

**CHU** de Liège Université de Liège

## Prevention of Perinatal Group B Streptococcal Disease

### POC test for GBS screening in delivery room


Pierrette Melin  
National Reference Centre for group B streptococci  
Clinical Microbiology, University Hospital of Liege, University of Liege, Belgium

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## BACKGROUND

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## Group B streptococcal diseases in neonates

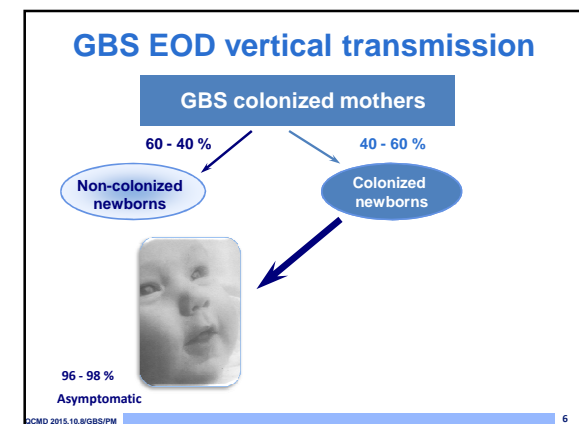
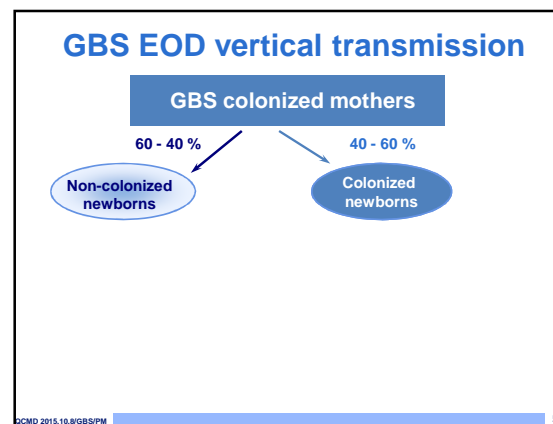
- Since the 1970s, leading cause of life-threatening infections in newborns
  - Neonatal illness/death
    - Early- & Late Onset Disease
    - Long-term disabilities

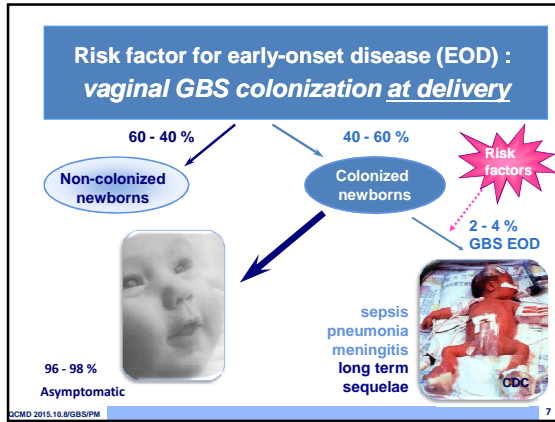
**GLOBAL public health major concern !**

Also in developing low income countries

- Early Onset Disease (EOD)
  - Incidence :
    - Before mid-1990s: 3/1000 live births
    - Today, prevention era : 0.3 - 1/1000 live births
  - Meningitis : 10 %
  - Mortality : 5 - 10 % (20-30% if premature)

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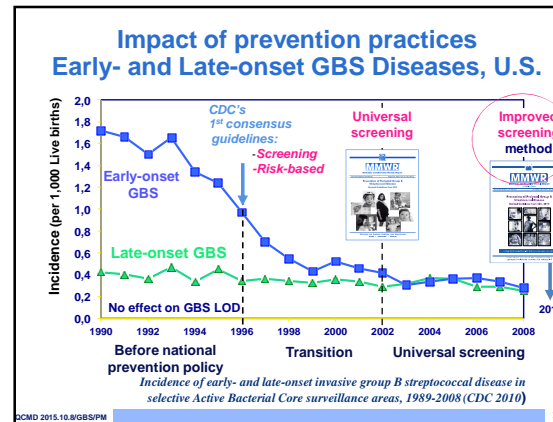
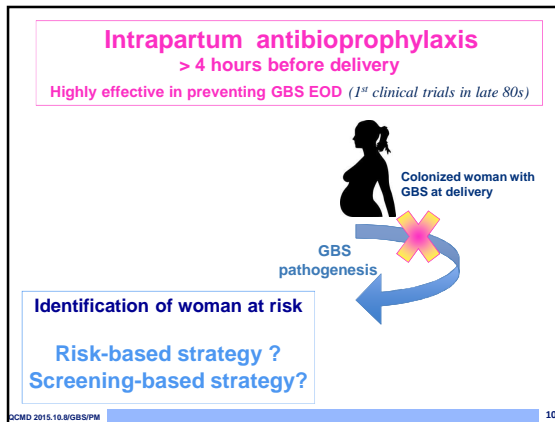
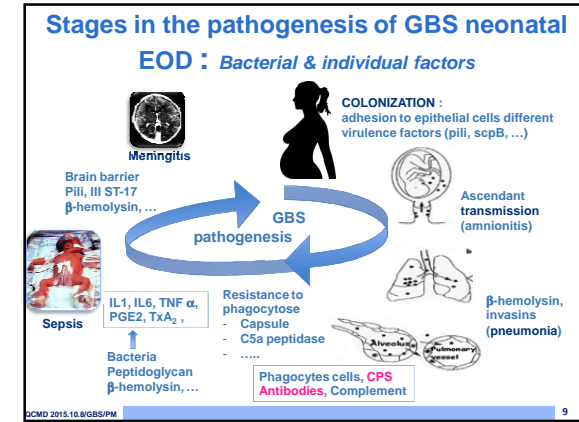




### GUIDELINES FOR PREVENTION OF GBS PERINATAL DISEASE

- ⊙ Intrapartum antibioprophyllaxis
  - Universal prenatal screening-based strategy
  - Risk-based strategy
  - No guideline
- ⊙ Immunoprophyllaxis

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### Antenatal GBS culture-based screening

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

Incidence to 0.3-1 per 1,000 live births

- Factors influencing accuracy
  - Swabbed anatomic sites
  - Timing of sampling
- Remaining burden of streptococcal early onset disease  
 Missed opportunities / False negative screening (antenatal culture based screening)
- Media

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### Antenatal GBS culture-based screening

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

- Critical factors influencing accuracy**
  - Swabbed anatomic sites
  - Timing of sampling (35-37 wks)
  - Screening methods (antenatal vs intrapartum)
    - Culture
      - Procedure
      - Media
    - Non-culture
      - Nucleic Acid Amplification Test (NAAT)

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### Theranostic approach

Alternative to GBS prenatal screening: intrapartum screening

**Turnaround time**  
collect specimen at admission

Optimal management of patient

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

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

Cost-effective

Full automation  
With internal QC  
Easy to perform,  
to interpret  
TRAINING!

Sensitivity > 90%  
Specificity > 95%

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CDC  
**MMWR**  
Morbidity and Mortality Weekly Report  
www.cdc.gov/mmwr

November 25, 2010 / Vol. 58 / No. RR-10

Prevention of Perinatal Group B Streptococcal Disease  
Revised Guidelines from CDC, 2010

THE JOURNAL OF  
**MATERNAL-FETAL & NEONATAL MEDICINE**

http://informahealthcare.com/jmf  
ISSN 1473-7058 (print); 1473-6554 (electronic)  
J Matern Fetal Neonatal Med. Early Online 1-17  
© 2014 Informa UK Ltd. DOI: 10.3109/14737058.2014.934804

informa healthcare

GUIDELINES

**Intrapartum GBS screening and antibiotic prophylaxis: a European consensus conference**

G. C. Di Renzo<sup>1</sup>, P. Melin<sup>2</sup>, A. Berardi<sup>3</sup>, M. Blennow<sup>4</sup>, X. Carbonell-Estrany<sup>5</sup>, G. P. Donzelli<sup>6</sup>, S. Hakansson<sup>7</sup>, M. Hod<sup>8</sup>, R. Hughes<sup>9</sup>, M. Kurtzer<sup>10</sup>, C. Poyart<sup>11</sup>, E. Shinwell<sup>12</sup>, B. Stray-Pedersen<sup>13</sup>, M. Wielgos<sup>14</sup>, and N. El Helali<sup>15</sup>

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### Intrapartum screening theranostic approach: Expected advantages & drawback

- 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
- No antimicrobial susceptibility results (in case of penicillin allergy)

IAP addressed to right target


- Reduction of inappropriate/unnecessary IAP
- Broader coverage of « at GBS risk women »

Improvement of prevention

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A POCT in the delivery room  
Xpert® GBS, Cepheid

**INTRAPARTUM SCREENING FOR GBS**




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### 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 (2 min hands on time)
- Result in 35-45 minutes

- a sample-processing control (SPC)
  - to monitor processing conditions
- internal control (IC)
  - to monitor PCR conditions and the absence of reaction inhibition



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### 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%	PPV	58.3%
Specificity	99.6%	NPV	92.1%
PPV	97.8%		
NPV	99.7%		

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### Xpert® GBS POC test in the delivery room study Objectives

Study in CHU Liège / UZ Antwerp, Belgium (900 patients)

- To assess the practical aspects and analytical performances
  - Tests performed by midwives
    - Evolving team of +/- 50 midwives
  - For screening all women at onset of labor
- To evaluate the cost-effectiveness of the intrapartum screening strategy

→ To consolidate the proposal of the European Expert Group

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### Specimen collection & processing

*Initial protocol*

#### Antenatal screening

- Vagino/rectal specimen
- Collected at 35-37 weeks' gestation

#### Intrapartum screening

- Vaginal specimen using a double swab
- Collected at onset of labor

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### Test Xpert® GBS: Procedure

- Mettre des gants
- Se procurer le cartouche et ouvrir le couvercle
- Retirer les accessoires du système de transport
- Frictionner doucement les accessoires l'un sur l'autre
- Remettre les accessoires dans le système de transport (à envoyer au labo). Utiliser l'autre pour le GeneXpert
- Insérer l'accessoire du GeneXpert dans le système de transport
- Localiser le marquage de lecture sur l'accessoire
- Insérer l'accessoire dans la cartouche (ouverture en bas à droite) au niveau du marquage
- Insérer la cartouche dans le système de transport
- Retirer les gants
- Insérer la cartouche dans le système de transport
- Insérer le système de transport dans le Xpert GBS

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

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### Xpert® GBS test Expression of results

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

Test Result: **POSITIVE** Presence of GBS

Test and Analyte Result	Ct	EndPt	Analyte Result	Probe Check Result
SFC	34.4	105.0	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 interrupted)

Test Result: **NO RESULT** Indeterminate status for GBS (test invalid)

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### Xpert® GBS test Use of results

- Criteria for giving intrapartum antibiotic prophylaxis
  - Presence of defined risk factors
  - Positive GBS result of the antenatal screening at 35-37 weeks' gestation
  - Positive result of intrapartum screening provided by Xpert® GBS test

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# Results

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## Global overview

	Liege	Antwerp
Study period	8.04.2014 – 3.10.2014	2.7.2014 – 24.9.2014
Number of deliveries	658	?
GBS antenatal colonization rate	19.4%	14.7%
Number tested intrapartum with Xpert® GBS test	486 (74% of deliveries)*	78
Xpert® GBS	Positive	11%
	Negative	83%
	Error	6%
	Invalid	0%

\*: lower inclusion rate among antenatally GBS positive screened women

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## Culture results (Liege)

- Colonization rate (35-37 wks)
  - 19.4% GBS positive
- Performances of the antenatal culture screening
  - Intrapartum culture as gold standard

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

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## Xpert® GBS results (Liege, 2014) Intrapartum (IP) culture as gold standard

	Pre-study
Number tested / Number GBS Positive IP Culture	112 / 16
Sensitivity Excluding enrichment	78.6%
Specificity	98.9%
PPV	91.7%
NPV	96.7%

- Bias : low inclusion rate of known GBS positive women
- Wrong handling

➔ Reminder of protocol and procedure

Objectives: Sensitivity > 90% & specificity > 95%

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## Xpert® GBS results (Liege, 2014) Intrapartum (IP) culture as gold standard

	Pre-study	Study
Number tested / Number GBS Positive IP Culture	112 / 16	225 / 32
Sensitivity Excluding enrichment	78.6%	46.7% !!
Specificity	98.9%	100%
PPV	91.7%	100%
NPV	96.7%	91.7%

Objectives: Sensitivity > 90% & specificity > 95%

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## Xpert® GBS results (Liege, 2014) Intrapartum (IP) culture as gold standard

	Study
In the lab, Liege	<ul style="list-style-type: none"> <li>GBS colonies from discrepant results tested POSITIVE with Xpert® GBS</li> </ul>

Checking if swab dropped in the bottom of the cartridge

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### Xpert® GBS results (Liege, 2014) Intrapartum (IP) culture as gold standard

Timeline: 08.04 (Pre-study) → 26.05 (Study) → 11.08 (Study)

	Pre-study	Study
Number tested / Number GBS Positive IP Culture	112 / 16	225 / 32
Sensitivity Excluding enrichment	78.6% 83.3%	46.7% !! 50% !
Specificity	98.9%	100%
PPV	91.7%	100%
NPV	96.7%	91.7%

**Checklist:**

- In the lab, Liege**
  - GBS colonies from discrepant results tested **POSITIVE** with Xpert® GBS
- In Cepheid**
  - Analysis of raw data from discrepant results
    - Mainly no Ct value for GBS
  - Discussion
    - No control for presence of specimen on board

*Checking if swab dropped in the bottom of the cartridge*

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### Xpert® GBS results (Liege, 2014) Intrapartum (IP) culture as gold standard

Timeline: 08.04 (Pre-study) → 26.05 (Study) → 11.08 (Study)

	Pre-study	Study
Number tested / Number GBS Positive IP Culture	112 / 16	225 / 32
Sensitivity Excluding enrichment	78.6% 83.3%	46.7% !! 50% !
Specificity	98.9%	100%
PPV	91.7%	100%
NPV	96.7%	91.7%

**Checklist:**

- In the lab, Liege**
  - GBS colonies from discrepant results tested **POSITIVE** with Xpert® GBS
- In Cepheid**
  - Analysis of raw data from discrepant results
    - Mainly no Ct value for GBS
  - Discussion
    - No control for presence of specimen on board
- To the midwives team**
  - Reminder of critical steps of the procedure
  - Intensive individual training of midwives on site

*Gentle rolling of the swab in order to eliminate excess of mucus*

*Checking if swab dropped in the bottom of the cartridge*

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### Xpert® GBS results (Liege, 2014) Intrapartum (IP) culture as gold standard

Timeline: 08.04 (Pre-study) → 26.05 (Study) → 11.08 (Revision) → 10.09 (Revision)

	Pre-study	Study	Revision
Number tested / Number GBS Positive IP Culture	112 / 16	225 / 32	89 / 15
Sensitivity Excluding enrichment	78.6% 83.3%	46.7% !! 50% !	93.3% 100%
Specificity	98.9%	100%	98.5%
PPV	91.7%	100%	93.3%
NPV	96.7%	91.7%	98.5%

**Objectives:** Sensitivity > 90% & specificity > 95%

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### Xpert® GBS results (Liege, 2014) Intrapartum (IP) culture as gold standard

Timeline: 08.04 (Pre-study) → 26.05 (Study) → 11.08 (Revision) → 10.09 (Following period)

	Pre-study	Study	Revision	Following period
Number tested / Number GBS Positive IP Culture	112 / 16	225 / 32	89 / 15	60 / 14
Sensitivity Excluding enrichment	78.6% 83.3%	46.7% !! 50% !	93.3% 100%	53.8% !! 54.5% !
Specificity	98.9%	100%	98.5%	97.6%
PPV	91.7%	100%	93.3%	87.5%
NPV	96.7%	91.7%	98.5%	87.2%

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### Xpert® GBS results (Antwerp, 2014) Intrapartum (IP) culture as gold standard

Timeline: 02.07 (Study) → 24.09 (Study)

	Study
Number tested	78
Sensitivity	50%
Specificity	100%
PPV	100%
NPV	94.7%

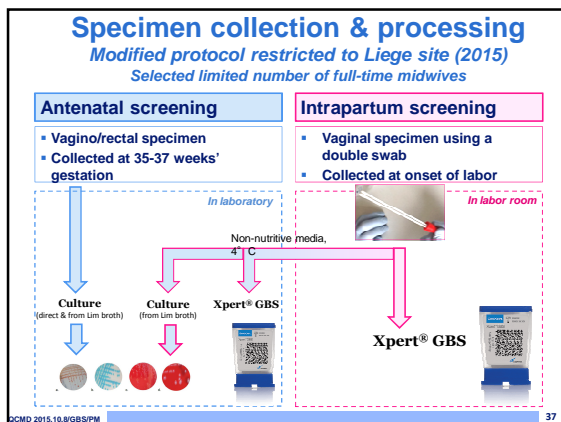
**Objectives:** Sensitivity > 90% & specificity > 95%

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### Xpert® GBS for intrapartum testing In Obstetric ward or in the lab !! (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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### Xpert® GBS results (Liege, July-sept.2015)

#### Intrapartum (IP) culture as gold standard

(61 deliveries ; 11 GBS positive in IP culture, 18%)

	PCR in delivery room	PCR in the lab 12-30 hours later
Number GBS Positive IP Culture	11 (18%)	8 (15%)
Number of tests performed/ number of positive results	61/8+1	53/8+1
Number of error /invalid	4 errors /3 invalid (11,5%)	3 errors (5.6%)
Sensitivity	<b>72,7%</b>	100%
Specificity	1 Pos with both PCR, not recovered in culture 100%	
Delta Ct values Delivery / Lab	+ 6.5 Ct (2.2 – 12.8)	

- Difference of operator ??
- Difference of mucus behaviour and interference with PCR, from time of collection to a few hours later ??

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## CONCLUSION

### Take home messages

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## Summary

### Xpert® GBS POCT in the delivery room

- Theoretical superior clinical value
  - versus antenatal screening
- Looks like easy to perform, BUT ...
  - Careful training of midwives
  - High turn-over in midwives team
  - Performances to be verified on EACH site !
  - To be supervised closely by the lab
  - Need for a internal specimen control
  - Role of excess of mucus ?

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## Summary

### Xpert® GBS POCT in the delivery room

- Not ready as a standalone screening
  - High specificity but varying sensitivities !
  - Could be combined with risk factor strategy ??
  - Some expected improvements to secure the result AND the patient management

Commutability from lab to POC  
Not always an unconditional success story

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## Acknowledgements

In Liege  
C.Meex  
J.Descy  
R.Sacheli  
Team of midwives

In Antwerp  
G.Leven  
K.Denis  
Team of midwives

Cepheid Belgian team

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