# PUBLIC HEALTH BENEFITS OF MATERNAL IMMUNIZATION

BMGF's portfolio and interests in maternal immunization and information expected from BMGF-sponsored studies

Keith P. Klugman
Director, Pneumonia
Bill & Melinda Gates Foundation
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# PNEUMONIA

Every person deserves the chance to live a healthy, productive life.

Our goal is to significantly reduce childhood deaths from pneumonia.

# PNEUMONIA IS THE LEADING KILLER OF CHILDREN UNDER THE AGE OF 5

- **Pneumonia was responsible for 1.3 million child deaths in 2011 (1.05M-1.48M)**
- **40% of child deaths are in neonatal period**
- **25% of neonatal deaths (10% of all <5 deaths) are due to infectious causes: pneumonia, tetanus, meningitis, and sepsis**

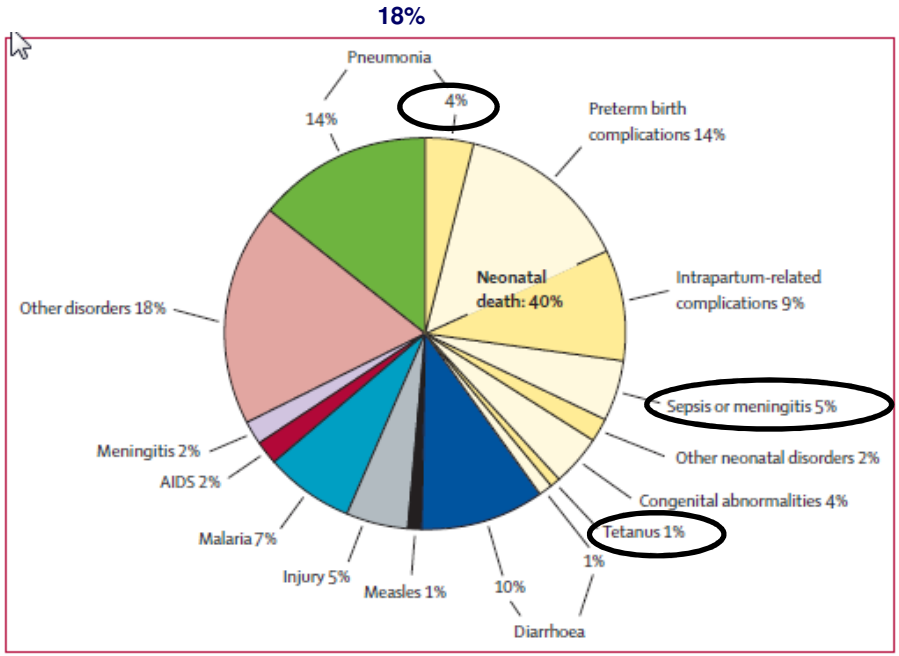
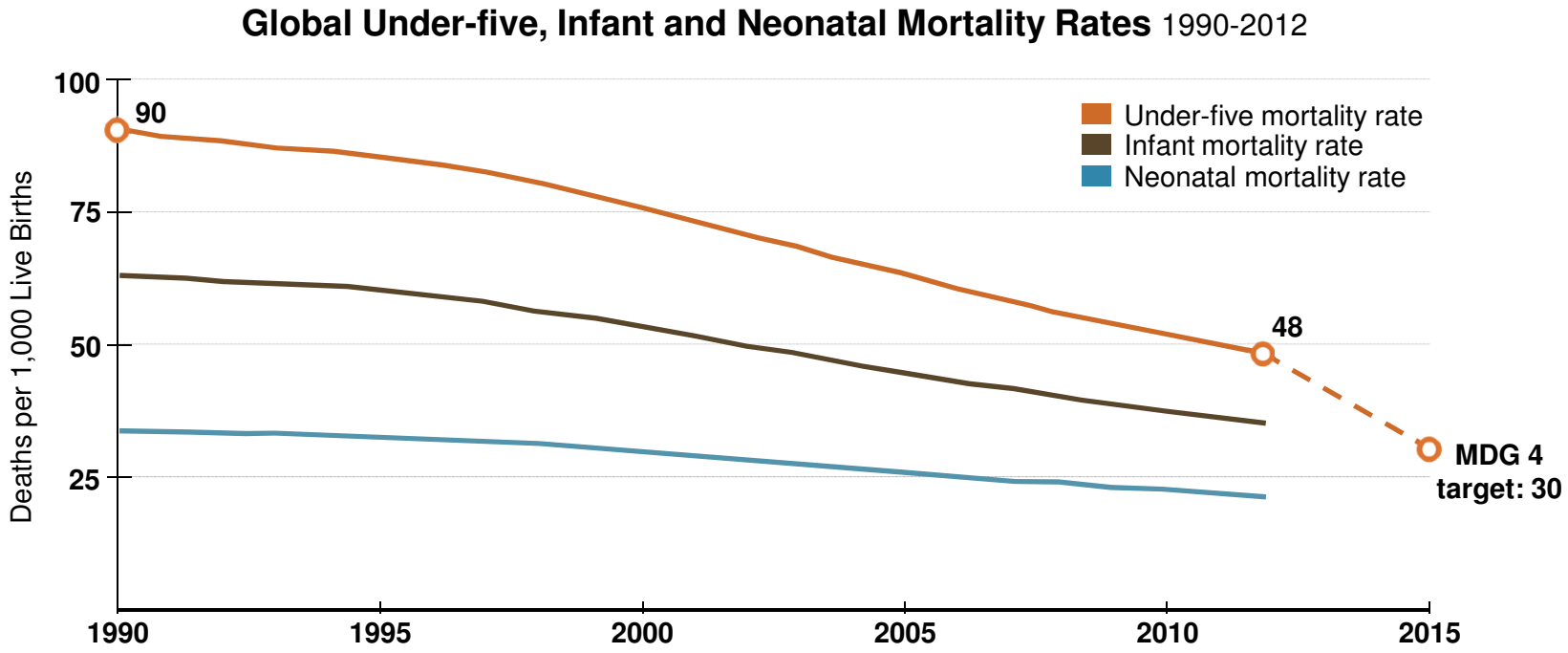



*Figure 2:* **Global causes of childhood deaths in 2010**
Causes that led to less than 1% of deaths are not shown.

Infectious causes of neonatal death

Walker et al. (2013). *The Lancet*, 381 (9875), 1405-1416. Liu et al. (2012). *The Lancet, 379 (9832), 2151-2161.*

# PROGRESS IN REDUCTION OF CHILD AND NEONATAL MORTALITY




Source: http://www.childinfo.org/mortality_underfive.php

# MATERNAL IMMUNIZATION

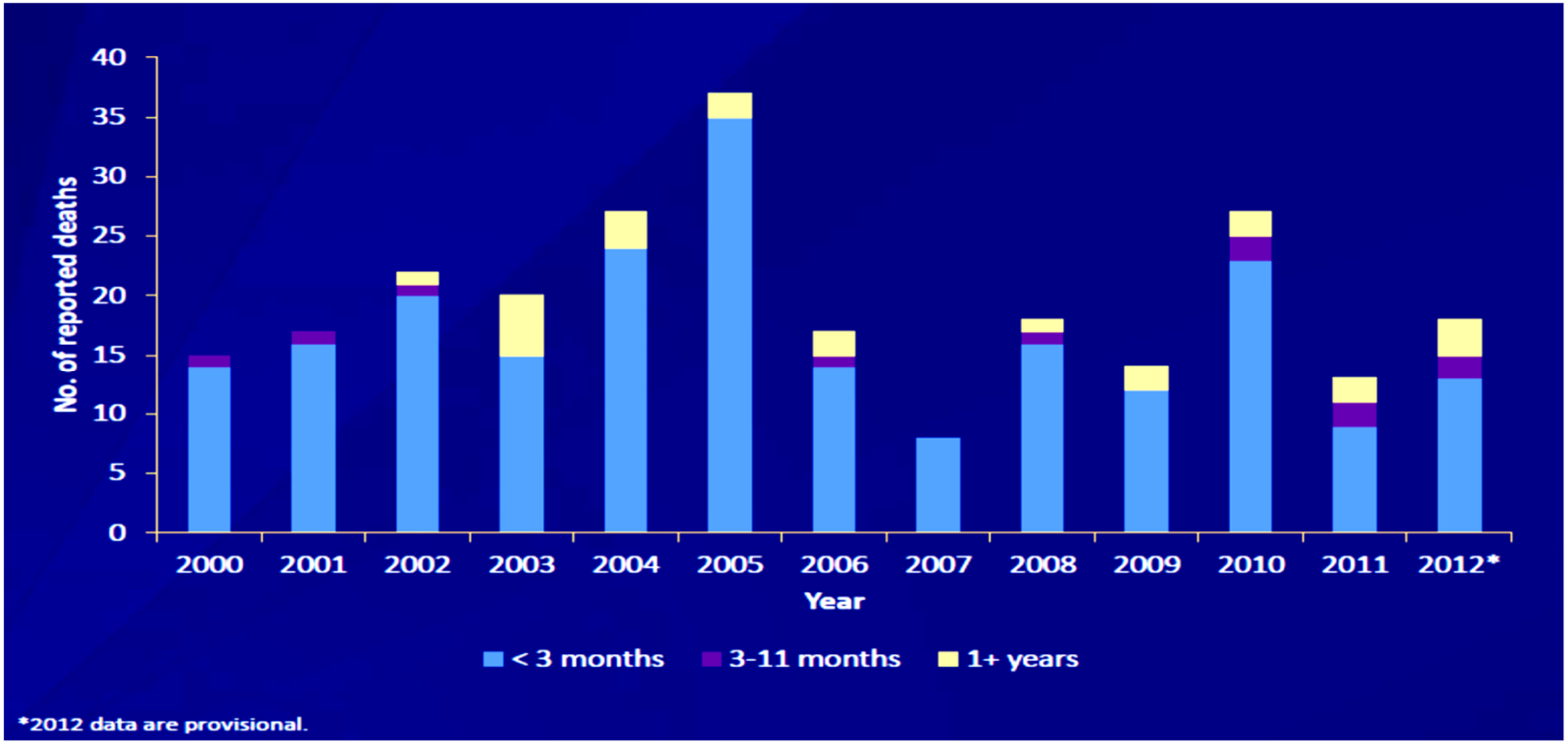
- Vaccinating pregnant women may protect young infants from infectious causes of mortality by passive immunization and by reduced transmission to the neonate from mother
- Existing vaccine interventions during infancy have not reduced neonatal mortality (beyond herd protection of neonates by PCV and Hib)
- Influenza trials in Nepal, Mali, and South Africa are studying a wide range of benefits to mother, unborn baby, and neonate

Maternal Immunization

# A SINGLE PLATFORM TARGETING FIVE DISEASES

| | Pathogen | Advantages | Challenges |
|---|---|---|---|
| Expanded Portfolio | **Influenza** | • Global recommendation targets pregnant women<br>• Maternal protection<br>• Potential impact on birth outcomes | • Limited demand/awareness<br>• Product label language<br>• Cost/seasonal supply |
| | **RSV** | • High global respiratory disease burden<br>• High infant case-fatality | • No licensed vaccine<br>• Limited correlates<br>• Safety issues |
| | **Pertussis** | • Burden in early infancy not addressed through EPI<br>• Maternal immunization recommended in US, UK<br>• Combination vaccine: Tdap could replace TT | • May inhibit infant vaccine response<br>• Limited burden data from developing countries |
| | **Group B Streptococcus** | • Leading cause of neonatal meningitis/sepsis<br>• Licensure trials planned for Novartis vaccine | • No licensed vaccine<br>• Unconfirmed correlate of efficacy<br>• Serotype coverage data limited<br>• Perceived lack of burden in Asia |
| | **Tetanus** | • Maternal immunization is an effective component of tetanus control programs<br>• Contribute to tetanus eradication | • Cost, logistical requirements of change unknown |

# PERTUSSIS DEATHS IN THE US BY AGE GROUP, 2000-2012*

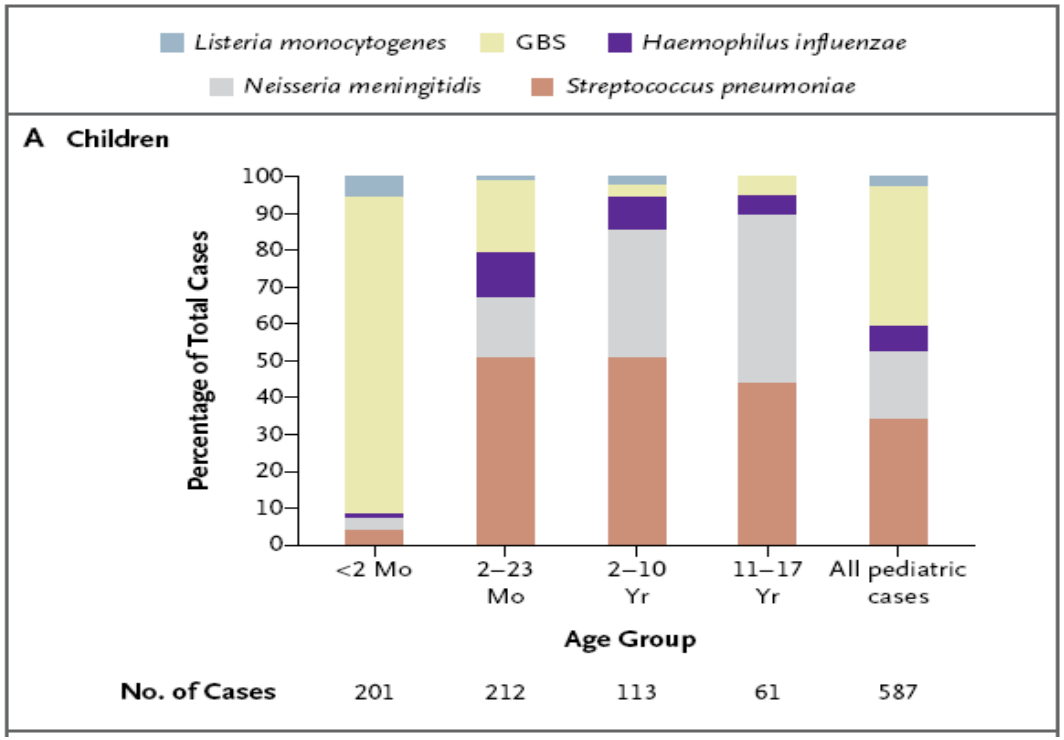



Source: CDC, National Notifiable Diseases Surveillance System, 2012.

# MATERNAL PERTUSSIS IMMUNIZATION ADDRESSES INCREASING INCIDENCE OF PERTUSSIS IN YOUNG INFANTS

- **JCVI recommendation 2013**
  - Temporary program in the UK to immunize pregnant women against pertussis
  - No safety concerns
  - Assess impact and cost-effectiveness of a range of pertussis control strategies
- **ACIP recommendation 2011/2012**
  - Implementation of a Tdap immunization program in the US for all pregnant women irrespective of prior history of receiving Tdap
- **WHO position paper 2010**
  - Insufficient evidence for recommendation of pertussis vaccination during pregnancy
  - Need to evaluate merits of neonatal versus maternal pertussis vaccination

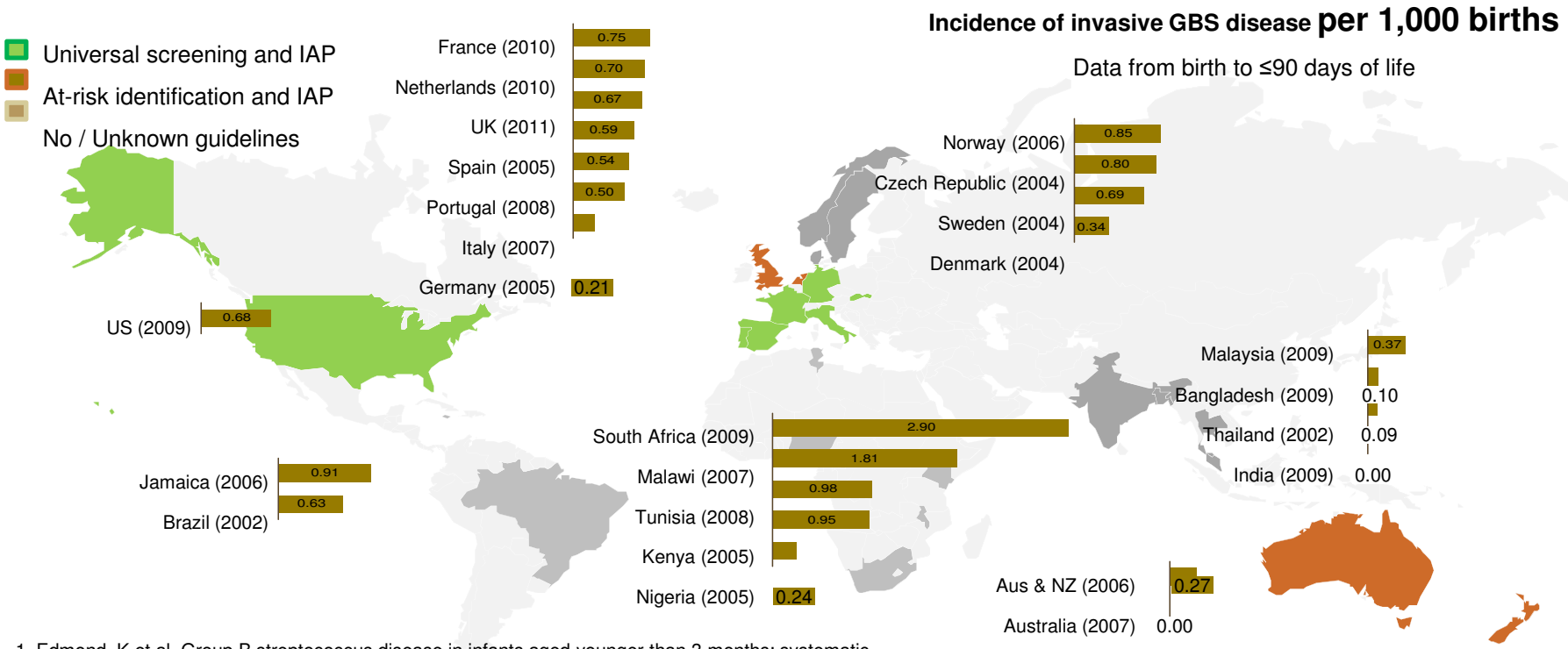
# GBS CAUSES >85% MENINGITIS IN INFANTS <2 MONTHS




Thigpen MC, et al. Bacterial meningitis in the United States 1998-2007. NEJM 364:2016, 2011

GBS

# SIGNIFICANT GBS BURDEN DEMONSTRATED IN AFRICA





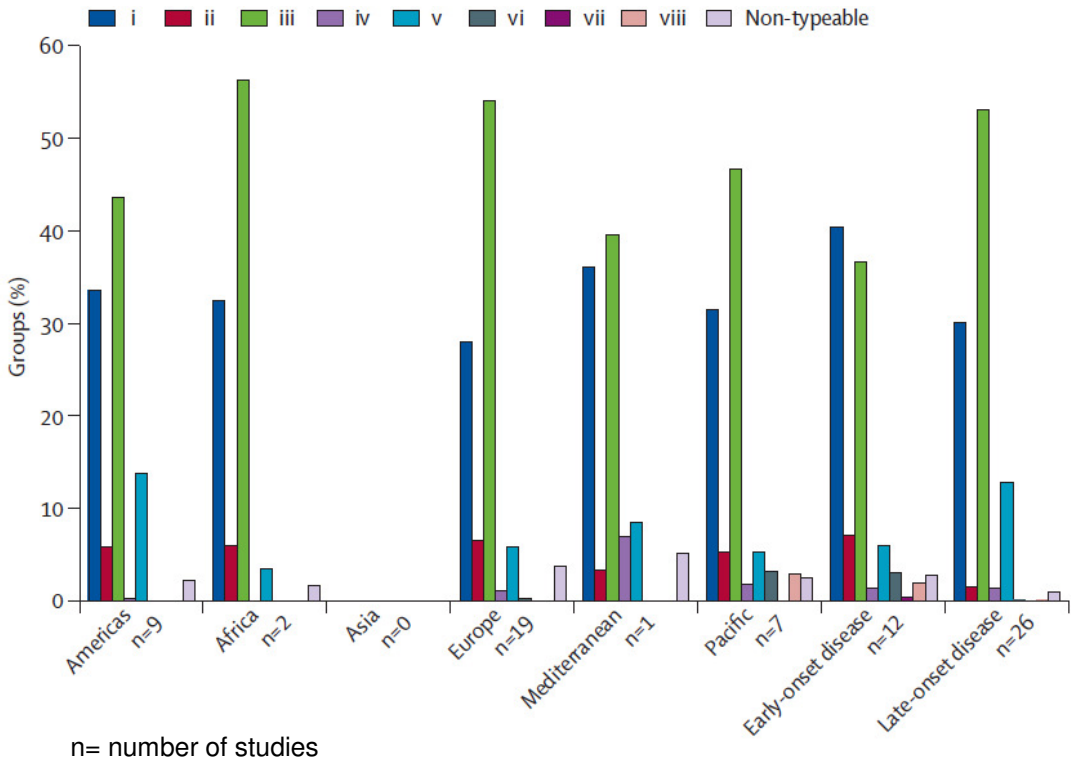
1 Edmond, K et al. Group B streptococcus disease in infants aged younger than 3 months: systematic review and analysis. *Lancet*, DOI:1016/S0140-6736(11)61651-6
2 Phares, C et al. Epidemiology of Invasive Group B Streptococcal Disease in the United States, 1999-2005
3 Cutland, C et al. Lancet 2009, 374:1909-1916

# ANTI-GBS CAPSULAR POLYSACCHARIDE (CPS) ANTIBODIES ARE PROTECTIVE

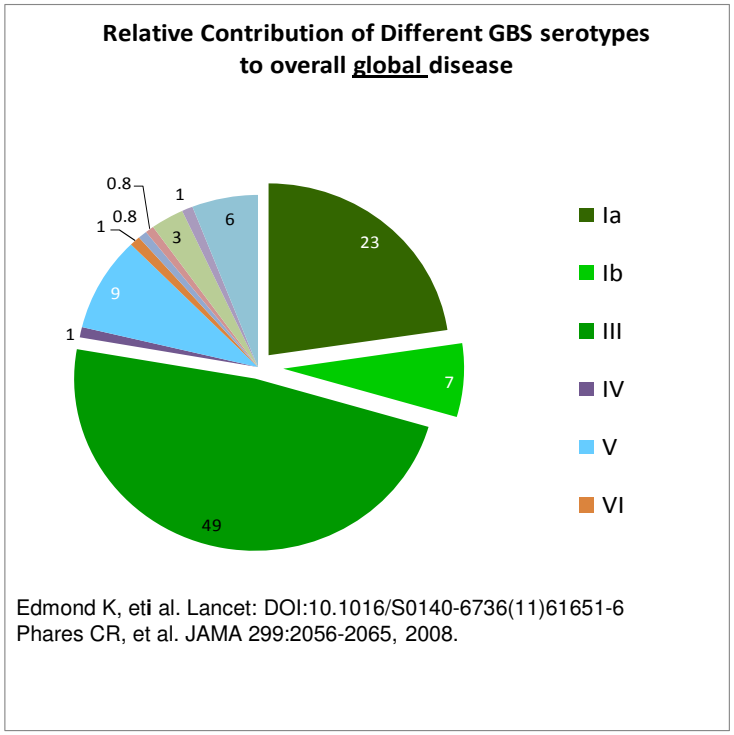
- GBS CPS-CRM protects newborn mouse pups born to vaccinated dams against lethal challenge with GBS[1]
- Passive transfer of anti-CPS Ab protects newborn mice against lethal challenge[2]
- Epidemiologic studies showed that *low* levels of maternal anti-CPS Ab correlates with neonatal disease *susceptibility*[3]
- Higher levels of maternal anti-CPS Ab correlate with reduced risk of neonatal disease[4,5,6] (case-control studies)

[1]Paoletti Vaccine 2001;19:2118-2126
[2]Rodewald JID 1992;166:635-639
[3]Baker NEJM 1976; 294:753-756
[4]Lin JID 2001;184:1022-1028
[5]Lin JID 2004;190:928-934
[6]Baker JID 2013

# GBS TRIVALENT CPS CONJUGATE VACCINE IN CLINICAL DEVELOPMENT *SEROTYPES IA, IB AND III PROVIDE ~ 79% COVERAGE*




n= number of studies




Edmond K, et**i** al. Lancet: DOI:10.1016/S0140-6736(11)61651-6
Phares CR, et al. JAMA 299:2056-2065, 2008.

# MOTHER'S GIFT: BANGLADESH NEONATAL OUTCOMES

| | No. (%) of infants | | | |
|---|---|---|---|---|
| | Control vaccine (n = 166) | Influenza vaccine (n=161) | p value | OR (95% CI) |
| **Birth weight, mean, g** | 3027 | 3117 | 0.09 | - |
| **Gestational age, mean, wk** | 39.4 | 39.5 | 0.6 | - |
| **Small for gestational age** | 63 (38.0) | 45 (28.0) | .05 | 0.63 (0.4 – 1.0) |
| **Weighed <2500 g** | 13 (7.8) | 1 (4.4) | 0.2 | 0.53 (0.2 – 1.4) |
| **Born before 37 weeks' gestation** | 14 (8.4) | 10 (6.2) | 0.4 | 0.72 (0.3 – 1.7) |

**Source**: Steinhoff MC et al. (2012). *CMAJ.*

RSV

# RSV F PROTEIN APPROACH APPEARS PROMISING FOR MATERNAL VACCINATION

- F protein exists in both pre-fusion and post-fusion forms
- F protein boost to protect infants for 4- 6 months through maternal immunization (preliminary evidence suggests better boosting with pre-fusion)
- Use of live vaccines, nucleic acid and gene-based vector vaccines, as well as novel adjuvants, face significant regulatory hurdles in pregnant women.
- Neutralizing antibodies to fusion (F) protein are cross-reactive across both A and B strains
- A correlate of protection for severe RSV disease is neutralizing antibody to F protein, as shown by efficacy of palivizumab and other monoclonal antibodies.
- Focusing on vaccines that induce neutralizing antibody to RSV F protein allows the use of this correlate to evaluate progress and success

RSV

# TIMING OF RSV DEATHS IN FIRST YEAR OF LIFE

*MORE DATA NEEDED FROM DEVELOPING COUNTRIES*

| | 0 to 3 months | | 0 to 6 months | | 0 to 12 months |
|---|---|---|---|---|---|
| | *n* | *%* | *n* | *%* | *n* |
| Argentina | 8 | 73% | 11 | 100% | 11 |
| South Africa | 5 | 56% | 7 | 78% | 9 |
| **Total** | **13** | **65%** | **18** | **90%** | **20** |

*Source: unpublished data from Fondacion INFANT/Vanderbilt University; data courtesy of Fernando Polack and the CDC SARI Surveillance Programme , South Africa; data courtesy of Shabir Madhi*

# RSV VACCINE INVESTMENT PRIORITIES

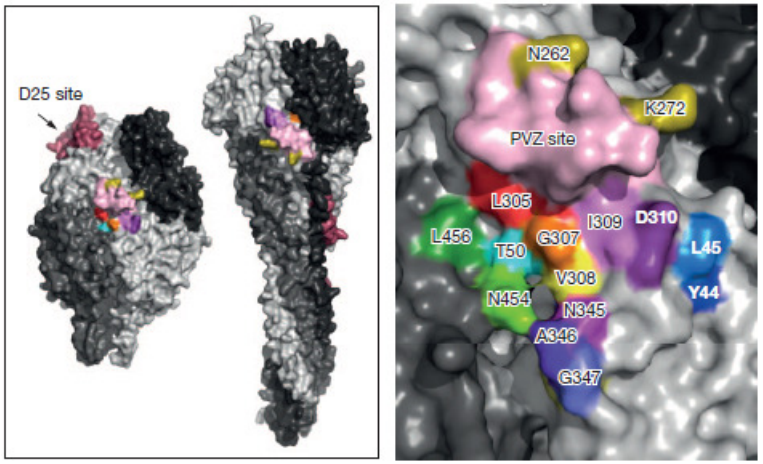
RSV vaccine development for maternal immunization

- F protein-based candidates, pre- or post-fusion
- Unadjuvanted or adjuvants already in licensed vaccines
- Single dose
- Given at 24-36 weeks
- Correlates of protection
- Promote Global Standardization (Assays, Clinical definition, regulatory pathways etc.)

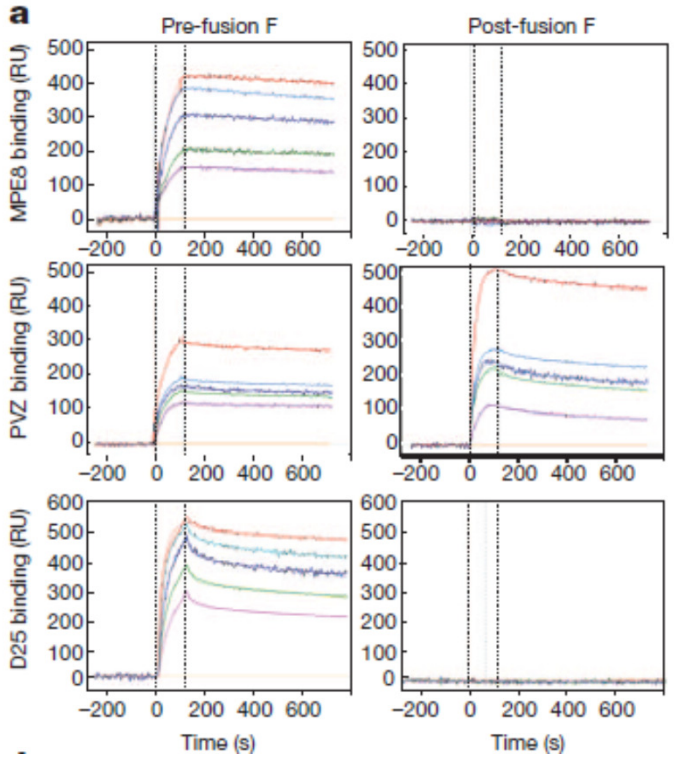
RSV

# A RECENTLY DISCOVERED HUMAN MONOCLONAL ANTIBODY (MPE8) TO THE RSV PRE-FUSION PROTEIN F CROSS NEUTRALIZES BOTH RSV AND HMV

- MPE8 binds to the pre-fusion but not the post-fusion form of the virus




Model of the trimeric pre-fusion (left) and post-fusion (right) F proteins shows the location of the D25 epitope (brown), the PVZ site (light pink), and the MPE8 site (as defined by residues T50, L305, G307, I309, and D310)




Corti et al. (19 September 2013). Nature, 501, 329

HMV= Human metapneumovirus


THE WORK IS
COMPLICATED.
WHY WE DO IT IS NOT.