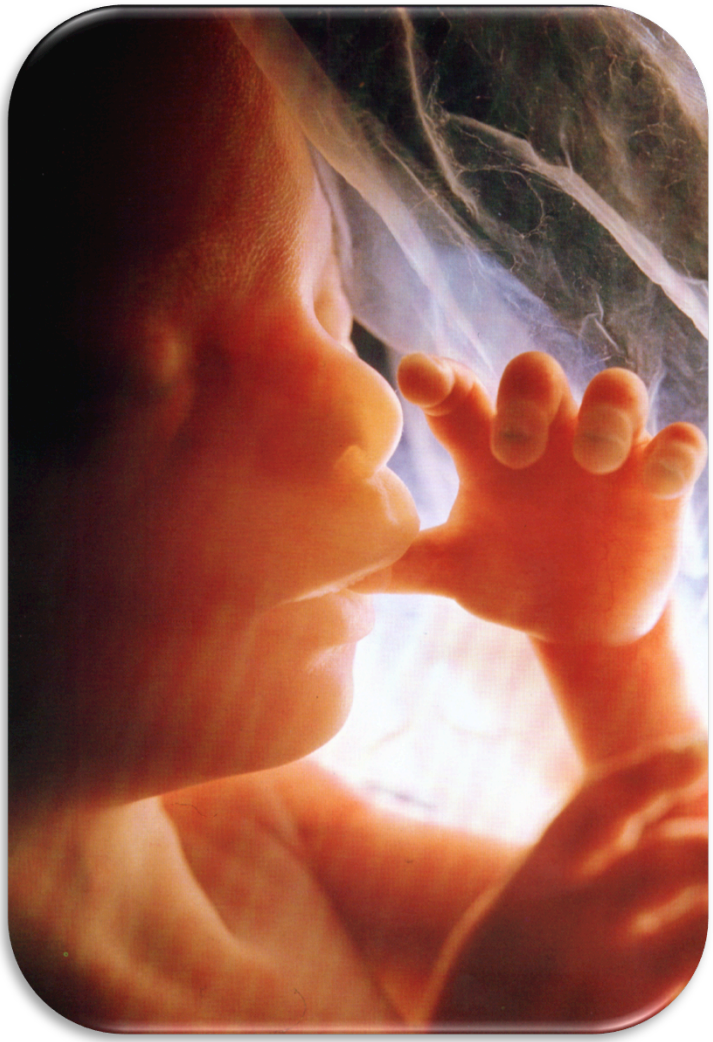


GBS SCREENING Belgium: current and future guidelines

Pierrette Melin

National Reference Centre for GBS
Microbiology, University of Liege
Medical Microbiology, University Hospital of Liege

INTRODUCTION & BURDEN

Streptococcus agalactiae or GBS

Gram positive cocci
- **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

➢**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

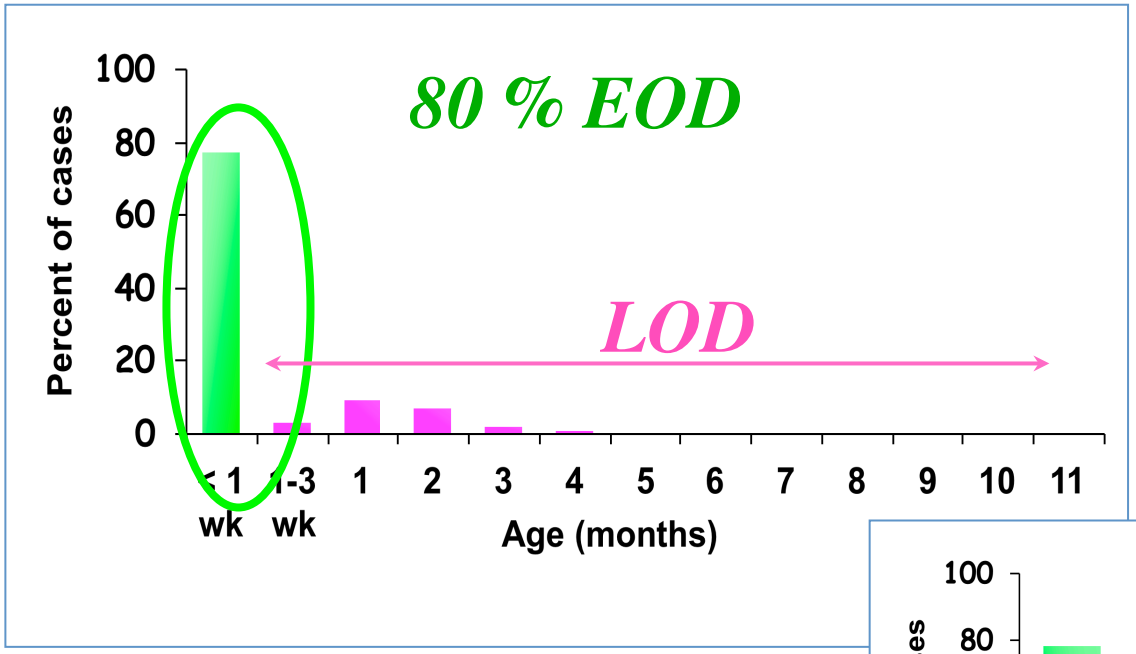
- Maternal morbidity
  - Along pregnancy
  - Peripartum
- Serious diseases among elderly and adults with underlying diseases
  - Significant mortality

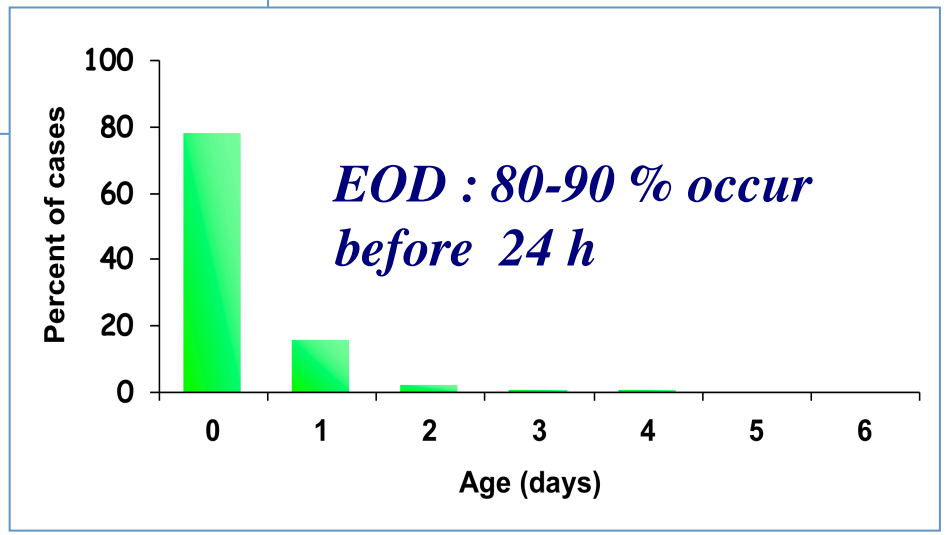
GBS Neonatal Infections

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

GBS Neonatal Infections

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





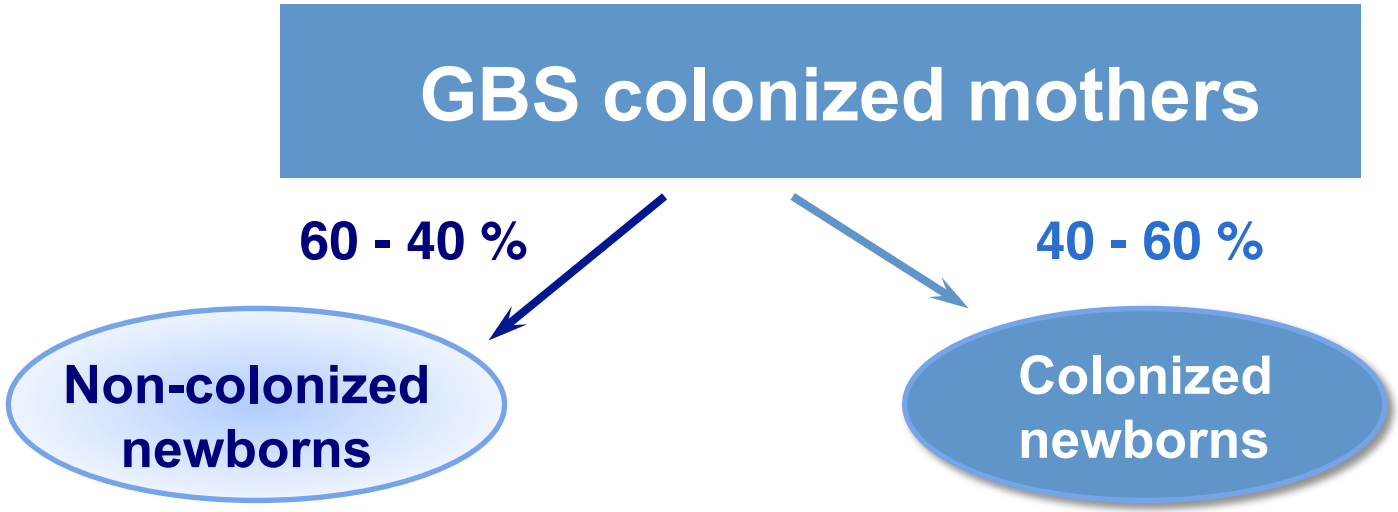
Burden of neonatal GBS early onset diseases in European countries

Location	Incidence per 1,000 live-births	*Reference*
Spain	2 (1996) to 0.45 (2008)	*Lopez Sastre et al. Acta Pediatr 2005*
Belgium	2	*Melin, Indian J Med Res 2004*
Eastern Europe	0.2 - 4	*Trijbels-Smeulders, Pediatr Infect Dis J 2004*
Western Europe	0.3 - 2	
The Netherlands	1.9	
Scandinavia	0.76 - 2	
Southern Europe	0.57 - 2	

- Carriage rate ?
- Ethnicity ?
- Sub-reporting?
- Systematic diagnostic approach?
- Virulence?

Data assessing more accurately the true burden are needed

GBS EOD vertical transmission



GBS EOD vertical transmission

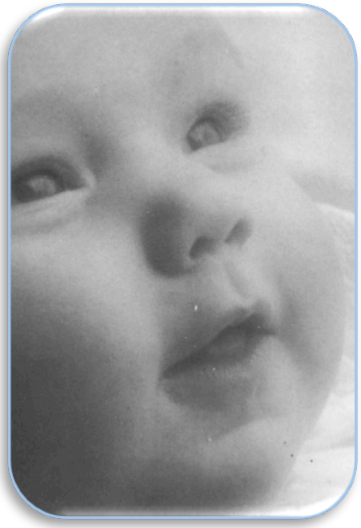
GBS colonized mothers

60 - 40 %

40 - 60 %

Non-colonized newborns

Colonized newborns



96 - 98 %

Asymptomatic

GBS EOD vertical transmission

GBS colonized mothers

60 - 40 %

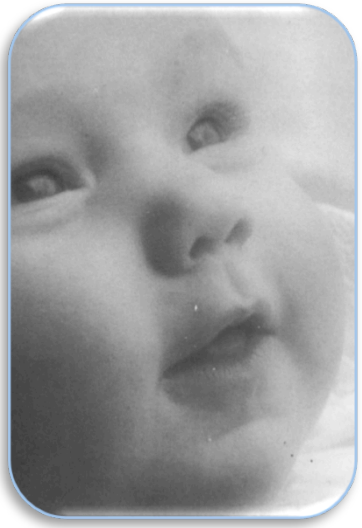
40 - 60 %

Non-colonized newborns

Colonized newborns

Risk factors

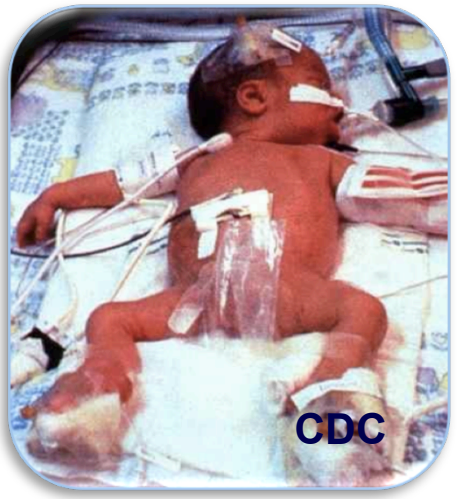
2 - 4 %
GBS EOD



96 - 98 %

Asymptomatic

sepsis
pneumonia
meningitis
long term sequelae



GBS maternal colonization

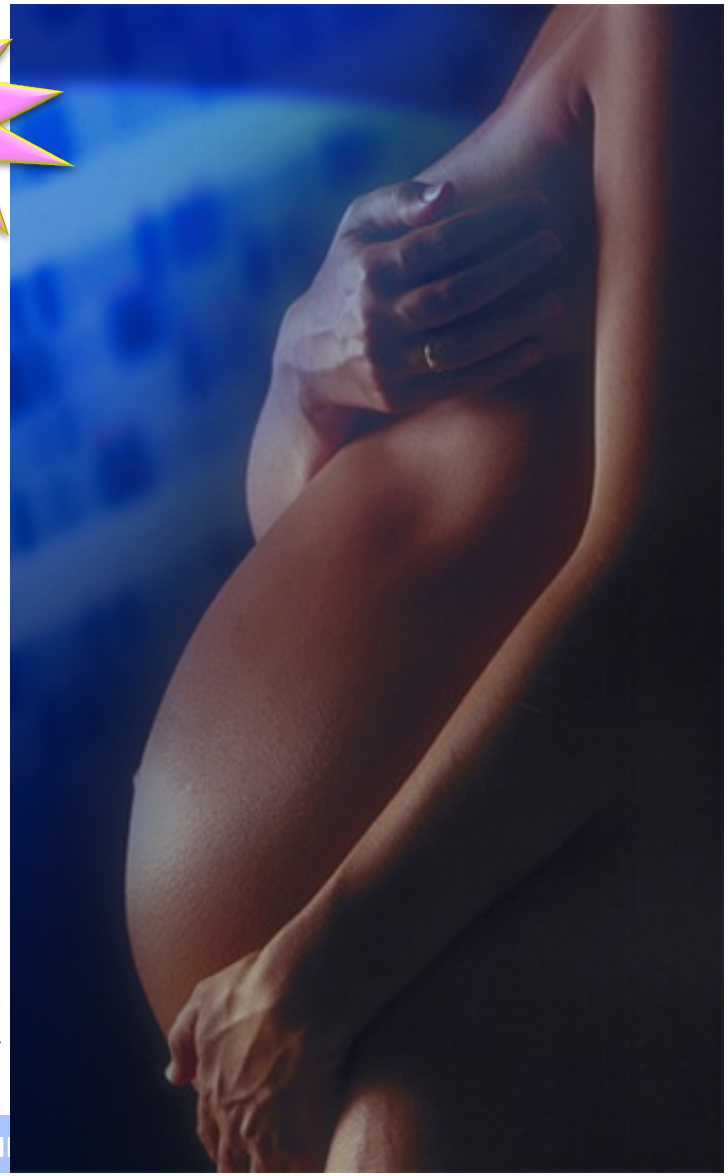
Risk factor for early-onset disease (EOD) :
vaginal GBS colonization at delivery

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

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

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.

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

GUIDELINES FOR PREVENTION OF GBS PERINATAL DISEASE

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

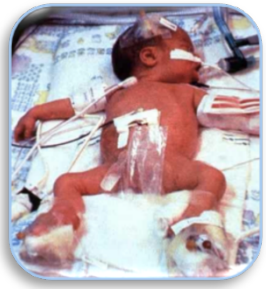
Meningitis

Brain barrier
Pili,
β-hemolysin, …

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

Ascendant **transmission** (amnionitis)

GBS pathogenesis

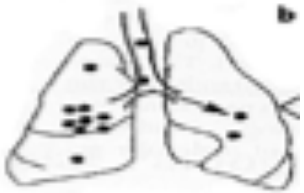


Sepsis

IL1, IL6, TNF α,
PGE2, TxA_2 ,

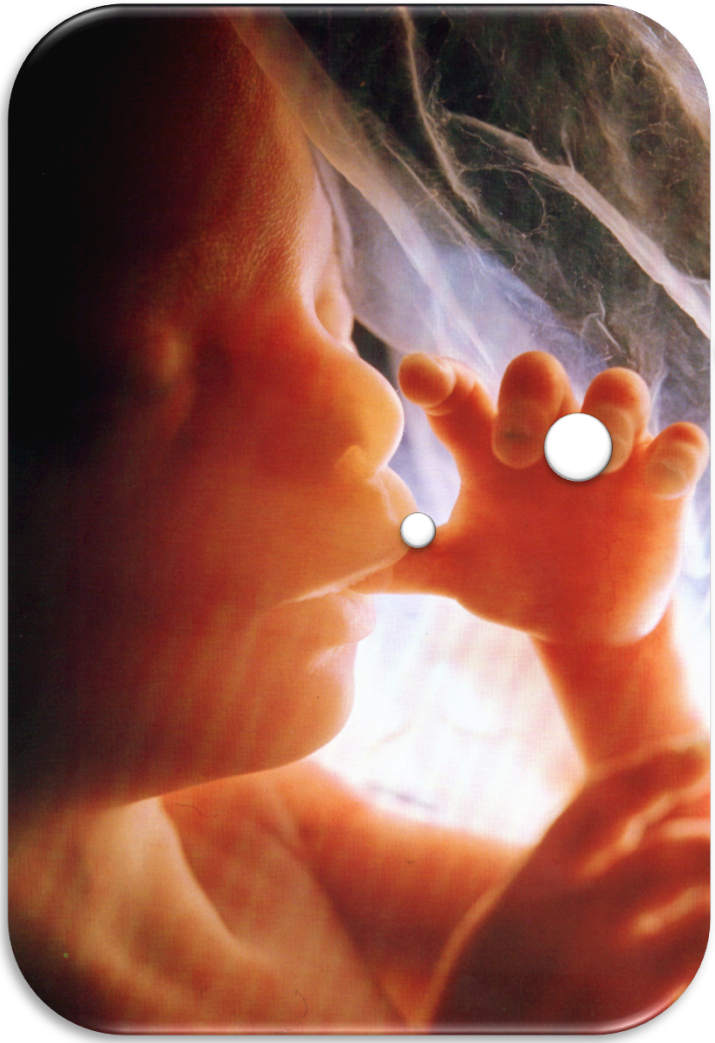
Bacteria
Peptidoglycan
β-hemolysin, …

Resistance to phagocytose
- Capsule
- C5a peptidase
- …..



β-hemolysin, invasins (**pneumonia**)

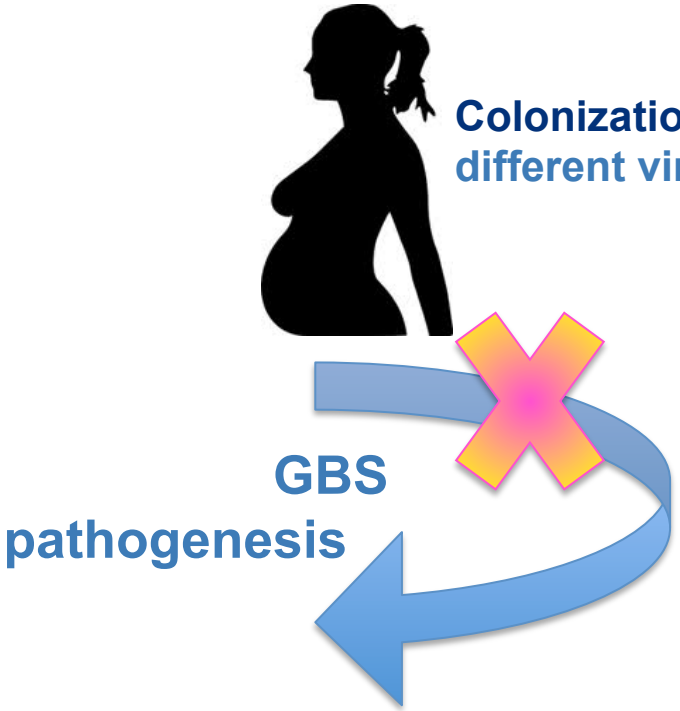
Phagocytes cells,
Antibodies, Complement



Which prevention strategy for GBS perinatal diseases ?

- **Intrapartum antibioprophylaxis**
- **Immunoprophylaxis**

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



Intrapartum antibioprophylaxis
> 4 (2) hours before delivery

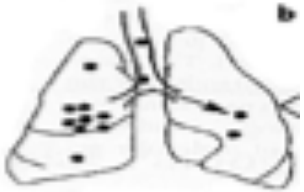
Stages in the pathogenesis of GBS neonatal EOD : *Bacterial & individual factors*

GBS vaccine
« still expected »

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

Ascendant transmission (amnionitis)

GBS pathogenesis



β-hemolysin, invasins (**pneumonia**)

Resi… phag… e
- Ca…
- C… pe… lase
- …..

Phagocytes cells,
Antibodies, Complement

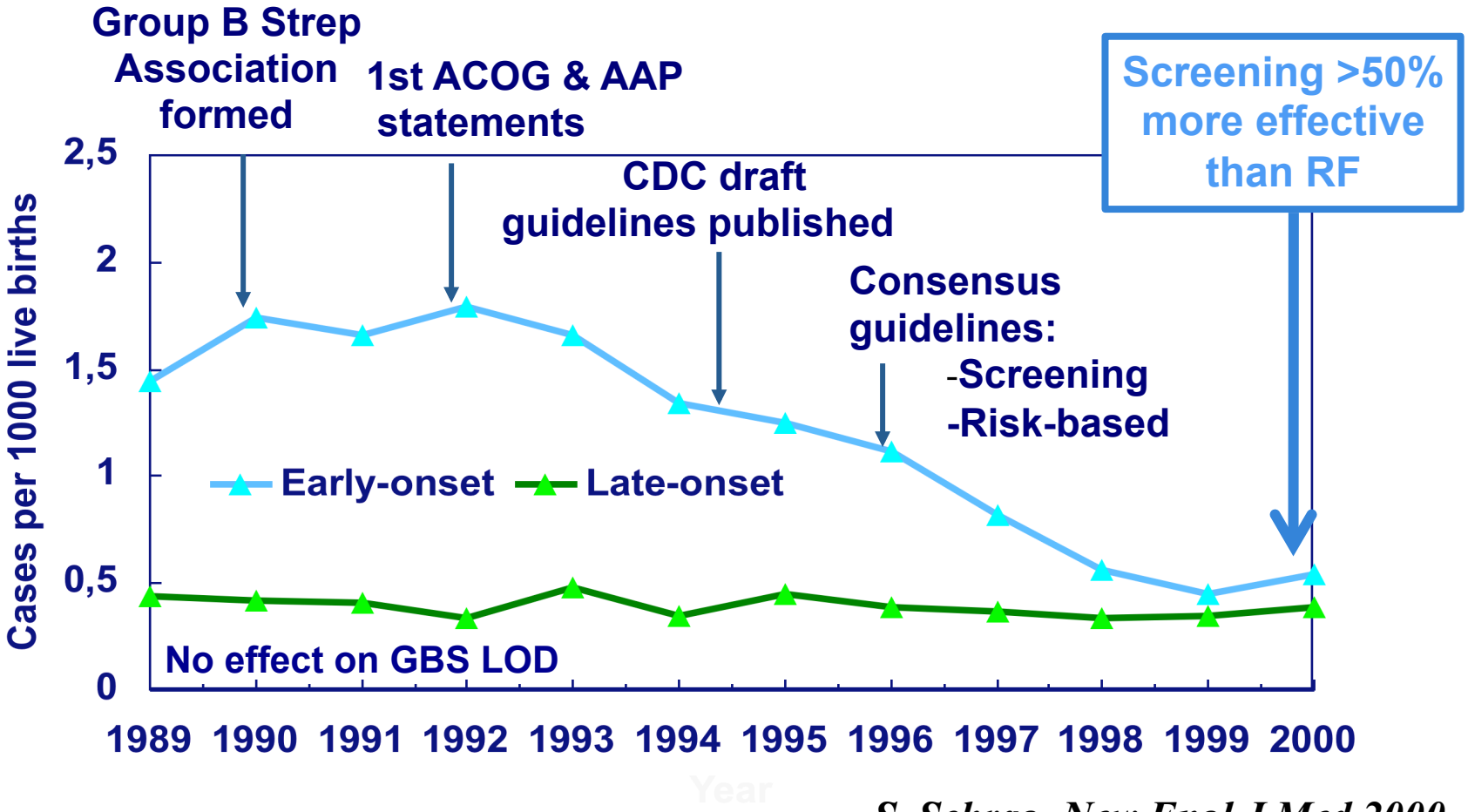
Prevention of perinatal GBS EOD

- **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

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

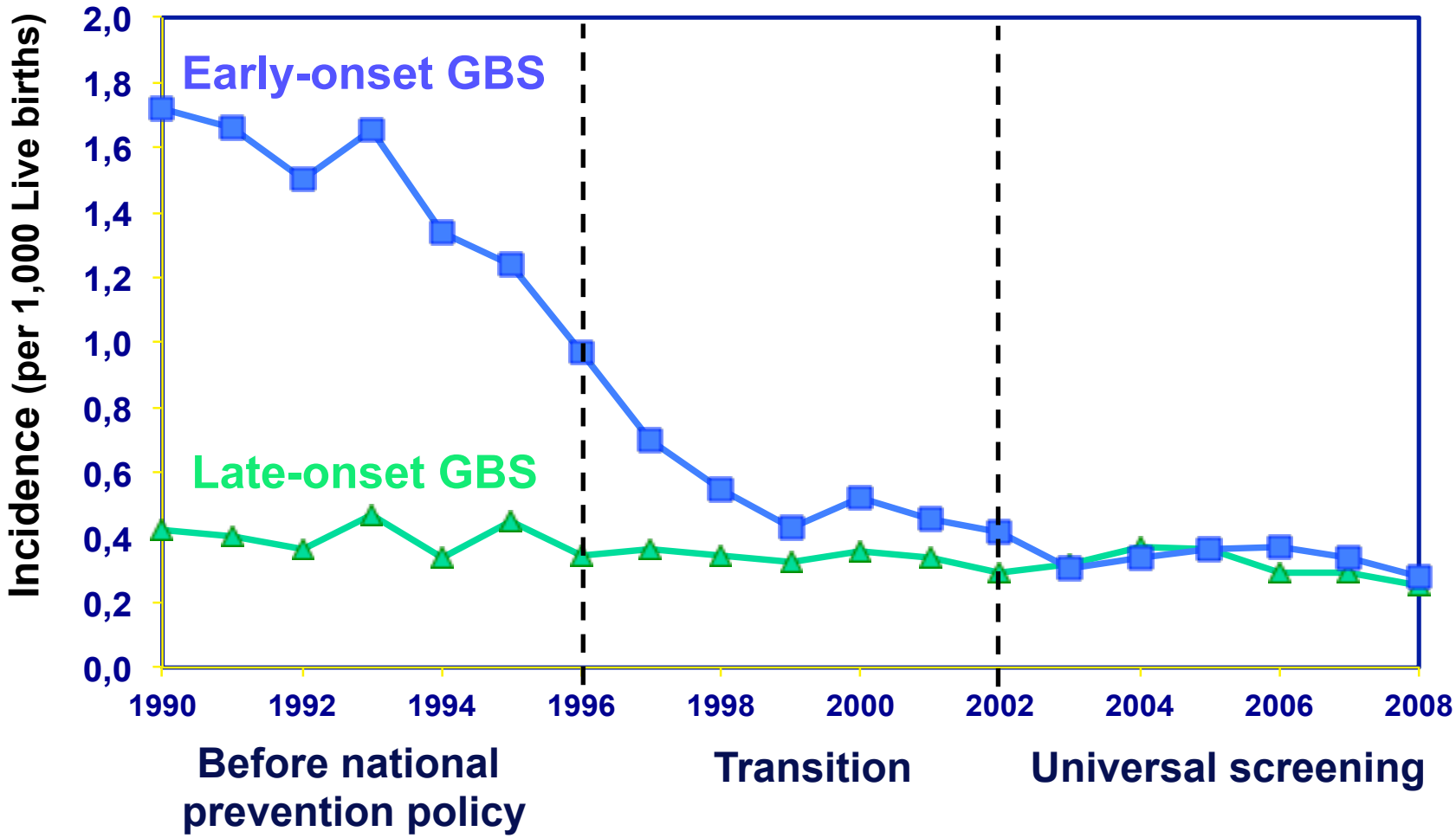
Why is Screening more protective than the risk-based approach ?

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

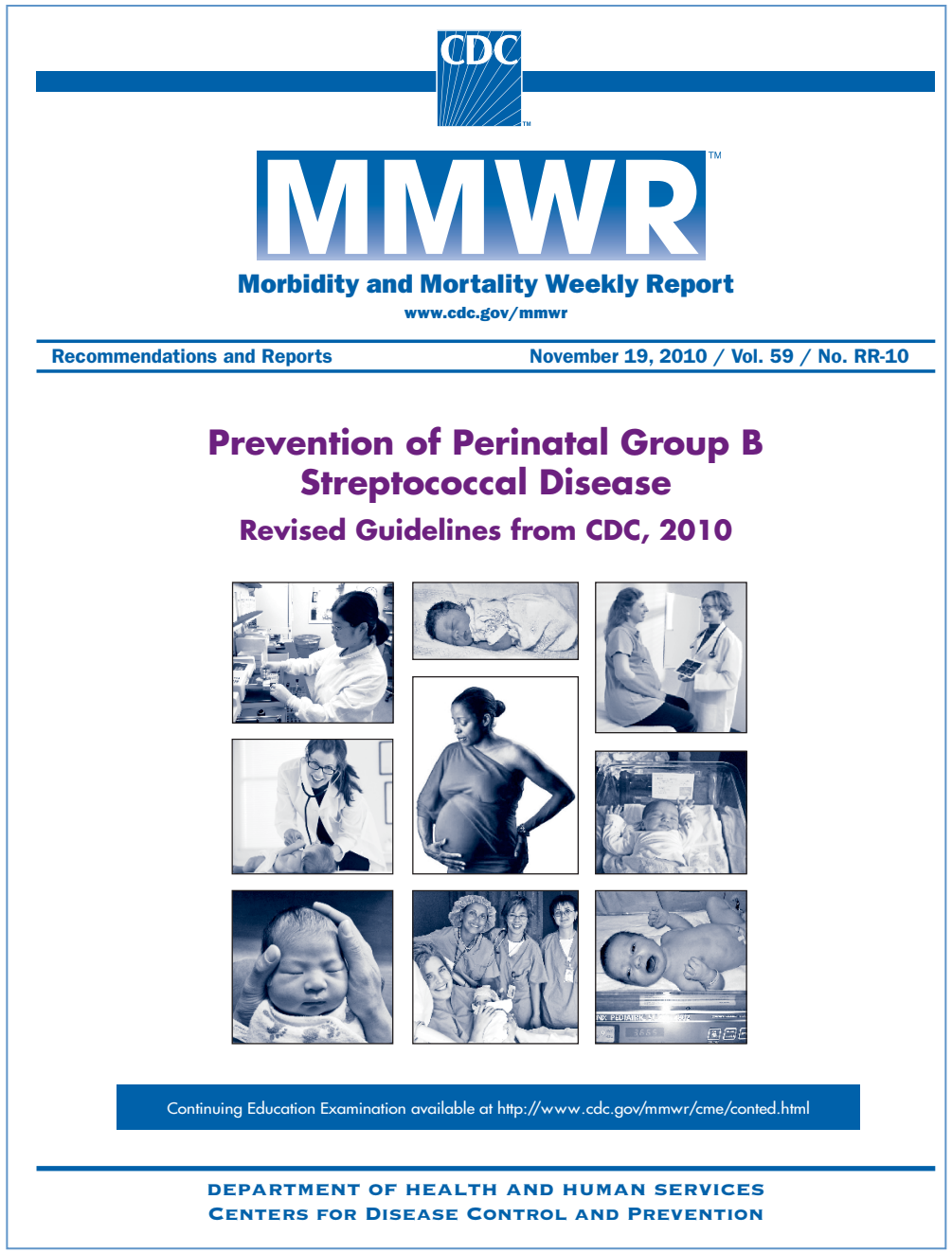
Broader coverage of « at-risk » population

- **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)



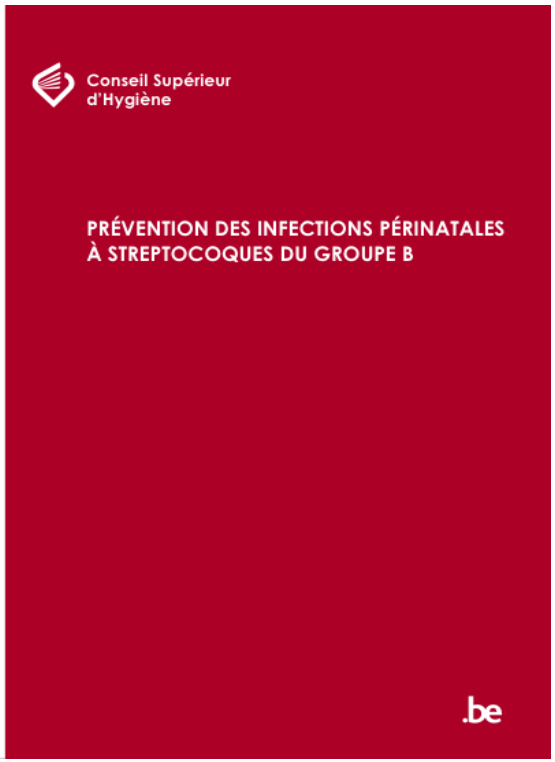
CDC, USA, MMWR, Vol 59 (RR-10) August 2010

Endorsed by

- ***AAP***
- ***ACOG***

SHC, Belgium July 2003

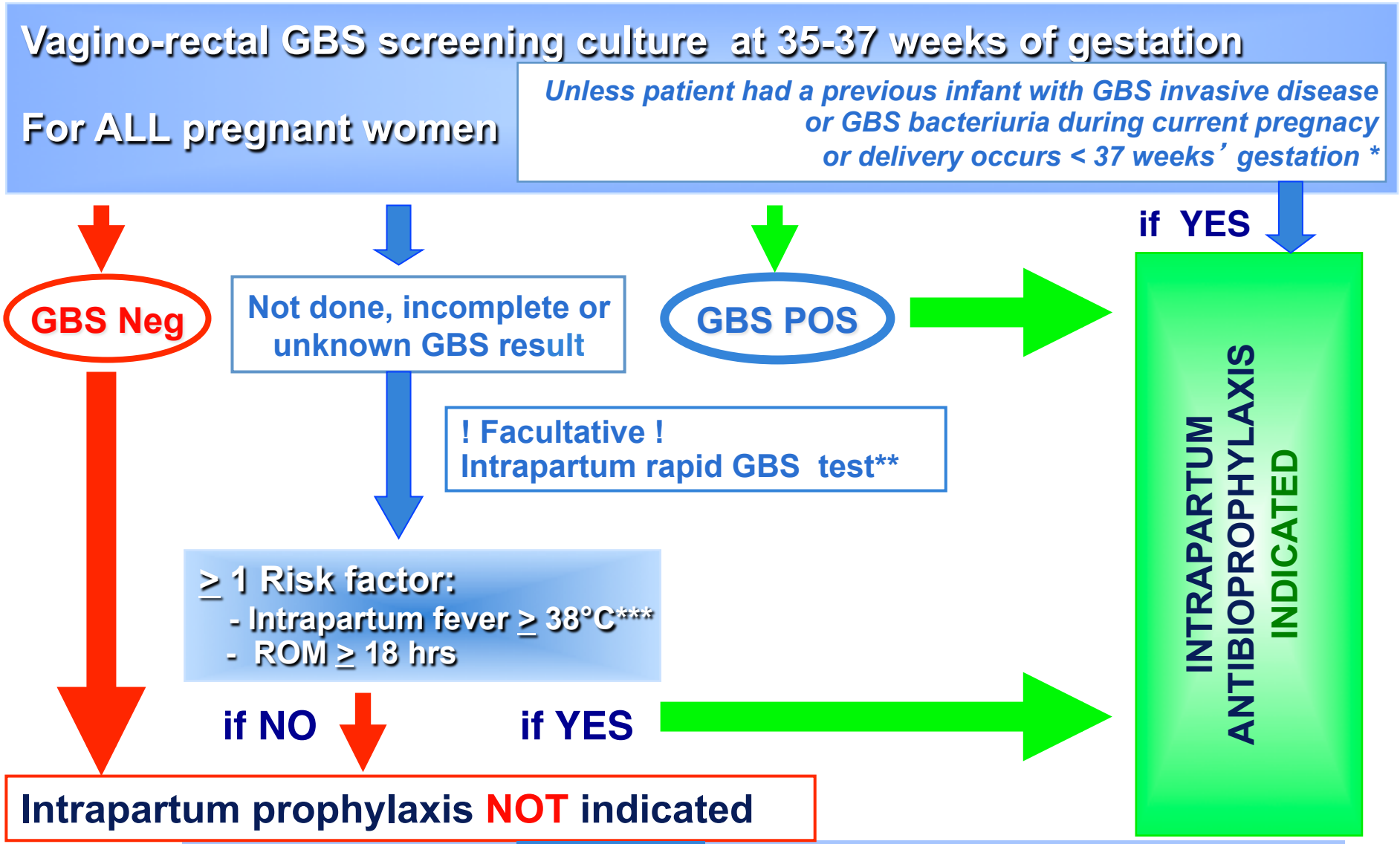
Revision ongoing

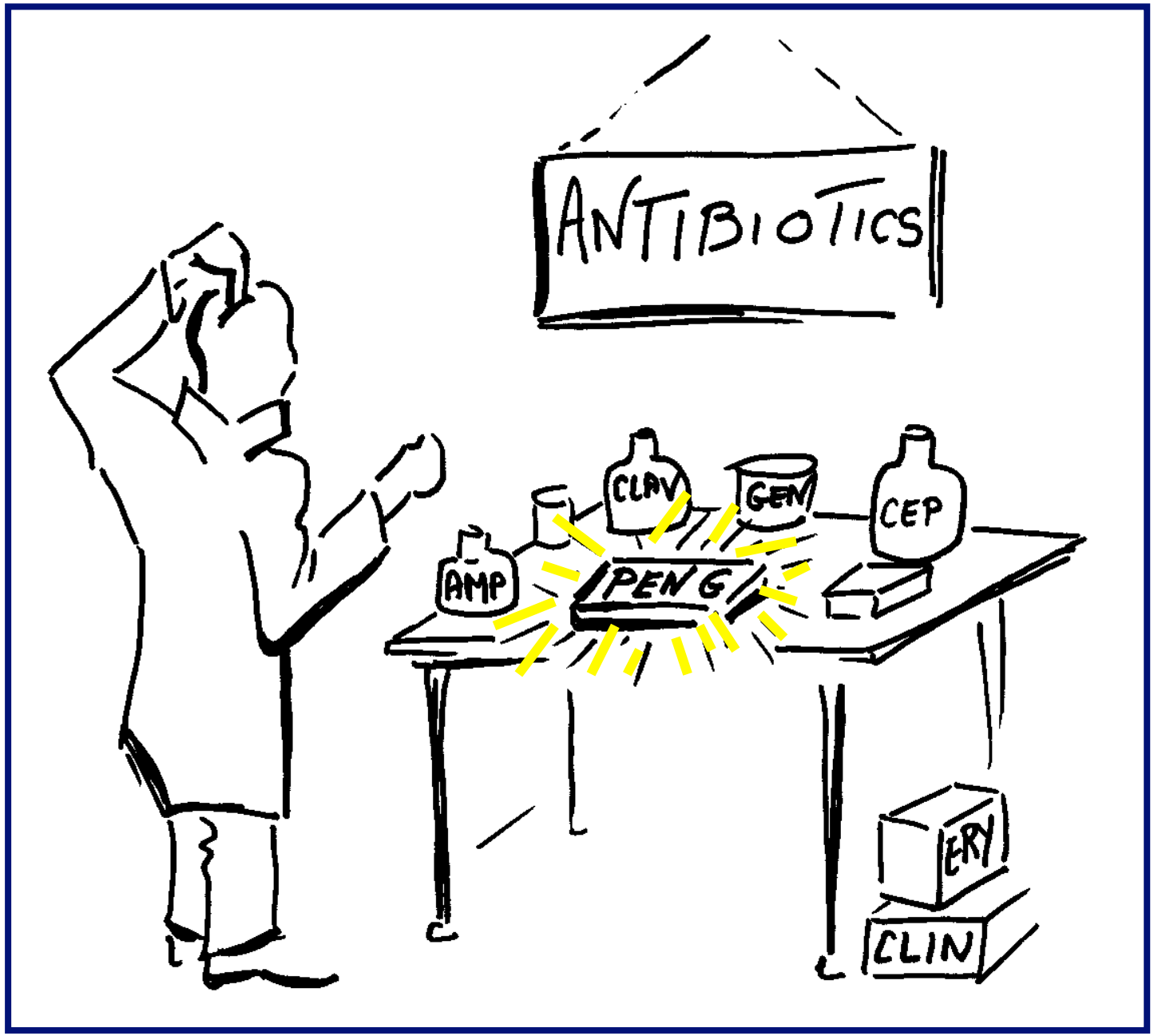


European strategies for prevention of GBS EOD

- Intrapartum antibioprophylaxis recommended
  - Screening-based strategy
    - Spain, 1998, 2003, revised 2012
    - France, 2001
    - Belgium, 2003, revision ongoing 2012
    - 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




ANTIBIOTICS
AMP
CLAV
GEN
PEN G
CEP
ERY
CLIN

Remaining burden of GBS EOD
Missed opportunities

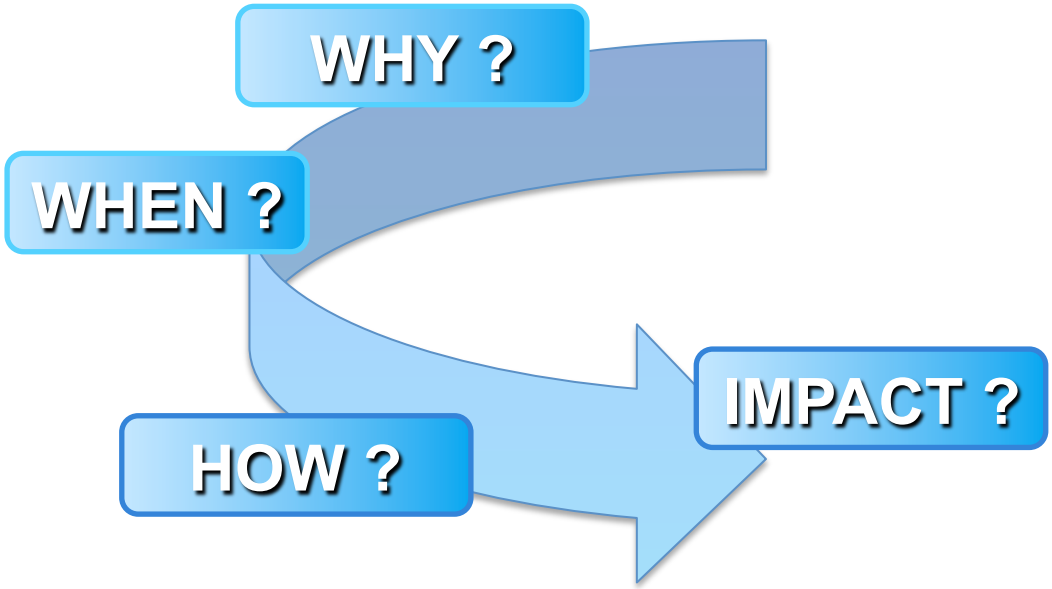
In spite of universal screening prevention strategy

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**
  - **Swabbed anatomic sites**
  - **Timing of sampling**
  - **Screening methods**
    - **Culture**
      - ***Procedure***
      - ***Media***
    - **Non-culture**

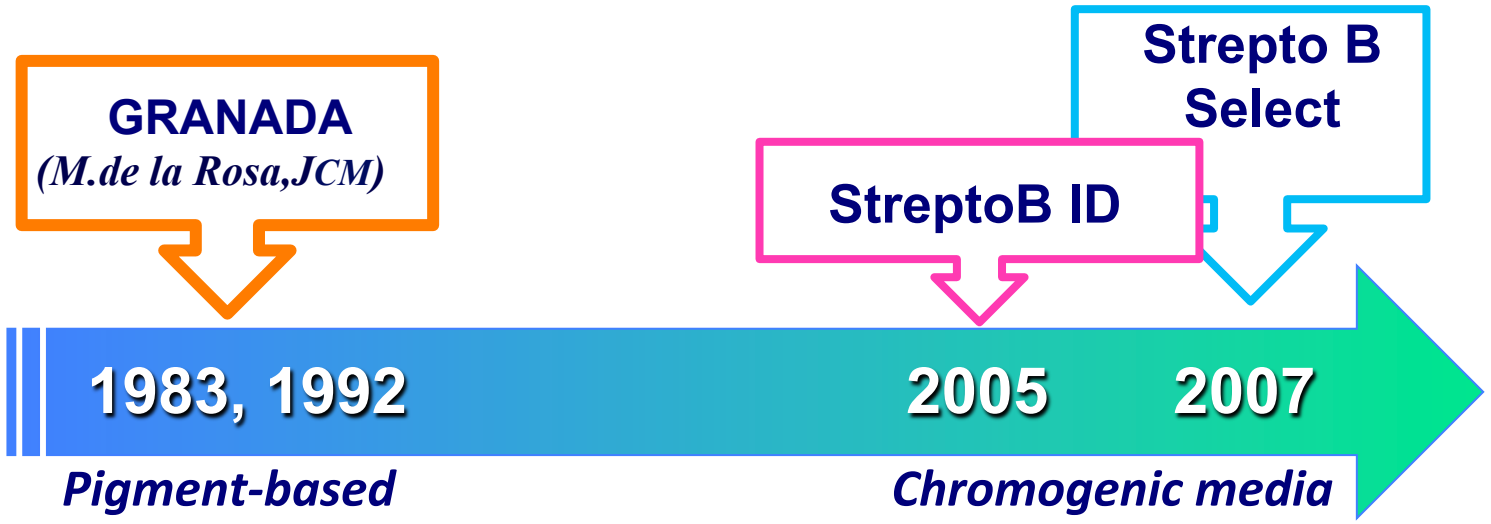
From direct plating on blood agar
Evolution of culture methods

Use of selective enrichment broth

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

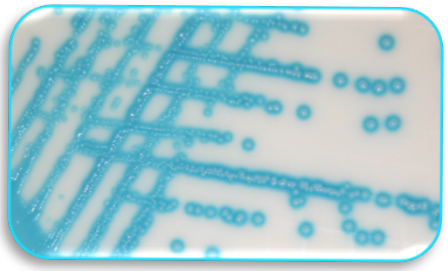
Use of differential agar media

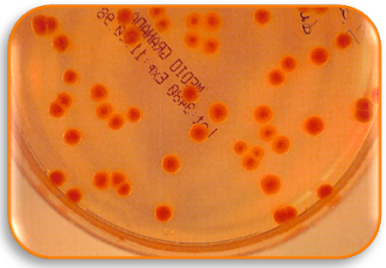
Recommended by some European guidelines (+ CDC 2010)

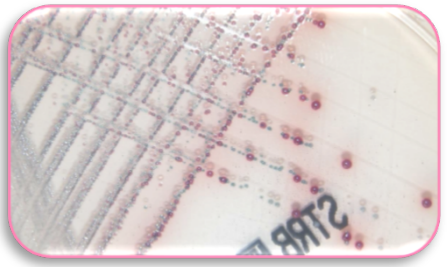


Which agar or which combination?

+/- Blood agar







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

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)

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
    - 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

Specimen Analysis "POCT" ?

Results

Optimal management of patient

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

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

Intrapartum screening theranostic approach: expected advantages

- **Identification of women without prenatal screening/ care**
- **Inclusion 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)

Xpert GBS for intrapartum screening

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** — **prenatal 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

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

Xpert GBS for intrapartum screening

Real-Time PCR Assay Provides Reliable Assessment of Intrapartum Carriage of Group B *Streptococcus*

Michelle J. Alfa, Shadi Sepehri, Pat De Gagne, Michael Helawa, Gunwat Sandhu, and Godfrey K. M. Harding

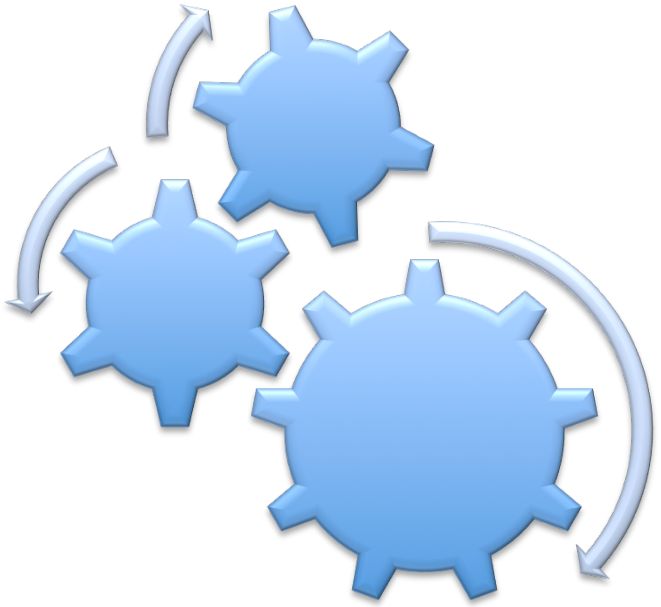
JCM, Sept. 2010, p. 3095–3099

- **205 Pregnant women**
- **Intrapartum Xpert GBS, Cepheid**
  - ***vs* intrapartum culture**

    24.5% GBS pos (vagino-rectal swab/LIM)
    - Sensitivity 91.7%
    - Specificity 99.3%
    - PPV 97.7%
    - NPV 97.3%

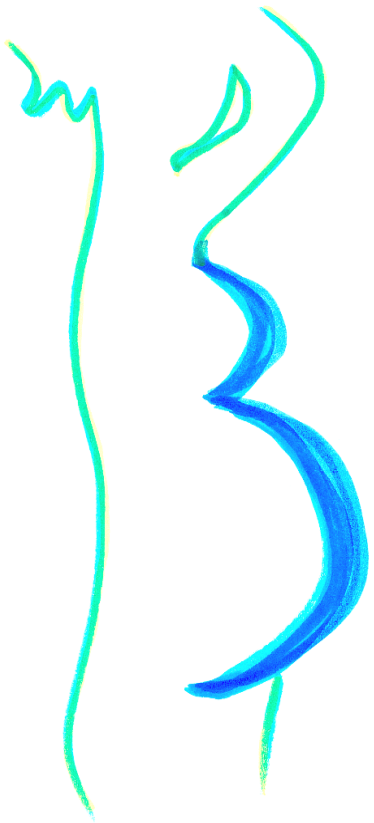
Real-time PCR, very promising, but …

- **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**
- **No antimicrobial result**
  - **In the future detection of R genes, but mixed microbiota !**



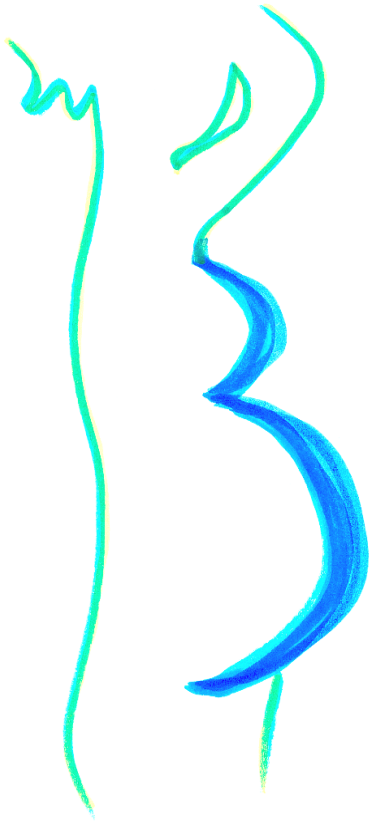
CONCLUSION
Take home messages

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**

Summary



“Screening” Prevention strategies

- **Culture-based GBS prenatal screening**
  - To optimize critical factors
  - Improved by selective differential agars
  - False +/False - !
- **Rapid intrapartum screening**

“From a dream to reality”

  - Real time PCR
    - Yes but costs, logistic, …
    - Need for more clinical trial and cost effectiveness evaluation

Thanks !

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

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 at low risk for anaphylaxis***
    - **Cefazolin, 2 g IV initial dose, then 1g IV every 8 h until delivery.**
  - ***Patients at high risk for anaphylaxis***
    - **Clindamycin, 900 mg IV every 8 hours until delivery.**
    - ***If GBS resistant to clindamycin : use vancomycin***