and RSV clinical trials currently underway, with South Africa at the fore in clinical development.