PROTECTING NEONATES: GROUP B *STREPTOCOCCUS*

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EARLY-ONSET GBS DISEASE IN NEONATES

- **Age at onset**: < 24 hrs in 92 - 95% of cases
- **Incidence:** 1 - 4/1000 live births (75% are born at term)
- **Features:** Sepsis (65%), pneumonia (25%), meningitis (5%)
- **Case-fatality:** 3 - 8%
- **Recurrence:** 1%

LATE-ONSET GBS DISEASE IN YOUNG INFANTS

- **Age at onset:** 7 - 89 days
- **Incidence:** 0.6/1000 live births
- **Manifestations:** Occult bacteremia (65%), meningitis (35%), other focal disease (5%)
- **Case-fatality:** 2 - 5%; 20% CNS sequelae

U.S. DISEASE BURDEN: INFANTS

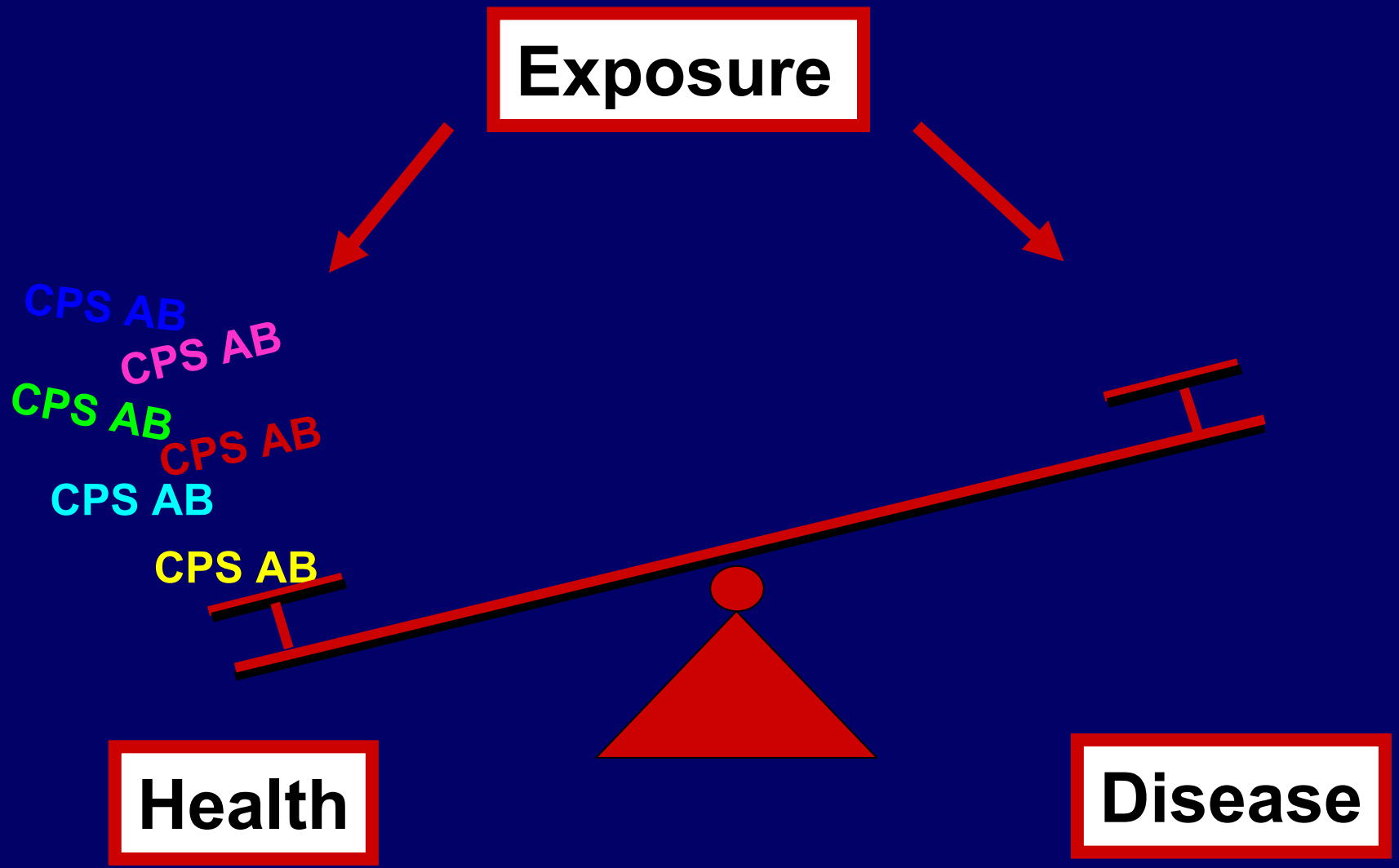
- Early-onset (0 - 6 days) disease
  - ➔ Cases ↓ 70 % with maternal IAP
  - ➔ Incidence 0.6/1000 live births
  - ➔ Mortality 5%
- Late-onset (7 - 89 days) disease
  - ➔ Incidence 0.6/1000 live births
  - ➔ Mortality 3%; CNS sequelae 20%
- Total disease burden: ~ 4800/year*

*Schrag SJ et al *N Eng J Med* 2000

ANTIBODIES TO GBS III CPS CORRELATE WITH HUMAN IMMUNITY

- Mouse protective assays of Lancefield*
- Low levels of maternal antibodies to GBS III CPS correlated with invasive infant disease†
- Maternal III-TT vaccination protects neonatal mice from lethal III GBS challenge#
- Maternal III CPS IgG ≥ 0.5 µg/ml are 99% protective against early-onset infant disease‡

•Lancefield RC et al. *J Exp Med* 1934; †Baker CJ, Kasper DL. *N Engl J Med* 1976; #Paoletti LC et al. *Infect Immun* 2000; ‡Baker CJ 2004.


Exposure
CPS AB
CPS AB
CPS AB
CPS AB
CPS AB
CPS AB
Health
Disease

PREVENTION OF GBS DISEASE BY IMMUNIZATION: RATIONALE

- Age at onset *and* ongoing disease burden
- IgG to CPS type of GBS is protective
- Immunization is simple, cost-effective and could last many years
- Maternal immunization is *only one* potential immunization strategy

GBS CONJUGATE VACCINES IN HEALTHY ADULTS

- Ia, Ib, II, III and V-TT CV → safe and immunogenic in healthy adults*,+,#,^
- Ia, Ib II, III and V-TT CV → CPS-specific IgG, functional Ab *in vitro*, and protective *in vivo**,#, ^

* Baker CJ et al. *J Infect Dis* 1999;179:142.
+ Paoletti LC et al. *Infect Immun* 2001;69:6696.
# Baker CJ et al. *J Infect Dis* 2000;182:1129.
^ Baker CJ et al. *J Infect Dis*, 2004:189:1103.

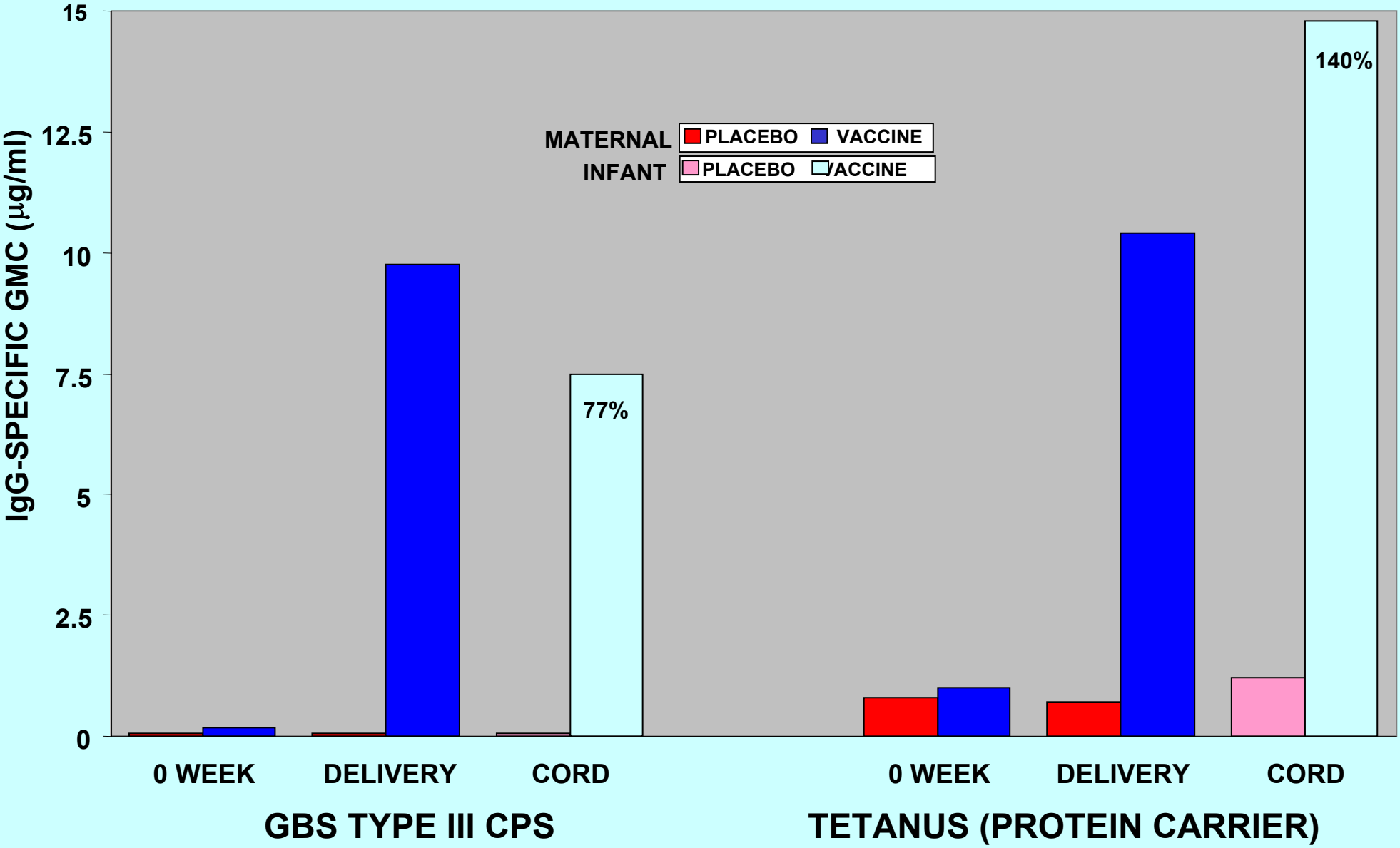
STUDY DESIGN*

- Prospective, randomized (2:1), double-blinded, placebo-controlled
- 30 "low risk for obstetrical complications" consenting women; 30-32 weeks' gestation
- Vaccine: III-TT (12.5 μg CPS; 15.9 μg TT) prepared under GMC conditions; Placebo = 0.9% NaCl
- Age: Mean 29 yrs; 30% ethnic minorities

*Baker et al. *Vaccine* 2003;21:3468.

IMMUNOGENICITY OF III-TT CV

Study Group	GMC (μg/ml) III CPS-Specific IgG			
	0 Wk	4 Wk	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


15
12.5
10
7.5
5
2.5
0
IgG-SPECIFIC GMC (μg/ml)
MATERNAL
INFANT
PLACEBO
VACCINE
PLACEBO
VACCINE
77%
140%
0 WEEK
DELIVERY
CORD
0 WEEK
DELIVERY
CORD
GBS TYPE III CPS
TETANUS (PROTEIN CARRIER)

INFANT SERUM CONCENTRATIONS

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

SUMMARY

- GBS III-TT was well-tolerated by women at 30-32 weeks' gestation; outcomes in vaccine and placebo groups similar
- Vaccine elicited ≥4-fold rises in III CPS-specific IgG in 95% of women; these rises persisted until delivery and at 2 mo
- Vaccinated women had III CPS-specific IgG GMC of 9.8 μg/ml at delivery; placebo recipients had 0.05 μg/ml (P <0.001)

SUMMARY

- Vaccine-induced III CPS-specific IgG was efficiently transported to infants (M:C ratio 0.8) as TT-specific IgG (M:C ratio 1.4)
- Maternal delivery-cord levels of III-TT induced IgG were correlated (r_s = 0.919; P <0.001)
- Sera from infants born to III-TT recipients uniformly promoted killing of III GBS at 1 and 2 mo when levels exceeded 0.5 μg/ml

ALTERNATIVE TARGET POPULATIONS FOR GBS VACCINE

- Non-pregnant women
  - → When and delivery via what system?
  - → Duration of "protective" serum levels?
- Adolescent vaccine (with MMR, Td, etc.)
  - → Boys and girls?
  - → Duration of "protective" serum levels?
- "High risk" adults (diabetes mellitus, healthy elderly, etc.)

SO WHY DON'T WE HAVE A GBS CONJUGATE VACCINE?

- ***Not*** **for lack of disease burden**
- ***Not*** **for lack of vaccine design technology**
- ***Not*** **for lack of safety and immunogenicity in healthy young men and women**
- ***Not*** **for lack of public health service, obstetrical care provider and patient desire**
- ***No pharmaceutical partner!***
- ***Liability issue because target population is perceived to be pregnant women***

SO WHO WANTS A GBS CONJUGATE VACCINE?

- *Pregnant women and parent groups*
- *Obstetricians and pediatricians*
- *Public health experts*
- *The babies (and me)*