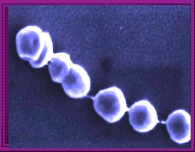


CNR-Strep



Current Statut of Group B Streptococcus Vaccine Research and Development

Claire Poyart

*CNR-Strep, Service de Bactériologie Hôpital Cochin,
Université Paris Descartes*



Current Status of GBS vaccine Research and Development

- Rational for the development of a GBS vaccine
- Which target candidate?
- Whom to vaccinate?
- Where are we ?

Leading Cause of Life-Threatening Infections in Newborns

- Sepsis
- Meningitis

In adults, usually causes no symptoms

- In rare cases, can lead to serious bloodstream infections, urinary tract infections, skin infections, and pneumonia; particularly at risk are people with weakened immune systems & other health problems, such as diabetes

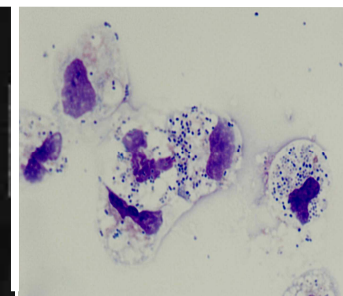
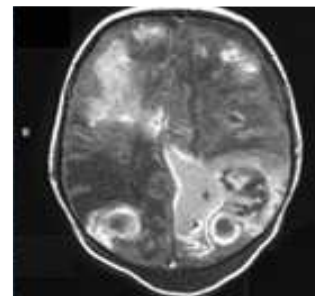
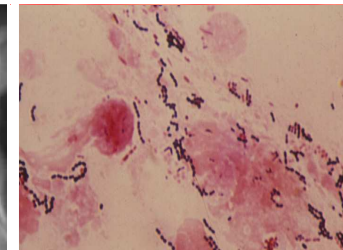
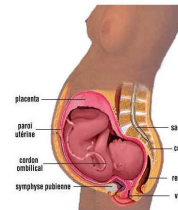
Statistics

- Incidence : 0.3/1000 birth
- Approximately 240 babies in France contract serious GBS disease each year
- Up to 30 of these babies die from it
- 20% of the babies who survive GBS-related meningitis are left permanently handicapped

Group B Streptococcus (GBS)

Streptococcus agalactiae

- Gram positive cocci,
- Beta-hemolytic
- Extra cellular pathogen
- Capsulated: 10 serotypes (**III**)
- Commensal of the lower intestine and the vagina of 10-35% of healthy women
- **Leading cause of life-threatening infections in newborns**
 - Sepsis
 - Meningitis
- Neonates are contaminated during delivery
 - **Early onset disease (EOD)**
 - (< 7 days)
 - **Late onset disease (LOD)**
 - (> 7 days, median: 3 weeks)

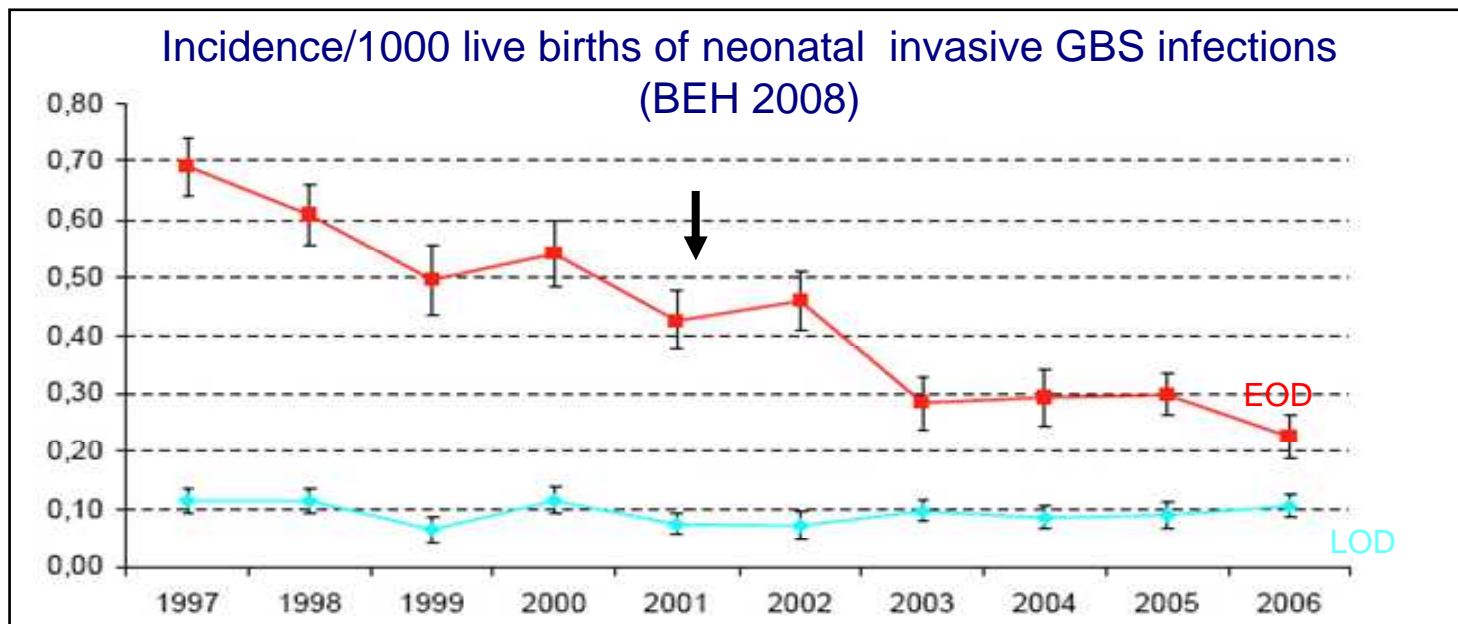


There are 2 types of GBS disease:

Early-Onset Disease

Late-Onset Disease

GBS neonatal invasive infections



- Since ANAES recommendations in 2001

—↘ EOD :

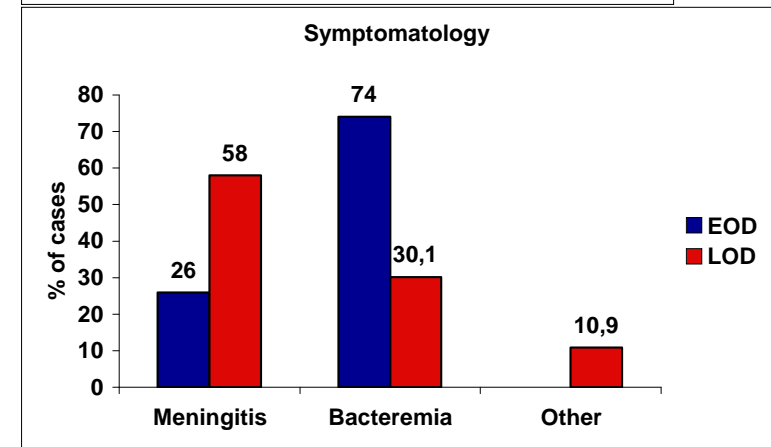
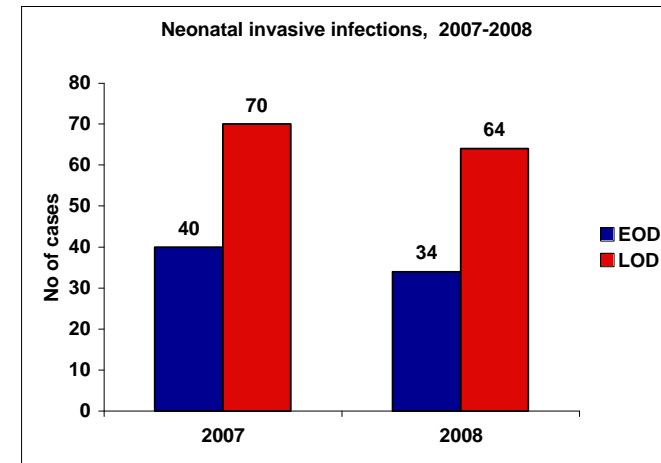
- 1997 : 0.69/1000 LB
- 2006 : 0.28/1000 LB

—→ LOD:

- 1997 : 0.12/1000 LB
- 2006 : 0.13/1000 LB

Main clinical features of GBS neonatal invasive infections

- 208 non redundant GBS strains were collected
- Approximately 1/3 of all invasive French GBS isolates responsible for NII
- EOD 36 % (n= 74)
- LOD 64 % (n= 134)
- 90% of EOD occur during the first 48h of birth
- 85% of LOD occur during the 8 weeks of life.
- There is a significant association between the clinical symptoms and the disease
 - EOD is mostly associated with sepsis (74% vs 30%)
 - LOD is more responsible for meningitis (58% vs 26%)



Pregnant Women who Carry GBS

Chance of Delivering a GBS Baby if
Antibiotics are Given: **1 in 4,000**

Chance of Delivering a GBS Baby if
Antibiotics are Not Given: **1 in 200**



MMWR

Morbidity and Mortality Weekly Report

Recommendations and Reports

August 16, 2002 / Vol. 51 / No. RR-11

Prevention of Perinatal Group B Streptococcal Disease

Revised Guidelines from CDC



CENTERS FOR DISEASE CONTROL AND PREVENTION
SAFER • HEALTHIER • PEOPLE™



ANTENATAL PREVENTION OF THE RISK OF EARLY NEONATAL BACTERIAL INFECTION

SEPTEMBER 2001

Clinical Practice Guidelines

Guidelines Department

- In 2001/02
- **one strategy:**
- screening for GBS colonization (34-37 w)
- A population-based comparison of strategies to prevent early-onset Group B streptococcal disease in neonates
- *Schrag et al. 2002 N Engl. J Med*

Antibiotics

- Giving antibiotics such as penicillin or amoxicillin intravenously during labor and delivery effectively eliminates most GBS infections in women and their newborns
- For best protection, should administered at least 4 to 6 hours before delivery

Intrapartum antibiotic prophylaxis: limitations

- Effective (80% reduction) but **only** for EOD (Cochrane review)
- Does **not** prevent LOD
- Costly; IV access; every pregnancy if GBS +; antibiotic pressure

Why only 80% effective?

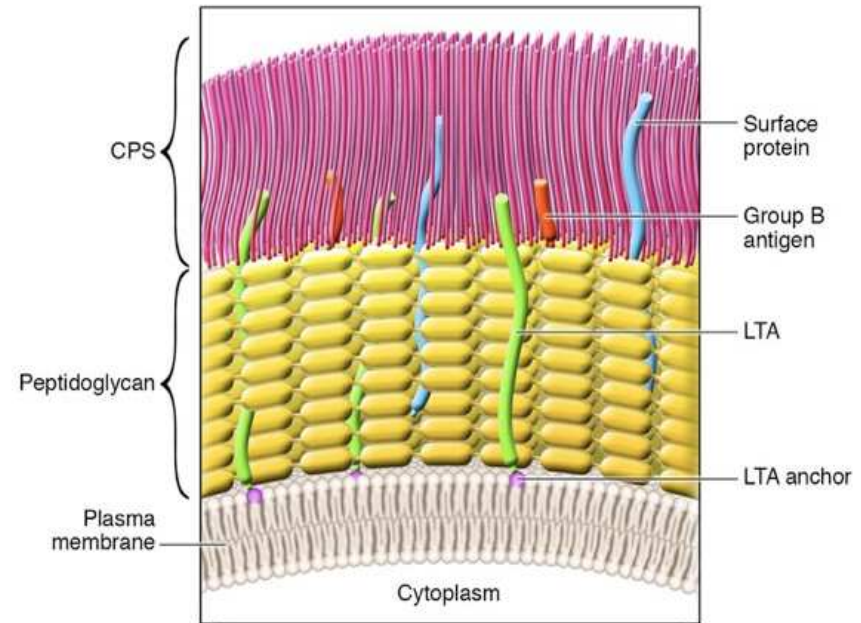
- Culture screen at 35-37 week's gestation not perfect (laboratory processing remains a problem)
- Failure to administer IAP > 4h before delivery
 - Precipitous delivery
 - Culture result not available
 - Preterm delivery

GBS vaccine

Which target?

Vaccine targets

- Capsular polysaccharide
- Surface proteins
- Other virulence factors



GBS CPS TT vaccine

- CPS main GBS virulence factor
- CPS ab protect against neonatal GBS infection
- Estimated protective levels of CPS-specific IgG in maternal sera at delivery: 0.5-2 μ g/mL

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

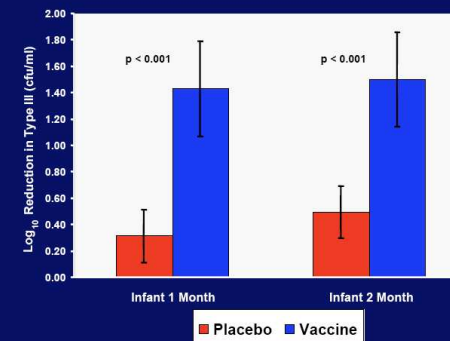
Study Group	GMC (μ g/ml) III CPS-Specific IgG			
	0 Wk	4 Weeks	Delivery	2 Month Post Delivery
III-TT (N=20)	0.18	9.98	9.76	10.80
Placebo (N=10)	0.06	0.05	0.05	0.08

* Baker CJ, et al. *Vaccine* 2003

INFANT SERUM CONCENTRATIONS*

Maternal Vaccine	GMC III CPS-Specific IgG (μ g/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

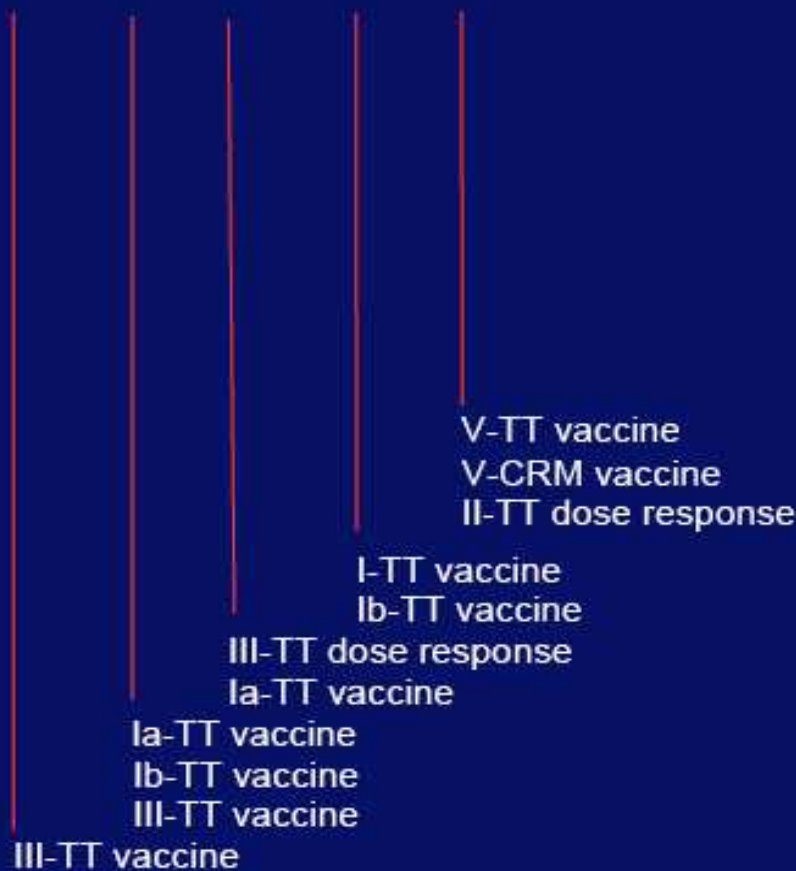


* Baker CJ, et al. *Vaccine* 2003

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

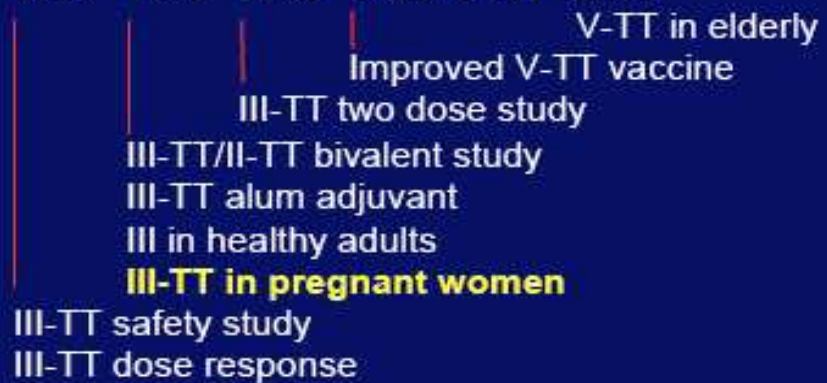
Group B Streptococcal Initiative

1992 1993 1994 1995 1996



The Streptococcal Initiative

1997 1998 1999 2000 2001 2002



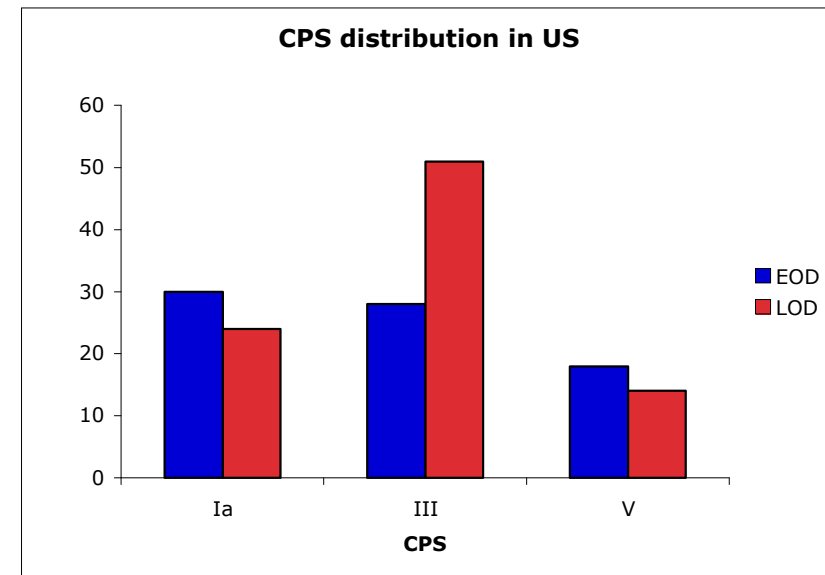
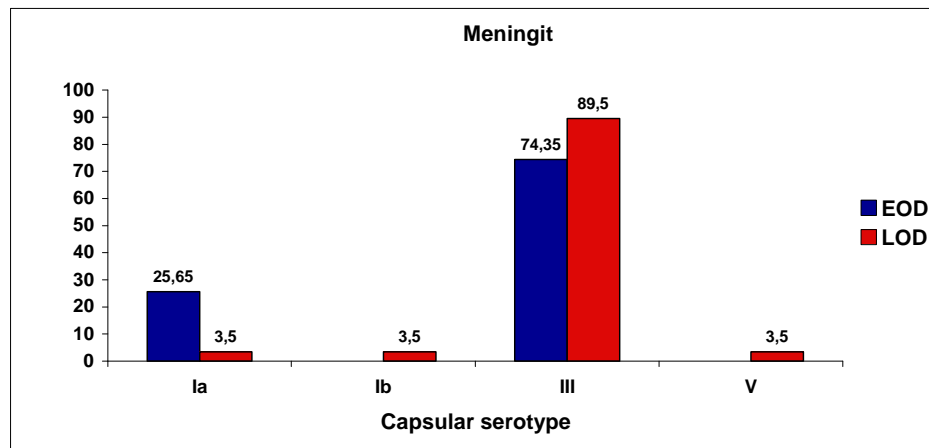
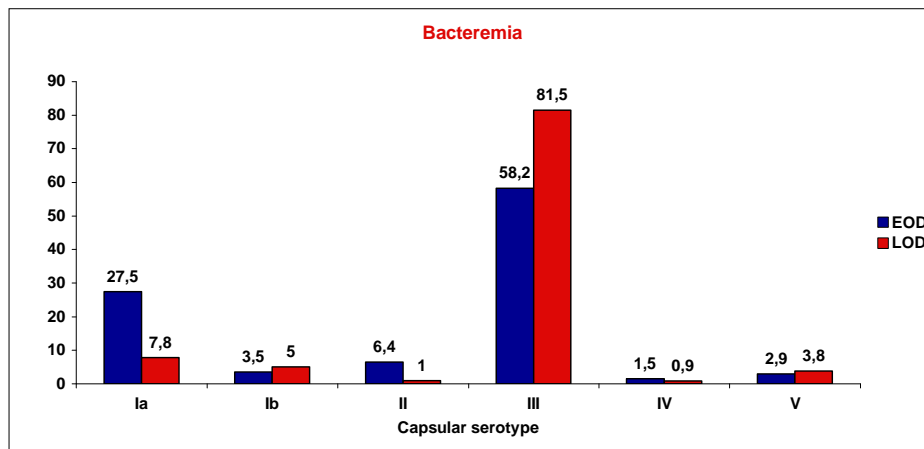
Prevention of GBS Disease

2003 2004 2005 2006 2007 2008

III-TT SPIN Study

From C.J. Baker et al 2008

Distribution of capsular serotypes CPS



Phares et al JAMA 2008

Poyart et al. Emerg Infec Dis 2008
Tazi et al. submitted



Conjugate multivalent CPS vaccine

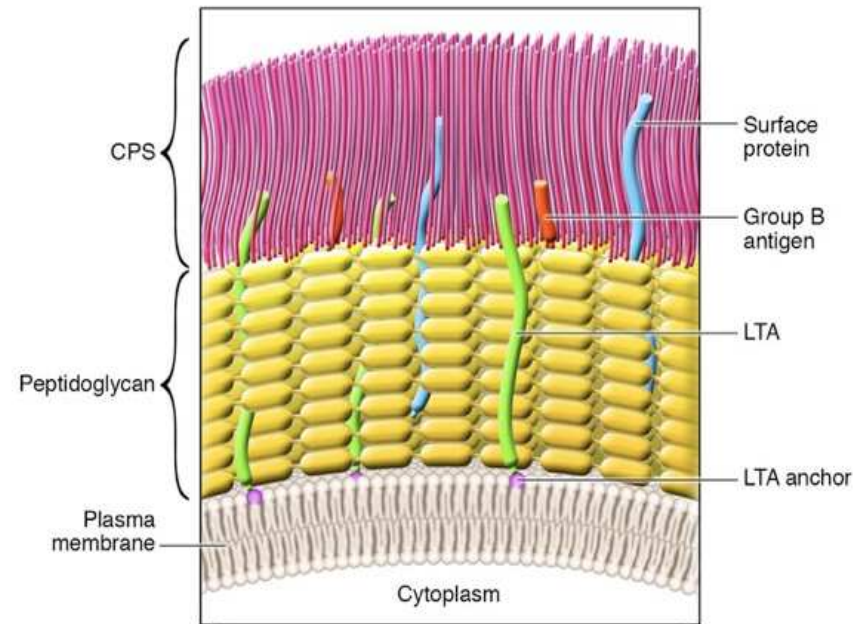
- Proposed that effective GBS vaccine in US includes 5 major CPS (Ia, Ib, II, III, and V).
- Are safe and induce IgG specific in non-pregnant adults 18-45 yrs
- Vaccine-induced IgG maternal IgG early in 3rd trimester → infant protective levels of ab through 2 months of age

Baker CJ et al JID 1999
Baker et al Vaccine 2003

Proteins as Vaccine targets

Surface proteins

- Reverse vaccinology
 - TIGER
 - Novartis

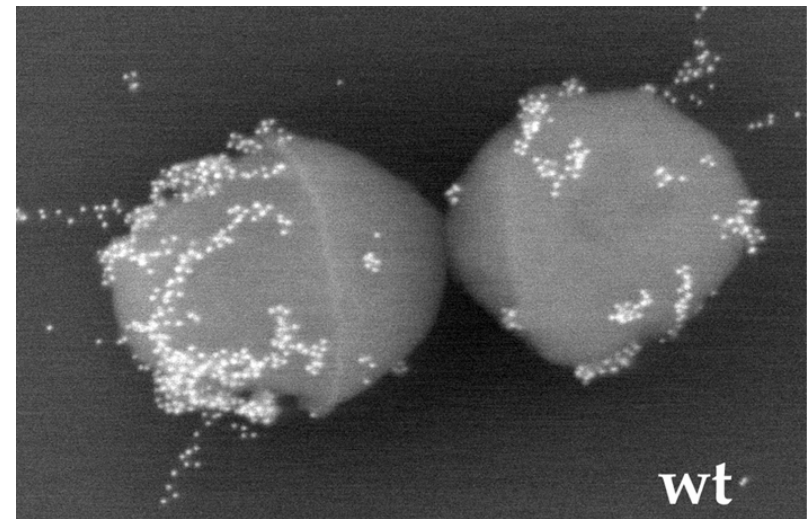


Protein vaccine candidates

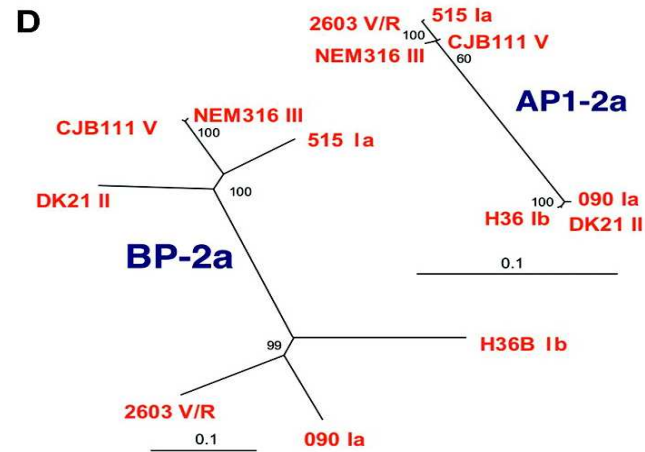
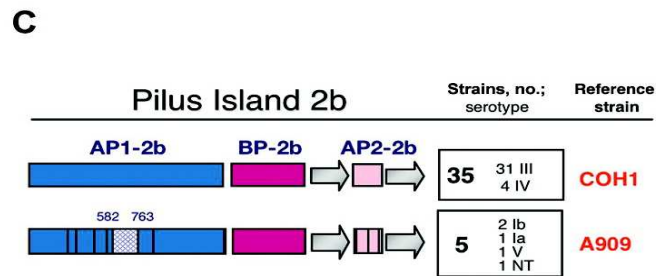
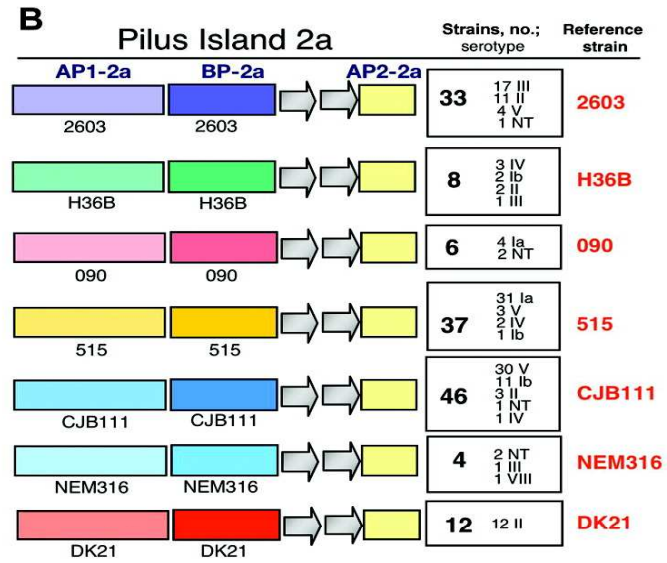
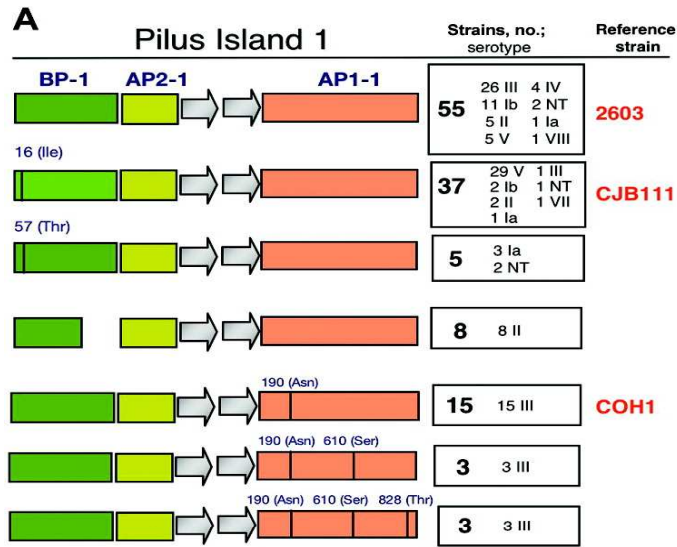
- C5a peptidase
- β -component C protein
- LmB
- Sip
- LrrG

AND

Pilus



Dramsai et al Mol Micro 2006



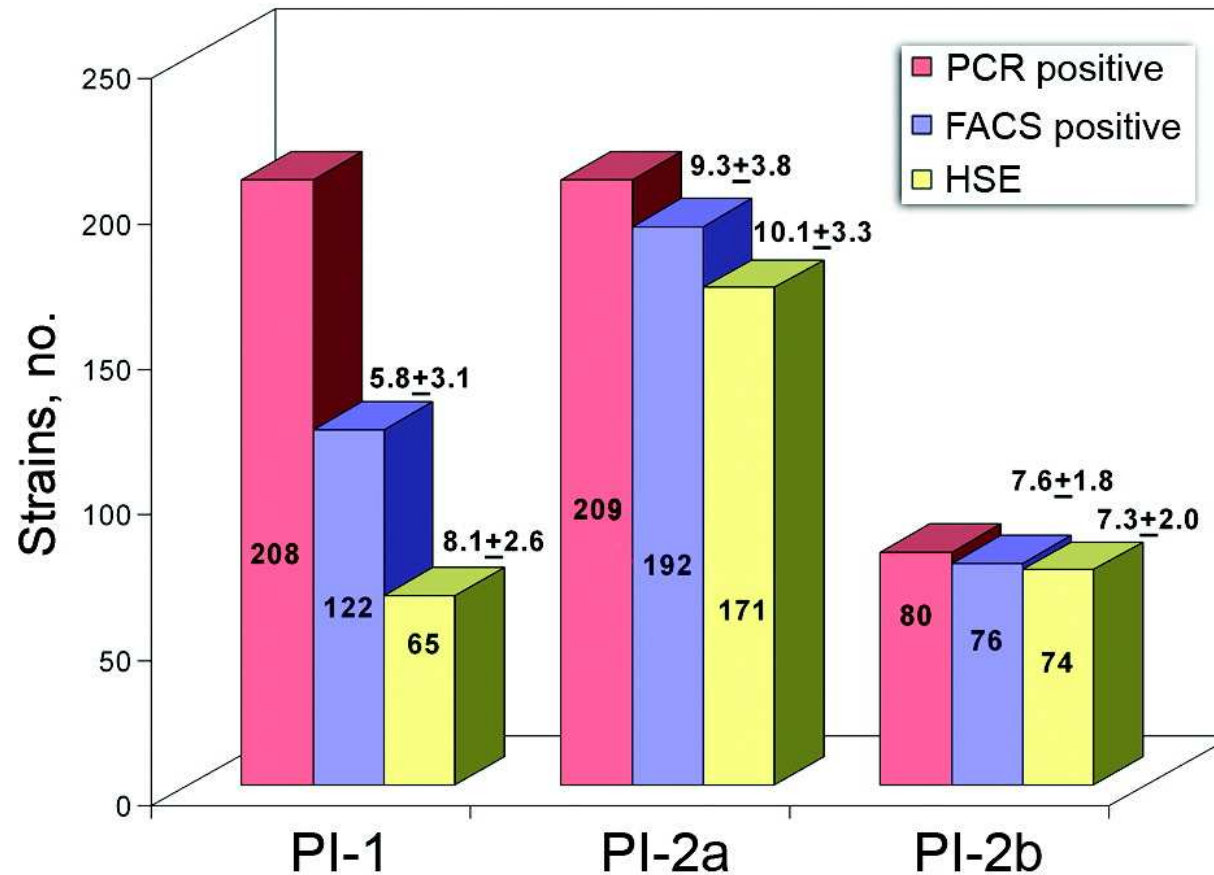


Figure 3. Analysis of pili expression in group B streptococci, showing the correlation between strains that were PCR positive for pilus islands (PIs) and strains for which flow cytometry detected surface - exposed (FACS positive) and highly surface - exposed (HSE) pili structural components. FACS - positive strains displayed a 2 - fold greater fluorescence intensity than those stained with preimmune sera, whereas HSE strains had a 5 - fold greater fluorescence intensity than those stained with preimmune sera. The mean fold - increases in fluorescence (\pm SD) are reported at the top of the columns.

Table 1. Results of an active maternal mouse immunization/neonatal pup challenge model to determine protection conferred by backbone protein of pilus 2b (BP-2b) and ancillary protein 1 of pilus 2b (AP1-2b) against group B streptococcus (GBS) strains.

Antigen, challenge strain ^a	Fluorescence ^b	Protection, % of mice	<i>P</i>
BP-2b			
COH1 (III)	7.7	72.4	<.001
M781 (III)	6.2	95.8	<.001
SMU071 (VIII)	11.6	56.0	<.001
CJB111 (V)	0 ^c	17.5	>.05
AP1-2b			
COH1 (III)	6.3	49.5	<.001
M781 (III)	6.3	82.1	<.001
SMU071 (VIII)	10.2	58.0	<.001
CJB111 (V)	0 ^c	14.5	>.05

NOTE. Groups of 4–8 female mice received 3 doses (on days 1, 21, and 35) of either 20 μ g antigen or buffer combined with Freund's adjuvant. Mice were then mated, and their offspring were challenged with a GBS dose calculated to kill 90% of the pups.

^a Serotype is indicated in parentheses.

^b Data are the fold-shift in fluorescence in cells stained with immune sera versus those stained with preimmune sera.

^c Gene was missing in this strain.

Questions remaining

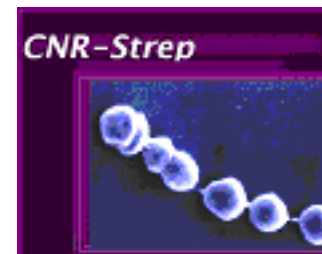
- Optimal combination of CPS's and/or proteins
- Optimal dose
- Need for booster dose(s)
- Need for adjuvant? Which one?
- Target population
 - Pregnant women
 - Adolescents
 - Pre-conception health visit

Conclusions

- 21st century GBS disease burden remains substantial
- Management of GBS diseases remains challenging
- A prevention strategy to further reduce disease burden (LOD)
- Maternal immunization is a promising strategy

Acknowledgements

- **All the correspondants**



- **To InVS**

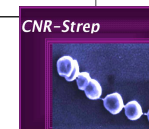
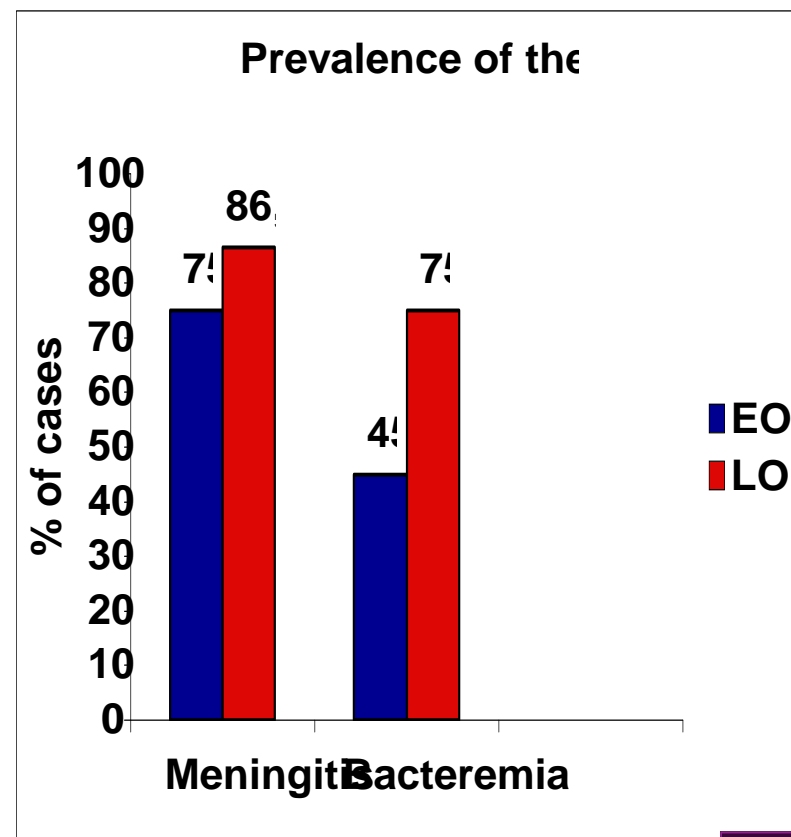


- **Members of the CNR-Strep**

- **Cochin : A. Doloy, H.Poupet, A. Tazi, A. Billoet, N. Dmytruk**
- **Hotel-Dieu : A. Bouvet**
- **Robert Debré : P. Bidet and E. Bingen**
- **Pasteur Institute : P. Trieu-Cuot**

Prevalence of the GBS ST-17 « hyper-virulent clone »

- The hyper virulent clone ST-17 accounts for :
 - 45% of sepsis and 75% of meningitis in EOD
 - 75% of sepsis and 86.5% of meningitis in LOD



Conclusions

- **GBS invasives infections occur at the 2 extremes of the life**
 - **in neonates**
 - **Incidence LOD>EOD**
 - **Capsular serotype III (>70%)**
 - **ST17 : > 90% of strains responsible for meningitis**
 - **in adults**
 - **age >65 ys**
 - **Osteoarticular infections (risk X 3 for male)**
 - **Serotype and ST repartition is identical to that of colonization GBS strains**

Incidence of the clone ST17 among type III GBS responsible for invasive infections

