GROUP B STREPTOCOCCAL INFECTIONS EARLY IN THE 21ST CENTURY

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OBJECTIVES

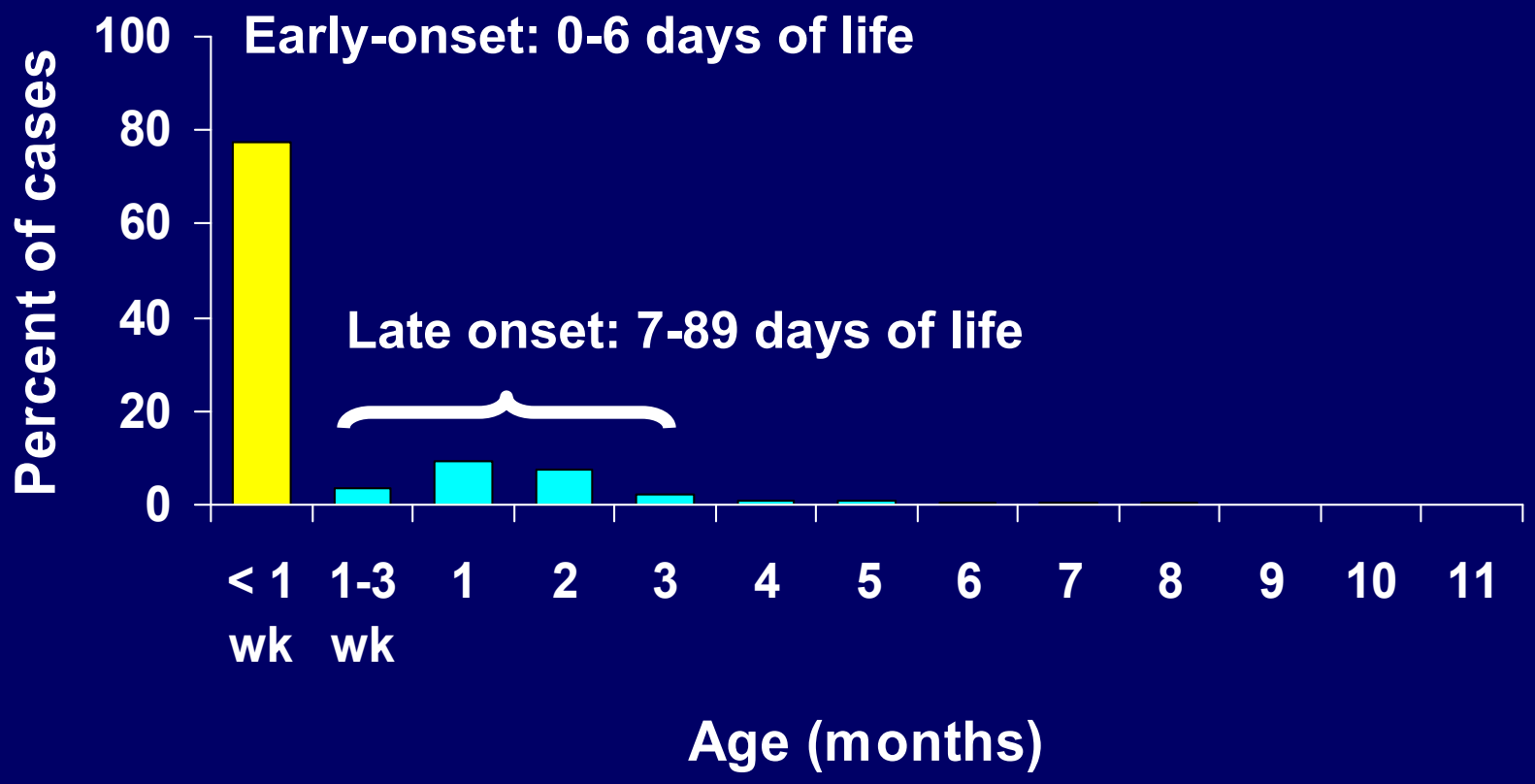
- Know the current GBS disease burden
- Understand 21st century GBS management issues
- Know the status of GBS disease prevention methods

DISEASE BURDEN

WHAT'S HAPPENED SINCE 1996?

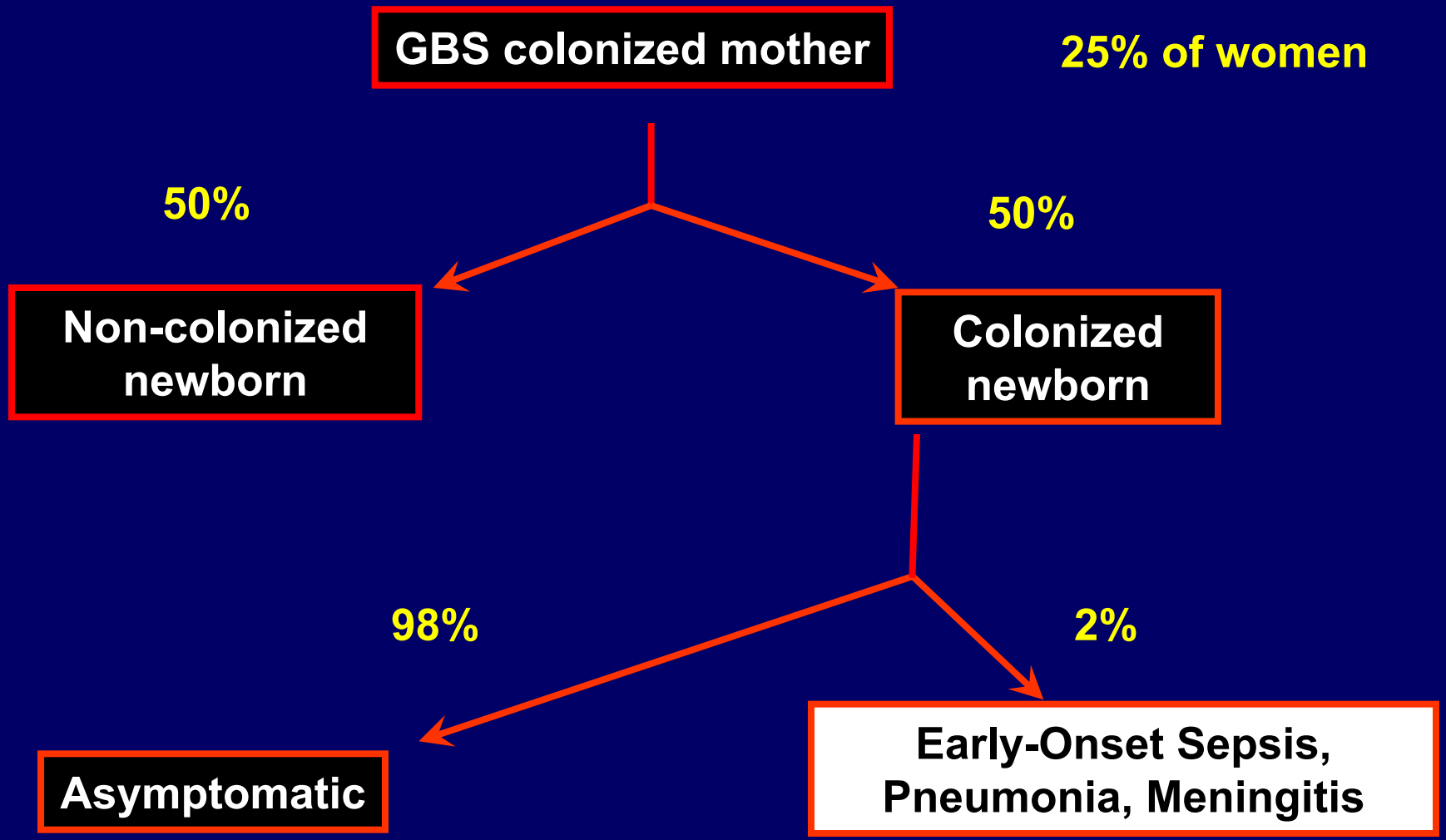
- Successful implementation of maternal intrapartum antibiotic prophylaxis (IAP)
- Disease remains in newborns, especially preterm infants and those with late-onset infections
- GBS disease increasing in adults

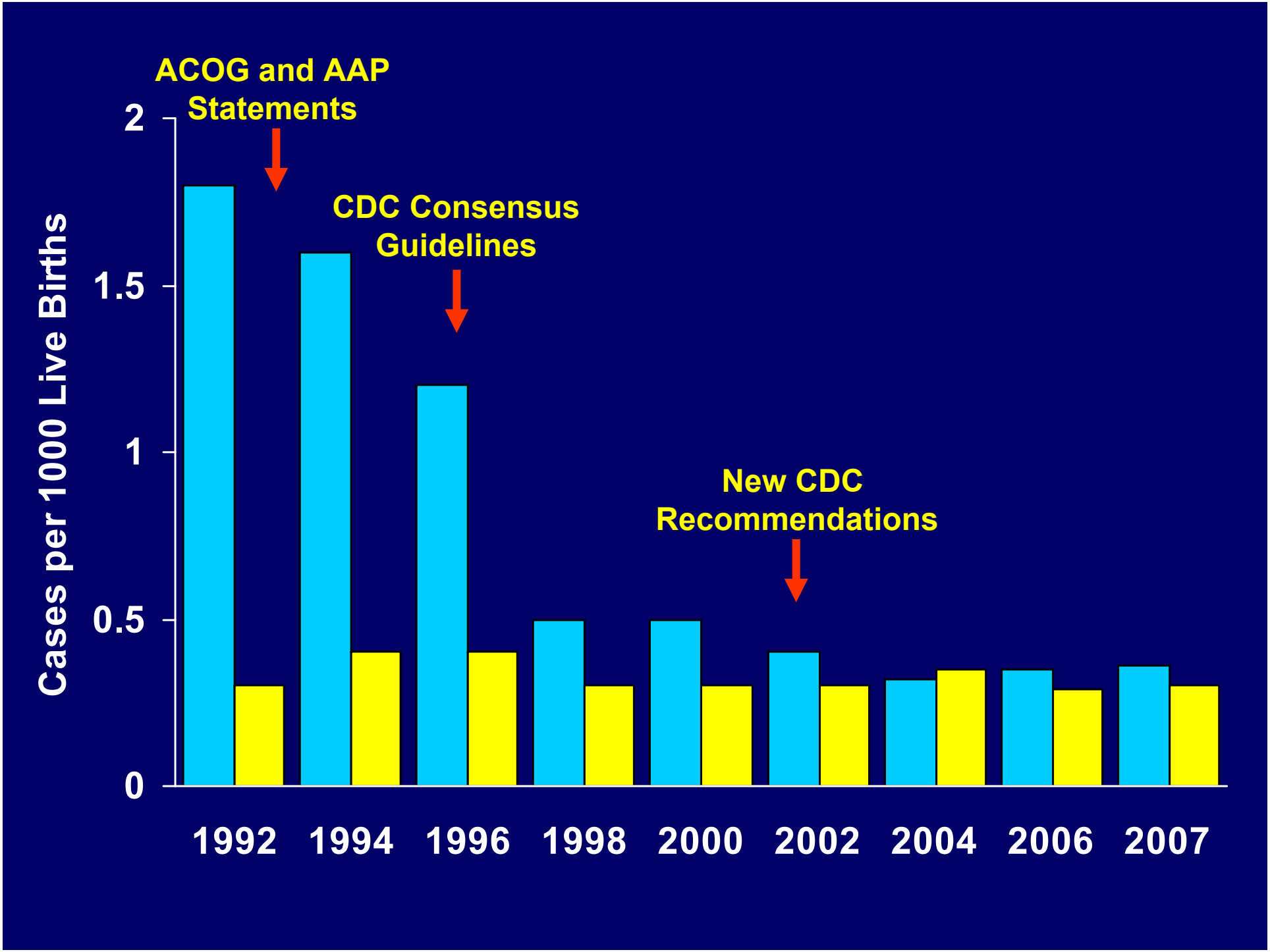
GBS DISEASE IN INFANTS BEFORE PREVENTION EFFORTS*

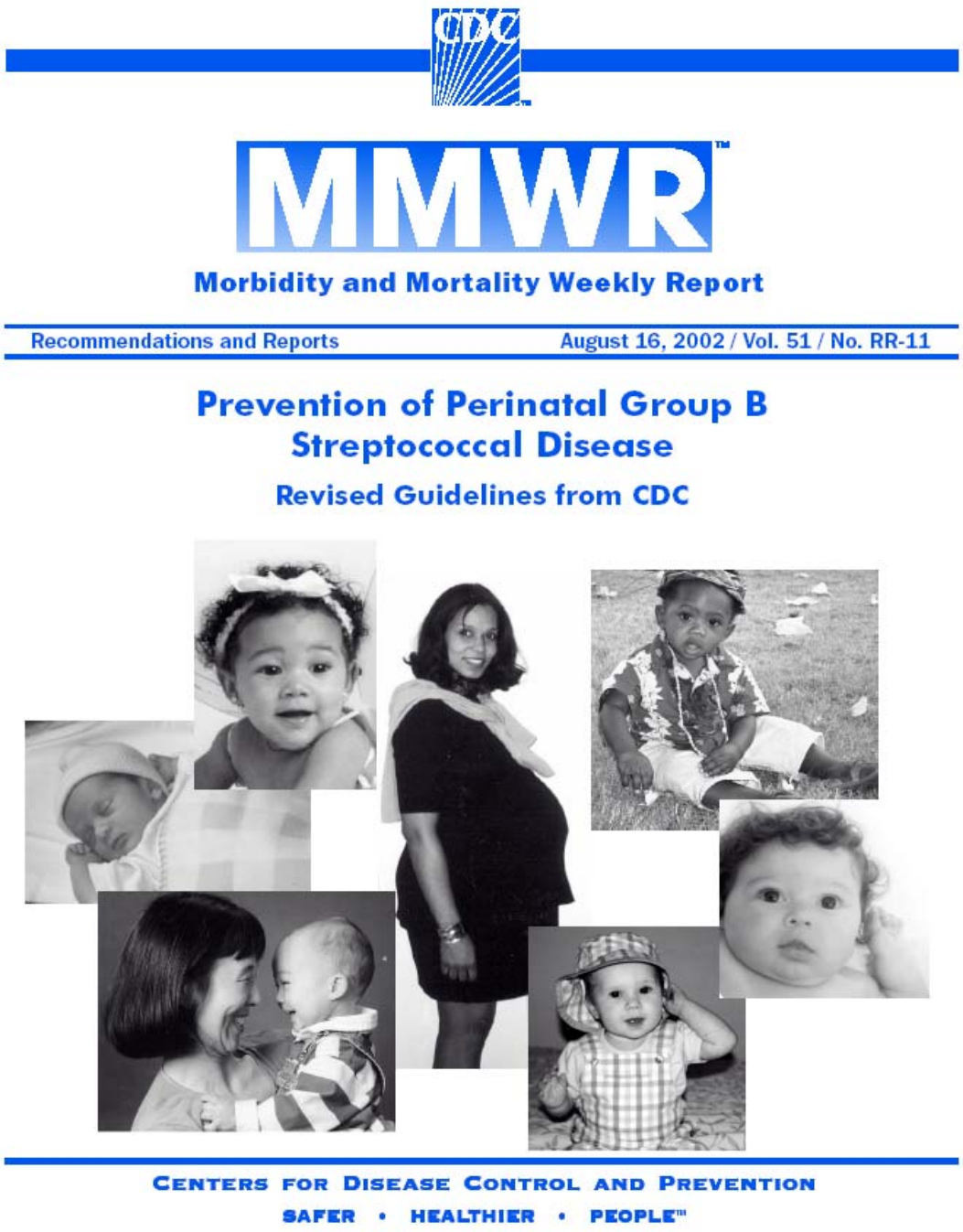


*A Schuchat. *Clin Micro Rev* 1998;11:497-513.

EARLY-ONSET DISEASE: MOTHER TO INFANT TRANSMISSION




ACOG and AAP Statements
CDC Consensus Guidelines
New CDC Recommendations
Cases per 1000 Live Births
2
1.5
1
0.5
0
1992
1994
1996
1998
2000
2002
2004
2006
2007



The 2002 Recommendations:

Universal Prenatal GBS Screening: Intrapartum Antibiotics for *All* GBS Colonized Women

MMWR, Vol 51 (RR-11)

www.cdc.gov/groupbstrep

GBS PERINATAL DISEASE: 1999 – 2005*

- **Incidence:** early- and late-onset nearly equal
- **Black vs. white relative risk:** 4 - 5 :1
- **Early-onset:** 1232 cases (96% sepsis; 7% mortality)
- **Late-onset:** 1036 cases (79% bacteremia [3% died]; 27% meningitis [7% died]; 52% preterm)
- **Pregnancy-associated:** 409 cases; 50% associated with upper genital tract infection; 1 death; 30% had healthy infants

*Phares C, et al. *JAMA* 2008;300 (May 7th)

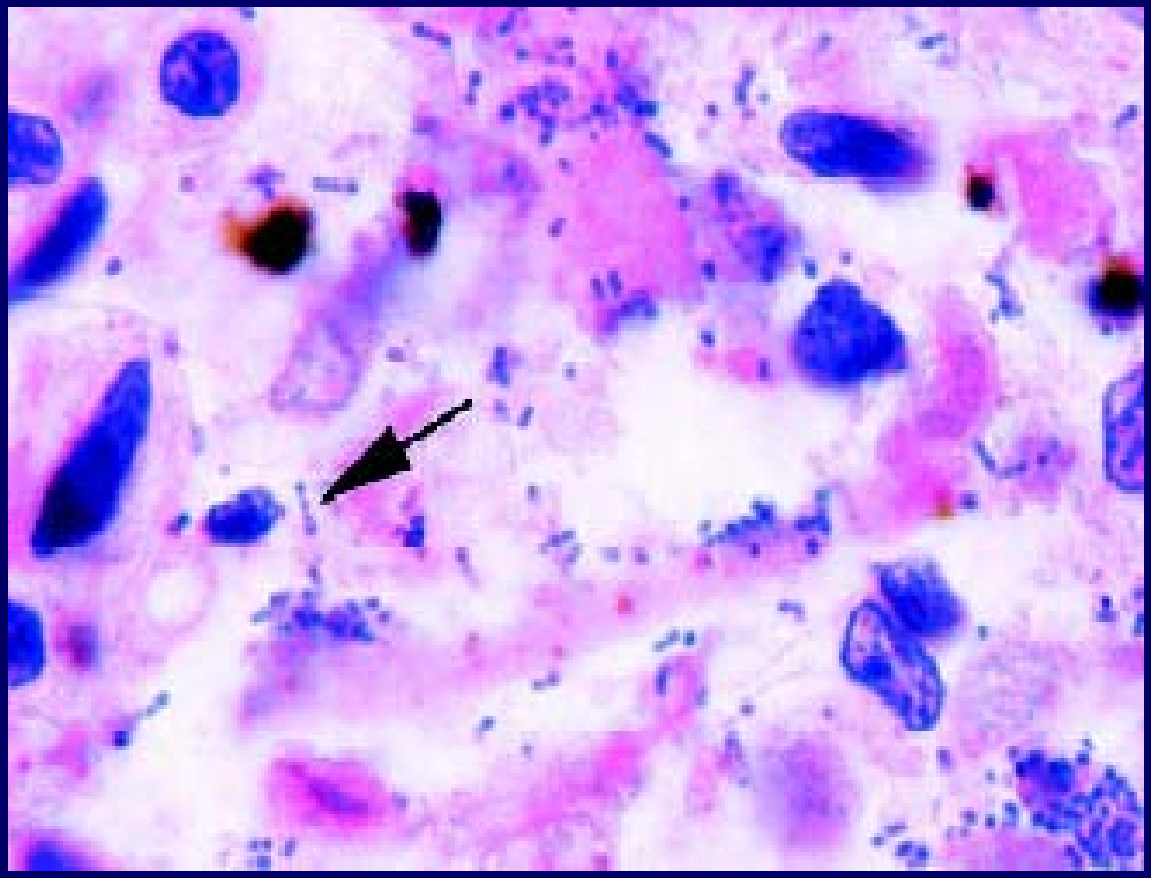
INTRAUTERINE DEATH DUE TO GBS

A 30-yr-old was admitted in active labor at term. Urine culture 24 wks had shown $<10^3$ cfu of a potential pathogen in mixed flora not further identified. Fetal movement was present at weekly visits from 36 to 39 wks of gestation.

On the day of admission, fetal movements ceased, contractions began and a 3.0 kg infant stillborn male was delivered vaginally. The amniotic fluid was clear.

Gibbs et al. *N Engl J Med* 2007:357;918.

GBS IN FETAL LUNG SPECIMEN



Gibbs et al. *N Engl J Med* 2007;357;918.

U.S. ESTIMATE OF INFANT GBS DISEASE BURDEN IN 2007

Early-Onset Cases: 1,475 (0.36/1000 live births)

Late-Onset Cases: 1,225 (0.30/1000 live births)

CDC 2008. ABCs Report, Emerging Infections Program Network, GBS.

LATE-ONSET GBS DISEASE*,+

- **Onset:** 7 – 89 days (median 37 days)
- **Mortality:** 5%
- **Meningitis:** 26% of cases; 4.3% fatal; incidence 3 x higher in blacks; 49% preterm
- **Term infants:** 48% of cases

*Phares et al. *JAMA* 2008;299:2056; +Jordan et al. *Pediatr Infect Dis J* 2008;27:1057.

PREGNANCY-ASSOCIATED GBS INVASIVE INFECTION

- **Incidence:** 0.12/1000 live births
- One-half of infections involve upper genital tract, amniotic fluid or placenta
- **Pregnancy outcome:**
  - ➔61% spontaneous abortion or stillbirth
  - ➔30% infants without illness
  - ➔5% infants with GBS invasive disease
  - ➔4% induced abortions

Phares CR et al. *JAMA* 2008;299:2056.

21st CENTURY

MANAGEMENT ISSUES

GBS DISEASE MANAGEMENT

- Twin and breast milk
- Recurrent GBS disease
- Lumbar Puncture
  - → diagnosis
  - → duration of therapy
- Drug(s), dose and duration

GBS IN TWINS

- Multiple gestation is not an independent risk factor for GBS infection
- If one infant from a multiple gestation has GBS infection, risk for disease in the other is substantial
- As many as 40% of apparently well twins may develop GBS infection
  - → Second twin ill in 4 of 11 sets
  - → Two of 3 triplets had early-onset disease

Edwards M et al. *JAMA 1981;245:2044-6.*
Moylett E et al. *Clin Infect Dis* 2000;30:282-7.

PATHOGENESIS OF GBS DISEASE IN TWINS

- GBS acquired from same source at delivery or postnatally
- Strain identity (by CPS type and PFGE) has been shown for maternal and infant colonizing and invasive strains
- CPS antibody status is the same
- GBS strain virulence the same

Benitz W et al. *Pediatrics* 1999;103:e77; Moylett EH et al. *Clin Infect Dis* 2000:282-7; Duran K et al. *J Perinatol J* 2002;22:326-30.

GBS IN TWINS: MANAGEMENT

- Interval between onsets: Hours to days
- Second twin should be evaluated for illness at time of first twin's presentation
- Outcome can differ between twins
- Consideration should be given to empirical evaluation and treatment of sibling(s) of affected multiples

Edwards M et al. *JAMA* 1981;245:2044-6.
Moylett E et al. *Clin Infect Dis* 2000;30:282-7.

BREAST MILK TRANSMISSION OF GBS DISEASE

- Attributed as a cause of late-onset and recurrent disease and disease in second of twins
- GBS is cultured from breast or breast milk
- Clinical mastitis may or may not be present
- Direct contact with breast not required

Kotiw M et al. *Pediatr & Devp Pathol* 2003;6:251-6.
Godambe S et al. *Pediatr Infect Dis J* 2005;24:381-2.

MECHANISM: GBS BREAST MILK TRANSMISSION

- Concept of "circular transmission"
- GBS colonizes infant's oropharynx
- Mammary ducts become infected during breast feeding
- Microbial concentration increases
- Infant infected or re-infected during feeding

Rench M et al. *Obstet Gynecol* 1989;73:875-7.
Godambe S et al. *Pediatr Infect Dis J* 2005;24:381-2.

RECURRENT GBS DISEASE

- Incidence ~ 1 - 5%
- Early- *and* late-onset disease
- Second or third episode can be more severe
- Typically same organism (persistent colonization / re-exposure) within the infant's household)

RECURRENT GBS DISEASE: MANAGEMENT

- Immune evaluation? NO
- Evaluation for “occult focus”? NO
- Assessment of colonization status? NO
- Susceptibility testing of GBS? YES
- Longer duration of therapy? NO

REPEAT LUMBAR PUNCTURE?

- At 24 - 48 hours to document sterility and assess complications
- End of therapy (optional)
  - → Determine "baseline" CSF values
  - → Assess intracranial complications
- Role of neuroimaging: Enhanced CT <u>not</u> MRI; late (2-3 weeks) not early

DRUG (S) FOR GBS DISEASE*

- **Empirical therapy**
  - → Ampicillin and gentamicin IV until blood and/or CSF are sterile (~3-5 days)
  - → Ampicillin should be 300 mg/kg/day *if* meningitis not excluded
- **Definitive therapy**
  - → Penicillin G IV (450,000–500,000 units per kg per day *if* meningitis)
  - → Others: ampicillin, ceftriaxone

*Early or late-onset disease. *2006 Red Book.*

DURATION AND ROUTE OF THERAPY FOR GBS DISEASE

- **Route:** IV or IM (never oral)
- **Duration:** Depends on site of infection
  - ➔ Sepsis: 10 days
  - ➔ Meningitis: 14-21 days
  - ➔ Osteoarthritis: 21-28 days
  - ➔ Ventriculitis: 28 days
  - ➔ Endocarditis: 4-6 weeks

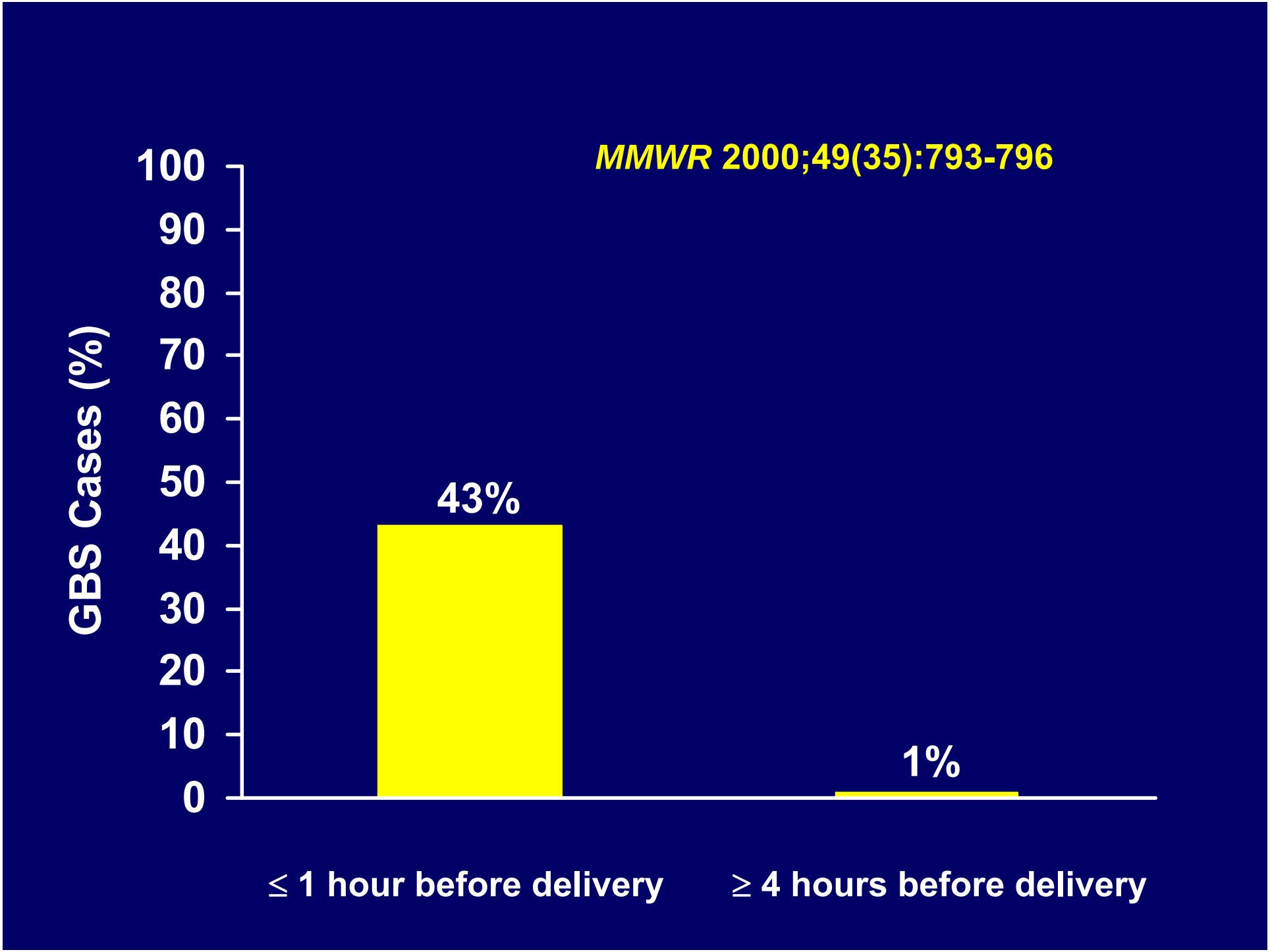
STATUS OF GBS PREVENTION

INTRAPARTUM ANTIBIOTIC PROPHYLAXIS: LIMITATIONS

- Effective (80% reduction) but ***only*** for early-onset disease (Cochrane review)
- Does ***not*** prevent late-onset disease
- Does ***not*** prevent GBS-related adverse pregnancy outcomes (eg, 2nd trimester losses, preterm labour, premature ROM, stillbirths)
- Costly; IV access; *every* pregnancy if GBS +; maternal adverse events; PCN-resistant GBS

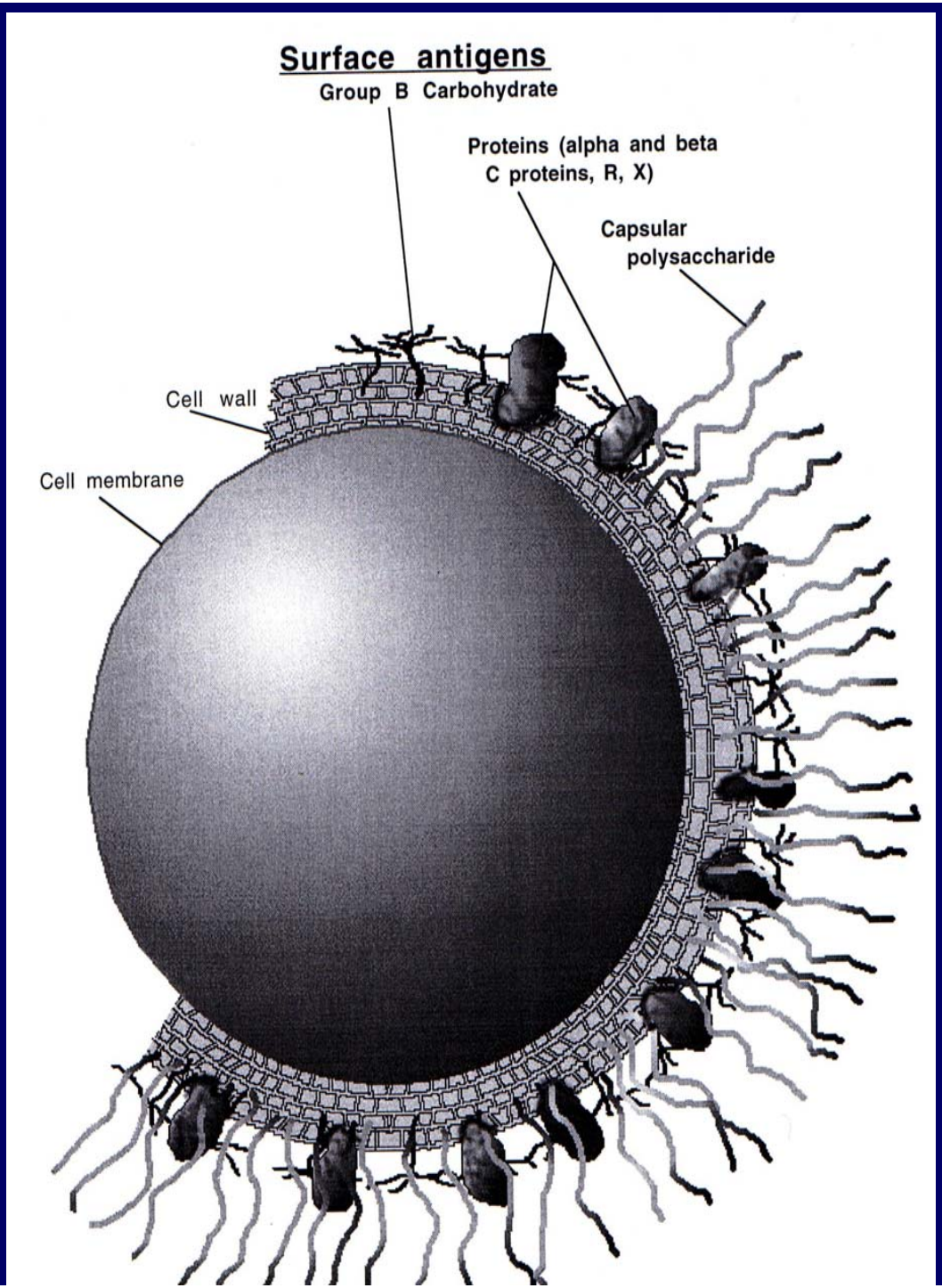
WHY ONLY 80% PERCENT EFFECTIVE?

- Culture screen at 35 - 37 weeks' gestation not perfect (laboratory processing remains a problem)
- Failure to administer IAP ≥ 4 hours before delivery
  - Precipitous delivery
  - Culture result not available
  - Preterm delivery
- Early treatment (not prophylaxis) for maternal chorioamnionitis (clinical/silent)


MMWR 2000;49(35):793-796
GBS Cases (%)
100
90
80
70
60
50
40
30
20
10
0
43%
1%
≤ 1 hour before delivery
≥ 4 hours before delivery

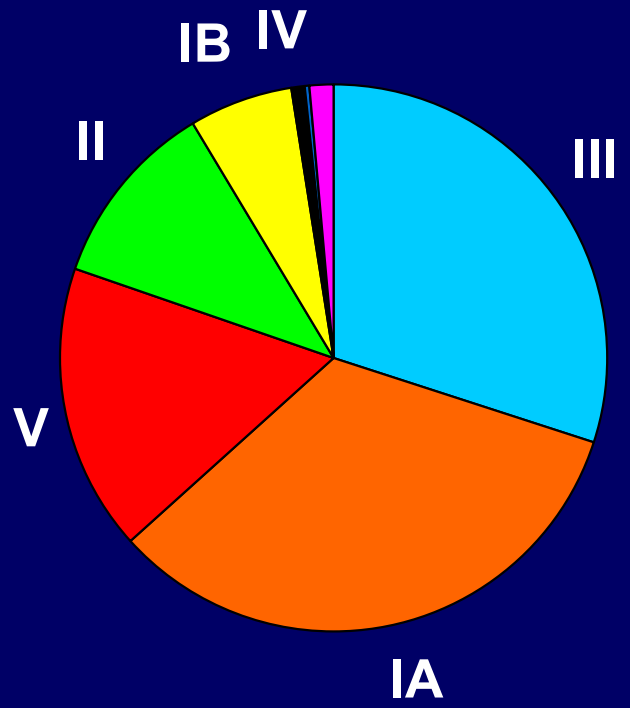
Only CPS and β-hemolytic toxin have been correlated with virulence.

Only antibody to CPS has been demonstrated to protect against neonatal GBS disease



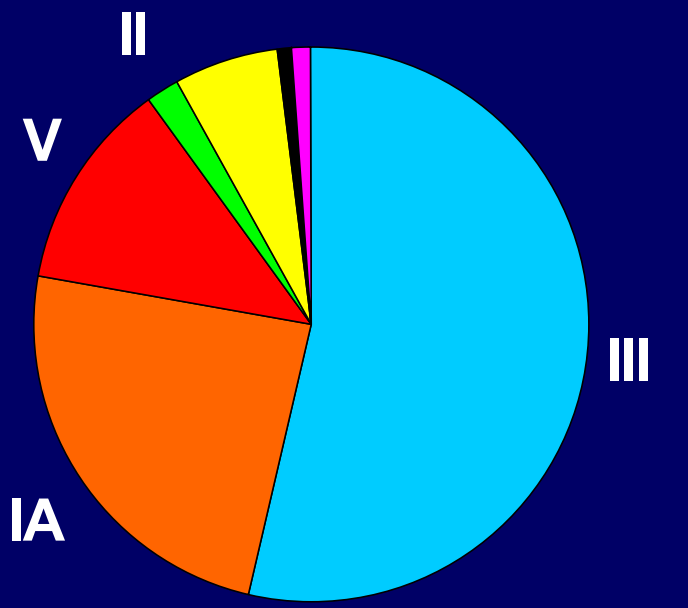
GBS SEROTYPE DISTRIBUTION: 1999 – 2005*

EOD (n=1057)



Remaining types: VI, NT

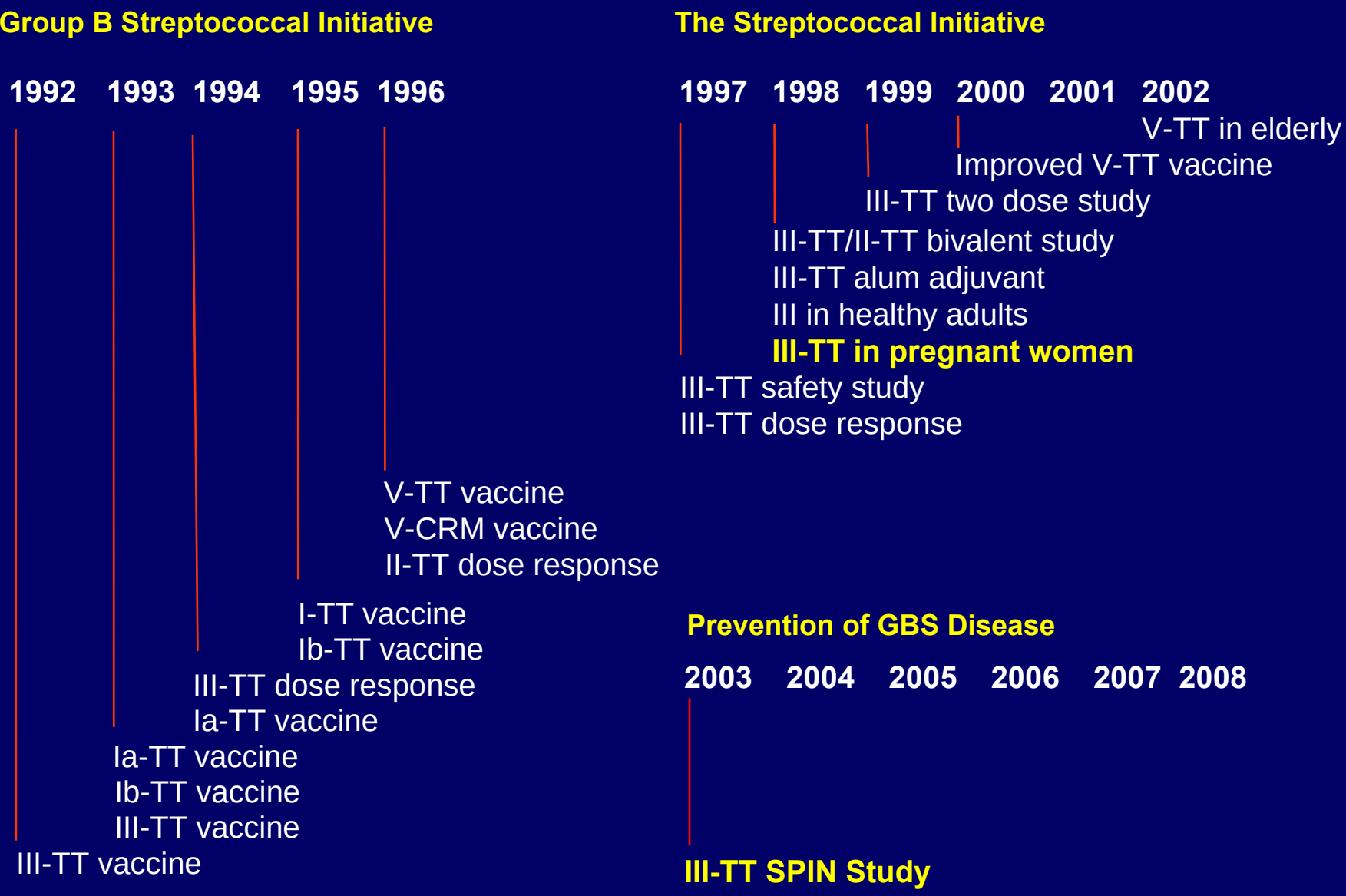
LOD (n=730)



Remaining types: Ib, IV, NT

*Phares C, et al. *JAMA* 2008;300 (May 7th)

TIMELINE OF NIAID-FUNDED GBS CONJUGATE VACCINE DEVELOPMENT AND CLINICAL TRIALS



ESTIMATED PROTECTIVE LEVELS OF CPS-SPECIFIC IgG IN MATERNAL SERA AT DELIVERY

- Ia ~ 1 – 2 µg/mL
- III ~ 0.5 - 1 µg/mL
- V ~ 1 – 2 µg/mL

IMMUNE RESPONSE TO GBS III-TT VACCINE IN PREGNANT WOMEN (28-32 WEEKS GA)*

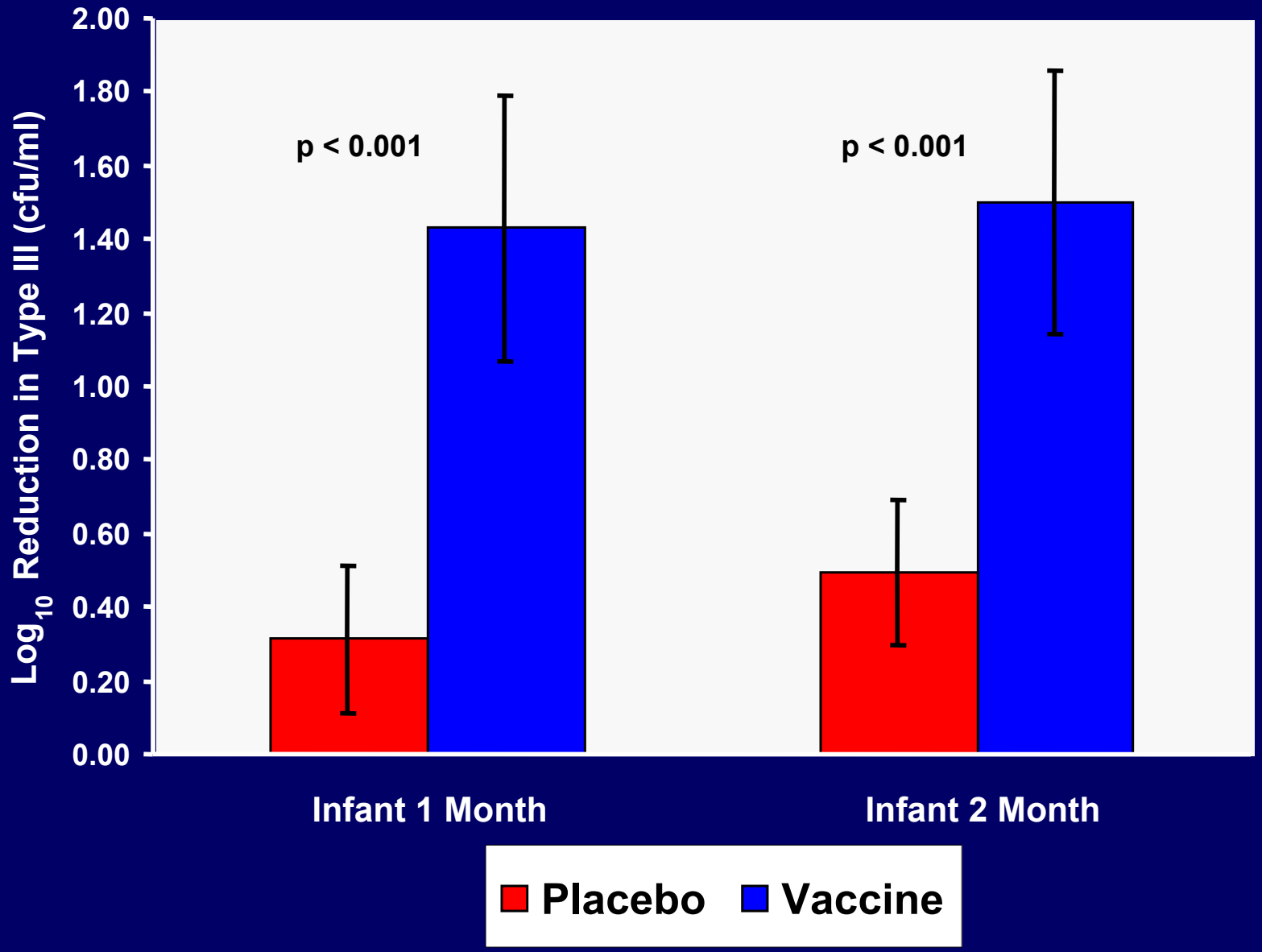
	GMC (μg/ml) III CPS-Specific IgG			
Study Group	0 Wk	4 Weeks	Delivery	2 Month Post Delivery
III-TT (N=20)	0.18	9.98	9.76	10.80
Placebo (N=10)	0.06	0.05	0.05	0.08

* Baker CJ, et al. *Vaccine* 2003

INFANT SERUM CONCENTRATIONS*

Maternal Vaccine	GMC III CPS-Specific IgG (µg/ml)		
	Cord	1 Month	2 Months
III-TT (N=20)	7.48	3.74	2.16
Placebo (N=10)	0.05	0.03	0.03

* Baker CJ, et al. *Vaccine* 2003



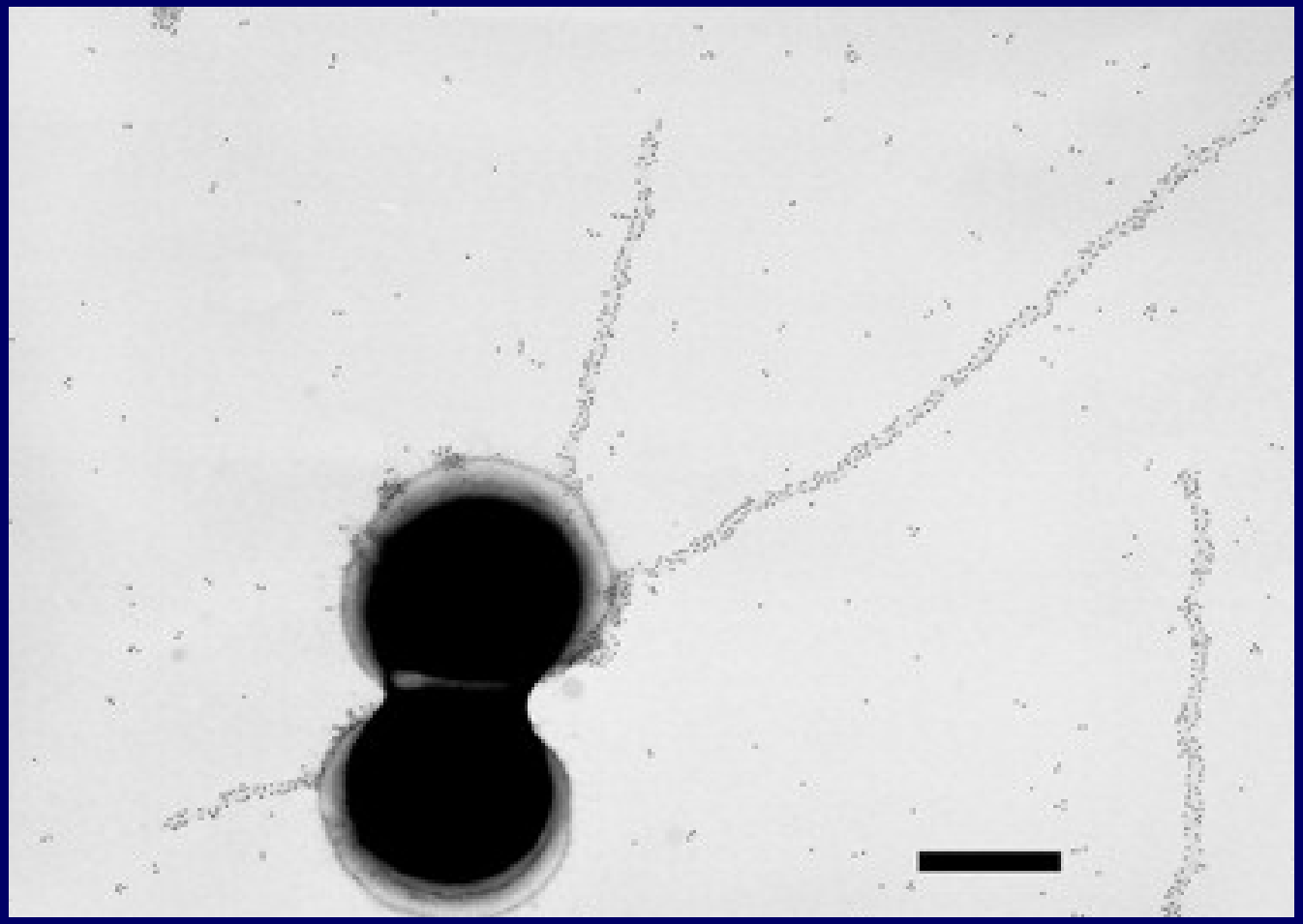
* Baker CJ, et al. *Vaccine* 2003

PREVENTION OF MATERNAL *AND* INFANT GBS DISEASE

- GBS conjugate vaccines are safe and induce IgG specific for the 5 major capsular types in non- pregnant adults 18 - 45 years of age *
- Vaccine-induced IgG maternal IgG early in 3rd trimester → infant protective levels of antibodies through 2 months of age +
- Problems: *societal value, political will, liability*

* Baker CJ et al. *J Infect Dis* 1999-2003
+ Baker CJ et al. *Vaccine* 2003;21:3468-72

PILUS ISLANDS IN GBS

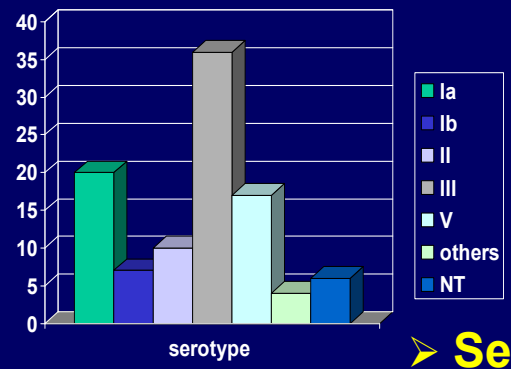


Lauer P et al. *Science* 2005:309;105.

PILUS ISLAND DISTRIBUTION*

A total of 290 GBS strains from neonatal (204) and adult (86) invasive disease

% Serotype Distribution



- 103 from Baylor College of Medicine (2002-2005)
- 100 from Centers for Disease Control (2000-2003)
- 87 from Italian NIH (1996-2004)

➢ Serotype distribution reflects circulating strains

By PCR amplification of the 3 LPXTG genes of each pilus

At least one pilus island is present in all GBS strains

* Margarit I, et al. *J Infect Dis 2009;199:108-15.*

QUESTIONS REMAINING?

- Optimal combination of CPS's and/or proteins
- Optimal dose
- Need for booster dose(s)
- Need for adjuvant? Which one?
- Target population
  - → Pregnant women
  - → Adolescents
  - → Pre-conception health visit

CONCLUSIONS

- 21ST century GBS disease burden remains substantial
- Management of GBS disease remains challenging
- A prevention strategy to further reduce disease burden is needed
- Maternal immunization (or immunization of 11-12 year olds with booster pre-pregnancy) is a promising strategy