Prevention of perinatal GBS disease in Europe

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GBS EOD in Europe

- No European epidemiology
- 0.3 to 2‰ live births
  - Different types of networks for declaration

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

Countries within the DEVANI consortium

Guidelines for prevention of GBS perinatal disease
Univesal prenatal screening

- **Spain since the end of 1990s**
  - Vagino-rectal screening
  - 2008, break-through in an area
    - Cases x 10 times during that period
- **Belgium**
  - Since the end of the 1990s in the French speaking Community
  - Since 2003, national official guidelines (Superior Council of Health)
    - Vagino-rectal screening
- **France**
  - +/- 2003 national official guidelines (ANAES)
    - Vaginal screening

Guidelines for prevention of GBS perinatal disease
Universal prenatal screening

- **Vagino-rectal or vaginal screening recommended by professional associations**
  - **Italy**
  - **Germany**
  - **The Netherlands**

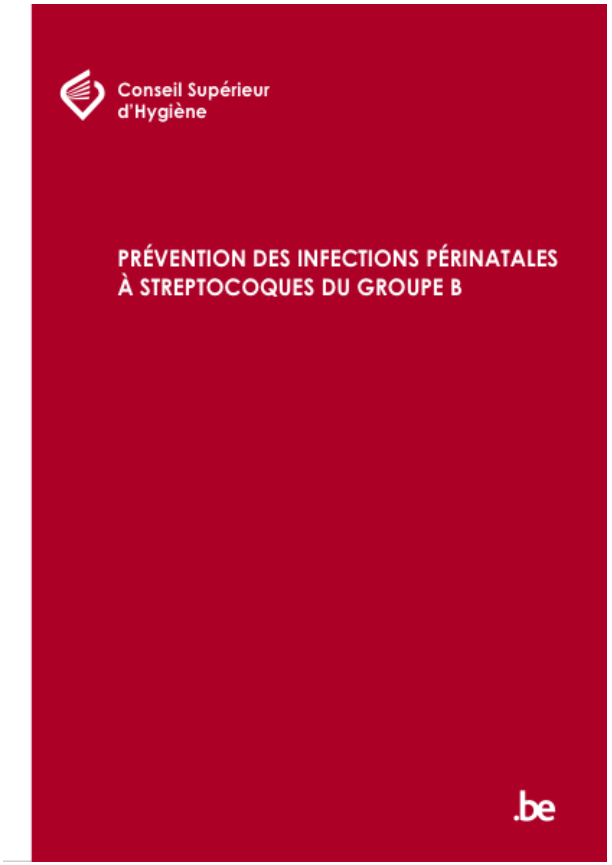
No Universal Screening Guidelines
for prevention of GBS perinatal disease

- Bulgaria
- Czech Republic

Risk-based strategy, but …

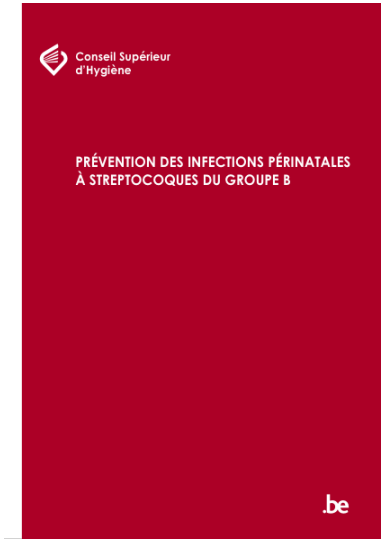
- Denmark
- Switzerland
- United Kingdom

Belgian recommendations Why Universal Screening?



- **Prospective investigation of 120 consecutive GBS EOD**
  - **French Community of Belgium**
  - **1999-2000**
  - **> 40 % had no "risk factor"**
- **Schrag SJ, Zell ER, Lynsfield R, et al.** ***N Engl J Med*** **; 2002 ;347 :233-9**

Belgian recommendations
Main differences vs CDCs guidelines

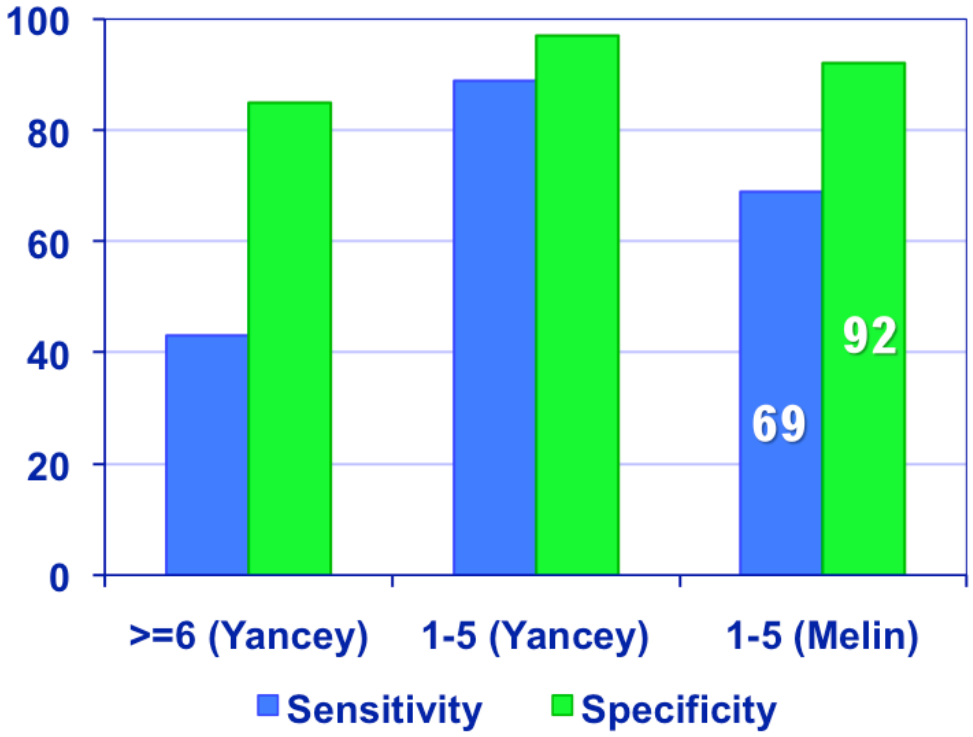


In 2003

- **SOP for laboratory**
  - **Selective enrichment broth + subculture on selective differential media like Granada agar**
  - **Facultative use of rapid intrapartum testing**
    - **Under analytical restrictive conditions**
    - **If positive: IAP**
    - **If negative: as if no additional result**

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

Melin et al. ICAAC 2000

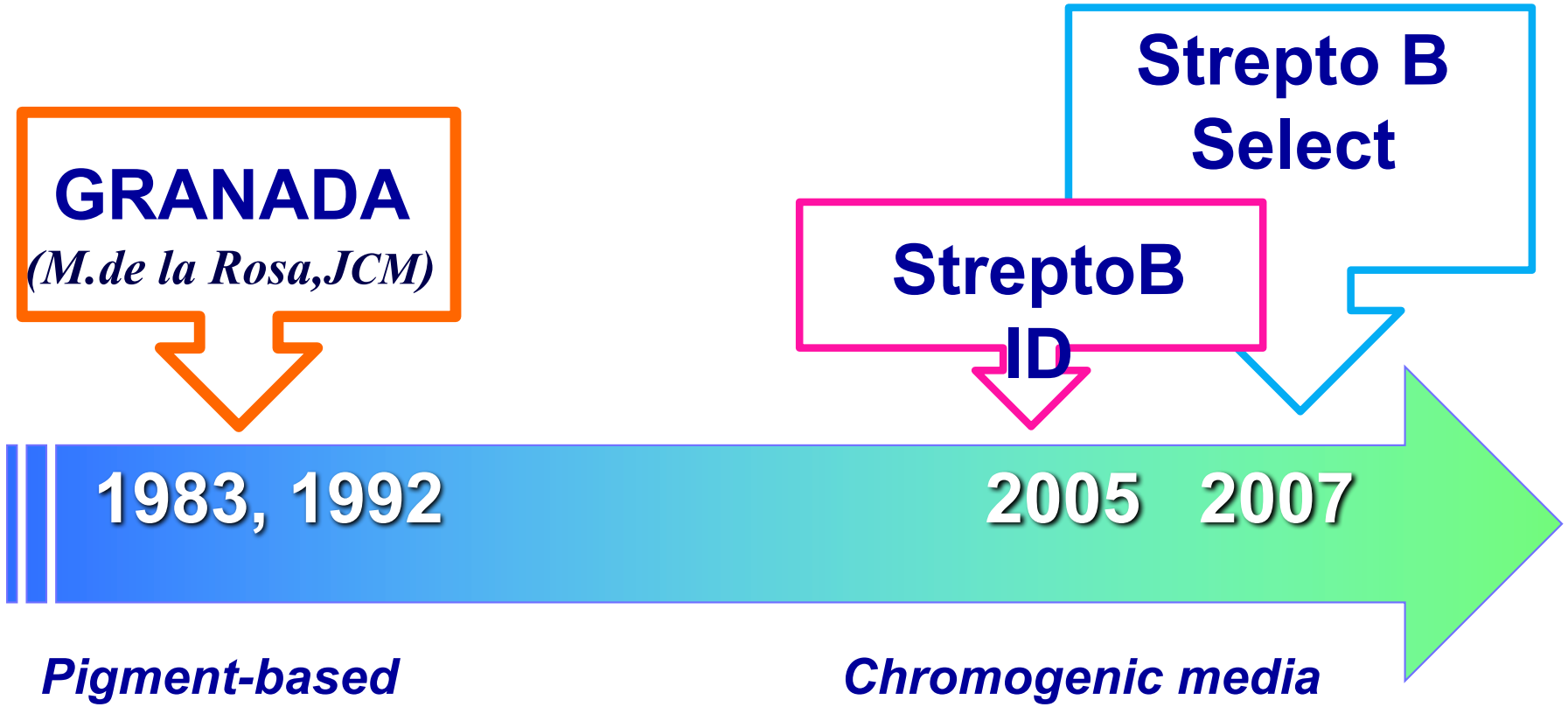
Evolution of culture methods

Revised guidelines from CDC (2002)

- Sub-culture < selective enrichment broth
  - Blood agar
    - Advantage
      - Growth of all GBS Isolates beta-hemolytic or not
    - Disadvantage
      - Difficulty in seeing GBS colonies within mixed flora (enterococci)
      - Difficulty in recognizing non-hemolytic GBS in mixed flora (enterococci)

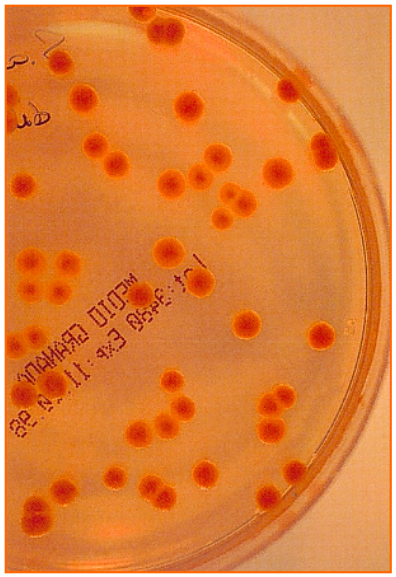
Evolution of culture methods
Use of differential agar media

Recommended by some European guidelines



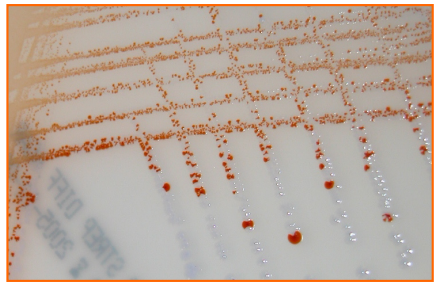
Granada medium agar

M de la Rosa Fraile, JCM 1983 & 1992



- **Orange color: GBS pigment, Granadaene**
- **100% specific for GBS // β-hemolysis**

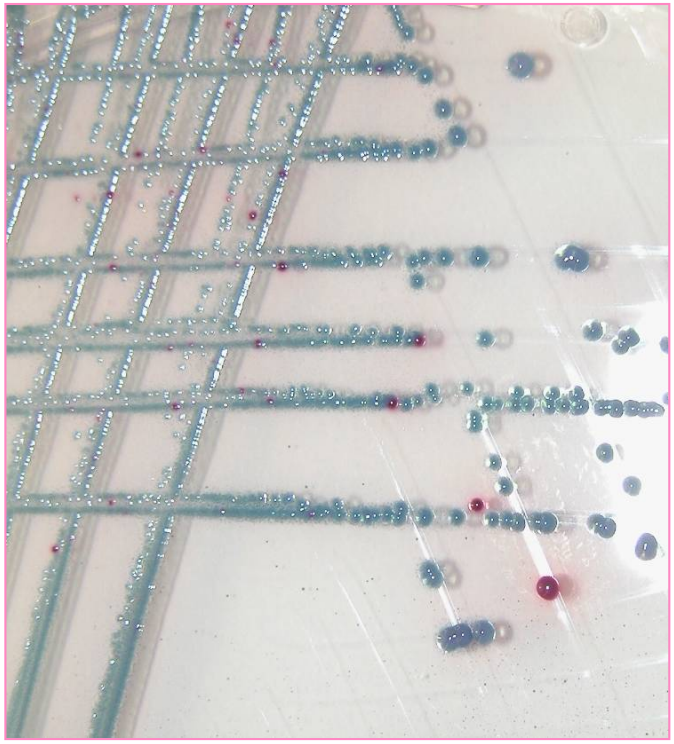
- **Group B Streptococcus Differential Modified Granada Medium™ (BD)**
- **Carrot Medium (Hardy)**

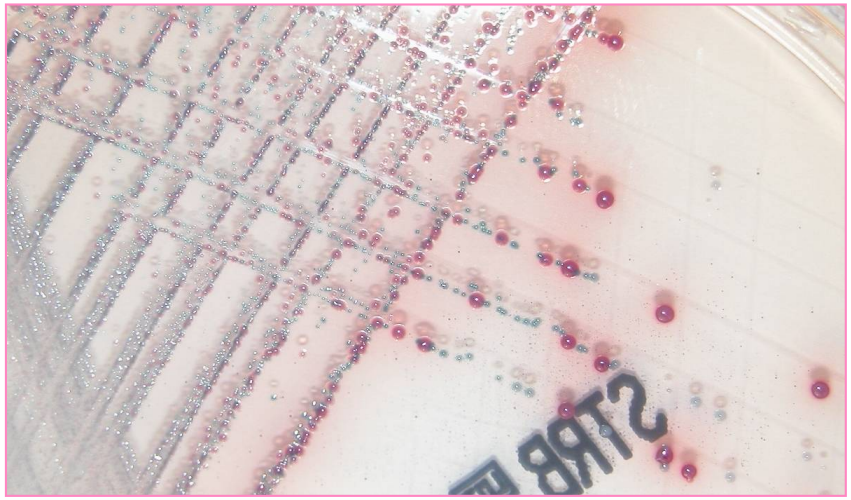


Does not show non-hemolytic strain !

(<5 % of invasive isolates)

Strepto B ID agar (BioMérieux)





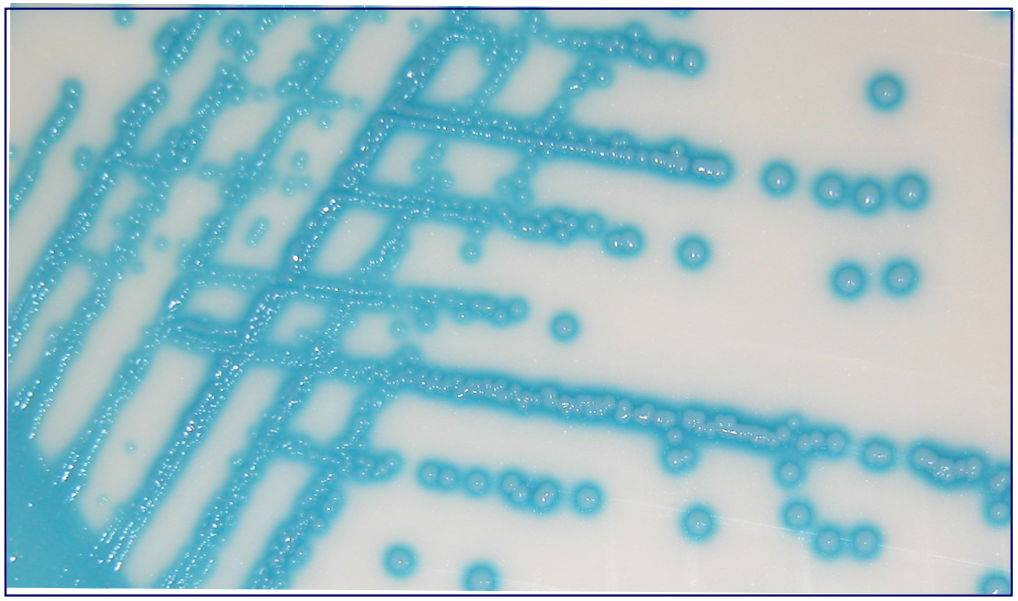
High sensitivity for growth of GBS

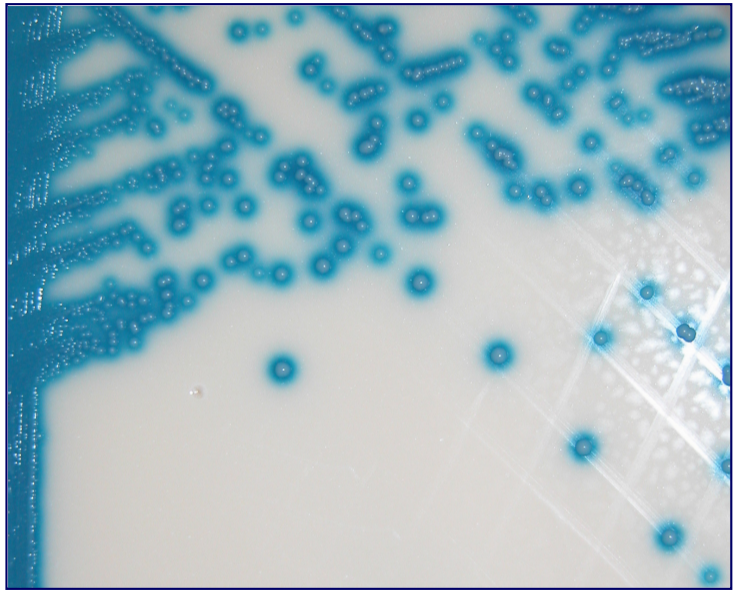
GBS = pink to red colonies

Chromogenic media

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

Strep B Select agar (BioRad)





GBS = pale to dark blue-turquoise colonies

Chromogenic media

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

Granada (BD) - StreptoB ID - StrepB Select *versus* Blood agar +/- CNA

500 genital swabs (29.4 % GBS Positive)

	Number of GBS Positive culture (%)		
	Direct culture	Lim sub-culture	Total
Strep B Select (BioRad)	103 **(70.1)**	134 **(91.1)**	139 **(94,6)***
« Granada » (BD)	90 **(61.2)**	123 **(83.7)**	124 **(84.4)**
Strep B ID (bioMérieux)	93 **(63.2)**	124 **(84.3)**	128 **(87.1)**
BA + CNA	76 **(51.7)**	113 **(76.9)**	120 **(80.6)**
>=1 Medium			147 **(100)**

* **StrepB Select > BA (p<0,5)**

P. Melin, 2008 ECCMID P1388

Granada (BD) - StreptoB ID - StrepB Select *versus* Blood agar +/- CNA

« False-Positive »

= Characteristic colonies not confirmed as GBS

	Identified as
Strep B Select	GAS, GCS, GDS-enterococci, Staphylococci, *S.bovis*, α-hemolytic colonies, (yeasts, Gram negative bacilli)
Granada	/
Strep B ID	GCS, Staphylococci, α-hemolytic colonies, (Gram negative bacilli)
BA +/- CNA	GAS, GCS, GFS, Staphylococci, GDS-enterococci, (Gram negative bacilli)

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Positive predictive value
Granada (BD) - StreptoB ID - StrepB Select *versus* Blood agar +/- CNA

	PPV Primoculture	PPV Lim sub-culture
Strep B Select	71,5 %	77,9 %
Granada	100 %	100 %
Strep B ID	80,9 %	87,9 %
BA +/- CNA	62,8 %	65,7 %

- **Sensitivity**

  Strep B Select > Granada - Strep B ID > CNA

- **Specificity**

  Granada > Strep B ID > Strep B Select > CNA

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Which agar or which combination?

+/- Blood agar

Workload – costs – extra-testing to be considered

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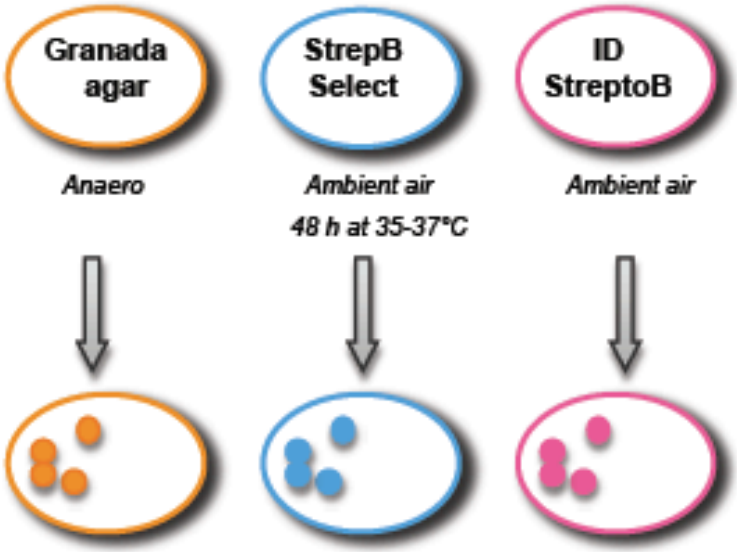
Vagino-rectal swab or
Vaginal & rectal swabs

Inoculate swab(s) in 1 Lim broth

LIM broth

Overnight And subculture following

at 35-37°C to one of the media



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

Prenatal culture-based screening

- **Limiting factors**
  - **Positive and negative predictive values**
    - **False-negative results**
      - **Up to 1/3 of GBS women at time of delivery**
      - **Continuing occurrence of EO GBS cases**
    - **False-positive**
      - **Unnecessary IAP**
  - **Need for more accurate predictor of intrapartum GBS vaginal colonization**

Alternative to prenatal GBS screening: intrapartum screening

Collect specimen at admision

Specimen analysis

Results

Optimal management of patient

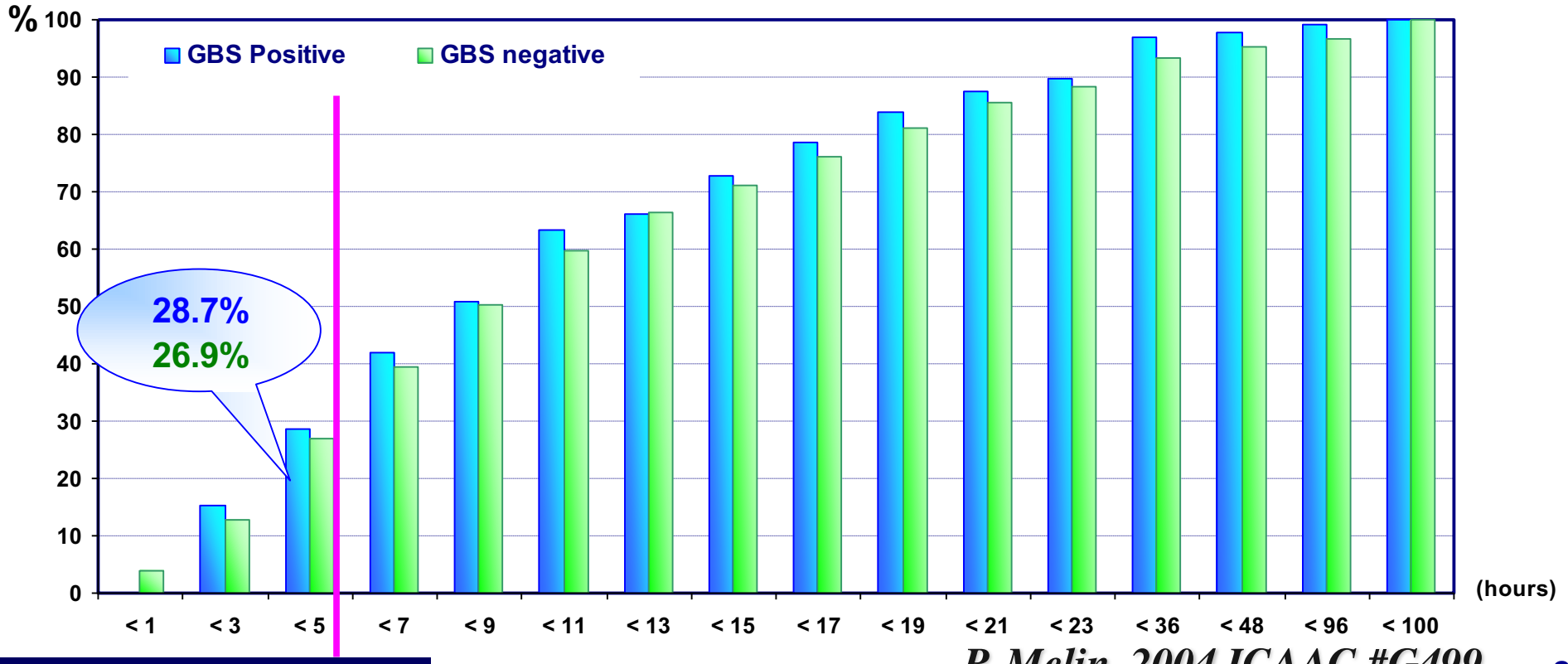
30-45 minutes, 24/24 hrs and 7/7 d, robust

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

Time between admission and delivery

Optimal time for IAP efficiency >= 4 hours

Cumulative histogram (% of patients) of time elapsed between admission to labor room and delivery for 532 women (sites CHR & CHBA)



P. Melin, 2004 ICAAC #G499

Rapid non-cultural GBS screening

- **Available antigenic tests**
  - **Variety of Immuno-assays**
  - **Lack of sensitivity**
    - **Announced 5.10^5 CFU, but not confirmed**
- **Hybridization tests**
  - **Not enough rapid**
  - **Lack of sensitivity if no enrichment step**

Real Time PCR for intrapartum screening

- **BD GeneOhm™ Strep B Assay (+/- 1 hr)**
- **Xpert GBS, Cepheid (+/- 75 min)**

(Gen Expert)

Rapid non-cultural GBS screening
Real-time PCR

- **IDI Strep B (BD GeneOhm)**
  - **Sensitivity : 94 %**
  - **Specificity : 96 %**
  - **PPV : 84 % and NPV : 98.6 %**

HD Davies et al., CID 2004

- **Xpert™ GBS**
  - **Sensitivity : 92 %**
  - **Specificity : 95.6 %**
  - **PPV : 86.7 % and NPV : 97.4 %**

Real-time PCR, very promising , but …

- Still an expensive technology
- Logistic
  - 24/24 hours and 7/7 days
  - In the lab?
  - In the obstetrical department ?
- In combination with prenatal screening strategy ?
- No antimicrobial result
  - In the future detection of R genes, but mixed flora !

SUMMARY

- Culture-based GBS prenatal screening
  - To optimize critical factors
  - Use of selective differential agars
  - False +/False - !
- Rapid intrapartum screening
  - Real time PCR
    - Yes but costs, logistic, …