Prevention of GBS disease

Perspective of a GBS vaccine

Prof. Pierrette Melin
National Reference Centre for *Streptococcus agalactiae*
Clinical Microbiology, University Hospital of Liege, University of Liege

CONTENT

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

INTRODUCTION & BURDEN

Group B streptococcal diseases in neonates

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

Group B streptococcal diseases in neonates

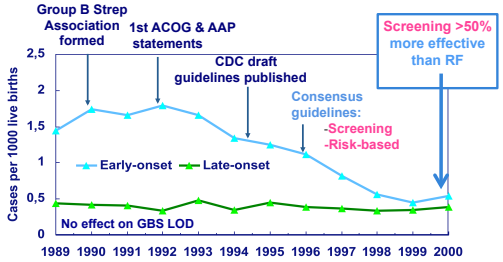
- Since the 1970s, leading cause of life-threatening infections in newborns
  - Neonatal illness/death
  - Long-term disabilities

EOD
0.3-3 per 1,000 live birth

LOD
0.4-0.5 per 1,000 live birth

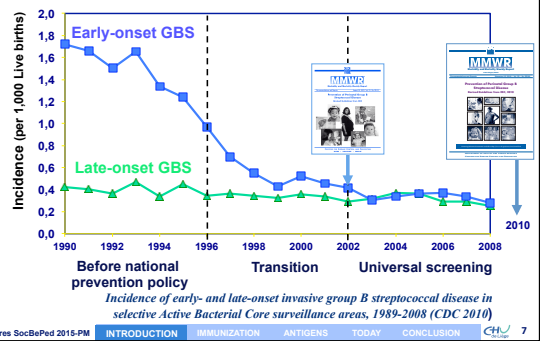
GLOBAL health major challenge !
Also in developing low income countries

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



S. Schrag, New Engl J Med 2000
Schrag S. et al. N Engl J Med 2002; 347:233-9

Impact of prevention practices Early- and Late-onset GBS Diseases, U.S.



Incidence of early- and late-onset invasive group B streptococcal disease in selective Active Bacterial Core surveillance areas, 1989-2008 (CDC 2010)

European strategies for prevention of GBS EOD

- Intrapartum antibioprophylaxis recommended
  - Screening-based strategy
    - Spain, 1998, 2003, revised 2012
    - France, 2001
    - Belgium, 2003, revised 2015
    - Germany, 1996, revised 2008
    - Switzerland, 2007
  - Risk-based strategy
    - UK, the Netherlands, Denmark
- No guidelines
  - Bulgaria, …

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, Sip, pilus islands 1, 2a & 2b, etc)

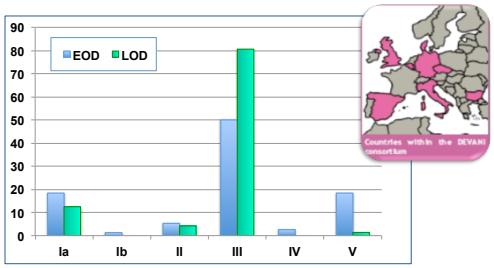
Rebecca Lancefield 1895-1981

1887, Noccard-Mollereau, bovine mastitis
1933, Group B Antigen
1964, severe neonatal sepsis, *Eickhoff et al N Eng J med*

➢ 1970, N°1 in neonatal infections

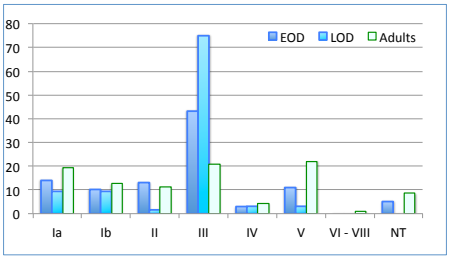
Distribution (%) of capsular types of GBS isolated in neonatal disease

(DEVANI project, 2008-2011, EU Fund FP7 programme)



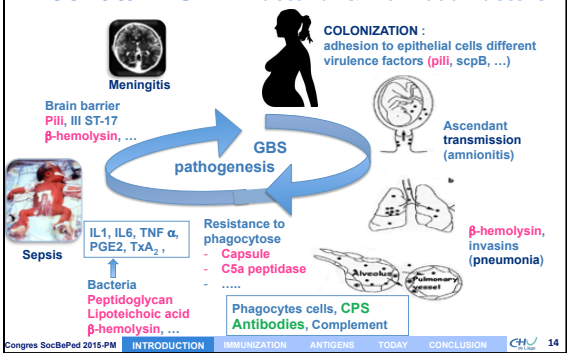
76 neonatal EOD; 72 neonatal LOD

Distribution (%) of capsular types of GBS isolated in Belgium from different groups of patients (1998-2007)

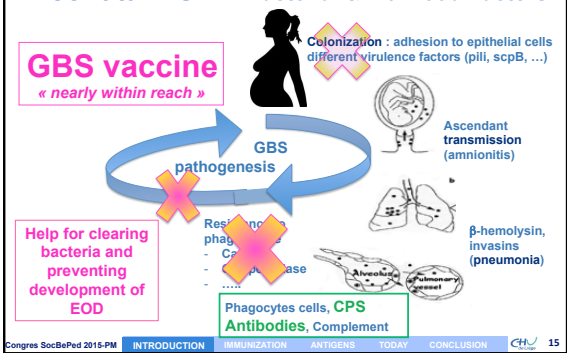


236 neonatal EOD; 64 neonatal LOD; 721 adults

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



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



History of vaccine development

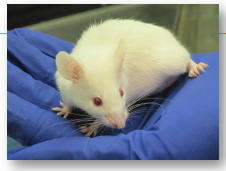
MATERNAL IMMUNIZATION

Background

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

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

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

- Correlate between maternal low level of CPS type Ab (III, Ia & Ib) at time of delivery and risk for development of GBS EOD
- Human serum containing sufficient concentrations of Ia, Ib, II, III and V CPS-specific IgG promotes efficient opsonization & phagocytosis of homologous strain in vitro and protection from experimental infection in vivo.

*Baker C et Kasper D, 1976, **NEJM***

Background
First generation of CPS vaccine

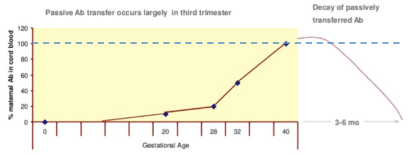
- Disappointment from studies of uncoupled first generation purified native GBS CPS vaccines in healthy adults
- Demonstration of feasibility of vaccine prevention of GBS disease
- Need for improvement of immunogens
- Success story of polysaccharide-protein conjugate vaccine technology in preventing *Hi* b 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



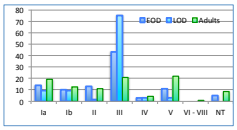
Vaccine for pregnant women:
Likely the most effective, sustainable and cost effective approach

CPS
Conjugate CPS
Surface proteins
Pili proteins
NN fusion protein

CANDIDATE VACCINES

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

Native capsular polysaccharide vaccines (1st gen)
- 10 serotypes
  - Different distributions
    - EOD, LOD, invasives infections in adults
    - Geographically, along time, ATB pressure

Conjugated vaccines (2nd gen)
(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

Capsular polysaccharide - TT vaccines
Capsular polysaccharide – CRM_{197} vaccines
(Second generation)

- **Dosage and route of administration**
- **Immune response**
- **Duration of immunity and protection**
- **Safety studies**

GBS Vaccines, since the 1980s Challenges

GBS Protein-based Vaccine

- **Ag = Surface proteins**
  - Cross protection against different serotypes
  - **Better immunogenicity**
    - **Humoral response T-cell dependent**
      = long lasting immunity

Protein-based Vaccines

Protein	Protective Ab (in mouse)	associated serotypes
Alpha-like proteins		
Alpha	**Yes**	**Ia, Ib et II**
Alp1		**Ia**
Rib	**Yes**	**III**
Alp2	**Yes**	**V, VIII**
Alp3	**Yes**	**V, VIII**
Beta C protein	**Yes**	**Ib**
C5a peptidase	Yes	All
Sip (1999)	Yes	All
BPS	Yes	All

Sip = Surface Immunogenic Protein (Brodeur, Martin, Québec)
BPS= Groupe B Protective surface Protein

Protein-based Vaccines

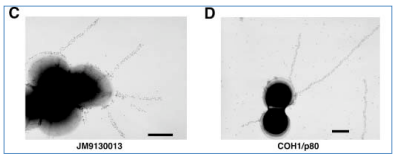
Reverse vaccinology approach
Knowledge of complete GBS genome

- **Comparaison of genomes from 8 different GBS serotypes (Novartis)**

D.Maione et al, Science 2006

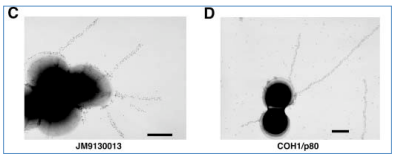
  - **312 surface proteins were cloned**
  - **4 provide a high protective humoral response in mouse**
    - **Sip and 3 others**
    - **The 3 other proteins = « pilus like structures »**
      - **PI 1, PI 2a & 2b**

GBS « pilus like structure »



GBS « pilus like structure »

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



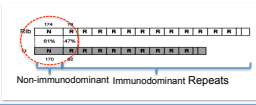
Protein-based Vaccines

GBS-NN fusion protein

From Rib and AlphaC surface proteins of GBS

- Based on novel vaccine epitopes identified in the N-terminal regions of the Rib and AlphaC surface-proteins of GBS
- Vaccine candidate is a non-glycosylated fusion protein

Rib and AlphaC surface proteins of GBS



GBS-NN Fusion protein

Cell Host & Microbes 2, 427-434, 2007

MINERVAX

Protein-based Vaccines

GBS-NN fusion protein

From Rib and AlphaC surface proteins of GBS

- Based on novel vaccine epitopes identified in the N-terminal regions of the Rib and AlphaC surface-proteins of GBS
- Vaccine candidate is a non-glycosylated fusion protein
- Highly immunogenic and anti-GBS-NN antibodies more protective than antibodies to full-length proteins

MINERVAX

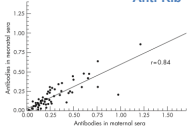
A novel protein-only, single component, GBS vaccine covering 95% of clinical isolates

Protein-based Vaccines

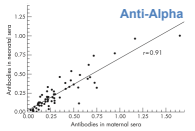
GBS-NN fusion protein

- Strong clinical correlation exists between naturally occurring maternal and neonatal levels of anti-Rib and anti-Alpha antibodies
- Strong correlation exists between levels of neonatal anti-Alpha (OR 0.0007) and Anti-Rib (OR 0.002) and invasive GBS infection
- **Anti-GBS-NN more protective than antibodies against full length Rib and Alpha in animal models**

Anti-Rib



Anti-Alpha

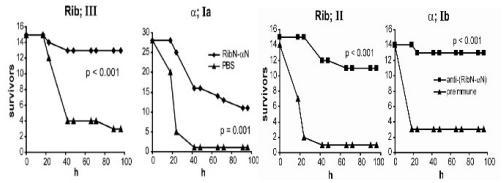


Arch Dis Child Fetal Neonatal Ed 91:F403-408, 2006

MINERVAX

Protein-based Vaccines

Vaccination with GBS-NN protects against lethal challenge with GBS Ia, Ib, II & III in adult mice



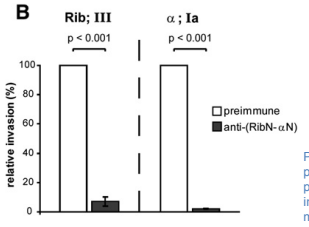
Mice immunized with GBS-NN in alum, boosted after 4 weeks and challenged 2 weeks later.

Cell Host & Microbe 2, 427-434, 2007

MINERVAX

Protein-based Vaccines

Anti-GBS-NN antisera prevents GBS invasion of epithelial cells



Potential Implications for pathogenesis and prevention of invasive disease by mucosal anti-NN IgG

Cell Host & Microbe 2, 427-434, 2007

MINERVAX

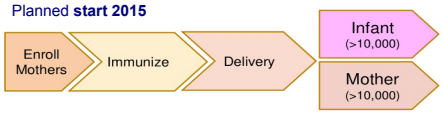
CRM-Conjugate CPS
NN Fusion protein
Cost effectiveness studies

CANDIDATE VACCINES
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)
    - Size: >10,000 mothers → >10,000 infants

Planned **start 2015**



- Eligibility: women between 28-35 wks gestation
- End-points: Mother/infant safety; vaccine immunogenictiy (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?

Vaccine
Volume 32, Issue 37, 20 August 2014, Pages 4778–4785

Prevention of group B streptococcal disease in the first 3 months of life: Would routine maternal immunization during pregnancy be cost-effective?

Gerry Oster[a], John Edelsberg[a], Kalin Hennegan[a], Clement Lewin[b], Vas Narasimhan[c], Karen Slobod[c], Morven S. Edwards[d], Carol J. Baker[d, e]

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 899 cases of GBS and an additional 35 deaths among infants in the US

GBS Maternal immunization
Would it be cost-effective?

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 (EO 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?

Vaccine
Volume 32, Issue 17, 7 April 2014, Pages 1954–1963

Cost-effectiveness of a potential group B streptococcal vaccine program for pregnant women in South Africa

Sun-Young Kim[a], Louise B. Russell[b], Jeehyun Park[b], Jennifer R. Verani[c], Shabir A. Madhi[d], Clare L. Cutland[d], Stephanie J. Schrag[c], Anushua Sinha[e]

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

Vaccine 31S (2013) D1–D2
Contents lists available at ScienceDirect
Vaccine
journal homepage: www.elsevier.com/locate/vaccine

Editorial
Introduction: Addressing the challenge of group B streptococcal disease

Vaccine 31S, 2013

- Introduction, *Rappuoli & Black*
- GBS Review, *Carol Baker*
- Overview GBS epidemiology, *Paul Heath*
- GBS epidemio and vaccine needs, *Melin & Efstratiou*
- GBS epidemiology in developping countries
- IAP in USA et Vaccine implications, *S.Schrag & Verani*
- GBS maternal vaccines Past Present and Future, *Chen & Kasper*
- GBS Public awareness etc
- Prevention through Vaccination, *M. Edwards*
- GBS Vaccination in pregnancy, *P. Ferrieri*
- GBS vaccine Phase III trial

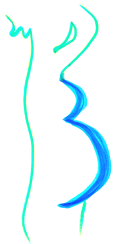
CONCLUSION
Take home messages

GBS vaccine - Conclusion

- CPS-glycoconjugate vaccine
  - 3 to 5-valent glycoconjugate vaccine (Ia, Ib, II, III and V)
- CPS-CRM_{197} / Pili vaccine
- NN-fusion protein vaccine

- Immunogenicity
- Safety
- Efficacy determination ongoing
- Impact on colonization : unknown

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 !