Trials and Tribulations of Performing Pregnancy Studies in Developing Countries

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Maternal Mortality Worldwide

- About 800 women died every day in 2010 due to complications of pregnancy and childbirth, including severe bleeding after childbirth, infections, hypertensive disorders, and unsafe abortions
  - 440 sub-Saharan Africa
  - 230 Southern Asia
  - 5 in high income countries

- Risk of a woman dying in a developing country from a pregnancy related cause is 25 times higher compared to a woman in a developed country
287,000 estimated women died in 2010 due to complications during pregnancy and childbirth (WHO 2012)

99% of maternal deaths occur in developing countries

The number of women dying due to complications during pregnancy and childbirth has decreased by 47% from 1990 to 2010

WHO Millenium Development Goal is 75% by 2015
The World Health Organization defines a maternal death as the death of a woman:

- While pregnant or within 42 days of a pregnancy termination
- Irrespective of the duration and site of the pregnancy
- From any cause related to or aggravated by the pregnancy or its management
- But not from accidental causes
Maternal Mortality rate (per 100,000 live births) 2010

WHO 2012 Interactive Map
### Maternal Mortality Ratio

**MMR per 100,000 live births**

<table>
<thead>
<tr>
<th>Country</th>
<th>MMR 1990</th>
<th>MMR 2010</th>
<th>Births attended by skilled personnel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singapore</td>
<td>6 (4-8)</td>
<td>3 (2-7)</td>
<td>99.7%</td>
</tr>
<tr>
<td>Finland</td>
<td>7 (4-10)</td>
<td>5 (3-8)</td>
<td>98.6%</td>
</tr>
<tr>
<td>United States of America</td>
<td>12 (11-14)</td>
<td>21 (18-23)</td>
<td>99.3%</td>
</tr>
<tr>
<td>Mexico</td>
<td>92 (80-100)</td>
<td>50 (44-56)</td>
<td>95.3%</td>
</tr>
<tr>
<td>Egypt</td>
<td>230 (140-370)</td>
<td>66 (40-100)</td>
<td>78.9%</td>
</tr>
<tr>
<td>Nepal</td>
<td>770 (430-1400)</td>
<td>170 (100-290)</td>
<td>36%</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>950 (570-1800)</td>
<td>350 (210-630)</td>
<td>10%</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>1300 (720-2500)</td>
<td>890 (510-1700)</td>
<td>30.7%</td>
</tr>
</tbody>
</table>

Global Health Observatory Data 2012 Interagency estimates
## Infant Mortality Rates
### Probability of Dying between Birth and 1 year of life per 1,000 live birth

<table>
<thead>
<tr>
<th>Country</th>
<th>IMR 1990</th>
<th>IMR 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singapore</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Finland</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>United States of America</td>
<td>8</td>
<td>7</td>
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<tr>
<td>Mexico</td>
<td>38</td>
<td>14</td>
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<tr>
<td>Egypt</td>
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<td>19</td>
</tr>
<tr>
<td>Nepal</td>
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<td>41</td>
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<tr>
<td>Ethiopia</td>
<td>111</td>
<td>68</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>161</td>
<td>114</td>
</tr>
</tbody>
</table>

Global Health Observatory Data 2012 Interagency estimates
Trend in infant mortality rate (per 1000 live births) Globally and by WHO region, 1980–2010

Over 70% of under 5 years of age deaths occur in the first year of life

58% of under-five deaths were caused by infectious diseases; Pneumonia, diarrhea and malaria accounted for more than one third of all under-five deaths in 2010
Causes of death among children aged under five years, 2010

- Neonatal deaths: 40%
- Pneumonia: 14%
- Birth asphyxia: 9%
- Neonatal sepsis: 6%
- Preterm birth complications: 14%
- Other conditions: 16%
- NCDs: 4%
- Injuries: 5%
- Malaria: 7%
- HIV/AIDS: 2%
- Measles: 1%
- Diarrhoea: 10%
- Other conditions: 2%
- Congenital abnormalities: 3%
- Neonatal tetanus: 1%

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What all this means to obstetric research in developing countries...

- Research is vital to continue to improve maternal and infant morbidity and mortality
- The design of research trails in low resource areas must take into consideration
  - Culture and country regulations
  - Available resources and standards of care
  - Baseline morbidity and mortality (cannot use US numbers and biases to monitor outcomes and safety assessments)
Nepal Maternal Influenza Vaccine Trial: Mother’s Gift Trial

Nepal Nutrition Intervention Project
Cincinnati Children’s Medical Center
Johns Hopkins Bloomberg School of Public Health

Seattle Children’s Hospital
University of Washington
Study Primary Aims

- To compare the incidence of influenza-like illness (ILI) among pregnant women and their newborns by performing a RCT of maternal influenza immunization vs. placebo

- To compare the incidence of laboratory confirmed influenza among pregnant women and their newborns by performing a RCT of maternal influenza immunization vs. placebo
Maternal tetanus toxoid recommended in pregnant women in limited resource areas (WHO, UNICEF)

- Decreases neonatal mortality significantly
- Elimination of Maternal and Neonatal Tetanus Program
  - 50-70% all pregnant women in Africa and south Asia receive antenatal tetanus
  - Several studies have proven programmatic feasibility for vaccine studies
Pregnant women are at increased risk of serious illness and complications as a result of pregnancy.

Vaccination using the trivalent inactivated influenza vaccine is the cornerstone of influenza prevention.

- Reduces respiratory febrile illnesses by 1/3 in pregnancy (Zaman et al 2008)
- Decreases stillbirth and neonatal death and preterm delivery (Sheffield and colleagues 2012)
Influenza Vaccine in Pregnancy


- Maternal vaccination decreases small for gestational age infants and in developing countries, may actually increase birth weight (Omer 2011, Steinhoff 2011)
CDC, The Advisory Committee on Immunization Practices and ACOG

- Since 2004, recommended vaccination of all women who will be pregnant during the influenza season regardless of trimester

- Cost effective strategy to decrease maternal and child morbidity

- Influenza vaccines are not licensed for infants under 6 months of age
To compare the incidence of influenza-like illness (ILI) among pregnant women and their newborns by performing a RCT of maternal influenza immunization vs. placebo

To compare the incidence of laboratory confirmed influenza among pregnant women and their newborns by performing a RCT of maternal influenza immunization vs. placebo
Influenza Worldwide

- Every year, seasonal influenza causes 3-5 million severe cases of disease
  - 250,000-500,000 deaths worldwide
  - Very high pregnancy complication rates
- Influenza vaccines are rarely used
  - Misperception that influenza is not a problem
  - Vaccine cost
  - Program implementation challenges
    - Maternal Neonatal Tetanus Elimination Initiative

Ortiz and colleagues 2011
Logistic issues: vaccine availability, expiration dates, optimal formulation

- Expiration date of <1 year
- Seasonal and annual variability
- Tropical year-round influenza season
  - Predominant circulating strains may differ from temperate regions
- Cost is very high in developing markets
  - Who is going to finance it?

Ortiz and colleagues 2011
Other special considerations for resource limited or constrained countries

- Malnutrition, HIV, other chronic infections and PTD may all impair immune responses to vaccines
  - TIV is less immunogenic in women with advanced AIDS and low CD4+ T-lymphocyte counts

Ortiz and colleagues 2011
Pregnant women are a high risk group for influenza

- TIV is safe to use in pregnancy
- Urged the WHO to recommend influenza vaccination
  - In 2005, the WHO encouraged countries to prioritize influenza vaccination for all pregnant women during the influenza season
    - WHO Strategic Advisory Group of Experts: consider pregnant women a vaccination priority
  - Currently Australia, Canada, the United Kingdom and the United States have recommendations for pregnancy
Nepal Maternal Influenza Vaccine Trial: Mother’s Gift Trial

Nepal Nutrition Intervention Project
Cincinatti Children’s Medical Center
Johns Hopkins Bloomberg School of Public Health

Seattle Children’s Hospital
University of Washington
Federal Democratic Republic of Nepal

- Southeast Asia between India and China
- Population 27 million
- 8 of the 10 tallest mountains in the world
- Hinduism >80% of the population
- Kathmandu (1,006,656)
Federal Democratic Republic of Nepal

- Influenza vaccine is not included in the Nepal Immunization program
- Evidence of vaccine efficacy and safety in their population is needed before influenza vaccine will be added
Sarlahi District, Nepal

- Tropical savannah along the Indian border
- 9 Village Development Committee
- 20 year history of research being conducted in this area
All pregnant women in a 9 village area

- One pregnancy per patient
- Identify by household surveys
  - Local female field workers visit household on a 5 week basis to ascertain pregnancy
Field workers

- Local married women who undergo extensive training
  - Each woman assigned an area of 80-100 families
  - They live in the assigned area and know the families
- Field interviewers and supervisors
- Field manager
Study Population

- All pregnant women receive
  - Clean delivery kit (government and non-government): soap, sterile blade and cord tie, plastic disc upon which to cut the cord, clean plastic sheet for delivery
  - Iron-Folic acid and deworming (hookworm)
  - Tetanus toxoid
  - Chlorhexidine cord cleansing for UC stump
  - Educational materials
Intervention

- Randomized placebo controlled community based trial
  - Pregnant women between 17 and 34 weeks gestation receive the TIV (use the vaccine version recommended by WHO for use in Asia)
  - Control group receives a saline injection
  - Monitored in a centralized clinic
At delivery

- Project staff visit the household within 12 hours to exam the infant and review any delivery complications
- Enrollment through 6 months after delivery
  - Weekly visits to conduct a short morbidity interview
  - Temperature and if respiratory symptoms, nasal swab
DSMB was convened to monitor both the study progress and the safety data

- Must take into account the baseline maternal and infant morbidity and mortality
- Must also take into account the logistics and complications that arise based on the rural nature of the study
- Currently monitoring the study which should be completed this year
Global Strategy for Women’s and Children’s Health

Each year, millions of women and children die from preventable causes. These are not mere statistics. They are people with names and faces. Their suffering is unacceptable in the 21st century. We must, therefore, do more for the newborn who succumbs to infection for want of a simple injection, and for the young boy who will never reach his full potential because of malnutrition. We must do more for the teenage girl facing an unwanted pregnancy; for the married woman who has found she is infected with the HIV virus; and for the mother who faces complications in childbirth.

United Nations Secretary-General Ban Ki-moon September 2010
In 2000, 189 nations made a promise to free people from extreme poverty and multiple deprivations. This pledge turned into the eight Millennium Development Goals.
Eight WHO 2015 Millenium Development Goals

- Eradicate extreme poverty and hunger
- Achieve universal primary education
- Promote gender equality and empower women
- Reduce child mortality
- Improve maternal health
- Combat HIV/AIDS, malaria and other diseases
- Ensure environmental sustainability
- Develop a global partnership for development
Women are not dying because of diseases we cannot treat... They are dying because societies have yet to make the decision that their lives are worth saving.

– Mahmoud Fathalla

Chair of the WHO Advisory Committee on Health Research