**Prevention of GBS disease**

**Perspective of a GBS vaccine**

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**Group B streptococcal diseases in neonates**

- Since the 1970s, leading cause of life-threatening infections in newborns
- Neonatal illness/death
- Long-term disabilities

- EOD: 0.3-3 per 1,000 live birth
- LOD: 0.4-0.5 per 1,000 live birth

**Impact of prevention practices Early- and Late-onset GBS Diseases in the 1990s, U.S.**

S. Schrag, New Engl J Med 2000


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**INTRODUCTION & BURDEN**

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**CONTENT**

- Introduction
- Maternal immunization
- History of development
- Different antigens / options
- Where are we today?
  - Different vaccines
  - Cost-effectiveness
- Take home messages

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**CHU of Liege – NRC for S.agalactiae (GBS)**

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**Société belge de Pédiatrie 13.03.2015**
**GBS still the leader!**

- GBS remains leading cause of EO sepsis & meningitis
- Up to 60% of occurring among women with negative antenatal screening
  - Highlighting limitation with screening and IAP
- IAP has no effect on incidence of GBS LOD

**Maternal GBS immunization**

Could maternal immunization be an alternative?

- Protection against both EOD & LOD?
- Bypassing concerns related to antimicrobial resistance?
- Cost-effectiveness?
- Adjunctive to screening & IAP?

**Streptococcus agalactiae or GBS**

- Gram positive cocci
- β-hemolytic
- Encapsulated
- 1 of major virulence factors
- 10 capsular serotypes (Ia, Ib, II-IX)
- Numerous surface proteins (α and β-C, Rib, SpI, pilus islands 1, 2a & 2b, etc)

**Distribution (%) of capsular types of GBS isolated in neonatal disease**

(DENVARI project, 2008-2011, EU Fund FP7 programme)
INTRODUCTION

Stages in the pathogenesis of GBS neonatal EOD: Bacterial & individual factors

GBS vaccine: Nearly within reach

History of vaccine development

Long-standing data supports protection of maternal anti-CPS Ab

Background

Lancefield's observations
- Demonstration of protection against lethal GBS infection in a mouse model by antibodies to the CPS of GBS
- Passive transfer of anti-CPS Ab protects newborn mice
Background
First generation of CPS vaccine
- Disappointment from studies of uncoupled first generation purified native GBS CPS vaccines in healthy adults
- Demonstration of feasibility of vaccine prevention of GBS disease
- Need for improvement of immunogens
- Success story of polysaccharide-protein conjugate vaccine technology in preventing *H. influenzae* and *S. pneumoniae* infections in infants

Background
- Expectation of polysaccharide-protein glycoconjugates
- T cell-dependent response
- Immunological memory & long term protection
- Predominantly IgG1 subclass → improved transplacental transport
- Increase likelihood of protection of mother and infant

Maternal vaccination allows infant protection
- Placental transfer increases markedly > 32 weeks

Vaccine for pregnant women:
Likely the most effective, sustainable and cost effective approach

GBS Vaccines, since the 1980s
Challenges
- 10 serotypes
  - Different distributions
    - EOD, LOD, invasives infections in adults
    - Geographically, along time, ATB pressure

Conjugated vaccines
(Channing laboratory, Harvard medical school, Boston)
- CPS III-Tetanus Toxoid
- Monovalent Ia, Ib, II and V CPS –TT
- Tested for immunogenicity in healthy adults
- Multivalent conjugated vaccines Ia, Ib, (II), III (and V)

GBS Vaccines, since the 1980s
Challenges
- Native capsular polysaccharide vaccines (1st gen)
- 10 serotypes
  - Different distributions
    - EOD, LOD, invasives infections in adults
    - Geographically, along time, ATB pressure
**GBS Vaccines, since the 1980s**

**Challenges**
- Capsular polysaccharide - TT vaccines
- Capsular polysaccharide – CRM197 vaccines (Second generation)
  - Dosage and route of administration
  - Immune response
  - Duration of immunity and protection
  - Safety studies

**INTRODUCTION**

**IMMUNIZATION**

**ANTIGENS**

**TODAY**

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**GBS Vaccines, since the 1980s**

**Challenges**
- Ag = Cross proteins
  - Humoral response T-cell dependent
  - long lasting immunity

**GBS Protein-based Vaccine**

- **Protein-based Vaccines**
  - Quality and route of administration
  - Immune response
  - Duration of immunity and protection
  - Safety studies

**Protein-based Vaccines**

- **GBS Protein-based Vaccine**
  - Knowledge of complete GBS genome
  - **Reverse vaccinology approach**
  - **Comparaison of genomes from 8 different GBS serotypes** (Novartis)
  - 312 surface proteins were cloned
  - 4 provide a high protective humoral response in mouse
  - Sip and 3 others
  - The 3 other proteins = « pilus like structures »
    - PI 1, PI 2a & 2b

**Protein-based Vaccines**

- **GBS Protein-based Vaccine**
  - Highly immunogenic proteins
  - Elicit protective and functional (opsonophagocytosis) antibodies
  - Virulence factor
    - Adhesion
    - Transcytose through cells

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**GBS « pilus like structure »**

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**GBS « pilus like structure »**

- Highly immunogenic proteins
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those obtained with the GBS proteins Rib and els, 1988

that apparently is immunodominant (protein, which has a centrally located B repeat region

nant. This conclusion is supported by a study of the M6

These data indicate that the N-terminal part of M22, which

2001
corresponding domains in M22, as shown by their ability

lacks of reactivity with M22-N and Sap22 was not caused

to intact M22 reacted well with C22 but showed little or

ous work had shown that antibodies to M22-N and

pose, we used three long peptides derived from M22:

opsonizing antibodies and a conserved C repeat region

lence factor with a variable N-terminal region targeted by

studied

M22 cannot be explained by a molar excess of repeats,

dition inhibitor C4BP, while an adjacent semivariable region binds hu-

met in animal models

From

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Figure 4

Anti-GBS-NN more protective than

Strong correlation exists between naturally occurring maternal

correlation exists between

Anti-GBS-NN more protective than antibodies against full length Rib and Alpha in animal models

Anti-Rib

Anti-Alpha

Anti-GBS-NN antiserum prevents GBS invasion of

Anti-GBS-NN antiserum prevents GBS invasion of

Anti-GBS-NN antiserum prevents GBS invasion of

Anti-GBS-NN antiserum prevents GBS invasion of

What is ongoing?
Novartis GBS Vaccine
Trivalent glycoconjugate vaccine
- CRM conjugated CPS Ia, Ib and III
- Trivalent conjugate coverage: 79 % globally
- Phase I completed, and Phase II ongoing
- Phase III study: (EU/US/Global)
- Eligibility: women between 28-35 wks gestation
- End-points: mother/infant safety; vaccine immunogenicity (efficacy); infant response to CRM-containing vaccines

Minervax GBS Vaccine
Single component NN fusion protein
- Anticipated coverage: 95% of isolates
- Clinical trial in healthy adults: Q2-2015
- EU funding FP7 Programme HEALTH for the development of a novel innovative GBS vaccine candidate
- Other sources of funding

GBS Maternal immunization
Would it be cost-effective?
- Cases prevented,
- Deaths averted,
- Life-years saved
- Quality-adjusted life-years (QALYs) gained
- Costs of
  - Acute care for infants with GBS disease
  - Chronic care for those with long term disability
  - Immunization per person
  - Assuming 85% coverage
    - Prevention of an additional 898 cases of GBS and an additional 35 deaths among infants in the US

In conclusion
Routine maternal immunization with a trivalent (Ia, Ib and III) vaccine at week 28 of pregnancy
- As an adjunct to screening and IAP
  - May address an important unmet public health need in the US
  - And further reduce the burden of GBS disease during infancy (ED and LOD)
  - May be comparable in cost-effectiveness to several other vaccines recently approved to use in children and adolescents

GBS Maternal immunization
Would it be cost-effective?
- Cost-effectiveness of a potential group B streptococcal vaccine program for pregnant women in South Africa
  - Sun Young Kim1, 2, LOUISE B. RUSSELL3, JHETHWYN PARK3, JENNIFER R. VERNON4, SHABE A. MADRI5, CLARA L. CULATNO6, STEPHANIE J. SCHLEG6, ANGELOSA BERTHO6

Trivalent (Ia, Ib and III) glycoconjugate vaccine
GBS Maternal immunization
Would it be cost-effective?

- In low and middle income countries:
  - no screening-based IAP strategy
  - +/- RF-based IAP strategy
- Comparison of 4 strategies
  - Doing nothing
  - Maternal GBS vaccination
  - RF-based IAP
  - Maternal GBS vaccination + RF-based IAP
- Assuming 50-90% coverage and 75% of women vaccinated
  - Vaccination / Doing nothing → prevents 30-54% of cases
  - RF-based IAP / Doing nothing → prevents 10% of cases
  - Vaccination + RF-based IAP → prevents 48% of cases
- Substantial reduction of the burden of infant GBS disease in South Africa and would be cost-effective by WHO-guidelines

CONCLUSION
Take home messages

Maternal GBS immunization
Conclusion

- Immunization at 28-32 weeks
- Prevention at least 85% of invasive GBS disease in neonates and young infants
- Potential reduction
  - of incidence of maternal invasive GBS infection
  - of premature births, stillbirths related to GBS infection
- Cost-effective in high and low income countries

Thank you!