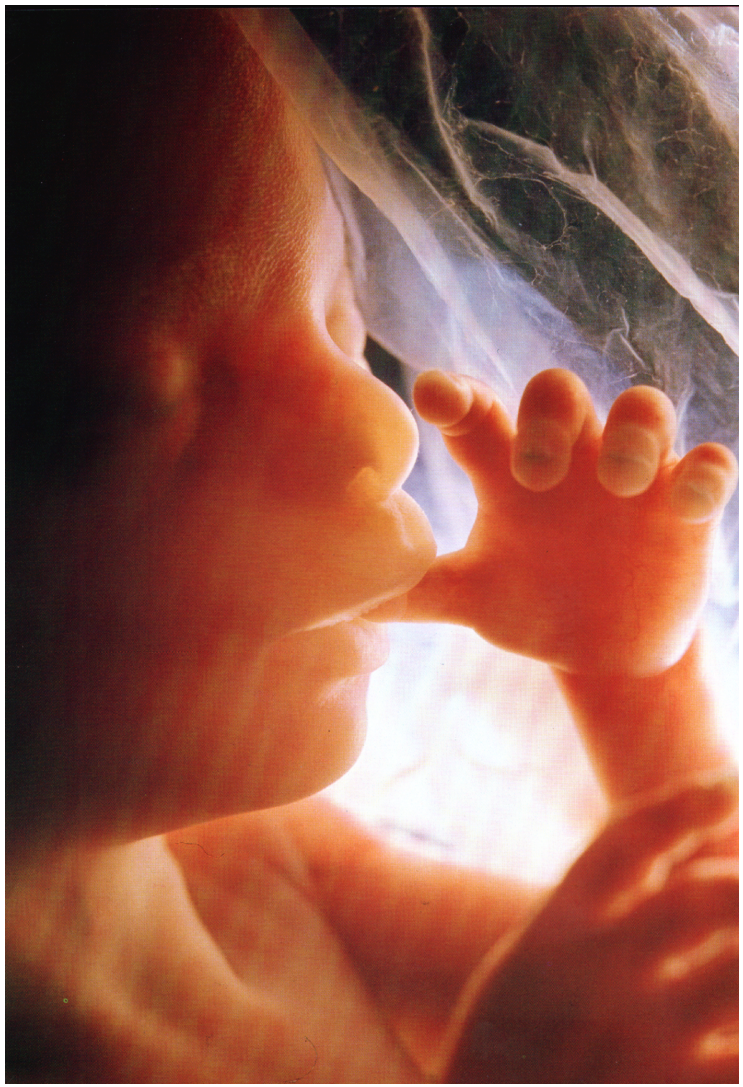


GBS AND THE NEONATE: PREVENTION STRATEGIES

Pierrette Melin

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

Disclosure

Communauté Française de Belgique

« Médecine préventive »
Epidémiologie et prévention des infections néonatales à streptocoques B

SEVENTH FRAMEWORK PROGRAMME

DEVANI

Wallonie

Waleo 3

RAIDGBS

Infectio Diagnostic

BD

BIOMÉRIEUX

BIO-RAD

INTRODUCTION & BURDEN

Streptococcus agalactiae or GBS

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

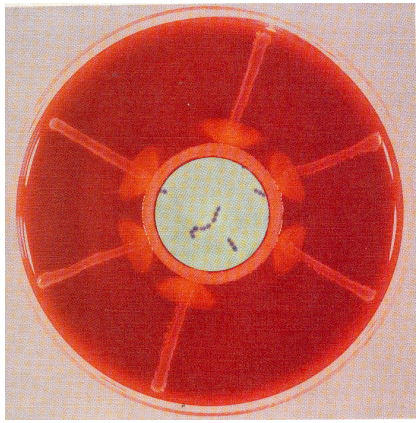
10 capsular serotypes (Ia, Ib, II-IX)

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

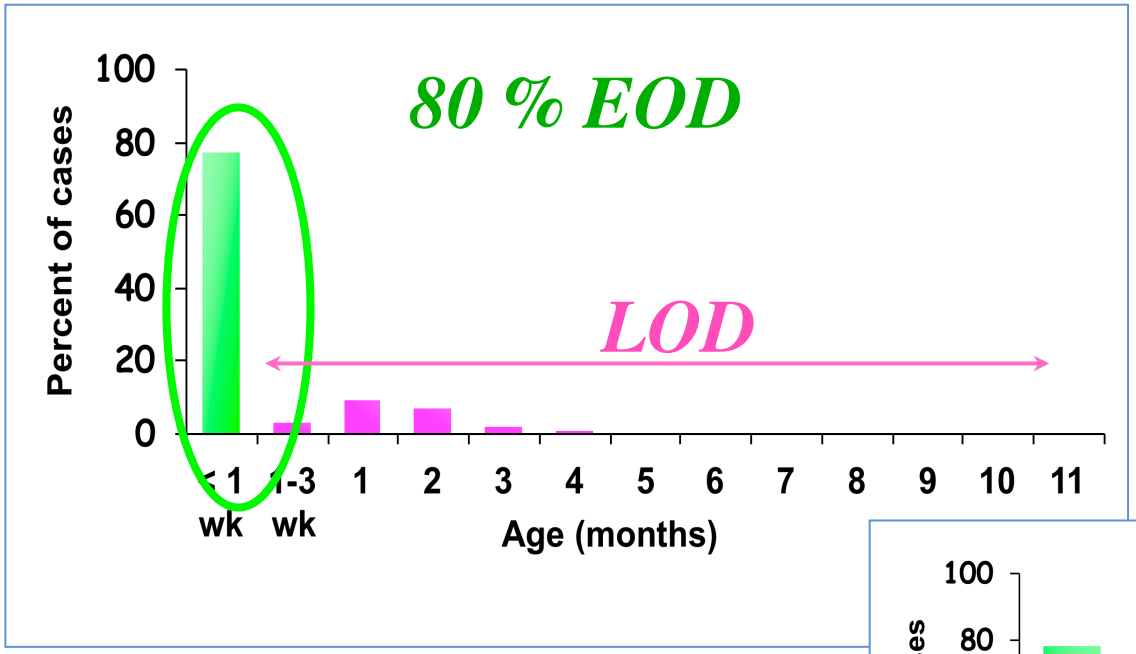
- **Maternal morbidity**
  - **Along pregnancy**
  - **Peripartum**
- **Serious diseases among elderly and adults with underlying diseases**
  - **Significant mortality**

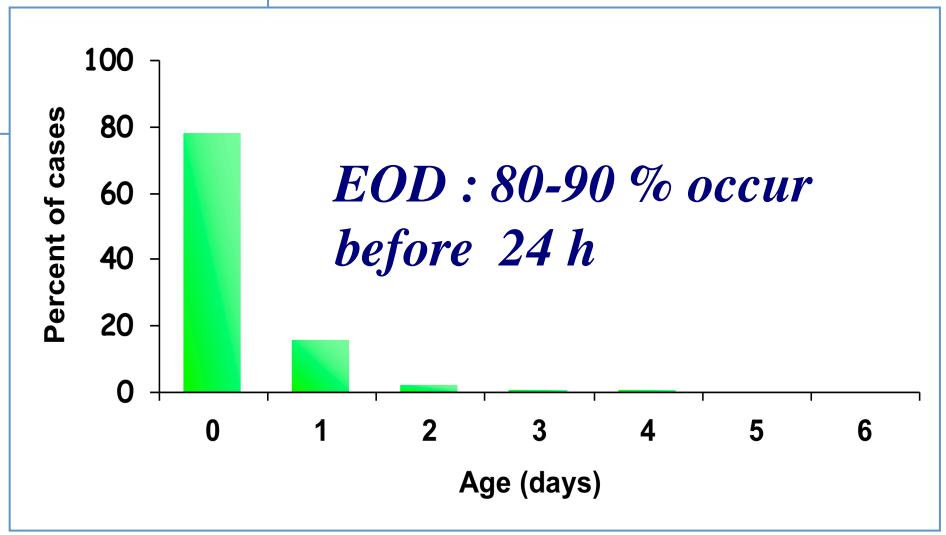
GBS Neonatal Infections

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

GBS Neonatal Infections

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





	EARLY Onset	LATE Onset
Incidence	0.5 - 4,7 per 1000	0.3 - 1,8 per 1000
Onset	≤ 6 days of live *(X : 1 - 10 h)*	> 6 days of live *(X : 1 mois)*
Transmission	Vertical *Intrapartum*	Horizontal *At delivery* *Nosocomial* *In the community*
Clinical signs	Respiratory distress with pneumonia Sepsis (Meningitis : 5-15 %)	Fever Bacteremia Meningitis (35%) (Cellulitis, Osteomyelitis)
Mortality	5 – 10%	0-6%
Sequelae	When meningitis : neurological sequelae Pulmonary weakness	
Serotypes	All (III, Ia & V)	III, mainly (Meningitis & Clone ST-17)

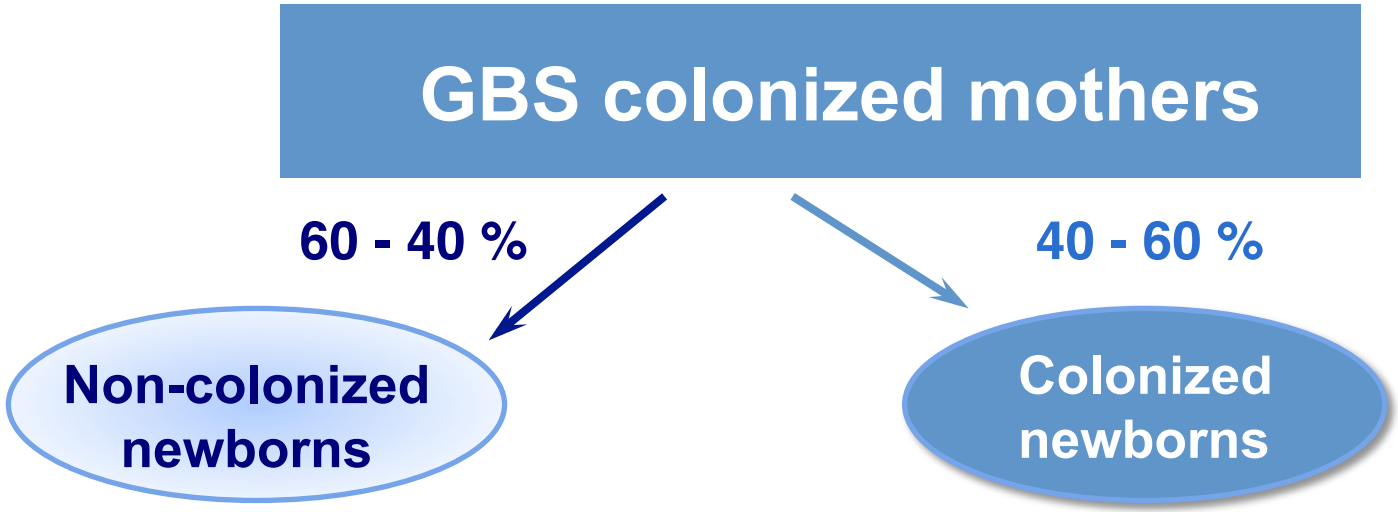
Burden of neonatal GBS early onset diseases in European countries

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

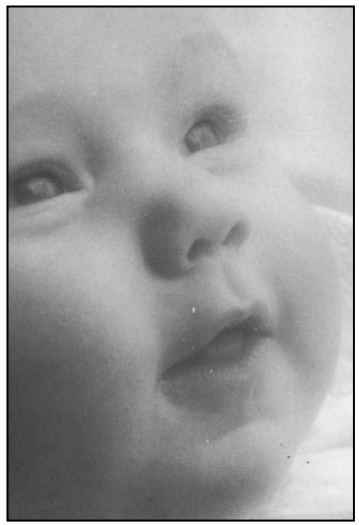
GBS colonized mothers

60 - 40 %

40 - 60 %

Non-colonized newborns

Colonized newborns



96 - 98 %

Asymptomatic

GBS EOD vertical transmission

GBS colonized mothers

60 - 40 %

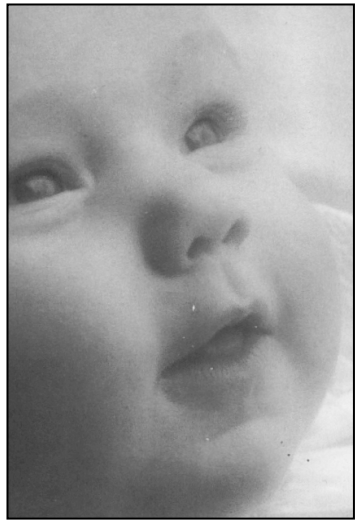
40 - 60 %

Non-colonized newborns

Colonized newborns

Risk factors

2 - 4 % GBS EOD



96 - 98 %

Asymptomatic

sepsis
pneumonia
meningitis
long term sequelae

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

Meningitis

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

Brain barrier
Pili,
β-hemolysin, …

Ascendant **transmission** (amnionitis)

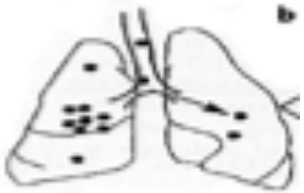
GBS pathogenesis

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

GBS maternal colonization

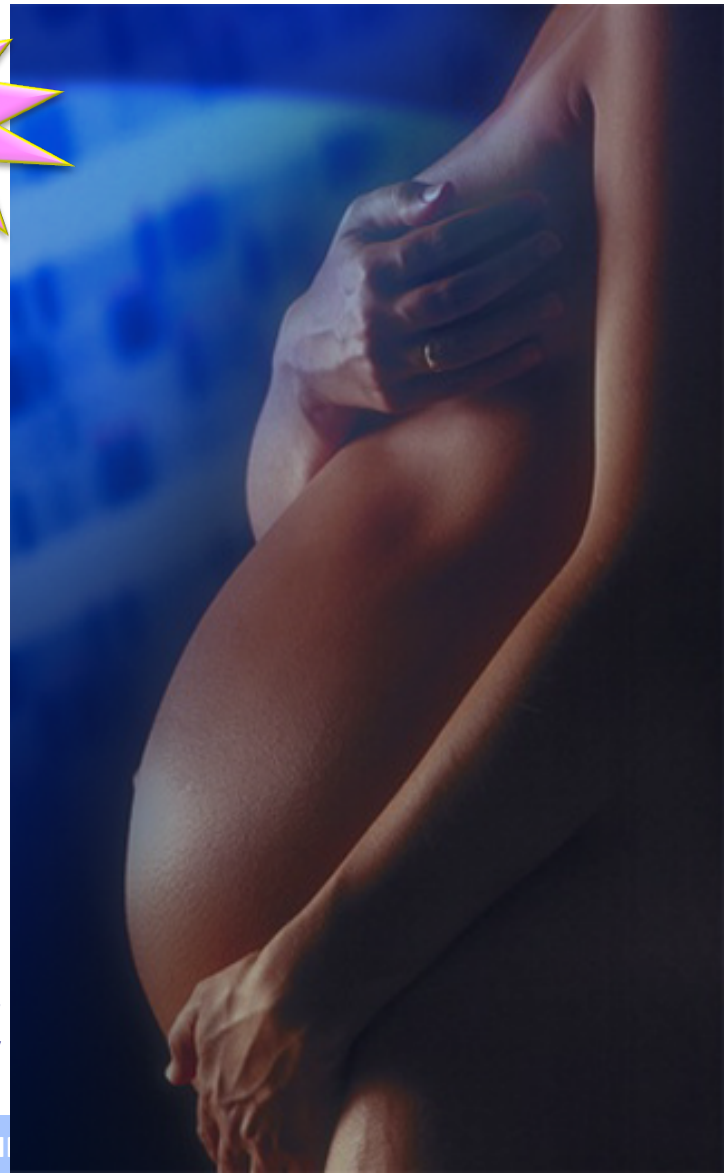
Risk factor for early-onset disease (EOD) :
vaginal GBS colonization at delivery

- **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.

Data from DEVANI Project (2008-2011)

Belgium – Bulgaria – Czech Republic – Denmark – Germany – Italy – Spain – United Kingdom

EUROPEAN DATA

Mothers of newborns with EOD

(Devani, 2008-2010 Europe)

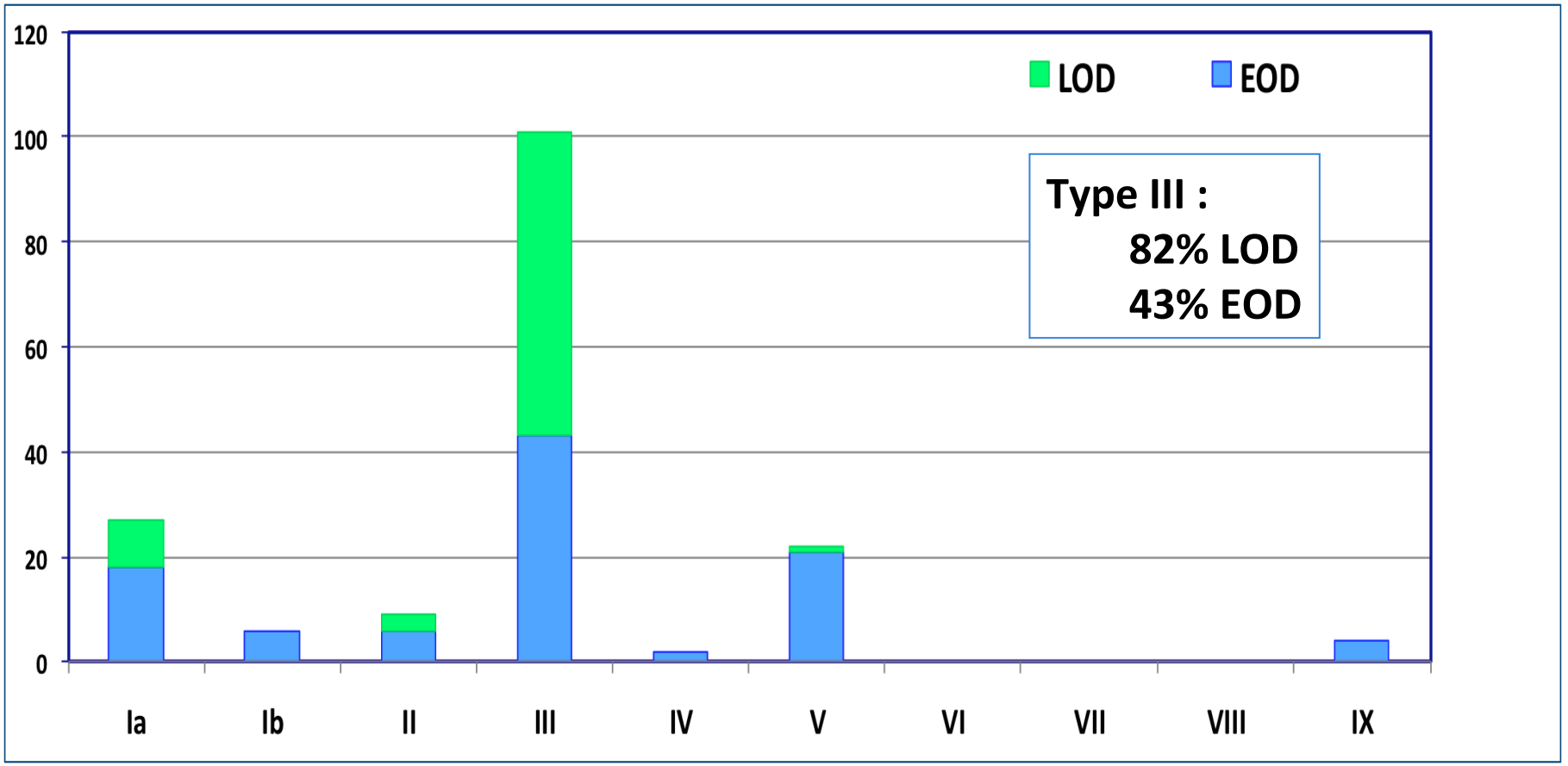
PW Screened in prenatal care

	Cases' mothers	GBS positive Control (mothers of healthy babies)
▪ Vagino-rectal swab	24%	
▪ IAP if GBS positive	41%	84%

Notified risk factors for EOD

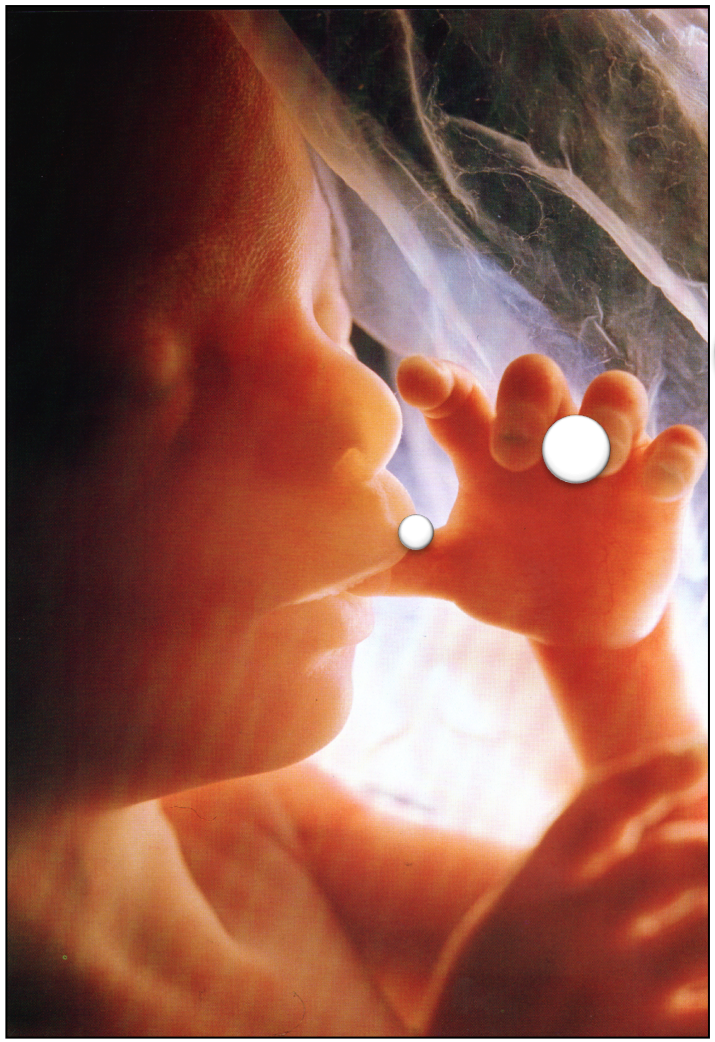
▪ ROM >18h	24.8%	5%
▪ T° >= 38°C	14.3%	1%
▪ GBS Bacteriuria	8.5%	3.9%
▪ Previous GBS sibling	0.9%	0.3%

Distribution of CPS serotypes among GBS from neonatal infections
(Devani, 2008-2010 Europe)



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

GUIDELINES



Which prevention strategy for GBS perinatal diseases ?

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

Prevention of perinatal GBS EOD

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

(clinical trials in late 80s)

Risk-based strategy
or
Screening-based strategy

Prevention of perinatal GBS EOD

- Screening-based strategy

INTRAPARTUM ANTIMICROBIAL PROPHYLAXIS

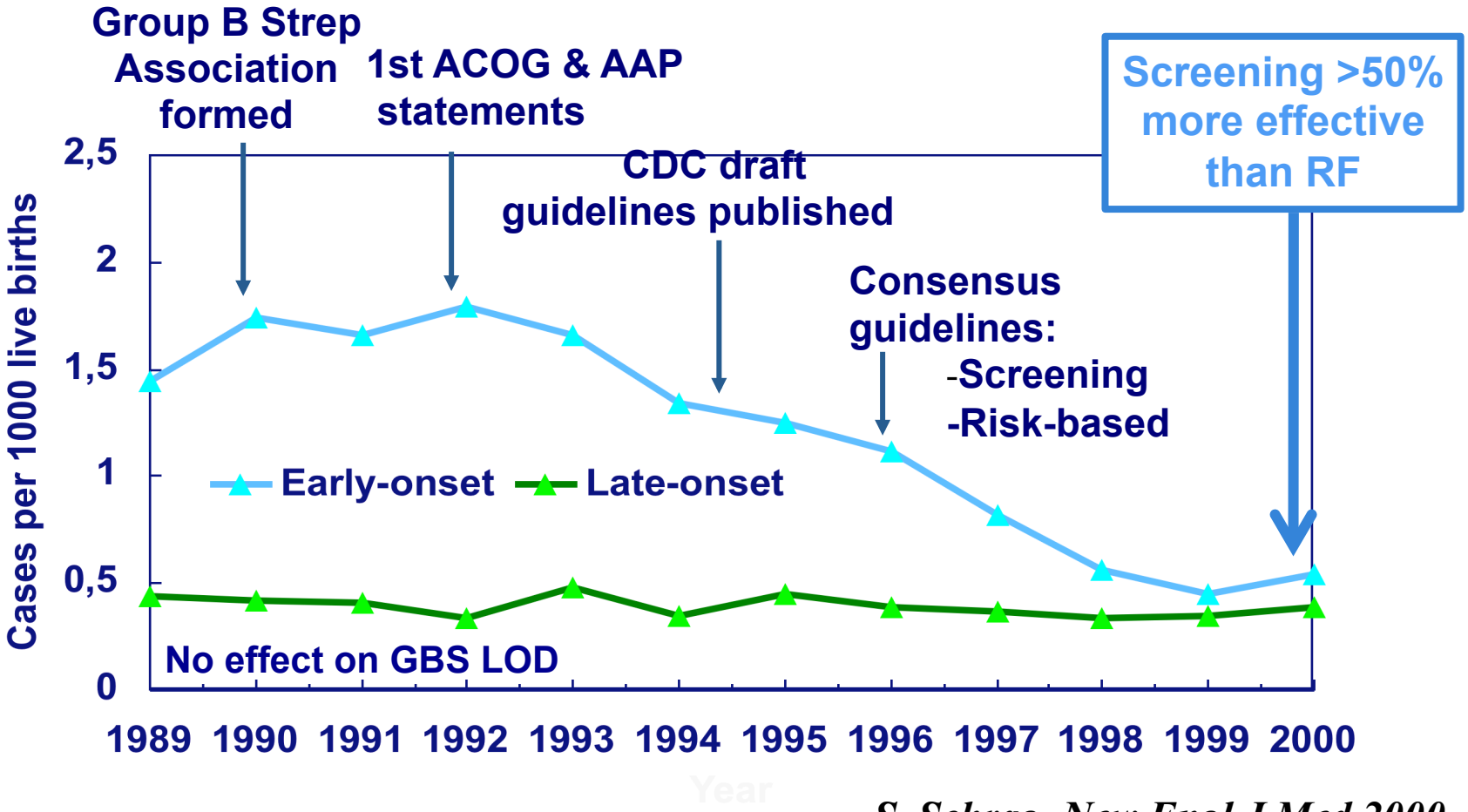
Main goal :

- To prevent 70 to 80 % of GBS EO cases

Secondary :

- To reduce peripartum maternal morbidity

Impact of prevention practices Early- and Late-onset GBS Diseases in the 1990s, U.S.



S. Schrag, New Engl J Med 2000
Schrag S. et al. N Engl J Med 2002; 347:233-9

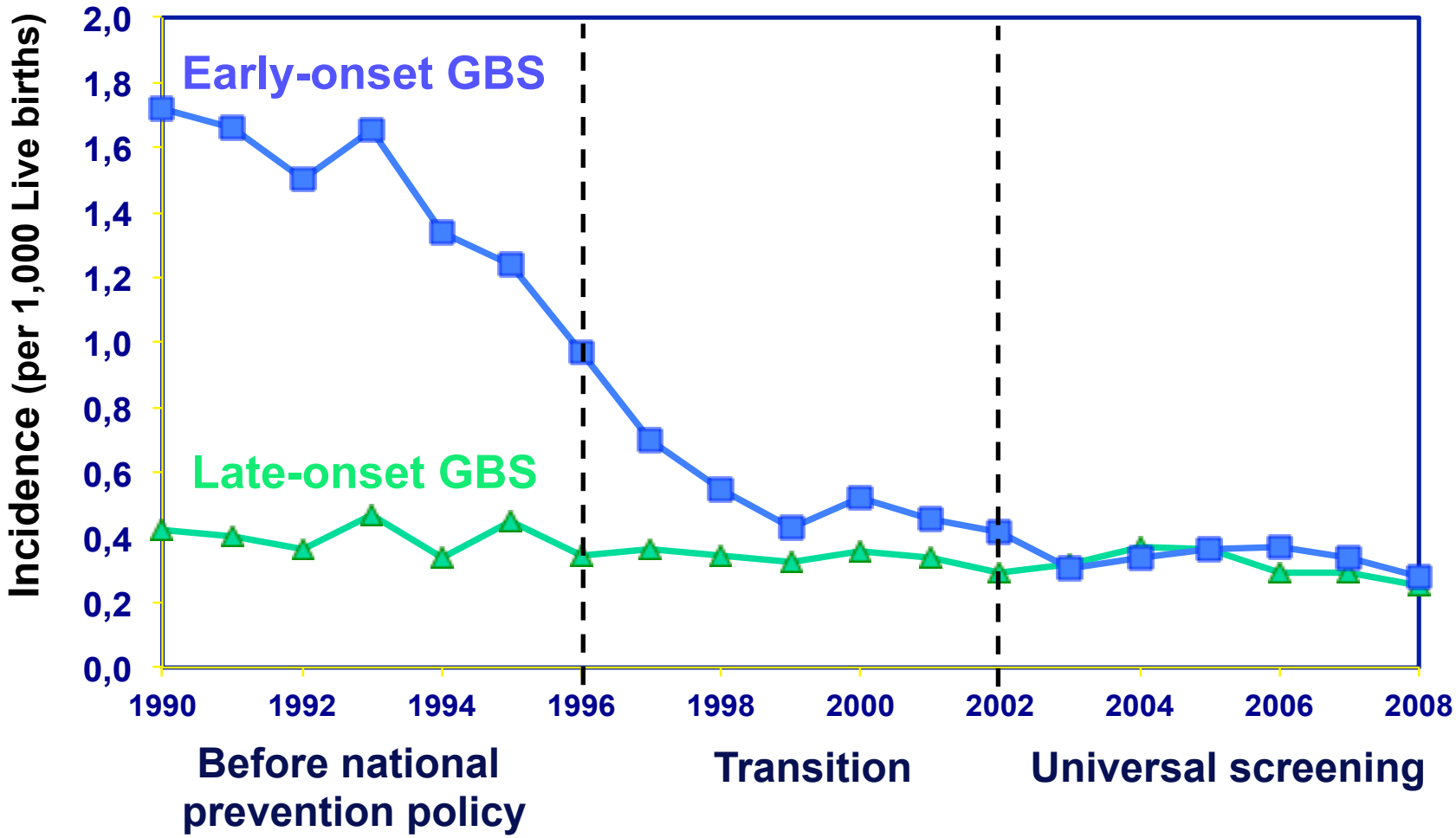
Why is Screening more protective than the risk-based approach ?

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

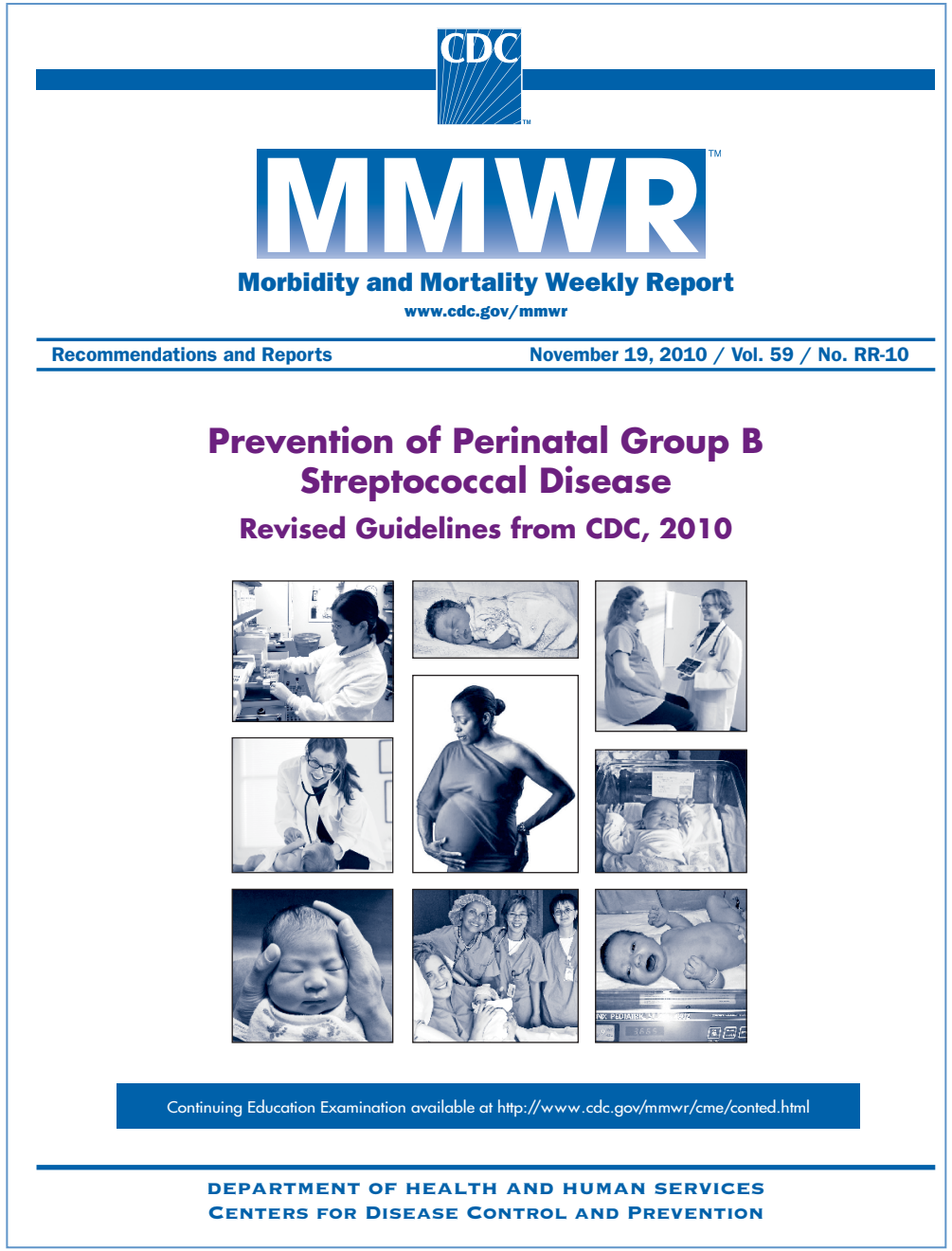
Broader coverage of « at-risk » population

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

Impact of prevention practices
Early- and Late-onset GBS Diseases, U.S.



Incidence of early- and late-onset invasive group B streptococcal disease in selective Active Bacterial Core surveillance areas, 1989-2008 (CDC 2010)

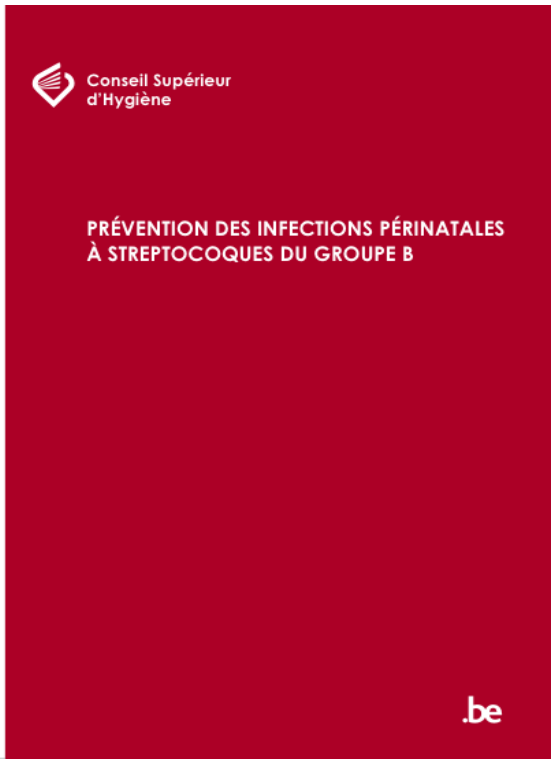


CDC, USA, MMWR, Vol 59 (RR-10) August 2010

Endorsed by

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

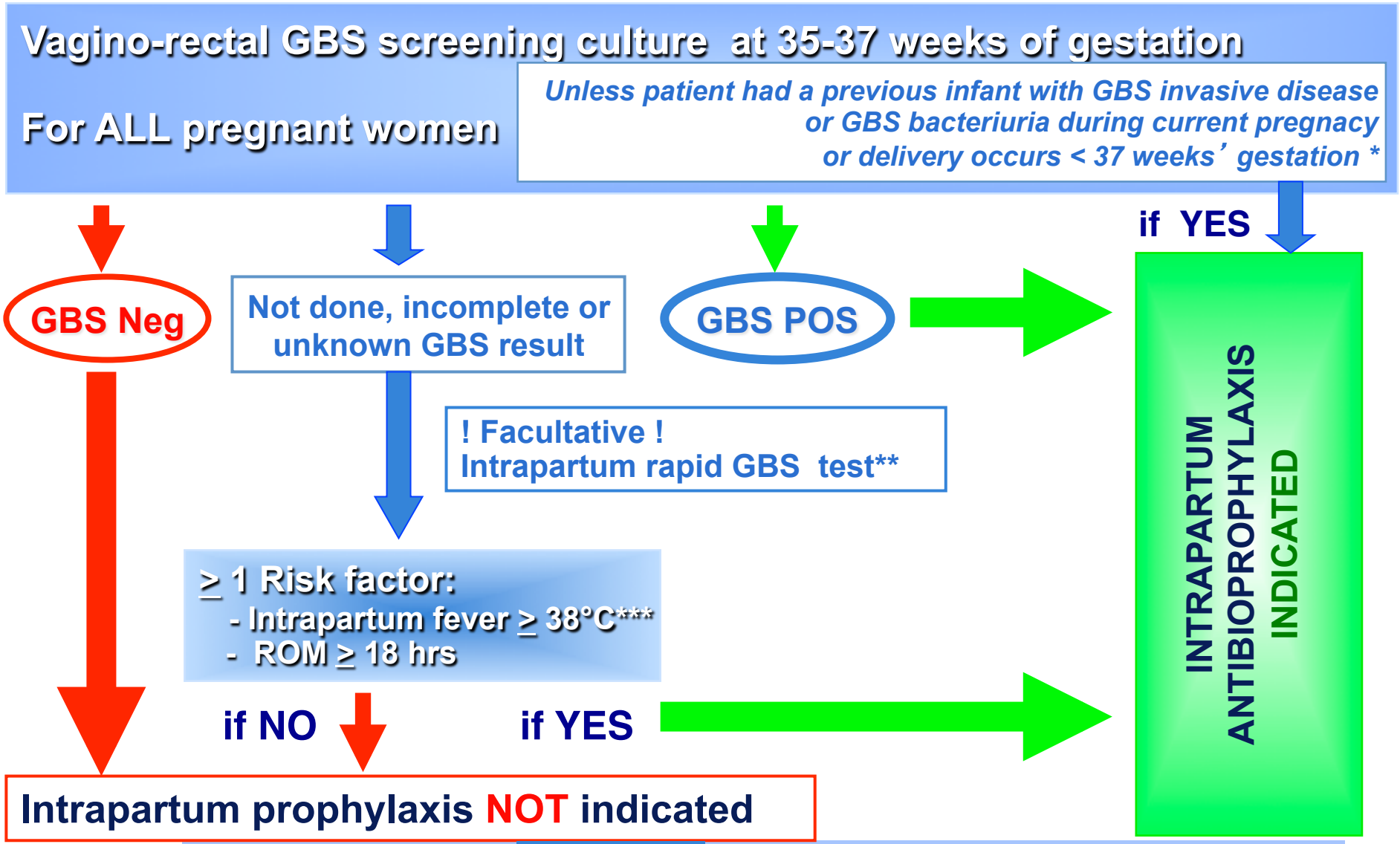
SHC, Belgium July 2003
Revision ongoing



European strategies for prevention of GBS EOD

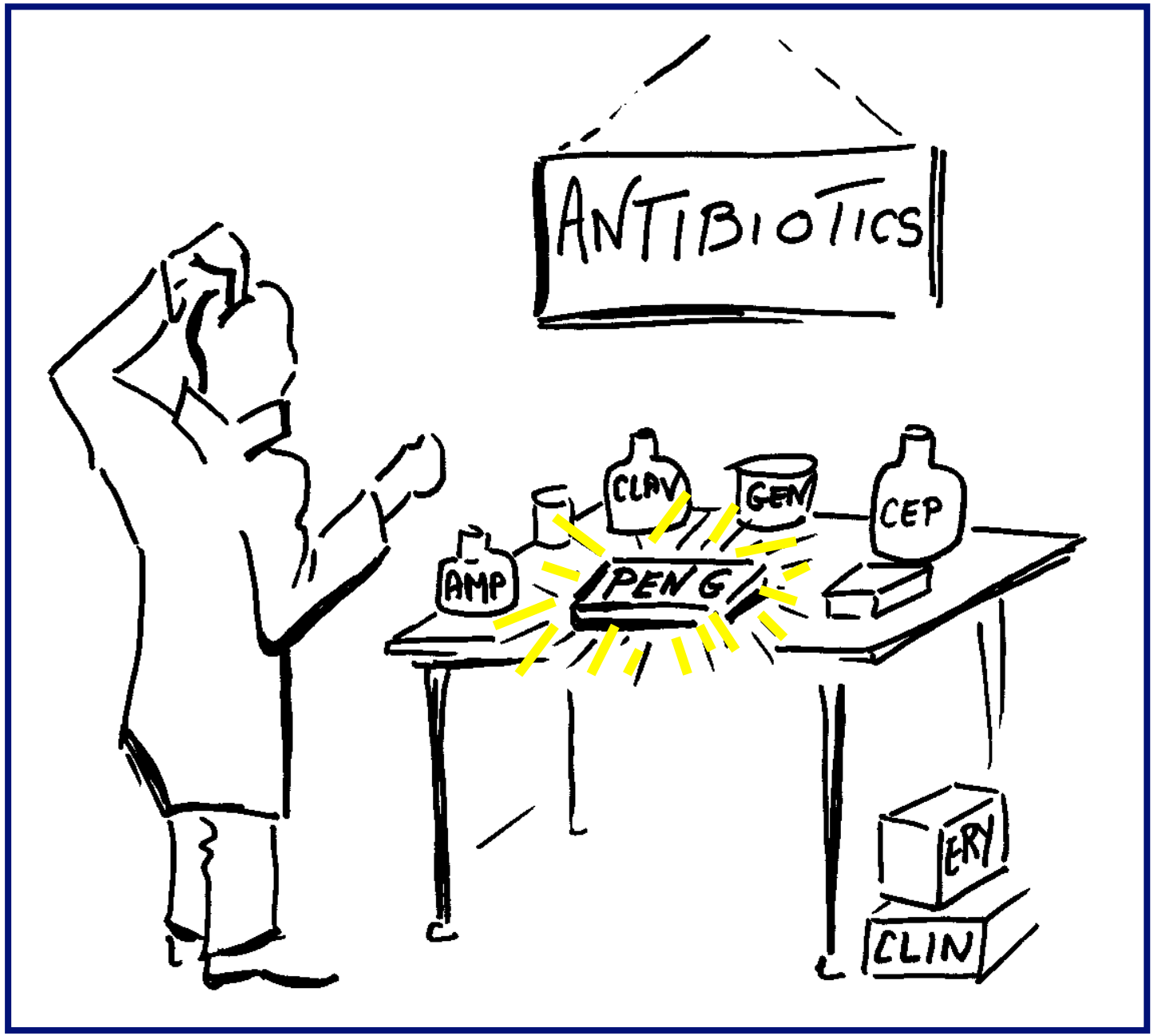
- Intrapartum antibioprophylaxis recommended
  - Screening-based strategy
    - Spain, 1998, 2003, revised 2012
    - France, 2001
    - Belgium, 2003, revision ongoing 2012
    - Germany, 1996, revised 2008
    - Switzerland, 2007
  - Risk-based strategy
    - UK, the Netherlands, Denmark
- No guidelines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

Universal screening-based strategy for prevention of GBS perinatal disease



Gynecologists
Obstetricians
Microbiologists
Midwives
Neonatalogists

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


ANTIBIOTICS
AMP
CLAV
GEN
PEN G
CEP
ERY
CLIN

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***

Concerns about potential adverse / unintended consequences of prophylaxis

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

Concerns : Clinically relevant antimicrobial resistance

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

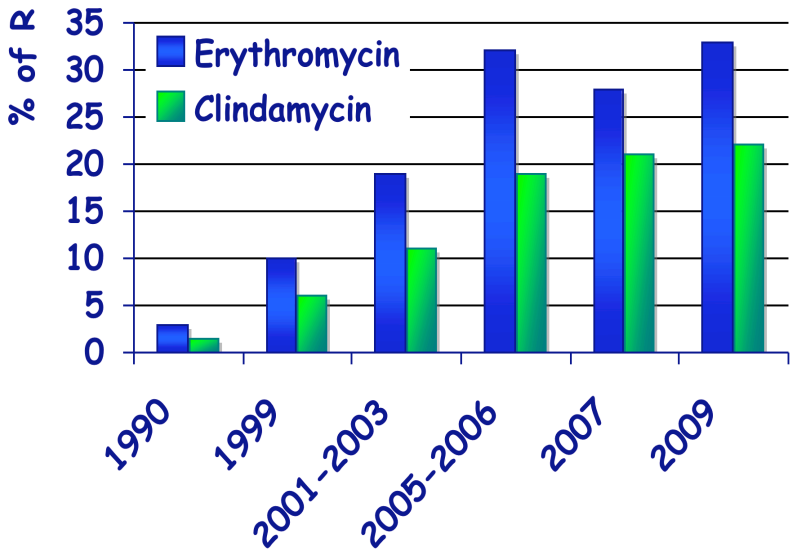
Noriyuki Nagano et al, AAC 2008

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

Erythromycin and clindamycin resistance

Erythromycin R

- USA, 15-35%
- Ireland, 15-20%
- Europe, 10-30%
- Belgium, 32%



GBS isolated in Belgium, from invasive diseases

Concerns about potential adverse / unintended consequences of prophylaxis

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

  →Algorithm for secondary prevention of EOD among newborns
    - **Symptoms; maternal chorioamnionitis; prophylaxis; gestational age; time of rupture of membrane**

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

Remaining burden of GBS EOD
Missed opportunities

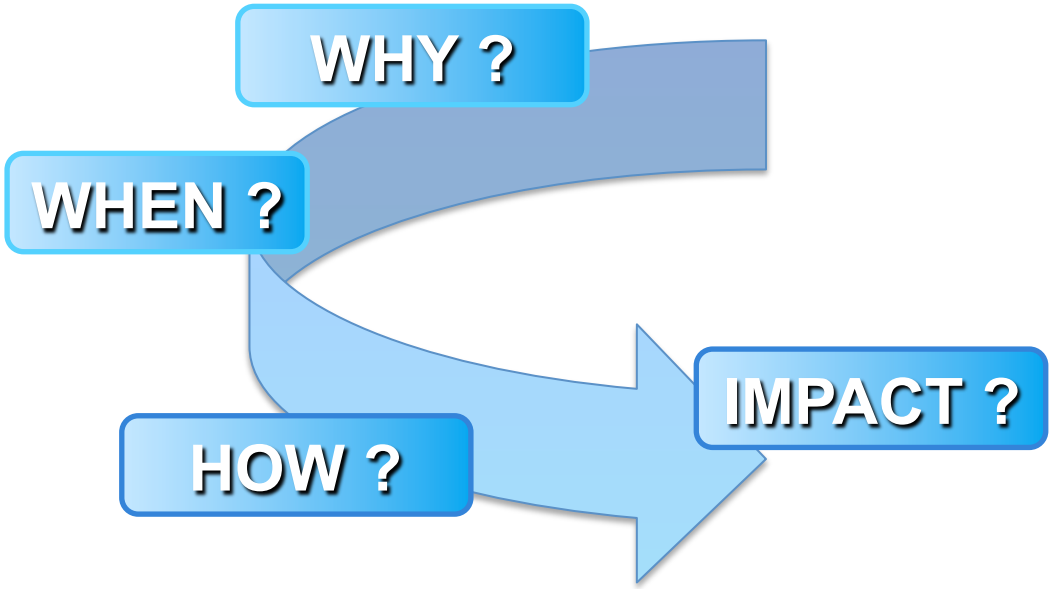
In spite of universal screening prevention strategy

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**

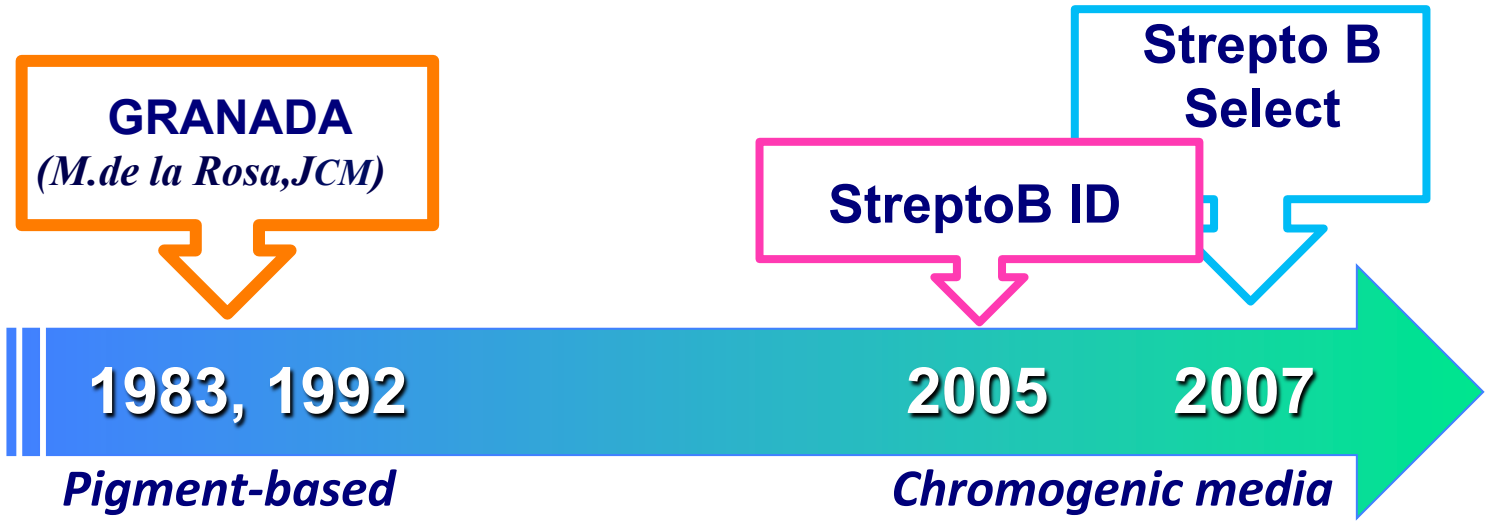
From direct plating on blood agar
Evolution of culture methods

Use of selective enrichment broth

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

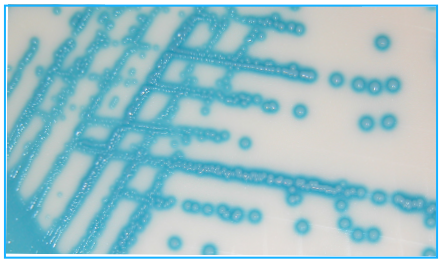
Use of differential agar media

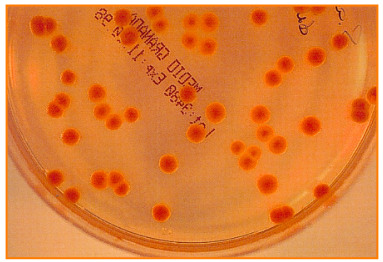
Recommended by some European guidelines (+ CDC 2010)

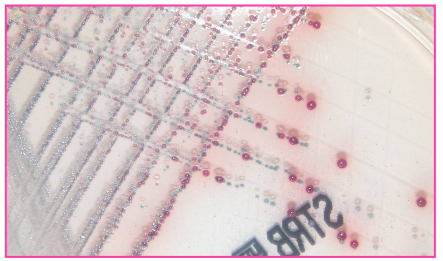


Which agar or which combination?

+/- 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

Alternative to GBS prenatal screening: intrapartum screening
Theranostic approach

Turnaround time

collect specimen at admission

Optimal management of patient

Specimen analysis

Results

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

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

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 (35-50 min) (can be performed as a POCT)**

Real-time PCR, very promising, but …

- **Still an expensive technology**
  - Cost effective ?
- **Logistic**
  - 24 hours 7 days
  - In the lab?
  - In the obstetrical department ?
- **In combination with prenatal screening strategy ?**
  - CDC 2010
- **No antimicrobial result**
  - In the future detection of R genes, but mixed microbiota !

Prevention of GBS EOD and LOD

VACCINE

Vaccines To Prevent GBS Disease

Improved use of intrapartum antimicrobial prophylaxis has resulted in a substantial reduction in early-onset GBS disease, but it is unlikely to prevent most late-onset neonatal infections, GBS-related stillbirths, or prematurity, and does not address GBS disease in nonpregnant adults. Immunization of women during or before pregnancy could prevent peripartum maternal disease and protect infants from perinatally acquired infection by transplacental transfer of protective IgG antibodies (*125,126*). This would eliminate the need for prenatal GBS screening and intrapartum antimicrobial prophylaxis, along with associated costs and concerns regarding the potential adverse effects of intrapartum antibiotic use discussed previously.

Background

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

Baker C et Kasper D, 1976, NEJM

Vaccine for pregnant women:

Likely the most effective, sustainable and cost effective approach

GBS Vaccines, since the 1980s Challenges

Capsular polysaccharide vaccines

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

GBS Vaccines

GBS Protein-based Vaccine

- **Ag = Surface proteins**
  - **Cross protection against different serotypes**
  - **Better immunogenicity**
    - **Humoral response T-cell dependent**
      = long lasting immunity

Protein-based Vaccines

Protein	Protective Ab (in mouse)	associated serotypes
Alpha-like proteins		
Alpha	**Yes**	**Ia, Ib et II**
Alp1		**Ia**
Rib	**Yes**	**III**
Alp2	**Yes**	**V, VIII**
Alp3	**Yes**	**V, VIII**
Beta C protein	**Yes**	**Ib**
C5a peptidase	**Yes**	**All**
Sip (1999)	**Yes**	**All**
BPS	**Yes**	**All**

Sip = Surface Immunogenic Protein (Brodeur, Martin, Québec)
BPS= Groupe B Protective surface Protein

Protein-based Vaccines

Reverse vaccinology approach

Knowledge of complete GBS genome

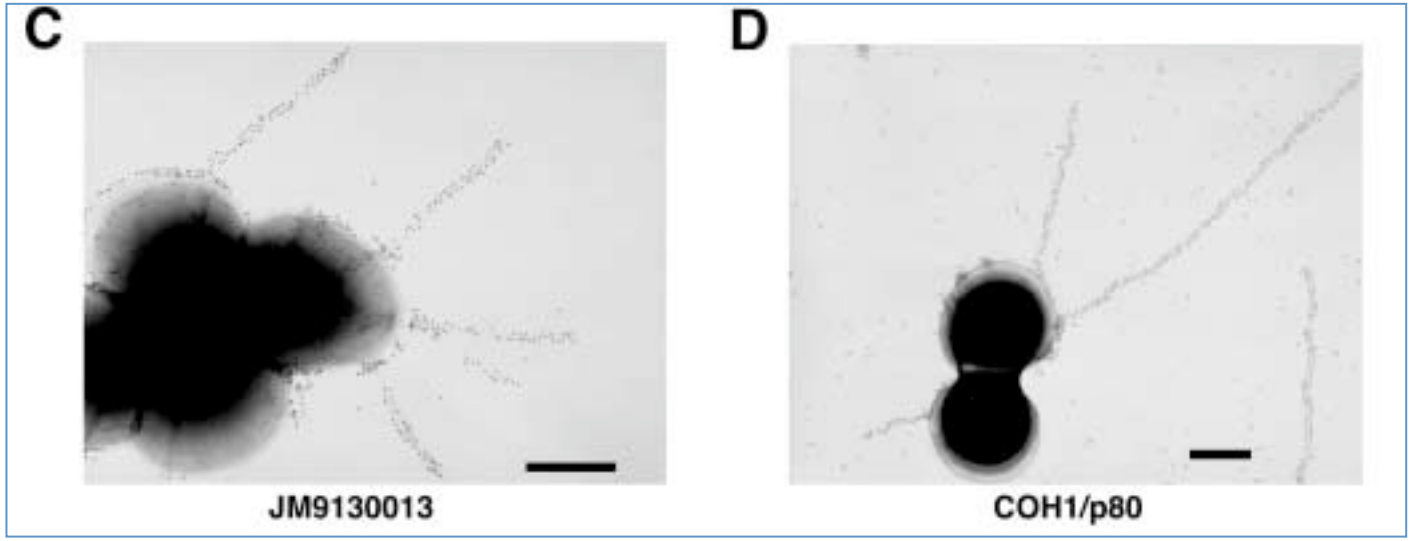
- **Comparaison of genomes from 8 different GBS serotypes**

D.Maione et al, Science 2006

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

GBS « pilus like structure »

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



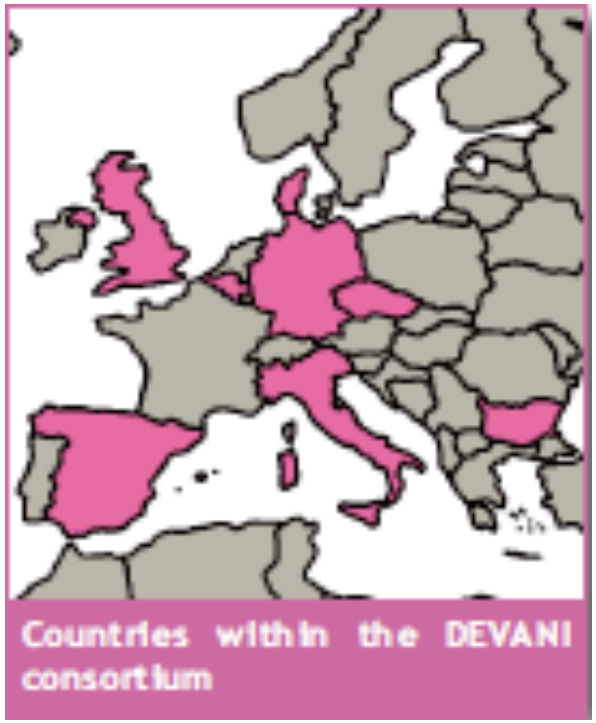
DEVANI

SEVENTH FRAMEWORK PROGRAMME

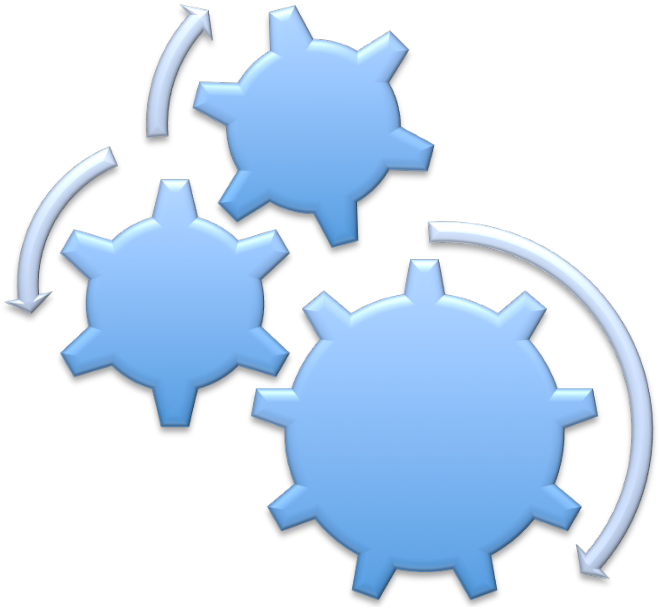
PROJECT

- European epidemiology
  - Genito-rectal colonizing strains
  - Invasive neonatal strains
- Identification of protective levels of specific antibodies

- Consortium of 8 European countries
- Development of a vaccine against pili proteins & major CPS serotypes



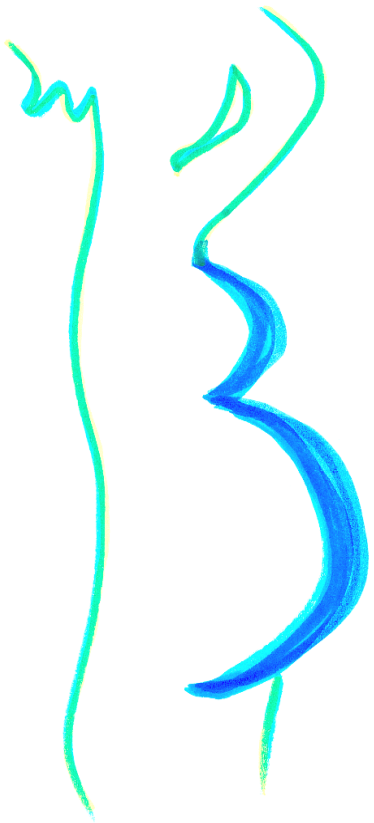
Countries within the DEVANI consortium



Good data - Coordination - Interaction

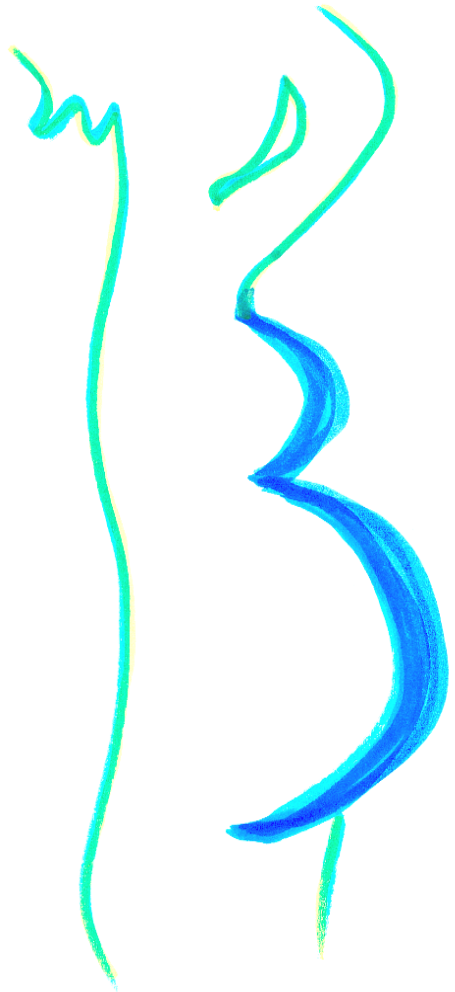
CONCLUSION
Take home messages

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



- Culture-based GBS prenatal screening
  - To optimize critical factors
  - Improved by selective differential agars
  - False +/False - !
- Rapid intrapartum screening
  - Real time PCR
    - Yes but costs, logistic, …
- Antimicrobial R
  - Surveillance of Penicillin by NRC
  - To perform AST for macrolides/clinda

Thanks !