# Perinatal Group B Streptococcal Disease

**Pierrette Melin**

*Belgian National Reference Centre for GBS*
*Microbiology, University of Liege, Belgium*
*Clinical Microbiology, University Hospital of Liege*



## Content

- History and historical context of perinatal GBS disease
- Early and contemporary epidemiology
- Pathogenesis and risk factors
- Prevention strategies through
  - Maternal intrapartum chemprophylaxis
    - Evolution of policies, effectiveness and concerns
    - Towards European consensus
  - Maternal immunization



## INTRODUCTION & BURDEN



## *Streptococcus agalactiae* or GBS

Rebecca Lancefield
1895-1981

**Gram positive cocci**
- Encapsulated
- Catalase -
- β-hemolytic
- CAMP test +
- Hippurate +
- Esculine-
- Orange pigment

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

**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**

## Group B streptococcal diseases in neonates

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

**GLOBAL public health major concern !**

**Also in developing countries**

- **Maternal morbidity**
  - **Along pregnancy**
  - **Peripartum**
- **Serious diseases among elderly and adults with underlying diseases**
  - **Significant mortality**



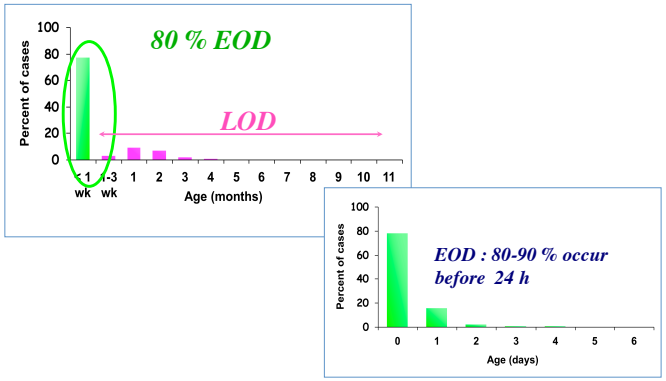
## GBS Neonatal Infections

*A. Schuchat, Clin Microb Rev 1998;11:497-513*



## GBS Neonatal Infections

*A. Schuchat, Clin Microb Rev 1998;11:497-513*

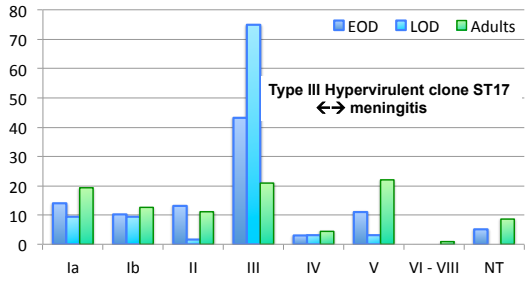





## GBS Neonatal Infections

| | EOD | LOD |
|---|---|---|
| **Incidence per 1,000 live births** | 0.3 – 3 | 0.5 |
| **Onset** | 0 – 6 days (or 0-72 hrs) | 1 week – 3 months (up 1 y) |
| **Mean age at onset** | 12 hrs | 1 month |
| **Transmission** | Vertical<br>Intrapartum | Horizontal (vertical ?)<br>At delivery<br>Nosocomial<br>In the community |
| **Portal of entry** | Inhalation → pneumonia → translocation into bloodstream | Likely intestinal |
| **Clinical presentation** | Respiratory distress with fulminant pneumonia<br>Sepsis<br>(Meningitis 5-15%) | Fever<br>Bacteremia<br>Meningitis (25-70%)<br>(Cellulitis, osteomyelitis) |
| **Mortality** | < 10 %<br>(→ 40 % in very premature) | 0 - 6% |
| **Capsular serotypes** | All (Ia, III, V) | III, mainly<br>Hypervirulent clone ST17 /meningitis |

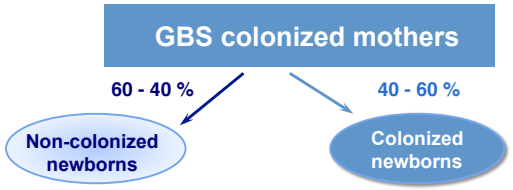
## Distribution (%) of capsular types of GBS isolated in Belgium from different groups of patients (1998-2007)




236 neonatal EOD; 64 neonatal LOD; 721 adults

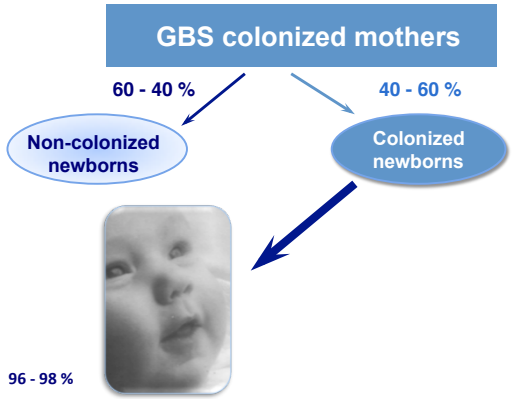
BIT Ped.2013.10/PM INTRODUCTION & BURDEN GUIDELINES SCREENING VACCINE CONCLUSION 9

## GBS EOD vertical transmission



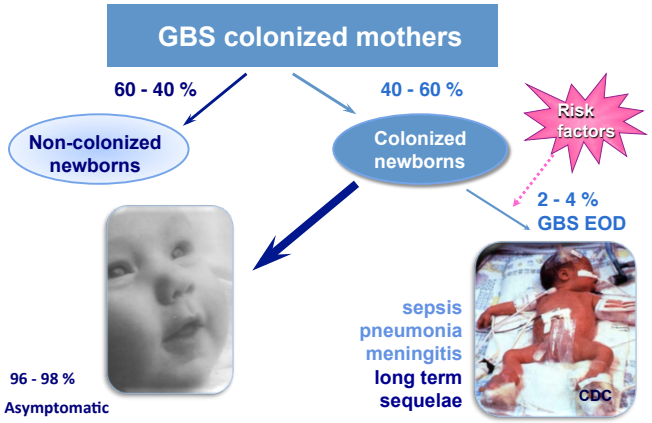

BIT Ped.2013.10/PM INTRODUCTION & BURDEN GUIDELINES SCREENING VACCINE CONCLUSION 10

## GBS EOD vertical transmission




BIT Ped.2013.10/PM INTRODUCTION & BURDEN GUIDELINES SCREENING VACCINE CONCLUSION 11

## GBS EOD vertical transmission




BIT Ped.2013.10/PM INTRODUCTION & BURDEN GUIDELINES SCREENING VACCINE CONCLUSION 12

## GBS maternal colonization

**Risk factor for early-onset disease (EOD) :**
***vaginal GBS colonization at delivery***

- **GBS carriers***
  - **10 - 35 % of women**
  - **Clinical signs not predictive**
  - **Dynamic condition**
  - **Intestinal reservoir**
  - **Prenatal cultures late in pregnancy can predict delivery status**

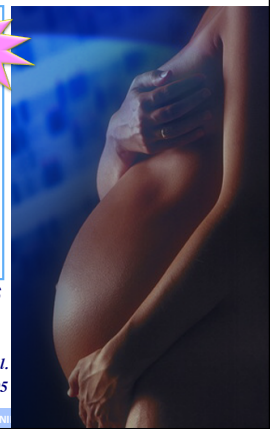
*: Carriage not restricted to women !

BIT Ped.2013.10/PM | INTRODUCTION & BURDEN | GUIDELINES | SCREENING | VACCINE | CONCLUSION | 13

## Additional Risk Factors for Early-Onset GBS Disease

- **Obstetric factors*:**
  - **Prolonged rupture of membranes,**
  - **Preterm delivery,**
  - **Intrapartum fever**
- **GBS bacteriuria***
- **Previous infant with GBS disease***
- **Immunologic:**
  - **Low specific IgG to GBS capsular polysaccharide**

Risk factors



***: No difference in occurrence either in GBS Positive or Negative women, except intrapartum fever***

*Lorquet S., Melin P. & al.*
*J Gynecol Obstet Biol Reprod 2005*

BIT Ped.2013.10/PM | INTRODUCTION & BURDEN | GUIDELINES | SCREENI

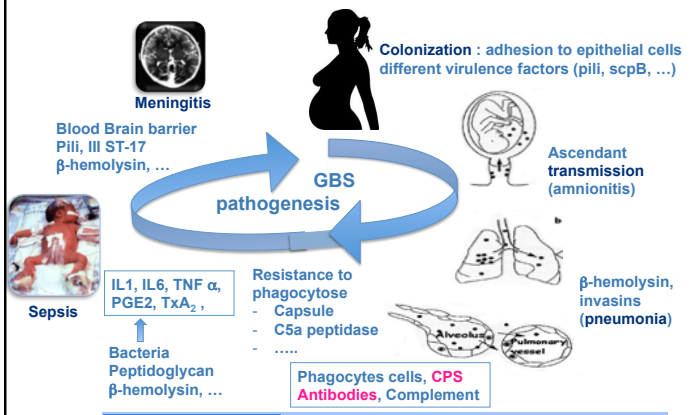
## GBS EOD - Belgian data

- **Incidence**
  - **1985 -1990: 3/1000 live births**
  - **1999, estimation : 2/1000 live births**
  - **2010, estimation : < 1/1000 live births**
- **Meningitis : 10 %**
- **Mortality : 5 -10 %**
- **60 % EOD (130 cases) : WITHOUT any maternal/ obstetric risk factor except colonization**
- **Prenatal screening**
  - **Recto-vaginal cultures : 13-35 % GBS Positive**

*P. Melin - 2001, 2007 - Reference laboratory for GBS.*

BIT Ped.2013.10/PM | INTRODUCTION & BURDEN | GUIDELINES | SCREENING | VACCINE | CONCLUSION | 15

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

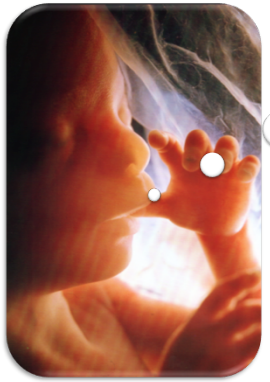



BIT Ped.2013.10/PM | INTRODUCTION & BURDEN | GUIDELINES | SCREENING | VACCINE | CONCLUSION | 17

- Universal prenatal screening-based strategy
- Risk-based strategy
- No guideline

## GUIDELINES FOR PREVENTION OF GBS PERINATAL DISEASE



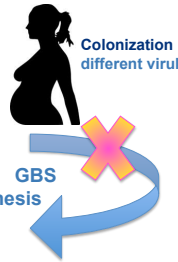


*Which prevention strategy for GBS perinatal diseases ?*

- Intrapartum antibioprophylaxis (IAP)
- Immunoprophylaxis



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



**Colonization** : adhesion to epithelial cells
different virulence factors (pili, scpB, …)

GBS pathogenesis

**Intrapartum antibioprophylaxis**
**> 4 (2) hours before delivery**



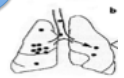
## Stages in the pathogenesis of GBS neonatal EOD : *Bacterial & individual factors*

**GBS vaccine**
*« still expected »*
*Nearly within reach*

**Colonization** : adhesion to epithelial cells
different virulence factors (pili, scpB, …)

GBS pathogenesis

Ascendant **transmission** (amnionitis)



β-hemolysin, invasins (**pneumonia**)


Phagocytes cells, CPS (& pili)
Antibodies, Complement

## Prevention of perinatal GBS EOD

- Intrapartum antibiotics
  - Highly effective at preventing EOD in women at risk of transmitting GBS to their newborns ( ≥ 4 h)

*(clinical trials in late 80s)*


Risk-based strategy
or
Screening-based strategy



## Prevention of perinatal GBS EOD

- Screening-based strategy

**INTRAPARTUM ANTIMICROBIAL PROPHYLAXIS**

**Main goal :**

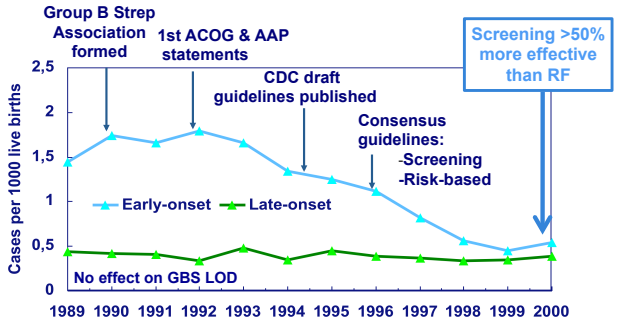
- To prevent 70 to 80 % of GBS EO cases

**Secondary :**

- To reduce peripartum maternal morbidity



## 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*



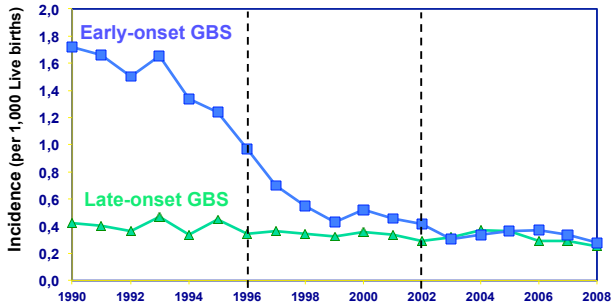
## Why is Screening more protective than the risk-based approach ?

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

Broader coverage of « at-risk » population

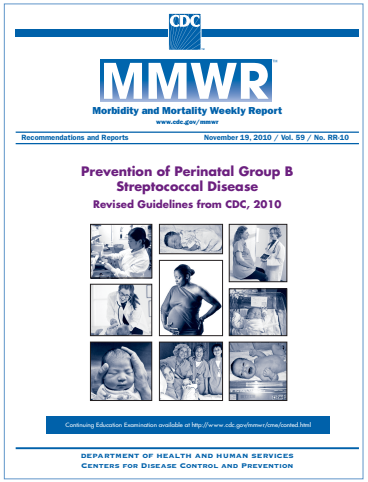
- Captures colonized women without obstetric RF
- High level of compliance with recommendations
- Enhanced compliance with risk-based approach cannot prevent as many cases as universal screening

## 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)*






**CDC, USA, MMWR, Vol 59 (RR-10) August 2010**
***Endorsed by***
***- AAP***
***- ACOG***

***SHC, Belgium July 2003***
***Revision ongoing***

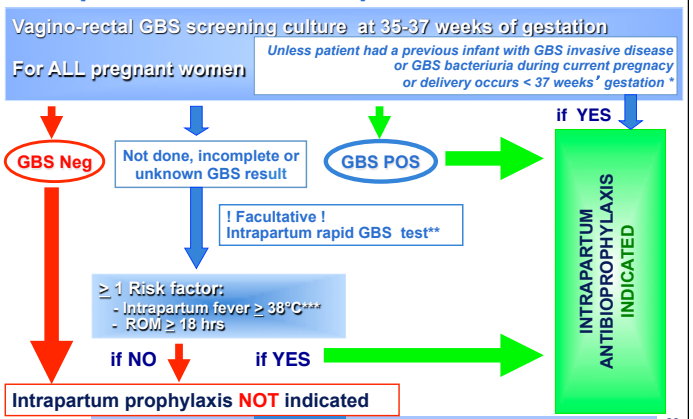



## European strategies for prevention of GBS EOD

- **Intrapartum antibioprophylaxis recommended**
  - **Screening-based strategy**
    - **Spain, 1998, 2003, revised 2012**
    - **France, 2001**
    - **Belgium, 2003, revision ongoing 2013**
    - **Germany, 1996, revised 2008**
    - **Switzerland, 2007**
  - **Risk-based strategy**
    - **UK, the Netherlands, Denmark**
- **No guidelines**
  - **Bulgaria, …**



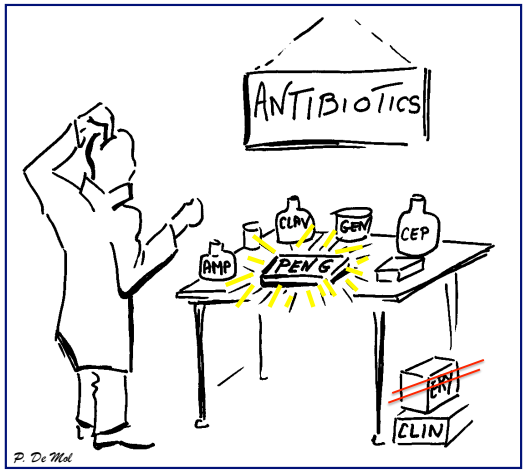
## Universal screening-based strategy for prevention of GBS perinatal disease




Gynecologists
Obstetricians
Microbiologists
Midwives
Neonatalogists

**Adhesion to a common protocol is a key of success**
**Multidisciplinary collaboration is mandatory**








## Intrapartum IV Antibio-Prophylaxis

*(CDC 2010, Belgian SHC 2003)*

- **Penicillin G**
  - ***5 millions U, IV initial dose, then 2,5 to 3 millions U IV every 4 hours until delivery.***
- **Ampicilline**
  - ***2 g IV initial dose, then 1 g IV everye 4 h until delivery.***
  - Acceptable **alternative , but broader spectrum, potential selection of R bacteria**
- ***If penicillin allergy***
  - ***Patients <u>at low risk for anaphylaxis</u>***
    - **Cefazolin, 2 g IV initial dose, then 1g IV every 8 h until delivery.**
  - ***Patients <u>at high risk for anaphylaxis</u>***
    - **Clindamycin, 900 mg IV every 8 hours until delivery.**
    - ***If GBS resistant to clindamycin : use vancomycin***



**Duration of antibiotherapy**

**Threatened preterm delivery**

**Planned caesarean delivery for GBS colonized women**

## Concerns about potential adverse / unintended consequences of prophylaxis

- **Allergies**
  - Anaphylaxis occurs but extremely rare
- **Changes in incidence or resistance of other pathogens causing EOD**
  - Data are complex …
  - BUT Most studies: stable rates of « other » sepsis
- **Changes in GBS antimicrobial resistance profile**



## Concerns : Clinically relevant antimicrobial resistance

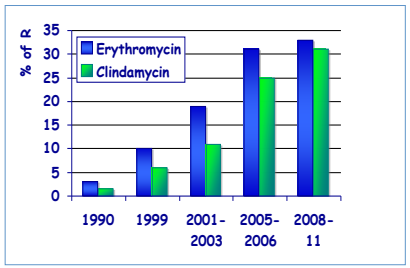
- **Increase of resistance to erythromycin and clindamycin**
- **Susceptibility to penicillin**
  - Very few « not S » **isolates recently characterized in Japan**
    - **Mutation in pbp genes, especially pbp2x**
    - **MIC= 0.25 -1 mg/L**
    - No clinical impact ?

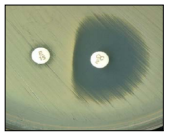
*Noriyuki Nagano et al, AAC 2008*

  - **Very few in the U.S.**
  - **All labs should send to reference lab**
    - **Any « non-S » isolate for confirmation**
    - **All invasive isolates for resistance surveillance**



## Erythromycin and clindamycin resistance among clinical isolates of GBS (Belgian data)



**Resistance to erythromycin :**
**Constitutive + Inducible R (± 75% CR / 25% IR)**

**→ D-Test recommended**



## Concerns about potential adverse / unintended consequences of prophylaxis

- **Management of neonates**
  - **Increase of unecessary evaluation**
  - **Increase of unecessary antimicrobial treatments**

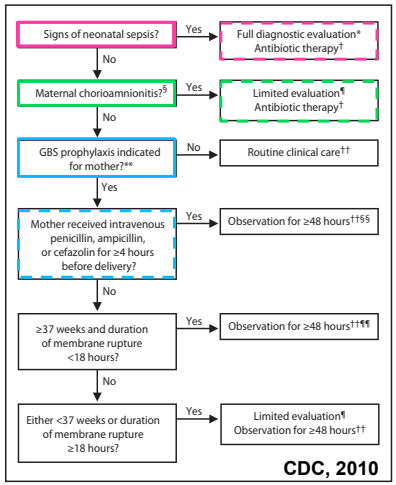
→Algorithm for secondary prevention of EOD among newborns

  - **Symptoms; maternal chorioamnionitis; prophylaxis; gestational age; time of rupture of membrane**

***Rem.:***
*80-90 % of GBS EOD are symptomatic < 24 h of live*

## Secondary prevention of GBS EOD among newborns

**Improved management according to clinical signs and risks**






## Secondary prevention of GBS EOD among newborns

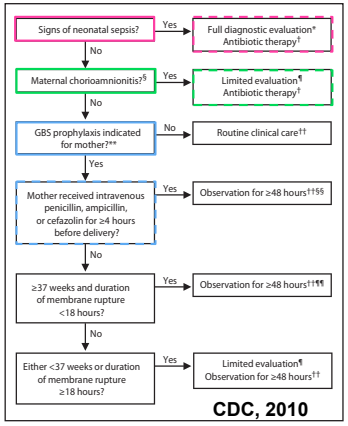
*Full diagnostic evaluation : blood culture + CBC + lumbar puncture (if patient stable) + chest X-ray if respiratory abnormalities

¶Limited evaluation : blood culture + CBC (at birth and/or at 6-12 hours of life)

†Antibiotic therapy should be directed towards the most common causes of neonatal sepsis

§§If ≥37 weeks' gestation, observation may occur at home after 24 hours if other discharge criteria have been met, access to medical care is readily available, and a person who is able to comply fully with instructions for home observations will be present.
If any of these conditions is not met, the infant should be observed in the hospital for ≥48 hours and until discharge criteria are achieved.

¶¶Somme experts recommend a CBC at age 6-12 hours.





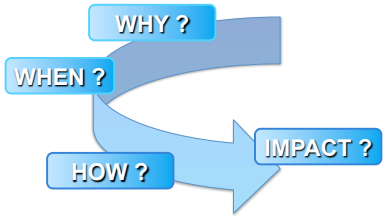

## Remaining burden of GBS EOD Missed opportunities

**In spite of universal screening prevention strategy**
**In spite the great progress**
**Cases still occur**

- **Among remaining cases of EOD**
  - Some may be preventable cases
    - **Missed opportunities for (appropriate) IAP**
    - False negative screening

*Van Dyke MK, Phares CR, Lynfield R et al. N Engl J Med 2009*
*CDC revised guidelines 2010*
*Poyart C, Reglier-Poupet H, Tazi et al. Emerg Infect Dis 2008*
*DEVANI project, unpublished data 2011*






## SCREENING FOR GBS COLONIZATION

## Antenatal GBS culture-based screening

**Goal of GBS screening**

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

- **Critical factors influencing accuracy**
  - Anatomic sites
  - Timing of sampling
  - Screening methods
    - Culture
      - *Procedure*
      - *Media*
    - Non-culture



## Crucial conditions to optimize 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°)
- Request form: To specify prenatal « GBS » screening
- Laboratory procedure

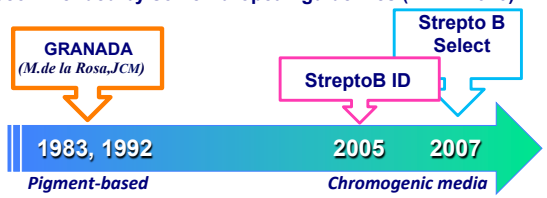
*(CDC 2010 - Belgian SCH 2003)*



## From direct plating on blood agar
## Evolution of culture methods

**Use of selective enrichment broth**
- To maximize the isolation of GBS
- To avoid overgrowth of other organisms

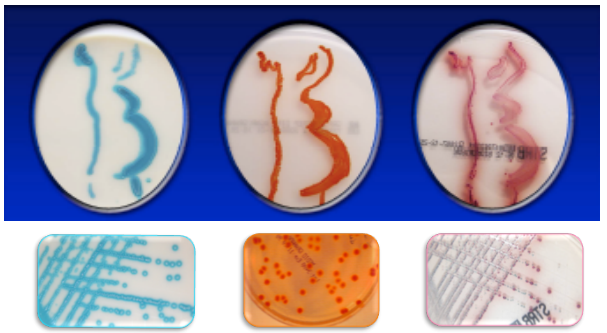
**Use of differential agar media**
Recommended by some European guidelines (+ CDC 2010)






## Which agar or which combination?

+/- Blood agar



**Workload - costs - extra-testing - non β-hemolytic GBS detection to be considered**

## Prenatal culture-based screening: Limiting factors

- **Positive and negative predictive values**
  - False-negative results
    - Failure of GBS culture (oral ATB, feminine hygiene) or new acquisition
    - Up to 1/3 of GBS positive women at time of delivery
    - Continuing occurrence of EO GBS cases
  - False-positive
    - Positive prenatal screening /negative at time of delivery
    - Unnecessary IAP

**Need for more accurate predictor of intrapartum GBS vaginal colonization**



## Prenatal culture-based screening: Limiting factors

- **Unknown GBS status at presentation for delivery**
  - Screening performed but result not available
  - Women with no prenatal care

→ Risk based strategy
- 60% at GBS risk not identified
- > 10% of unnecessary IAP

**Need for rapid accurate predictor of intrapartum GBS vaginal colonization**



## Alternative to GBS prenatal screening: intrapartum screening
### Theranostic approach

**Turnaround time**
collect specimen at admission

Optimal management of patient

Specimen Analysis "POCT" ?

Results

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

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



## Intrapartum screening theranostic approach: expected advantages

- Inclusion of women without prenatal screening/care
- Identification of women with change of GBS status after 35-37 wks gestation
- Increased accuracy of vaginal GBS colonization status at time of labor & delivery

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

→ Improvement of prevention

## Real Time PCR for intrapartum screening

- **Advance in PCR techniques & development of platforms**
  - **BD GeneOhm™ Strep B Assay (+/- 1 hr) (in laboratory)**
  - **Xpert GBS, Cepheid (35-45 min)** (can be performed as a POCT)




## Real-time PCR, very promising, BUT …

- **Rapid, robust & accurate technology**
- **Still an expensive technology** (specific equipment)
  - Cost effective ?
    - *Need for more cost-effective clinical study*
- **Logistic**
  - 24 hours 7 days
  - In the lab?
  - In the obstetrical department as a POCT ?
- **In combination with prenatal screening strategy ?**
  - CDC 2010 : for women with premature delivery or no prenatal care
- **No antimicrobial result**
  - In the future detection of R genes, but mixed microbiota !



**Prevention of GBS EOD and LOD**

**Prevention of maternal diseases**

## VACCINE



## Background

- **Correlate between maternal low level off CPS type Ab at time of delivery and risk for development of GBS EOD**

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

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

## GBS Vaccines, since the 1980s Challenges

### Capsular polysaccharide vaccines

- 10 serotypes
  - Different distributions
    - EOD, LOD, invasives infections in adults
    - Geographically and along time
- Conjugated vaccines
- Multivalent vaccines Ia, Ib, III, V
- Clinical studies
  - Immunogenicity
  - Safety
  - Efficacy: scheduled/ongoing (Phase 3 studies)



## GBS Vaccines

### 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

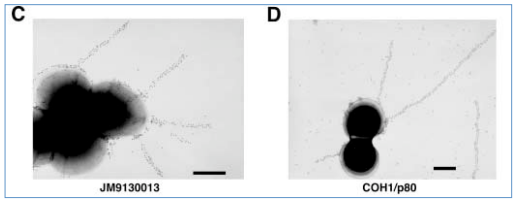
- Comparaison of genomes from 8 different GBS serotypes

*D.Maione et al, Science 2006*

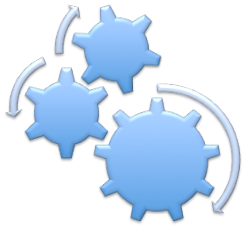
  - 312 surface proteins were cloned
  - 4 Provide a high protective humoral response in mouse
    - Sip and 3 others
    - The 3 other proteins = « pilus like structures »

## GBS « pilus like structure »

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





## CONCLUSION
## Take home messages



## In Europe, as globally

### Neonatal GBS diseases

- EOD and LOD, a public health concern
- IAP efficient for prevention of EOD
  - Best strategy still a matter of debate
  - Not 100% efficient
  - No effect on LOD
- IAP not widely recommended
- Need better data assessing more accurately the true burden

### GBS vaccine eagerly expected

- Appears to be within reach



## Summary

### "Screening" Prevention strategies

- Culture-based GBS prenatal screening
  - To optimize critical factors
  - Improved by selective differential agars
  - False +/False - !
  - Expected improvement from transport ssystem
- Rapid intrapartum screening
  - Real time PCR
    - Yes but costs, logistic, …
    - Need for more clinical and cost effectiveness trials