Current Statut of Group B Streptococcus Vaccine Research and Development

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Current Status of GBS vaccine Research and Development

• Rational for the development of a GBS vaccine
• Which target candidate?
• Whom to vaccine?
• 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

Incidence/1000 live births of neonatal invasive GBS infections (BEH 2008)

- 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%)

Poyart et al 2008 Emerg Infec Dis
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
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

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: 0.5-2µg/mL

<table>
<thead>
<tr>
<th>Study Group</th>
<th>0 Wk</th>
<th>4 Weeks</th>
<th>Delivery</th>
<th>2 Month Post Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>III-TT (N=20)</td>
<td>0.18</td>
<td>9.98</td>
<td>9.76</td>
<td>10.00</td>
</tr>
<tr>
<td>Placebo (N=10)</td>
<td>0.06</td>
<td>0.05</td>
<td>0.05</td>
<td>0.08</td>
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</tbody>
</table>


<table>
<thead>
<tr>
<th>Maternal Vaccine</th>
<th>GMC III CPS-Specific IgG (µg/ml)</th>
<th>Cord</th>
<th>1 Month</th>
<th>2 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>III-TT (N=20)</td>
<td>7.48</td>
<td>3.74</td>
<td>2.16</td>
<td></td>
</tr>
<tr>
<td>Placebo (N=10)</td>
<td>0.05</td>
<td>0.03</td>
<td>0.03</td>
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</tr>
</tbody>
</table>

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

Group B Streptococcal Initiative


- V-TT vaccine
- V-CRM vaccine
- II-TT dose response
- I-TT vaccine
- lb-TT vaccine
- III-TT dose response
- la-TT vaccine
- III-TT vaccine

The Streptococcal Initiative


- V-TT in elderly
- Improved V-TT vaccine
- III-TT two dose study
- III-TT/II-TT bivalent study
- III-TT alum adjuvant
- III in healthy adults
- III-TT in pregnant women
- III-TT safety study
- III-TT dose response

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

Tazi et al. submitted

Phares et al JAMA 2008
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

Dramsi 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 (±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.

<table>
<thead>
<tr>
<th>Antigen, challenge strain&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Fluorescence&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Protection, % of mice</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP-2b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COH1 (III)</td>
<td>7.7</td>
<td>72.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>M781 (III)</td>
<td>6.2</td>
<td>95.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SMU071 (VIII)</td>
<td>11.6</td>
<td>56.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CJB111 (V)</td>
<td>0&lt;sup&gt;c&lt;/sup&gt;</td>
<td>17.5</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>AP1-2b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COH1 (III)</td>
<td>6.3</td>
<td>49.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>M781 (III)</td>
<td>6.3</td>
<td>82.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SMU071 (VIII)</td>
<td>10.2</td>
<td>58.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CJB111 (V)</td>
<td>0&lt;sup&gt;c&lt;/sup&gt;</td>
<td>14.5</td>
<td>&gt;.05</td>
</tr>
</tbody>
</table>

**NOTE.** Groups of 4–8 female mice received 3 doses (on days 1, 21, and 35) of either 20 µg 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.

<sup>a</sup> Serotype is indicated in parentheses.

<sup>b</sup> Data are the fold-shift in fluorescence in cells stained with immune sera versus those stained with preimmune sera.

<sup>c</sup> 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

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  - 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

![Prevalence of the GBS ST-17](image)
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