Maternal Vaccination Strategies:

Influenza, GBS, RSV

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The Potential of Maternal Immunization

- **Influenza**
  - Disease Burden
  - Evidence of benefit of maternal immunization strategies
- **Group B Streptococcal Disease**
  - Disease Burden
  - Prevention strategies
  - Current status
- **Respiratory Syncytial Virus**
  - Disease Burden
  - History of Vaccine Development
  - Prevention Strategies
  - Current status

- Other Potential Targets
  - Pertussis
  - Meningococcal Disease
  - CMV
  - Listeria

Influenza

US Target Groups for Influenza Vaccination

- All persons who want to reduce their risk of becoming ill with influenza or of transmitting disease to others
- All persons **6 months of age and older**
- Especially taregeting Individuals at high risk for influenza and its complications:
  - ≥50 years of age
  - Residents of nursing homes and chronic-care facilities
  - Persons with chronic pulmonary, cardiovascular, renal, hepatic, hematologic, or metabolic disorders
  - Immunocompromised persons
  - People with conditions that compromise respiration or increase risk for aspiration
  - Women who will be pregnant during influenza season

Reference: 1. CDC. *MMWR*. 2008;57(RR-7).1

Influenza is a frequent infection in young infants, but often not recognized.

In the U.S., in some winters as many as **9%** of all infants 0-6 months of age require care in a clinic, emergency room or hospital (Neuzil, 2000)

Hospitalization rates for infants 0 to 6 months in the U.S. range from **45-104/10,000** infants (Poehling 2006)

Of all U.S. children 0- 5 years who are hospitalized with influenza, **48%** are 0-6 months of age (Neuzil, Poehling)

Little data from resource-constrained regions

Influenza Disease Burden

Highest in The First Months of Life

TABLE 3. RELATIVE RISK OF HOSPITALIZATION FOR ACUTE RESPIRATORY DISEASE AMONG CHILDREN WITHOUT HIGH-RISK CONDITIONS DURING PERIODS IN WHICH INFLUENZAVIRUS PREDOMINATED.

STUDY SITE AND AGE GROUP	NO. HOSPITALIZED	NO. OF PERSON-MONTHS	RATE/100,000 PERSON-MONTHS	RELATIVE RISK (95% CI)*	P VALUE
Northern California Kaiser					
0–1 yr	155	66,964	231	12.1 (9.1–16.1)	<0.001
2–4 yr	42	79,280	53	2.8 (1.8–4.1)	<0.001
5–17 yr	74	384,887	19	1.0†	—
Group Health Cooperative					
0–1 yr	86	44,589	193	11.7 (8.2–16.8)	<0.001
2–4 yr	11	52,137	21	1.3 (0.7–2.4)	0.455
5–17 yr	54	327,652	16	1.0†	—

*CI denotes confidence interval.

†This group served as the reference group.

Izurieta et al NEJM Jan 2000

Maternal Influenza Vaccination:

Table 4. Efficacy of IIV3 Vaccination in Mothers and Infants until 24 Weeks after Birth, Intention-to-Treat Population.

Efficacy End Point	HIV-Uninfected Cohort				
	IIV3 (N=1026)	Placebo (N=1023)	Vaccine Efficacy	P Value	
Infants					
RT-PCR–confirmed influenza — no. (%); (95% CI)					
With inclusion of B/Yamagata	19 (1.9); (1.1 to 2.9)†	37 (3.6); (2.6 to 5.0)†‡	48.8 (11.6 to 70.4)	0.01	
With exclusion of B/Yamagata	13 (1.3); (0.7 to 2.2)	25 (2.4); (1.6 to 3.6)	48.2 (−0.8 to 73.3)	0.05	
Influenza-like illness — no. (%); (95% CI)	595 (58.0); (54.9 to 61.0)	584 (57.1); (54.0 to 60.1)	−1.6 (−9.4 to 5.7)	0.68	
Any respiratory illness — no. (%); (95% CI)	706 (68.8); (65.9 to 71.6)	697 (68.1); (65.2 to 71.0)	−1.0 (−7.1 to 4.8)	0.74	
	IIV3 (N=1062)	Placebo (N=1054)	Vaccine Efficacy	P Value	
Women					
RT-PCR confirmed influenza — no. (%)					
With inclusion of B/Yamagata	19 (1.8); (1.1 to 2.8)¶	38 (3.6); (2.6 to 4.9)¶	50.4 (14.5 to 71.2)	0.010	
With exclusion of B/Yamagata	19 (1.8); (1.1 to 2.8)	35 (3.3); (2.3 to 4.6)	46.1 (6.4 to 69.0)	0.03	
Influenza-like illness — no. (%)	175 (16.5); (14.3 to 18.8)	181 (17.2); (14.9 to 19.6)	4.0 (−16.0 to 20.6)	0.67	
Any respiratory illness — no. (%)	674 (63.5); (60.5 to 66.4)	687 (65.2); (62.2 to 68.1)	2.6 (−3.7 to 8.6)	0.41	

- **Therefore protection in Mothers and their Infants is sub-optimal with unadjuvanted vaccine alone**

Madhi, Shabir A., et al. "Influenza vaccination [illegible]nt women and protection of their infants." *New England Journal of Medicine* 371.10 (2014): 918-9

Safety Studies in Pregnant Women: Adjuvanted Vaccine

- A passive reporting database within Novartis reviewed for doses of MF-59 influenza vaccine inadvertently administered during pregnancy
- Overall, 43 reports from MF-59 vaccine and 60 from unadjuvanted influenza.
  - ~70% of pregnancies normal in each group
  - 22% with abnormal pregnancy outcome: one each: C section, spontaneous abortion, ectopic pregnancy, still birth
    - Rate of these events reported for unadjuvanted vaccine = 29%
  - Three induced abortions
- Rates of events the same as reported for unadjuvanted vaccine.

Tsai, Theodore, et al. "Exposure to MF59-adjuvanted influenza vaccines during pregnancy —a retrospective analysis." Vaccine 28.7 (2010): 1877-1880.

Meta-analysis of MF-59 seasonal influenza vaccine in Pregnant Women in Italy, the Netherlands and Argentina

TABLE 2
Pregnancy and neonatal outcomes in 4492 pregnant women

Variable	Vaccinated (n = 2295) (column %)[a]	Unvaccinated (n = 2213) (column %)[a]	Total (n = 4508) (column %)[a]	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)[b]
Gestational diabetes	25 (1.1)	49 (2.2)	74 (1.6)	0.49 (0.30–0.79)	0.48 (0.29–0.80)
Preeclampsia	81 (3.5)	75 (3.4)	156 (3.5)	1.04 (0.76–1.44)	1.12 (0.81–1.55)
Spontaneous abortion	0	9 (0.4)	9 (0.2)	n/a	n/a
Elective termination	0	3 (0.1)	3 (0.1)	n/a	n/a
Stillbirth	3 (0.1)	2 (0.1)	5 (0.1)	1.45 (0.24–8.67)	1.44 (0.23–8.90)
Live birth[c]	2310 (99.9)	2212 (99.3)	4522 (99.6)		
Low birthweight	64 (2.8)	68 (3.1)	132 (2.9)	0.90 (0.64–1.28)	0.88 (0.61–1.26)
Preterm birth	84 (3.7)	108 (4.9)	192 (4.3)	0.74 (0.55–0.99)	0.75 (0.55–1.01)
Neonatal death[c]	2 (0.1)	1 (<0.1)	3 (0.1)	1.93 (0.17–21.29)	1.81 (0.16–20.23)
Congenital malformation[c,d]	56 (2.4)	41 (1.9)	97 (2.1)	1.32 (0.88–1.98)	1.33 (0.88–2.00)

[a] Total pregnancies enrolled of which 4492 were followed up until termination (2291 and 2201 among the vaccinated and unvaccinated cohorts, respectively); [b] The estimates for all outcomes were adjusted for parity, smoking, and maternal age. The automated SAS procedure Stepwise (SAS Institute, Inc., Cary, NC) selected type of health care professional enrolling and previous history of the same outcome to adjust the estimates for the outcomes preeclampsia, gestational diabetes, low birthweight, and preterm birth; [c] Percentages are based on the total number of pregnancy outcomes; [d] Percentages are based on the number of live births and elective terminations, therapeutic terminations, fetal deaths, or stillbirths associates with congenital malformations in each cohort.

Heikkinen. Safety of MF59-adjuvanted influenza vaccination during pregnancy. Am J Obstet Gynecol 2012.

Maternal Influenza Vaccination:

What about benefits?

Incidence of Influenza Virus Infection in Early Infancy: A Prospective Study in South Asia

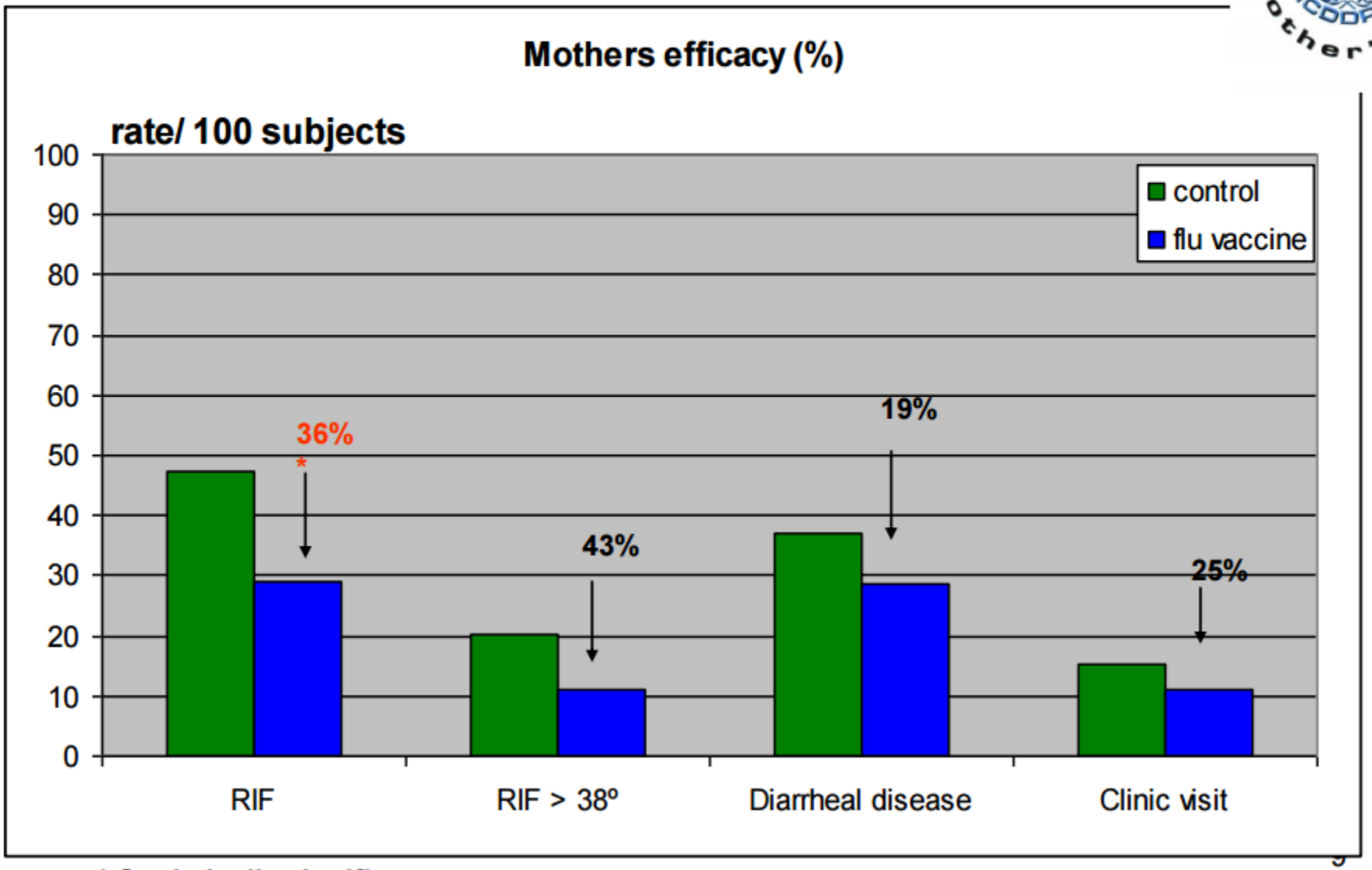
Henkle, Emily; Steinhoff, Mark C.Omer, Saad B. Roy, Eliza ; Arifeen, Shams E. ; Raqib, Rubhana McNeal, Monica Breiman, Robert F. Moss, William J. Zaman, K.

close follow-up of 131 infants in Mother'sGift trial cohort

- We evaluated infants of mothers who did not receive 'flu vaccine
- Weekly home visits to detect respiratory illness,
- Rapid test for influenza on nasal swabs of ill children.
- Serum specimens obtained from cord, 10 weeks, 20-24 weeks
- Sera were analyzed for antibody titers to the three influenza vaccine strains

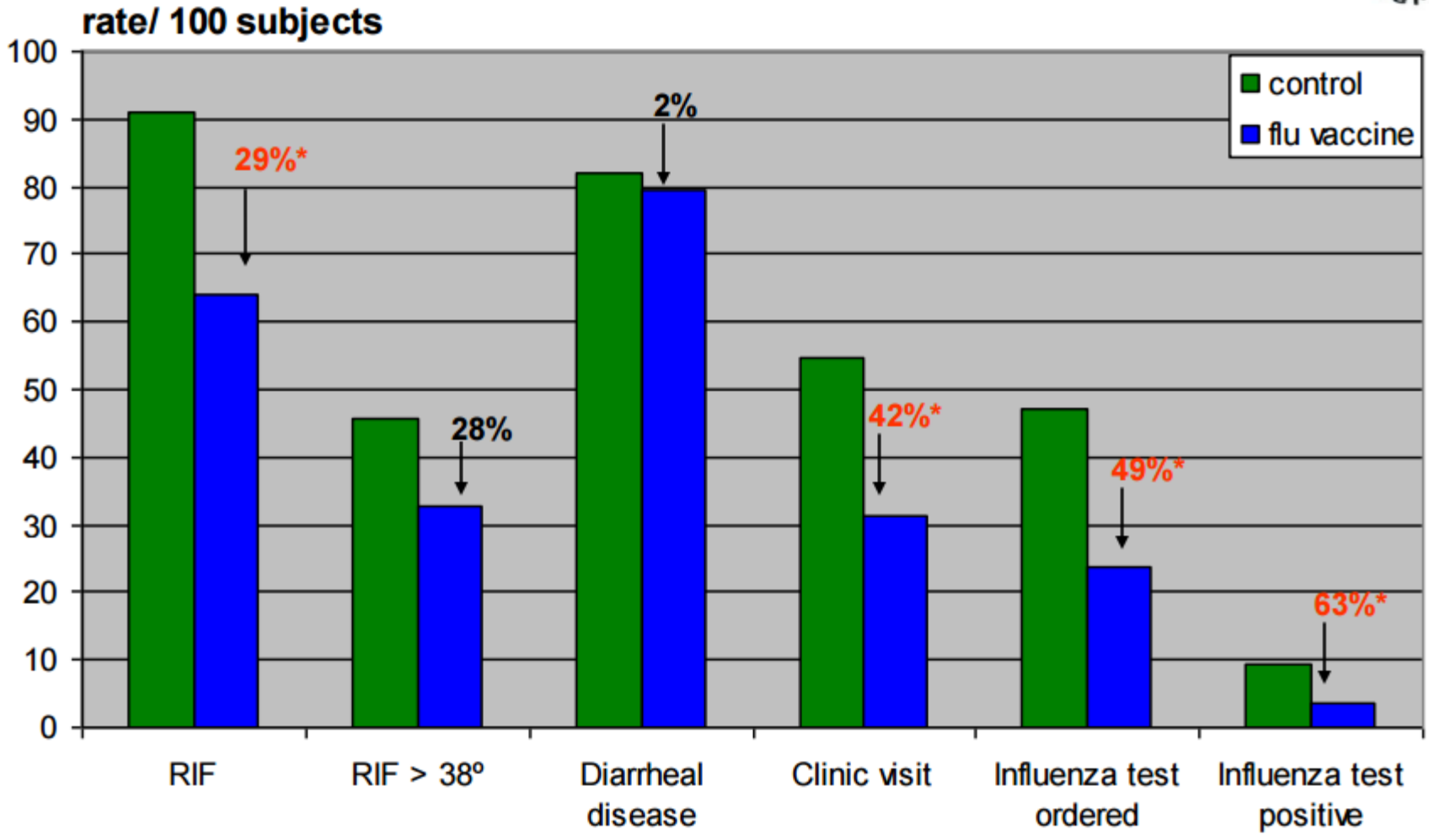
Pediatric Infectious Disease Journal: 2011;30:170-173

Maternal antepartum Influenza vaccine data



* Statistically significant

maternal 'flu vaccine efficacy in infants 0-6months



* Statistically significant

N American studies confirm Bangladesh infant protection data

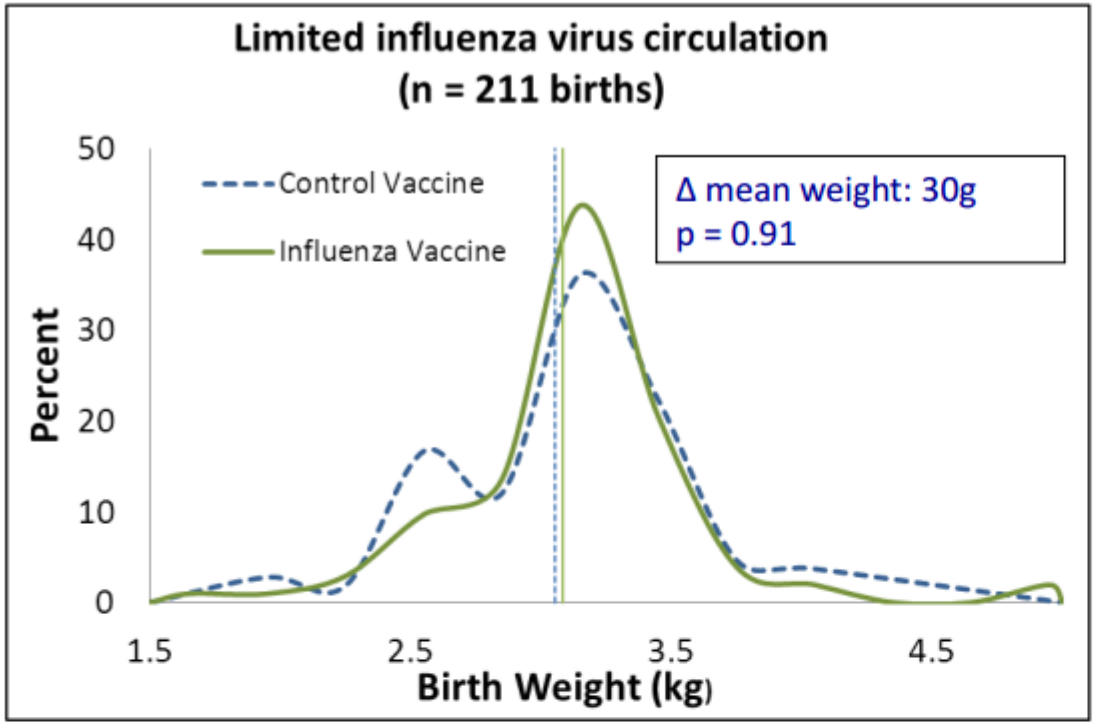
TABLE 1
Antenatal influenza immunization and infant outcomes at 0–6 months

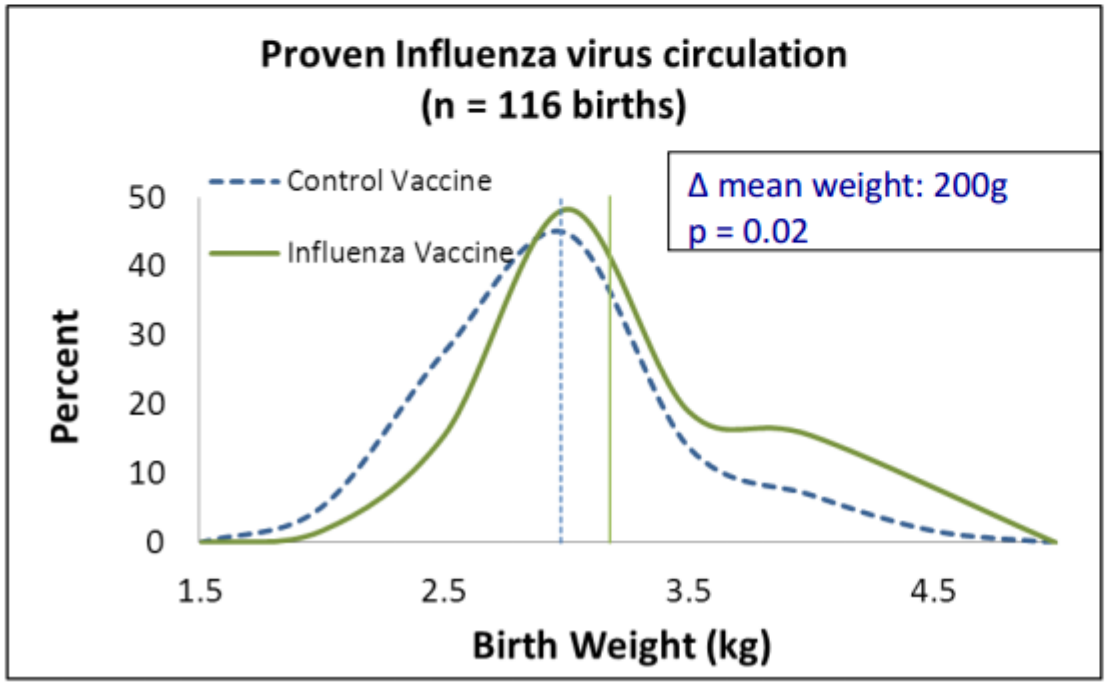
Author	Site	Design	Vaccine	Control	Effect in infant[a]
Zaman et al, 2008[4]	Bangladesh, 2004–2005	Randomized controlled trial of vaccine	172	168	36% ILI 69% rapid test influenza illness
Benowitz et al, 2010[9]	Connecticut, 2000–2009	Case-control	91	156	91.5% DFA or PCR influenza hospitalization
Poehling et al, 2011[8]	Tennessee, Ohio, New York, 2002–2009	Case-control	151	1359	45–48% viral culture or PCR in influenza hospitalization
Eick et al, 2011[7]	Apache, Navajo, 2002-2005	Observational prospective cohort	573	587	41% serologically defined influenza episode

DFA, direct fluorescent antibody; *ILI*, influenza-like illness; *PCR*, polymerase chain reaction.

[a] Expressed as efficacy (percent reduction of infant outcome).

Steinhoff. Antenatal influenza Immunization. Am J Obstet Gynecol 2012.





Mother'sGift Study

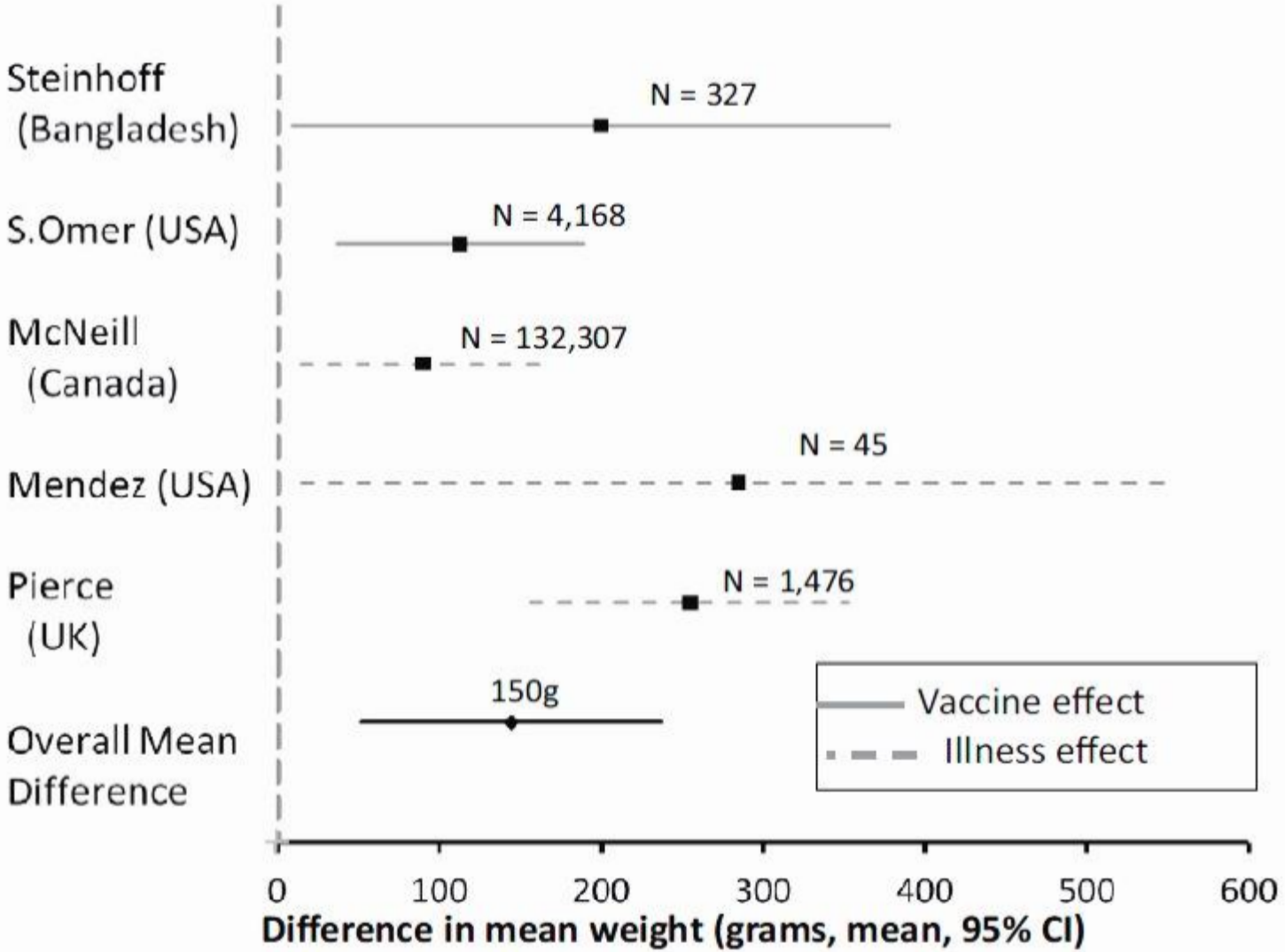
Distribution of Birth Weights during flu virus circulation in Dhaka, Bangladesh:

FETAL EFFECT OF ANTENATAL FLU VACCINE

Steinhoff, CMAJ, 2012

FIGURE 4

Difference in mean birthweights associated with maternal influenza vaccination or illness status



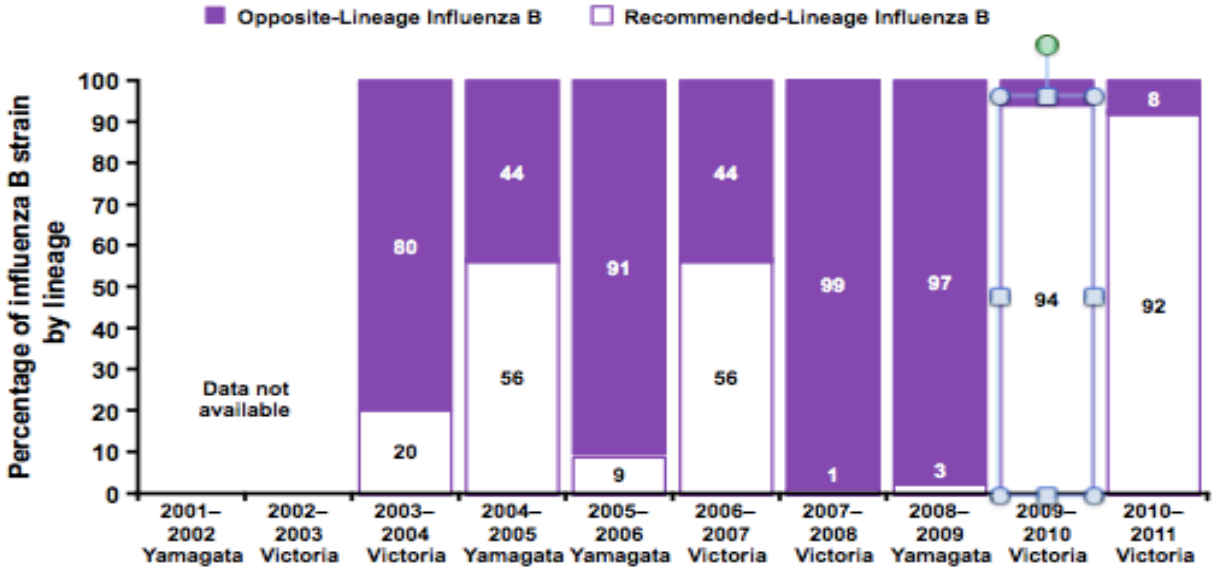
CI, confidence interval.

Steinhoff. Antenatal influenza Immunization. Am J Obstet Gynecol 2012.

Classes of New Influenza Vaccines

- Quadrivalent vaccines containing two A and two B strains
- Adjuvanted vaccines
- Vaccines not dependent on eggs for production
  - Cell culture based technology
  - Recombinant vaccines
- Live attenuated influenza vaccine

The rationale for quadrivalent vaccines



- Accuracy of selection for B strains has been very poor
- There are two strain lineages.
- Doubling the number of strains included increases the chance of obtaining a “correct” match
- However, efficacy against B in children of adjuvanted vaccine has been low

Maternal Influenza Vaccination Summary

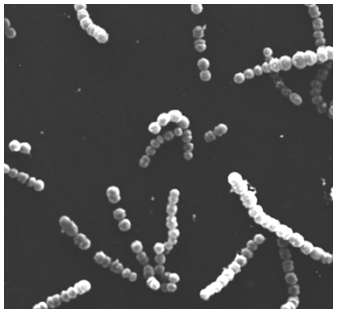
- Infants have the highest disease burden due to influenza – second only to the elderly
- Current influenza vaccines are not effective in children less than six months of age
- Maternal influenza immunization has multiple benefits to the mother and infant.
- Current CDC recommendations
  - Women who are or will be pregnant during influenza season should receive IIV.
  - Live attenuated influenza vaccine (LAIV) is not recommended for use during pregnancy.

GBS

Group B Streptococcal Disease: A potentially preventable cause of neonatal mortality

Group B Streptococcus (GBS) as major cause of neonatal invasive disease

- GBS are Gram positive bacterial cocci that colonize the genital and/or lower GI tract of 10-40% of women



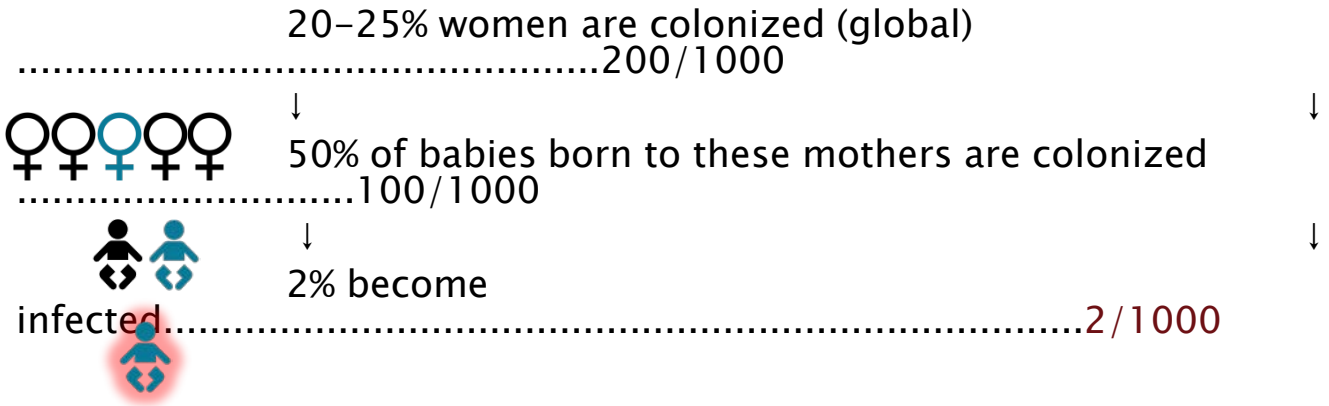
- GBS are a leading cause of neonatal sepsis and meningitis in the first three months of life, causing high mortality, morbidity and sequelae
  - EOD (Early Onset Disease): days 0-7
  - LOD (Late Onset Disease): days 8-90

GBS neonatal disease

- Early-onset:
  - Incidence: 0.3-3.0/1000 live births
  - Mortality: 25-50%
  - Meningitis: 25%
  - Many preterm infants thought to have HMD
- Late-onset:
  - Incidence: 0.5/1000 live births
  - Mortality: 20-25%
  - Meningitis: 80%; permanent sequelae, 50%
- Term infants: 80%
- Pregnancy-related: early postpartum fever

Group B streptococcus (GBS) transmission

- Mother to infant:



- 95% of 'early' onset disease (EOD: 0-6 days) occurs within 48 hrs
- Median age of 'late' onset disease (LOD: 7-89 days) is 37 days (3rd quartile is 53 day

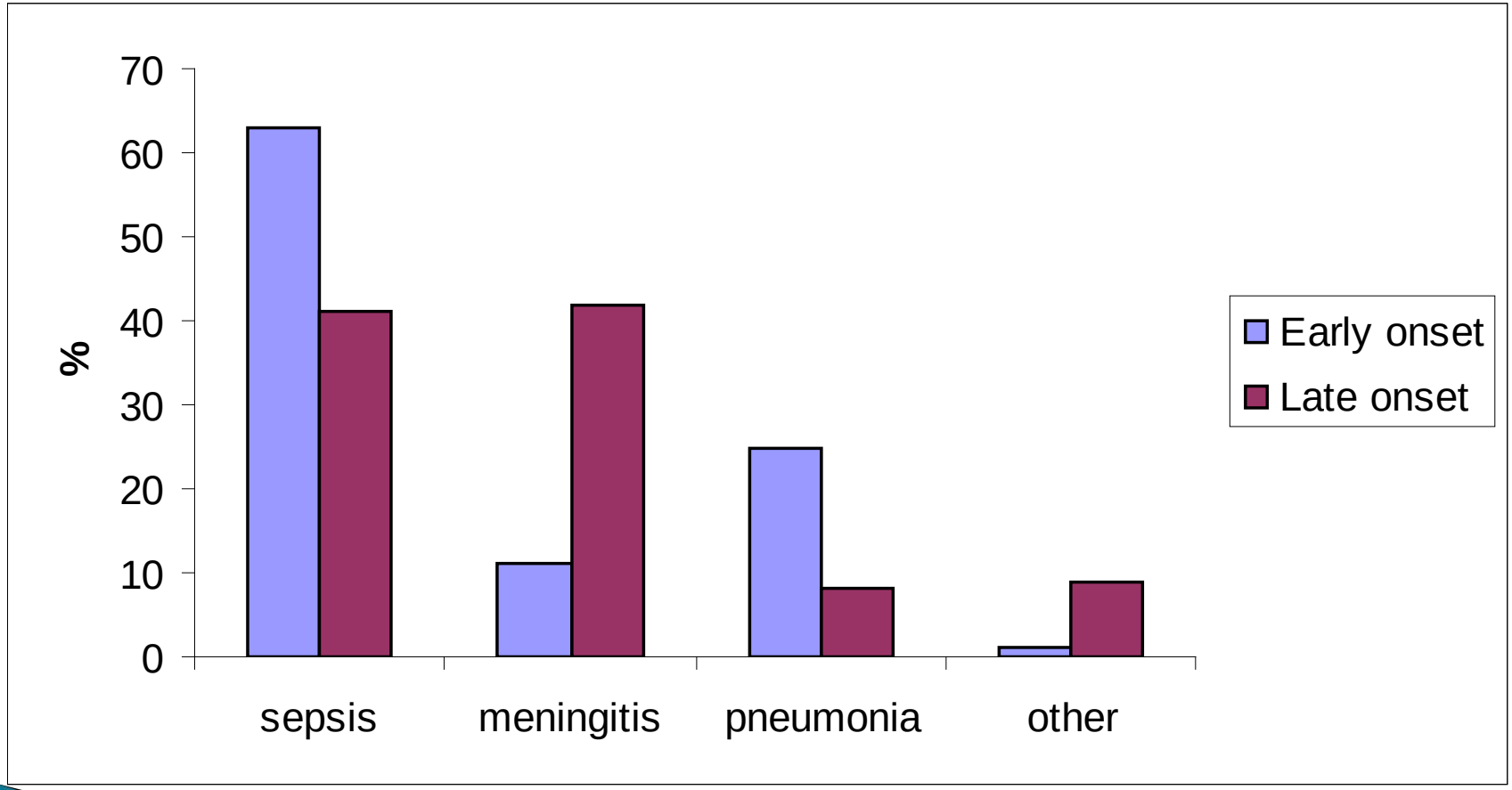
GBS Neonatal Infection

Frequent cause of neonatal sepsis/meningitis

- 800,000 to 1 million neonatal deaths/yr worldwide due to sepsis[1]
- GBS is a leading cause of neonatal sepsis and meningitis in the first 3 months of life[2]
  - US incidence: EOD + LOD = 0.68 cases/1000 live births[3] (~2725 cases/yr)
  - Mortality: Case fatality rate 4-6% among term infants[4]
- Morbidity: Meningitis is associated with long-term neurologic sequelae/disability in 35-44% of cases[5,6]

[1]Lawn JE, et al. Lancet 365:891; 2005
[2]Edwards MS. Human Vaccine 4:444, 2008
[3] Phares CR, et al. JAMA, 299:2056-2065, 2008.
[4] MMWR 2005;54(47):1205-8)
[5] NEJM 357:918-25, 2007
[6]Colbourn 2007 Health Technologies Assess (11) No 29; 2007

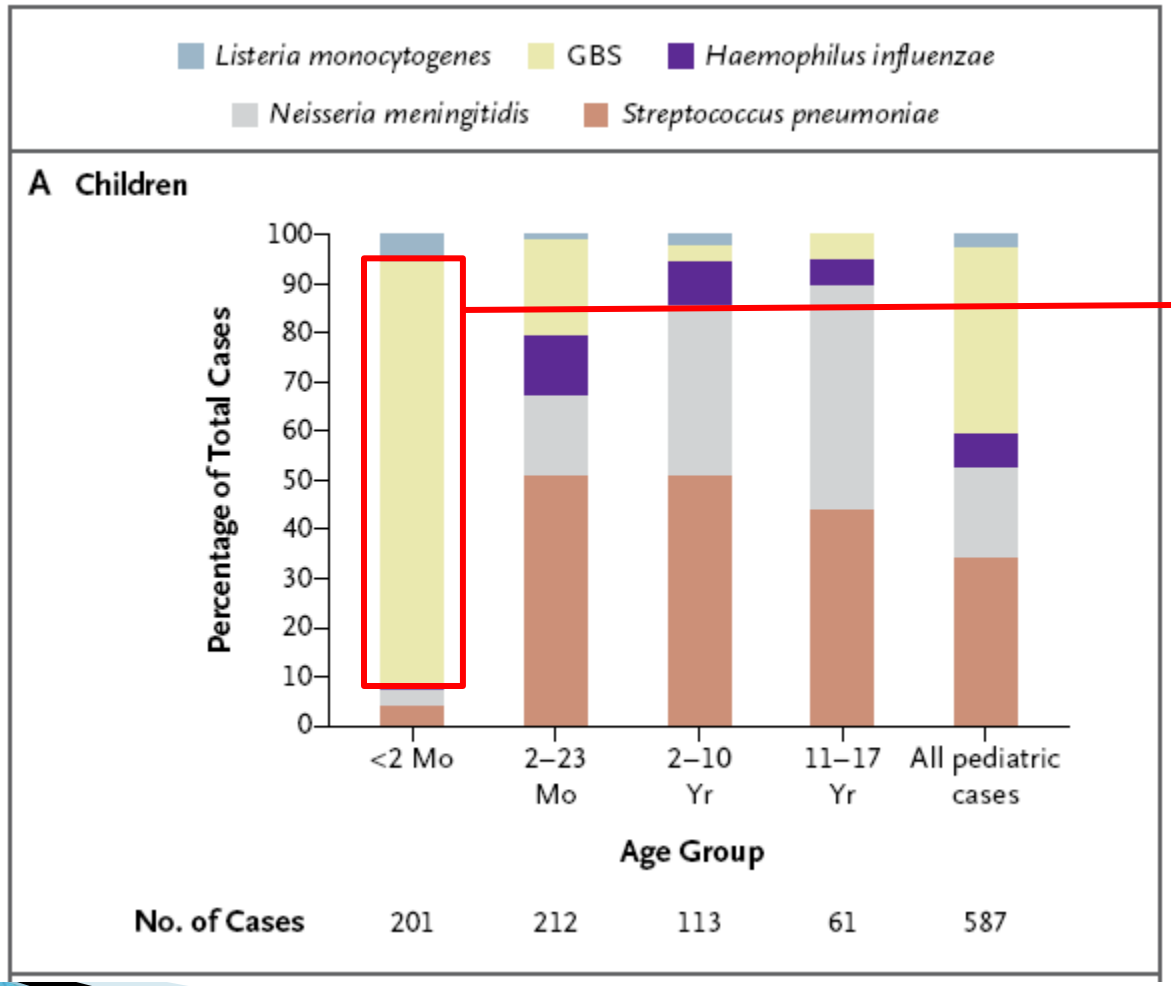
GBS neonatal infections: Clinical presentation



Lancet 2004; **363:** 292–94

GBS: Leading Cause Neonatal Meningitis (US)

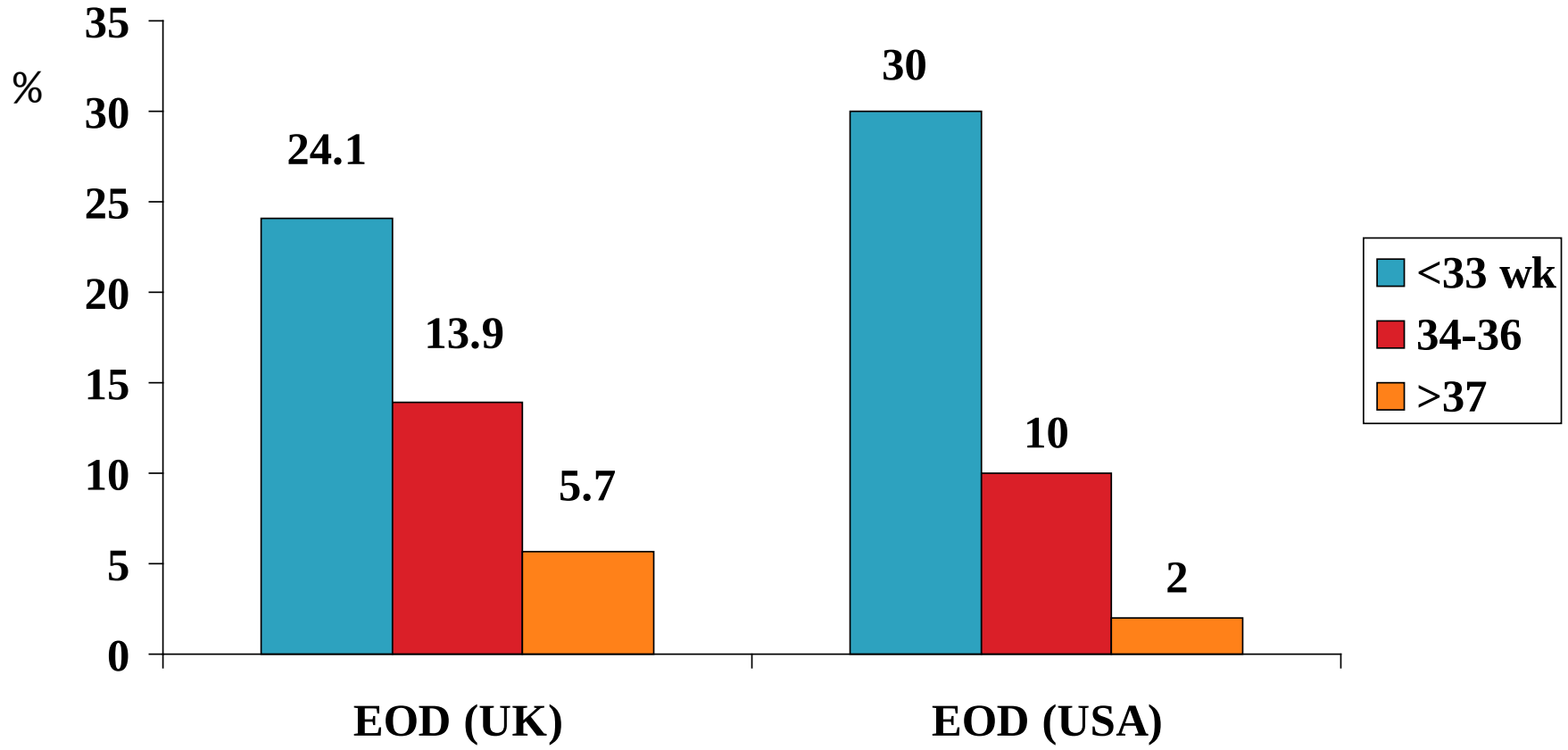
Causes >85% of disease among infants < 2 mo (US)[1]



GBS = 86.1%

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

EOD GBS case fatality rates by gestational age



Overall: 10% UK (2000–1) vs. 7% USA (1999–2005)

GBS Morbidity

- 98 children with GBS meningitis (1985 – 1987); follow- up at 5 years of age:

- 13% severe disability
- 17% moderate disability
- 18% mild disability

~ 50% have disability at 5 years of age

BMJ 2001;323:533-6

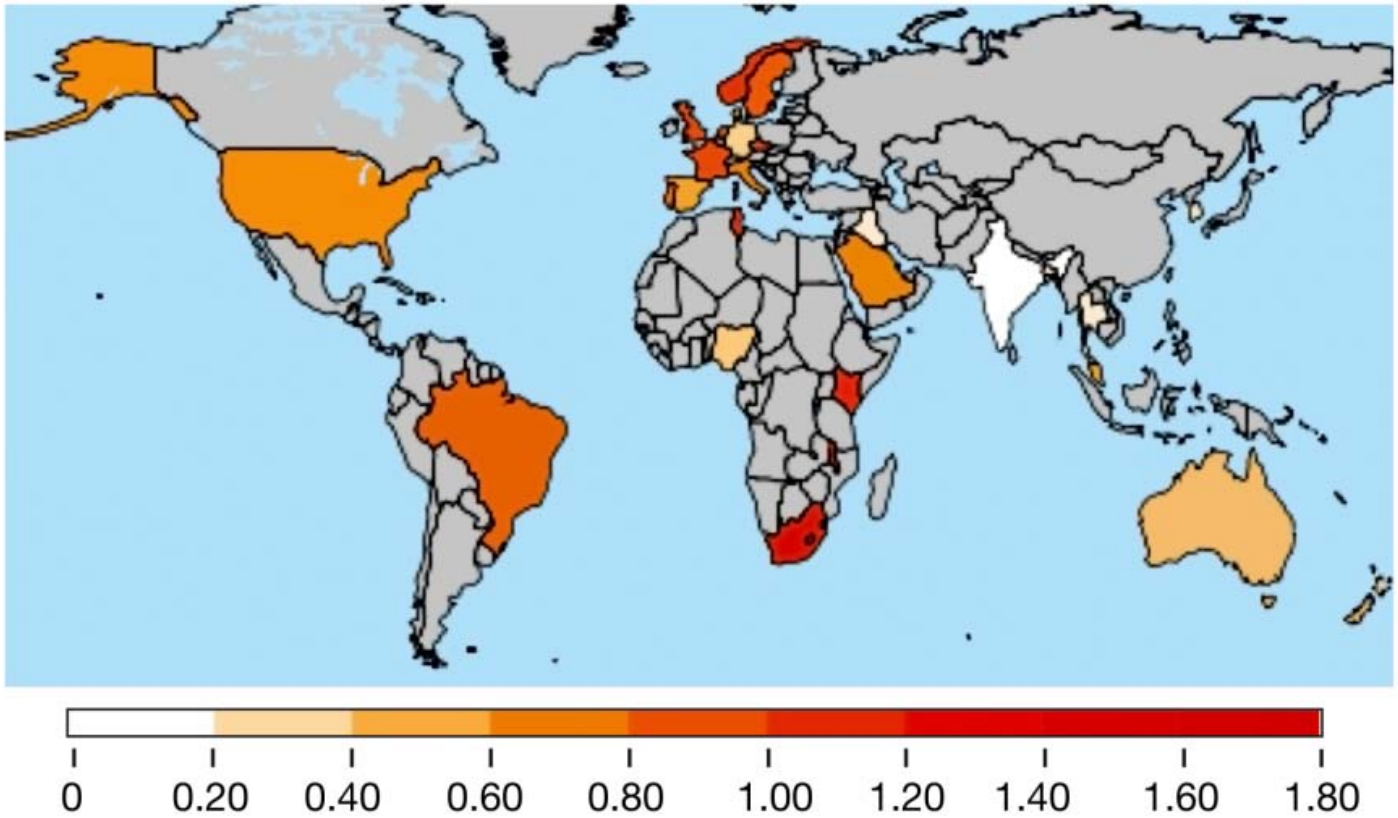
Risk factors for Late Onset GBS (USA)

JID 2003;188:267–71

Risk factor	OR (95% CI)
Prematurity by decreasing week of gestation	1.34 (1.15-1.56)
Black mother	3.7 (1.36-10.1)
Mother GBS +ve	4.15 (1.27-13.6)
TERM BABIES ONLY	
Male infant	2.81 (0.99-7.94)
Black mother	3.83 (1.0-14.6)
Mother GBS +ve	5.37 (1.11-26.0)

Reported Global Incidence of GBS infant disease

Estimated number of cases per 1000 live births in infants <90 days of age



Edmond K M et al, *Lancet* **379**, 547–556 (2012)
Black S, Margarit I, Rappuoli R. *Sci. Transl. Med.* 2013 Jul 24;5(195):195ps11.

GBS Can Be Difficult to Detect

- Poor blood collection technique: contamination
- Small blood volumes: optimal blood volume 0.75 to 1.0 mL for 90% sensitivity in neonates
- No pediatric blood culture bottles: dilution factor
- Lack of proper media/supplies for GBS isolation and identification: agar base, sheep's blood, etc.

Potential Maternal Impact

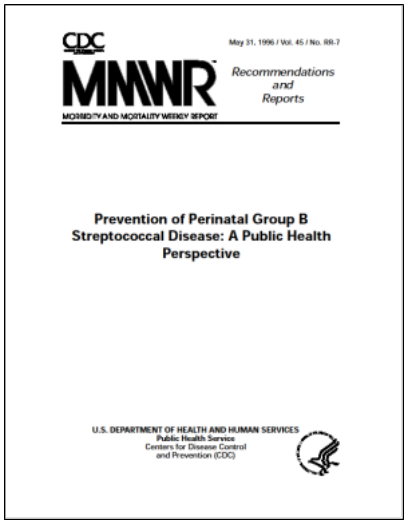
- GBS is a known cause of chorioamnionitis in the mother
- GBS is a cause of UTI in pregnant women
- Both of these entities have been associated with the early onset of labor and complications of labor.

Prevention: No vaccine yet licensed

Intrapartum antibiotic prophylaxis (IAP) only prevention

- IAP = Intravenous ampicillin q4h during labor for women at risk. Risk determined:
  - Universal screening: All pregnant women are screened at ~35-37 wks gestation → *all* colonized women receive IAP (e.g. USA)
  - Clinical factors: previous infant with GBS disease, prematurity, PROM, fever (e.g. UK)

CDC Guidelines for Prevention of Early Onset GBS Disease

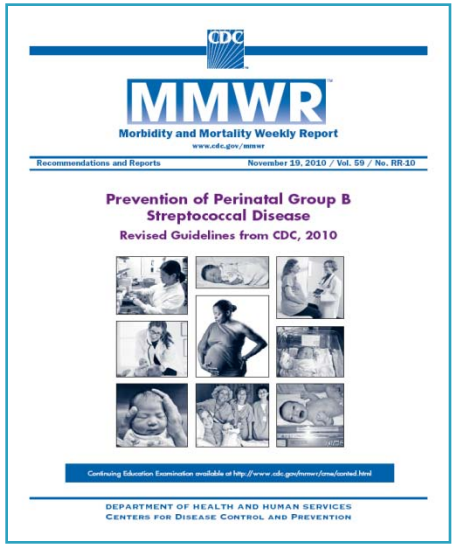


- 1996—IAP introduced
- Antenatal GBS screening-based approach

  OR
- Intrapartum risk-based approach

- Supported by key obstetric and pediatric organizations
- Lack of direct evidence to prefer one strategy over the other

Universal screening



- 2002—First recommended
  - Culture-based screening at 35–37 weeks
  - IAP for GBS+
- 2010: Fundamentals unchanged
  - Expansion/refinement of some areas of challenge
  - Management of threatened preterm delivery
  - Management of newborns
  - Laboratory processing of screening specimens
  - Endorsed by ACOG, AAP, AAFP, ASM, ACNM

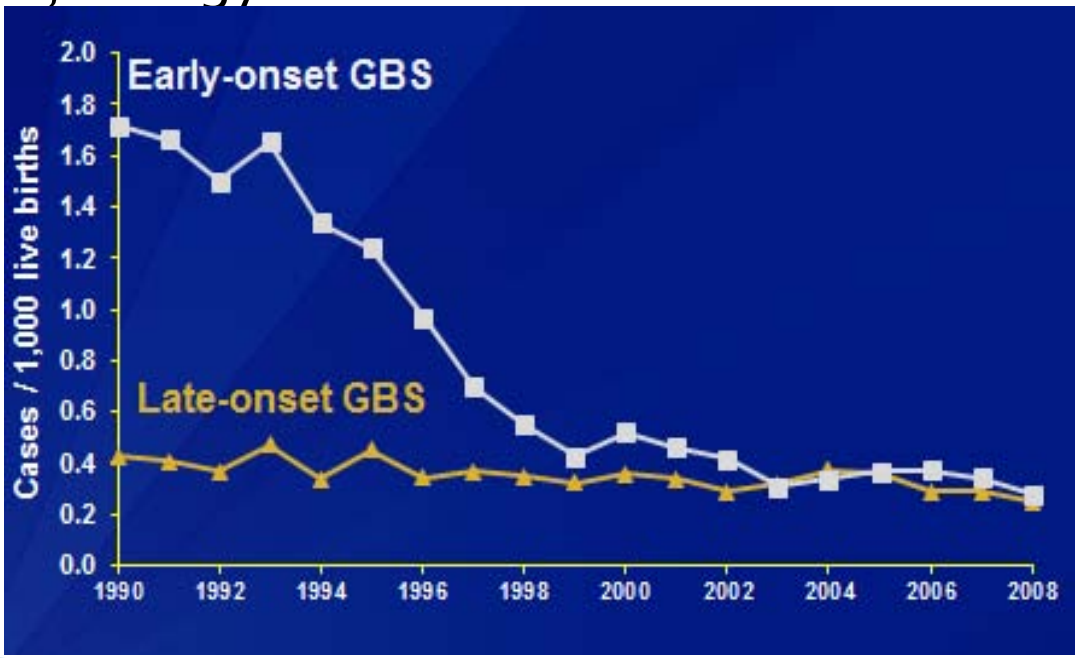
GBS: Universal screening and IAP have reduced but not eradicated the disease

- Incidence of invasive GBS disease among infants in US prior and after recommendations issued in 1993

Limitations of IAP:

ineffectiveness in preventing LOD, false

negative screening results, allergy



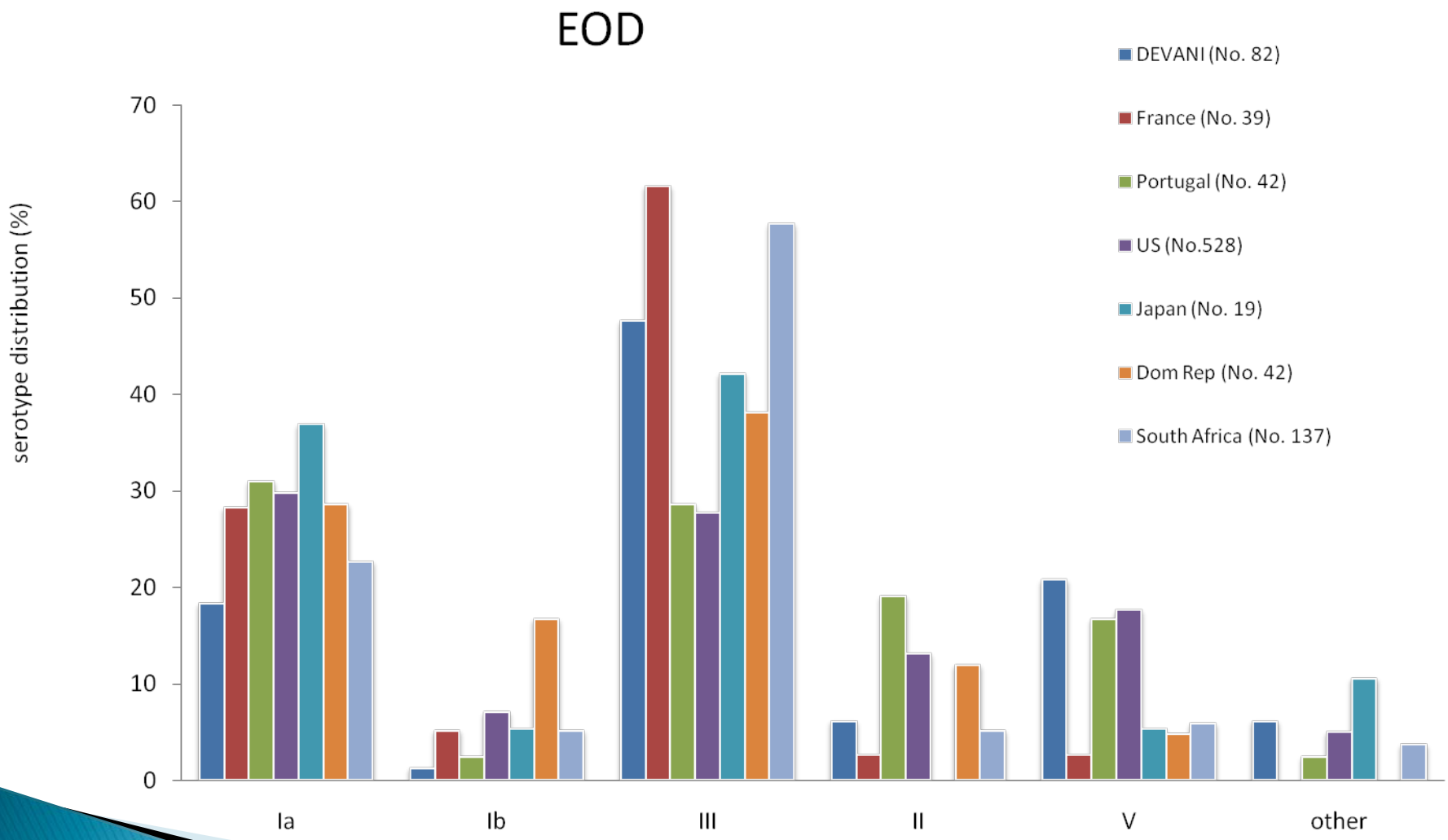
MMWR 2010 59:RR10 Jordan et al. 2008 PIDJ

A vaccine against GBS

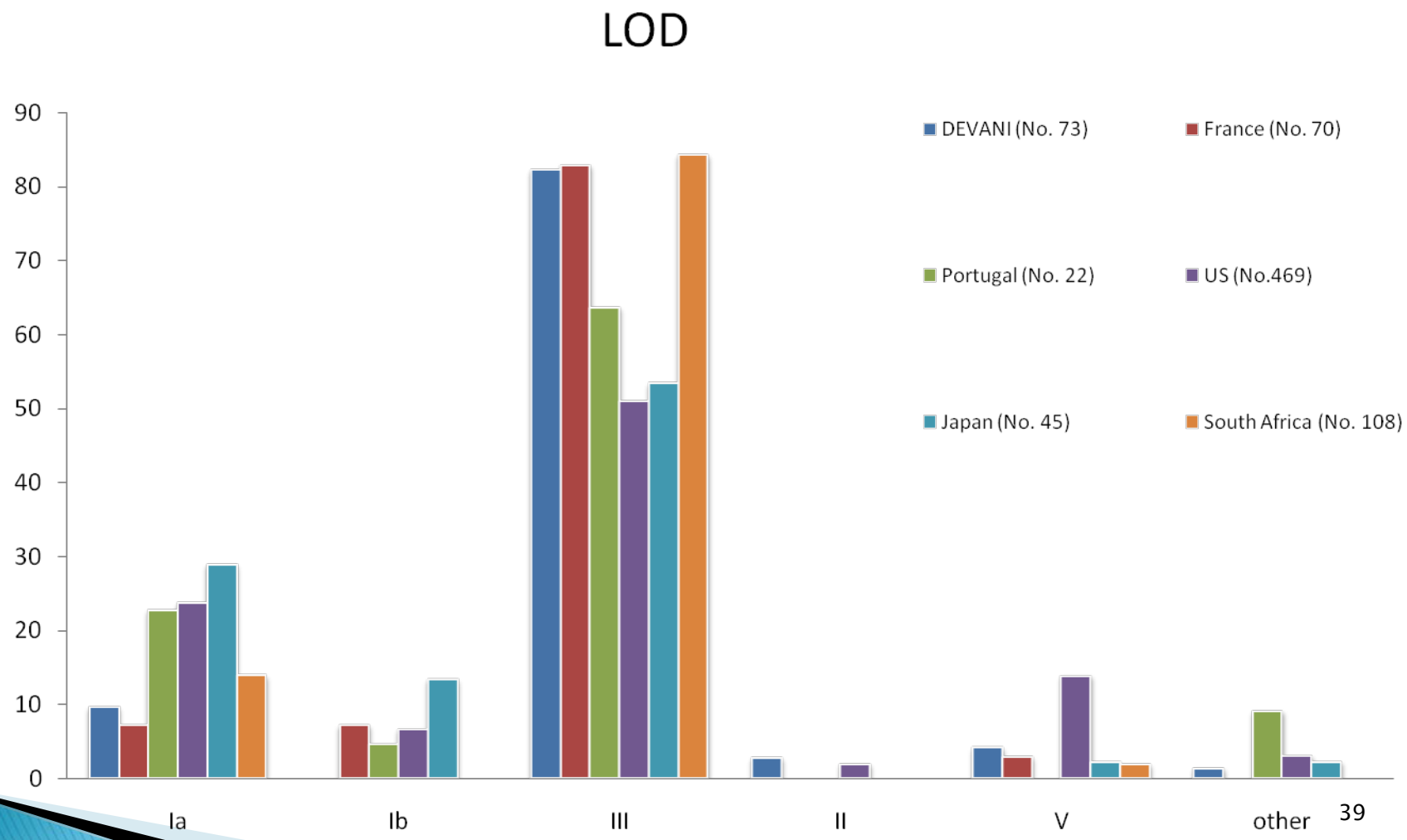
Scientific Rationale

- The polysaccharide capsule of GBS is a major virulence factor preventing complement deposition and bacterial killing by phagocytes
- Maternal antibodies to GBS capsular polysaccharides (CPS) mediate bacterial opsonopahgocytic killing and correlate with neonatal mouse & human protection
- Ten existing GBS serotypes (Ia, Ib, II, III, IV, V, VI, VII, VIII and IX) based on CPS composition and protective activity is type-specific
- Serotype distribution of neonatal isolates does not differ significantly worldwide

Detailed serotype distribution of GBS neonatal disease

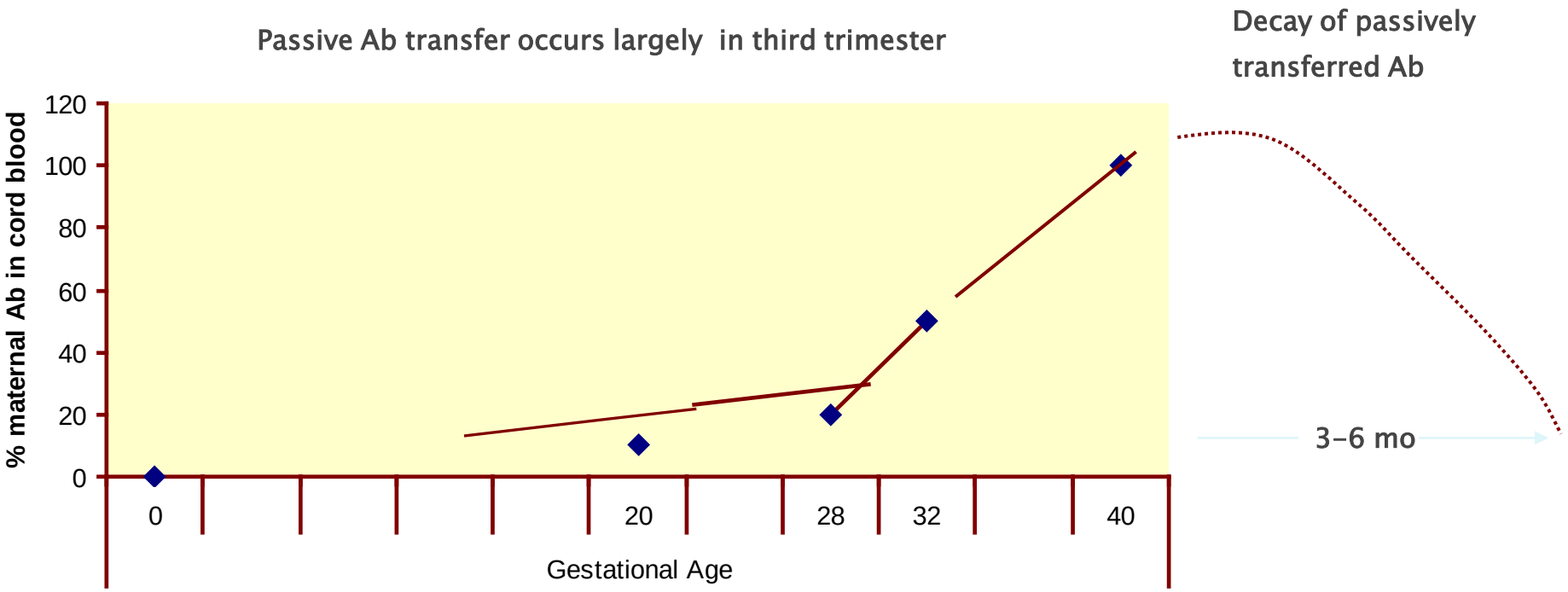


Detailed serotype distribution of GBS neonatal disease



GBS: Maternal vaccination allows infant protection

- Placental transfer increases markedly >32 wks



GSK GBS vaccine under development

Trivalent glycoconjugate vaccine

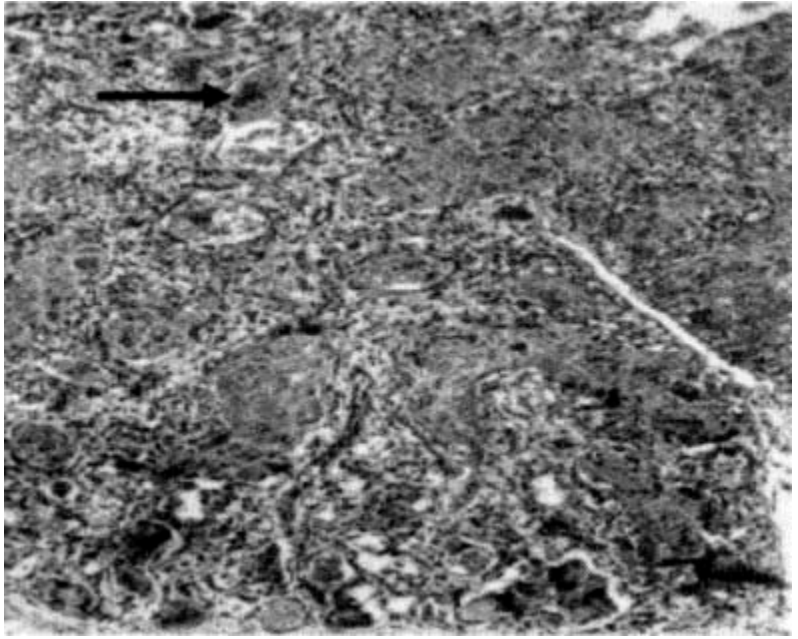
- Vaccine: CRM_{197} conjugated capsular polysaccharide representing three serotypes (at 1:1:1 ratio):
  - Ia
  - Ib
  - III

Bacterial capsular polysaccharide | CRM protein | Glycoprotein conjugate

- Same carrier as successfully used for pneumococcal and Hib vaccines
- Trivalent coverage ≈ 79% globally
- Has been shown to be safe and immunogenic in phase one and two studies in Europe and South Africa

Summary

- Group B streptococcus is a major pathogen in the neonate
- Risk is often underestimated due to difficulty in ascertaining diagnosis.
- Prenatal screening and intrapartum prophylaxis has been effective against early onset disease
- Vaccines are in development that offer the potential to prevent both early and late onset disease in neonates.



RSV

Respiratory Syncytial Virus

It has been a long journey

RSV Disease

- Respiratory syncytial virus (RSV) is the leading viral cause of severe lower respiratory tract disease in infants and young children worldwide.
- WHO has estimated that the global annual burden of infections and mortality due to human RSV are 64 million and 160,000, respectively [WHO 2009].
- Almost all children will have had an RSV infection by their second birthday. When infants and children are exposed to RSV for the first time,
  - 25 to 40 out of 100 of them have signs or symptoms of bronchiolitis or pneumonia.
  - Children hospitalized for RSV infection are younger than 6 months of age.The most severe disease occurs within the first 2 to 8 months of life, particularly in infants born prematurely and infants with underlying chronic lung and congenital heart diseases.
- RSV bronchiolitis in early life is associated with an increased risk of reactive airway disease later.

RSV Disease Burden in the US

- RSV infection in the first two years of life is almost universal
- **Highest morbidity and mortality in the first two months of life**
- Infants with CHD, BPD at highest risk

Table I.

RSV hospitalizations per 100 child-years by age and risk group

Age (mo)	Normal	CHD	BPD	≤28 wk GA	29–32 wk GA	33–35 wk GA
0–5	4.4	12.1	56.2	9.4	8.2	8.0
6–11	1.5	6.3	21.4	4.6	5.0	3.5
12–23	0.4	1.8	7.3	3.0	0.9	1.1
24–35	0.1	0.5	1.3	0.0	0.2	0.1

The burden of respiratory syncytial [illegible] (RSV) and the value of prevention. Welliver in Journal of Pediatrics Volume 143, Issue 5, Supplement, November [illegible] pages 112-117

Risk of Hospitalization and Gestational Age

TABLE 1

Average RSV Hospitalization Rates Among Children Younger Than 24 Months (2000–2005)[34]

Children <24 mo	N[a]	RSV Hospitalization Rate/1000	95% CI
All infants regardless of gestational age	559[b]	5.2	4.8–5.7
All term infants (≥37 wk gestation)	479	5.3	4.9–5.8
All preterm infants (<37 wk gestation)	56	4.6	3.4–5.8
≥35 wk gestation	494	5.1	4.7–5.5
32–34 wk gestation	23	6.9	4.3–10.1
29–31 wk gestation	6	6.3	2.0–12.4
<29 wk gestation	12	19.3	8.4–34.0
All very preterm (<30 wk gestation)	15[c]	18.7	10.0–30.0

[a] Among 2149 enrolled hospitalized children from a birth cohort of 132 085 children.

RSV Hospitalization and Underlying Risk Favors

TABLE 2

RSV Hospitalizations per 1000 Children From >248 000 Child-Years of Follow-up[38]

Age Stratum/Risk Group	0 to <6 mo	6 to <12 mo	12 to <24 mo	IRR (95% CI) for 0 to <6 mo	Adjusted IRR (95% CI) for first 12 mo
Low-risk infants	44.1	15.0	3.7	Comparator	Comparator
Infants with CHD	120.8	63.5	18.2	2.7 (2.2–3.4)	2.8 (2.3–3.3)
Infants with CLD	562.5	214.3	73.4	12.8 (9.3–17.2)	10.7 (8.4–13.6)
≤28 wk gestation	93.8	46.1	30.0	2.1 (1.4–3.1)	2.4 (1.8–3.3)
29 to <33 wk gestation	81.8	50.0	8.4	1.9 (1.4–2.4)	2.2 (1.8–2.7)
33 to <36 wk gestation	79.8	34.5	10.8	1.8 (1.5–2.1)	1.8 (1.6–2.1)
Other condition[a]	122.3	55.2	24.1	2.8 (2.5–3.1)	2.3 (2.1–2.6)

IRR, incidence rate ratio.

[a] Asthma, cystic fibrosis, cancer, HIV infection, immunodeficiency, steroid therapy, chronic renal disease, diabetes mellitus, congenital anomalies of the respiratory tract, or respiratory distress syndrome.

Source AAP RSV Report 2014

RSV in Adults

TABLE 3

RSV pneumonia in adults

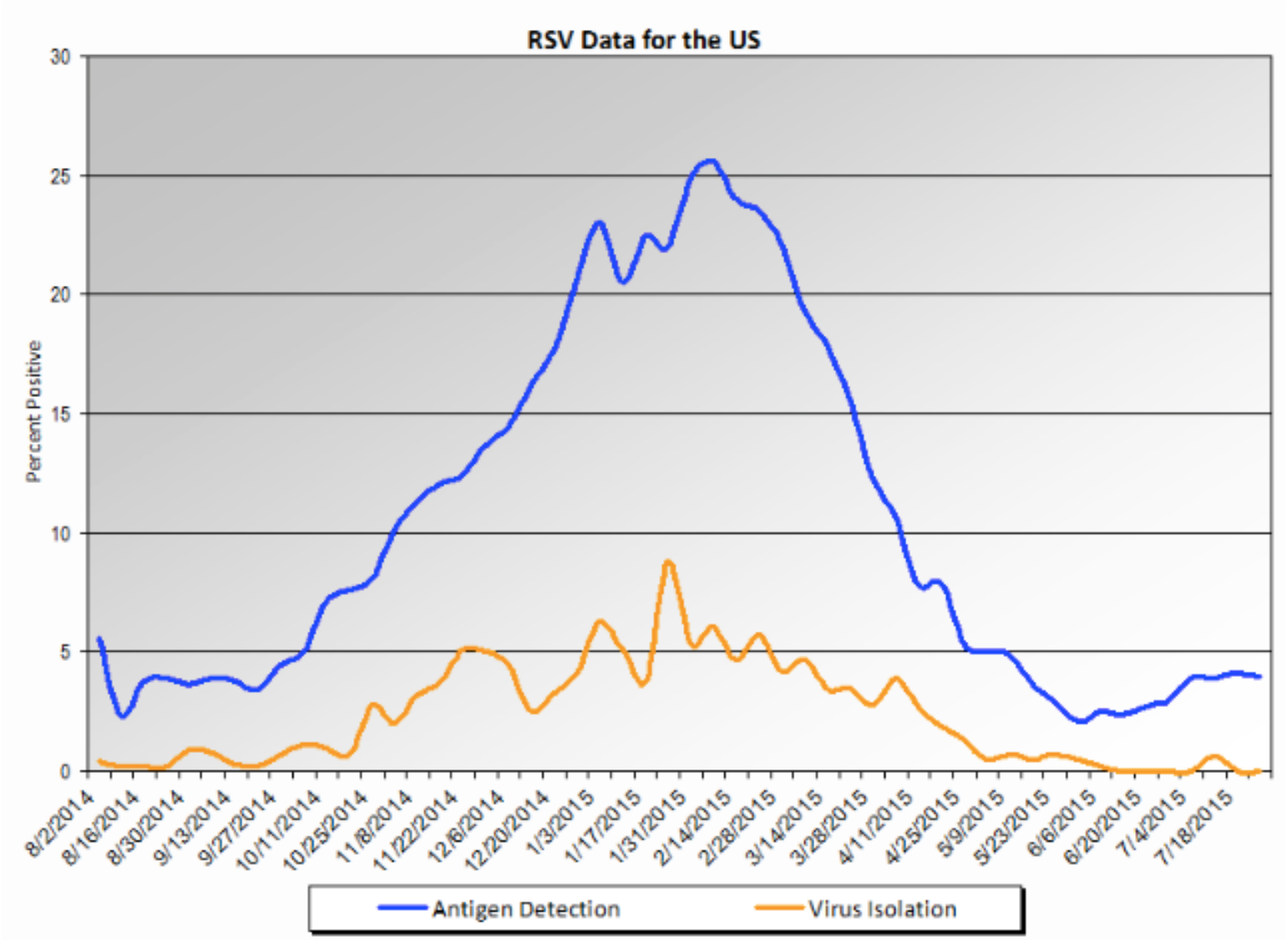
Study (reference)	Location, dates	Diagnostic test(s)[a]	No. positive/no. tested (% positi
Fransen et al. (54)	Sweden, 1963–66	CF	31/598 (5.2)
Hers et al. (96)	Netherlands, 1967–68	CF	10/207 (4.3)
Vikerfors et al. (178)	Sweden, 1971–80	CF, Ag, IgM	57/2,400 (2.0)
Kimball et al. (109)	USA, 1980–81[b]	Culture, CF	2/100 (2.0)
Stanek and Heinz (169)	Czechoslovakia, 1983–85	Culture, CF	2/74 (2.7)
Zaroukian and Leader (194)	USA, 1987–88[b]	IAH, Ag, culture	3/55 (5.4)
Melbye et al. (128)	Norway, 1988–89[b]	CF	5/36 (13.9)
Falsey et al. (42)	USA, 1989–92[b]	Culture, Ag, EIA	69/483 (14.3)
Marrie (121)	Canada, 1991–94	CF	0/149 (0)
Dowell (27)	USA, 1990–92	EIA	53/1,195 (4.4)
Ruiz et al. (159)	Spain, 1996–97	Serology not specified	5/204 (2.4)

[a]CF, complement fixation; Ag, antigen; IAH, immune adherence hemagglutination.
[b]Winter seasons only evaluated.

Clin Microbiol Rev. 2000 Jul; 13(3): 371–384.

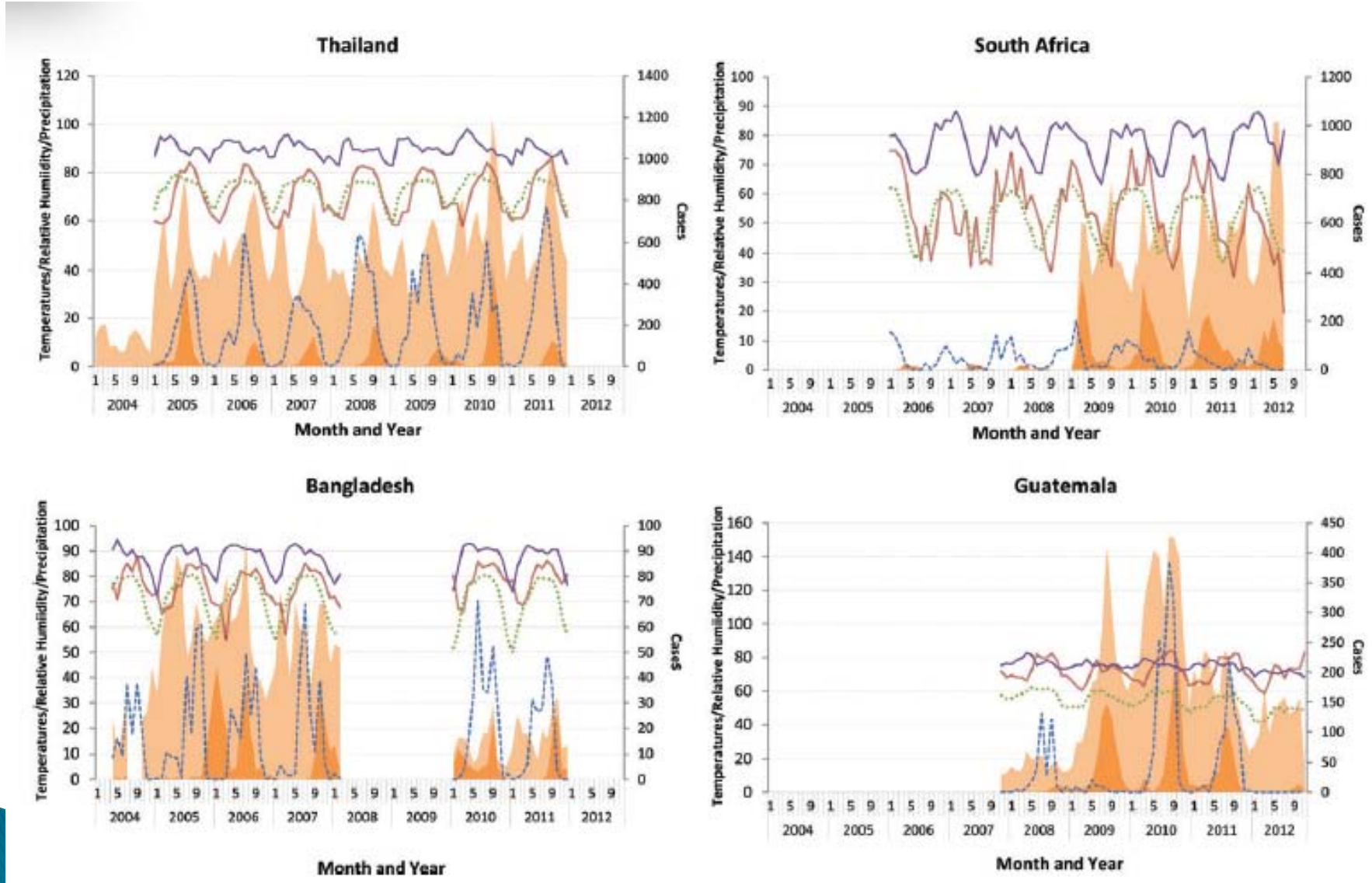
RSV Seasonality

Respiratory Syncytial Virus (RSV)



CDC Viral Disease Surveillance Network

RSV is a Global Problem



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RSV in Argentina

- Lower respiratory tract infections, in which RSV is a frequent pathogen in children under 2 years of age [Marguet 2009], are the second leading cause of death in children under 5 years of age in Argentina [Marconi 2010].
- A recent publication by Ferolla and coworkers confirmed the incidence of severe RSV infections as a major burden of respiratory illness among young children in Argentina [Ferolla 2013], in agreement with similar studies [Moisi 2011, Nair 2010], and stressed the central role of RSV on hospital admissions among children younger than 2 years.
  - Specifically, this study revealed that over 60% of the respiratory infections in 1,293 hospitalized children in Buenos Aires within a catchment population of over 360,000 children, were due to RSV.
  - Almost 20% of these children had life-threatening disease (as assessed by oxygen saturations below 87%), a finding that helps explain the high mortality rates associated with RSV.
  - The attributable mortality rate for RSV was estimated to be 7% in this study sample. The gravity of the RSV burden in Argentinean children is exemplified by noting that in the Buenos Aires metropolitan area, the burden of illness due to RSV in 2011 outweighed that of 2009 H1N1 influenza A virus during the pandemic year: 14-fold in hospitalizations and 4-fold in virus-confirmed deaths [Libster 2010].

RSV: The Virus

- RSV is a pleomorphic virus belonging to the *Paramyxoviridae* family.
  - Two major subtypes, A and B, that co-circulate.
    - The two major surface glycoproteins of RSV, F and G, are the primary targets of neutralizing antibodies, which are associated with protection [Graham 2011]
    - The F protein mediates fusion of the viral envelope with the plasma membrane and syncytium formation, while the G protein is essential for viral attachment. There is a high degree of genetic and antigenic homology in the F proteins across RSV/A and B viruses, and among individual isolates, whereas the G protein is much more variable [Johnson 1987].
  - Immunization with vaccinia virus containing the F gene protected animals against homologous and heterologous subtype A and B viral challenge; whereas, animals immunized with the G gene expressed in the same system were only protected against the homologous virus [Olmsted 1986, Stott 1987]. These data demonstrate the ability of anti-F neutralizing antibodies to generate immunity across RSV/A and B subtypes.

RSV Virus Structural Proteins

TABLE 1

RSV structural proteins in order of gene sequence, 3′ to 5′

Protein	Size (kDa)	Designation	Comments
N[a]	44	Nucleocapsid protein	Major target of CTL in humans
P[a]	34	Phosphoprotein	
M	28	Matrix protein	
SH	7.5–30	Small hydrophobic protein	Glycosylated transmembrane protein; no neutralizing epitope known; participates in cell fusion (91)
G	90	Attachment protein	Antigenic variation between strains; neutralizing epitopes; truncated secreted form (Gs) from second open reading frame (158)
F	70	Fusion protein	Sequence conserved between strains; contains neutralizing epitopes
M2-1, M2-2	22	Transcription regulation	Two open reading frame products (ORF1 and ORF2) important for full-length mRNA production by polymerase and transcription regulation (23)
L[a]	~200	Polymerase protein	

[a]N, P, and L together constitute the viral replicase.

Clin Microbiol Rev. 2000 Jul; 13(3): 371–384.

Prior Vaccine History

- In the 1960s, a formalin activated F protein vaccine was given to naïve children.
  - This vaccine was associated with an increased risk of severe disease and mortality in vaccine recipients.
  - Subsequently a cotton rat model of this enhanced disease has been used to screen vaccine candidates
  - This prior history has slowed development of vaccines.

Approaches to Protection

- Passive immunization with monoclonal antibody to F protein
  - Highly effective
  - Very expensive
  - Limited to high risk infants
- Immunization of young infants
  - Fusion protein vaccines have required multiple doses for immunogenicity – misses the high risk period
- Maternal immunization
  - Offers the most promise for protection early in life.

RSV Vaccines in Development

Table 1. Respiratory Syncytial Virus Vaccines Under Development: Undergoing Clinical Evaluation

Vaccine	Manufacturer/ Institution	Experimental Approach	Clinical Evaluation Status	Target Population
MEDI-559	Medimmune LLC	Live attenuated/ genetically engineered	Phase 1/2a (completed August 2012)	Seronegative pediatric populations
MEDI-534	Medimmune LLC	Viral vector based (RSV/PIV-3)	Phase 1/2 (completed October 2012)	Seronegative pediatric populations
MEDI-ΔM2-2	NIAID	Live attenuated	Phase 1	Seronegative pediatric populations
RSV F nanoparticle vaccine	Novavax	Subunit vaccine	Phase 2 (young women), phase 1 elderly)	Women of childbearing age (18–35 years), elderly, adults

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Candidate: Live Attenuated MEDI-ΔM2-2

- Target population in very young infants
- Caused nasal congestion and upper airway symptoms – perhaps not sufficiently attenuated.
- Concern for increased risk of SIDS in infants due to the above.
- Further development stopped after phase 1.

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Candidate: Further Attenuated Live Attenuated Live Vaccines

- Target population in very young infants
- Three vaccine candidates developed in response to results with MEDI-ΔM2-2
- All of these candidates developed by reserve genetics to include multiple attenuating mutations.
- However, these candidates have not been stable and have a tendency to develop reversion towards the wild type strain.
- It is not clear with these candidates will be pursued.

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Candidate: Viral Vector Vaccine

- The RSV/parainfluenza virus type 3 (PIV-3) vaccine candidate
- (MEDI-534) is based on the bovine PIV3 backbone with substituted human PIV3 fusion and hemagglutinin-neuraminidase
- Surface glycoproteins and engineered to express the RSV F
- In phase 1 studies in adults, RSV-PIV-3-seropositive
- children (aged 1-9 years), and RSV-PIV3-seronegative young
- children (aged 6 to <24 months), MEDI-534 demonstrated acceptable safety, virus shedding, and immunogenicity.
- A phase 1/2a study in RSV-PIV-3-seronegative young children (aged 6 months to <24 months) and in 2-month-old infants was completed
- No results have been published to date.

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Candidate:
Noravax F protein vaccine

- Novavax' has developed an RSV F vaccine.
  - Based on a purified, recombinant near full-length RSV fusion (F) glycoprotein.
  - The RSV F is produced using the baculovirus/*Spodoptera frugiperda* (*Sf9*) insect cell system, and assembles into trimers, which further associate via hydrophobic interactions into nanoparticles resembling the previously-described 40nm protein-protein micelles of isolated RSV F protein [Calder 2000].
  - The purified F protein is adsorbed to aluminum phosphate and contains 120µg of RSV F protein and 0.4mg of aluminum per 0.5mL injection.
  - The vaccine contains no viable viruses.

Noravax F protein vaccine

- Four clinical trials completed in humans thus far in 1022 healthy adults and 973 pregnant women
  - No safety concerns to date
  - Phase III efficacy trial currently underway
  - Primary outcome is RSV disease in the first months of life.

Another Candidate: GSK RSV Vaccine

- More than one candidate in development
- One candidate utilizes a self replicating RNA platform to induce early immune to F protein
- Currently only animal data available.

RSV Summary & Questions for the future

- RSV is a very significant cause of respiratory disease morbidity and mortality globally
- Current treatment and prevention strategies are suboptimal
- Toxicity with a prior vaccine candidate has slowed the field.
- Remaining questions:
  - Will maternal immunization provide protection in the first months of life for infants?
  - Can an effective infant immunization strategy be developed?

Conclusion

- Maternal immunization is an effective strategy that can provide protection to mother and infant
- Current recommendations globally include recommendations for tetanus toxoid, influenza, and pertussis in some countries
- Vaccines are in development for RSV and Group B streptococcus.
- Other potential targets include meningococcal vaccination.