Streptocoque groupe B

Nouveaux tests de dépistage: PCR

Pharm.biol. Cécile Meex

Perspectives vaccinales

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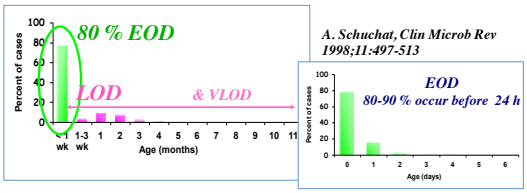
CONTENT

- Introduction & burden
- GBS Screening: new tools
- Maternal immunization
  - Different antigens / options
  - Where are we today?
- 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

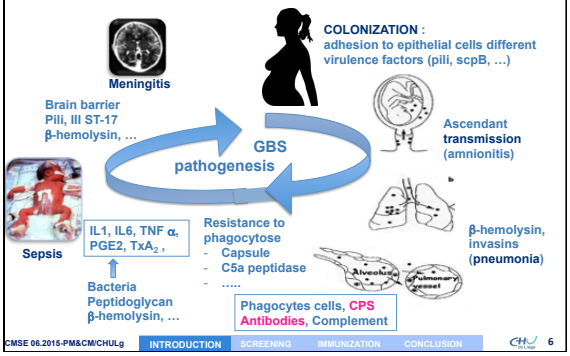
- Since the 1970s, leading cause of life-threatening infections in newborns
  - Neonatal illness/death
  - Long-term disabilities

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

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



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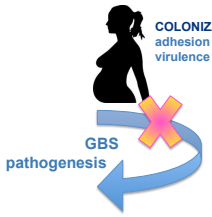
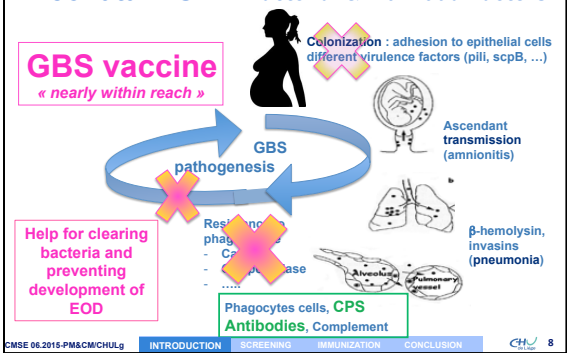


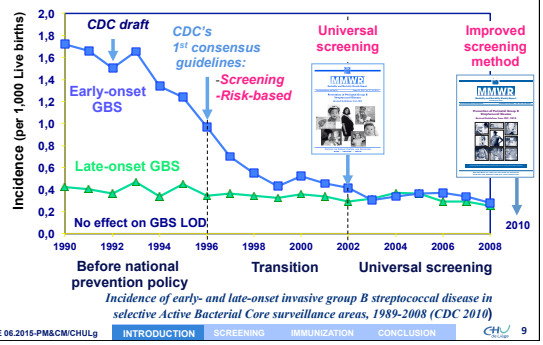
Intrapartum antibioprophylaxis
> 4 hours before delivery
Highly effective in preventing GBS EOD (*1st clinical trials in late 80s*)

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

GBS vaccine
« nearly within reach »



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 rec… ended
  - Screening-based st…
    - Spain, 19…
    - …, 2003, revised 2015
    - Germany, 1996, revi…
    - Switzerl…
    - …Denmark
- …o guidelines
  - Bulgaria, …

Incidence to 0.3-1 per 1,000 live births

Remaining burden of streptococcal early onset disease
Missed opportunities / False negative screening
(antenatal culture based screening)

Screening for GBS colonization
OLD & NEW TOOLS

Screening for GBS colonization

Goal of GBS screening
To predict GBS vaginal (rectal) colonization at the time of delivery

Expected high predictive values
- **False negative**
  → **Missed IAP**
- **"False" positive**
  → **Unnecessary IAP**

Screening for GBS colonization

Goal of GBS screening

To predict GBS vaginal (rectal) colonization at the time of delivery

- **Critical factors influencing accuracy**
  - **Swabbed anatomic sites** *(distal vagina + rectum)*
  - **Timing of sampling**
  - **Screening methods** (antenatal vs intrapartum)
    - **Culture**
      - *Procedure*
      - *Media*
    - **Nucleic Acid Amplification Test (NAAT)**

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Crucial conditions to optimize universal antenatal SCREENING

WHEN	**35-37 weeks**
WHO	**ALL the pregnant women**
Specimen	**Vaginal + rectal swab(s)**
Collection	**WITHOUT speculum**
Transport	**Transport/collection device/condition** (non nutritive medium: Amies/Stuart or Granada like tube) (type of swab)(Length and T°) → Lim broth
Request form	**To specify prenatal « GBS » screening**
Laboratory procedure	

(CDC 2010 - Belgian SCH 2003)

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Antenatal culture-based screening: Limiting factors

- **Positive and negative predictive values**
  - **False-negative results**
    - **Failure of GBS culture** *(reduced viability during transport, oral ATB, feminine hygiene)* **or new acquisition**
    - **Up to 1/3 of GBS positive women at time of delivery**

Eargerly expected, a more accurate predictor
For intrapartum GBS vaginal colonization

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Detection of EOD risk = GBS positive colonization at delivery

Antenatal screening	Intrapartum screening
• VPP 60 à 87% • VPN 88 à 96%	• Expected PPV and NPV >90%
• False negative: missed IAP • False positive: unnecessary IAP	• Better targeted IAP
	• No susceptibility testing

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Intrapartum screening theranostic approach
Expected advantages: pro & con

- Inclusion of women without prenatal screening/care
- Identification of women with change of GBS status after 35-37 wks gestation *(new acquisition, false negative)*
- Increased accuracy of vaginal GBS colonization status at time of labor & delivery
- Drawback: no antimicrobial susceptibility result

→ **IAP addressed to right target**
- **Reduction of inappropriate/unnecessary IAP**
- **Broader coverage of « at GBS risk women »**

→ **Improvement of prevention**

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Prevention strategy for GBS EOD
TOWARDS A EUROPEAN CONSENSUS ?

Conference held in June 2013, Florence, Italy

A European working party: Neonatologists, obstetricians, microbiologists

Representing countries
- **with screening-based IAP,**
- **with risk-based IAP strategies**
- **or nothing**

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Towards « European Consensus »

Decision taken by the European working party

Main recommendations

- **Universal screening at time of delivery**
  - POCT with high PPV and NPV
    - Real time PCR or other methods
  - TAT < 1 hour
- **IAP for all GBS positive pregnant women**
  - documented by intrapartum testing (or late pregnancy test if performed)
- **Late pregnancy antenatal screening in known penicillin allergic women**
  - Determination of clindamycin susceptibility if GBS positive screening

Intrapartum GBS screening and antibiotic prophylaxis : a European consensus conference. J Matern Fetal Neonatal Med 2014;27:1-17.

Alternative to GBS antenatal screening: intrapartum screening

Theranostic approach

€€€ Cost-effective

Turnaround time
collect specimen at admission

Optimal management of patient

- Full automation
- With internal QC
- Easy to perform, to interprete

TRAINING !

- Sensitivity > 90%
- Specificity > 95%

Results

30-45 minutes, 24 hrs/7 d, robust

Benitz et al. 1999, Pediatrics, Vol 183 (6)

Test Xpert GBS

- Real Time PCR on GeneXpert system (Cepheid).
  - Amplification of a conserved region adjacent to the cfb gene of GBS
- On vaginal or vagino/rectal swab
- Fully automated
- Easy handling
- Result in 45 minutes

Ongoing study in CHU Liège/UZ Antwerp: Objectives (→ 900 patients)

1. To assess the practical and analytical aspects of the implementation of the PCR test Xpert GBS® in Belgium
   - Performed by midwives
   - For all women at onset of labor
2. To evaluate the cost-effectiveness of the intrapartum screening strategy

→ To consolidate the proposal of the European Expert Group

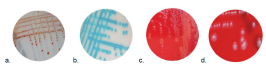
Material and methods

Specimen collection
Test Xpert GBS

Specimen collection

Prenatal screening	Intrapartum screening
• vagino/rectal specimen collected at 35-37 weeks' gestation	• vaginal specimen using a double swab • From ALL women at onset of labor

Culture



Test Xpert GBS

a/Granada, b/StrepB Select, c,d/GS-CNA

Test Xpert GBS: Procedure

- Procedure performed by midwives
- GeneXpert system installed at the Obstetrics facility

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Test Xpert GBS: Expression of results

Assay Information

Assay	Assay Version	Assay Type
Xpert GBS G3	3	In Vitro Diagnostic

Test Result: POSITIVE — Presence of GBS

Test and Analyte Result

Analyte Name	Ct	EndPt	Analyte Result	Probe Check Result
SPC	34.4	108.0	NA	PASS
GBS	34.1	188.0	POS	PASS
IC	31.0	149.0	NA	PASS

Test Result: NEGATIVE — Negative for GBS

Test Result: ERROR — Indeterminate status for GBS

Test Result: NO RESULT

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Test Xpert GBS: Use of results

- Algorithm proposed to clinicians:

  Integration of the intrapartum Xpert result in addition to :
  - patient's clinical data
  - Result of the antenatal screening at 35-37 weeks' gestation

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Preliminary results

Culture results
PCR results

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Global overview

- Study period : 8/4 au 03/10/2014 (still ongoing)
- 658 deliveries
- Included patients : 486 Xpert® GBS tests performed (74%)
  - Inclusion rate lower among antenatally positive screened patients.

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Culture results

- Colonization rate (35-37 weeks): 19.4%
- Performances of the antenatal culture screening

Sensitivity	Specificity	PPV	NPV
67.3 %	94.2 %	68.8 %	93.8 %

  - intrapartum culture as gold standard

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PCR results

- Not yet available for presentation
- Difficulties encountered:
  - Wrong manipulations
  - Invalid results

- Study still ongoing, with a revised protocol

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Discussion

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Xpert® GBS for intrapartum testing (main papers)

Authors	Year/journal	Nb patients	Site	S %	Sp %	PPV %	NPV %
Mueller et al.	2014 Eur J Obstet Gynecol Reprod Biol.	150 150	Lab Obst.	85.71 85.71	95.9 95.66	82.76 85.71	96.69 95.65
Poncelet-Jasserand et al.	2013 BJOG	225	Lab	66.7	94.9	64.3	95.4
Abdelazim IA	2013 Aust N Z Obstet Gynaecol	Authors	Lab	98.3	99	97.4	99.4
Park JS et al.	2013 Ann Lab Med	175	Lab	86.6	95.6	65	98.7
Church DL et al.	2011 Diag Microbiol Infect Dis	231	Lab	100	100	100	100
De Tejada BM et al.	2011 Clin Microbiol Infect	695	Obst.	85	96.6	85.7	96.3
Young BC et al.	2011 Am J Obstet Gynecol	559	Lab	90.8	97.6	92.2	97.1
El Helali N et al.	2009 Clin Infect Dis	968	Lab	98.6	99.6	97.8	99.7

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Intrapartum PCR: Inclusion rate

- Bias linked to low inclusion of antenatally positive detected women
- 100% inclusion rate is utopian:
  - Delay before delivery too short, high workload
  - Technical problems, lack of involvement in the study.

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Intrapartum PCR: Handling

- Test easy to perform « a priori » BUT…
- Many difficulties encountered by midwives :
  - Sample preparation
  - Proper breaking into the cartridge
  - Loading in the instrument
- Large team, high turn-over

→ **Continuous training required**

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Conclusion (1)

- **Intrapartum screening:**
  - Proven clinical value
  - Recommended by new European directives
  - Cost-effectiveness remains to be demonstrated
- **Test Xpert GBS :**
  - Sensible et specific
  - Fully automated
  - Fast result
  - Feasible in point-of-care, 24h/24
  - Easy to perform…

BUT…

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Conclusion (2)

Necessary supervision by the lab :

- Careful training of operators
- Verification of test performance before routine implementation
- Daily technical supervision
- Involvement of gynecologists:
  - ensure adequate inclusion rates
  - integrate the result of the rapid test in the care of the patient

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Conclusion (3)

Is the Xpert® GBS test enough robust to be universally recommended as a POCT ?

Desired developments at Cepheid :

- Internal control checking for human cells
- Simplifying the interface of the GeneXpert system

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Today GBS is 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**

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History of vaccine development

MATERNAL IMMUNIZATION

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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 ?**

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CONTENT

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

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Streptococcus agalactiae or GBS

Gram positive cocci
β-hemolytic
Encapsulated → 1 of major virulence factors

10 capsular serotypes (Ia, Ib, II-IX)

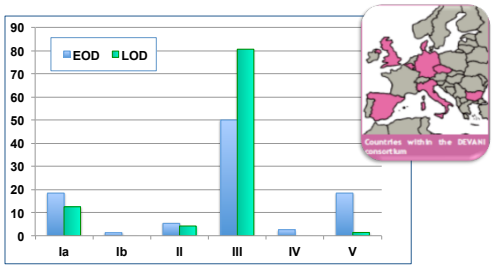
Numerous surface proteins (α- and β-C, rib, Sip, pilus islands 1, 2a & 2b, etc)

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

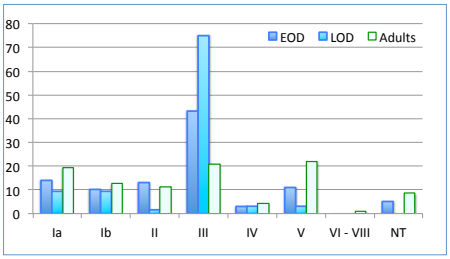
Distribution (%) of capsular types of GBS isolated in neonatal disease

(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)



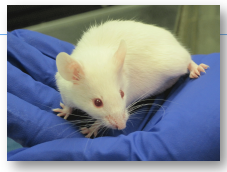
236 neonatal EOD; 64 neonatal LOD; 721 adults

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

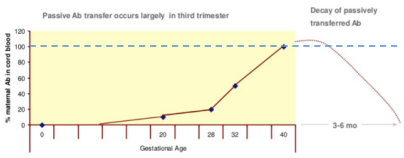
Long-standing data supports protection of maternal anti-CPS Ab

- 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***

Maternal vaccination allows infant protection

- Placental transfer increases markedly > 32 weeks



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

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

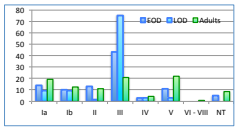
CPS
Conjugate CPS
Surface proteins
Pili proteins
NN fusion protein

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

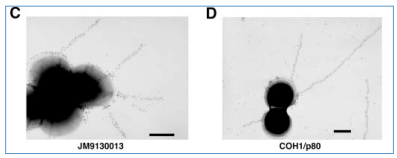
Knowledge of complete GBS genome

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

D.Maione et al, Science 2006

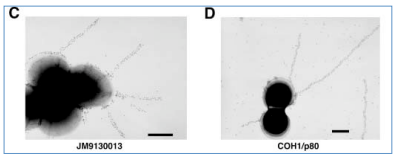
  - 312 surface proteins were cloned
  - 4 provide a high protective humoral response in mouse
    - Sip and 3 others
    - The 3 other proteins = « pilus like structures »
      - PI 1, PI 2a & 2b

GBS « pilus like structure »



GBS « pilus like structure »

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

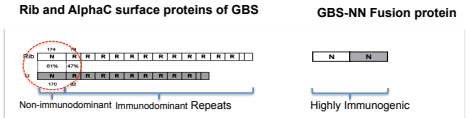


Protein-based Vaccines

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



Cell Host & Microbes 2, 427-434, 2007

MINERVAX

Protein-based Vaccines

GBS-NN fusion protein

From Rib and AlphaC surface proteins of GBS

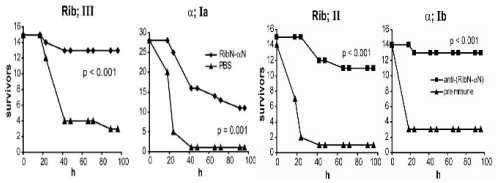
- Based on novel vaccine epitopes identified in the N-terminal regions of the Rib and AlphaC surface-proteins of GBS
- Vaccine candidate is a non-glycosylated fusion protein
- Highly immunogenic and anti-GBS-NN antibodies more protective than antibodies to full-length proteins

MINERVAX

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

Protein-based Vaccines

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



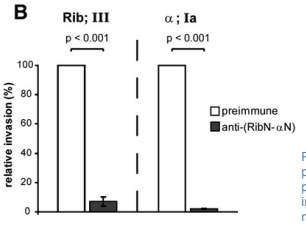
Mice immunized with GBS-NN in alum, boosted after 4 weeks and challenged 2 weeks later.

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

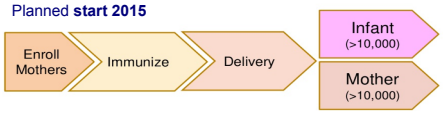
CANDIDATE VACCINES
What is ongoing ?

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

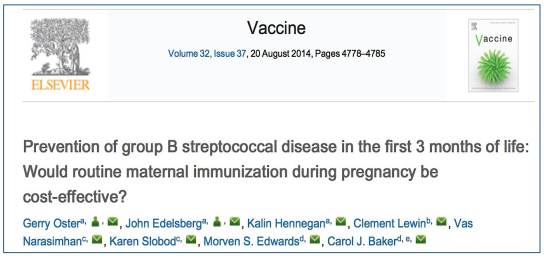
Minervax GBS Vaccine

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**

- **Phase 1 study will start in UK (announced 2 june 2015)**

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*
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- GBS vaccine Phase III trial


CONCLUSION
Take home messages
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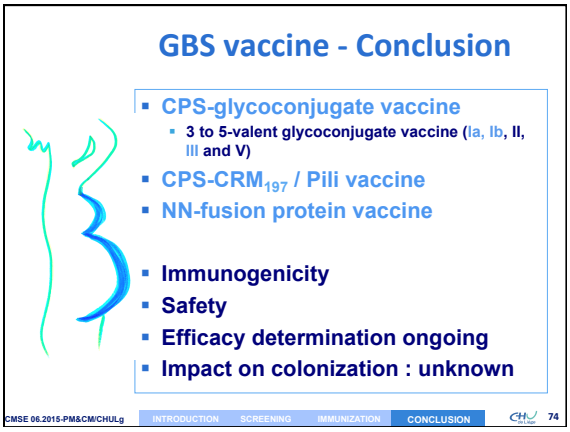
GBS vaccine - Conclusion
CPS-glycoconjugate vaccine
3 to 5-valent glycoconjugate vaccine (Ia, Ib, II, III and V)
CPS-CRM197 / Pili vaccine
NN-fusion protein vaccine
Immunogenicity
Safety
Efficacy determination ongoing
Impact on colonization : unknown
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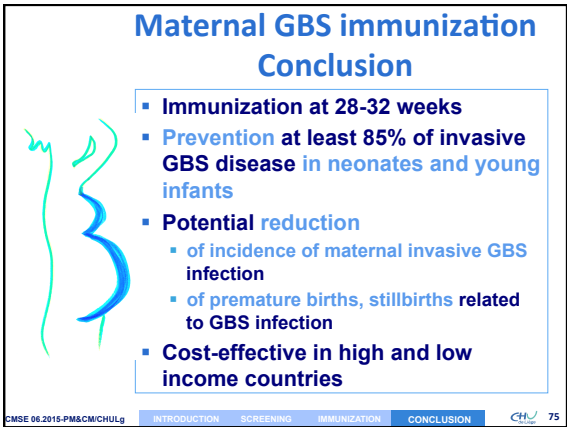
Maternal GBS immunization
Conclusion
Immunization at 28-32 weeks
Prevention at least 85% of invasive GBS disease in neonates and young infants
Potential reduction
of incidence of maternal invasive GBS infection
of premature births, stillbirths related to GBS infection
Cost-effective in high and low income countries
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Thank you
for your attention !
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