Prevention of GBS disease

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CONTENT

- Introduction
- Screening for GBS colonization
  - Old and new tools
- Antibiotic resistance
  - Threat to therapy ?
- Maternal immunization
- Take home messages

INTRODUCTION & BURDEN

Streptococcus agalactiae or GBS

Rebecca Lancefield 1895-1981

Gram positive cocci
β-hemolytic
Encapsulated

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

Streptococcus agalactiae or GBS

Streptococcus agalactiae clones infecting humans were selected and fixed through the extensive use of tetracycline

- Genome-based phylogeny reveals the expansion of a few clones
- Human GBS belong mainly to a small number of TcR clones

V.Dacunha, MR.Davies, …, C.Poyart and P.Glaser
In *Nat Commun.* 2014 Aug 4;5:4544. doi: 10.1038/ncomms5544.

1887, Noccard-Mollereau, bovine mastiti
1933, Group B Antigen
1964, severe neonatal sepsis, *Eickhoff et al 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

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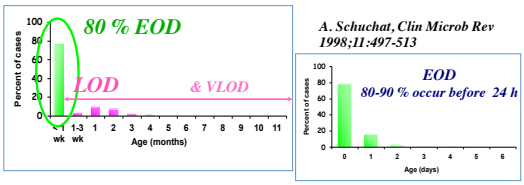

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Group B streptococcal diseases in neonates

- 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

GLOBAL health major challenge !
Also in developing countries

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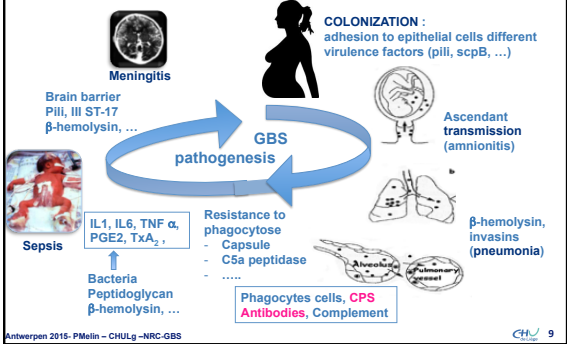
Stages in the pathogenesis of GBS neonatal EOD : *Bacterial & individual factors*



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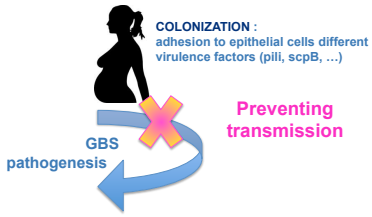
Stages in the pathogenesis of GBS neonatal EOD : *Bacterial & individual factors*



Intrapartum antibioprophylaxis
> 4 (2) hours before delivery

Highly effective in preventing GBS EOD *(1st clinical trials in late 80s)*

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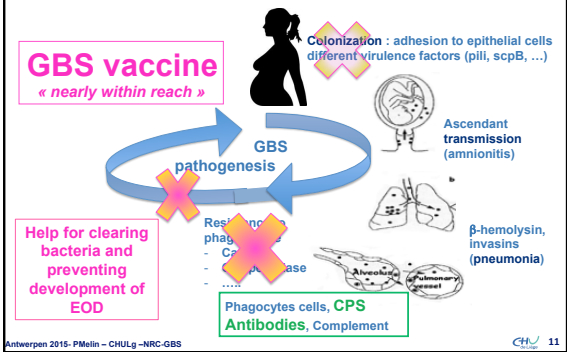
Stages in the pathogenesis of GBS neonatal EOD : *Bacterial & individual factors*

GBS vaccine
« nearly within reach »



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Screening for GBS colonization
OLD & NEW TOOLS

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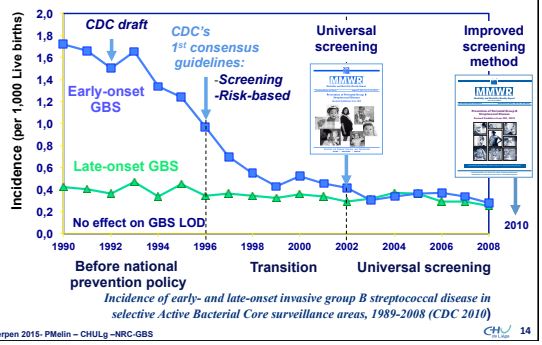
OBJECTIVES

To provide a comprehensive picture of current and coming practices for GBS screening

Culture methods *versus* NAAT
Antenatal *versus* intrapartum

- To emphasize critical criteria for success
- To identify some possibilities for improvement
- To point out advantages and drawbacks

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, …

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
    - Culture
      - *Procedure*
      - *Media*
    - Nucleic Acid Amplification Test (NAAT)

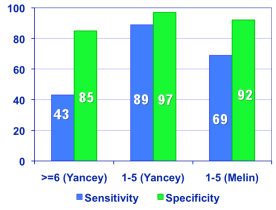
Crucial conditions to optimize universal antenatal SCREENING

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°)
Request form	To specify prenatal « GBS » screening
Laboratory procedure	

(CDC 2010 - Belgian SCH 2003)

Optimal time for screening
35-37 weeks gestation

Culture-based screening done 1 to 5 or ≥ 6 weeks before delivery *(Yancey, 860 cases; Melin, 531 cases)*



Not 100 % as colonization is dynamic

Yancey MK et al. Obstet Gynecol 1996;88:811-5

Optimal time for culture-based screening
35-37 weeks gestation

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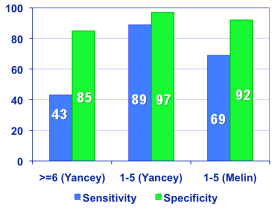


Melin, 13-16% GBS Pos
PPV= 56%
NPV= 95%
or 5% False negative
or 30% of GBS pos in labor not detected with antenatal screening !

Yancey MK et al. Obstet Gynecol 1996;88:811-5

Remaining burden of GBS EOD
Missed opportunities

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

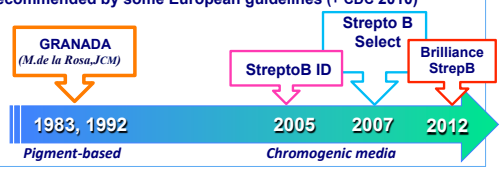
- Among remaining cases of EOD
  - Some may be preventable cases
    - Missed opportunities for (appropriate) IAP
    - False negative screening

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

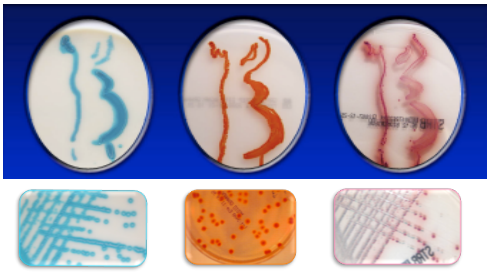
From direct plating on blood agar
Evolution of culture methods

Use of selective enrichment broth (Lim broth, e.g.)
- 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

Crucial conditions to optimize SCREENING

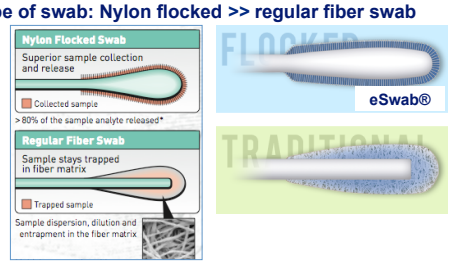
- WHEN — 35-37 weeks
- WHO — ALL the pregnant women
- Specimen — Vaginal + rectal swab(s)
- Collection — WITHOUT speculum
- **Transport** — **Transport/collection device/condition**
  (non nutritive medium: Amies/Stuart or Granada like tube) (type of swab)(Length and T°)
- Request form — To specify prenatal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

(CDC 2010 - Belgian SCH 2003)

Crucial conditions to optimize SCREENING

Transport-collection system & transport-storage condition

- Type of swab: Nylon flocked >> regular fiber swab



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Crucial conditions to optimize SCREENING

Transport-collection system & storage condition

- Recommandations CDC, USA (2010)
  - Non nutritive media: Amies or Stuart without charcoal
  - Storage at 4°C or RT 1-4 days
    - Or Granada like tubes ??
- Recommandations CSS, Belgium (2003)
  - Non nutritive media: Amies or Stuart without charcoal
  - Storage maximum 48h at 4°C

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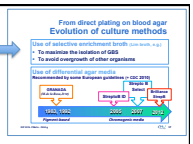
ICAAC 2013
53rd ICAAC | SEPT 10-13 | Denver, CO



IMPROVEMENT OF TRANSPORT CONDITION OF SWABS FOR GROUP B STREPTOCOCCAL (GBS) SCREENING

P. Melin, M. Dodémont, G. Sarlet, R. Sacheli, et al.
National Reference Centre for GBS, University Hospital of Liège, Liège, Belgium

To sustain viability
Whatever is storage T° for a few days

Use of a selective enrichment Lim broth as transport media

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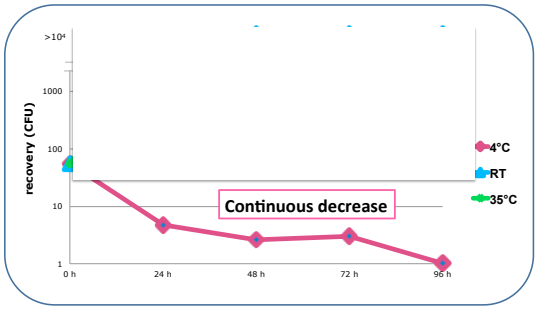
Results:

Recovery of GBS in Lim BD at 4°C, RT and 35°C

(Clinical studies ongoing)



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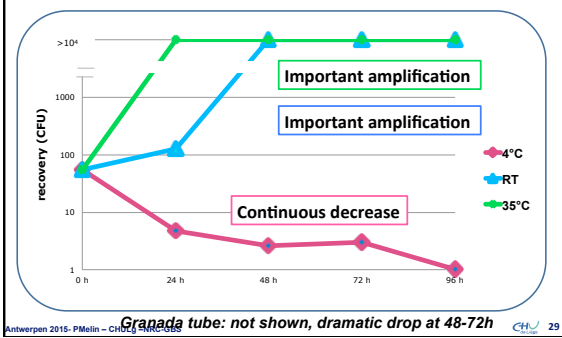
Results:

Recovery of GBS in Lim BD at 4°C, RT and 35°C

(Clinical studies ongoing)



Granada tube: not shown, dramatic drop at 48-72h

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Transport conditions to be recommended for optimizing GBS antenatal screening

Belgian Health Superior Council, 2015

- Transport system
  - Use of a selective enrichment Lim broth with a flocked swab *(BD, Copan, bioMérieux, i.e.)*
- Transport and storage condition
  - At RT° (up to 35°C)
  - As soon as possible
    - Viability sustained at least 4 days
- Remark
  - If use of Amies or Stuart medium (non nutritive medium)
    - To be processed as soon as possible within 24 hours (max 48 h)

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Antenatal culture-based screening combined with amplification molecular test

NAAT performed from Lim enrichment broth Broth
- ❑ The Xpert GBS LB assay
- ❑ The LAMP Illumigene GBS Assay

Clinical evaluations
- Speed: time to result minus one day
- Accuracy: good comparison to reference culture
- Cost, logistic, training: very important to consider

Antenatal culture-based screening combined with *illumigene*® Group B Streptococcus assay

A loop mediated isothermal amplification (LAMP) assay by Meridian Bioscience, Inc
- Broth enrichment followed by *illumigene*® GBS
  - Speed and accuracy

Evaluation of the *illumigene*® GBS assay for antenatal screening from Lim broth

CHU Liege & UZ St Lucas, 2012
- Speed and "accuracy"
- Good comparison to reference culture method
- "Easy" to perform BUT not as easy as claimed and training very important

- 90% → 95% sensitivity (PCR)
- 100% specificity
- Identification of an 0.8% additional GBS positive specimen
- Overall cost and logistic to be considered

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

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)

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

Real Time PCR for intrapartum screening

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

Already recommended by CDC for women with no prenatal care, …

Required analytical specification for rapid intrapartum test

- High sensitivity and specificity
  - Minimum 90% and 95% respectively
- Full automation with integrated internal controls
- Easy to perform and interpret by nurses
- Time to result: < 1 hour
- 24 h / 7 days availability

Di Renzo G, Melin P et al. Intrapartum GBS screening and antibiotic prophylaxis : a European consensus conference. J Matern Fetal Neonatal Med 2014;27:1-17

Xpert® GBS for intrapartum screening

- Real Time PCR on GeneXpert system
  - 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

Xpert® GBS for intrapartum screening

(selected paper amongst many others)

Diagnostic Accuracy of a Rapid Real-Time Polymerase Chain Reaction Assay for Universal Intrapartum Group B Streptococcus Screening

Najoua El Helali, Jean-Claude Nguyen, Aïcha Ly, Yves Giovangrandi and Ludovic Trinquart

Clinical Infectious Diseases 2009;49:417–23

- 968 Pregnant women
- Intrapartum Xpert GBS, Cepheid (performed in lab)
  - *vs* intrapartum culture — antenatal culture *(French recom.)* (vaginal swab/CNA-BA)

Sensitivity	98.5%		
Specificity	99.6%		
PPV	97.8%	PPV	58.3%
NPV	99.7%	NPV	92.1%

Xpert® GBS for intrapartum screening

(selected paper amongst many others)

Cost and effectiveness of intrapartum group B streptococcus polymerase chain reaction screening for term deliveries.

El Helali N, Giovangrandi Y, Guyot K, Chevet K, Gutmann L, Durand-Zaleski I

Obstet Gynecol 2012 Apr;119 (4):822-9

2009	2010
Antenatal screening	Xpert GBS intrapartum screening *Performed by midwives as a POCT !!*
11.7% GBS POS	16.7% GBS POS Less GBS EOD & less severe

Cost neutral per delivery

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

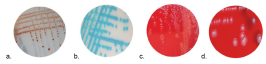
1. To assess the practical and analytical aspects of the implementation of the PCR test Xpert GBS® in Belgium
   - Performed by midwives
   - For all women at onset of labor
2. To evaluate the cost-effectiveness of the intrapartum screening strategy

→ To consolidate the proposal of the European Expert Group

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

Lim & Sub-Culture



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

Test Xpert GBS

Test Xpert GBS: Procedure

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

Test Xpert GBS: 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

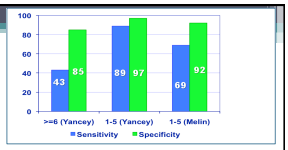
Preliminary results

Culture results
PCR results

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.

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

PCR results

- « Not yet available »
- Difficulties encountered:
  - Wrong manipulations
  - Invalid results

- Pause of the study and revision of protocol

Xpert® GBS for intrapartum screening

(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	85.7 85.7	96 95.6	82.7 85.7	96.7 95.6
Poncelet et al	2013, BJOG	225	Lab	66.7	94.9	64.3	95.4
Abdelazim	2013, Aust NZ Obstet Gynaecol	445	Lab	98.3	99	97.4	99.4
Park et al	2013 Ann Lab Med	175	Lab	86.6	95.6	65	98.7
Church et al	2011 Diag Microbiol Infect Dis	231	Lab	100	100	100	100
De Tejada et al	2011 Clin Microbiol Infect	695	Obst	85	96.6	85.7	96.3
Young et al	2011, Am J Obstet Gynecol	559	Lab	90.8	97.6	92.2	97.1
El Helali et al	2009, Clin Inf Dis	968	Lab	98.6	99.6	97.8	99.7

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Real Time PCR for intrapartum screening

- **Advance in PCR techniques & development of platforms & to be used as a POCT**
  - **Xpert® GBS, Cepheid (35-45 min)**
    - **Already recommended by CDC for women with no prenatal care, …**
- **Easy BUT …**
- **Midwives teams: numbers, turn-over**
- **TRAINING is essential**
  - **Sample preparation**
  - **Proper breaking the swab into the cartridge**
  - **Loading the instrument**
- **To be used under lab control**

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TAKE-HOME MESSAGES

GBS screening

Acknowledged need for improvement of predictive values & logistics

Antenatal screening

- Identified possibilities for improvement of culture method
- NAAT on enrichment broth as an alternative approach

Intrapartum screening or « the desirable approach »

- NAAT available *(but no clindamycin susceptibility result)*
- Some evidence of cost-effectiveness
- Additional studies needed for validation as a POCT

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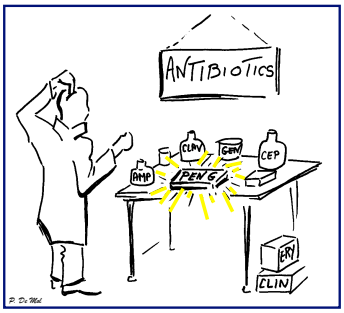

GBS and Antibiotic Resistance

Threat to Therapy ?

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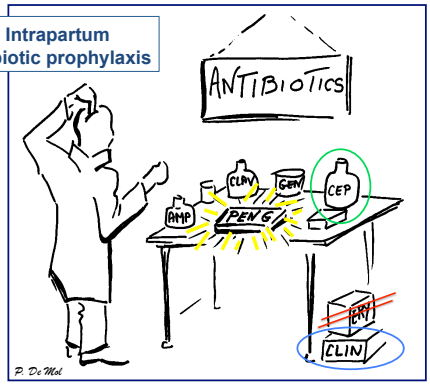
IAP: Intrapartum antibiotic prophylaxis



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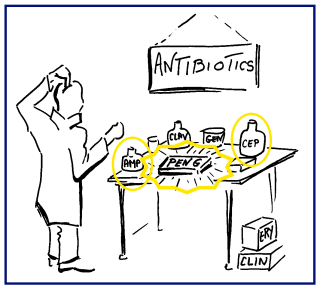
Background

- Intrapartum antimicrobial prophylaxis (IAP)
  - Penicillins = first line drugs
    - In case of IgE mediated allergy (risk of anaphylaxis)
      - Clindamycin, if susceptible
      - Vancomycin, if clindamycin resistant or unknown status
- Treatment of infections
  - Penicillins = first line drugs
    - +/- combination with aminoglycosides in severe infections
  - According to site of infections
    - Macrolides, clindamycine, fluoroquinolones

Antibiotics and GBS in 2014

- Penicillins
  - GBS still fully susceptible to P and most β-lactams
  - Very rare non S GBS (Japan, USA, Canada, … ?)
- Macrolides and lincosamides
  - R on the rise
    - 5 – 35 % R, even more to erythromycin and clindamycin
    - Geographical differences
- Gentamicin
  - High level resistance reported (up to 13% in Argentina)
- Fluoroquinolones
  - Increasing for a decade, mainly in Japan, Korea, China (up to 37%)



Will penicillins remain the gold standard ?

GBS and non-S to β-lactams

- Existence and molecular mechanisms of clinical isolates with reduced Penicillin susceptibility (PRGBS)
  - First report in Japan by Kimura K et al, AAC 2008
  - Following reports from Japan, USA, Canada
    - Penicillin MIC 0.25-1 mg/L
    - Ceftizoxime MIC 4-128 mg/L

Acquisition of amino-acid substitutions in PBP2X and in PBP1A

→ elevation of cephalosporins'MICs

PR GBS versus PR *S.pneumoniae*

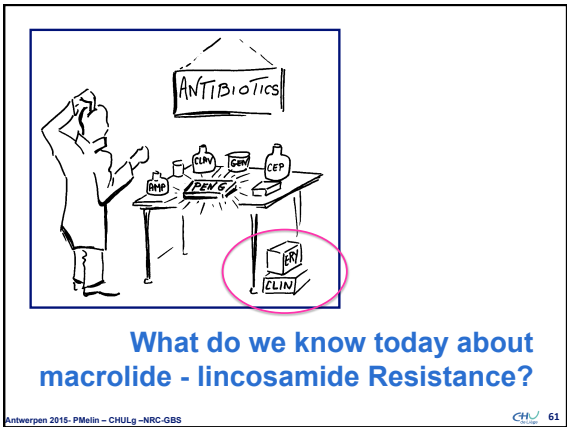
- PR *S.pneumoniae*
  - Penicillin MICs increased by acquiring various amino-acid substitutions in PBPs, including PBP1A and PBP2X
- Why should we not see the same in GBS?
  - Risk of highly resistant cephalosporin GBS
  - Risk of increase of MICs to penicillin

PR GBS detection

→ possibly unrecognized by standard antimicrobial susceptibility methods !!

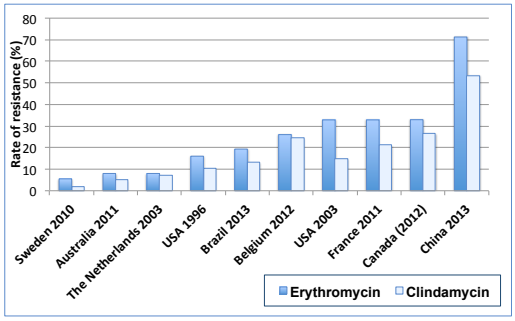
- Recommended methods for initial screening
  - 3-Disk diffusion
    - Oxacillin, ceftizoxime,
    - Ceftibuten (no zone)
  - MICs to oxacillin and ceftizoxime
    - Usually high for PR GBS

Kimura et al, J Clin Microbiol 2009



What do we know today about macrolide - lincosamide Resistance?

Resistance to macrolides/lincosamides
Wide geographical variation of rates



Resistance to macrolides/lincosamides
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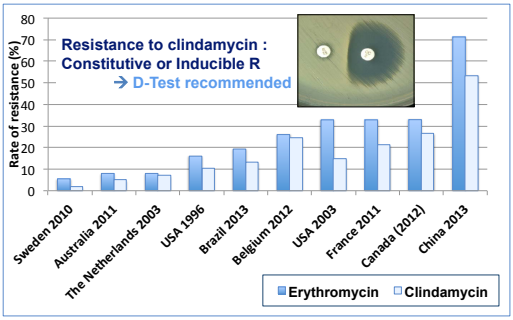
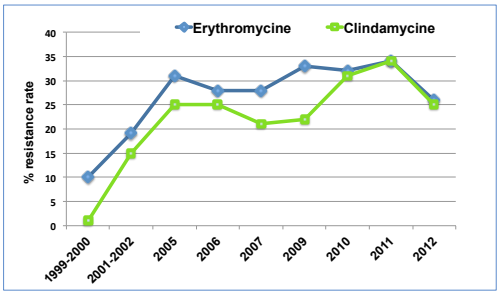


Resistance to macrolides/lincosamides
on the rise (Invasive isolates of GBS Belgium 1999-2012)



MLS acquired Resistance
Phenotypes and genotypes

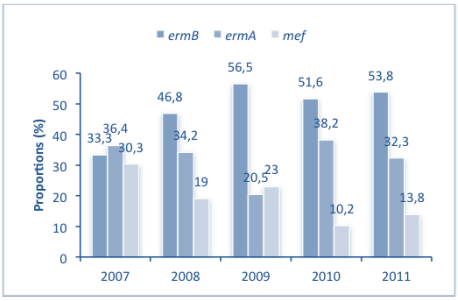
- **Target modification** (*erm* family genes)
  - **Constitutive MLS resistance**
  - **Inducibe MLS resistance (D-zone test)**
  - **Serotype associated** (higher rates: IV, V > III > others)

  Cross resistance to macrolides, lincosamides and streptogramin B

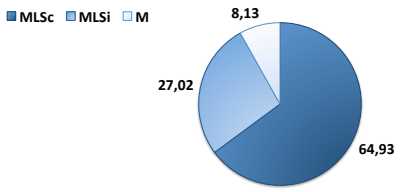
- **Active efflux** (*mef*A gene) → **M phenotype**

  Resistance to 14- & 15- membered ring macrolides (as erythromycin and azithromycin)

Distribution of erythromycin R genes
(French GBS NRC 2007 – 2011)



Distribution of erythromycin R genes among invasive isolates
(Belgian GBS NRC, 2012)



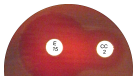
MLS acquired Resistance Phenotypes and genotypes

- Target modification (*erm* family genes)
  - Constitutive MLS resistance
  - Inducibe MLS resistance

  Cross resistance to macrolides, lincosamides and streptogramin B
- Active efflux (*mef*A gene)

  Resistance to 14- & 15- membered ring macrolides (as erythromycin and azithromycin)

- **Enzymatic inactivation or ?** (lnu genes, lsa genes)
  - Clindamycin resistance



Phenotypes L

- L phenotype
  - Inactivation by lincosamide nucleotidyltransférases (*lnu*(B) and *lnu*(C) genes)
    - New Zealand, Canada, USA, Asia, Argentina
- LS_A or LS_AP phenotype
  - Cross resistance to lincosamides, streptogramin A and pleuromutilin
  - *lsa*(C) gene
    - New Zealand *(Malbruny et al., AAC, 2011)*
    - Belgium *(J.Descy et al, LISSSD abstract 100)*
      - *0.6% from1329 isolates (2008-2013)*

Aminosides

Emergence of high-level resistance to gentamicin and streptomycin in *Streptococcus agalactiae* in Buenos Aires, Argentina

U.E.Villar et M.B.Jugo, Rev Esp Quimioter 2013;26:112-115

141 GBS from vagino-rectal swabs

HLR Gentamicin : 13.5%

HLR Streptomycin: 16.3%

Detection methods
- Disks GEN (120 µg) and STR (300 µg)
- MICs to GEN and STR (Etests)
- Agar screening plates (GEN 100mg/L; GEN 500mg/L; STR 2000 mg/L)

Very rarely reported in Europe

Fluoroquinolones

Emerging fluoroquinolone resistance *in Streptococcus agalactiae* in South Korea

M.Ki et al, Eur J Clin Microbiol Infect Dis, 2012:3199-3205

221 GBS from pregnant women + 838 patients

2006-2008

R unexpectly high:

Ciprofloxacine 9.3%; Levofloxacine 9.5%; Moxifloxacine 0.8%

Mutation detected in gyrase and topoisomerase genes

+/- 4% in Belgian isolates

Fluoroquinolones

High prevalence of Fluoroquiolone-resistant Group B Streptococci among clinical isolates in China and predominance of sequence type 19 with serotype III

Hui Wang et al, AAC, 2013:1538-41

146 GBS from different locations in China, 2011

Levofloxacine 37.7%

80% belonged to GBS ST19/serotype III clone

with GyrA-ParC-ParE triple substitution

this clone carrying *erm* and *mef* genes

Clonal expansion of multi-drug-resistant GBS
→ concerns about it s future spread

Tetracycline Resistance

- The most frequent antimicrobial resistance marker
- > 85% of GBS isolated from human infection

Streptococcus agalactiae clones infecting humans were selected and fixed through the extensive use of tetracycline

By V. Dacunha, MR. Davies, …, C. Poyart and P. Glaser

In *Nat Commun.* 2014 Aug 4;5:4544. doi: 10.1038/ncomms5544.

GBS Antibiotic Resistance : where are we going?

EPILOGUE

- Emergence of resistance is unavoidable
  - But how fast ?
- Transmission of Resistant genes « in package » !
  - → Risk of increase of multi-resistance
  - → Threat for both prophylaxis and therapy
- Emphasize the need for
  - careful epidemiologic monitoring
  - good clinical laboratory AST practice

Antibiotics	About Resistance	Epidemio. surveillance by Nat.Ref.C.	AST - Routine lab methods
Penicillin and other β-lactams	• *Still very rare* • *Possibly unrecognized*	Mandatory	Initial screening by with 3-disks diffusion *To implement in clinical labs worldwide ?*
Erythromycin – Clindamycin	• *Globally on the rise* • *National differences* • *Evolution of genetic supports* • *L phenotype emerging*	Mandatory	• AST for E & C • D-zone Test synergy testing if E R *Already recommended*
Gentamicin	• *Emerging in some countries* • *Not routinely screened*	Mandatory	HLR determination for severe infections Method ???
Fluoroquinolones	• *Emerging in Asia* • *Rare elsewhere*	Mandatory	No special trick

History of vaccine development

MATERNAL IMMUNIZATION

Maternal GBS immunization

Could maternal immunization be an alternative ?

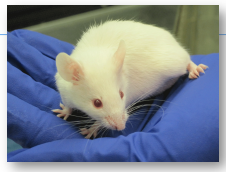
- Protection against both EOD & LOD ?
- Bypassing concerns related to antimicrobial resistance ?
- Cost-effectiveness ?
- Adjunctive to screening & IAP ?

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

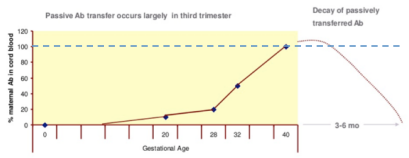
- Disappointment from studies of uncoupled first generation purified native GBS CPS vaccines in healthy adults
- Demonstration of feasibility of vaccine prevention of GBS disease
- Need for improvement of immunogens
- Success story of polysaccharide-protein conjugate vaccine technology in preventing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

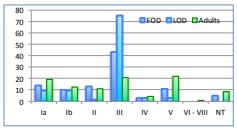
CPS
Conjugate CPS
Surface proteins
Pili proteins
NN fusion protein

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

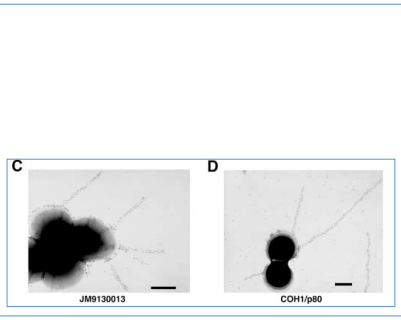
Knowledge of complete GBS genome

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

D.Maione et al, Science 2006

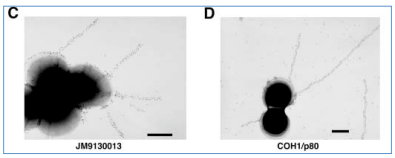
- 312 surface proteins were cloned
- 4 provide a high protective humoral response in mouse
  - Sip and 3 others
  - The 3 other proteins = « pilus like structures »
    - PI 1, PI 2a & 2b

GBS « pilus like structure »



GBS « pilus like structure »

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

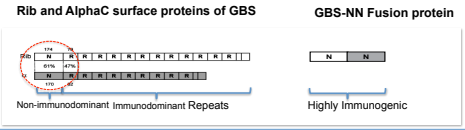


Protein-based Vaccines

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



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

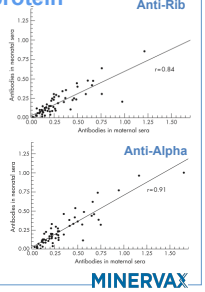
MINERVAX

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**

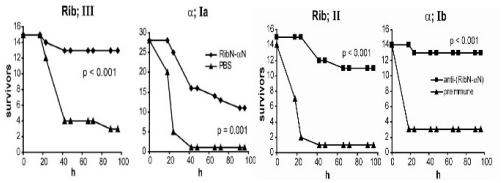


Arch Dis Child Fetal Neonatal Ed 91:F403-408, 2006

MINERVAX

Protein-based Vaccines

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



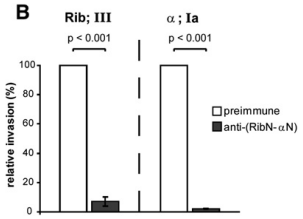
Mice immunized with GBS-NN in alum, boosted after 4 weeks and challenged 2 weeks later.

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

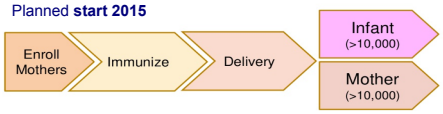
CRM-Conjugate CPS
NN Fusion protein
Cost effectiveness studies

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?

ELSEVIER
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

GBS VACCINE 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

Antwerpen 2015- PMelin – CHULg –NRC-GBS 109

Thank you !

Antwerpen 2015- PMelin – CHULg –NRC-GBS 110