Perinatal Group B Streptococcal Disease

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Content

- Introduction & burden
  - History and historical context of perinatal GBS disease
  - Early and contemporary epidemiology
  - Pathogenesis and risk factors
- Guidelines - Prevention strategies
  - Maternal intrapartum chemprophylaxis (IAP)
    - Evolution of policies, effectiveness and concerns
    - Towards European consensus
  - Maternal immunization
- Conclusion

INTRODUCTION & BURDEN

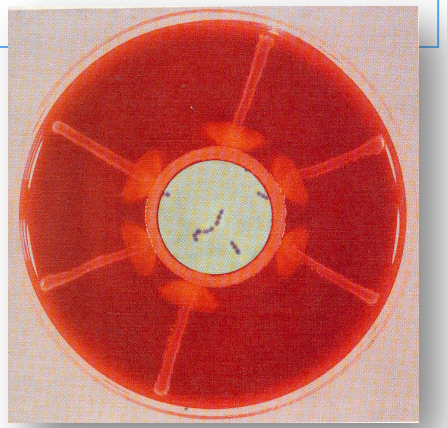
Streptococcus agalactiae or GBS

Rebecca Lancefield 1895-1981

Gram positive cocci

- Encapsulated
- Catalase -
- β-hemolytic
- CAMP test +
- Hippurate +
- Esculine-
- Orange pigment

10 capsular serotypes (Ia, Ib, II-IX)
3 pilus types (P1, P2a & P2b) alone or combined



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**

Streptococcus agalactiae or GBS

***Streptococcus agalactiae* clones infecting humans were selected and fixed through the extensive use of tetracycline**

- **Genome-based phylogeny reveals the expansion of a few clones**
- **Human GBS belong mainly to a small number of TcR clones**

V.Dacunha, MR.Davies, …, C.Poyart and P.Glaser

In *Nat Commun.* 2014 Aug 4;5:4544. doi: 10.1038/ncomms5544.

1887, Noccard-Mollereau, bovine mast

1933, Group B Antigen

1964, severe neonatal sepsis, *Eickhoff et … 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

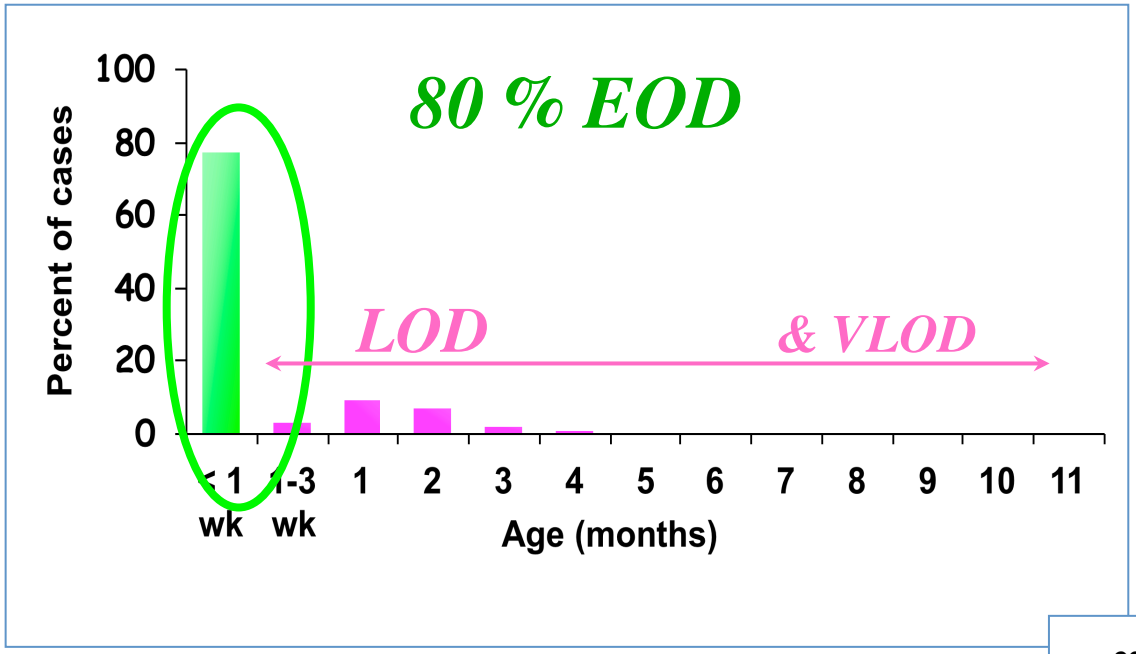
- **Maternal morbidity**
  - **Along pregnancy**
  - **Peripartum**
- **Serious diseases among elderly and adults with underlying diseases**
  - **Significant mortality**

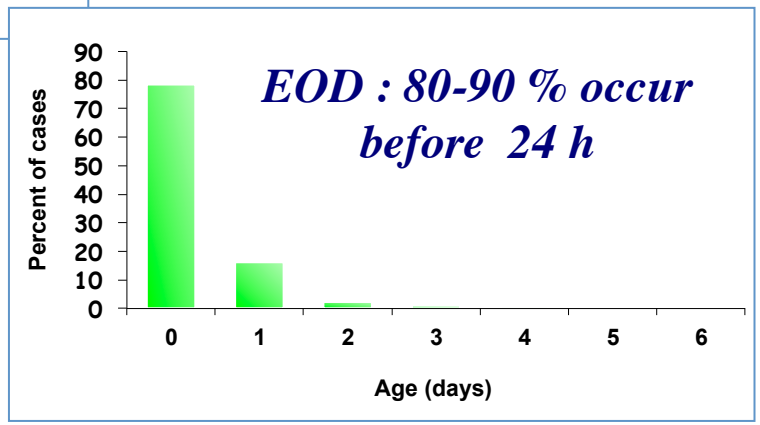
GBS Neonatal Infections

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

GBS Neonatal Infections

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

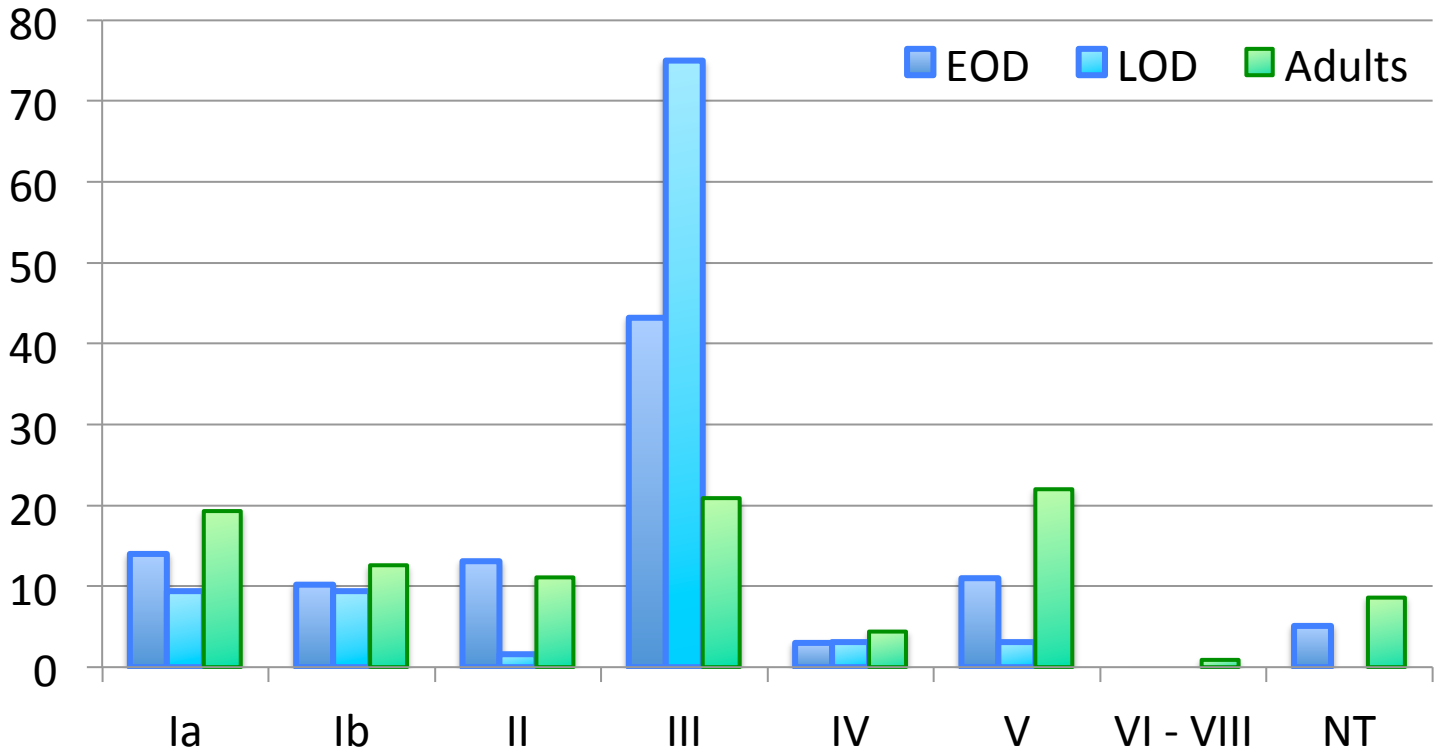




GBS Neonatal Infections

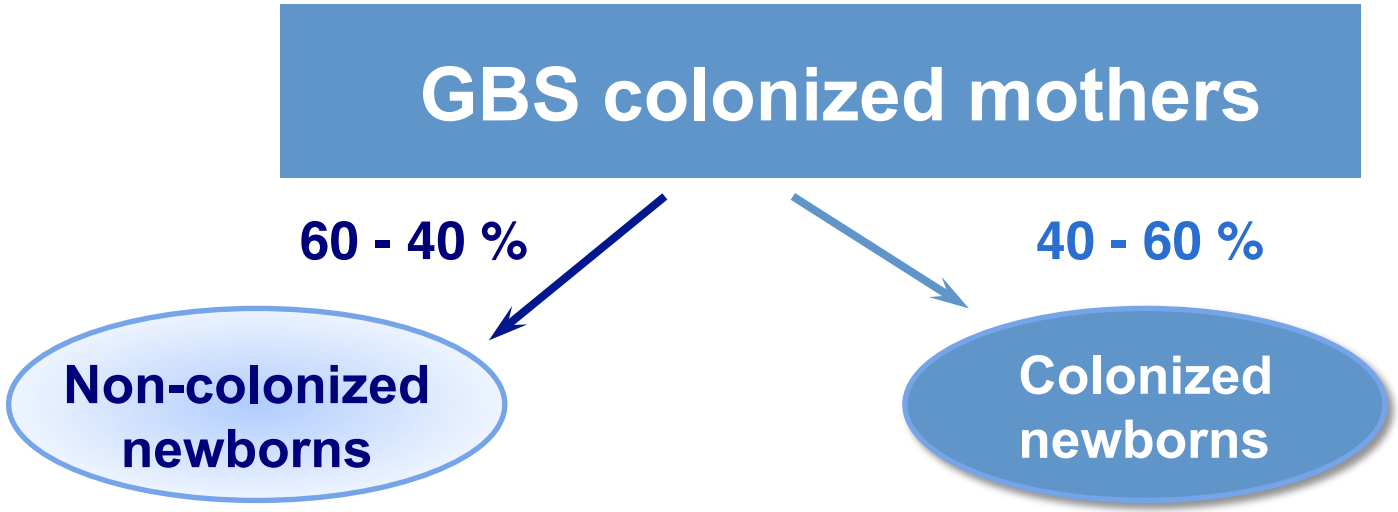
	EOD	LOD
Incidence per 1,000 live births	0.3 – 3	0.5
Onset	0 – 6 days (or 0-72 hrs)	1 week – 3 months (up 1 y)
Mean age at onset	12 hrs	1 month
Transmission	Vertical Intrapartum	Horizontal (vertical ?) At delivery Nosocomial In the community
Portal of entry	Inhalation → pneumonia → translocation into 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)

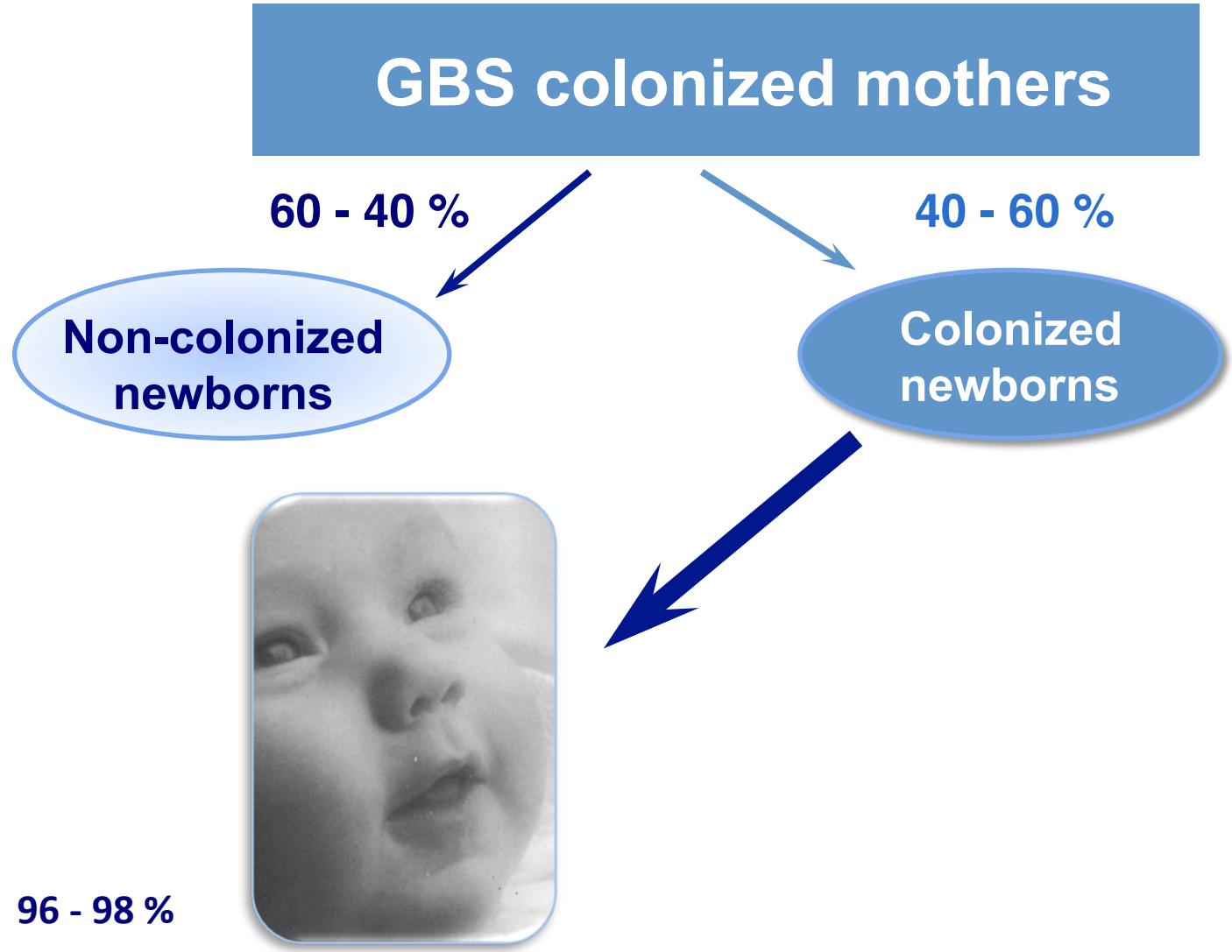


236 neonatal EOD; 64 neonatal LOD; 721 adults

GBS EOD vertical transmission



GBS EOD vertical transmission



GBS EOD vertical transmission

GBS colonized mothers

60 - 40 %

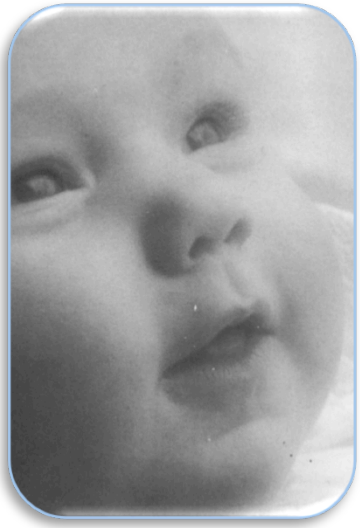
40 - 60 %

Non-colonized newborns

Colonized newborns

Risk factors

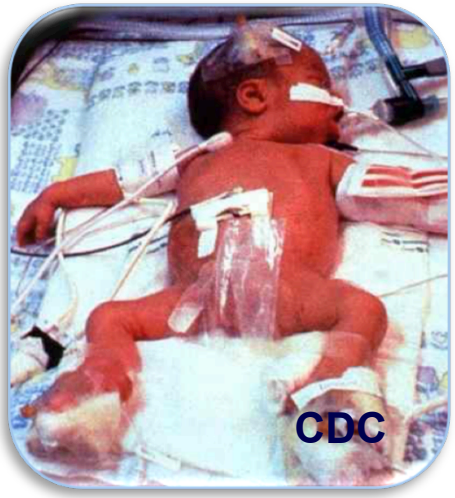
2 - 4 %
GBS EOD



96 - 98 %

Asymptomatic

sepsis
pneumonia
meningitis
long term sequelae



GBS maternal colonization

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

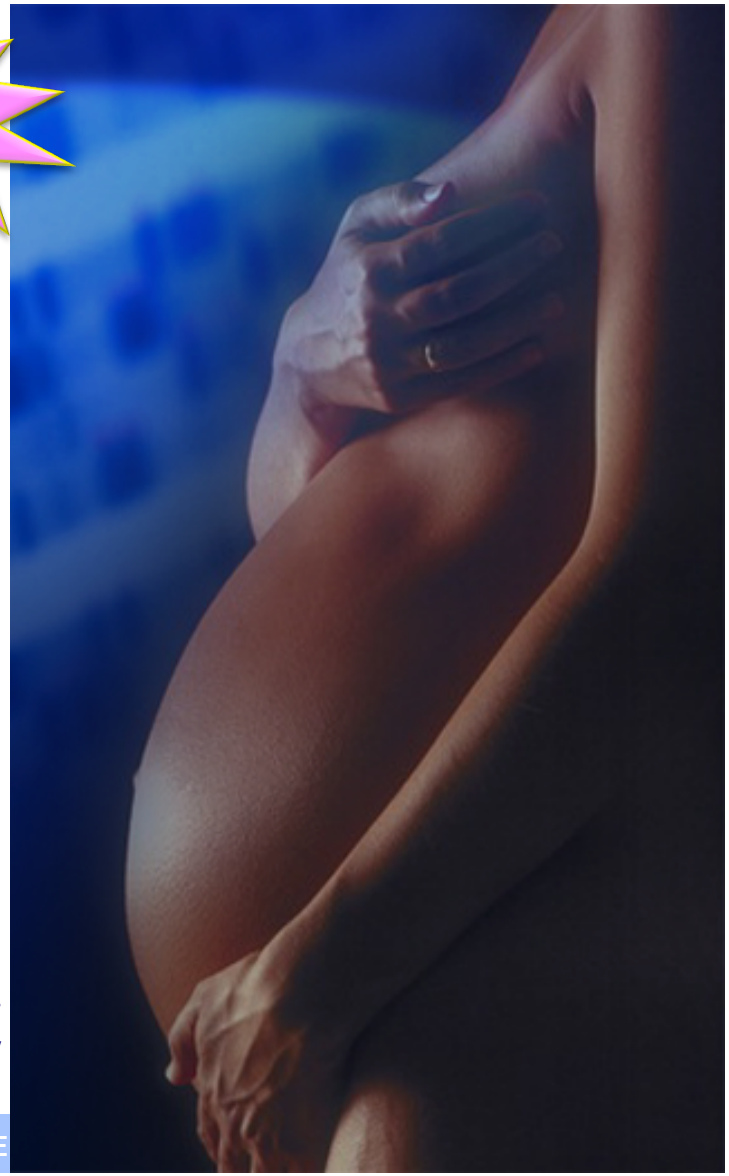
- **GBS carriers***
  - **10 - 35 % of women (Be: 20-25%)**
  - **Clinical signs not predictive**
  - **Dynamic condition**
  - **Intestinal reservoir**
  - **Prenatal cultures late in pregnancy can predict delivery status**

***: 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.

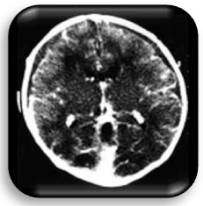
Burden of neonatal GBS early onset diseases in European countries

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*



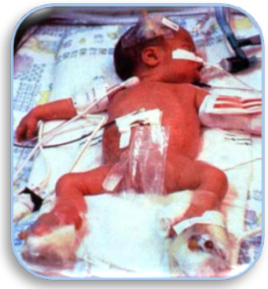
Meningitis

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, …

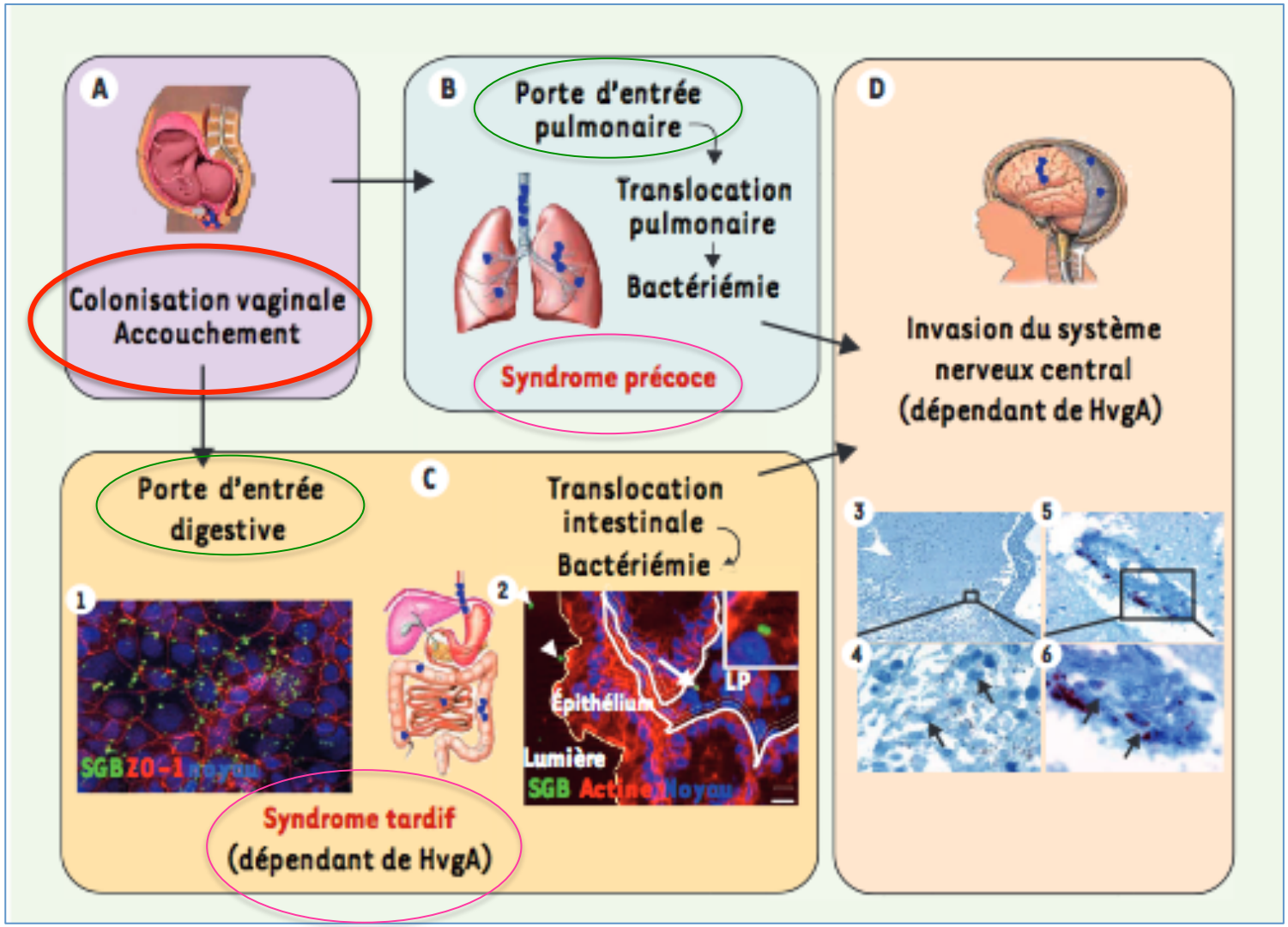
Resistance to
phagocytose
- **Capsule**
- C5a peptidase
- …..

β-hemolysin,
invasins *(pili, …)*
(pneumonia)

Phagocytes cells, **CPS**
Antibodies, Complement

Stages in the pathogenesis of GBS neonatal disease (EOD & LOD)

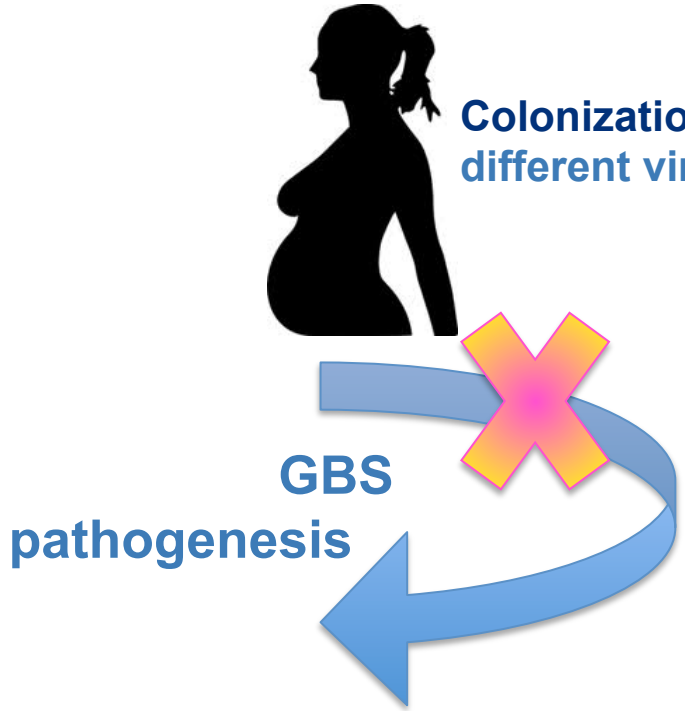
Tozi A et al. 2011 http://dx.doi.org/10.1051/medsci/2011274010



- **Intrapartum antibioprophylaxis**
  - **Universal prenatal screening-based strategy**
  - **Risk-based strategy**
  - **No guideline**
- **Immunoprophylaxis**

GUIDELINES FOR PREVENTION OF GBS PERINATAL DISEASE

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



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

Intrapartum antibioprophylaxis
> 4 (2) hours before delivery

Highly effective in preventing GBS EOD *(1st clinical trials in late 80s)*

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

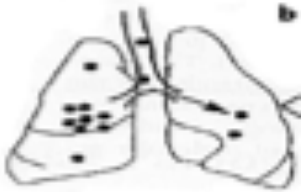
GBS vaccine

« nearly within reach »

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

Ascendant transmission (amnionitis)

GBS pathogenesis



β-hemolysin, invasins (**pneumonia**)

Help for clearing bacteria and preventing development of EOD

Resi… phag…
- Ca…
- C… …ase
- …..

Phagocytes cells, **CPS**
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

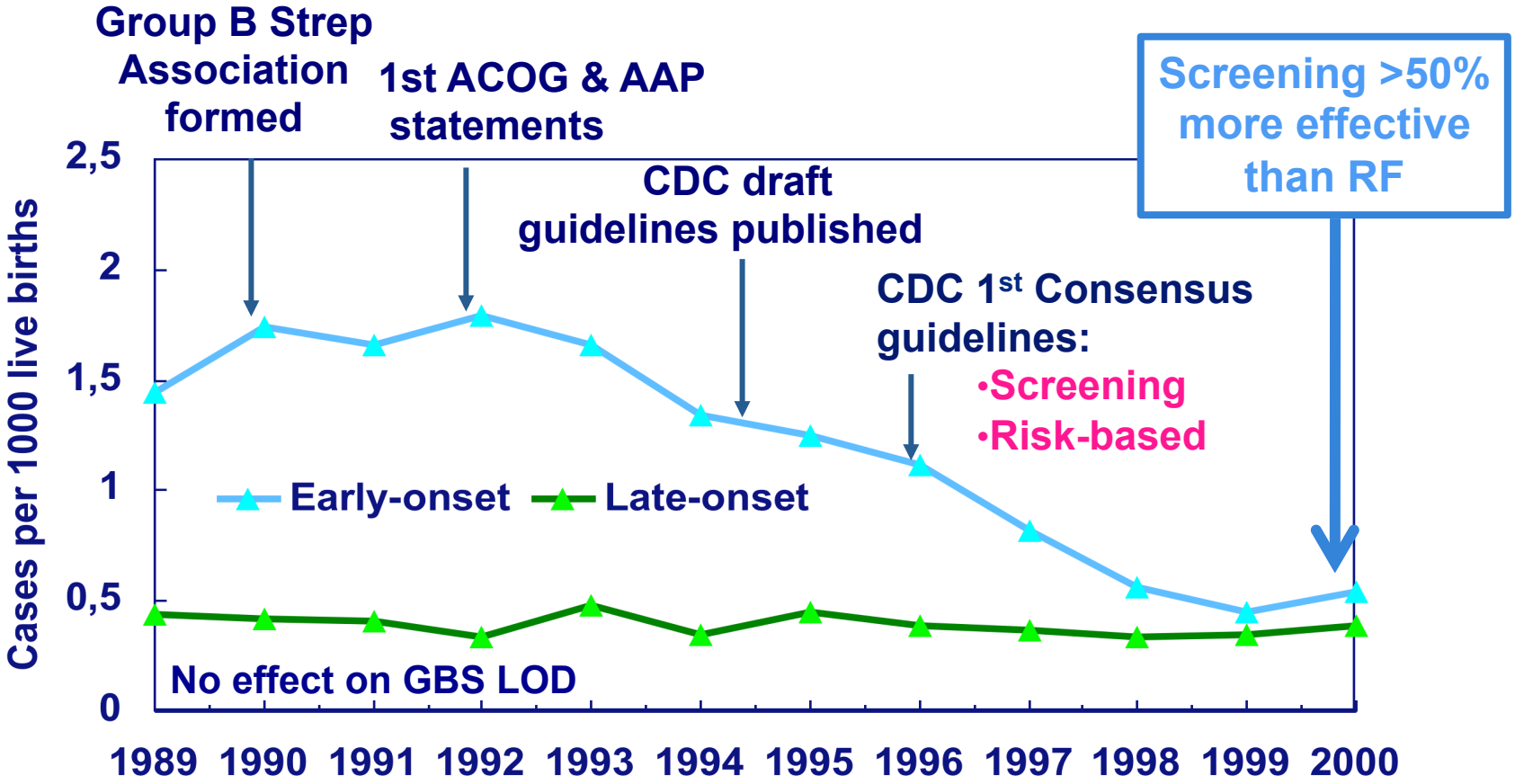
Main goal :

- 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

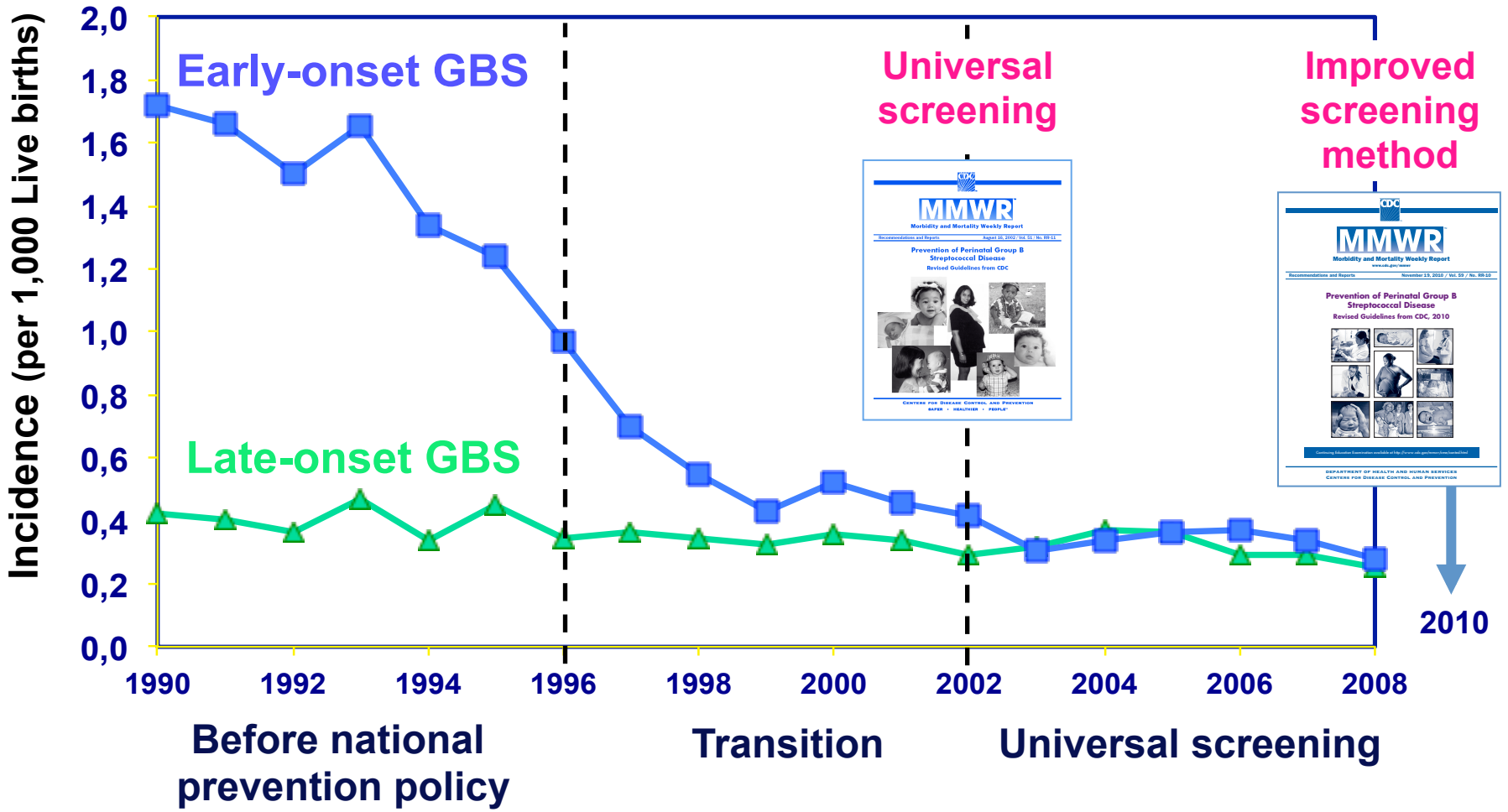
Why is Screening more protective than the risk-based approach ?

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

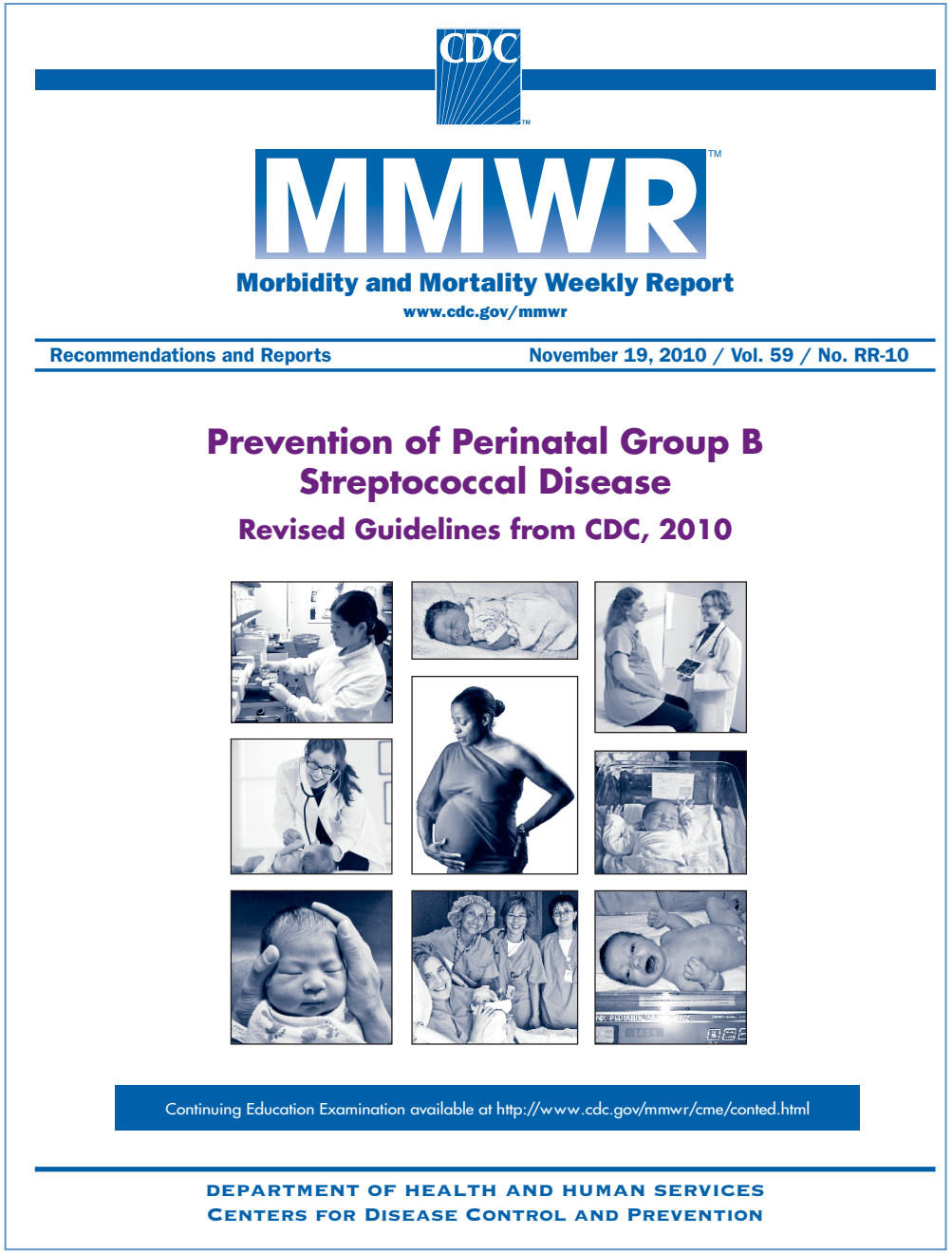
Broader coverage of « at-risk » population

- **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)

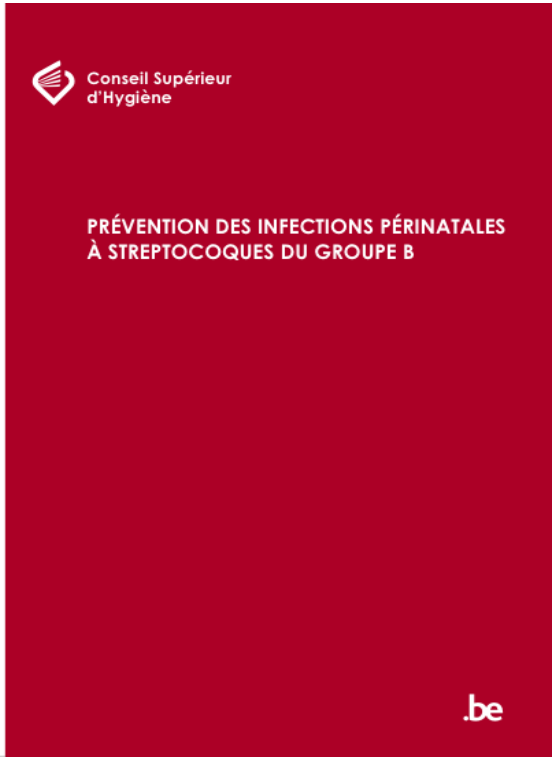


CDC, USA, MMWR, Vol 59 (RR-10) August 2010

Endorsed by

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

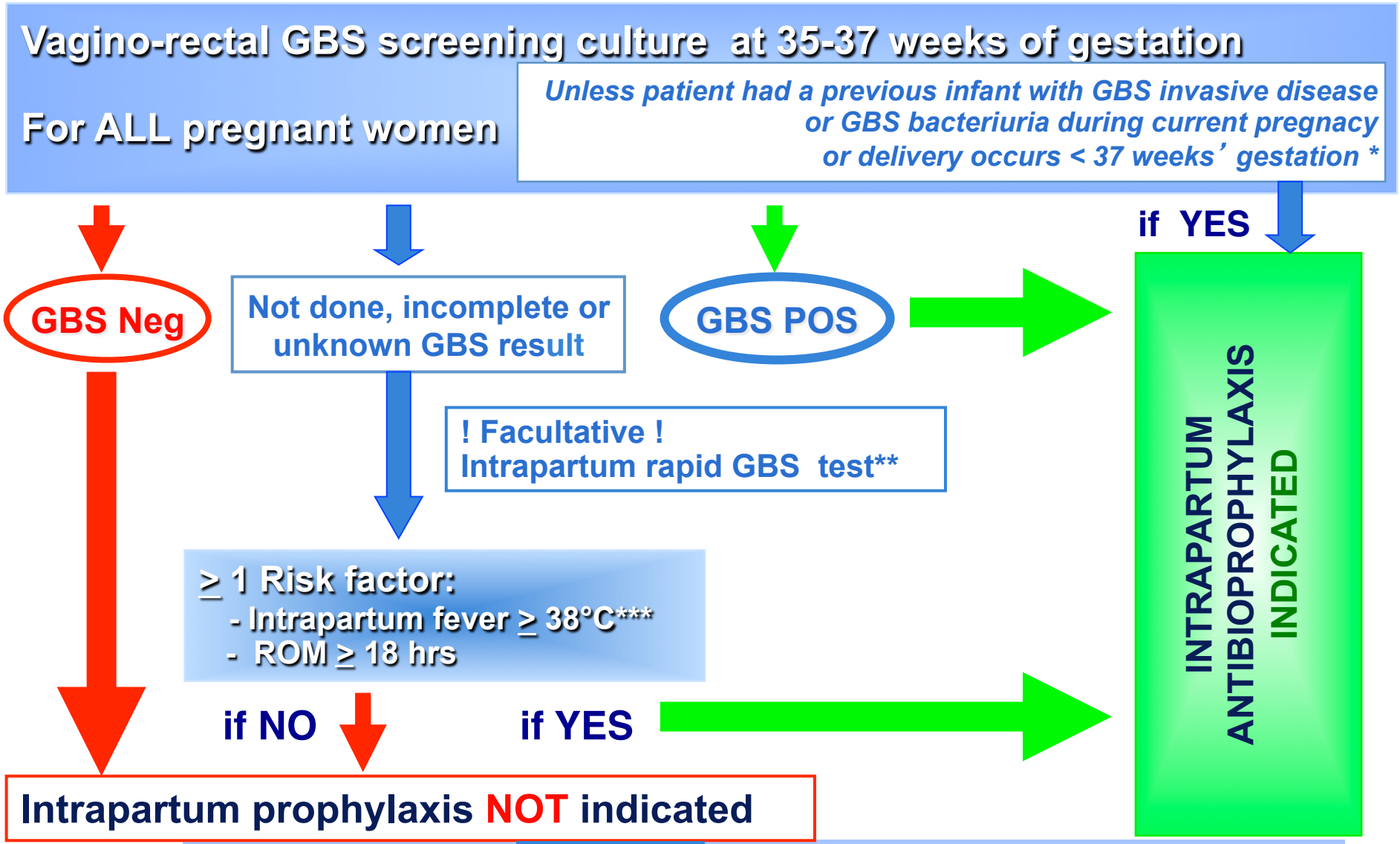
SHC, Belgium July 2003
Revision ongoing



European strategies for prevention of GBS EOD

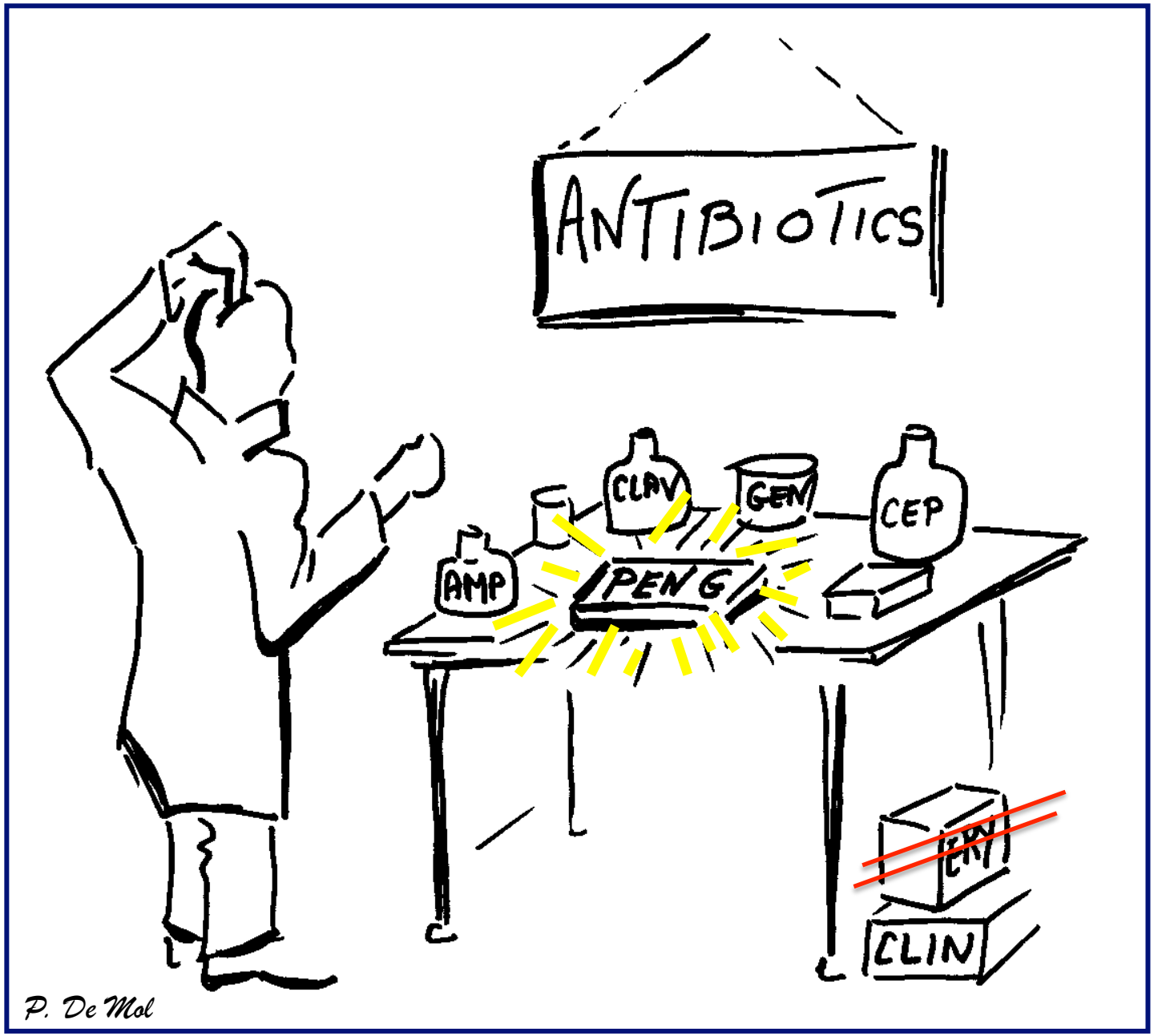
- Intrapartum antibioprophylaxis recommended
  - Screening-based strategy
    - Spain, 1998, 2003, revised 2012
    - France, 2001
    - Belgium, 2003, revision ongoing
    - Germany, 1996, revised 2008
    - Switzerland, 2007
  - Risk-based strategy
    - UK, the Netherlands, Denmark
- No guidelines
    - 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
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 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, 1 g IV q12h***

Intrapartum IV Antibio-Prophylaxis & antibiotherapy

- **Intrapartum antimicrobial prophylaxis (IAP)**
  - **Penicillins = first line drugs**
    - **In case of IgE mediated allergy (risk of anaphylaxis)**
      - **Clindamycin, if susceptible**
      - **Vancomycin, if clindamycin resistant or unknown status**

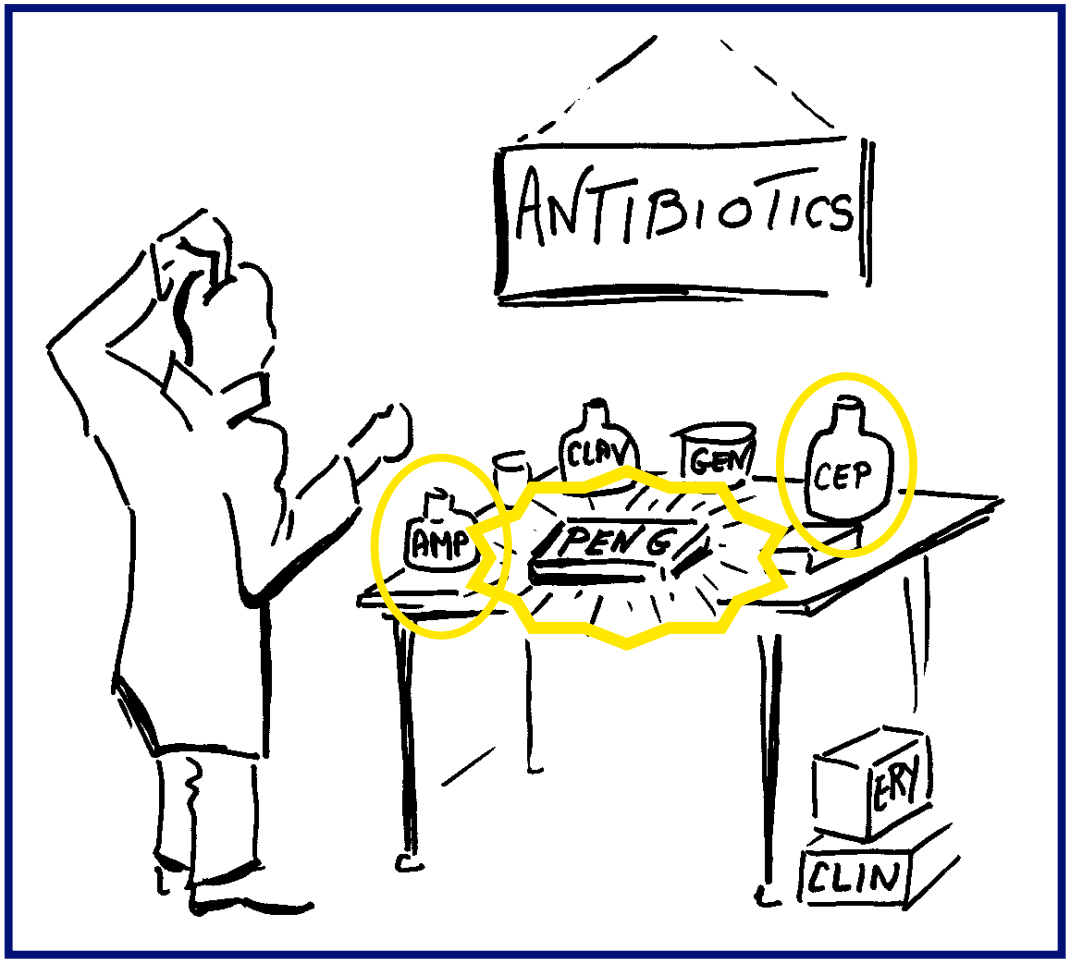
- **Treatment of infections**
  - **Penicillins = first line drugs**
    - **+/- combination with aminoglycosides in severe infections**
  - **According to site of infections**
    - **Macrolides, clindamycine, fluoroquinolones**

Concerns : Clinically relevant antimicrobial resistance

- **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**



Will penicillins remain the gold standard ?

GBS and non-S to β-lactams

- **Existence and molecular mechanisms of clinical isolates with reduced Penicillin susceptibility (PRGBS)**
  - **First report in Japan by Kimura K et al, AAC 2008**
  - **Following reports from Japan, USA, Canada**

- **Penicillin MIC 0.25-1 mg/L**
- **Ceftizoxime MIC 4-128 mg/L**

Acquisition of amino-acid substitutions in PBP2X and in PBP1A

→ elevation of cephalosporins'MICs

PR GBS versus PR *S.pneumoniae*

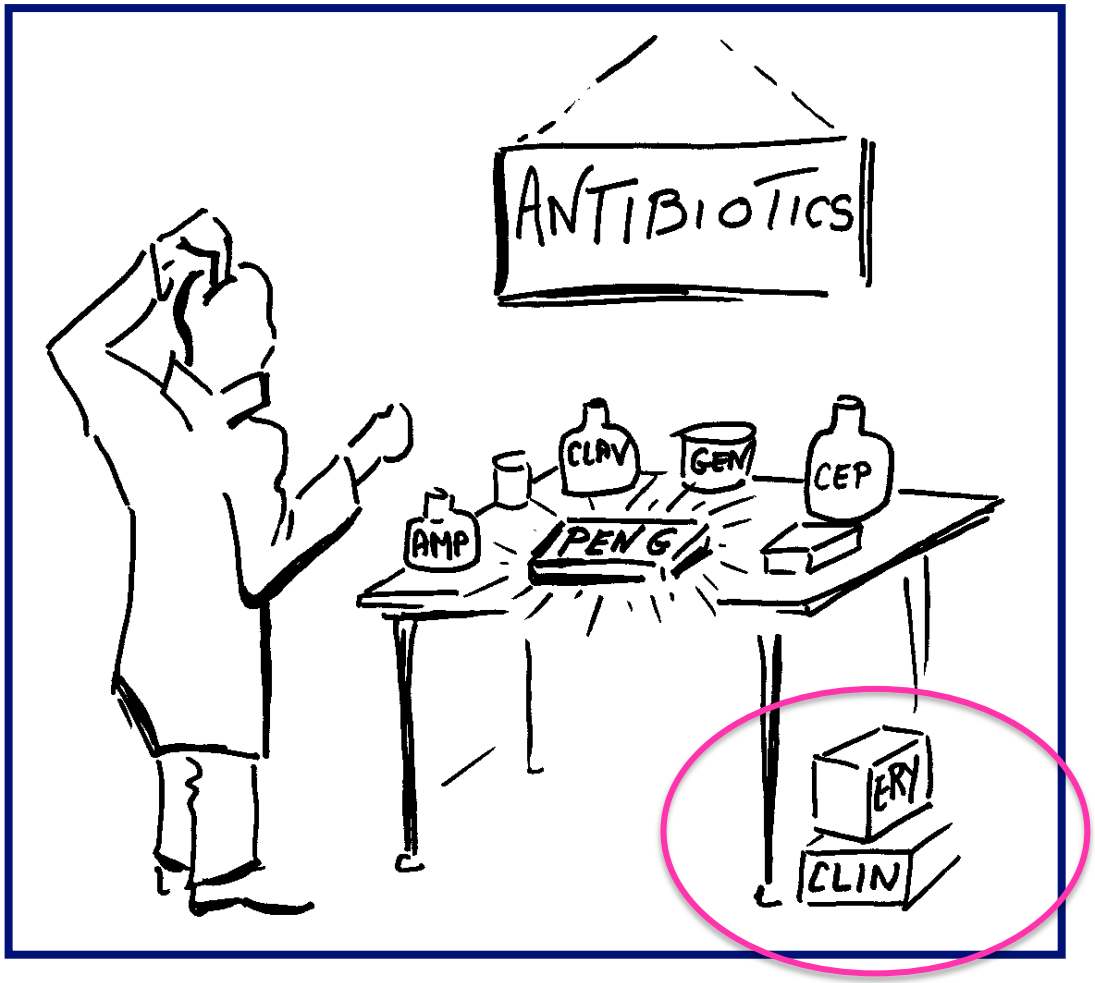
- PR *S.pneumoniae*
  - Penicillin MICs increased by acquiring various amino-acid substitutions in PBPs, including PBP1A and PBP2X
- Why should we not see the same in GBS?
  - Risk of highly resistant cephalosporin GBS
  - Risk of increase of MICs to penicillin

PR GBS detection

→ possibly unrecognized **by standard antimicrobial susceptibility methods !!**

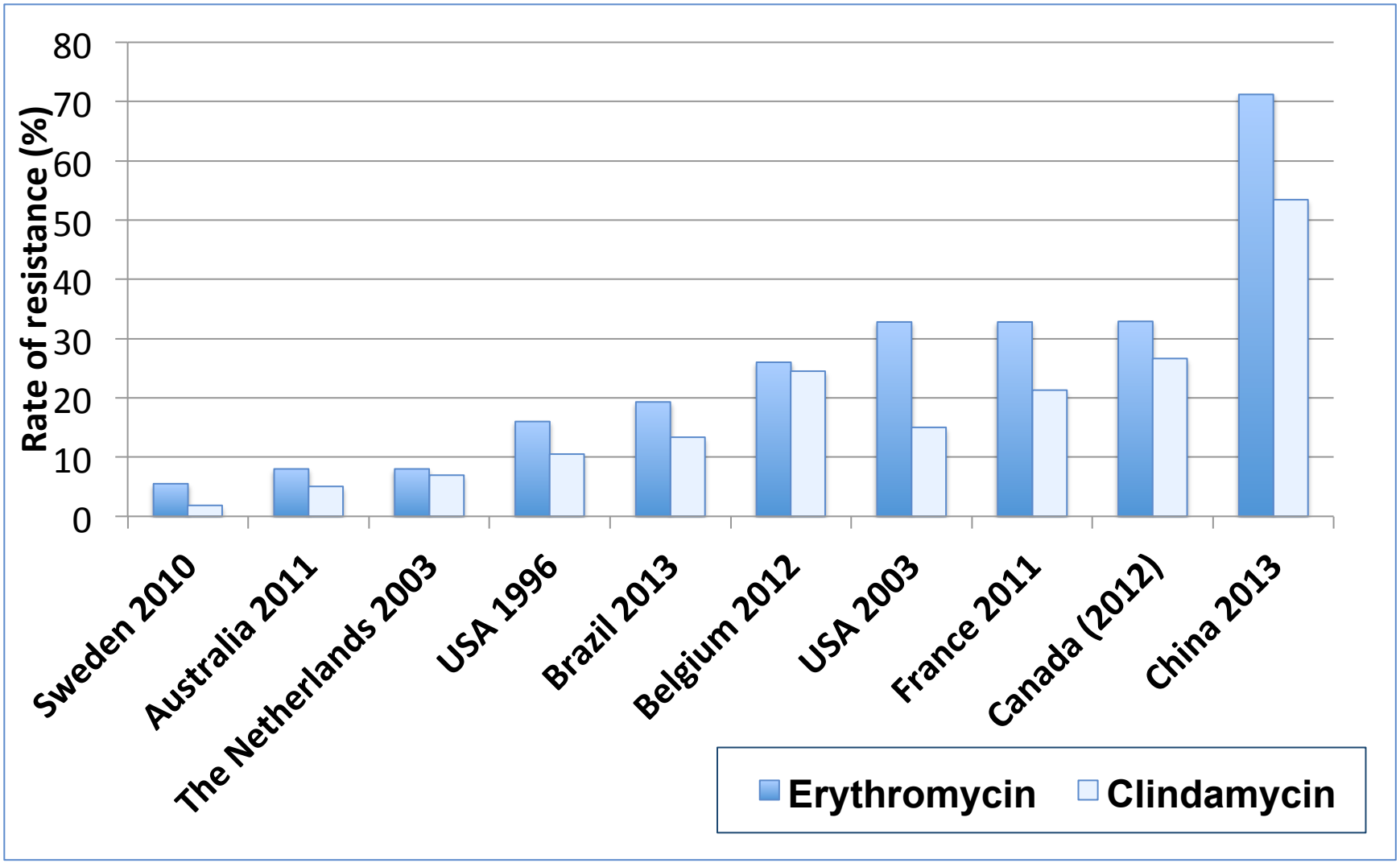
- **Recommended methods for initial screening**
  - **3-Disk diffusion**
    - **Oxacillin, ceftizoxime,**
    - **Ceftibuten (no zone)**
  - **MICs to oxacillin and ceftizoxime**
    - **Usually high for PR GBS**

Kimura et al, J Clin Microbiol 2009



What do we know today about macrolide - lincosamide Resistance?

Resistance to macrolides/lincosamides
Wide geographical variation of rates



Resistance to macrolides/lincosamides
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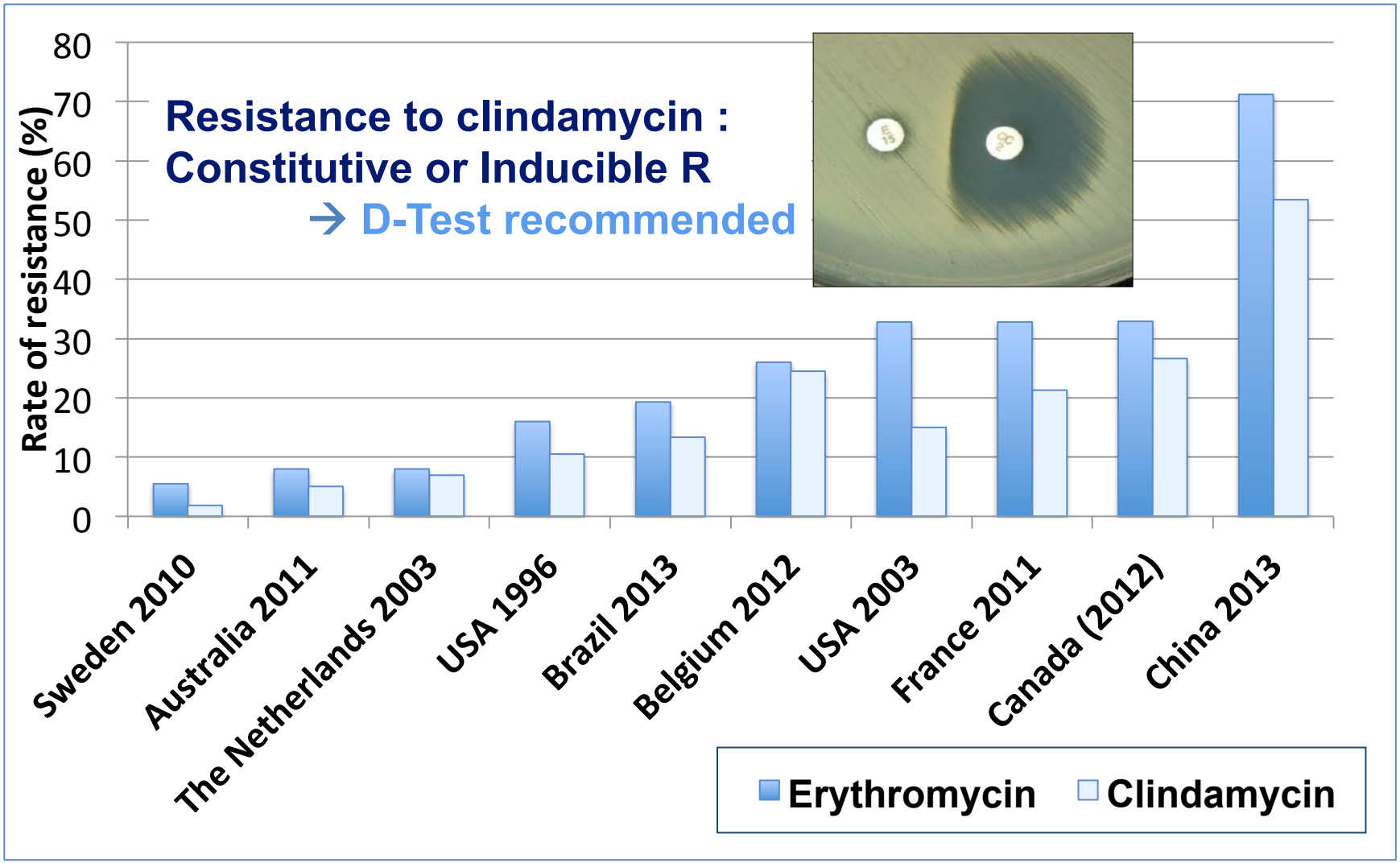
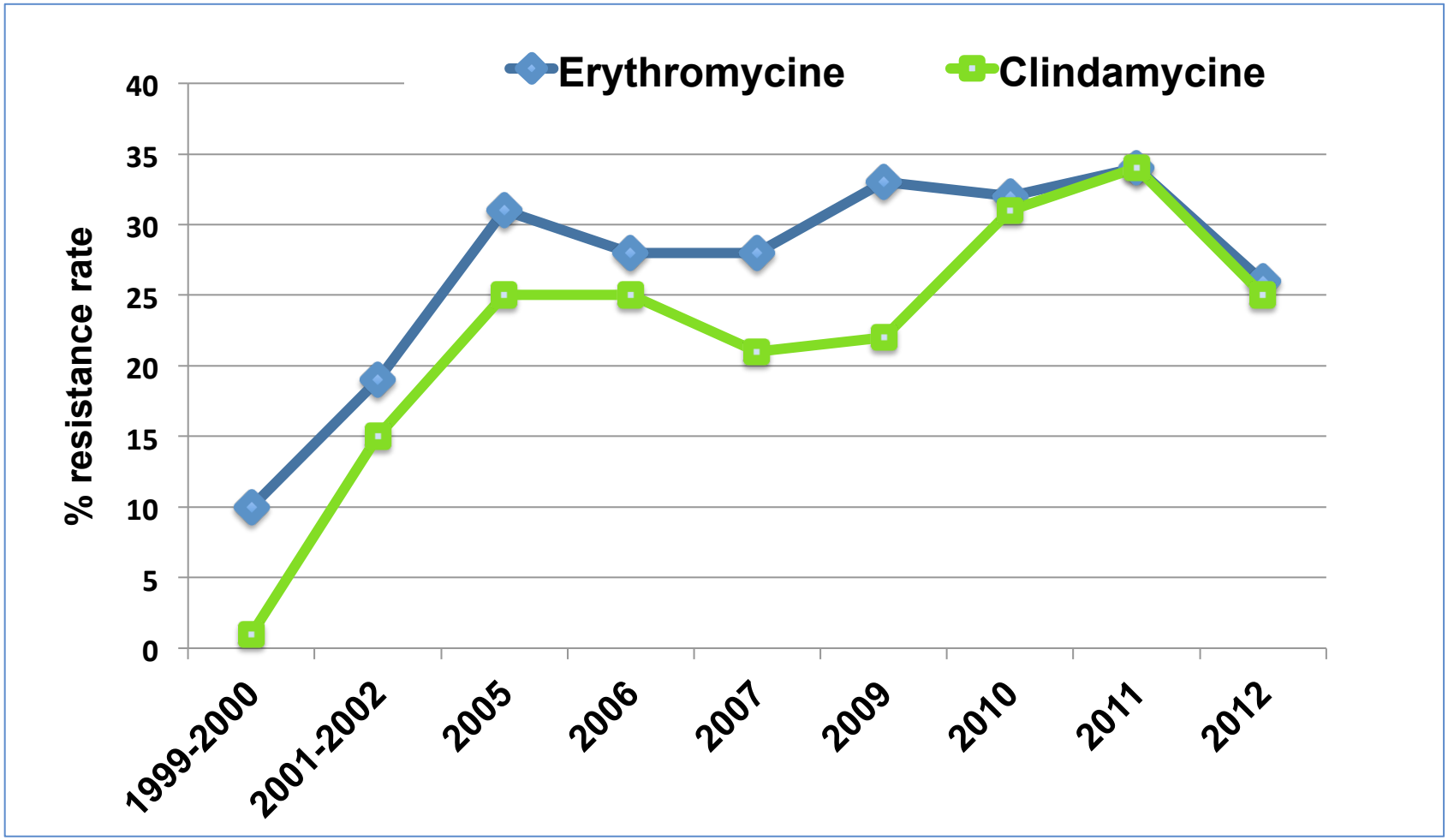


Resistance to macrolides/lincosamides on the rise (Invasive isolates of GBS Belgium 1999-2012)



MLS acquired Resistance Phenotypes and genotypes

- **Target modification (*erm* family genes)**
  - **Constitutive MLS resistance**
  - **Inducibe MLS resistance (D-zone test)**
  - **Serotype associated (higher rates: IV, V > III > others)**

  Cross resistance to macrolides, lincosamides and streptogramin B

- **Active efflux (*mef*A gene) → M phenotype**

  Resistance to 14- & 15- membered ring macrolides (as erythromycin and azithromycin)

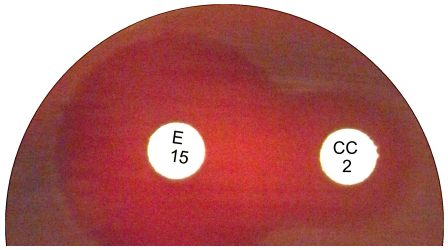
MLS acquired Resistance
Phenotypes and genotypes

- Target modification (*erm* family genes)
  - Constitutive MLS resistance
  - Inducibe MLS resistance

  Cross resistance to macrolides, lincosamides and streptogramin B
- Active efflux (*mef*A gene)

  Resistance to 14- & 15- membered ring macrolides (as erythromycin and azithromycin)

- **Enzymatic inactivation or ? (lnu genes, lsa genes)**
  - **Clindamycin resistance**



Phenotypes L

- **L phenotype**
  - **Inactivation by lincosamide nucleotidyltransférases (*lnu*(B) and *lnu*(C) genes)**
    - **New Zealand, Canada, USA, Asia, Argentina**

- **LS_A or LS_AP phenotype**
  - **Cross resistance to lincosamides, streptogramin A and pleuromutilin**
  - ***lsa*(C) gene**
    - **New Zealand *(Malbruny et al., AAC, 2011)***
    - **Belgium *(J.Descy et al, LISSSD abstract 100)***
      - ***0.6% from1329 isolates (2008-2013)***

- **Emergence of resistance is unavoidable**
  - **But how fast ?**
- **Transmission of Resistant genes « in package » !**
  - **→ Risk of increase of multi-resistance**
  - **→ Threat for both prophylaxis and therapy**
- **Emphasize the need for**
  - **careful epidemiologic monitoring**
  - **good clinical laboratory AST practice**

Antibiotics	About Resistance	Epidemio. surveillance by Nat.Ref.C.	AST - Routine lab methods
Penicillin and other β-lactams	• *Still very rare* • *Possibly unrecognized*	Mandatory	Initial screening by with 3-disks diffusion *To implement in clinical labs worldwide ?*
Erythromycin – Clindamycin	• *Globally on the rise* • *National differences* • *Evolution of genetic supports* • *L phenotype emerging*	Mandatory	• AST for E & C • D-zone Test synergy testing if E R *Already recommended*
Gentamicin	• *Emerging in some countries* • *Not routinely screened*	Mandatory	HLR determination for severe infections Method ???
Fluoroquinolones	• *Emerging in Asia* • *Rare elsewhere*	Mandatory	No special trick

Concerns about potential adverse / unintended consequences of prophylaxis

Management of the neonate at risk for early onset Group B streptococcal disease (GBS EOD): new paediatric guidelines in Belgium

L. Mahieu, J.-P. Langhendries, V. Cossey, C. De Praeter, P. Lepage, P. Melin **- Acta Clinica Belgica 2014:313-9**

- **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

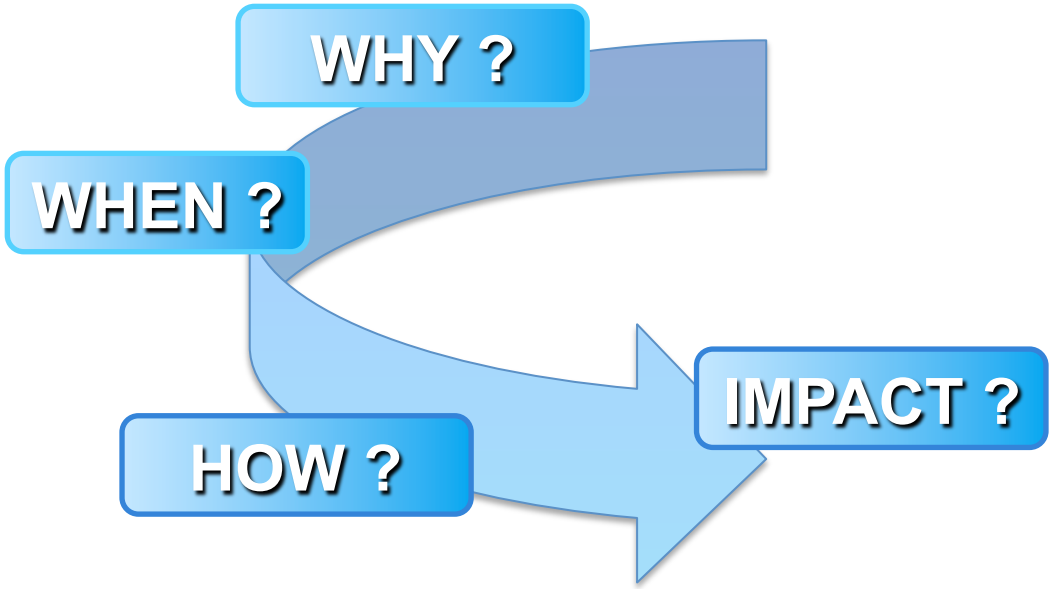
In spite of universal screening prevention strategy

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

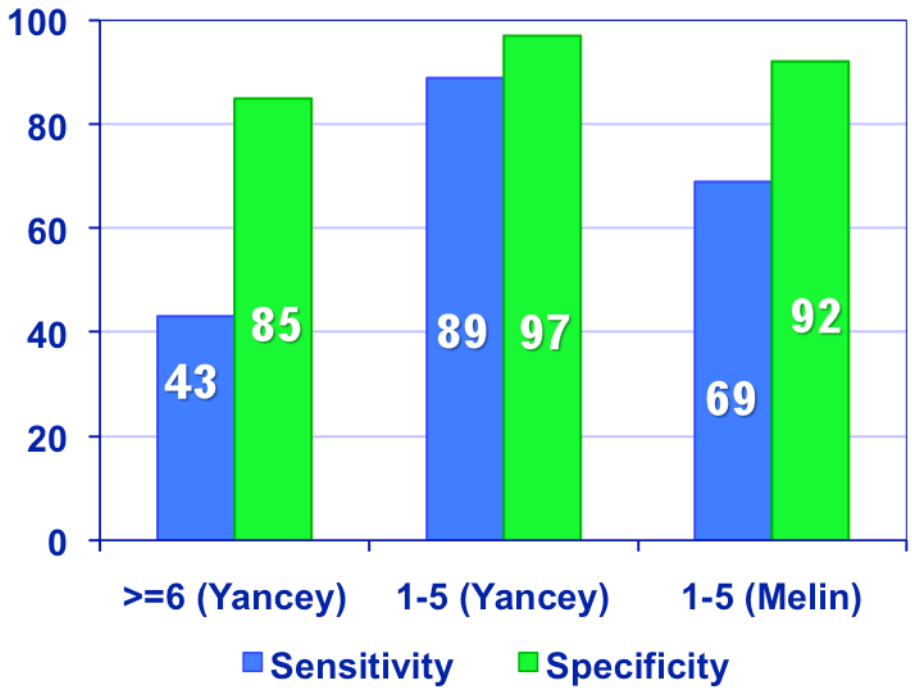
To predict GBS vaginal (rectal) colonization at the time of delivery

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

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)***



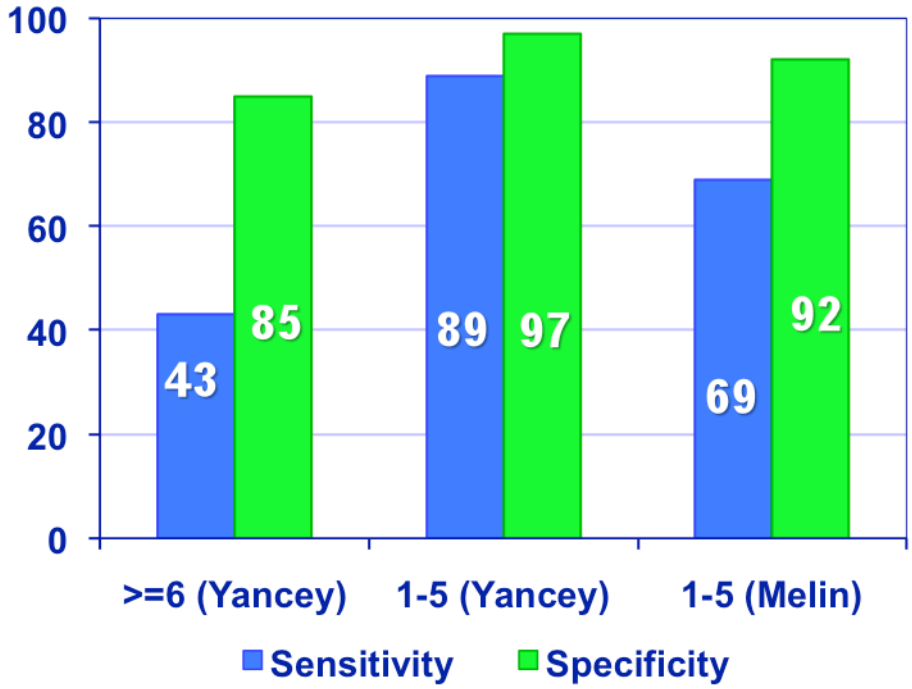
Not 100 % as colonization is dynamic

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

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)

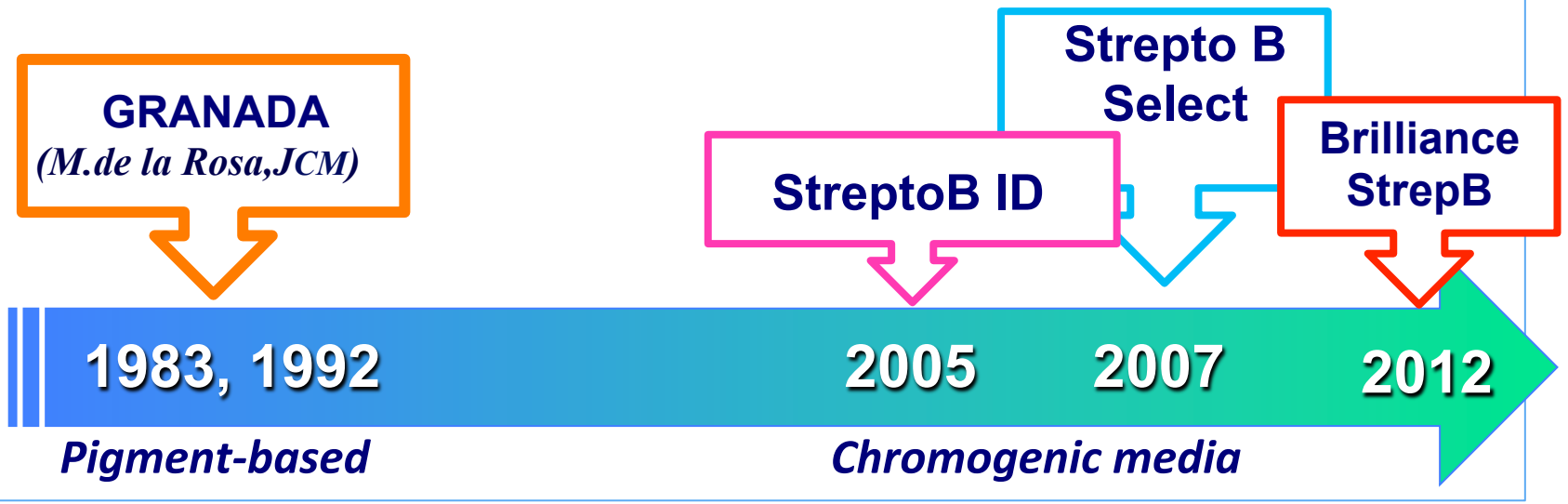
From direct plating on blood agar
Evolution of culture methods

Use of selective enrichment broth

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

Use of differential agar media

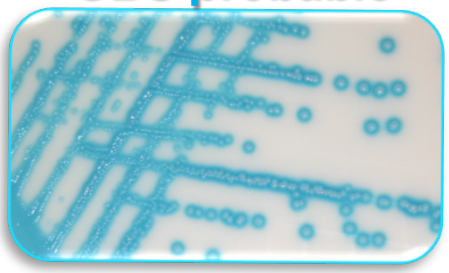
Recommended by some European guidelines (+ CDC 2010)



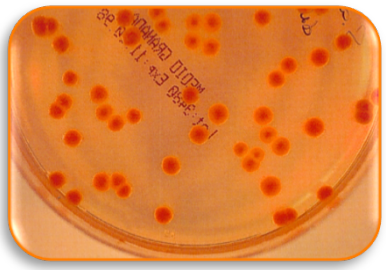
Which agar or which combination?

+/- Blood agar

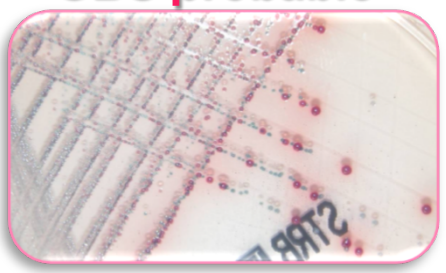
= GBS probable



= GBS



= GBS probable



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

Standard procedure

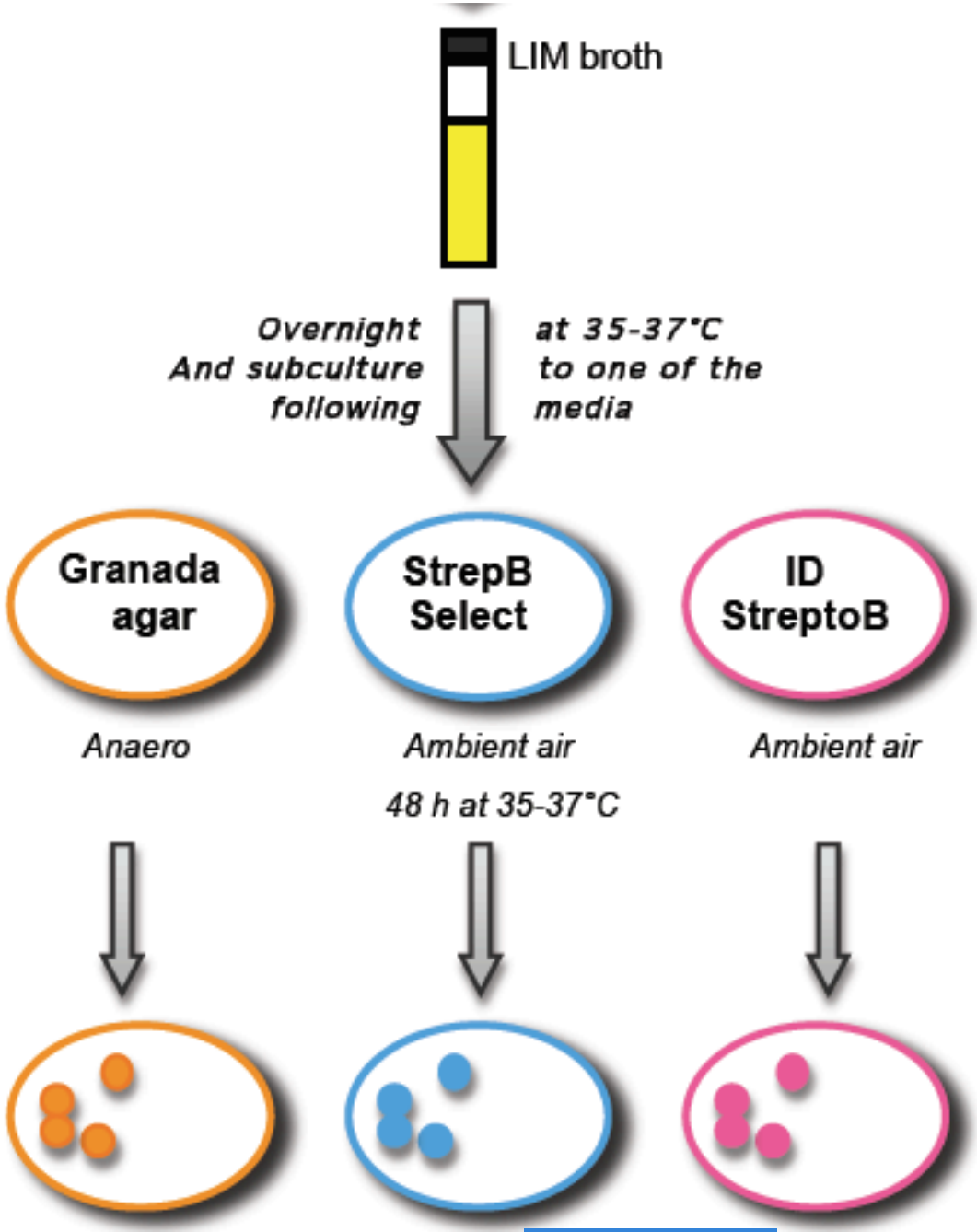
Vagino-rectal swab or
Vaginal & rectal swabs

Inoculate swab(s) in 1 Lim broth

LIM broth

Overnight
And subculture
following

at 35-37°C
to one of the
media


LIM broth
Overnight
And subculture
following
at 35-37°C
to one of the
media
Granada
agar
StrepB
Select
ID
StreptoB
Anaero
Ambient air
Ambient air
48 h at 35-37°C

Optional procedure

Vagino-rectal swab or
Vaginal & rectal swabs

And

Inoculate swab and streak to at least one of the following media

- ID StreptoB
- StrepB Select
- Blood agar ± CNA

18 h at 35-37°C in appropriate atmosphere

LIM broth

Overnight *at 35-37°C*

If no GBS identified on direct plate(s) :

proceed as in standard procedure.

Reading and processing of the cultures

POSITIVE GBS Screening if	Orange colonies = GBS	Blue-turquoise colonies = suggestive GBS Id. to confirm	Pink colonies = suggestive GBS Id. to confirm	Beta-hemolytic colonies = suggestive GBS Id. to confirm
Negative GBS Screening if	No orange colonies	No blue-turquoise colonies	No pink colonies	No beta-hemolytic colonies

Identification: Group B Antigen or MALDI-TOF MS

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

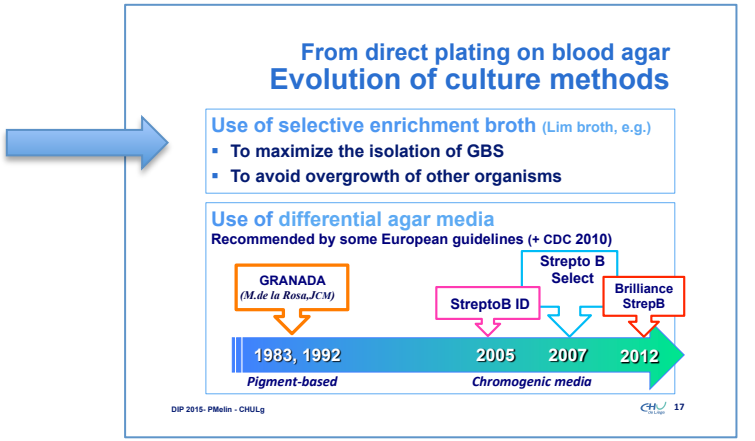
Recovery of group B streptococci (GBS) was assessed in 1,204 vaginorectal swabs stored in Amies transport medium at 4 or 21°C for 1 to 4 days either by direct inoculation onto Granada agar (GA) or by culture in blood These data indicate that viability of GBS is not fully preserved by storage of vaginorectal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

ICAAC 2013
53rd ICAAC | SEPT 10-13 | Denver, CO



IMPROVEMENT OF TRANSPORT CONDITION OF SWABS FOR GROUP B STREPTOCOCCAL (GBS) SCREENING

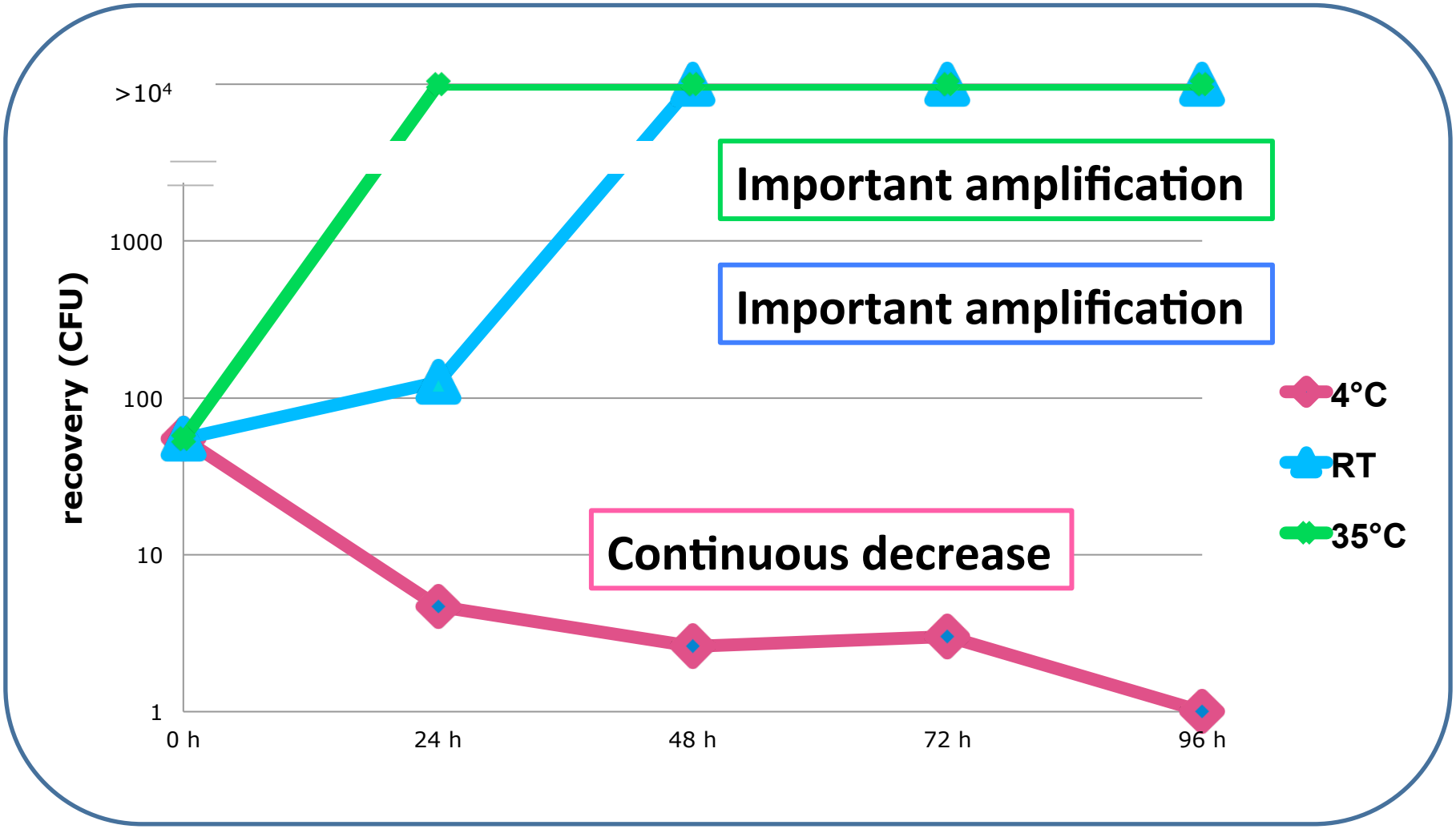
P. Melin, M. Dodémont, G. Sarlet, R. Sacheli, et al.
National Reference Centre for GBS, University Hospital of Liège, Liège, Belgium

To sustain viability
Whatever is storage T° for a few days

Use of a selective enrichment Lim broth as transport media

Results:

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



Granada tube: not shown, dramatic drop at 48-72h

Transport conditions to be recommended for optimizing GBS antenatal screening

Belgian Health Superior Council, 2015

- **Transport system**
  - Use of a **selective enrichment Lim broth with a flocked swab** *(BD, Copan, bioMérieux, i.e.)*
- **Transport and storage condition**
  - At RT° (up to 35°C)
  - As soon as possible
    - Viability sustained at least 4 days
- **Remark**
  - If use of Amies or Stuart medium (non nutritive medium)
    - To be processed as soon as possible within 24 hours (max 48 h)

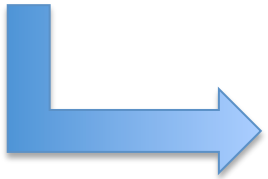
Prenatal culture-based screening: Limiting factors

- **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

€€€
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)

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

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 « 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 guidelines

- 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

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

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)

Required analytical specification for rapid intrapartum test

- High sensitivity and specificity
  - Minimum 90% and 95% respectively
- Full automation with integrated internal controls
- Easy to perform and interpret by nurses
- Time to result: < 1 hour
- 24 h / 7 days availability

Di Renzo G, Melin P et al. Intrapartum GBS screening and antibiotic prophylaxis : a European consensus conference. J Matern Fetal Neonatal Med 2014;27:1-17

Xpert® GBS for intrapartum screening

- **Real Time PCR on GeneXpert system**
  - **Amplification of a conserved region adjacent to the cfb gene of GBS**
- **On vaginal or vagino/rectal swab**
- **Fully automated**
- **Easy handling** ***(2 min hands on time)***
- **Result in 35-45 minutes**

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

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 for intrapartum screening

(selected paper amongst many others)

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
POC test in the delivery room study
Objectives

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

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

2. **To evaluate the cost-effectiveness of the intrapartum screening strategy**

→ To consolidate the proposal of the European Expert Group

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 → 2014-2015 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 !**

Real-time PCR, very promising, BUT …

Xpert® GBS POCT in the delivery room

- **Theoretical superior clinical value**
  - ***versus*** **antenatal screening**

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

Real-time PCR, very promising, BUT …

Xpert® GBS POCT in the delivery room

Not ready as a standalone screening

- **High specificity but varying sensitivities !**
- **Could be combined with risk factor strategy ??**
- **Some expected improvements to secure the result AND the patient management**

Prevention of GBS EOD and LOD

Prevention of maternal diseases

VACCINE

Maternal GBS immunization

Could maternal immunization be an alternative ?

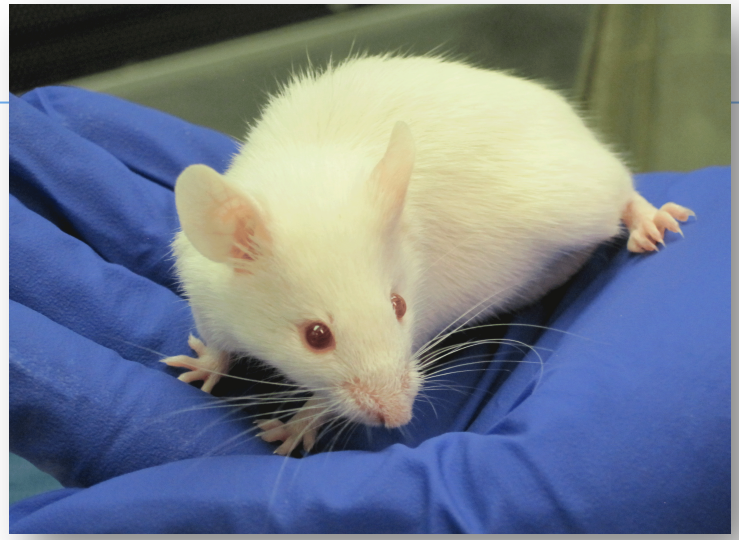
- **Protection against both EOD & LOD ?**
- **Bypassing concerns related to antimicrobial resistance ?**
- **Cost-effectiveness ?**
- **Adjunctive to screening & IAP ?**

Background

Long-standing data supports protection of maternal anti-CPS Ab

Lancefield's observations

- **Demonstration of protection against lethal GBS infection in a mouse model by antibodies to the CPS of GBS**
- **Passive transfer of anti-CPS Ab protects newborn mice**



Background

Long-standing data supports protection of maternal anti-CPS Ab

- **Correlate between maternal low level of CPS type Ab (III, Ia & Ib) at time of delivery and risk for development of GBS EOD**

- **Human serum containing sufficient concentrations of Ia, Ib, II, III and V CPS-specific IgG promotes efficient opsonization & phagocytosis of homologous strain in vitro and protection from experimental infection in vivo.**

***Baker C et Kasper D, 1976*, NEJM**

Background
First generation of CPS vaccine

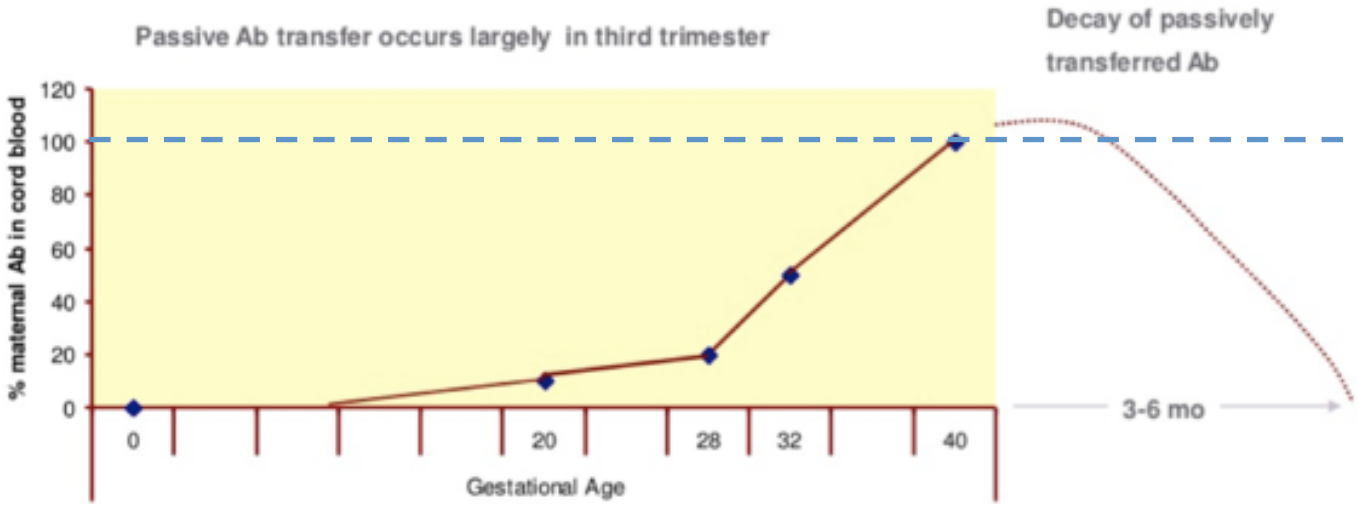
- Disappointment from studies of uncoupled first generation purified native GBS CPS vaccines in healthy adults
- Demonstration of feasibility of vaccine prevention of GBS disease
- Need for improvement of immunogens
- Success story of polysaccharide-protein conjugate vaccine technology in preventing *Hi* b and *S.pneumoniae* infections in infants

Background

- **Expectation of polysaccharide-protein glycoconjugates**
  - **T cell-dependent response**
  - **Immunological memory & long term protection**
  - **Predominantly IgG1 subclass → improved transplacental transport**
  - **Increase likelihood of protection of mother and infant**

Maternal vaccination allows infant protection

- **Placental transfer increases markedly > 32 weeks**



Vaccine for pregnant women:

Likely the most effective, sustainable and cost effective approach

CPS

Conjugate CPS

Surface proteins

Pili proteins

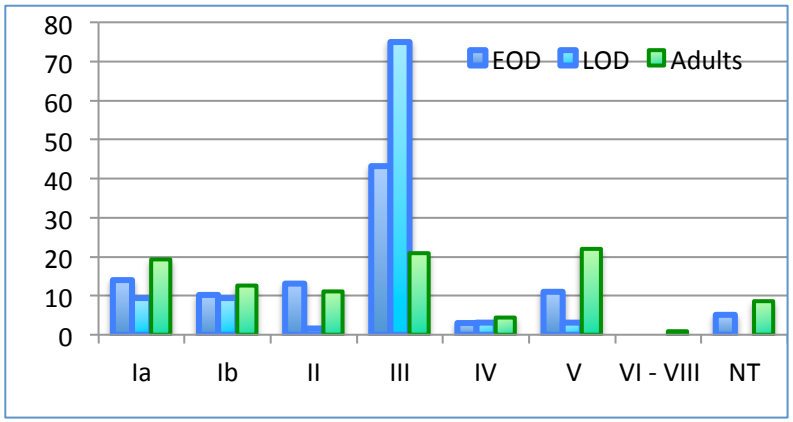
NN fusion protein

CANDIDATE VACCINES

GBS Vaccines, since the 1980s Challenges

Native capsular polysaccharide vaccines (1st gen)

- **10 serotypes**
  - **Different distributions**
    - **EOD, LOD, invasives infections in adults**
    - **Geographically, along time, ATB pressure**



GBS Vaccines, since the 1980s Challenges

Native capsular polysaccharide vaccines (1st gen)

- **10 serotypes**
  - **Different distributions**
    - **EOD, LOD, invasives infections in adults**
    - **Geographically, along time, ATB pressure**

Conjugated vaccines (2nd gen)

(Channing laboratory, Harvard medical school, Boston)

- **CPS III-Tetanus Toxoid**
- **Monovalent Ia, Ib, II and V CPS –TT**
- **Tested for immunogenicity in healthy adults**

- **Multivalent conjugated vaccines Ia, Ib, (II), III (and V)**

GBS Vaccines, since the 1980s Challenges

Capsular polysaccharide - TT vaccines
Capsular polysaccharide – CRM_{197} vaccines
(Second generation)

- **Dosage and route of administration**
- **Immune response**
- **Duration of immunity and protection**
- **Safety studies**

GBS Vaccines, since the 1980s Challenges

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

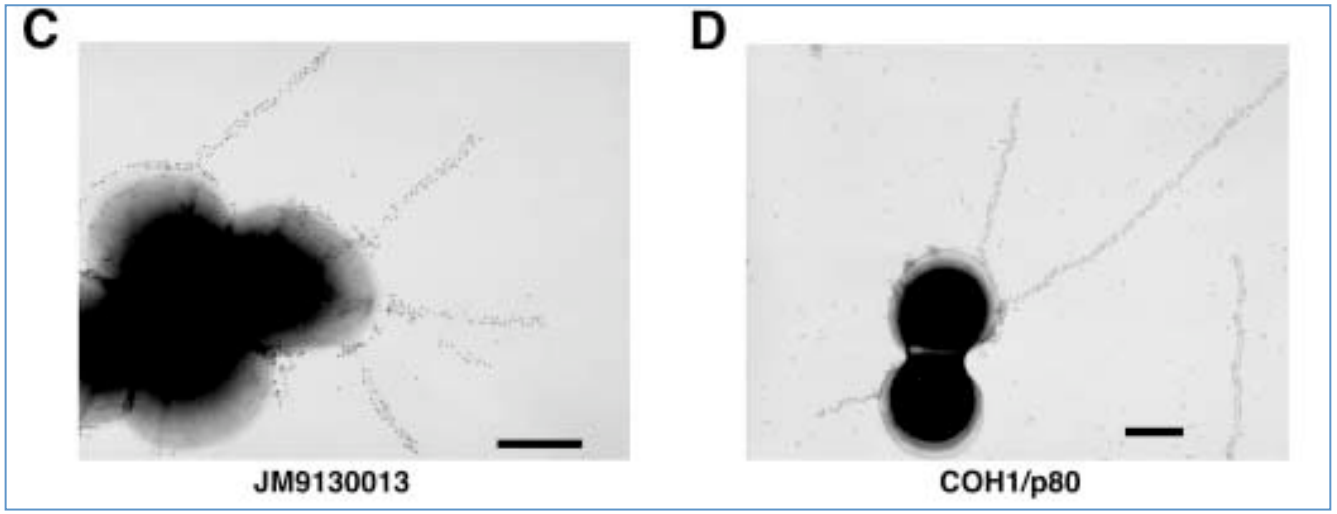
- **Comparaison of genomes from 8 different GBS serotypes (Novartis)**

  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 »**
      - **PI 1, PI 2a & 2b**

GBS « pilus like structure »

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

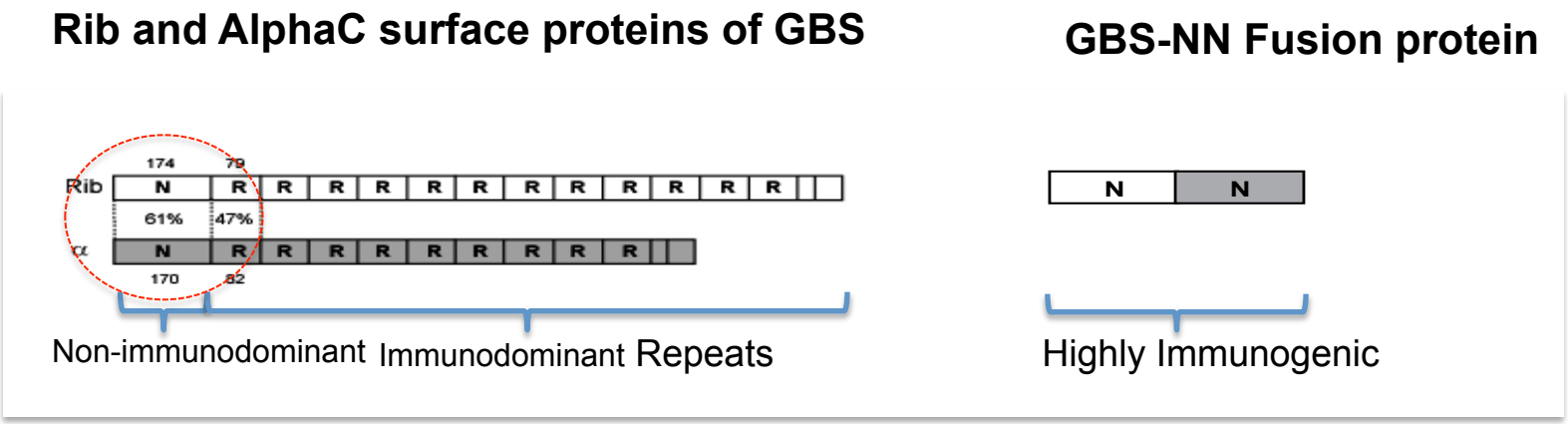


Protein-based Vaccines

GBS-NN fusion protein

From Rib and AlphaC surface proteins of GBS

- Based on novel vaccine epitopes identified in the N-terminal regions of the Rib and AlphaC surface-proteins of GBS
- Vaccine candidate is a non-glycosylated fusion protein



Cell Host & Microbes 2, 427-434, 2007

MINERVAX

Protein-based Vaccines

GBS-NN fusion protein

From Rib and AlphaC surface proteins of GBS

- Based on novel vaccine epitopes identified in the N-terminal regions of the Rib and AlphaC surface-proteins of GBS
- Vaccine candidate is a non-glycosylated fusion protein
- Highly immunogenic and anti-GBS-NN antibodies more protective than antibodies to full-length proteins

MINERVAX

A novel protein-only, single component, GBS vaccine covering 95% of clinical isolates

CRM-Conjugate CPS

NN Fusion protein

Cost effectiveness studies

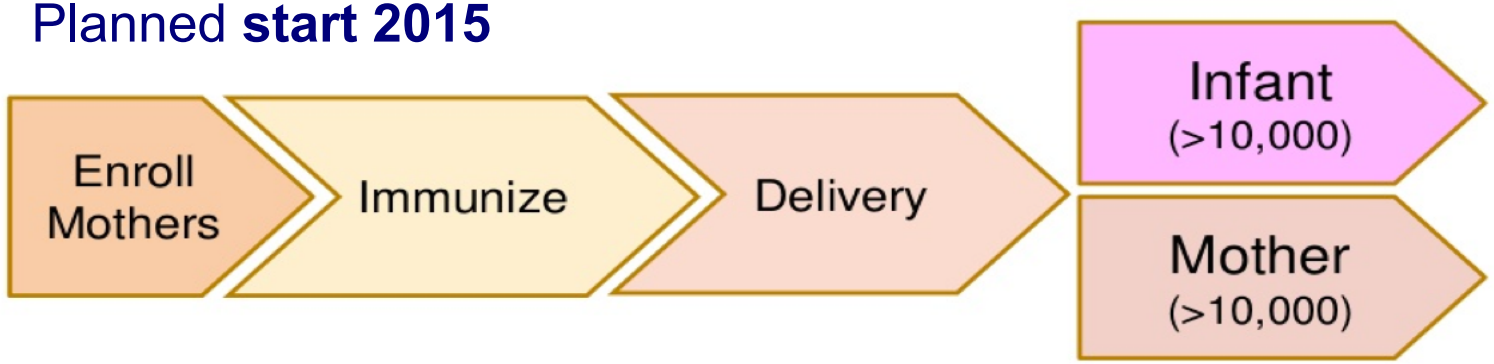
CANDIDATE VACCINES
What is ongoing in 2015?

Novartis GBS Vaccine

Trivalent glycoconjugate vaccine

- **CRM conjugated CPS Ia, Ib and III**
- **Trivalent conjugate coverage: 79 % globally**
- **Phase I completed, and Phase II ongoing**
  - Phase III study: (EU/US/Global)
    - Size: >10,000 mothers → >10,000 infants

Planned **start 2015**



- Eligibility: women between 28-35 wks gestation
- End-points: Mother/infant safety; vaccine immunogenictiy (efficacy); infant response to CRM-containing vaccines

Minervax GBS Vaccine

Single component NN fusion protein

- Anticipated coverage : 95% of isolates
- Clinical trial in healthy adults : Q2-2015
- EU funding FP7 Programme HEALTH for the development of a novel innovative GBS vaccine candidate
- Other sources of funding

Vaccine 31S (2013) D1–D2

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

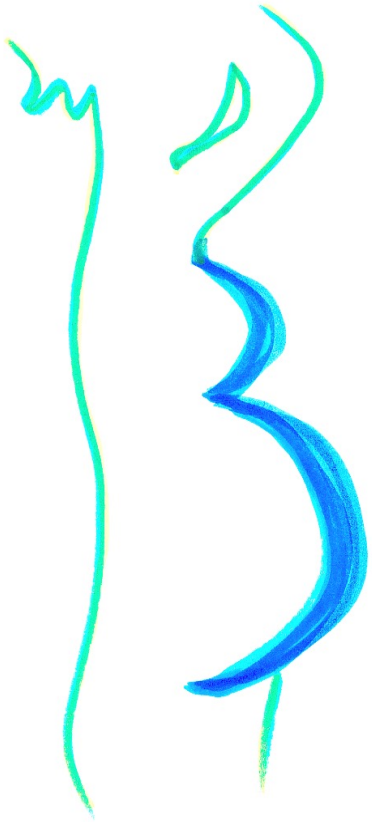
Editorial

Introduction: Addressing the challenge of group B streptococcal disease

Vaccine 31S, 2013

- **Introduction**, *Rappuoli & Black*
- **GBS Review**, *Carol Baker*
- **Overview GBS epidemiology**, *Paul Heath*
- **GBS epidemio and vaccine needs**, *Melin & Efstratiou*
- **GBS epidemiology in developping countries**
- **IAP in USA et Vaccine implications**, *S.Schrag & Verani*
- **GBS maternal vaccines Past Present and Future**, *Chen & Kasper*
- **GBS Public awareness** etc
- **Prevention through Vaccination**, *M. Edwards*
- **GBS Vaccination in pregnancy**, *P. Ferrieri*
- **GBS vaccine Phase III trial**

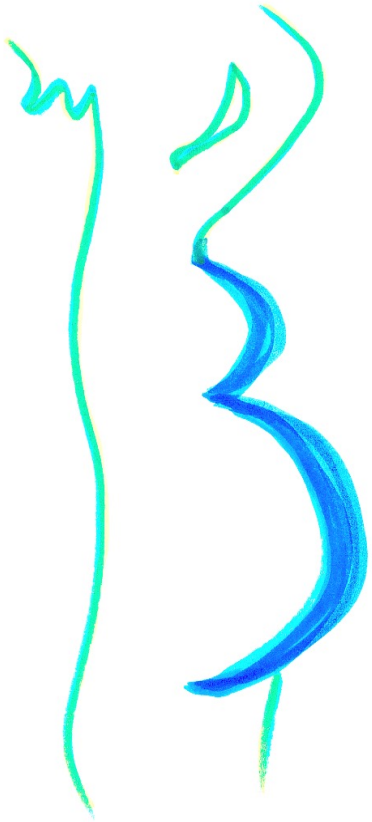
GBS vaccine - Conclusion



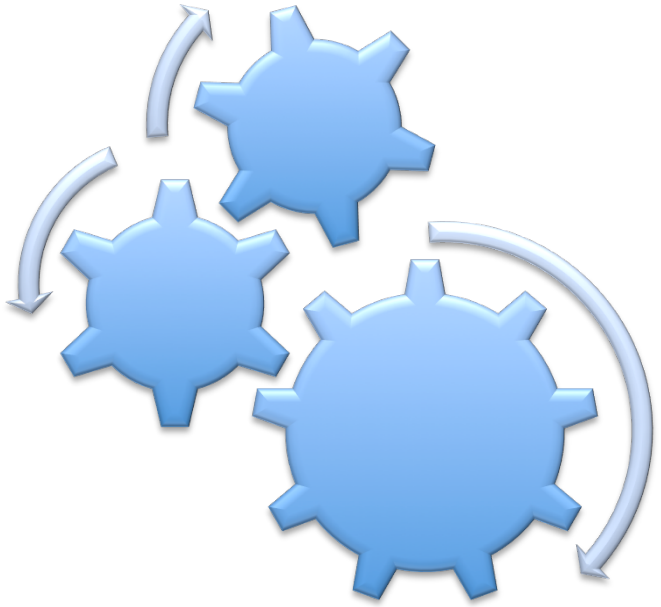
- CPS-glycoconjugate vaccine
  - 3 to 5-valent glycoconjugate vaccine (Ia, Ib, II, III and V)
- CPS-CRM_{197} / Pili vaccine
- NN-fusion protein vaccine

- Immunogenicity
- Safety
- Efficacy determination ongoing
- Impact on colonization : unknown

Maternal GBS immunization Conclusion

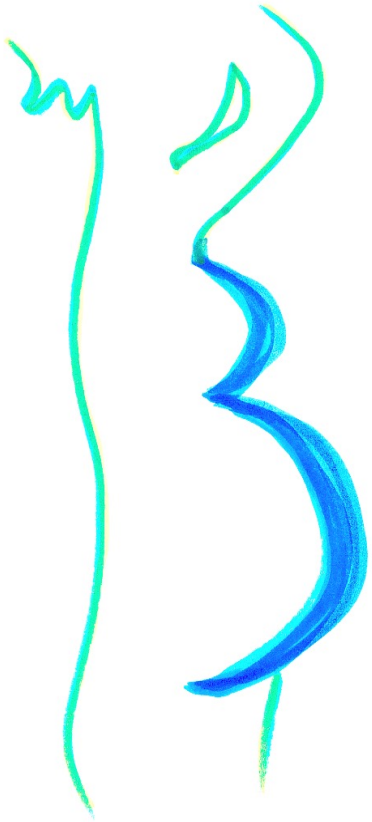


- **Immunization at 28-32 weeks**
- **Prevention at least 85% of invasive GBS disease in neonates and young infants**
- **Potential reduction**
  - **of incidence of maternal invasive GBS infection**
  - **of premature births, stillbirths related to GBS infection**
- **Cost-effective in high and low income countries**



CONCLUSION
Take home messages

In Europe, as globally



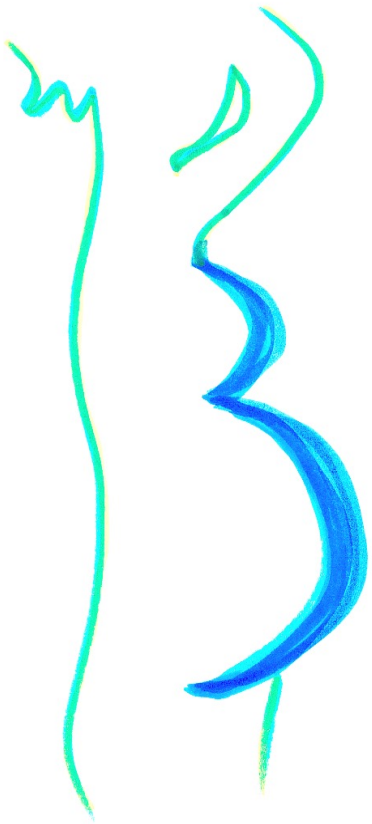
Neonatal GBS diseases

- 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