Prevention des infections périnatales par streptocoques du groupe B et perspectives vaccinales

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Centre national de référence des GBS

- Contexte
- Recommandations
- Limites d'efficacité de IAP et controverses
- Alternative vaccinale et défits
  - Historique
  - Vaccin « CPS »
  - Vaccin « protéine »
  - Projet DEVANI

Background
Group B streptococci or *S.agalactiae*

- **Since the 1970s, leading cause of life-theatening infections in newborns**
  - **Neonatal illness/death**
  - **Long-term disabilities**

Of major concern

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

GBS VERTICAL TRANSMISSION

GBS colonized mothers

60 - 40 %

Non-colonized newborns

96 - 98 %
Asymptomatic

40 - 60 %

Colonized newborns

Risk factors

2 - 4 %
GBS EOD

sepsis
pneumonia
meningitis
long term sequelae

CDC

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**
  - **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**

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

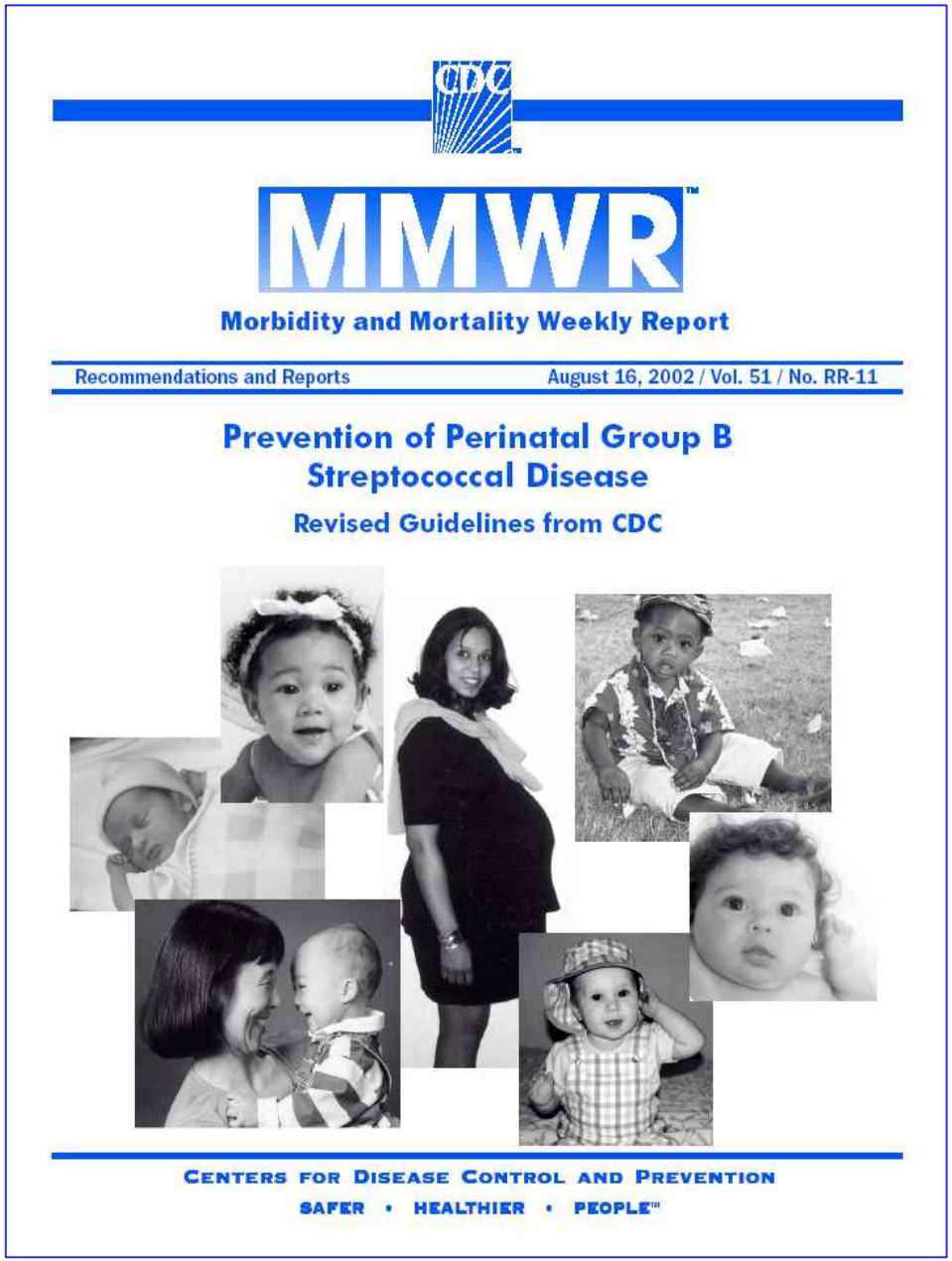
GBS EOD - Belgian data

- **Incidence**
  - **1985: 3/1000 live births**
  - **1990: 3 cases + 4 likely cases/1000 live births**
  - **1999, estimation : 2/1000 live births**
- **Meningitis : 10 %**
- **Mortality > 14 %**
- **60 % EOD (130 cases) : WITHOUT any maternal/obstetric risk factor**
- **Prenatal screening**
  - **Recto-vaginal cultures : 13-35 % GBS Positive**

GBS EOD - Belgian data

- **Réseau des laboratoires vigies**
  - **Enregistrement infections néonatales < 28 jours**
  - **1991-2001**
    - **> 300 sepsis ± méningite /an**
    - **Parmi les EOD (<= 5j)**
      1. **GBS : 37 %**
      2. ***E.coli* : 11 %**

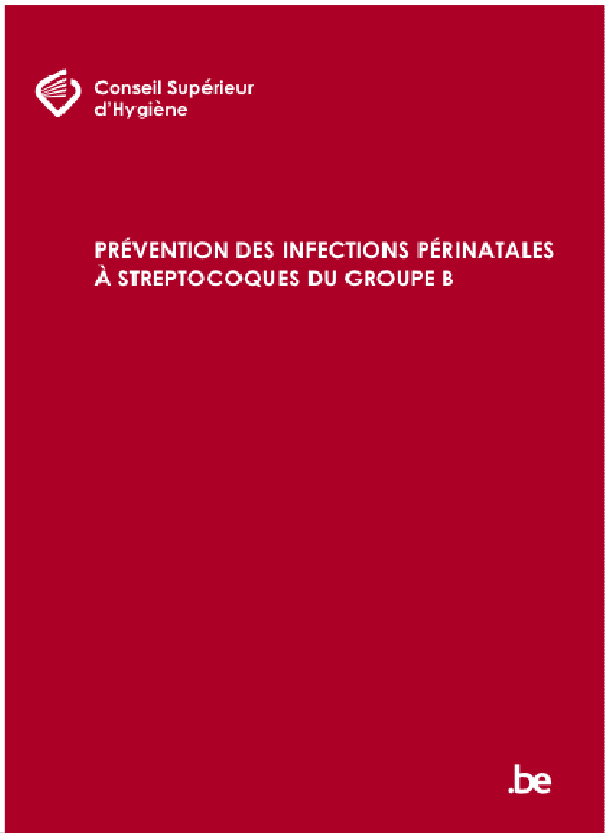
P. Melin - ICAAC 2003.



CDC, USA, MMWR, Vol 51 (RR-11) August 2002

Endorsed by AAP and by ACOG in 2002

SHC*, Belgium July 2003



***SHC= Superior Health Council = CSS**

Intrapartum antimicrobial prophylaxis-IAP

Universal prenatal screening at 35-37 weeks gestation

Risk-based approach reserved for women with unknown GBS status at time of labor.

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

Prevention of perinatal GBS EOD

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

INTRAPARTUM ANTIMICROBIAL PROPHYLAXIS

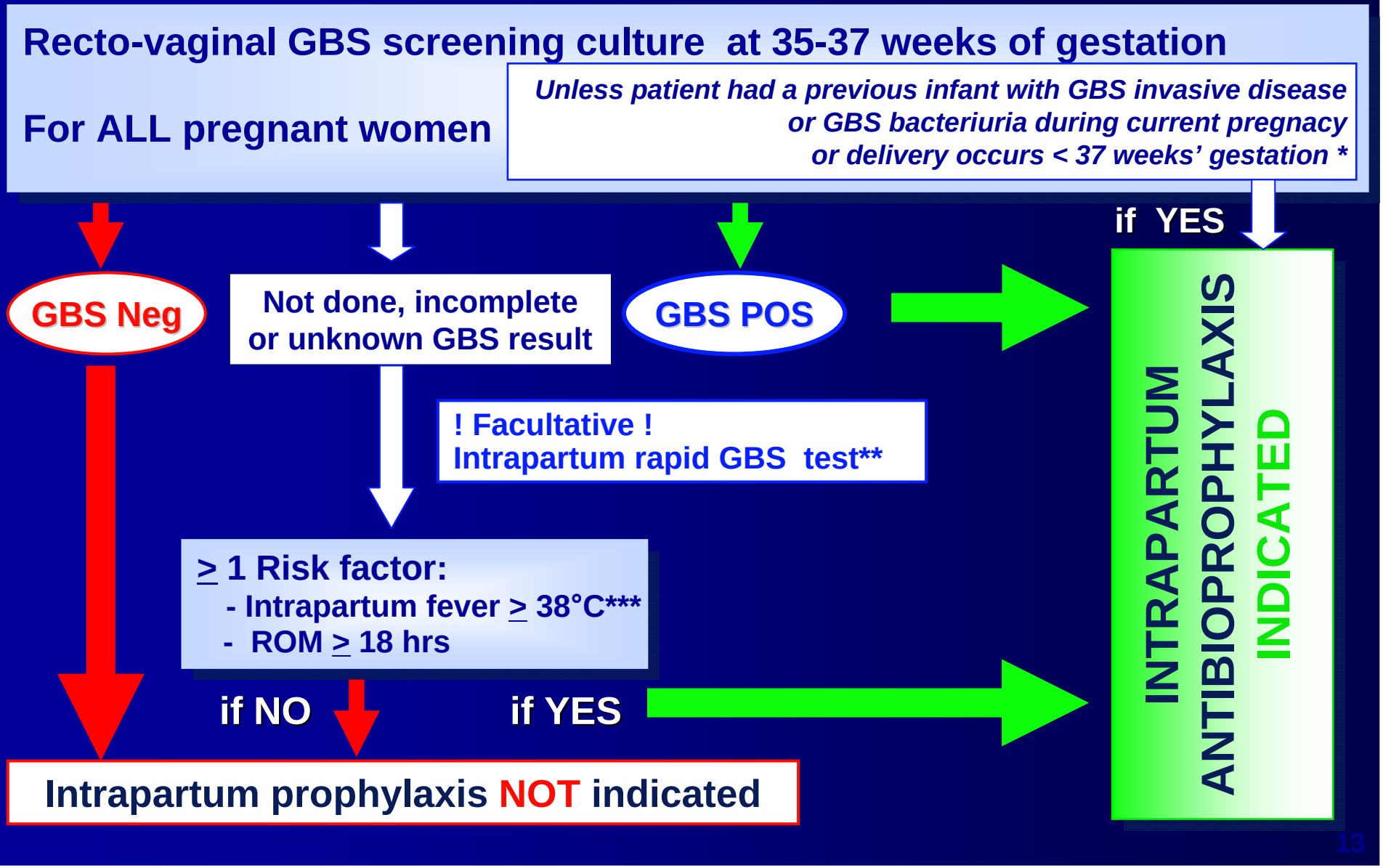
Main goal :

- **To prevent 70 to 80 % of GBS EO cases**

Secondary :

- **To reduce peripartum maternal morbidity**

Screening-based strategy for prevention of GBS perinatal disease *(Belgian SHC, 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 (non nutritive medium: Amies/Stuart)
Request form	To specify prenatal « GBS » screening + *expected address for delivery*

(CDC 2002 - Belgian SHC 2003)

Prenatal GBS screening : Laboratory procedure *(Belgian SHC, 2003)*

Minimum:

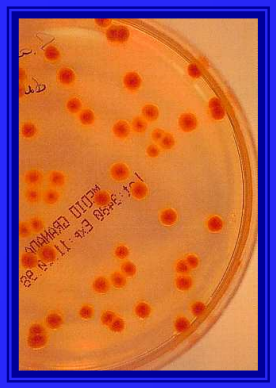
35-37 wks V+R

↓

Selective enrichment broth (eg.LIM)

Overnight, 35-37°C

↓



Sub-culture onto "Granada" agar

Overnight, 35-37°C anaerobically

Presence of orange colonies = GBS

Absence of orange colonies

POSITIVE screening

Negative screening

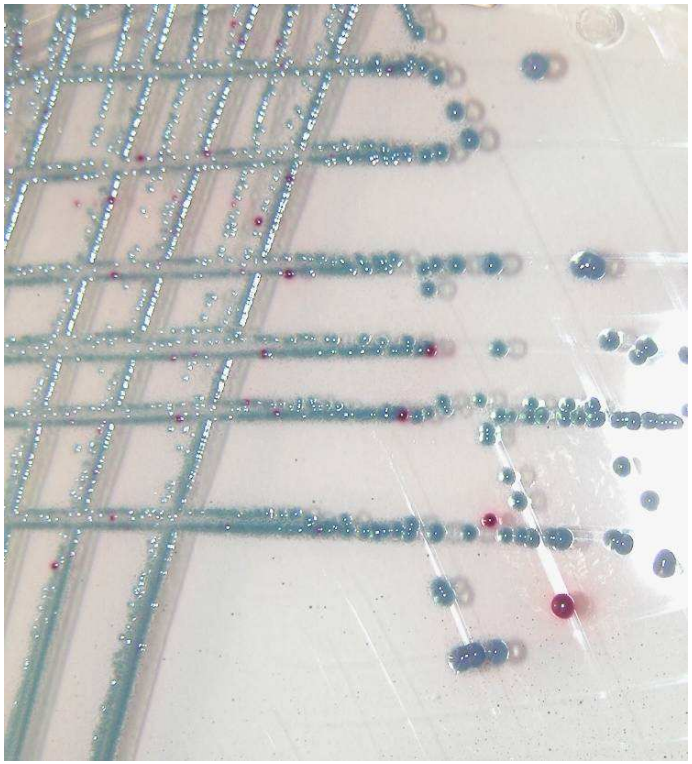
Granada medium agar or BD™ Group B Streptococcus Differential Modified Granada Medium

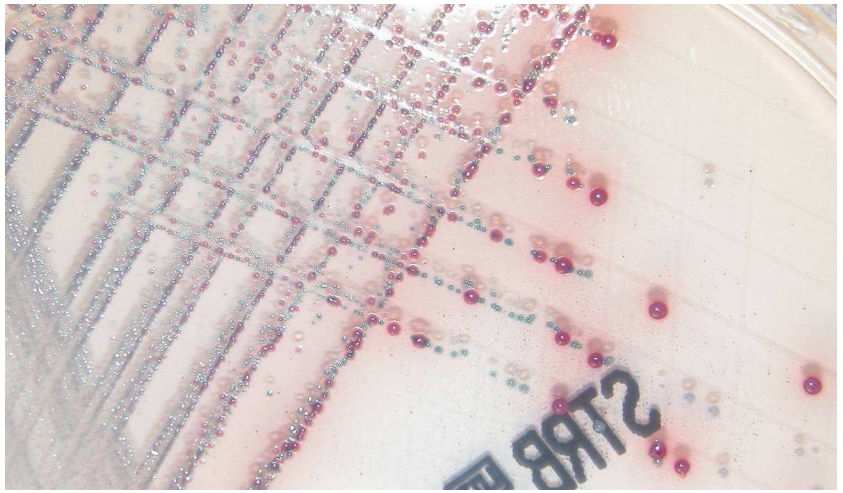
Orange color
= GBS pigment:

Specific for GBS
// β-hemolysis

Strepto B ID agar - BioMérieux

Melin, ASM 2005 #C-318



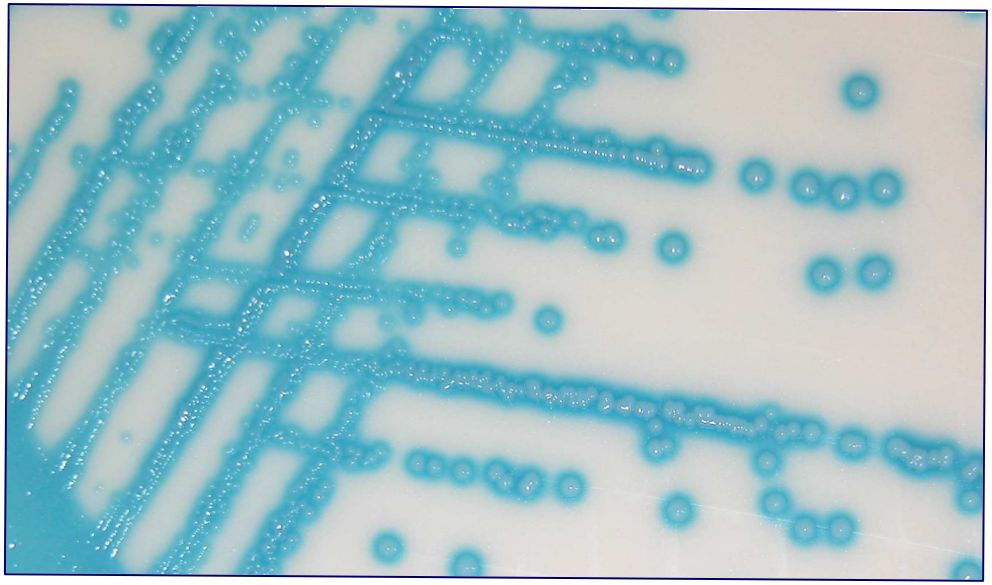


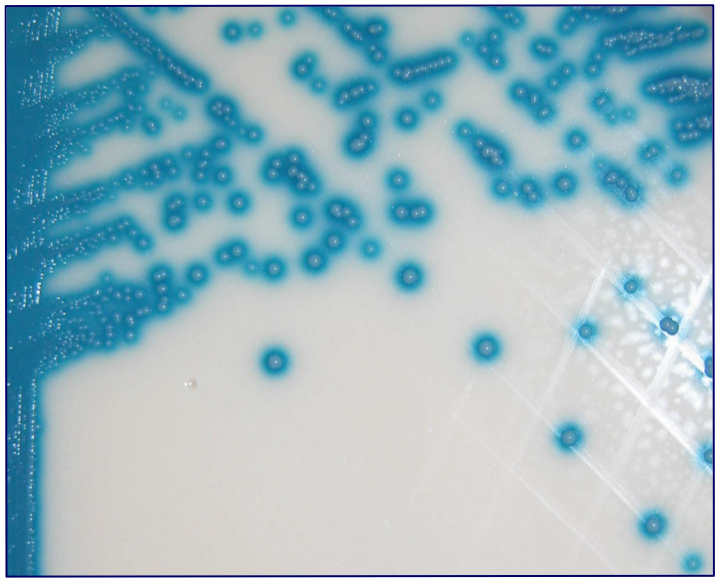
High sensitivity
for growth of GBS
GBS = pink to red colonies

Chromogenic media
Not 100 % specific for GBS: Id to confirm (latex)

Strep B Select agar – BioRad

P.Melin et al. ECCMID 2008, P 1388





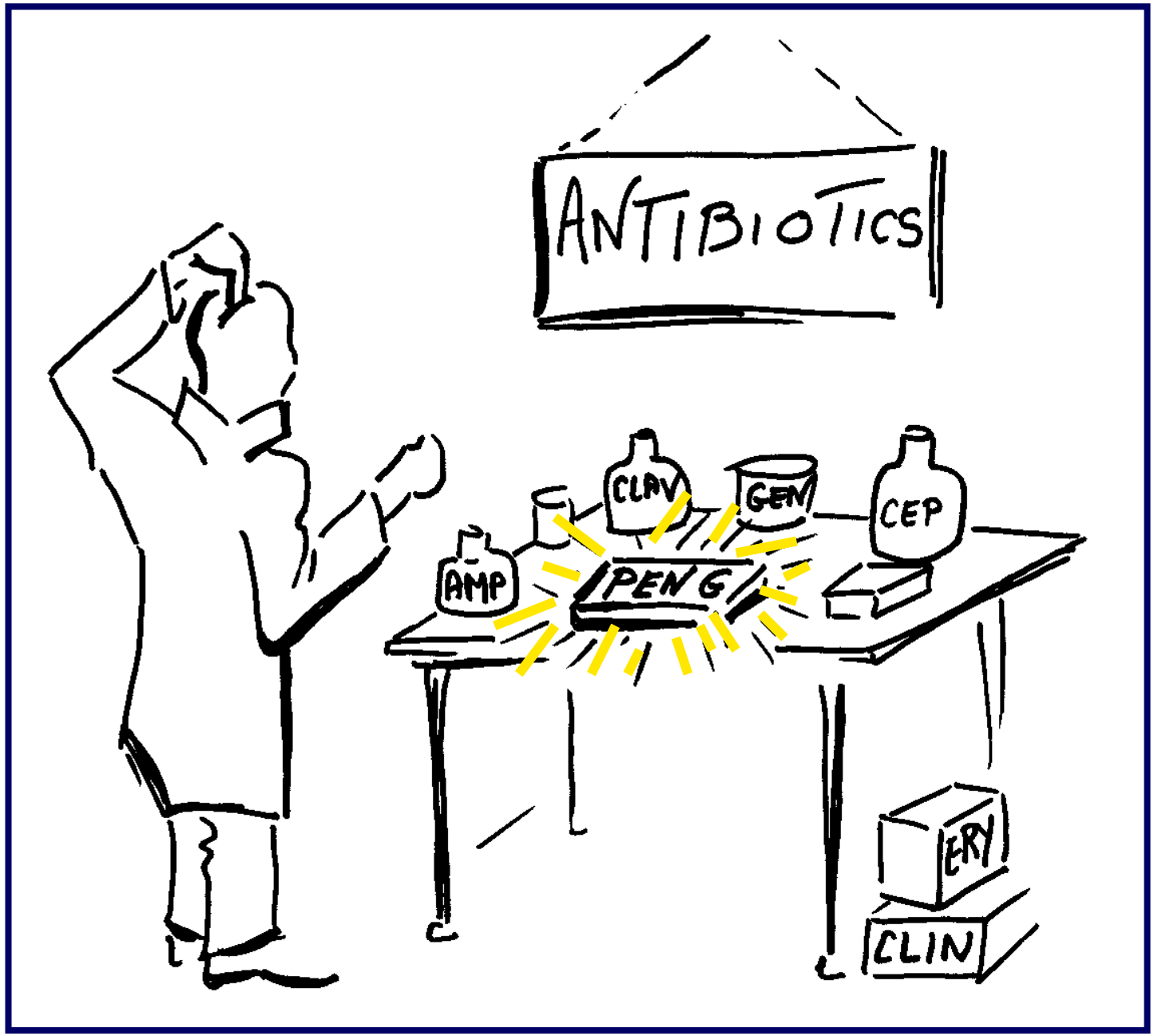
GBS = pale to dark blue-turquoise colonies

Chromogenic media

Not 100 % specific for GBS: Id to confirm (latex)

What to do in case of Positive GBS screening ? *(Belgian guidelines SHC 2003)*

- **Send results to requesting doctor *and a copy to expected site for delivery***
- **DO NOT treat during pregnancy if asymptomatic**
  - ***(! To treat If GBS bacteriuria !)***
- **To schedule IAP**


ANTIBIOTICS
AMP
CLAV
GEN
PEN G
CEP
ERY
CLIN

Intrapartum Antibio-Prophylaxis

(Belgian guidelines SHC 2003)

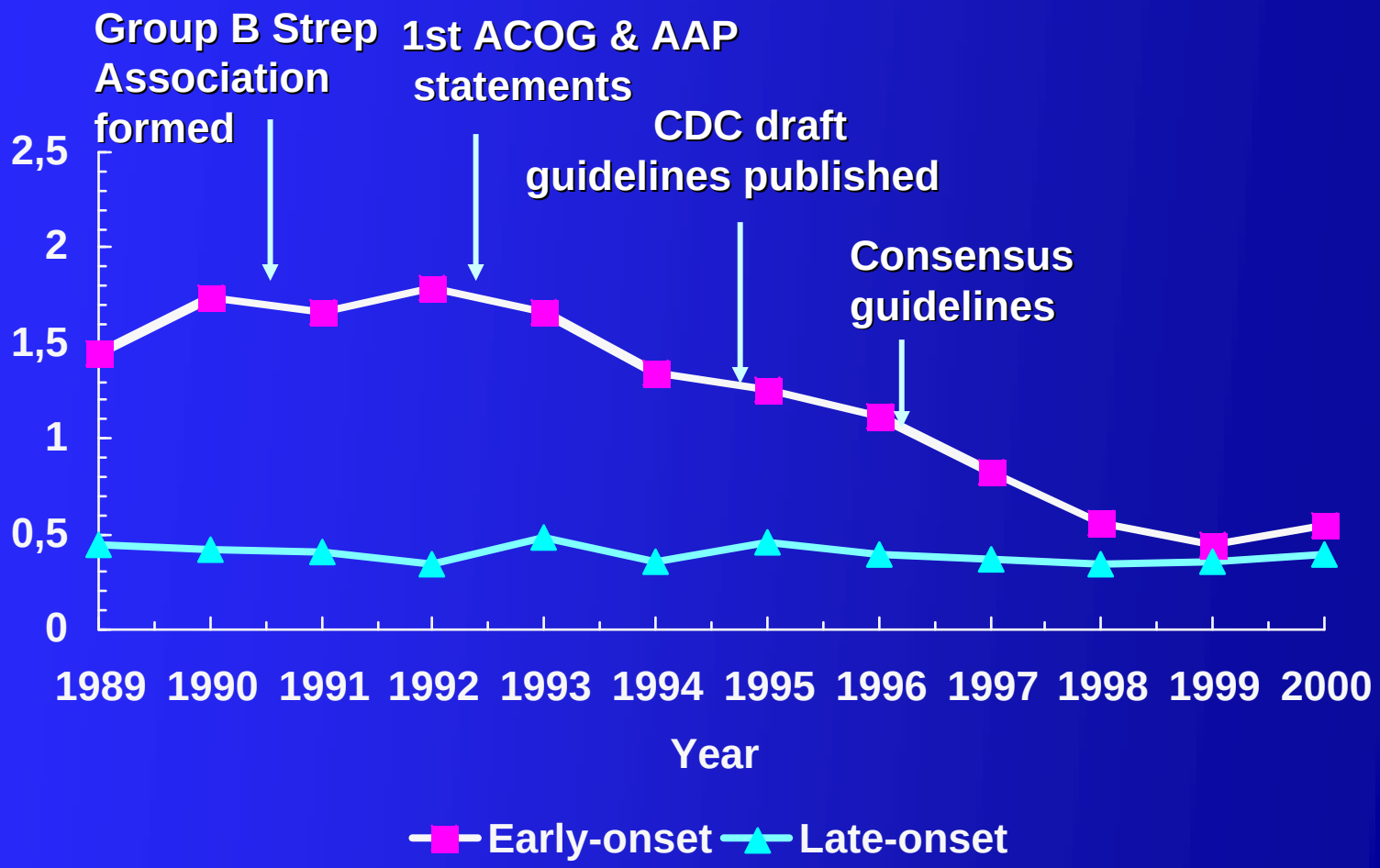
- **Penicillin G**
  - ***5 millions U, IV initial dose, then 2,5 millions U IV every 4 hours until delivery.***

- **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**

Intrapartum Antibio-Prophylaxis
If penicillin allergy *(Belgian guidelines SHC 2003)*

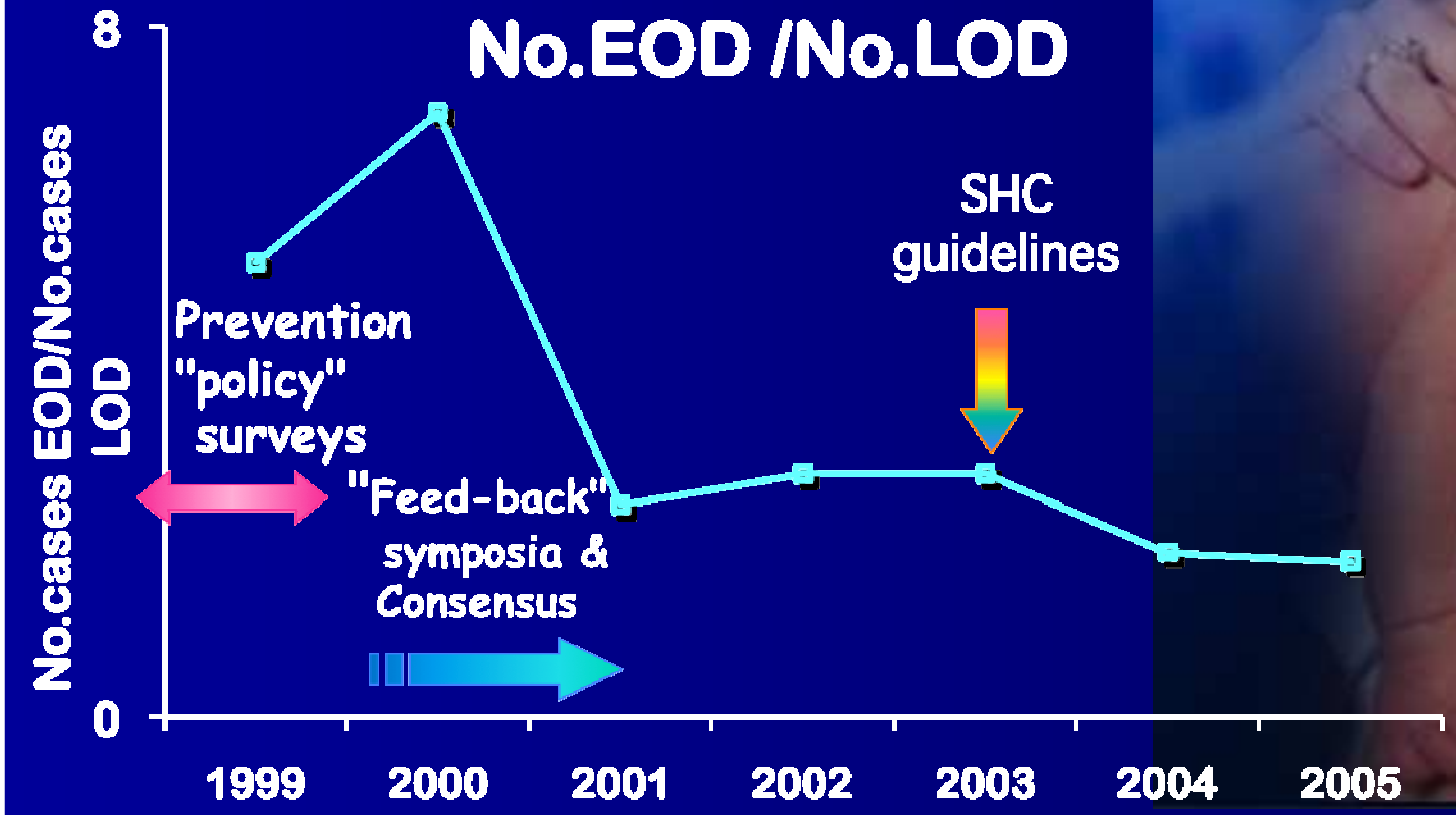
- ***Patients at low risk for anaphylaxis***
  - **Cefazolin**
    - **2 g IV initial dose, then 1g IV every 8 h until delivery.**
- ***Patients at high risk for anaphylaxis***
  - **Clindamycin**
    - **900 mg IV every 8 hours until delivery.**
    - ***If GBS resistant to clindamycin : ask for infectiologist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

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



S. Schrag, New Engl J Med 2000

Preventive strategies
Current Belgian benefits



Melin P. et al. Belgian GBS Ref.Lab, ICAAC2006, Abstract #G-0864

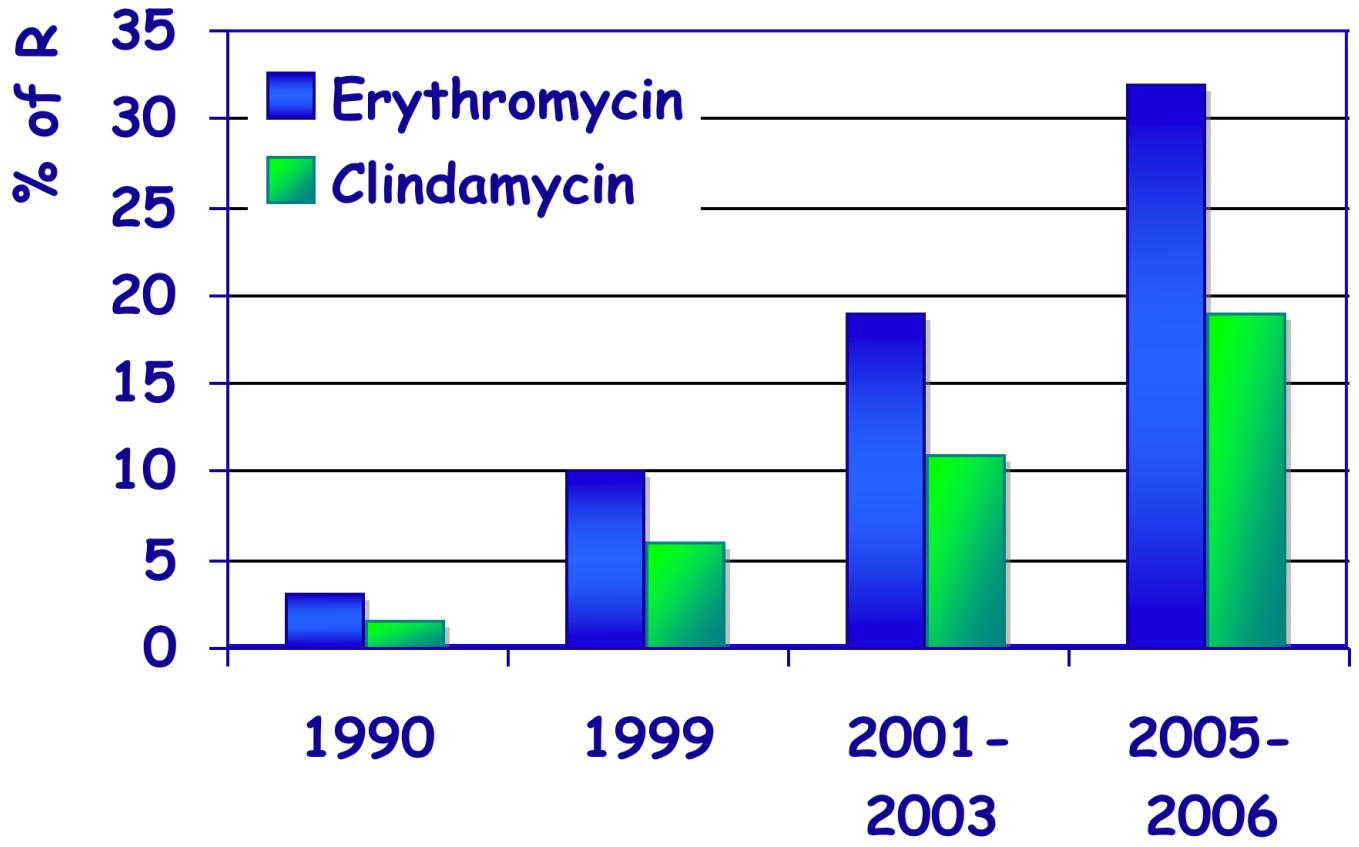
Concerns about potential adverse / unintended consequences of prophylaxis

- **Allergies**
  - Anaphylaxis occurs but rarely
- **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**

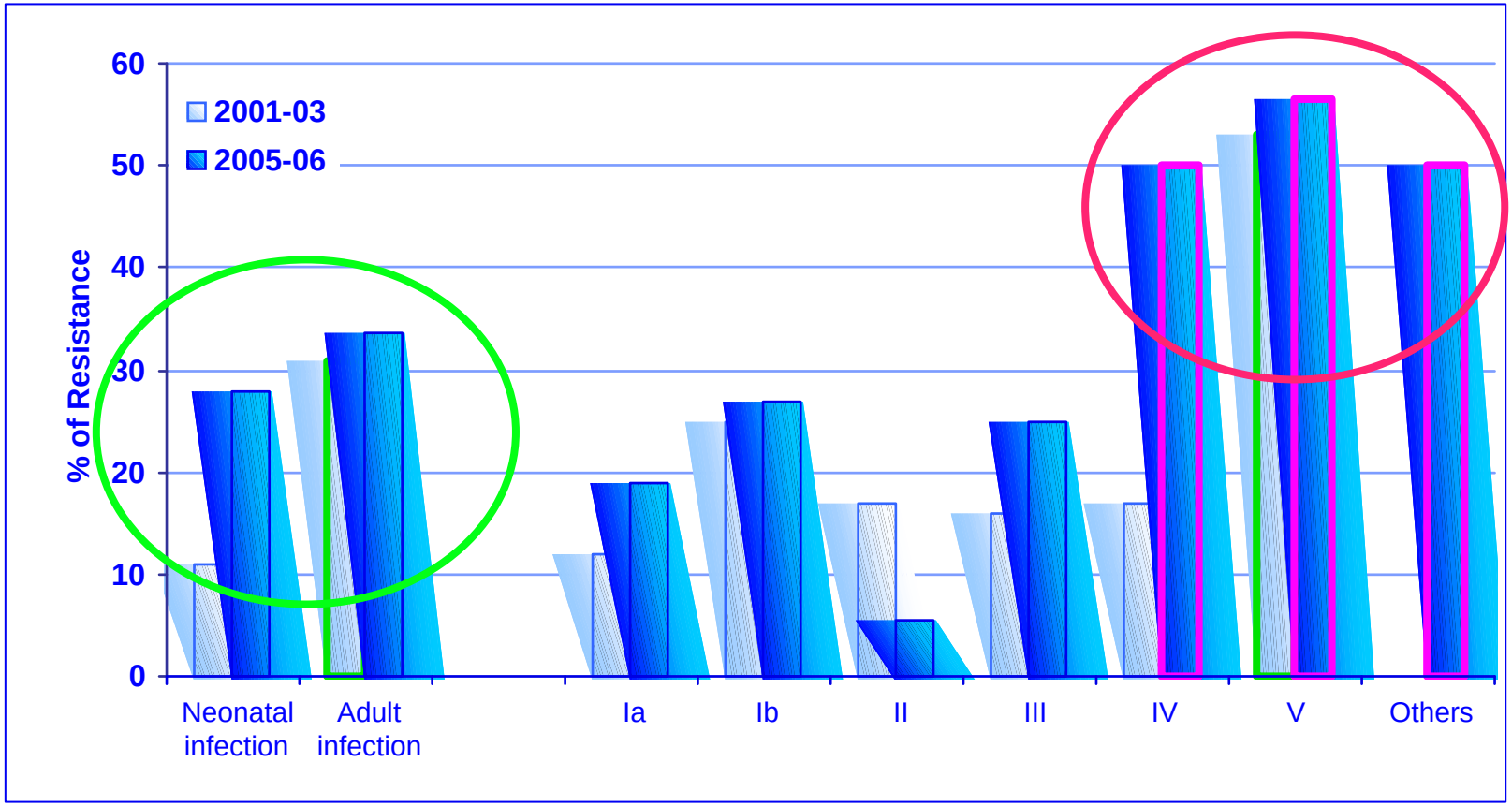
Concerns

- **Increase of resistance to erythromycin and clindamycin**
- **Susceptibility to penicillin**
  - **Very few R isolates recently characterized in Japan**

Results
Erythromycin and clindamycin resistance Evolution among Belgian GBS isolates



Erythromycin Resistance of Belgian clinical GBS isolates



Erythromycin Resistance:

1990: 3%; 1999: 10%; 2001-03: 19%; 2005-06: 32%

Concerns about potential adverse / unintended consequences of prophylaxis

- **Management of neonates**
  - **Increase of unecessary evaluation**
  - **Increase of unecessary antimicrobial treatments**
    - **Propositions Recommandations +/- standardisées**

Management of neonates at risk for GBS EOD

***Rem.**: 95 % of GBS EOD are symptomatic < 24 h of live*

Neonates born to women who received IAP

Symptomatic NN / asymptomatic NN

At low/at high risk

To minimize unnecessary evaluation and antimicrobial treatment

Management of symptomatic newborns at risk for GBS EOD

Clinical signs of sepsis

1- Full diagnostic evaluation *

2- Empiric antibiotherapy

(Ampicillin + aminoside)

:- *Full blood cell count (FBC) + differential

- CRP

- Blood culture

- (Lumbar P.)

- Chest Xray

- Endotracheal culture (if intubated or if resp.distress. or Rx infiltrate)

Rem : NOT recommanded :

1- Urinary GBS Ag

2- « Monitoring » cultures

Management of asymptomatic newborns « *at high risk* » for GBS EOD *(Belgian guidelines SHC 2003)*

If antibiotherapy given to mother for

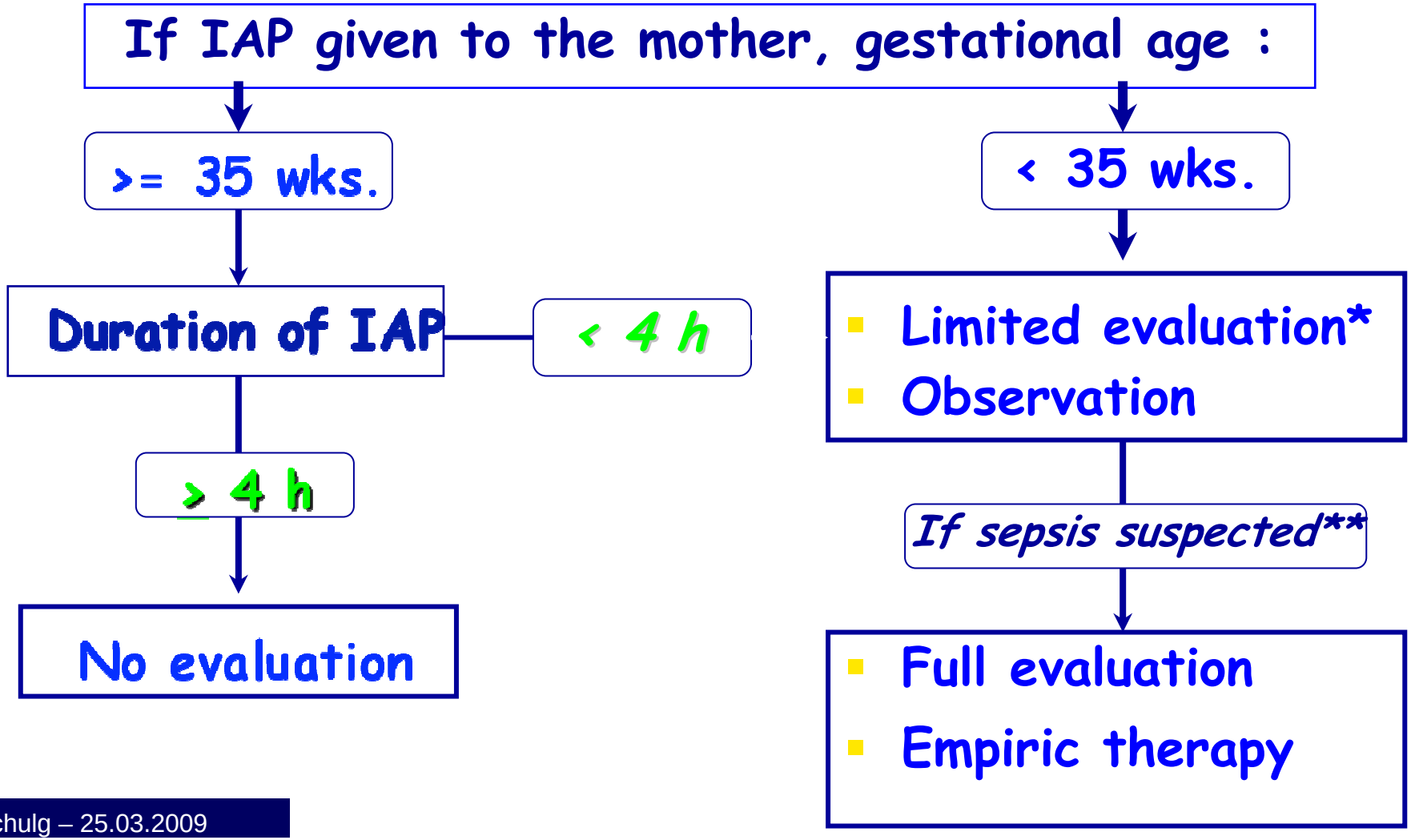
- Suspicion of chorioamnionitis or

- Premature AND prolonged rupture of membranes

Full evaluation

Empiric therapy

Management of asymptomatic newborns « *at low risk* » for GBS EOD



Duration of antibiotherapy

Threatened preterm delivery

Planned caesarean delivery for GBS colonized women

(Cf. texte complet des recommandations belges CSS 2003)

Conclusions & perspectives

Prevention of GBS perinatal Diseases
SCREENING-BASED

Currently the best choice but NOT the ideal strategy

Temporary, waiting for vaccines, other approach

Revision of CDC's guidelines scheduled June 2009

- **To implement in the daily practice**
- **V+R Screening method (*prenatal/ intrapartum ?)***
- **!! Transmission of results !!**

Alternative to prenatal GBS screening: intrapartum screening

Collect specimen at admision

Specimen analysis

Results

Optimal management of patient

30 - 45 minutes

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

Real Time PCR for intrapartum screening

- **Cost-benefit and feasability to investigate in Belgium**

(GenExpert - Cepheid)

Recommandations actuelles = stratégie intérimaire dans attente vaccins

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.

Vaccins : Historique

- **Correlation entre déficience Ac CPS type maternels à l'accouchement et risque EOD néonatal**

Baker C et Kasper D, 1976, NEJM

Vaccination femme enceinte pourrait devenir une stratégie prophylactique très intéressante de EOD néonatal

Montée Ac maternels et passage transplacentaire

= Protection nouveau-né

Vaccins : Défits

Recherche des Ag les plus immunogènes

Immunité protectrice et durable

Vaccins « CPS »

- 9 sérotypes
  - Distribution variable
    - EOD, LOD, infections invasives adultes
    - Géographique et dans le temps !!

- Ag sérotypes capsulaires
  - Unités répétées de 4 de 5 sucres
    - glucose, galactose, N-acétylglucosamine, rhamnose et acide sialique
  - Acide sialique: rôle majeur
    - Caractéristique structure antigénique
    - Facteur de virulence
      - Pas d'activation de v.alterne du complément

Vaccins « CPS »

- **1978, 33 adultes vaccin CPS III**
  - **Sécurité : ok**
  - **Immunogénicité : faible**
    - **Méthode extraction Ag**
- **1980, > 300 adultes, dont 40 femmes enceintes (3ème trimestre)**
  - **Sécurité : ok**
  - **Immunogénicité: faible (indepdt dose)**
- **Fin des années 80**
  - **Vaccin CPS: trop peu immunogènes**

Vaccins « CPS » conjugués

- 1990: CPS III conjugué au toxoid du tétanos (TT)
  - Modèle animal
    - Immunogénicité augmentée
    - Ac protecteur fonctionnel
- Ia-TT, Ib-TT, II-TT et III-TT + V-TT
  - Vaccin multivalent
- III CPS conjugué à CRM (toxoïde diphtérie)
- III CPS conjugué à Protéine C (beta)
- III CPS conjugué à C5a peptidase

Essais cliniques divers chez adultes et femmes enceintes (30-32 sem): Immunogénicité et sécurité

Vaccins « protéines de GBS »

Alternative au vaccin CPS

Vaccin GBS basé sur protéine ubiquitaire

- **Si Ag = Protéines de surface**
  - **Induction immunité protectrice croisée pour différents types**
  - **Conjugaison à « porteur » pas nécessaire**
    - **Réponse Ac T-cell dépendante = Immunité long-terme**
- **Premières candidates (Ac protecteurs chez souris)**
  - **Protéine R**
  - **Sous unités α et β de protéine c**
  - **Protéine Rib**

Vaccins « protéines de GBS »

Protéine	Ac protecteur (modèle murin)	Sérotypes associés
Alpha-like protéines		
Alpha	**Oui**	**Ia, Ib et II**
Alp1		**Ia**
Rib	**Oui**	**III**
Alp2	**Oui**	**V, VIII**
Alp3	**Oui**	**V, VIII**
Beta C protéine	**Oui**	**Ib**
C5a peptidase	**Oui**	**Tous**
Sip (1999)	**Oui**	**Tous**
BPS	**Oui**	**Tous**

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

Vaccins « protéines de GBS »

- **Reverse vaccinology approach**
  - **Connaissance du génome complet de GBS**
    - **Exploration systématique de l'expression de protéines de surface et identification comme Ag potentiel**

Très prometteur

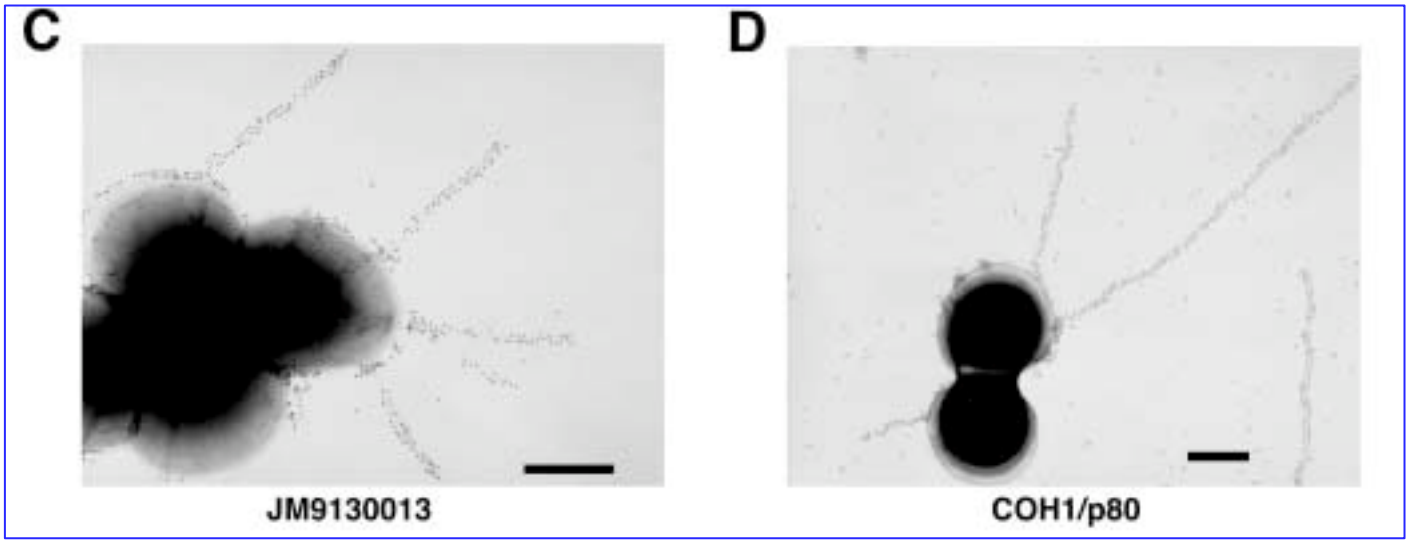
- **Comparaison génomes 8 GBS CPS différents**

D.Maione et al, Science 2006

  - **312 protéines de surface clonées**
  - **4 confèrent Ac très protecteurs chez la souris**
    - **Sip et 3 autres**
    - **Les 3 autres protéines = « pilus like structures »**

Structure « pilus like » chez GBS

- **Mise en évidence grâce à génomique**
- **Protéines très immunogènes**
- **Confèrent réponse Ac protecteurs, fonctionnels**
- **Rôle dans virulence des GBS // Gram négatif**
- **Aussi mis en évidence chez GAS et *S.pneumoniae***



Structure « pilus like » chez GBS

- **Construction plasmide avec gènes des 3 pili (1a, 1b et 2)**
- **Expression chez *Lactococcus lactis***
- **Vaccin vivant potentiel dans modèle murin**
  - **Sous-cutané**
  - **Intrapéritonéal**
  - **Intra-nasal**

- **Protection contre challenge différents types de GBS**
- **Pas de toxicité**
- **IgG et IgA**

S Buccato, D. Maione et al, JID 2006:194 331-340

Vaccins : Défits

- Taux Ac élevé fin gestation; passage transplacentaire
- Diversité des sérotypes capsulaires
  - Ia, Ib, II à IX
- Faible immunogénicité Ag CPS type
  - Conjugaison à protéine porteuse (TT, CRM, protéine de GBS)
- Vaccins « protéines de GBS »
- Marqueurs efficacité
  - Pas diminution incidence EOD et LOD
    - Incidence trop faible
  - Taux protecteurs d'anticorps et fonctionnalité
- Quand l'administrer ?
  - Pendant grossesse, quels trimestre
  - En dehors grossesse mais quand?
- Impact sur colonisation / sérotypes

EUROPEAN COMMISSION
Community Research

SEVENTH FRAMEWORK PROGRAMME

DEVANI

Vaccine Against Neonatal Infections

Design of a vaccine to immunize neonates against GBS infections through a durable maternal immune response

DEVANI

www.devaniproject.org

- **Infections néonatales // déficit d'anticorps spécifiques contre les polysaccharides de type.**
- **Effet protecteur réponse immune vaccinale**
  - **Pas si vaccination directe nné**
- **Vaccin capable induire**
  - **Réponse protectrice durable et de haut niveau**
  - **Ac protecteurs transférables par v.transplacentaire**
  - **A administrer aux femmes**

Autorisation du comité d'éthique CHU-ULg obtenue

DEVANI

PROJET

- Epidémiologie européenne des
  - Souches de colonisation génitales pendant la grossesse
  - Souches d'infections néonatales
- Identification des taux protecteurs d'anticorps spécifiques
- Corrélation taux Ac et colonisation

- Consortium de 8 pays européens
- Développement d'un vaccin dirigé contre des protéines de pili et CPS

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Moyens, par pays

Infection néonatale	Patients	Souche de GBS isolé	Serum	CRF	Nombre /pays
EOD ou LOD	Nouveau-né	OUI	Serum mère OUI	OUI	+/- 20
Non	Mère colonisée	OUI	OUI	OUI	125
	Mère non colonisée	NON	OUI	OUI	50

Durée: +/- 12 mois pour la Belgique

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Moyens, par pays

Infection néonatale	Patients	Souche de GBS isolé	Serum	CRF	Nombre /pays
EOD ou LOD	Nouveau-né	OUI	Serum mère OUI	OUI	+/- 20
Non	Mère colonisée	OUI	OUI	OUI	125
	Mère non colonisée	NON	OUI	OUI	50

Durée: +/- 12 mois pour la Belgique

Devenir des prélèvements – analyses des données

- GBS isolés
  - < frottis vagino-rectal prénatal/accouchement
  - < hémoculture/LCR de nouveau-né
    - Typage capsulaire *(pays)*
    - Génotypage “pili” *(Rome, ISS)*
    - Génotypages complémentaires
- Serum
    - Sérologie, Novartis Vaccines & Diagnostics (Sienne)
- Data base
    - E-platform, développée par CHU Lg & LambdaPlus
    - Analyses des données CHU Lg & ULg

DEVANI

Pour tout renseignement

Pierrette Melin ou Grisel Rodriguez Cuns

Microbiologie médicale

Centre national de référence des GBS

CHU de Liège

04.366.24.38

04.366.24.52

http://www.devaniproject.org


DEVANI
Current Insights
into Group B Streptococcal Diseases
Golden Bay Beach Hotel, Larnaca, Cyprus, May 27-28, 2009
European Workshop
Day 1: Wednesday, May 27, 2009
Morning Session
Chairs: Dr. Androulla Efstratiou (Health Protection Agency Centre for Infections, London - UK) and Dr. Graziella Orefici (Istituto Superiore di Sanità, Rome - Italy)
Key Opening Lecture
Overview history of GBS
Prof. Carol Baker (Baylor College of Medicine, Houston, Texas - USA)
Global epidemiology of GBS and screening strategies
Dr. Monica Farley (Emory University School of Medicine, Atlanta, Georgia - USA)
Pathogenesis of GBS
Prof. Barbara Spellerberg (University of Ulm, Ulm - Germany)
Epidemiology of GBS in France
Dr. Claire Poyart (Université Paris Descartes, Paris - France)
Afternoon Session
Chairs: Dr. Manuel De La Rosa Pelle (University Hospital, Granada - Spain) and Dr. Pavla Krizova (National Institute of Public Health, Prague - Czech Republic)
Epidemiology of GBS in Finland
Dr. Jaana Vuopio-Varkila (KTL National Public Health Institute, Helsinki - Finland)
Streptococcus agalactiae infections in Greece: an overview
Dr. Lavrentia Zacharioudou ("Aghia Sophia" Children's Hospital, Athens - Greece)
Changing epidemiology of invasive GBS disease in England and Wales
Dr. Theresa Lamagni (Health Protection Agency Centre for Infections, London - UK)
Day 2: Thursday, May 28, 2009
Morning Session
Chairs: Prof. Mogens Kilian (Aarhus University, Aarhus - Denmark) and Prof. Reinhard Berner (University Children's Hospital, Freiburg - Germany)
Overview of DEVANI
Dr. Graziella Orefici (Istituto Superiore di Sanità, Rome - Italy)
GBS vaccine developments
Dr. John Telford (Novartis Vaccines and Diagnostics, Siena - Italy)
Clinical management of GBS diseases: a paediatrician's perspective
Dr. Maria Kolios (Archbishop Makarios III Hospital, Nicosia - Cyprus)
GBS: screening, diagnosis and clinically relevant antimicrobial resistance
Dr. Pierrette Melin (Centre Hospitalier Universitaire de Liège, Liège - Belgium)
Overview of GBS molecular typing methods
Dr. Ulla Skov Sørensen (Institute of Medical Microbiology and Immunology, Aarhus - Denmark)
Afternoon Session
Chairs: Raheela Afsher (Health Protection Agency Centre for Infections, London - UK) and Dr. Anicarela Dobreva (National Center of Infectious and Parasitic Diseases, Sofia - Bulgaria)
GBS genomics and proteomics
Dr. Philippe Glaser (Institut Pasteur, Paris - France)
Poster session
Scientific Committee:
Organizing Committee:
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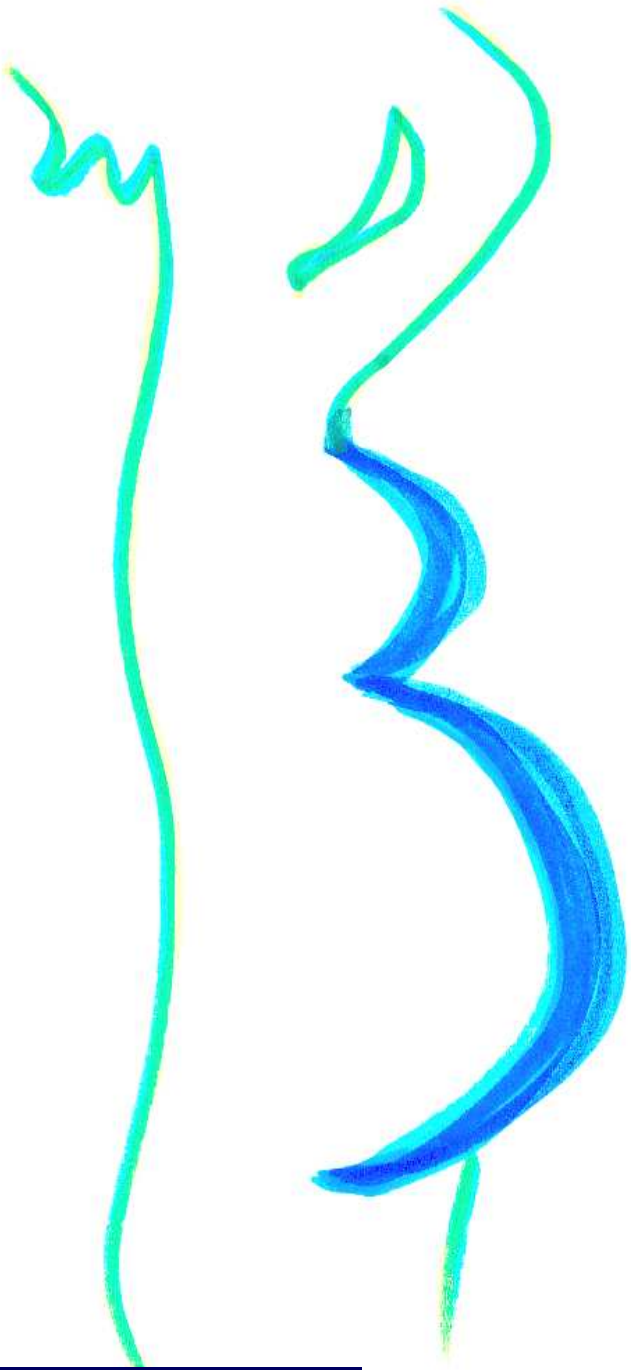
ALTA
Graphic by Francesco Grassia



Key GBS Resources

MMWR : August 16, 2002 / 51(RR11); 1-22

ACOG Comm Opin 2002, N°279

Obstet Gynecol, 2002;100:1405-12

CDC ’s GBS Internet page

http://www.cdc.gov/groupBstrep/

Conseil Supérieur de la Santé

(brochure strep B)

http://www.health.fgov.be

Conseil Supérieur Santé / Avis et recommandations (CSH7721)