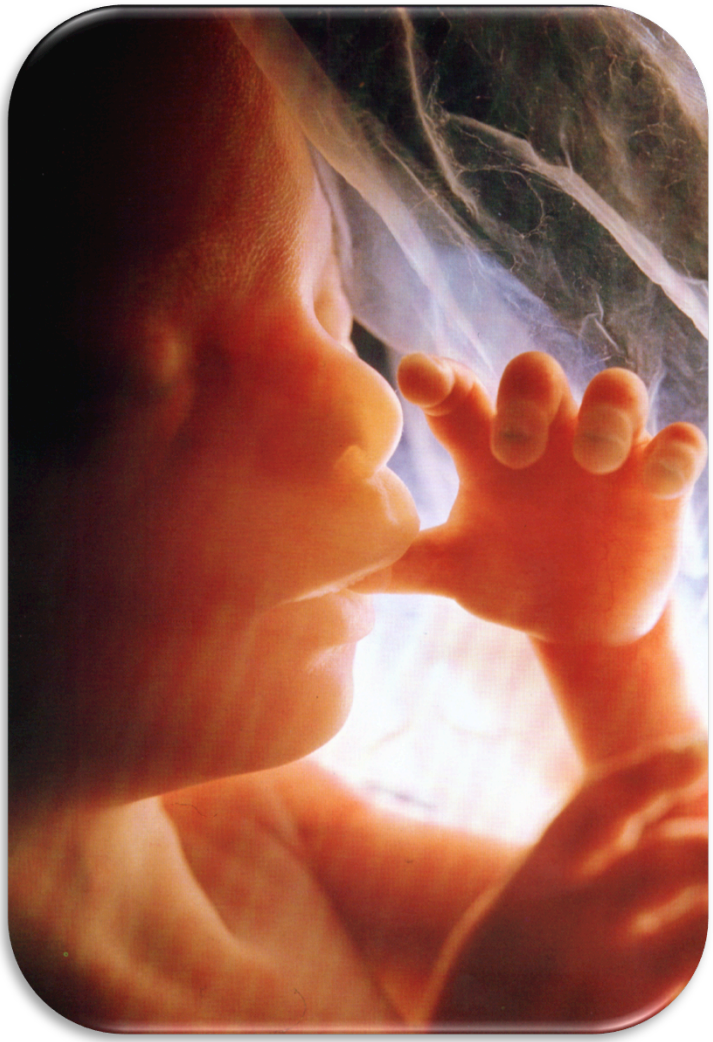


Perinatal Group B Streptococcal Disease

Towards a European consensus for prevention of GBS perinatal disease: old and new tools

Pierrette Melin

National Reference Centre for GBS

Clinical Microbiology, University Hospital of Liege

Content

- History and historical context of perinatal GBS disease
- Early and contemporary epidemiology
- Pathogenesis and risk factors
- Prevention strategies through
  - Maternal intrapartum chemoprophylaxis
    - Evolution of policies, effectiveness and concerns
    - Towards European consensus and revised Belgian guidelines
  - Maternal immunization

INTRODUCTION & BURDEN

Streptococcus agalactiae or GBS

Rebecca Lancefield
1895-1981

Gram positive cocci

- Encapsulated
- 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, *Eickhoff et al N Eng 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

GLOBAL public health major concern !

Also in developing countries

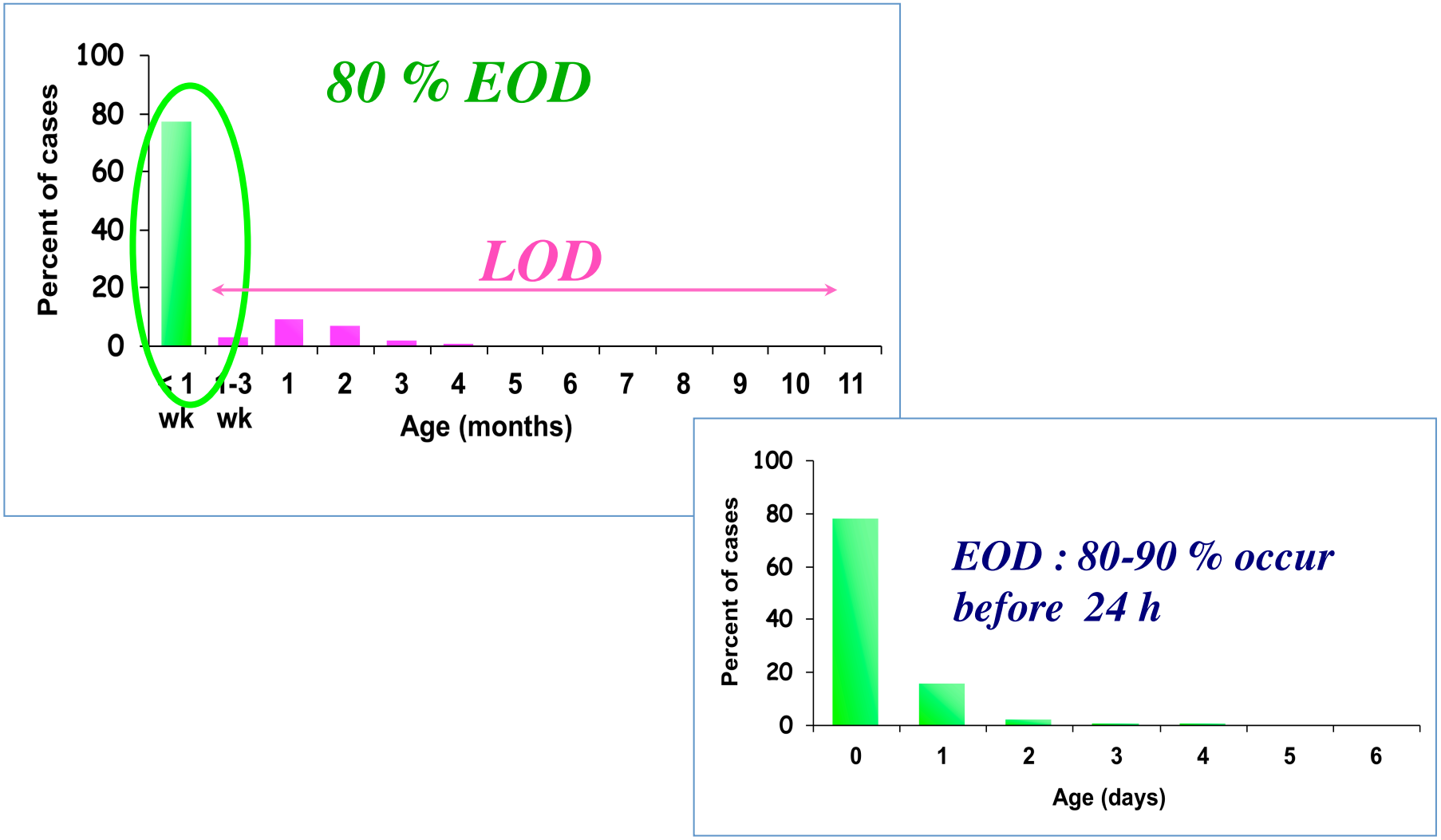
- Maternal morbidity
  - Along pregnancy
  - Peripartum
- Serious diseases among elderly and adults with underlying diseases
  - Significant mortality

GBS Neonatal Infections

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

GBS Neonatal Infections

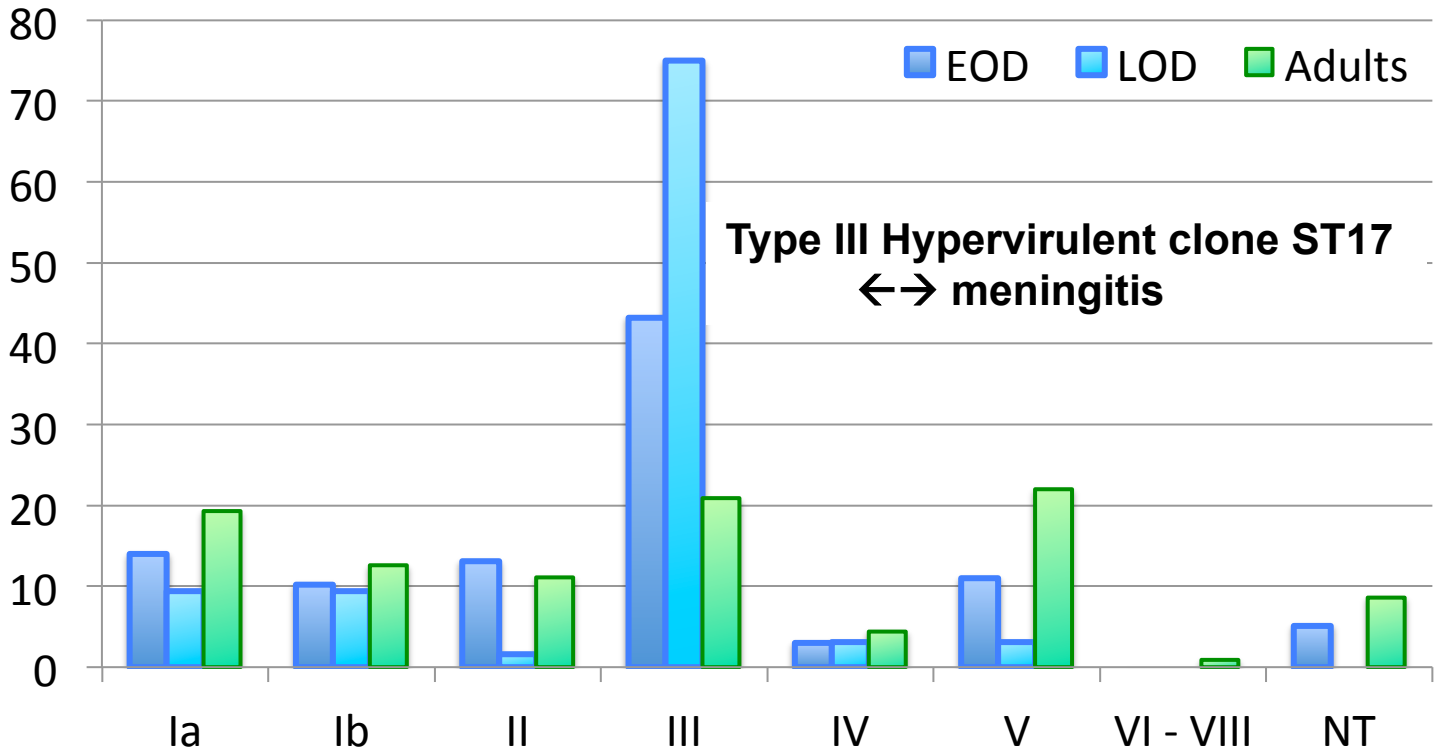
A. Schuchat, Clin Microb Rev 1998;11:497-513



GBS Neonatal Infections

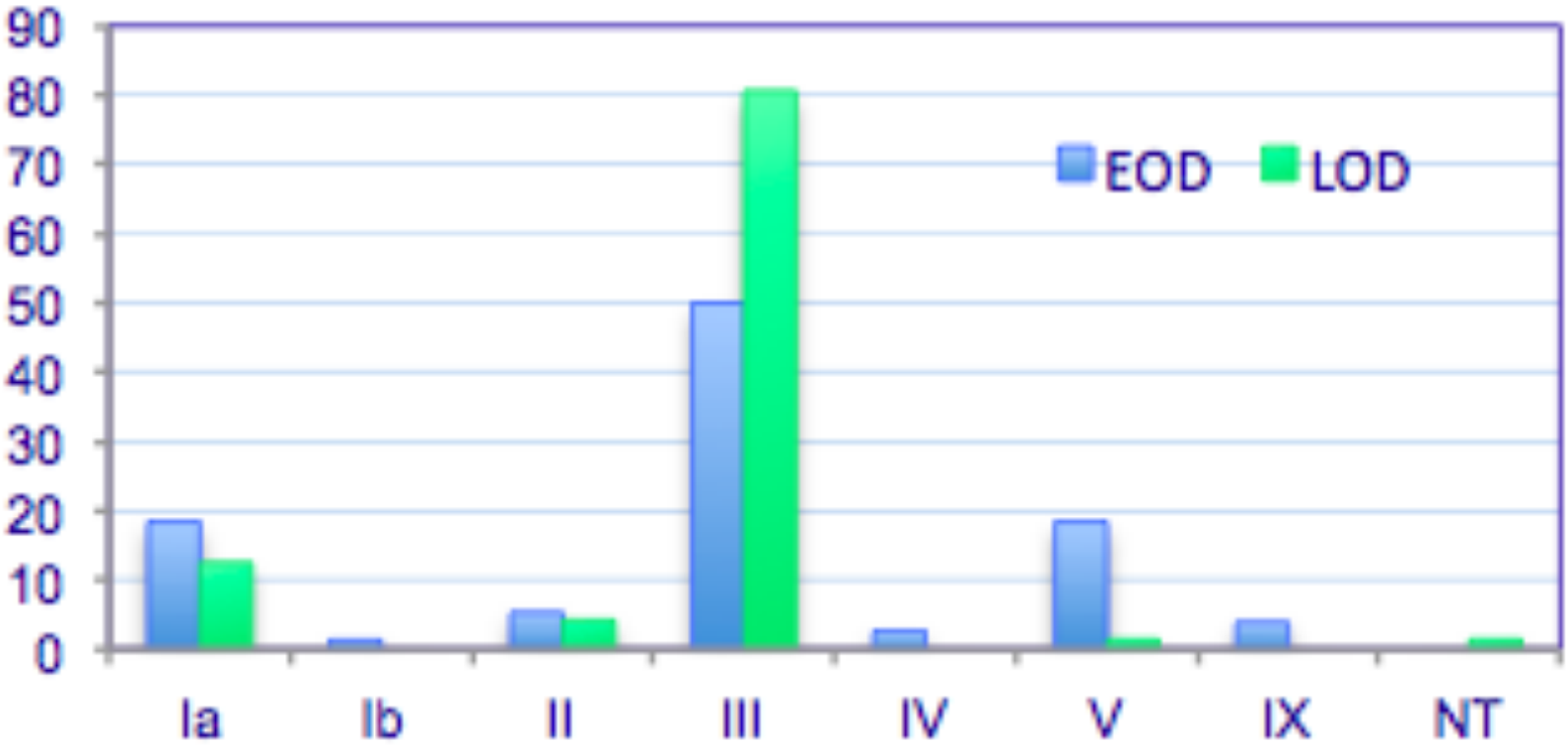
	EOD	LOD
Incidence per 1,000 live births	0.3 – 3	0.5
Onset	0 – 6 days (or 0-72 hrs)	1 week – 3 months (up 1 y)
Mean age at onset	12 hrs	1 month
Transmission	Vertical Intrapartum	Horizontal (vertical ?) At delivery Nosocomial In the community
Portal of entry	Inhalation → pneumonia → translocation into bloodstream	Likely intestinal
Clinical presentation	Respiratory distress with fulminant pneumonia Sepsis (Meningitis 5-15%)	Fever Bacteremia Meningitis (25-70%) (Cellulitis, osteomyelitis)
Mortality	< 10 % (→ 40 % in very premature)	0 - 6%
Capsular serotypes	All (Ia, III, V)	III, mainly Hypervirulent clone ST17 /meningitis

Distribution (%) of capsular types of GBS isolated in Belgium from different groups of patients (1998-2007)



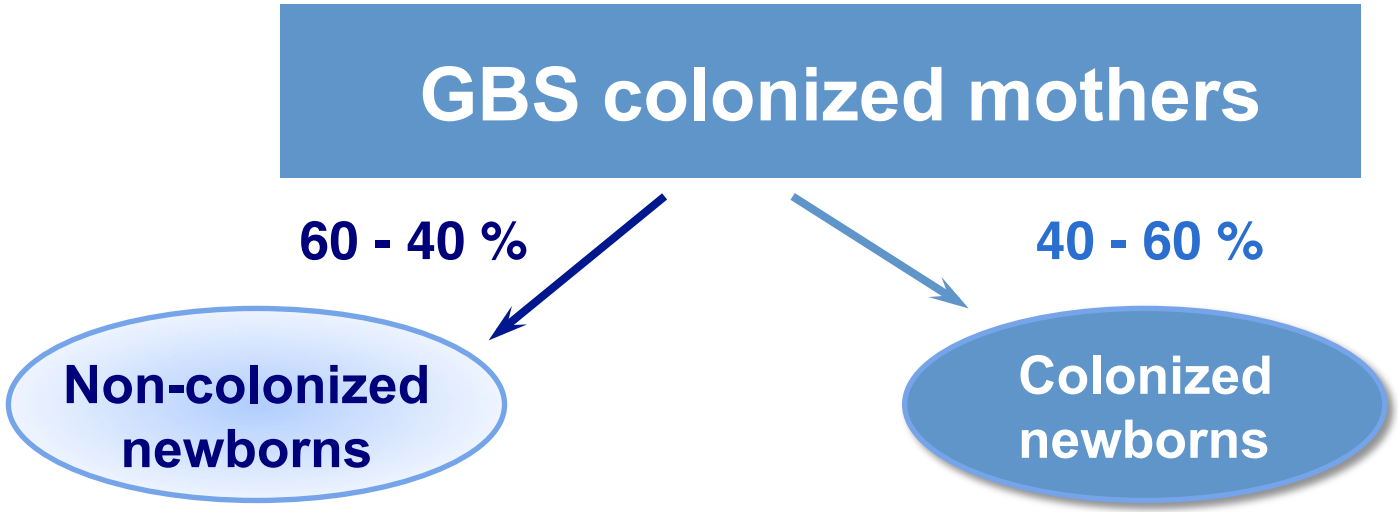
236 neonatal EOD; 64 neonatal LOD; 721 adults

Distribution (%) of capsular types of GBS isolated from 159 neonates, European DEVANI project (2008-2010)



51.6% neonatal EOD; 45.9 neonatal LOD; 2.5% neonatal D

GBS EOD vertical transmission



GBS EOD vertical transmission

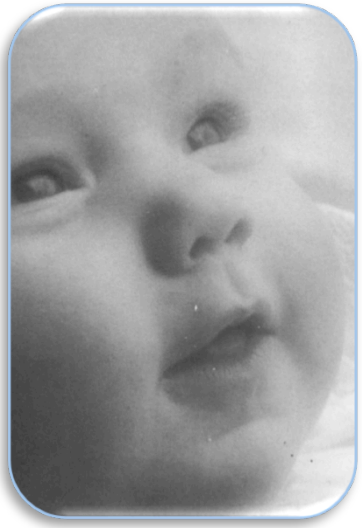
GBS colonized mothers

60 - 40 %

40 - 60 %

Non-colonized newborns

Colonized newborns



96 - 98 %

Asymptomatic

GBS EOD vertical transmission

GBS colonized mothers

60 - 40 %

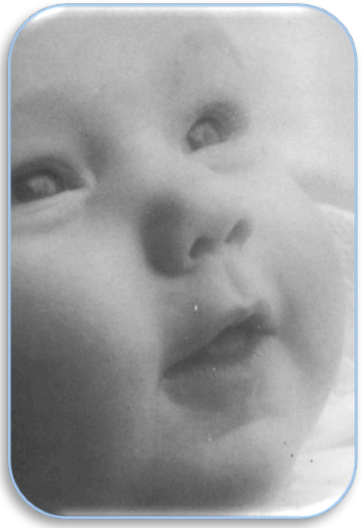
40 - 60 %

Non-colonized newborns

Colonized newborns

Risk factors

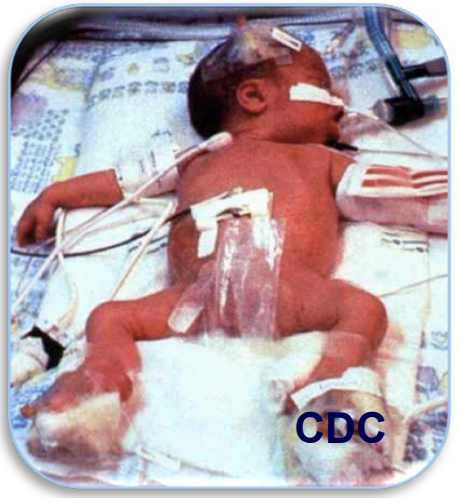
2 - 4 %
GBS EOD



96 - 98 %

Asymptomatic

sepsis
pneumonia
meningitis
long term sequelae



GBS maternal colonization

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

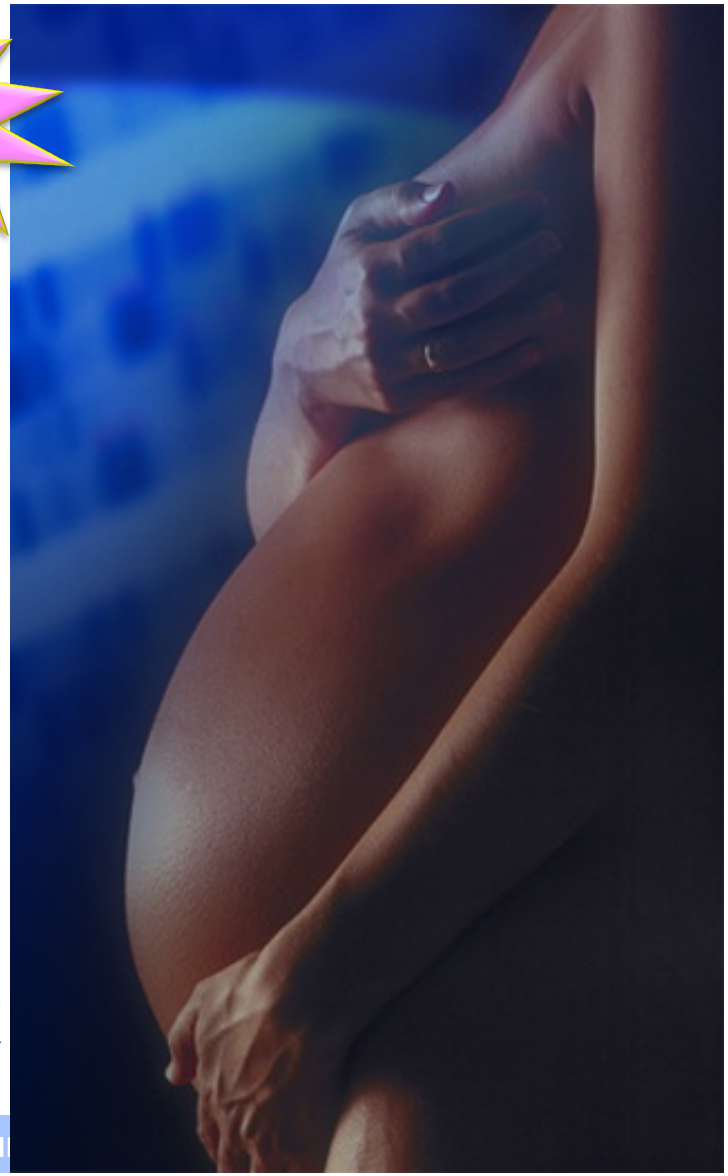
- **GBS carriers***
  - **10 - 35 % of women**
  - **Clinical signs not predictive**
  - **Dynamic condition**
  - **Intestinal reservoir**
  - **Prenatal cultures late in pregnancy can predict delivery status**

***: Carriage not restricted to women !**

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.

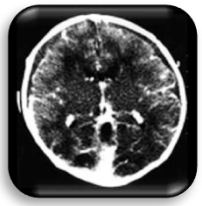
Burden of neonatal GBS early onset diseases in European countries

Location	Incidence per 1,000 live-births	*Reference*
Spain	2 (1996) to 0.45 (2008)	*Lopez Sastre et al. Acta Pediatr 2005*
Belgium	3 (1985) to <1 (2010)	*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

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



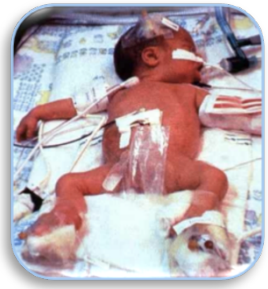
Meningitis

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

Brain barrier
Pili, III ST-17
β-hemolysin, …

Ascendant **transmission** (amnionitis)

GBS pathogenesis

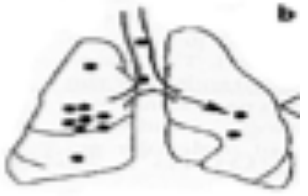


Sepsis

IL1, IL6, TNF α,
PGE2, TxA_2 ,

Bacteria
Peptidoglycan
β-hemolysin, …

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

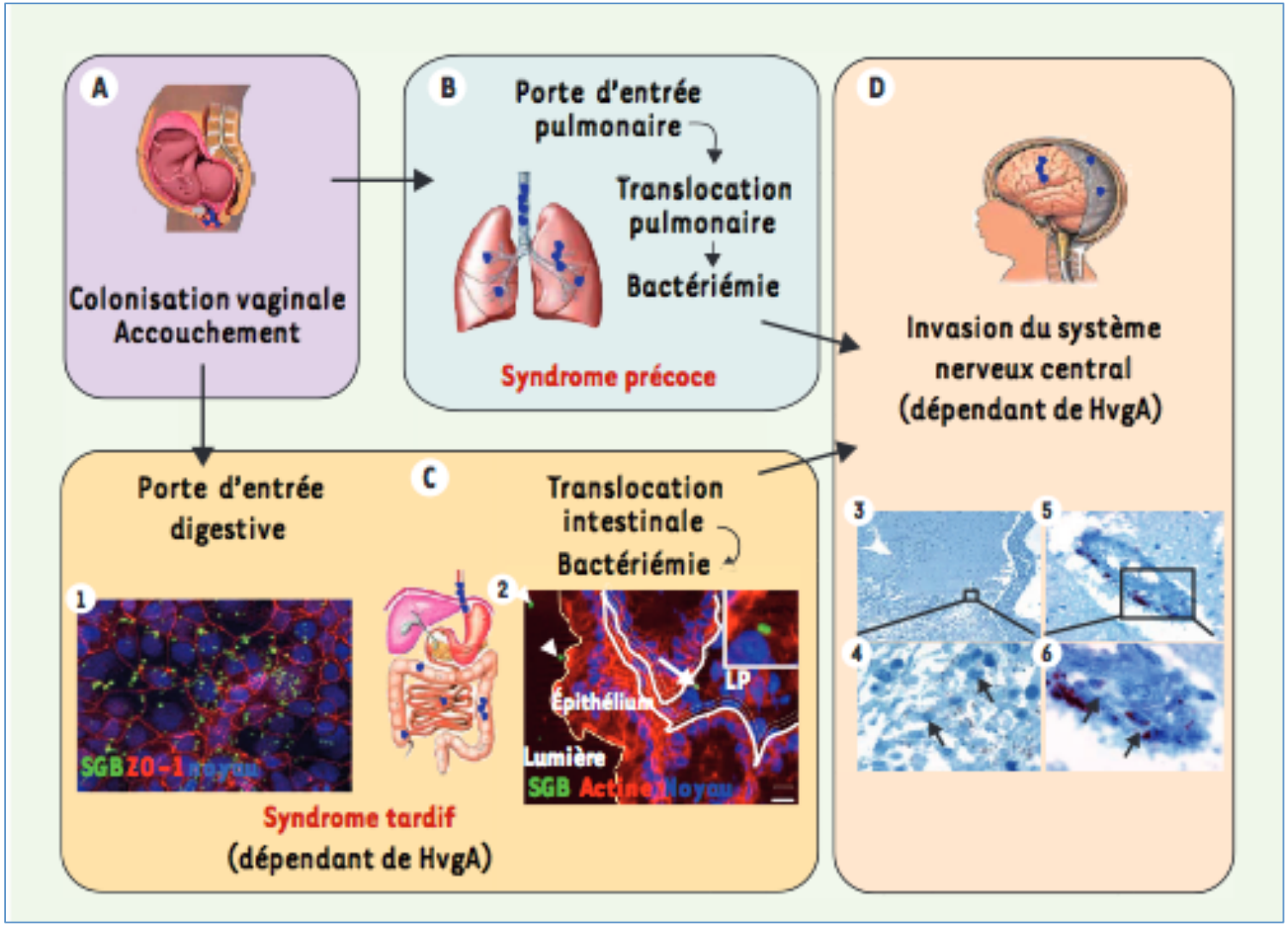


β-hemolysin, invasins (**pneumonia**)

Phagocytes cells, CPS
Antibodies, Complement

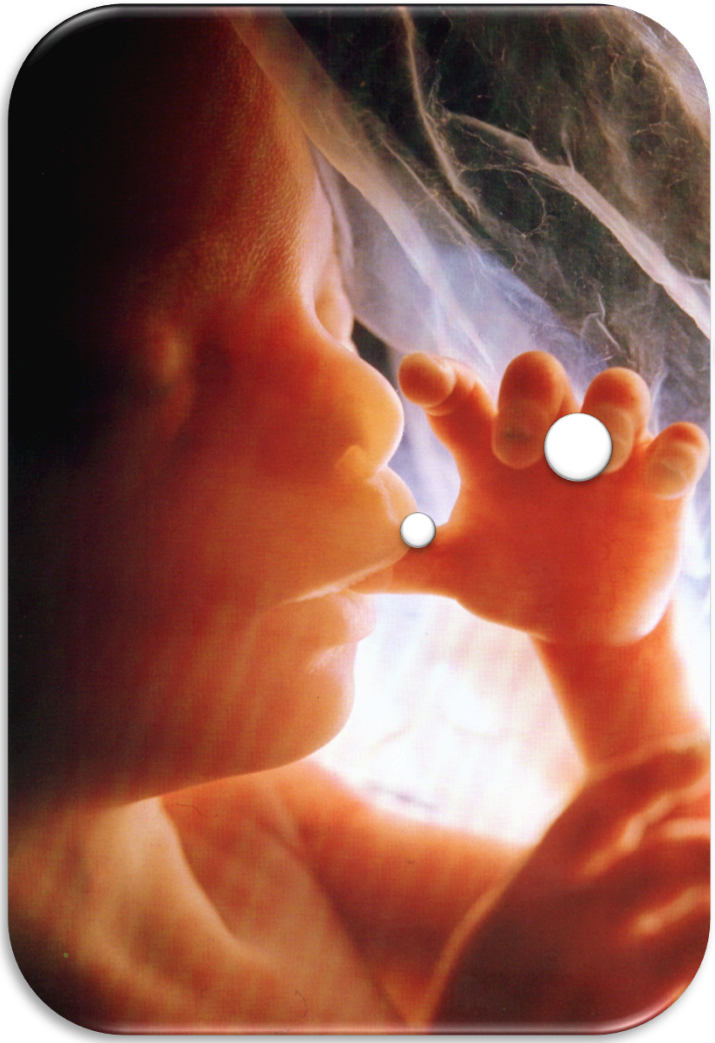
Stages in the pathogenesis of GBS neonatal EOD

Tozi A et al. 2011 http://dx.doi.org/10.1051/medsci/2011274010



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

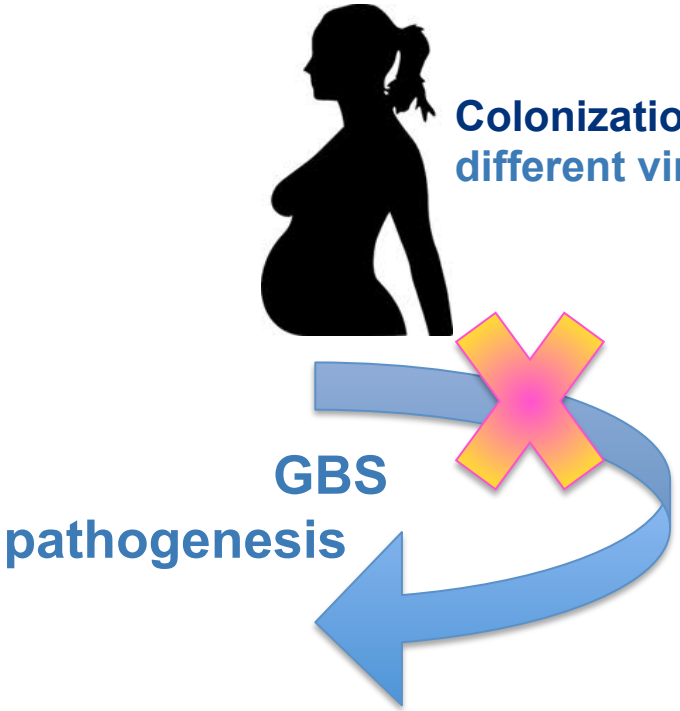
GUIDELINES FOR PREVENTION OF GBS PERINATAL DISEASE



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*

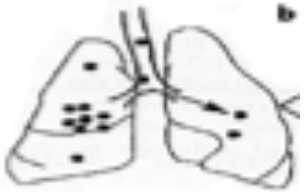
GBS vaccine

« 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

Prevention of perinatal GBS EOD

- Screening-based strategy

INTRAPARTUM ANTIMICROBIAL PROPHYLAXIS

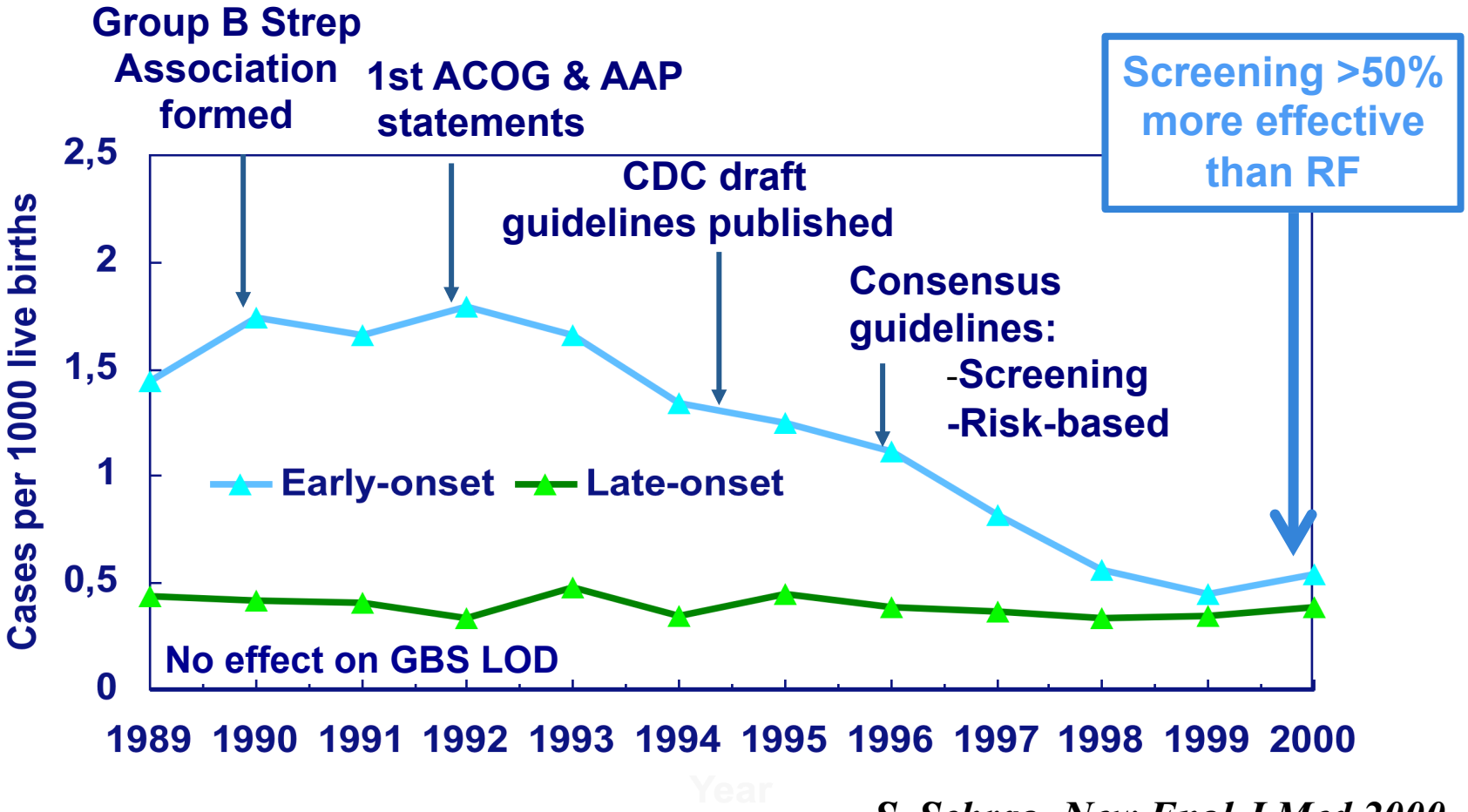
Main goal :

- 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

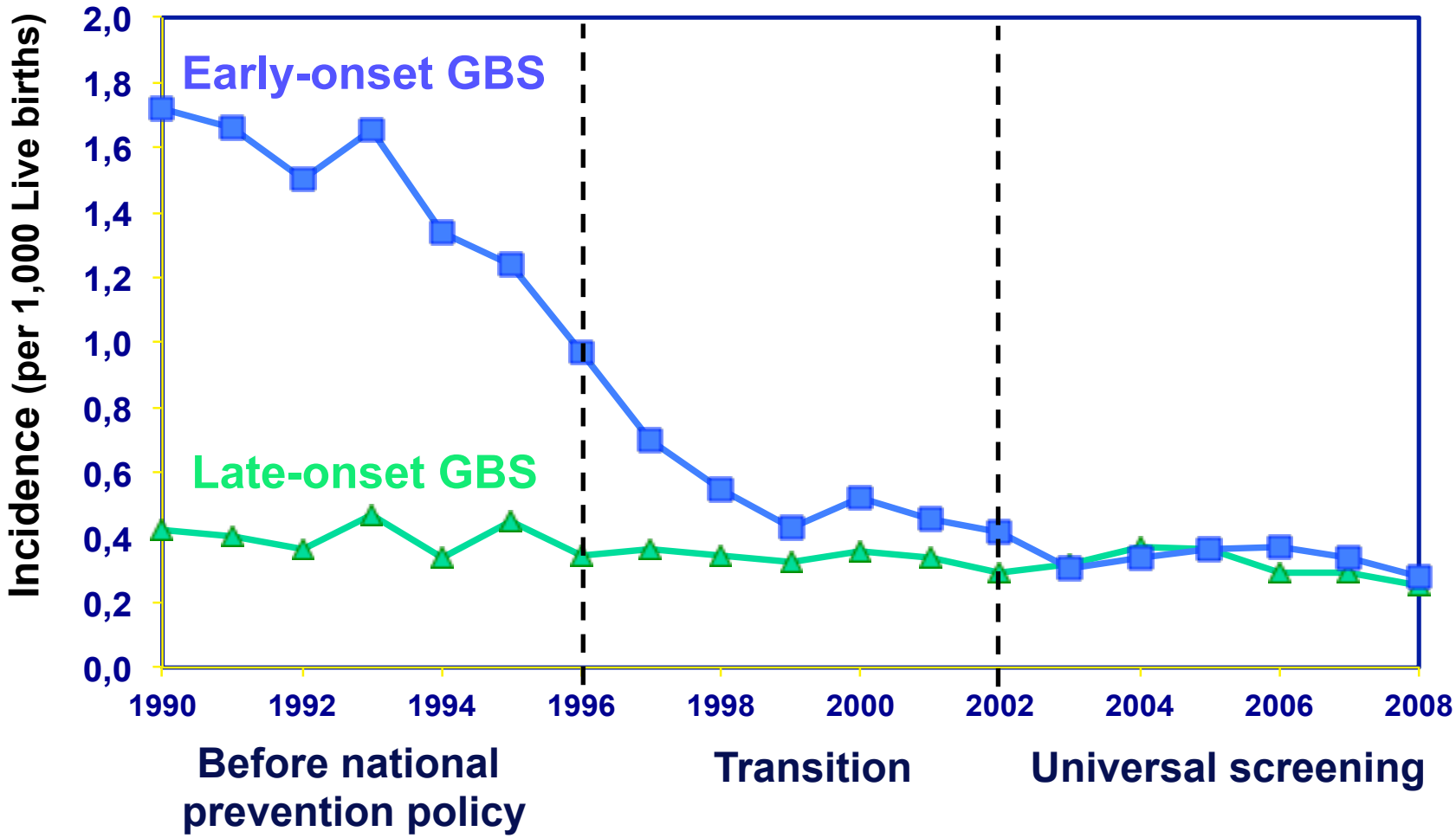
Why is Screening more protective than the risk-based approach ?

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

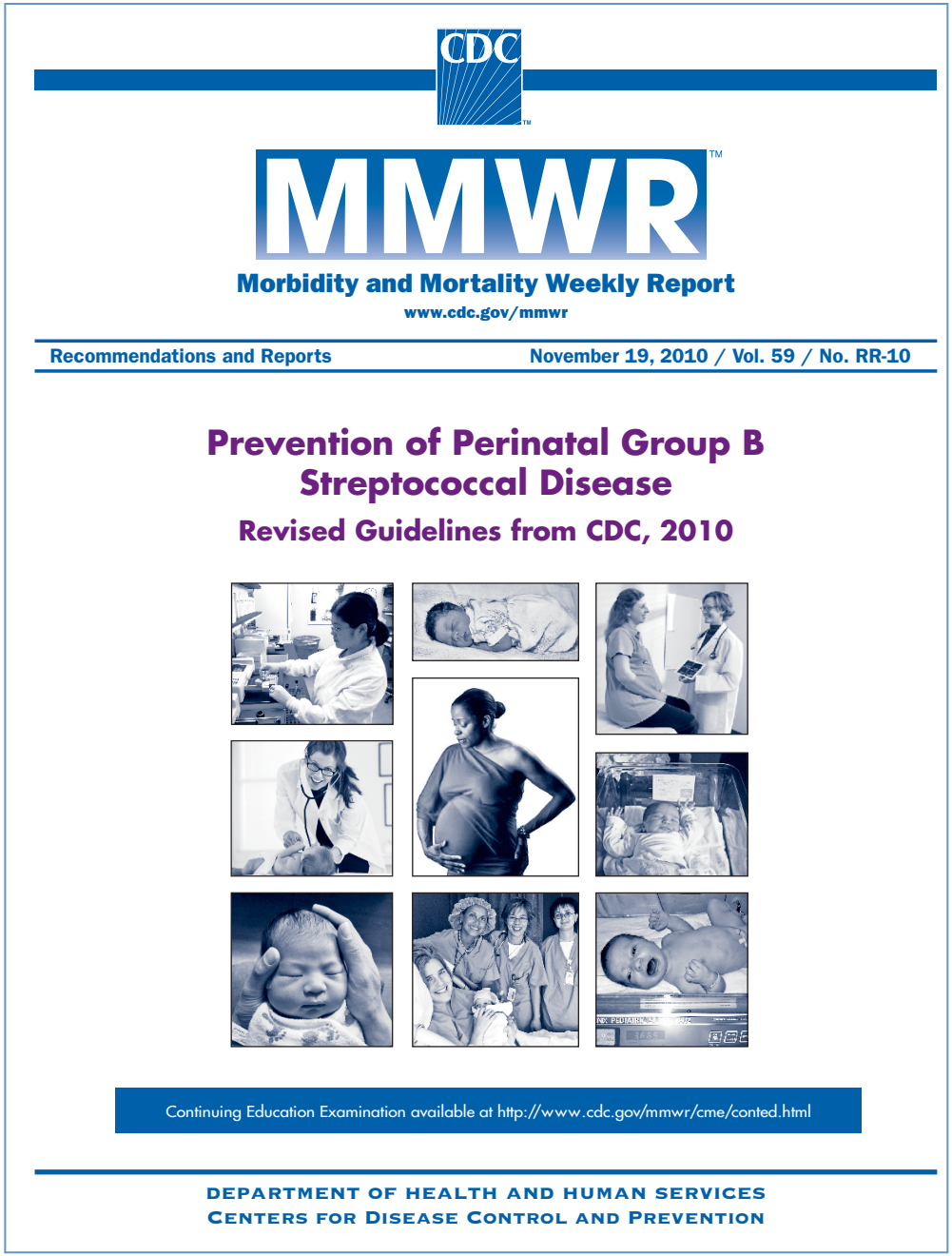
Broader coverage of « at-risk » population

- **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)

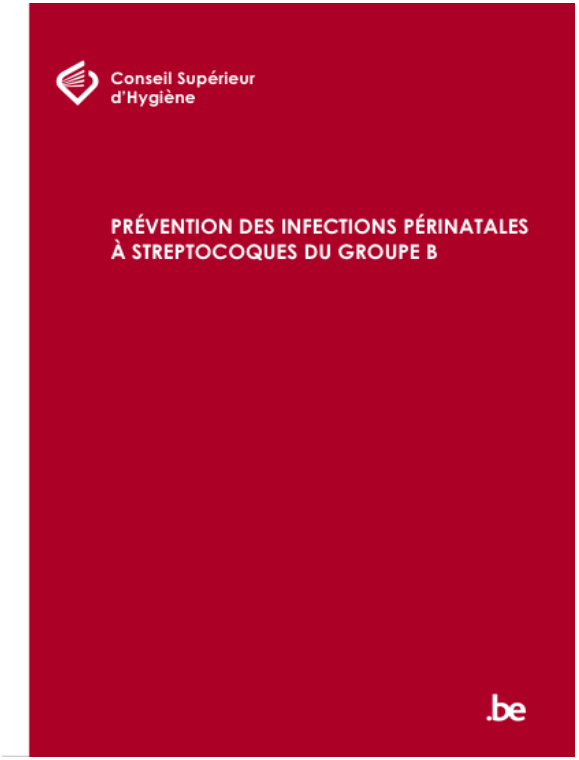


CDC, USA, MMWR, Vol 59 (RR-10) August 2010

Endorsed by

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

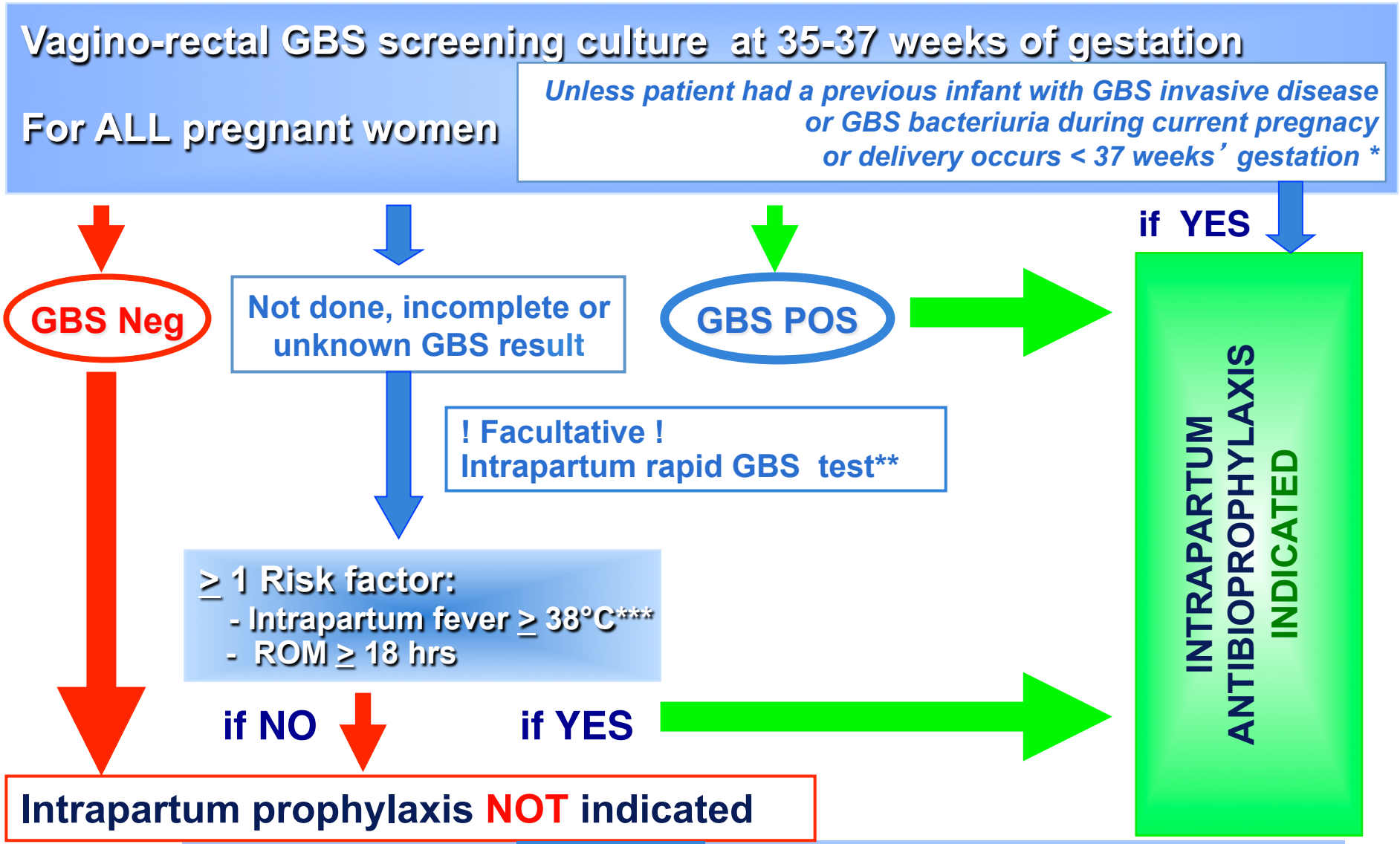
SHC, Belgium July 2003
Revision ongoing



European strategies for prevention of GBS EOD

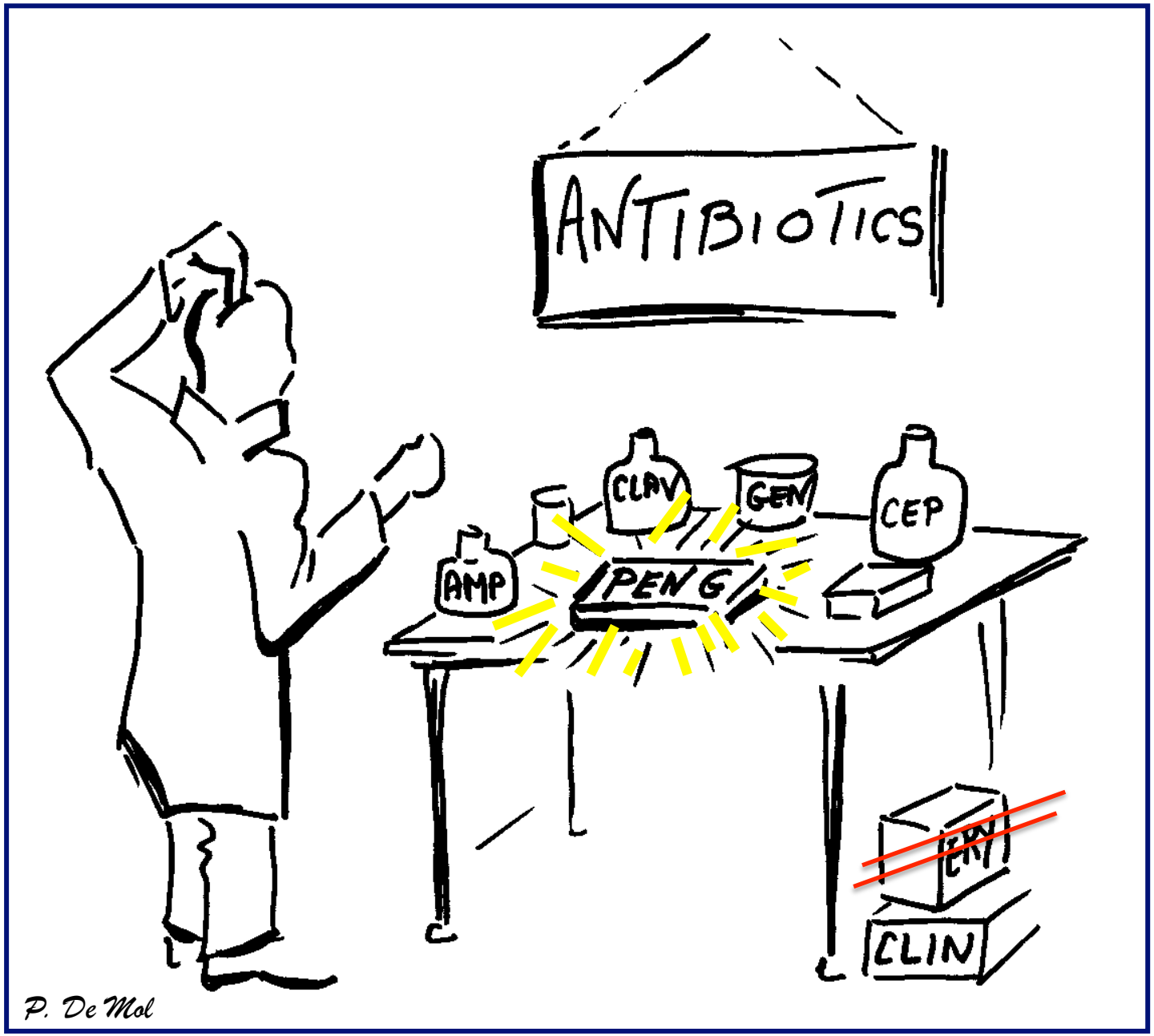
- Intrapartum antibioprophylaxis recommended
  - Screening-based strategy
    - Spain, 1998, 2003, revised 2012
    - France, 2001
    - Belgium, 2003, revision ongoing 2013
    - Germany, 1996, revised 2008
    - Switzerland, 2007
  - Risk-based strategy
    - UK, the Netherlands, Denmark
- No guidelines
    - 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
CLAV
GEN
CEP
AMP
PEN G
CLIN
P. De Mol

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 every 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**

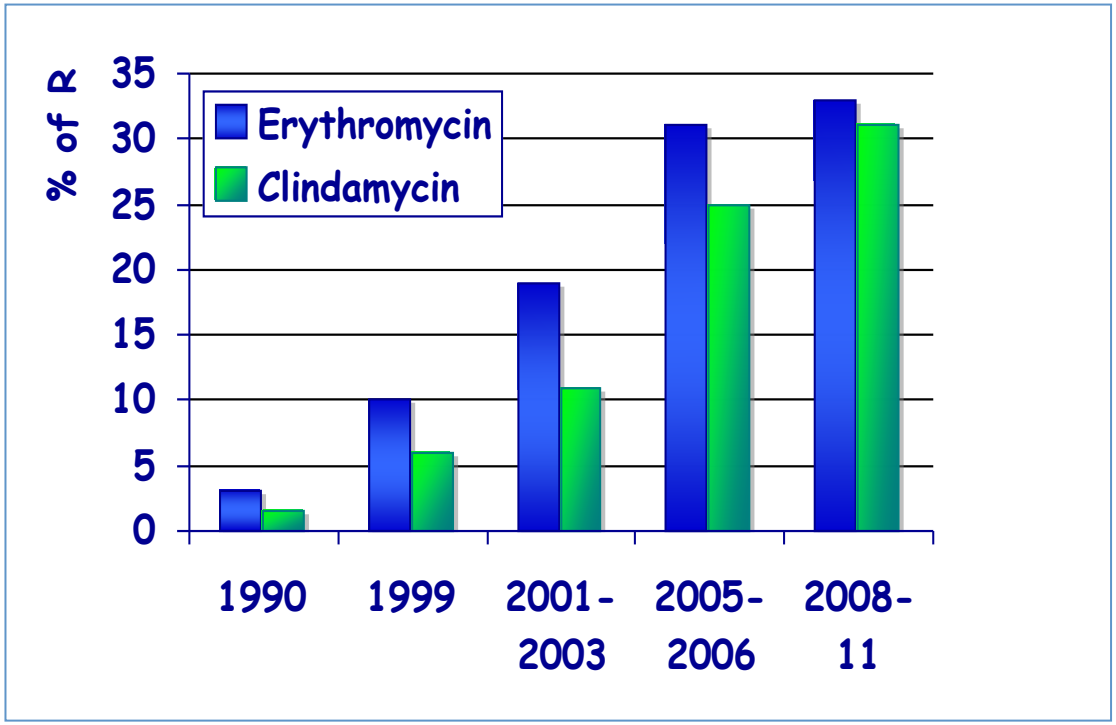
Concerns : Clinically relevant antimicrobial resistance

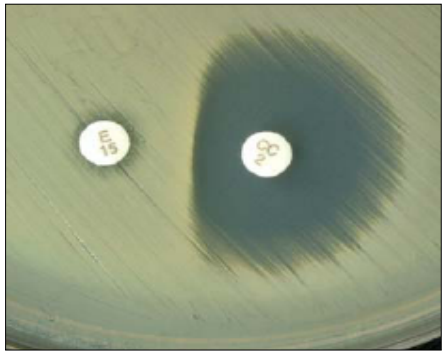
- **Increase of resistance to erythromycin and clindamycin**
- **Susceptibility to penicillin**
  - **Very few « not S » isolates recently characterized in Japan**
    - **Mutation in pbp genes, especially pbp2x**
    - **MIC= 0.25 -1 mg/L**
    - **No clinical impact ?**

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 among clinical isolates of GBS (Belgian data)





Resistance to erythromycin :
Constitutive + Inducible R (+ 75% CR / 25% IR)

→ D-Test recommended

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

- **Negative impact on intestinal flora**

Remaining burden of GBS EOD
Missed opportunities

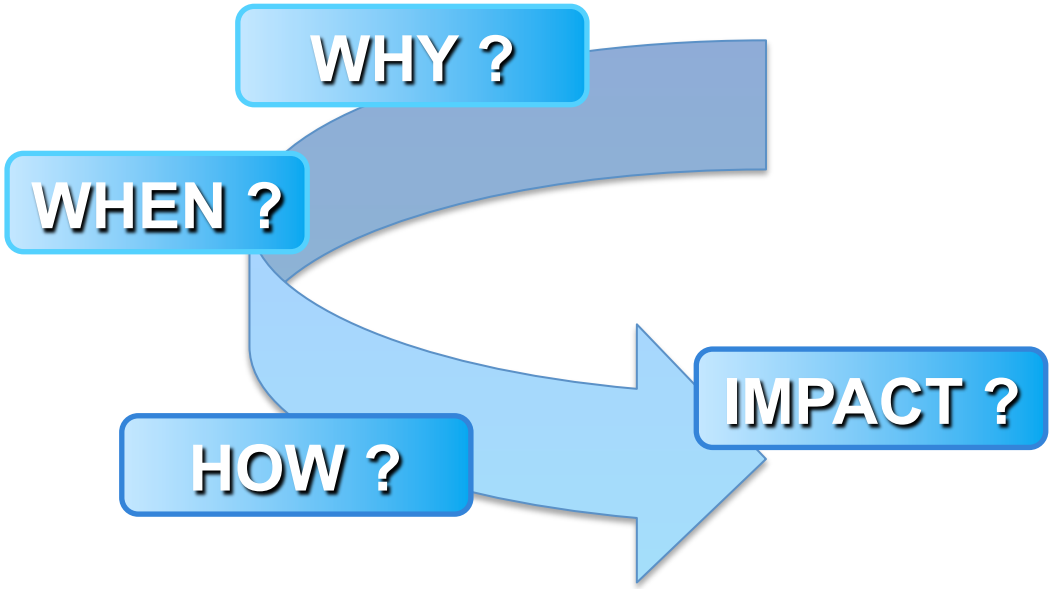
In spite of universal screening prevention strategy

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

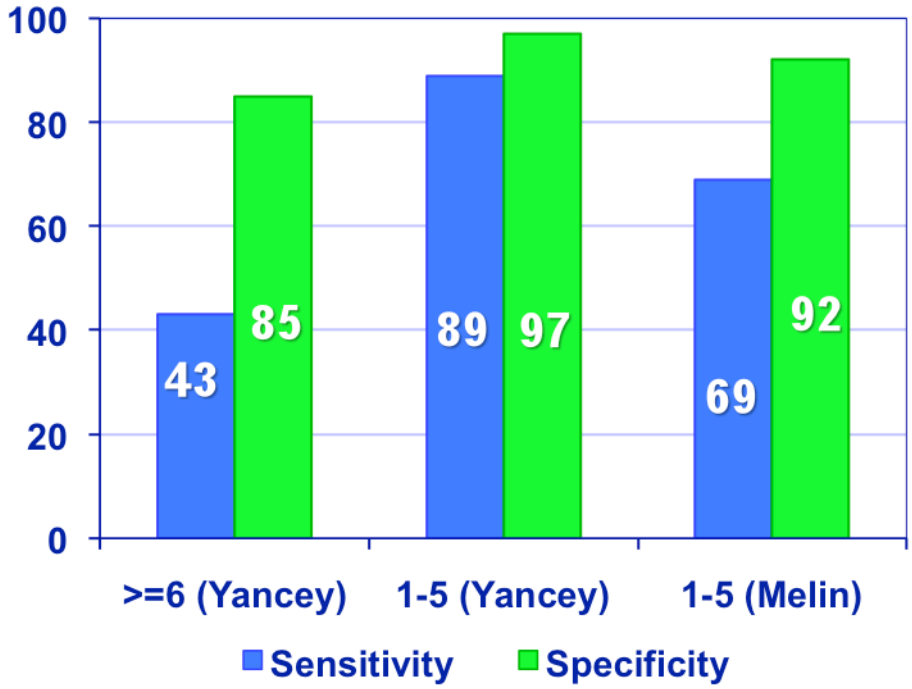
To predict GBS vaginal (rectal) colonization at the time of delivery

- **Critical factors influencing accuracy**
  - **Swabbed anatomic sites**
  - **Timing of sampling**
  - **Screening methods**
    - **Culture**
      - ***Procedure***
      - ***Media***
    - **Non-culture**

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)***



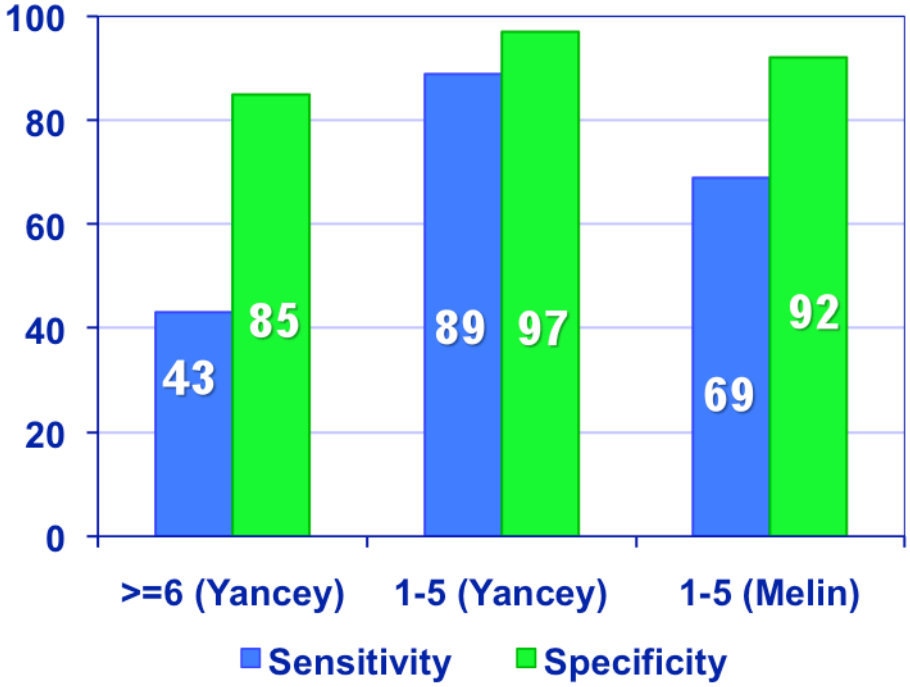
Not 100 % as colonization is dynamic

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

Optimal time for screening

35-37 weeks gestation

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



Melin, 13-16% GBS Pos

PPV= 56%

NPV= 95%

or 5% False negative

or 30% of GBS pos in labor not detected with prenatal screening !

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

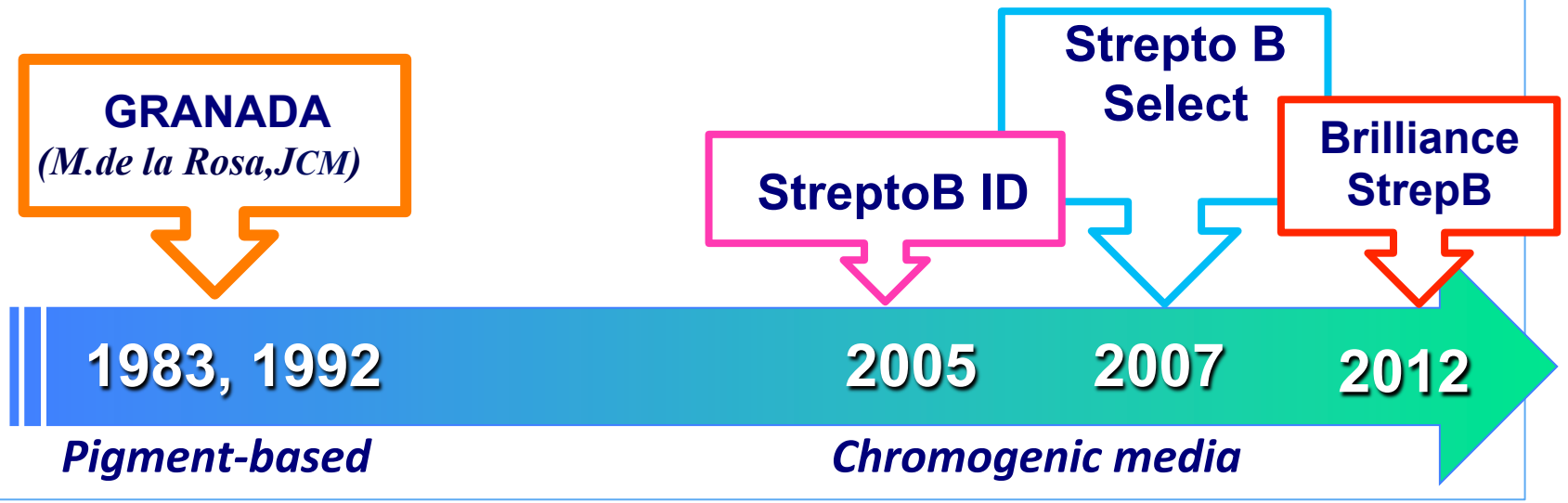
From direct plating on blood agar
Evolution of culture methods

Use of selective enrichment broth

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

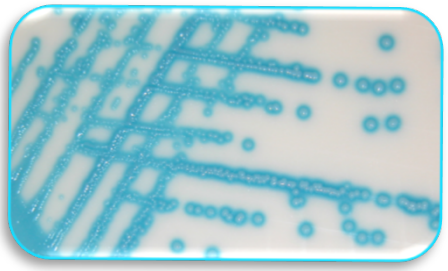
Use of differential agar media

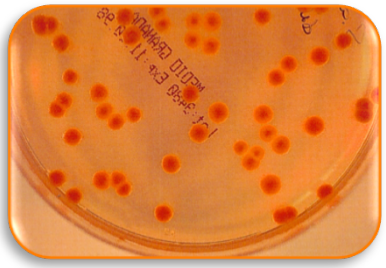
Recommended by some European guidelines (+ CDC 2010)

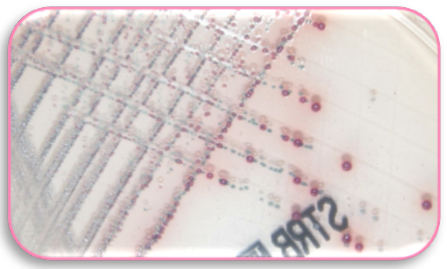


Which agar or which combination?

+/- 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)

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

- **Specimen storage in transport medium and detection of group B streptococci by culture.**

Rosa-Fraile M. et al. J Clin Microbiol 2005, 43: 928-930

Recovery of group B streptococci (GBS) was assessed in 1,204 vaginorectal swabs stored in Amies transport medium at 4 or 21°C for 1 to 4 days either by direct inoculation onto Granada agar (GA) or by culture in blood These data indicate that viability of GBS is not fully preserved by storage of vaginorectal swabs in Amies transport medium, mainly if they are not stored under refrigeration.

➢ Belgian Guidelines (2003, SHC)

"Specimens should be placed in a non-nutritive transport medium (e.g., Amies or Stuart's without charcoal). In these conditions, viability of GBS is warranted for at least 48 h at room temperature or in a fridge (2 - 8°C).

Specimen labels should clearly identify that specimens are for group B streptococcal culture. Swabs should reach the lab within 48 h of collection."

Crucial conditions to optimize SCREENING

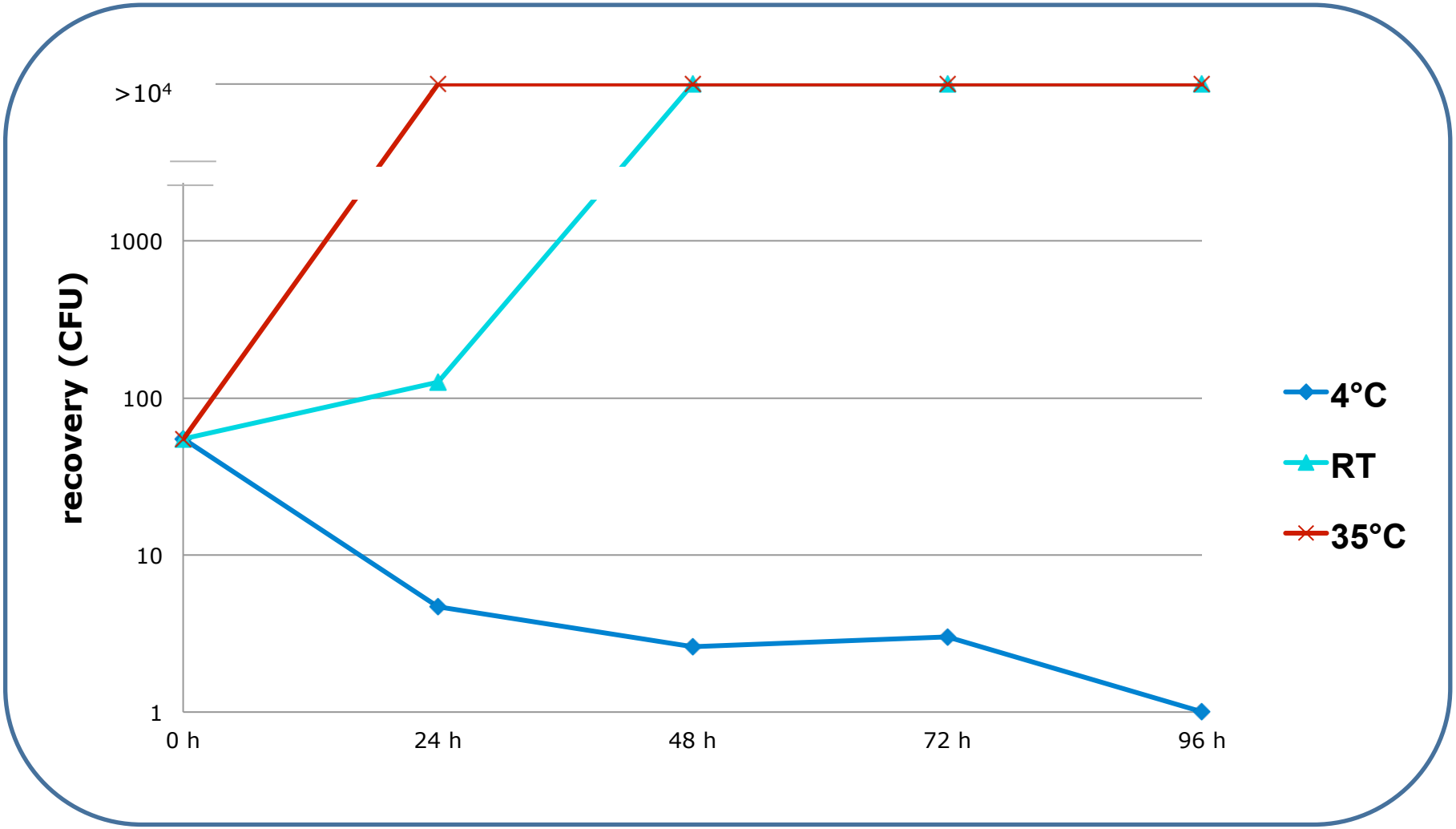
Transport-collection system & transport-storage condition

(2012, NRC GBS)

- **Use of a selective enrichment Lim broth** *(BD, Copan, bioMérieux)*
  - **At RT° up to 35°C**
  - **Between 4-8°C**

- **Use of a selective enrichment Granada medium** *(bioMérieux)*
  - **At RT° up to 35°C**
  - **Between 4-8°C**

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



Crucial conditions to optimize SCREENING

Transport-collection system & transport-storage condition

***Results** (2012, NRC GBS)*

- **Use of a selective enrichment Lim broth** ***(BD, Copan, bioMérieux)***
  - **At RT° up to 35°C**
    - **Rapid important amplification of GBS initial inoculum**
    - **Sustained viability > 4 days**
  - **Between 4-8°C**
    - **≥ 24 hours, continuous decrease of life GBS**

- **Use of a selective enrichment Granada medium** ***(bioMérieux)***
  - **At RT° up to 35°C**
    - **Rapid important amplification of GBS initial inoculum**
    - **Sustained viability at RT°**
    - **Abrupt lost of viability at 35°C ≥ 48-72h**
  - **Between 4-8°C**
    - **≥ 24 hours, continuous decrease of life GBS**

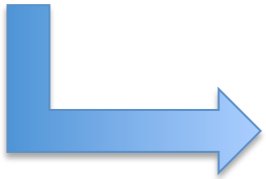
Prenatal culture-based screening: Limiting factors

- **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
    - Positive prenatal screening /negative at time of delivery
    - 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

- 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

IAP addressed to right target

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

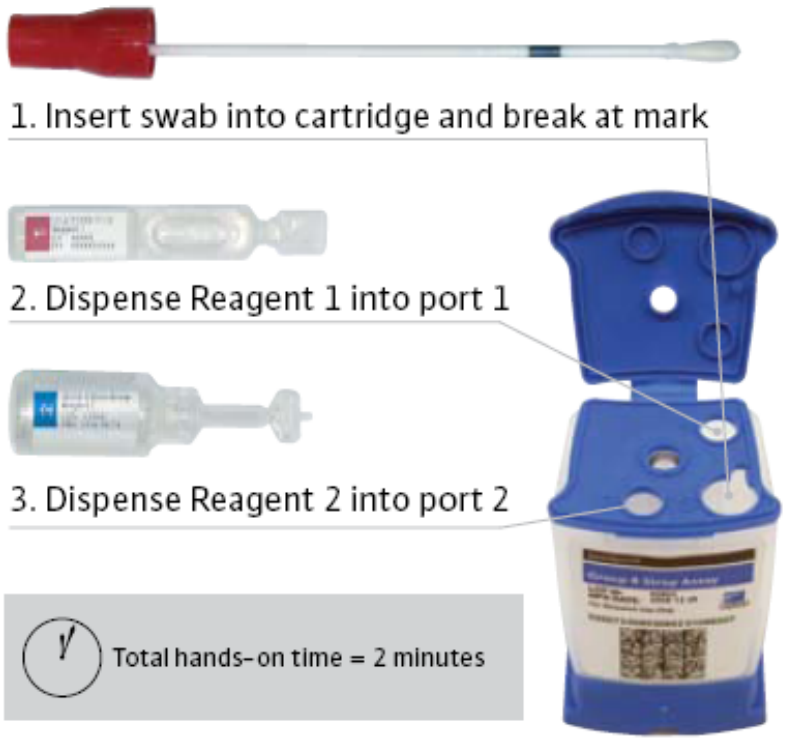
Improvement of prevention

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)

The Xpert GBS™ Advantage: Simplicity

- Fully automated process reduces handling time to just minutes
- Random access for flexibility and workflow optimization
- Rapid results to improve patient management
- Fully integrated reagent and instrument system for accuracy and reproducibility



4. Insert cartridge and start assay

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%

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 → 2014 CHULg & UIA*
- **Logistic**
  - 24 hours 7 days
  - In the lab?
  - In the obstetrical department as a POCT ?
- **In combination with prenatal screening strategy ?**
  - CDC 2010 : for women with premature delivery or no prenatal care
- **No antimicrobial result**
  - In the future detection of R genes, but mixed microbiota !

Revised Belgian guidelines

(Superior Health Council, expected autumn 2014)

(Neonatologists, obstetricians, microbiologists, midwives)

Main recommendentions

- Universal antenatal screening at 35-37 wks gestation
  - Lim broth as transport media
  - Selective differential culture media
  - Determination of clindamycin susceptibility *(if IgE mediated penicillin allergy)*
- Universal screening at time of delivery can be used
  - If POCT with high PPV and NPV
    - Real time PCR or other methods
    - TAT < 1 hour
  - In case of known IgE mediated penicillin allergic women
    - Determination of clindamycin susceptibility for GBS positive screening
- IAP for all GBS positive pregnant women
  - documented by antenatal testing (or intrapartum testing if performed)

Towards « European Consensus »

Decision taken by a European working party

(Neonatologists, obstetricians, microbiologists)

including countries with screening-based IAP, with risk-based IAP strategies or nothing (June 2013, Florence, Italy)

Main recommendentions

- Universal screening at time of delivery
  - 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 prenatal screening in known penicillin allergic women
  - Determination of clindamycin susceptibility if GBS positive screening

Towards « European Consensus »

Decision taken by a European working party

(Neonatologists, obstetricians, microbiologists)

including countries with screening-based IAP, with risk-based IAP strategies or nothing (June 2013, Florence, Italy)

Main recommendentions

- Provisionally , for countries with antenatal screening
  - Improved antenatal screening method
    - Use of Lim broth for transportation
    - Use of selective differential media

The Journal of Maternal-Fetal & Neonatal Medicine

Intrapartum GBS screening and antibiotic prophylaxis: a European Consensus Conference.

Journal:	*The Journal of Maternal-Fetal & Neonatal Medicine*
Manuscript ID:	DJMF-2014-0242
Manuscript Type:	Guidelines
Date Submitted by the Author:	20-Mar-2014
Complete List of Authors:	Di Renzo, Gian Carlo; University Hospital of Perugia, Dept. of Ob/Gyn and Centre for Perinatal Medicine Melin, Pierrette; University Hospital of Liege, Department of Clinical

Prevention of GBS EOD and LOD

Prevention of maternal diseases

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, (II), III and V
- Clinical studies (phases 1, 2 and 3)
  - Immunogenicity
  - Safety
  - Efficacy: scheduled/ongoing

GBS polysaccharide-based Vaccines new challenges

Capsular Switching in Group B *Streptococcus* CC17 Hypervirulent Clone: A Future Challenge for Polysaccharide Vaccine Development

S. Bellais, A.Six, A. Fouet, M. Longo, N. Dmytruk, P. Glaser, P. Trieu.Cuot and C. Poyart

J Infect Dis. (2012) 206 (11): 1745-1752.

doi: 10.1093/infdis/jis605 **First published online: September 21, 2012**

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

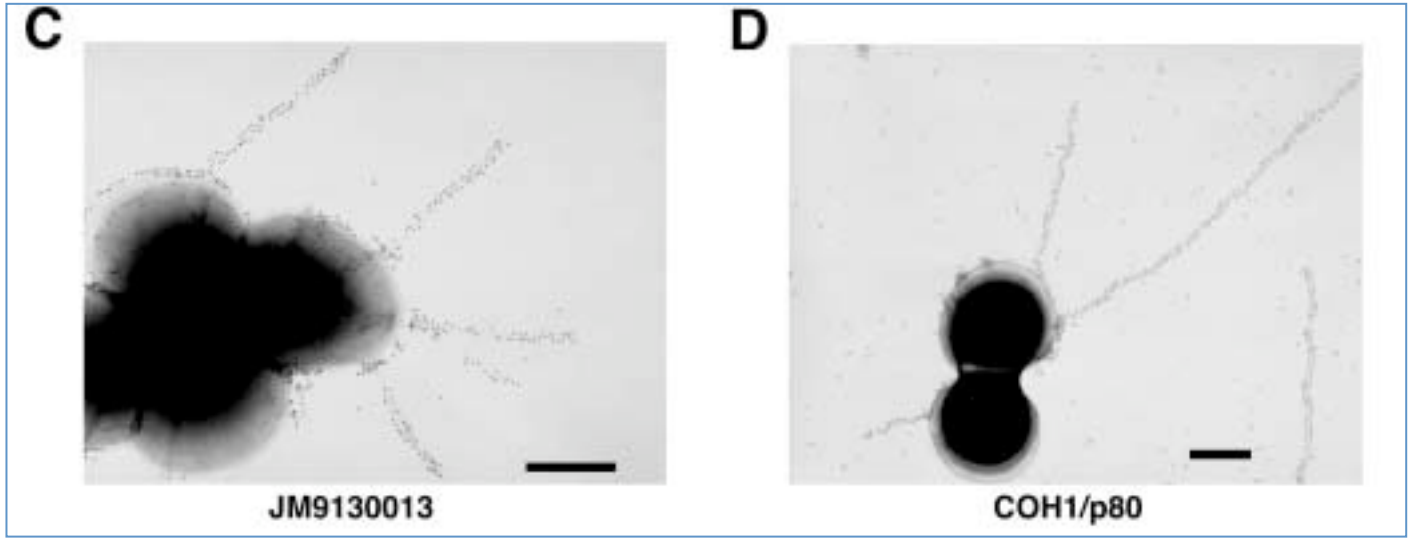
- **Comparaison of genomes from 8 different GBS serotypes**

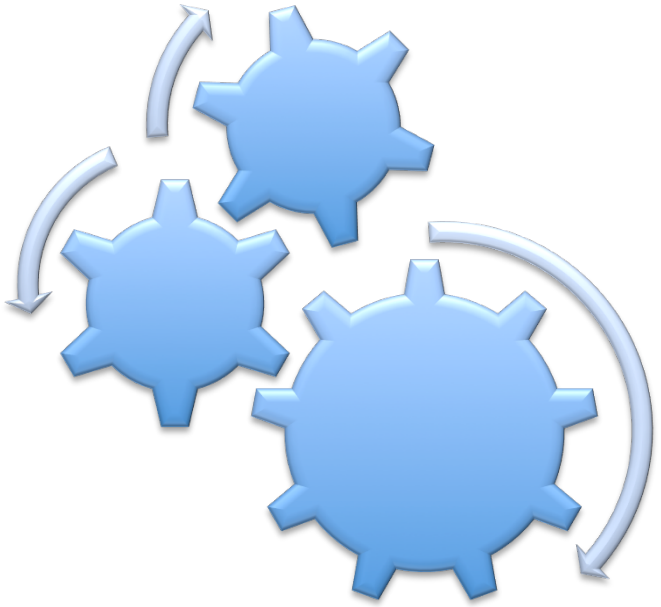
D.Maione et al, Science 2006

  - **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 »

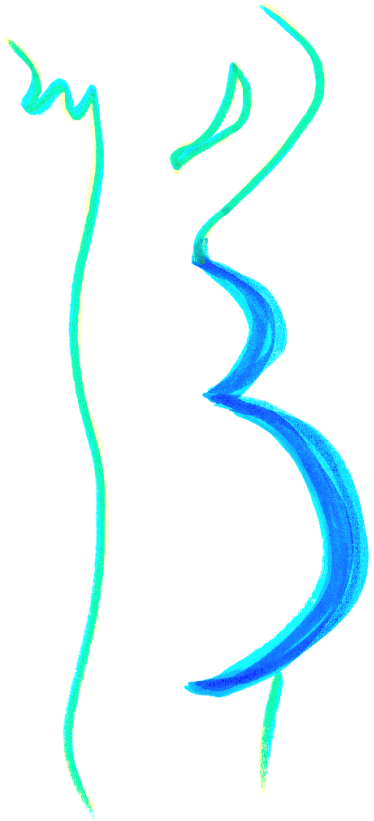
- Highly immunogenic proteins
- Elicit protective and functional antibodies
- Virulence factor
  - Adhesion
  - Transcytose through cells





CONCLUSION
Take home messages

In Europe, as globally



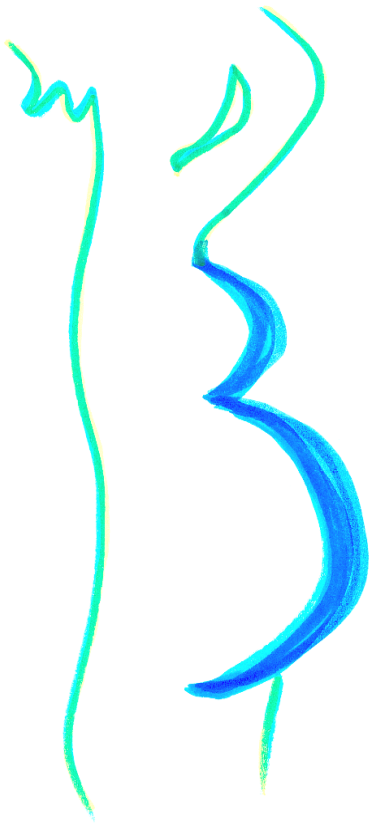
Neonatal GBS diseases

- 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
- Towards European consensus
- Need better data assessing more accurately the true burden

GBS vaccine eagerly expected

- Appears to be within reach

Summary



“Screening” Prevention strategies

- **Culture-based GBS prenatal screening**
  - To optimize critical factors
  - Improved by selective differential agars
  - False +/False - !
  - Expected improvement from transport system
- **Rapid intrapartum screening**
  - Real time PCR
    - Yes but costs, logistic, …
    - Need for more clinical and cost effectiveness trials

Vaccine 31S (2013) D31–D42

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Review

Group B streptococcal epidemiology and vaccine needs in developed countries

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Thank you !