Maternal Immunizations: Protects Mothers, Fetuses and Newborn Infants

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The American Academy of Pediatrics Committee on Infectious Diseases recognizes

S. Michael Marcy, M.D., FAAP

For his contributions to the field of pediatric infectious diseases.

- Service on AAP COID from 1993 to 1999
- Contributions as COID member to AAP Red Book,1994, 1997, and 2000 editions
- CDC ACIP member from 2008 to 2012
- AAP PREP:ID Course Director from 2007 to 2013

Wisdom, insight, and humor characterize Dr. Marcy's tremendous contributions to the field, for the betterment of children's health throughout the United States and the world.

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Maternal Immunizations

WHY Immunize Mothers?

- Globally-each year:
  - 600,000-800,000 neonatal deaths due to infections.
  - 10-50% of still births are estimated to be due to maternal/fetal infections.

- Most fatal neonatal infections:
  - Occur prior to completion of routine infant immunization schedules e.g. pertussis, rotavirus, meningococcus, etc.

OR

  - Caused by agents for which there are no currently approved vaccine, e.g. group B streptococcus, RSV, HSV, etc.

Maternal Immunization

Balancing Risks and Benefits

- Potential to protect mothers, fetuses, and infants from vaccine-preventable diseases.

VS.

- Potential to cause harm to mothers and/or fetuses and/or infants by administering vaccines.

Maternal Immunizations

Intent: American Academy of Pediatrics

Ethical Considerations for Vaccine and Drug Trials in Pregnant Women and their Infants: The Pediatrician's Perspective

Committee on Infectious Diseases (COID)

Committee on Bioethics (COB)

Maternal Immunization

- Immune response to different vaccines during pregnancy might be affected by pregnancy trimester.

- Most studies to date do not provide any evidence that pregnancy significantly impacts immune responses to vaccines administered during pregnancy; immune responses appear to be unrelated to maternal age, parity, socioeconomic status, or body weight.

Omer SB NEJM 376: 1256-1267, 2017
Healy CM Clin Infect Dis 56:539-544, 2013
Sperling RS Obstet Gynecol 119: 632-369, 2012
Baker CT Vaccine 21:3468-3472, 2003

Maternal Transfer of Antibodies

- IgG antibodies are the primary antibody transferred across the placenta
- IgG antibodies are *actively* transported through the placenta by neonatal Fc receptor
- IgG transported by Fc receptors on syncytotrophoblasts of chorionic *villae* by transcytosis into fetal circulation

Malek A Am J Reprod Immunol 36:248-255, 1996
Stapleton NM Immunol Rev 268:253-260, 2015
Rooopenian DC Nat Rev Immunol 7:715-725, 2007

Maternal Immunization

Transfer of Antibody from Mother to Fetus

- IgG>>>IgM, IgA; IgE
- IgG1> IgG2, IgG3, IgG4 (may vary based on trimester)
  - Streptococcal Abs: IgG2
  - RSV: IgG1 and IgG2
- Maternally-acquired antibodies **may** inhibit both serum and mucosal antibodies production in newborn/young infant.

Crowe JE Clinical Infect Dis 2001; 33: 1720-1727

Maternal Immunization

Factors Influencing Maternal Transfer of Antibodies

- Gestational age of the infant.
- Maternal antibody level:
  - Prior infection (s)
  - Prior immunization(s)
- Type of Ig class and IgG subclass
- Health of the placenta

Transport of Maternal Antibodies
Impact of Antigen-specific Antibodies

Antigen	Fetal: Maternal Ab Ratio (Term)
Pertussis	0.7-1.9
Group B strep	0.7
Influenza	0.7-1.0

Bahl R Bull World Health Organ 83: 418-426, 02005
Victoria CG Lancet 387: 475-490, 2016
Schlaudecker EP Plos One 8: e70867; 2013

Maternal Transfer of Antibodies

- The half-life of IgG is affected by:
  - IgG subclass.
  - Total IgG concentration: higher IgG levels→ higher IgG catabolism.
  - Varies by antigen-specific antibody.

Antigen	Ab Half-life in Infant
Pertussis	30-40 days
Tetanus	50-days
Group B Strep	60-days

Vidorsson G I Front Immunol 5:520, 2014
Garty KZ Clin Diag Lab Immunol 1:667-669, 1996
deVoer RM Clin Infect Dis 49:58-64, 2009
Munoz FM Vaccine 20:826-837, 2001

Maternal Transfer of Antibodies Impact of Prematurity

- Pre-term births: 5-18% of pregnancies globally
- IgG transport across the placenta starts at 26-28 weeks gestation
- Transport across placenta is restricted at earlier gestation
  - 28-32 weeks gestation: 0.5-0.6 fetal: maternal ratio
  - Full term : $\geq$ 1.0 fetal: maternal ratio
- IgG1 transport is more restricted earlier in gestation than IgG2

Van den Berg JP Early Hum Der 87:67, 2011
Van den Berg JP Plos One 9:c94714, 2014

Maternal Vaccinations and Neonatal Morbidity/Mortality

- 413,034 live births (Tdap/influenza vs. no vaccine)
  - CDC Vaccine Safety Datalink (2004-2014)
  - 25,222 infants hospitalized
  - 157 infant deaths in first 6 months of life

- No association found between infant hospitalization and/or infant mortality and maternal Tdap or influenza vaccine

Maternal Immunization During Pregnancy

Routinely Recommended In Pregnancy in US	Not Routinely Recommended in Pregnancy in US But Are Safe	Contraindicated in Pregnancy
Influenza-inactivated	Anthrax (high risk only)	BCG
Tdap	Hepatitis A	Influenza-live
		Japanese encephalitis
	Hepatitis B	virus-inactivated *
	HPV	MMR
	MenACWY	MMRV
	MenB	Typhoid*
	PCV13	Varicella
	PPSV23	Zoster
	Polio-IPV	
	Rabies (exposure or high-risk)	
	Smallpox (exposure)	
	Yellow fever (high-risk)	

*inadequate safety data

Maternal Active Immunization

When To Immunize

- Due to safety concerns, most vaccines administered during pregnancy are recommended to be given in the later half of pregnancy: 2nd & 3rd trimesters

- Tdap during pregnancy*
  - GMT for PT and FHA are higher when given 13-25 wk gestation as compared to > 26 weeks gestation (approximately double)

***Eberhardt CS Clin Infect Dis 2016; 62-829-836**

Maternal Antibodies and Interference with Infant Immunization

- Passively-acquired maternal antibodies have the **potential** to affect not only the concentration of antibodies produced following infant immunization but also the quality of antibody.

- Passively-acquired maternal antibodies do not affect T-cell responses to infant immunization.

- The impact of passively-acquired maternal antibodies is affected by the concentration of maternal antibodies at the time of immunization and the antigen content of the vaccine.

Stegrist CA Vaccine 21:2406-3412, 2003

Favoette An Hum Repord Updates 21:119-135, 2015

Initial Use of Maternal Vaccines

- Smallpox results in more severe disease in pregnant women.
- Smallpox vaccine given to pregnant women in late 1800s:
  - Reduced smallpox in mothers.
  - Protected young infants from smallpox early in life.
- Fetal demise was rare.

Burkhardt AE Arch Klin Med 1879; 24:506.
Badell ML Obstet Gyneol 2015, 125: 1439-51

Currently Available Maternal Immunizations

Tetanus: Risk Factors and Outcomes

Mother	Child
Unhygienic delivery	Unhygienic care of umbilical stump
Abortion	Poor perinatal hygiene
Miscarriage	Inadequate material tetanus immunization

Thwaites CL Lancet 385:362-370,2015

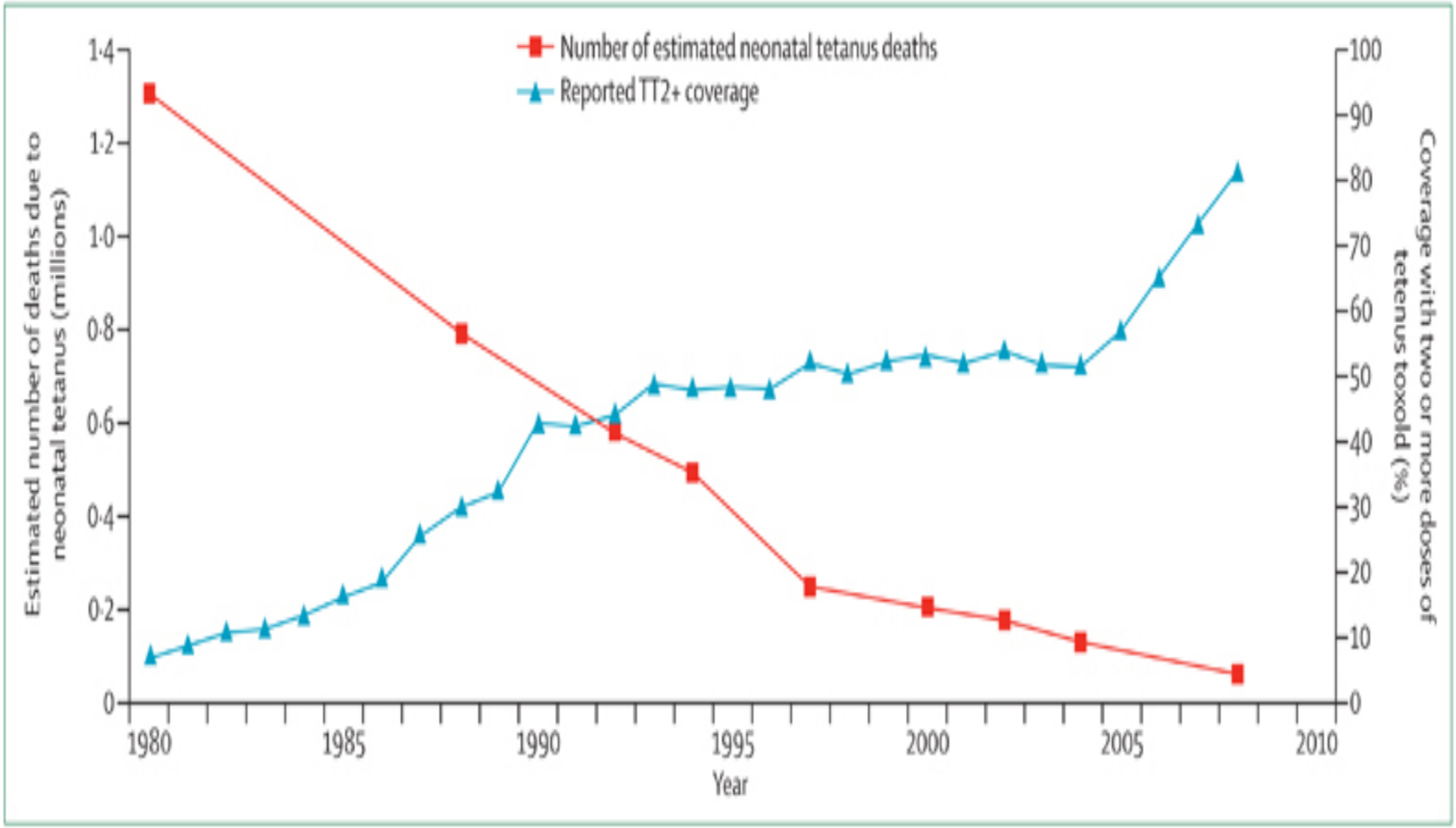
Tetanus Immunization During Pregnancy

- For women with no prior tetanus immunization prior to pregnancy WHO recommends:
  - 2 doses of a tetanus-containing vaccine for the first pregnancy.
  - 1 dose of a tetanus-containing vaccine for each subsequent pregnancy (maximum of 5 doses).

- Tetanus mortality decreased by 92%.

Heoly CM Clin Obstet Gynecol 2012; 55:74-86

Impact of Tetanus Immunization (2 doses) on Neonatal Tetanus Deaths



Thwaites CL Lancet 385: 362-370; 2015

Influenza Vaccine: Pregnancy Outcomes

- Influenza morbidity is greater in pregnant women, particularly influenza in 2nd and 3rd trimester. [1,2]
- Maternal influenza increases risk of fetal death.[3]
- Vaccine safety: Pregnant women =non-pregnant women.[4]
- Vaccine efficacy: Pregnant women=non-pregnant women.[5]
- Pregnancy outcomes (mothers):
  - Reduced respiratory illness/hospitalizational.[5]
  - Reduced stillbirths.[5]
  - Reduced preterm labor/deliveries.[6]

1. Dodds L CMAJ 2007: 176:463-468
2. Louie JK NEJM 2010: 362: 27-3
3. Haberg SE NEJM 2013; 368: 333-340
4. Thompson MG Clin Infect Dis 2014; 58: 449-457
5. Regan AK Clin Infect Dis 2016; 62: 1221-1227
6. MMWR 2011; 60: 1193-1196

Influenza Vaccine and Neonatal Outcomes

- 12,223 pregnant women.
- 1958 (16%) of these women received seasonal influenza vaccine.
- Neonatal outcomes in vaccinated mothers:
  - Pre-term birth – 25% less likely
  - Low-birth-weight – 27% less likely

Legge A: CMAJ 2014; 186: E157-64

Maternal Immunization

Influenza Vaccine: Infant Outcomes

- Maternal influenza immunization results in passive transfer of vaccine-generated antibodies to fetus.

- Infant outcomes (<6 months of age):
  - Reduced laboratory-confirmed influenza infection. [1,2]
  - Reduced influenza illnesses.[3]
  - Reduced febrile respiratory illnesses.[1]
  - 80% reduction in influenza-related hospitalization.[2]

1. Zaman K NEJM 2008; 359-1555-1564
2. Shakib JH Pediatrics 2016; 137: e20152360
3. Eick AA. Arch Pediatr Adolesc Med 2011; 165: 104-111

Efficacy of maternal IIV3 vaccination in preventing influenza illness in the infants until 6 months of age

Study	Period, country	Control group	Population	Outcomes	Vaccine efficacy
Zaman K, *et al. N Engl J Med* 2008; 359:1555 –64	2004-2005 Bangladesh	23-valent pneumococcal vaccine	IIV3 161 Control 166	Rapid test-confirmed influenza	**62.8%** **(95%CI: 5.0%, 85.4%)**
Madhi SA, *et al. N Engl J Med* 2014; 371:918–31	2011-2012 South Africa	Saline placebo	IIV3 1026 Control 1023	PCR-confirmed influenza	**48.8%** **(95%CI: 11.6%, 70.4%)**
Tapia MD, *et al. Lancet ID* 2016	2011-2013 Mali	Meningococcal vaccine	IIV3 2064 Control 2041	PCR-confirmed influenza	**33.1%** **(95%: 3.7%, 53.9%)**
Steinhoff MC, *et al Lancet ID* 2017	2011-2013 Nepal	Saline placebo	IIV3 1,831 Control 1,835	PCR-confirmed influenza	**30%** **(95% CI: 5%, 48%)**

Vaccination of pregnant women in preventing Influenza-related hospitalization in their infants

Study	Year, country	Design	Population	Outcomes	VE
Black SB, et al. 2004	1997-2002 USA	Retrospective cohort	3652 infants of immunized moms 44987 infants of non-immunized moms	Hospitalization for pneumonia and influenza	**4% (95%CI: -3, 11)**
France EK, et al. 2006	1995-2001 USA	Retrospective matched cohort	3160 infants of immunized moms 37969 infants of non-immunized moms	Medically attended ARI	**4% (95%CI: -1, 1)**
Benowitz I, et al. 2010	2000-2009 USA	Matched case-control	<12 months old (113 cases; 192 matched controls)	Lab-confirmed influenza hospitalization	**92% (95%CI: 62, 98) in <6 months**
Eick AA, et al. 2011	2002-2005 USA	Prospective cohort	1169 infant mother pairs	Lab-confirmed influenza; ILI hospitalization	**41% (95%CI: 7, 63) 39% (95%CI: 16, 55)**
Poehling KA, et al. 2011	2002-2009 USA	Active population-based case-control	<6 months old (151 cases; 1359 controls)	Lab-confirmed influenza hospitalization	**48% (95%CI: 9, 70)**
Dabrera G, et al. 2014	2013-2014 England	Retrospective study using the screening method	<6 months old (43 cases)	Lab-confirmed influenza; Lab-confirmed influenza hospitalization	**71% (95%CI: 24, 89) 64% (95%CI: 6, 86)**
Regan AK, et al. 2016	2012-2013 Australia	Retrospective population-based cohort	3169 infants of immunized moms 27859 infants of non-immunized moms	Hospitalization for respiratory illness during influenza season	**aHR: 0.75 (95%CI: 0.56, 0.99)**

Black SB, *et al. Am J Perinatol* 2004;21:333–9; France EK, *et al. Arch Pediatr Adolesc Med* 2006;160:1277–8; Benowitz I, *et al. Clin Infect Dis* 2010;51:1355–61; Eick AA, *et al. Arch Pediatr Adolesc Med* 2011;165:104–11; Poehling KA, *et al. Am J Obstet Gynecol* 2011;204:S141–8; Dabrera G, *et al. Euro Surveill* 2014;19:20959; Regan AK, *et al. Pediatr Infect Dis J* 2016,35:1097-1103

The American College of
Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

ACOG COMMITTEE OPINION

Number 732 • April 2018

(Replaces Committee Opinion Number 608, September 2014)

Committee on Obstetric Practice

This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Immunization and Emerging Infections Expert Work Group and the Committee on Obstetric Practice in collaboration with Neil S. Silverman, MD, and Richard Beigi, MD.

Influenza Vaccination During Pregnancy

ABSTRACT: Influenza vaccination is an essential element of prepregnancy, prenatal, and postpartum care because influenza can result in serious illness, including a higher chance of progressing to pneumonia, when it occurs during the antepartum or postpartum period. In addition to hospitalization, pregnant women with influenza are at increased risk of intensive care unit admission and adverse perinatal and neonatal outcomes. The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices and the American College of Obstetricians and Gynecologists recommend that all adults receive an annual influenza vaccine and that women who are or will be pregnant during influenza season receive an inactivated influenza vaccine as soon as it is available. In the United States, the influenza season typically occurs from October to May. Ideally, an influenza vaccination should be given before the end of October, but vaccination throughout the influenza season is encouraged to ensure protection during the period of circulation. Any of the licensed, recommended, age-appropriate, inactivated influenza vaccines can be given safely during any trimester. Therefore, it is critically important that obstetrician–gynecologists and other obstetric care providers recommend and advocate for the influenza vaccine. Obstetrician–gynecologists are encouraged to stock and administer the influenza vaccine to their pregnant patients in their offices, and should get the influenza vaccine themselves every season. If the influenza vaccine cannot be offered in a practice, obstetrician–gynecologists and obstetric care providers should refer patients to another health care provider, pharmacy, or community vaccination center. This updated Committee Opinion includes more recent data on the safety and efficacy of influenza vaccination during pregnancy and recommendations for treatment and postexposure chemoprophylaxis.

Influenza Vaccine: Prevention of Influenza and Pertussis

- Study in South Africa: 2011-2012.
- Influenza vaccine (1062) and Placebo (1054).
- Efficacy in infants (reduction of infection):
  - Influenza – 50%
  - Pertussis – 40%

Nunes Mc: NEJM 2018; 378: 1257-58.

Pertussis During Pregnancy

- Overall morbidity of pertussis among pregnant women compared with non-pregnant women is not increased.

- Maternal pertussis is “tiresome” by not associated with obstetric complications or preterm delivery/disease.

MacLean DW Scott Med J 26: 250-253, 1981

Granstrom G. Scand J Infect 71 (Suppl): 237-29, 1990

Complications of Pertussis in Infants United States, 1997-2000

Age	No. With Pertussis	Hospitalizations	Pneumonia	Seizures	Encephalopathy
< 6 Months	7,203	4,543(63%)	847(12%)	103(1%)	15(.2%)
6-11 Months	1,073	301(28%)	92(8%)	7(.6%)	1(.1%)

CDC. *MMWR*. 2002;51:73-76

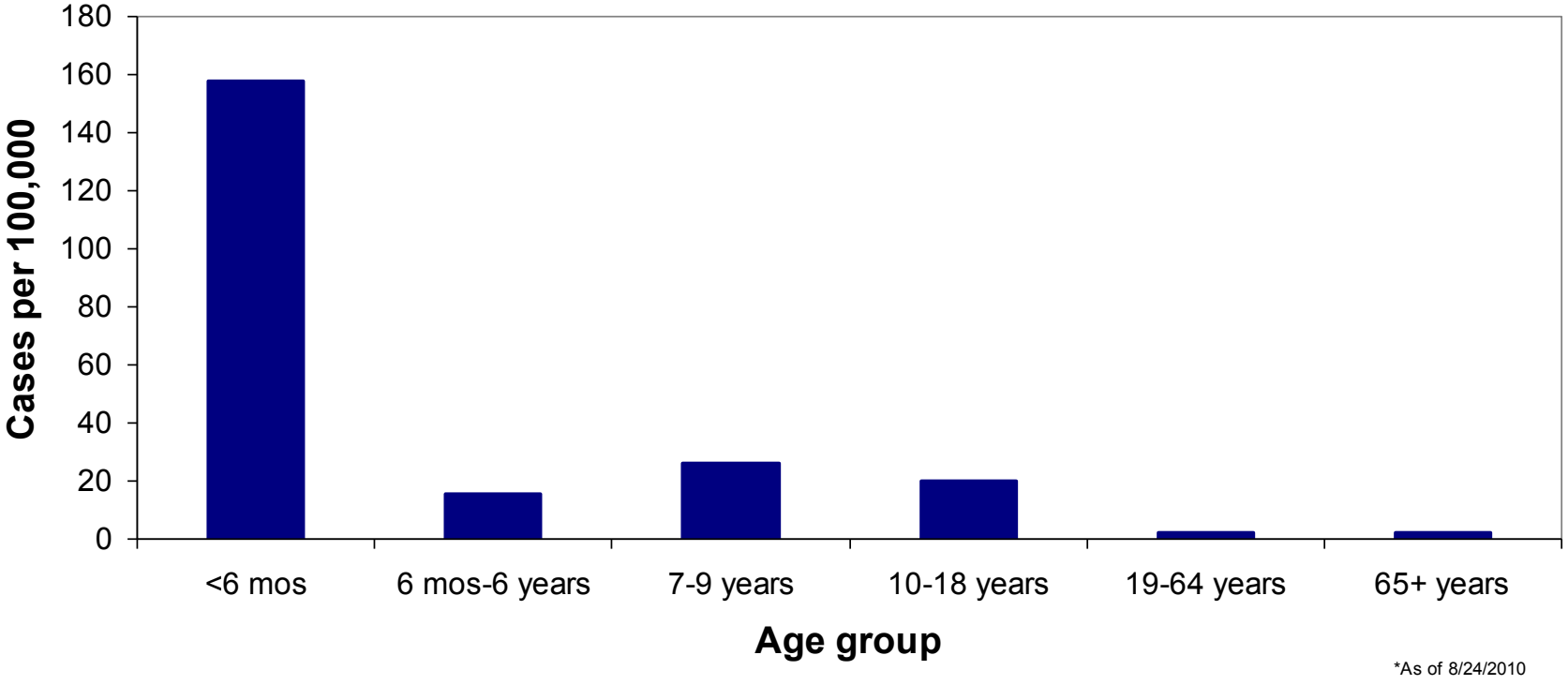
CA Pertussis Cases (12/31/2010)

- 9,143 confirmed, probable and suspect cases, 24.3 cases/100,000

- This was the most cases reported in California since 1955 and the highest incidence since 1962

- 10 deaths (case fatality rate <3 months = 1.6%)
  - 9 infants <2 months; no DTaP doses
  - 1 premature infant, age 2 months: 1 DTaP
  - Cough illness **common** in parents or sibs

Rates of reported pertussis by age -- California, Jan 1 - Aug 24, 2010



Vaccine Safety
Tdap: Maternal Immunization

- Injection site reactions/pain were common
- No serious adverse events in mothers nor infants
- Possible increase in chorioamnionitis

Cayton JB Vaccine 35: 4072-4078, 2017
Munoz FM JAMA 311: 1760-1769, 2014

Pertussis Immunization During Pregnancy

- Booster doses of Tdap increase pertussis antibodies in pregnant women.

- Maternal Tdap given at 27 through 30 weeks gestation results in higher cord blood pertussis antibodies than when Tdap is administered at ≥31 weeks gestation.

Munoz FM: Clin Infect Dis 2014; 59 (Suppl.7):5415-27
Abu Raya B: Vaccine 2014: 32:5787-93

Efficacy of Maternal Tdap

- Maternal Tdap vaccine effectiveness in preventing pertussis in infants:
  - ✓91.4% in first 2 months of life
  - ✓69% during first year of life

- Maternal Tdap during pregnancy provided additional and earlier protection than pre-pregnancy DTaP and/or Tdap alone.

Baxter R Pediatrics 139: e20164091 May 2017
Amirthalingham G Lancet 384: 1521- 1528, 2014

Maternal Vaccines Strategies

in Development

Immunity To RSV Infection

- Neutralizing antibodies directed against the RSV F and G proteins are the primary antibodies assumed to confer immunity against RSV infection.
-
- Repeated RSV infections suggest that the immune response following natural RSV infection does not provide life-long immunity/ protection

Hall C NEJM 360: 588-598; 2009.

Prevention of RSV in Infants by Passive Antibody Therapy

- RSV-IGIV (RespiGam)-high-titer RSV polyclonal IGIV
- Palivizumab (Synagis)
- Motavizumab (Numax)

RSV Vaccines: Early attempts Hampered by Adverse Events

- Formalin-inactivated RSV vaccine given to RSV seronegative children→ "enhanced RSV disease" following natural exposure to RSV.

- Formalin-inactivated RSV vaccine:
  - Antigens not processed in cytoplasm→ lack of protective antibodies and CD4 + helper T-cell priming.
  - Pathogenic Th2 memory response.
  - RSV exposure → excess eosinophils, neutrophils, monocytes and immune complex deposition in lungs.

Omer SB NEJM 376: 1256-1267, 2017
KIM HW. Am J Epidemiol 89:533-434, 1969
Fulginiti VA AM J Epidemiol 89:435-448, 1969
Acosta PL Clin Vaccin Immunol 23: 189-195, 2015

Candidate RSV Vaccines

- Live attenuated virus vaccines
- Whole inactivated virus vaccines
- Particle-based subunit vaccines
- Nucleic acid vaccines
- Gene-based vector vaccines

Omer SB NEJM 376: 1256-1267, 2017

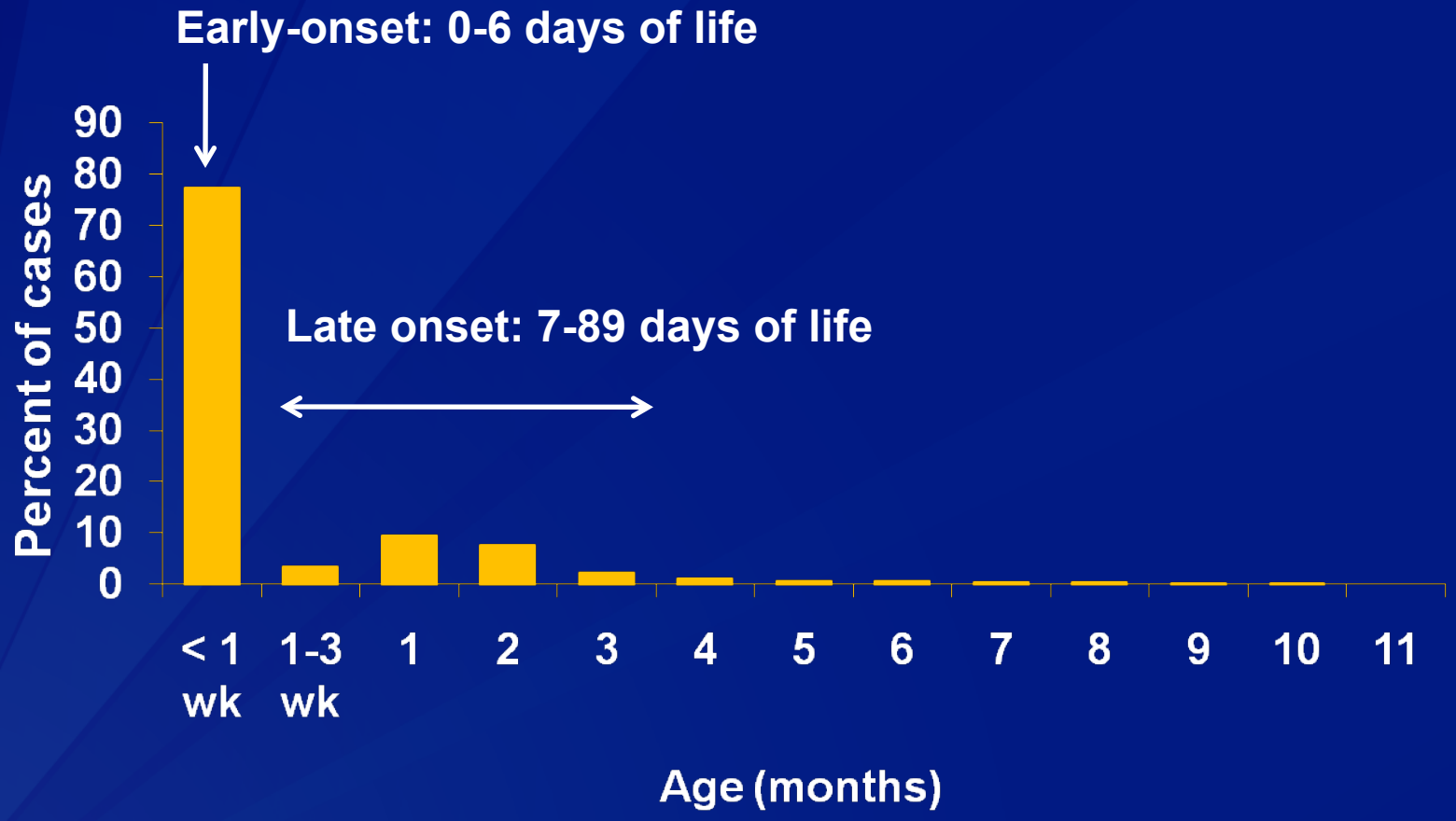
Maternal Active Immunization

The Case for Maternal RSV Immunization

- Transfer of material RSV Abs to full term infants are 100% of maternal levels.[1]
- Maternally-derived Abs decline rapidly but are still detectable at 5-7 months of age.[2]
- Maternally-derived RSV Abs protect against severe RSV during first 5-7 months of age. [2]
- Maternal Immunization with a nanoparticle RSV vaccine:[3]
  - -Safe.
  - - Immunogenic.
  - -Passive transfer to fetus.
  - -Reduced hospitalizations.

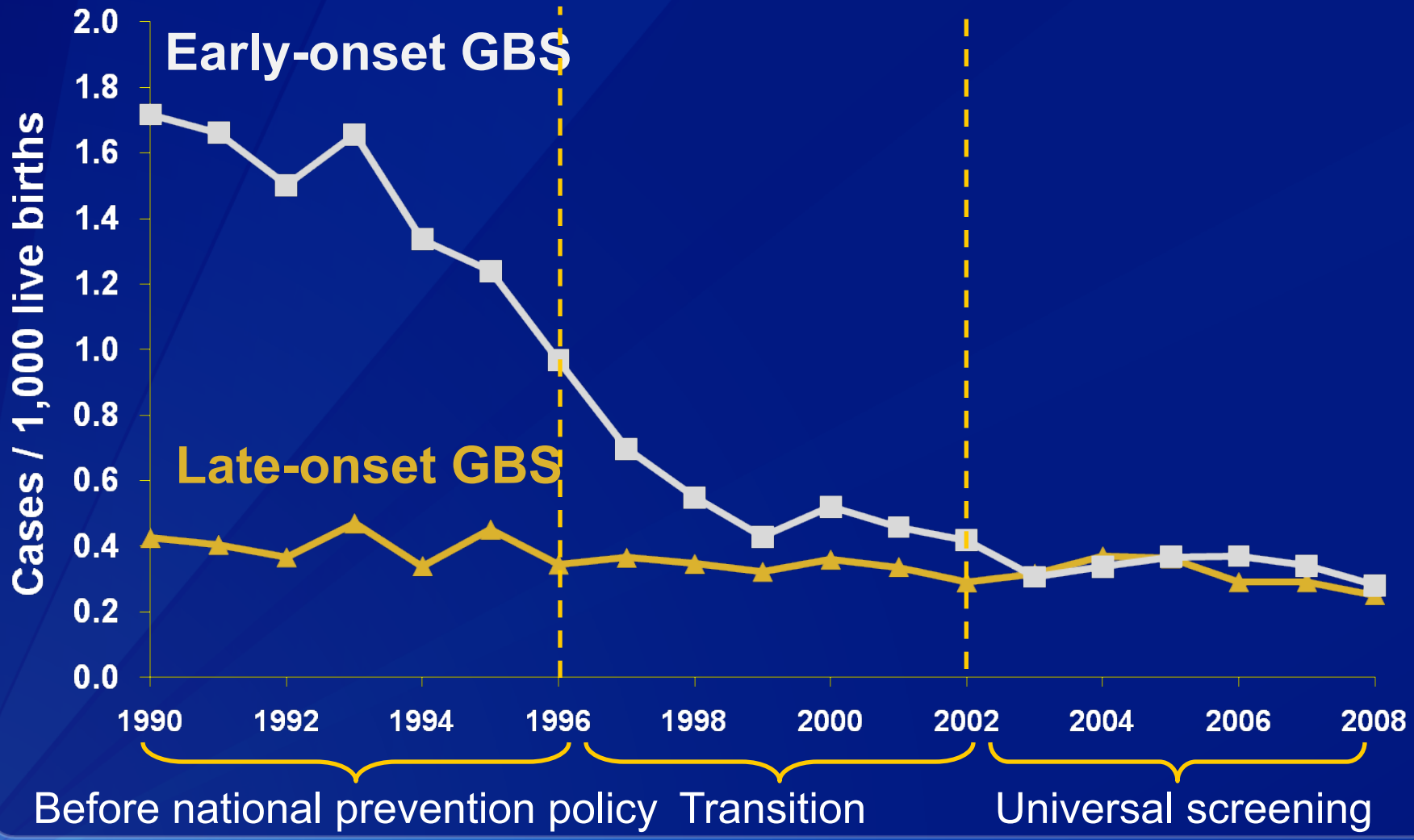
1. Chu HY J Infect Dis 2014; 210: 1582-1589
2. Ochola R PLoS One 2009; 4(12):e8088
3. Glenn GM J Infect Dis 2016; 213; 411-422

GBS Disease in Infants Before Prevention Efforts



A Schuchat. Clin Micro Rev 1998;11:497-513.

Rate of Early- and Late-Onset GBS, 1990-2008



Source: Active Bacterial Core surveillance / Emerging Infections Program

Risk Factors for Early-onset GBS Disease

- **Obstetric risk factors:**
  - Preterm delivery
  - Prolonged rupture of membranes
  - Infection of the placental tissues or amniotic fluid / fever during labor
- **GBS in the mother's urine during pregnancy (marker for heavy colonization)**
- **Previous infant with GBS disease**
- **Low maternal levels of anti-GBS antibodies**
- **Demographic risk factors**
  - African American
  - Young maternal age

Group B streptococcal Vaccines

- Polysaccharide vaccines
- Conjugated polysaccharide vaccines
  (in current clinical trials)

Group B streptococcal Vaccines

- Conjugated polysaccharide vaccines:
  - Monovalent
  - Trivalent (Ia, Ib and III)

- Serotypes Ia, Ib and III cause majority of GBS in Americas and Europe

- Globally, Serotypes II and V cause GBS disease in addition to Ia, Ib and III.

Omer SB NEJM 376: 1256-1267, 2017
Edmund KM Lancel 379:547-556, 2012.

Group B Streptococcal Vaccines

- Trivalent Serotypes Ia, Ib and III Vaccine has undergone phase I and 2 trials:

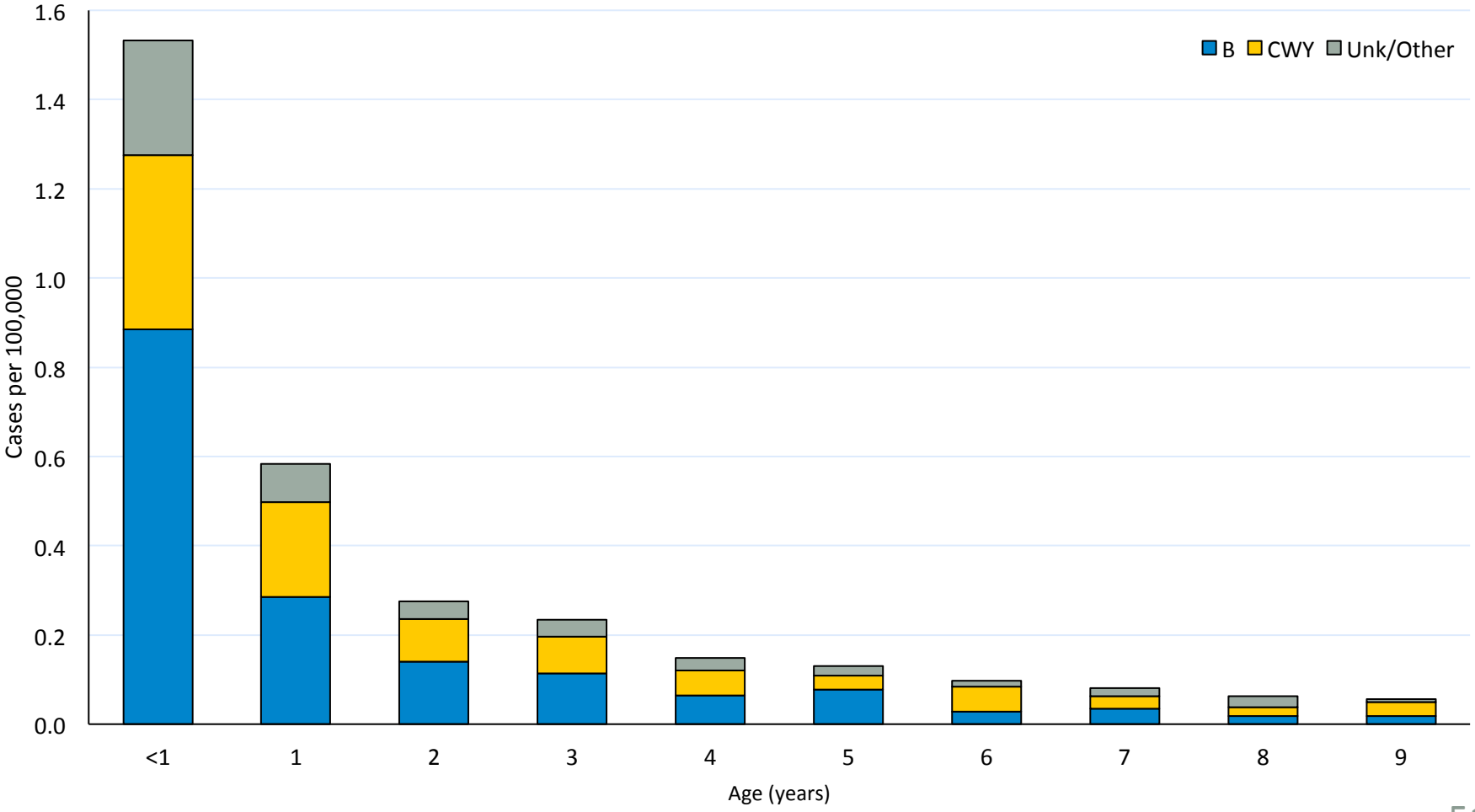
  -Safe.

  -Immunogenic.

  - Maternal Abs transferred to newborn.

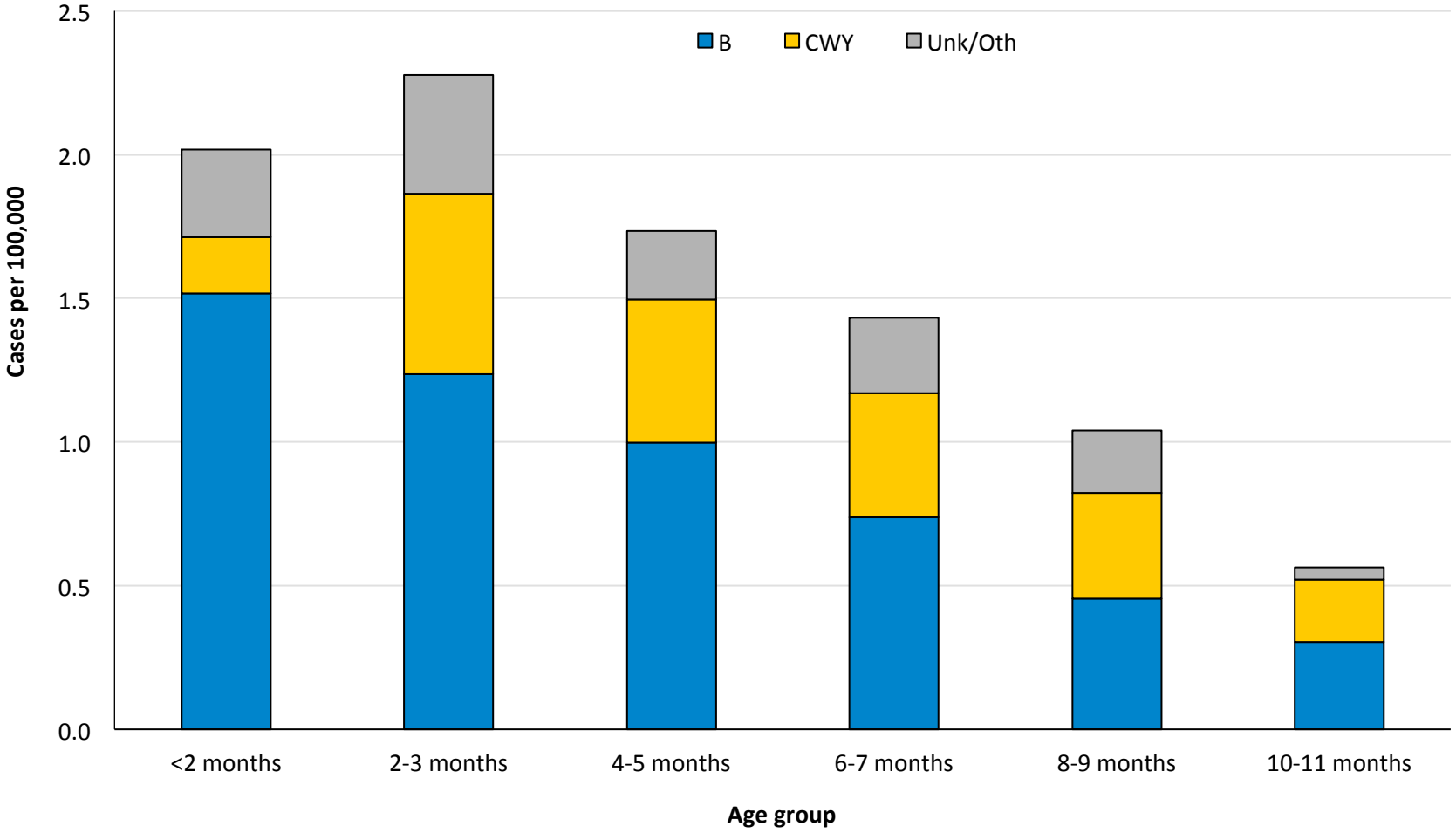
Madhi SA Lancet Infect Dis 16:923-934, 2016
Madhi SA Vaccine 31(Suppl 4): D52-D57, 2013
Donders GG Obstet Gynecol 127:213-221, 2016
Heyderman RS Lancet Infect Dis 16: 546-555, 2016
Baker C Vaccine 21: 3468-3472; 2003.

Incidence of meningococcal disease in children aged <10 years, by age and serogroup— United States, 2010-2016



Source: National Notifiable Diseases Surveillance System (NNDSS) data with additional serogroup data from Active Bacterial Core surveillance (ABCs) and state health departments

Incidence of meningococcal disease among infants aged <1 year by age group and serogroup – United States, 2010-2016



Source: National Notifiable Diseases Surveillance System (NNDSS) data with additional serogroup data from Active Bacterial Core surveillance (ABCs) and state health departments

Meningococcal Vaccines Available in the US

- **MenACWY**: polysaccharide capsule conjugated with carrier protein for meningococcal serogroups A, C, W and Y.
- **MenB**: vaccine developed using outer-membrane proteins of meningococcal serogroup B.
- Safety and efficacy studies in pregnancy are in early stages.
- Since different serogroups might be more relevant in other countries, alternate vaccines might be appropriate for different countries.

Maternal Immunization

Maternal Immunization with Pneumococcal Polysaccharide Vaccine (PPV)

- Safe; well tolerated.
- Infants had high titers of pneumococcal Abs out to 4 months of age.
- Response to PPV in infants at 7 to 17 weeks of age resulted in fair responses to a few PPV antigens but most were poor.
- Revaccination at 3 years of age with PPV resulted in a good response to all PPV antigens
  (no immune tolerance).

Pneumococcal Vaccine During Pregnancy

- Pregnant women who receive pneumococcal polysaccharide vaccine in 3rd trimester:
  - Vaccine is safe and immunogenic.
  - Transplacental transfer of pneumococcal antibodies related strains in pneumococcal polysaccharide vaccine.
  - Antibody half-life of 35 days.
  - Breast milk had detectable antibodies until 5 months of age.

Shahid NS: Lancet 1995;346:1252-57
Munoz FM: infect Dis Clin North Am 2001:15:253-271

Haemophilus Influenzae b Vaccine During Pregnancy

- Maternal immunization with Hib vaccine in 3rd trimester:
  - Safe and immunogenic.
  - Conjugate vaccine results in better Hib antibody levels in both mother and newborn infant than polysaccharide vaccine.
  - Infants whose mothers received Hib vaccine during pregnancy had no interference with infant response to Hib vaccine series.
  - May play a role in non-industrialized countries without infant Hib vaccine program.

Mulholland: JAMA: 1996; 275:1182-1188
Englund: Vaccine: 2003; 21:3455-3459
Englund: Pediatr infectDis J 1997; 16:1122-30
Englund: J Infect Dis 1995; 171:99-105

Neonatal HSV

- Infants exposed natally to HSV who had higher titers of transplacentally-derived HSV neutralizing antibodies had better outcomes/ lower infection rates than infants with low Ab titers

- An effective maternal HSV vaccine could:
  - Reduce risk of acquiring a primary genital HSV infection.
  - Boost maternal antibody levels to provide infants with higher neutralizing antibodies at birth.

Yeager AS Infect Immun 29: 532-538; 1980
Arvin AM Rev Infect Dis 13 (Suppl 11):S953-956; 1991
Sullender WM J Infect Dis 157: 164-171; 1988.
Harger JH J Perinatol 10: 16-19; 1990