Point of care testing of GBS, isn't it obvious?

Professor Pierrette Melin

National Reference Centre for Streptococcus agalactiae
Clinical Microbiology, University Hospital of Liege,
University of Liege, Belgium

Content

- **Background**
  - Burden - Transmission - Prevention strategies
- **POCT for GBS, isn't it clinically obvious?**
  - Risk-based or antenatal screening-based Intra-partum antibioprophylaxis
  - Reduction of incidence of EOD, advantages & drawbacks
  - Room for improvement
- **POCT for GBS, is it technically obvious?**
  - Advantages & drawbacks
  - Expected characteristics
  - Available or coming POCTs
- **Take home message**

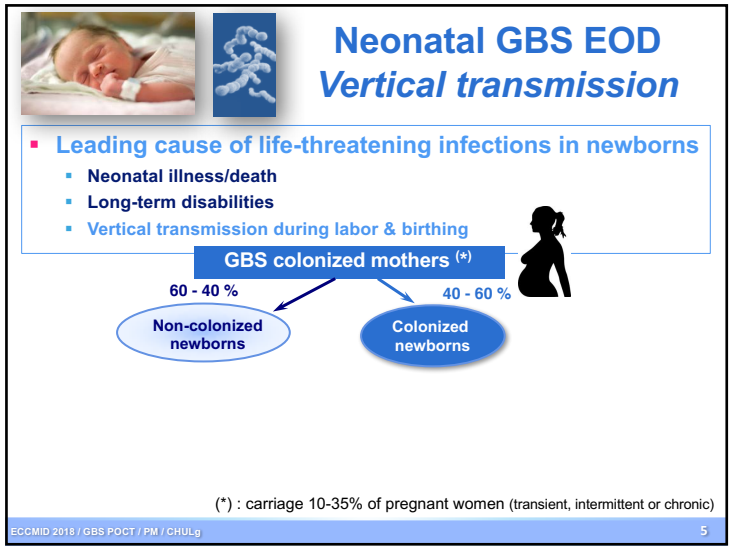
Burden
Transmission
Prevention strategies

BACKGROUND

Group B streptococcus or GBS *(Streptococcus agalactiae)*

- **Since the 1970s, leading cause of life-threatening infections in newborns**
  - Neonatal illness/death
    - **Early & Late Onset Disease** (EOD, LOD)
  - Long-term disabilities
- **GBS EOD**
  - **Before mid-1990s: 2-3/1000 live births**
  - Today, prevention era : 0.2 - 1/1,000 live births
    - Meningitis : 10 %
    - Mortality : 4 - 10 % (20-30% if premature)
- **GBS LOD**
  - **0.3 – 0.5 /1,000 live births**

GLOBAL public health major concern !
WHO
Also in developing low income countries


Neonatal GBS EOD
Vertical transmission
Leading cause of life-threatening infections in newborns
Neonatal illness/death
Long-term disabilities
Vertical transmission during labor & birthing
GBS colonized mothers (*)
60 - 40 %
40 - 60 %
Non-colonized newborns
Colonized newborns
(*) : carriage 10-35% of pregnant women (transient, intermittent or chronic)
ECCMID 2018 / GBS POCT / PM / CHULg
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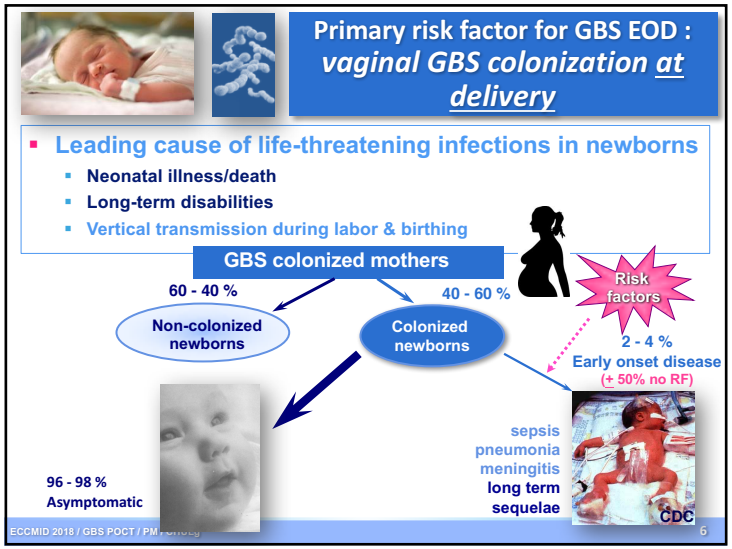
Primary risk factor for GBS EOD :
vaginal GBS colonization at delivery
Leading cause of life-threatening infections in newborns
Neonatal illness/death
Long-term disabilities
Vertical transmission during labor & birthing
GBS colonized mothers
60 - 40 %
40 - 60 %
Non-colonized newborns
Colonized newborns
Risk factors
2 - 4 %
Early onset disease
(+ 50% no RF)
96 - 98 %
Asymptomatic
sepsis
pneumonia
meningitis
long term sequelae
CDC
ECCMID 2018 / GBS POCT / PM
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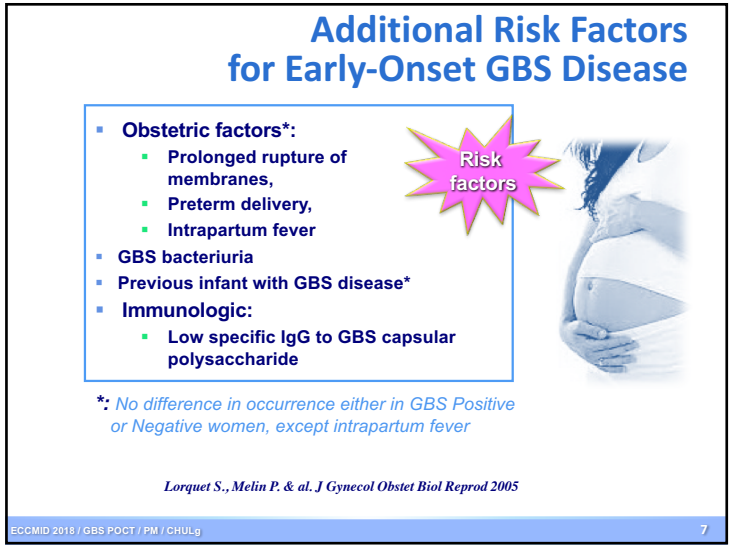
Additional Risk Factors
for Early-Onset GBS Disease
Obstetric factors*:
Prolonged rupture of membranes,
Preterm delivery,
Intrapartum fever
GBS bacteriuria
Previous infant with GBS disease*
Immunologic:
Low specific IgG to GBS capsular polysaccharide
Risk factors
*: No difference in occurrence either in GBS Positive or Negative women, except intrapartum fever
Lorquet S., Melin P. & al. J Gynecol Obstet Biol Reprod 2005
ECCMID 2018 / GBS POCT / PM / CHULg
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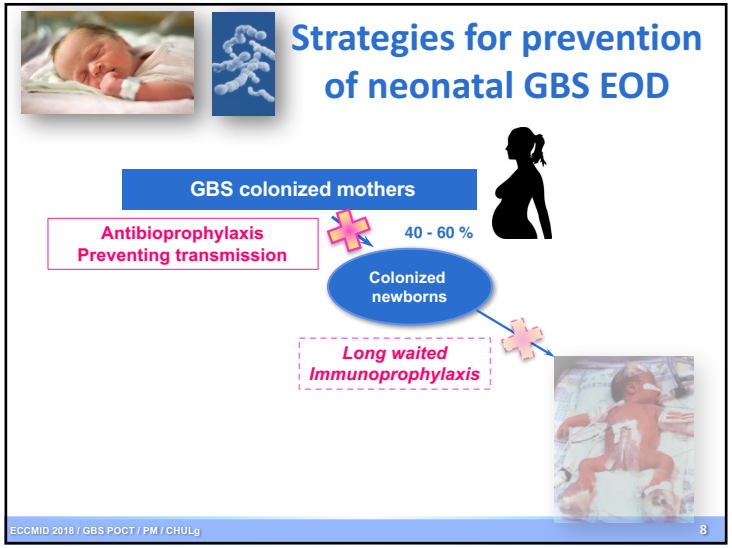
Strategies for prevention
of neonatal GBS EOD
GBS colonized mothers
Antibioprophylaxis
Preventing transmission
40 - 60 %
Colonized newborns
Long waited
Immunoprophylaxis
ECCMID 2018 / GBS POCT / PM / CHULg
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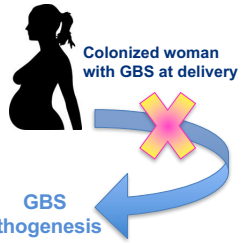
Strategies for prevention of neonatal GBS EOD

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

To mitigate transmission and reduce chance of invasive infection.

Challenge:
Identification of woman at risk

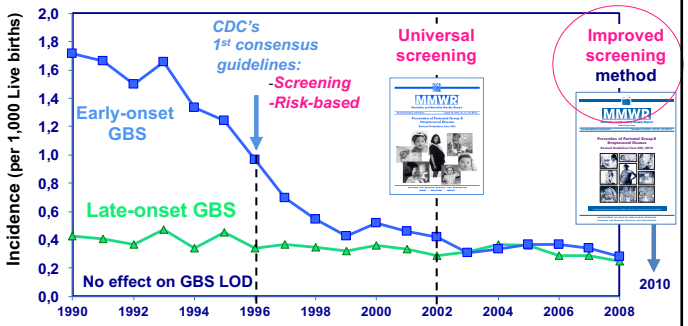
Risk-based strategy ?
Screening-based strategy?



Guidelines for prevention
Efficacy, concerns & drawbacks
Room for improvement

POCT FOR GBS,
ISN'T IT CLINICALLY OBVIOUS ?

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**
    (issued by prof.societies; by public health authorities)
    - Spain, 1998, 2003, revised 2012
    - France, 2001, 2017
    - Belgium, 2003, revised 2015
    - Germany, 1996, revised 2008
    - Switzerland, 2007
  - **Risk-based strategy**
    - UK, the Netherlands, Denmark
- **No guidelines**
  - Bulgaria, …

Antenatal GBS culture-based screening

Goal of GBS screening

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

- **Crucial factors influencing accuracy**
  - **Swabbed anatomic sites** (distal vagina & rectum)
  - **Timing of sampling** (35-37 wks)
  - **Collection devices & Transport conditions**
  - **Screening methods**
    - **Culture**
      - ***Procedure***
        - *± selective enrichment broth further sub-cultured (LIM)*
      - ***Media***
        - *Blood agar (β-hemolysin), Granada & chromogenic agars*

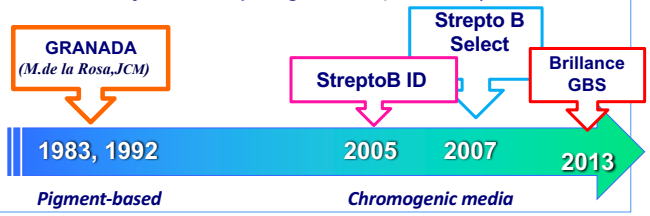
From direct plating on blood agar
Evolution of culture methods

Use of selective enrichment broth

- **To maximize the isolation of GBS**
- **To avoid overgrowth of other organisms**

Use of differential agar media (>> CNA Blood agar)

Recommended by some European guidelines (+ CDC 2010)



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

Antenatal culture-based screening for GBS detection combined with real-time NAAT from enriched Lim Broth

illumigene® Group B Streptococcus assay	BD MAX™ GBS assay	XPERT® GBS LB assay	GenePOC™ GBS LB Test
A loop mediated isothermal amplification (LAMP) assay by Meridian Bioscience, Inc	Fully-automated, real-time PCR method. (High throughput)	GeneXpert® Systems	revogene™ Instrument Throughput up to 8 samples/run
Speed & accuracy			
Assay performances	**Assay performances**	**Assay performances**	**Assay performance**
Sensitivity: 95.7-98.6%	Sensitivity: 95.0%	Sensitivity: 95.7-98.6%	Sensitivity: 96%
Specificity: 93.2-100%	Specificity: 96.7%	Specificity: 93.2-100%	Specificity: 96%

About analytically reliable diagnostic devices/systems for Real-time NAAT GBS LB assays

Impact on diagnostics ?

Impact on patient management, care ?

Impact on Turn-around-time?

Clinical significance of ... ?

... benefits ?

Could NAAT GBS LB assays replace favourably GBS Screening culture ?

Rem.: antimicrobial susceptibility results not available, if positive, first subculture.

When to use which techniques?
For selected patients?
Alone or combined with conventional methods?
Will results be able to change behaviour?

About analytically reliable diagnostic devices/systems for Real-time NAAT GBS LB assays

Impact on diagnostics ?
Could improve it in some labs !

Impact on patient management, care ?
Could be improved for some pregnant women and neonates

Impact on Turn-around-time?
Up to 48h shorter, but not essential as antenatal. Elegant, streamlined solution.

Clinical significance of results?
→ Accurate, High PPV & NPV

Cost-benefits ?
For lab/global? Country, reimbursement, availability of human resources, quality of culture procedures, etc.

When to use which techniques?
For selected patients?
Alone or combined with conventional methods?
Will results be able to change behaviour?

Antenatal GBS culture-based screening

Goal of GBS screening

To predict GBS vaginal (rectal) ... the time ...

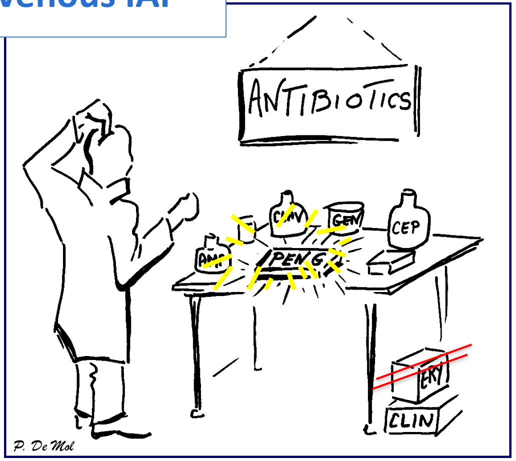
➘ Incidence to 0.2-1 per 1,000 live births

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

Negative and positive predictive values to be improved

- Non-culture
  - *Nucleic Acid Amplification Test (NAAT)*

Intra-venous IAP



Concerns about potential adverse / unintended events related to IAP

- 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
- Impact on development of the neonatal intestinal microbiome.

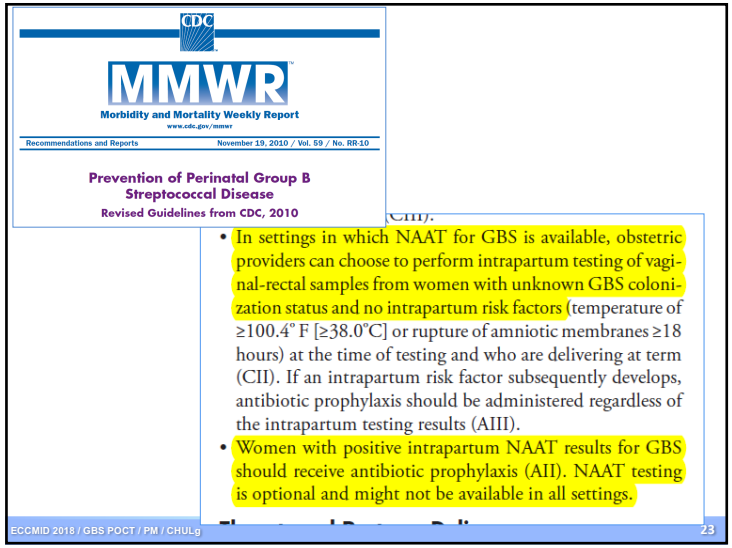
- Changes in GBS antimicrobial resistance profile
  - Increase of resistance to clindamycin (10 to 40% in Europe, USA; up to 70% in Asia)
  - Very very rare decrease of susceptibility to penicillin

Concerns about preventive strategies & IAP

	Risk-based approach	Antenatal screening-based approach

No IAP when needed	• A lot of missed opportunities
	  ▪ Lack of adhesion
	  ▪ Incomplete assessment of risks
	• Up to 65% of cases not associated to RF
		• Some missed opportunities
		  ▪ Results not available
		• False Negative screening
		  30 - 60 % of true +
		  ▪ Change of GBS status
		  ▪ Colonization dynamics
		  ▪ Lack of viability
		  ▪ Transport conditions, antibiotherapy, personal hygiene
		  ▪ Poor sensitivity of culture

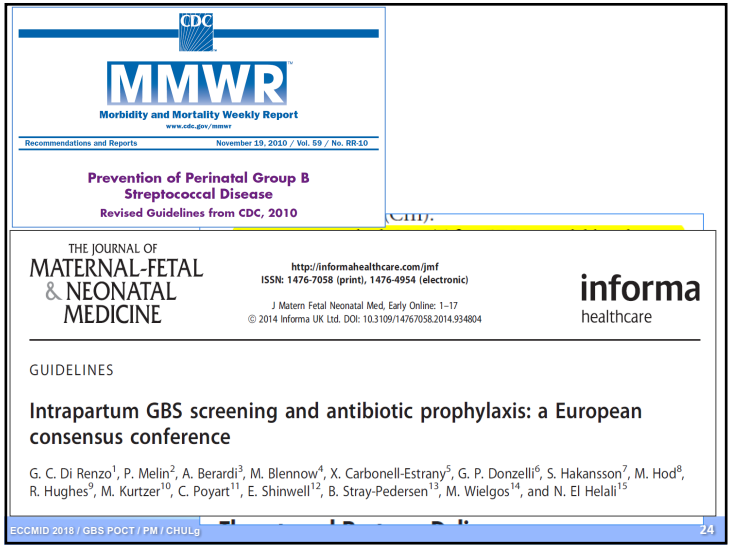
Unnecessary IAP	• Half up to 80% of women with RF are not GBS colonized (except intrapartum fever)	• False Positive screening
		  ▪ Change of GBS status
		  ▪ Colonization dynamics
		Up to 30 % of antenatal positive



CDC MMWR Morbidity and Mortality Weekly Report
www.cdc.gov/mmwr
Recommendations and Reports November 19, 2010 / Vol. 59 / No. RR-10

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

- In settings in which NAAT for GBS is available, obstetric providers can choose to perform intrapartum testing of vaginal-rectal samples from women with unknown GBS colonization status and no intrapartum risk factors (temperature of ≥100.4° F [≥38.0°C] or rupture of amniotic membranes ≥18 hours) at the time of testing and who are delivering at term (CII). If an intrapartum risk factor subsequently develops, antibiotic prophylaxis should be administered regardless of the intrapartum testing results (AIII).
- Women with positive intrapartum NAAT results for GBS should receive antibiotic prophylaxis (AII). NAAT testing is optional and might not be available in all settings.



CDC MMWR Morbidity and Mortality Weekly Report
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THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE

http://informahealthcare.com/jmf
ISSN: 1476-7058 (print), 1476-4954 (electronic)
J Matern Fetal Neonatal Med, Early Online: 1–17
 DOI: 10.3109/14767058.2014.934804

informa healthcare

GUIDELINES

Intrapartum GBS screening and antibiotic prophylaxis: a European consensus conference

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

Towards a « European Consensus »

Decision taken by a European working party

(Neonatologists, obstetricians, microbiologists)

including countries with screening-based IAP, with risk-based IAP strategies or no strategy at all *(June 2013, Florence, Italy)*

Main recommendations

- Universal screening at time of delivery ***(when appropriate POCT available)***
  - **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**

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Intrapartum screening
Expected advantages & drawback

- ❑ **Inclusion of women without antenatal 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, antenatal screening)

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

Improvement of prevention

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Intrapartum screening
Expected advantages & drawback

GBS POCT
performed on vaginal specimen
at admission for delivery
=
Valuable alternative method for accurate identification of GBS colonized women at delivery

Improvement of prevention

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Old or new tools to detect GBS ?
Response to a 30 year "dream" but also an obvious need.

POCT FOR GBS,
IS IT TECHNICALLY OBVIOUS ?

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XXIst century, Medical evolutionary background

Factors impacting on development and daily practice of microbiology

- **Medical environment**
  - Increasing emphasis on **evidence-based medicine** and adherence to **guidelines**
- **Economic environment**
  - Cost-effective use of available resources
  - Reimbursement system, regulation

- **Evolution of technological background**
  - Exponential progress: molecular biology and robots
  - New platforms from "sample-in / result-out"
  - Continuation of advance to accelerate in the near future
- **Quality assurance, traceability, LIS**
- **Global increase of antimicrobial resistance**

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Theranostic approach

Alternative to GBS prenatal screening: intrapartum screening

€€€ 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)

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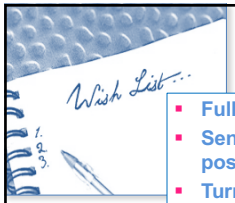

- **Fully automated and robust test & platform**
- **Sensitivity >90%, specificity>95%, negative and positive predictive values**
- **Turn Around Time (TAT) < 1 hour**
- **Internal QC / embedded process control / control for presence of specimen on board**
- **Workflow; very limited hands-on-time**
- **Easyness to perform and to interprete** *(clear-cut result)*
  - *Low rate of invalid / error results*
- **Availability 24h/7d**
- **Limited training** *(high turnover among nurses/midwives)*
- **Cost-effective**
- **Traceability, connectivity to electronic medical files**
- **Small footprint, low noise level**
- **Minimized waste**

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Xpert® GBS Assay, Cepheid

GenePOC™ GBS DS Assay, GenePOC

A POCT in the delivery room

INTRAPARTUM SCREENING FOR GBS

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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%
    - Specificity 99.6%
    - PPV 97.8% — PPV 58.3%
    - NPV 99.7% — NPV 92.1%

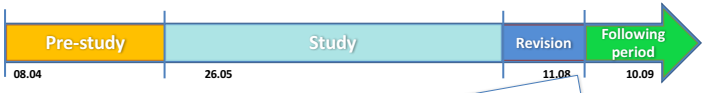
Xpert® GBS
POC test in the delivery room study
Objectives

Study in CHU Liège / UZ Antwerp, Belgium (900 patients), 2014-2015

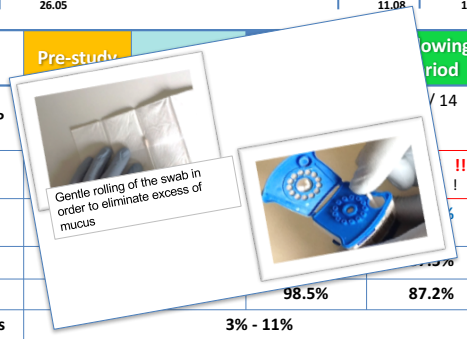
1. **To assess the practical aspects and analytical performances**
   - Tests performed by midwives
     - *Evolving team of +/- 50 midwives /hospital*
   - For screening all women at onset of labor
2. **To evaluate the cost-effectiveness of the intrapartum screening strategy**

→ To consolidate the proposal of the European Expert Group

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



	Pre-study	Study	Revision	Following period
Number tested / Number GBS Positive IP Culture				/ 14
Sensitivity *Excluding enrichment*				!! !
Specificity				
PPV				
NPV		98.5%		87.2%
Error + Invalid results	3% - 11%			



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

	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%
Error + Invalid results	3% - 11%			

Antenatal screening culture *(Melin et al, 2000)*

>> PPV : 68.8%

> NPV : 93.8%

Key message

Xpert® GBS POCT in the delivery room

- High specificity but varying sensitivities !
- Some invalid or error results
  - Time, cost to retest ???
- Some expected improvements to secure the result AND the patient management (specimen control)
- Mucus interference
- Higher Ct when test perform immediately after collection: better results a few hours later

Commutability from lab to POC:

Not always an unconditional success story !

→ **Clinical validation of GBS POCT:**

crucial to be performed on site, by midwives and on fresh specimens

A POCT in the delivery room

GenePOC™ GBS DS test, *CE-marked, 2017*

& the revogene™ instrument, *CE-marked & FDA cleared*

INTRAPARTUM SCREENING FOR GBS

GenePOC™ GBS DS test for intrapartum screening

- Real Time PCR on revogene™ instrument
  - Detection of a *cfb* gene sequence specific of the GBS genome
- On vaginal or vagino/rectal swab
- Fully automated
- Easy to use *: 3 steps in 1 min*
- Result in 70 minutes
- Single-use microfluidic cartridges
  - Testing 1 up to 8 samples in one run

- ***Embedded process control*** *to monitor sample processing conditions*
- ***internal control*** *to monitor PCR conditions and the absence of reaction inhibition*

GenePOC™ GBS DS Assay, validation by the Belgian NRC GBS

- Currently tested in parallel with reference culture
- Results: so far so good, evaluation still ongoing

GenePOC™ GBS DS test for intrapartum screening

Clinical performances characteristics of the GBS DS Assay in comparison to reference method

PI GBS DS IVD EN V2(2017-10) ; No. document: 133392-EN

Overall performance		Reference Method		
		Positive	Negative	Total
GBS DS Assay	Positive	107	31[B]	138
	Negative	4[A]	277	281
	Total	111	308	419

Sensitivity	96.4%.
Specificity	89.9%
PPV	77.5%
NPV	98.6%

[A]: GBS DNA detected in ½ false negative specimens tested using a second NAAT method
[B]: GBS DNA detected in 13/15 false positive specimens tested using a second NAAT method

Limit of detection

GBS Strain	LoD in simulated matrix
Serotype III (ATCC 12403)	750 CFU/mL
Non-hemolytic (ATCC 13813)	375 CFU/mL

→ P0810

Intrapartum group B *Streptococcus* (GBS) detection by point-of-care real-time PCR testing (POCT)

Lutz Von Müller*, Germany

CONCLUSION
Take home messages

Summary

Neonatal GBS diseases & prevention

- GBS still a perinatal threat
- EOD and LOD, a public health concern
- Immunoprophylaxis , highly desirable but not yet available
- IAP efficient for prevention of EOD
  - Up to 80% reduction of EOD
  - Best strategy still a matter of debate
    - Antenatal screening >> risk factors ??
- IAP not widely recommended
- Towards European consensus 2014
  - Universal screening, intrapartum when appropriate GBS POCT available

Summary

Intrapartum GBS POCT

- Clinically OBVIOUS to reduce
  - Missed opportunities of IAP
  - Unnecessary IAP
  - Inappropriate management of newborn
- Clinically OBVIOUS
  - To better address the right target for IAP
- But no AST result for penicillin allergic woman
- A lot of papers relating the superiority of intrapartum GBS POCT–based IAP (*Xpert® GBS)*
  - Which "reference method" ?
  - Testing in lab versus on delivery site ?
  - Room for technical improvement ?
- Hope in the new GenePOC™ GBS DS test & coming others still in the pipeline of development