GBS: To screen or not to screen?

To screen!!!!!!!!!!!!!!!!!!!!!!!!

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17/05/2010

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- Background on GBS disease and prevention
- Important issues

- Data in Israel
- Policy in Israel

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Background on GBS disease and prevention

GBS

Group B streptococcus (strep agalactiae):

- Aerobic, gram positive, β hemolytic
- Capsular polysaccharides : Ia, Ib, II, III, IV, V, VI, VII and VIII
- Cell wall proteins : C, R, X, α and Rib
- All serotypes can cause neonatal disease

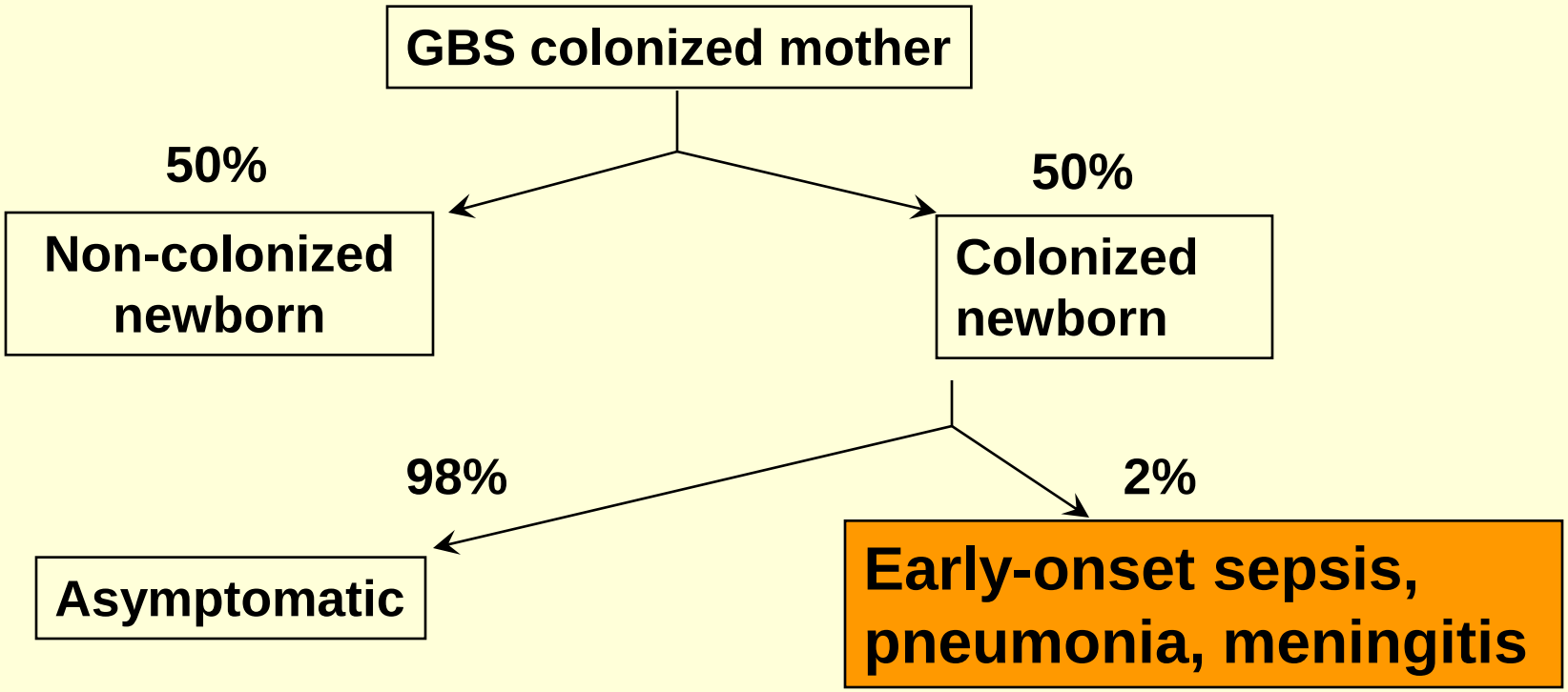
Smith et al, Infect Dis Obstet Gynecol, 2002;10:165-169

GBS

- Silent carrier state in intestinal, urinary and genital tracts of healthy individuals (reservoir: large bowel)
- Most often asymptomatic
- Maternal morbidity:
  - Sepsis, amnionitis, postpartum wound infection, stillbirth
- Vertical transmission or ascending during delivery
- Reported carrier rates in pregnant women 4-40% (20%)
- Carrier state can be chronic, transient or intermittent
- Risk factors for carrier state:
  - low socio-economic status, African American or Hispanic race, maternal age younger than 20

Regan, Obstet Gynecol, 1991;77:604-610; Oddi, BMJ, 2002:325:1-5

Mother to Infant Transmission

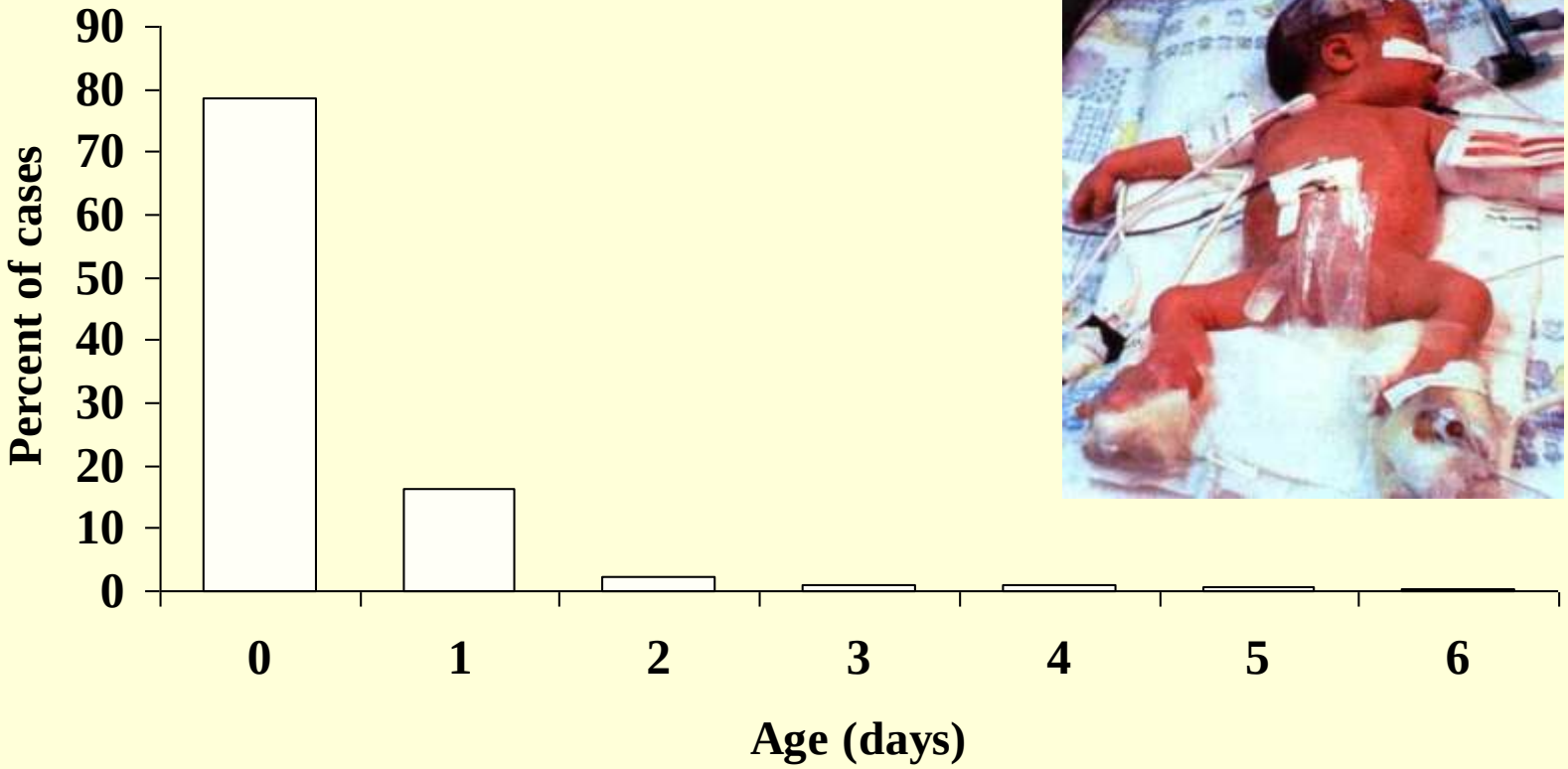


Early-Onset GBS

- Most common cause of early onset neonatal sepsis
- Sepsis, meningitis, pneumonia
- 0.2-3.7/1000 live births before AB Rx
- 0.5-0.7/1000 live births with AB Rx
- 0.5-2% of infants to carrier mothers become sick (did not receive AB Rx)
- Mortality rate 5-16%
- Most disease states can be prevented with maternal AB Rx given at delivery but not throughout pregnancy
- Most common serotypes Ia,III,V
- Long term effects:
  - Hearing loss, impaired vision, developmental problems

Oddi, BMJ, 2002:325:1-5, Gotoff, Pediatr Rev, 2002;23:381-86

Early-Onset Neonatal GBS Disease – 80%



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

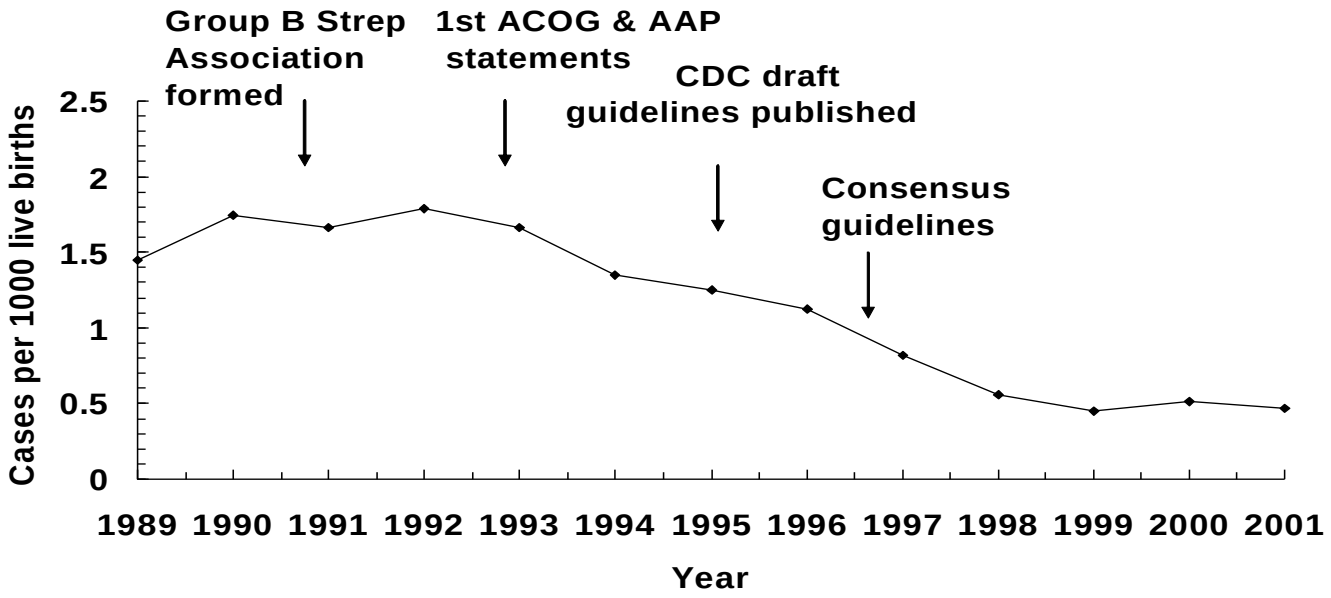
Risk Factors for Early-Onset GBS Disease

- GBS colonization at delivery
- Prenatal cultures in late pregnancy predict delivery status
- Obstetric:
  - prolonged rupture of membranes, preterm delivery, intrapartum fever, multiple pregnancy
- GBS bacteriuria
- Previous infant with GBS disease
- Demographic (African American race, young age)
- Immunologic (low IgG antibody to GBS capsular polysaccharide – MIN 1-2 µg/ml required, present in only 20% of laboring women, low in premies)

Lin et al, J Infect Dis, 2001;184:1022-1028

Attack rate

Incidence of early-onset invasive group B streptococcal disease, selected Active Bacterial Core Surveillance areas, 1989-2001, and activities for prevention of group B streptococcal disease



80% decrease in EOGBS since strategy implementation (Jeffrey et al, Pediatrics, 1998;101:e2)

Factors associated with early-onset GBS disease: multivariable analysis

Characteristic	Adjusted RR (95% CI)
GBS screening	0.46 (0.36-0.60)
Prolonged ROM (≥ 18 h)	1.41 (0.97-2.06)
Pre-term delivery	1.50 (1.07-2.10)
Black race	1.87 (1.45-2.43)
Maternal age < 20 y	2.22 (1.59-3.11)
Previous GBS infant	5.54 (1.71-17.94)
Intrapartum fever	5.36 (3.60-7.99)

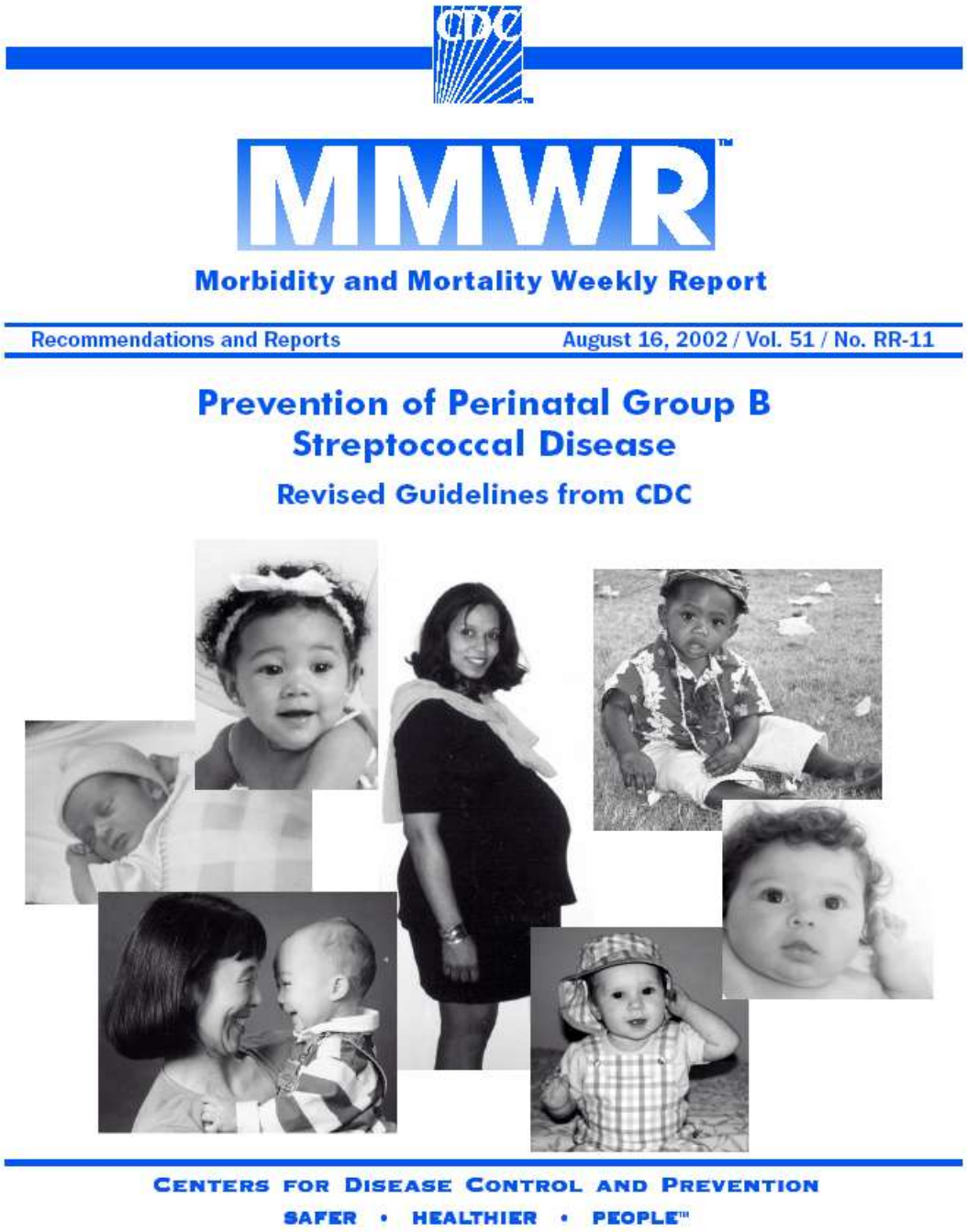
Schrag et al, NEJM 2002, 347:233-9

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

Broader coverage of at-risk population

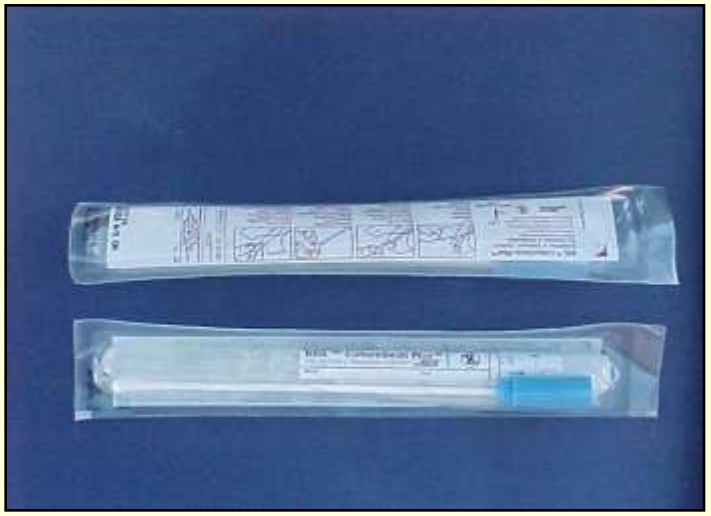
- **Captures colonized women without obstetric risk factors (18% of all deliveries)**
- **Antibiotic effectiveness in this cohort, based on birth survey data: 89% (versus 61% treated in risk factor approach)**

Schrag et al, NEJM 2002, 347:233-9



The Recommendations

MMWR, Vol 51 (RR-11)



Obstet Gynecol 2002;100: 1405-12

AAP News 2002;21(3):118

Indications for IAP under universal prenatal screening

- **Previous infant with invasive GBS disease**
- **GBS bacteriuria during current pregnancy** (2-4%)
- **Positive GBS screening culture during current pregnancy (unless a planned cesarean delivery, in the absence of labor or amniotic membrane rupture)**
- **Unknown GBS status AND any of the following:**
  - **Delivery at <37 weeks' gestation**
  - **Amniotic membrane rupture ≥18 hours**
  - **Intrapartum temperature (≥ 38.0 °C)**

MMWR Aug. 16,2002 (RR-11)

Agents for intrapartum prophylaxis

- 5,000,000 iu Penicillin G immediately
- 2,500,000 iu every 4 hours until delivery
- Alternatively:
- Ampicillin 2 g immediately and 1 g every 4 hours until delivery

MMWR Aug. 16,2002 (RR-11)

Important issues

Anticipated intrapartum antibiotic use does not differ between strategies

Reason for IAP	Deliveries (%)	
	Screening cohort	Risk cohort
GBS indication	24	24
Other reasons*	4	5
Treatment of screen negative with fever	2	--
Total IAP use	**30**	**29**

- Screening: based on use in screen negative, no risk factors;
- Risk: based on use in risk factor negative

Schrag et al, NEJM 2002, 347:233-9

Adverse consequences of intrapartum antibiotics

- Allergies:
  - 10% report previous penicillin allergy
  - Anaphylaxis is rare – 0.4-4.0/10,000 women receiving AB Rx.
  - In hospital setting – less concern

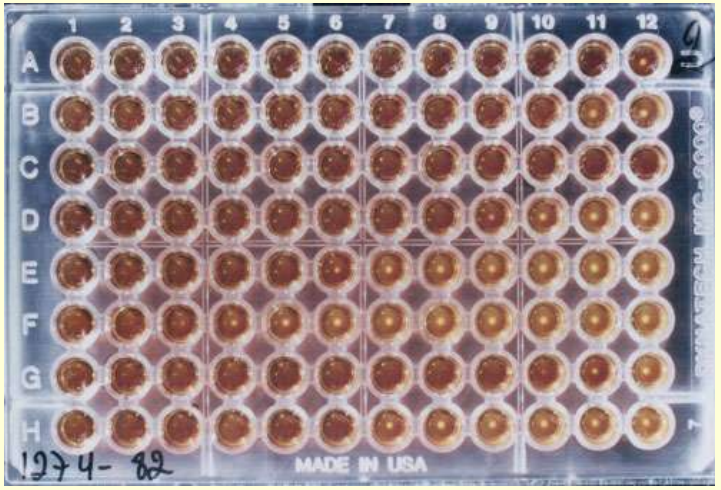
- Resistance: Clindamycin & Erythromycin resistance now more common in GBS
  - Penicillin resistance unlikely

- Changes in incidence or resistance of other pathogens: E. coli, other gram negatives

MMWR Aug. 16,2002 (RR-11)

Epidemiology US 1999-2005

- ABC system covers 26 million residents
- 1232 EOGBS, 83 deaths (6.8%)
- 0.34/1000 after 2002 ($p<0.001$)
- Reduction 27%
- 528 had serotype testing:
  - Ia – 30%
  - III – 28%
  - V – 18%
  - II – 13% (overall 96%)
- 23% premies (mean 31 w)
- **Susceptibility to Penicillin and Ampicillin maintained**



Phares et al, JAMA 2008;299:2056-2065

Trends in “other pathogens”?

- A few hospitals reported increased rates of gram negative sepsis
- One multicenter study of very LBW infants found increase in *E coli* rates (Stoll et al, NEJM 347:240-7)
- Pop-based (multicenter) studies find stable rates of total nonGBS and *E coli*
- % of *E. coli* sepsis w/ amp resistance may be increasing
- **Increases restricted to low birth weight or preterm deliveries, NICU,** and may not be related to GBS prophylaxis
- **THESE CONCERNS DO NOT OVERWEIGH THE BENEFIT OF PREVENTION OF EOGBS**

MMWR Aug. 16,2002 (RR-11)

When to screen

- Colonization is often intermittent
- Positive urine or GI culture in tri1 – 70% will have positive culture at delivery
- Negative screening at tri 2 – 8% will be positive at delivery
- Culture at 35-37 weeks:
  - NPV – 97%
  - PPV – 89%

Oddi, BMJ, 2002:325:1-5,

Recurrence of GBS in subsequent pregnancy

- Taipei, 2002-2006
- Known carrier rate – 11.1 - 18.3%
- 251 women
- Policy – universal screening + sensitivity testing, answer 72 hours
- Excluded: previous EOGBS, bacteriuria
- Recurrence 38.2%
- Risk factors for recurrence:
  - **Heavy colonization – 1.7**
  - **Time interval between pregnancies < 12months (36mo) – 1.6**
  - Smoking – 1.47
  - GDM 1.42

- **GBS colonization stable over a long period of time: only 18% change carrier status within 1 year of delivery**

Cheng et al, Obstet Gynecol 2008;111:704-9, Hansen et al, J Clin Microbiol 2004;42:83-9

Can EOGBS occur in babies whose mothers had a negative screening culture?

- 25/67260 EOGBS 1997-2003 Boston (0.37/1000)
- Screening based protocol – 21 were screened, 16 were negative
- 19/25 had delivery risk factors, only 4 received AB
- 17 term infants: 14 mothers were screened GBS negative, 1 unknown, 2 positive (no AB: clinical error, precipitous delivery).
- 8 had intrapartum risk factors but did not receive AB
- 8 preterm: 3 were culture positive, 2 negative, 2 unknown
- 1 received AB but the isolate was resistant (Clindamycin)
- 4/25 – procedural errors

- New colonization in interval from culture and delivery
- False negative, inadequate technique, poor specimen handling, poor communication of screen results

- Efforts to evaluate and treat intrapartum risk factors should be made even in screen negative women

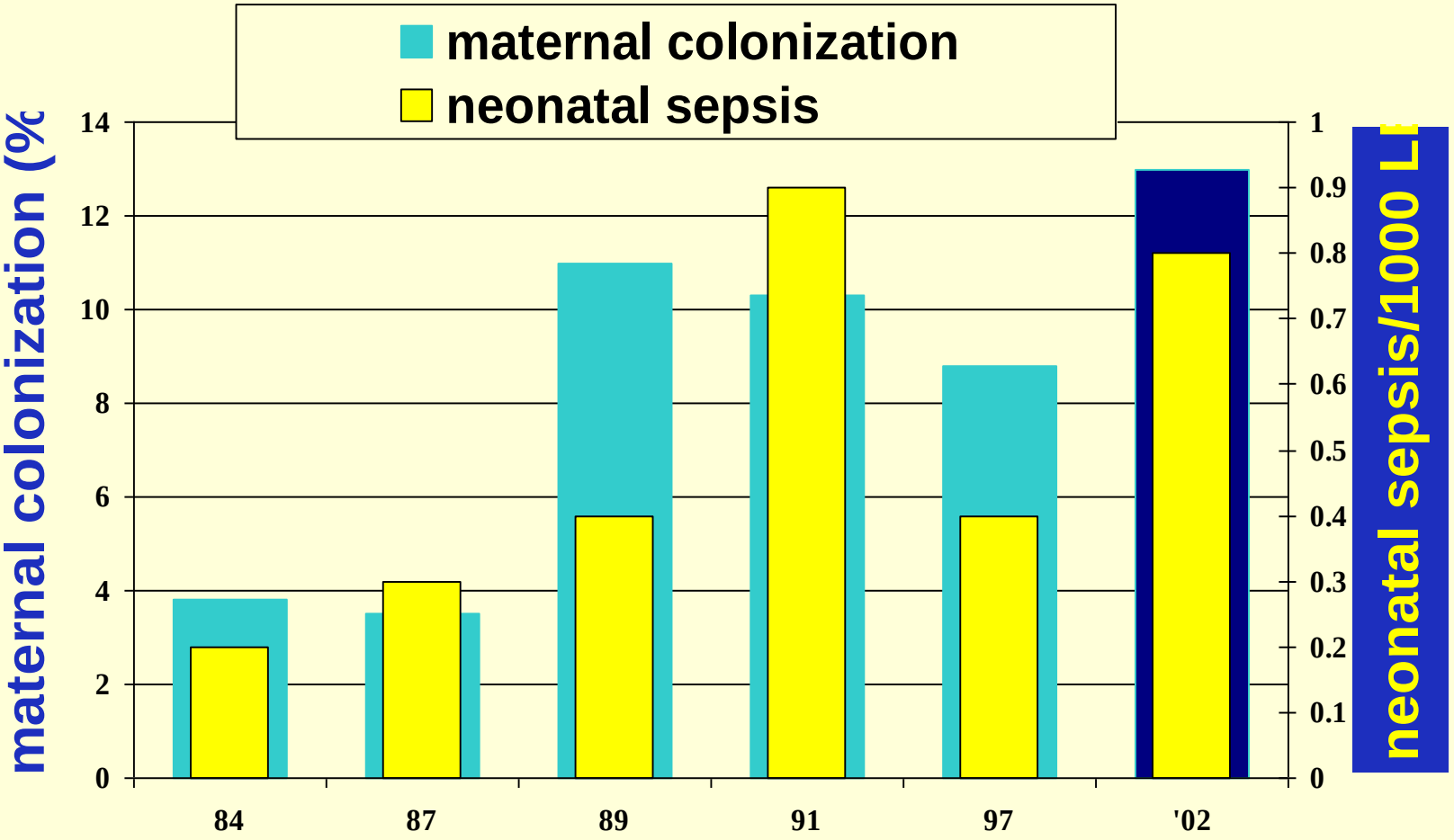
Puopolo et al, Pediatrics 2005;115:1240-46

Data from Israel

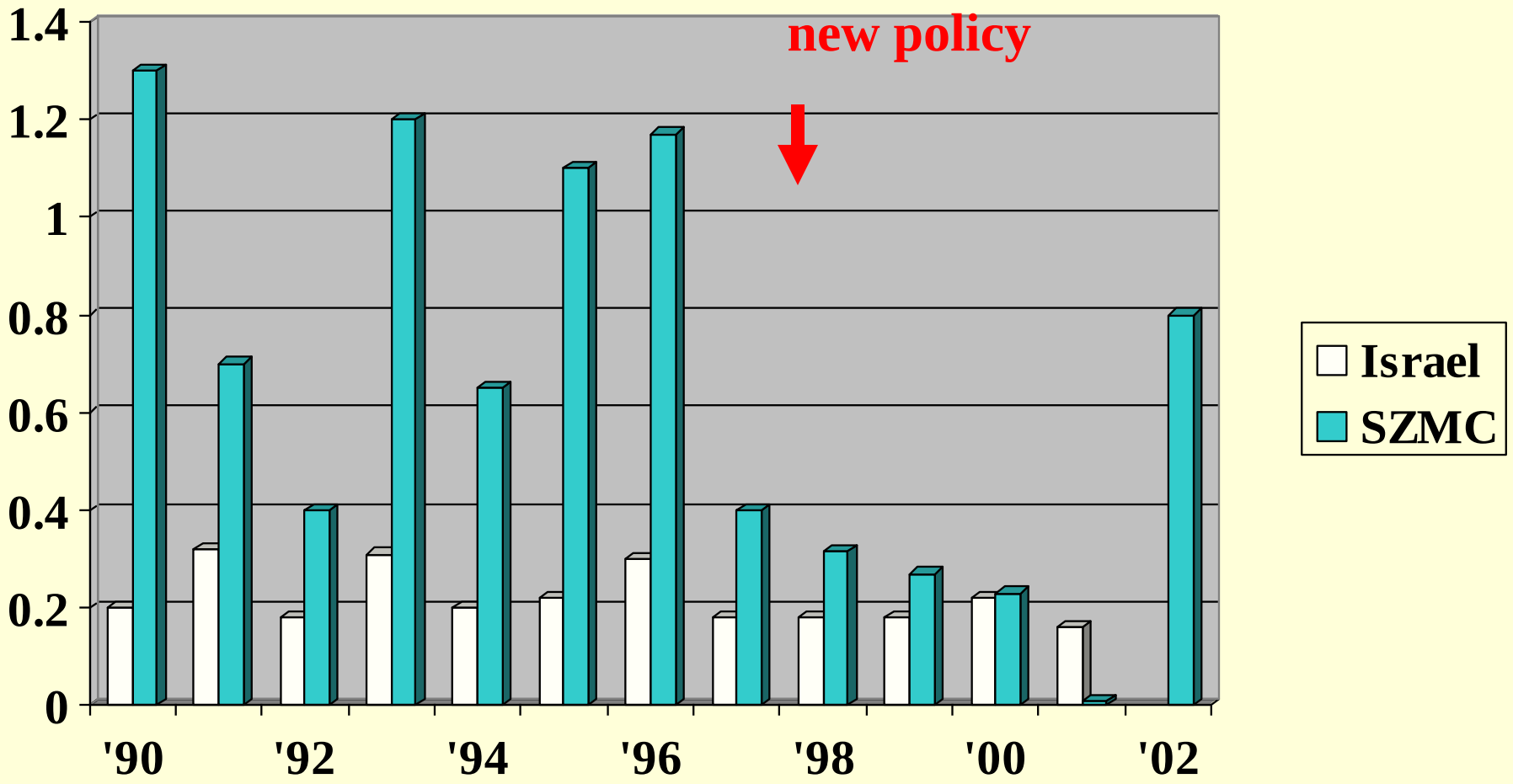
Reference	Location	Numbers	Carrier rate (%)	Neonatal positive culture (%)	Attack rate (/1000 LB)
Nitzan et al 1980	Hasharon	NA	**11.8 (high risk)**	NA	0.5-0.6
Weintraub et al 1983	Jerusalem Haifa	300 85	**2.6** **3.5**	NA 2.1	0.08
Eidelman et al 1983	Jerusalem	283	**5.3**	4.1	0.2
Eidelman et al 1990	Jerusalem 1984,1987	562	**1.6-5.4**	1.1-1.8	0.2
Hagay et al 1993	Rehovot	NA	**7.5% (high risk)**	NA	NA
Schimmel et al 1994	Jerusalem 1989,1991	556	**10.3-11**	NA	0.95
Hannah et al 1996	Israel, PROM	319	**6.8**	NA	NA
Yaakobi et al 1996	Haifa	NA	**4**	NA	0.27-0.56
Brosh et al 1998	Sheba 1994-1996	764 hospitalized	**19 (high risk)**	1.3	NA
Eisenberg et al 2006	Jerusalem 2002	629	**13.7**	NA	0.8
Marchaim et al 2003	Southern Israel	681	**12.3**	1.2	0.1
German et al 2006	Northern Israel	700	**16.4**	NA	0.15
Efrat et al 2006-2007	Carmel, Hadera, Nahariya, TAU	732	**14.3**	NA	NA

Shaare Zedek experience

- Maternal Screening: ’84, ’87, ’89, ’91, ’97 and 2002



National vs. SZMC
GBS Disease (/1000LB)



Prevention of Early-Onset Neonatal Group B Streptococcal Infection: is Universal Screening by Culture Universally Applicable?

Vered H. Eisenberg MD MHA[1]*, David Raveh MD[2], Yair Meislish MD[3], Bernard Rudensky PhD[4]*, Yossef Ezra MD[1], Arnon Samueloff MD[1], Arthur I. Eidelman MD[3,5] and Michael S. Schimmel MD[3]

- Consecutive deliveries (low risk)
- Vaginal and rectal cultures prior to vaginal examination
- GBS isolated using a selective broth medium (Todd-Hewitt), containing gentamicin, polymyxin, crystal violet & Tween; identified by latex agglutination and antigen B assay. Control – Antigen F. Serotyping at Central MOH Lab
- Prospective follow-up
- culture proven sepsis/meningitis

- 4650 women (6 months)
- **Carrier rate 13.7% (21%, p=0.048)**
- **Attack rate 0.8/1000 (3.8/1000, p=0.002)**
- **Serotype V – 20% most common (NA, shift in serotype prevalence)**
- **Resistance to Clindamycin – 8%**
- **Resistance to Erythromycin – 19%**

SZMC - Neonatal Disease - 2002

- 8 newborns had proven sepsis/meningitis
- In all cases GBS status was unknown
- 5/8 - term infants without risk factors, no Rx at time of delivery
- 3 premies, 2 delivered within less than 1 hr of arrival, single dose AB; 1 arrived at 25 gest weeks reporting weeks of PROM and delivered immediately; neonate died
- 3 NA origin
- None of the screened women had EOGBS

SZMC study comparison

	1984	2002	p
Maternal colonization rate (%)	**5.4**	**13.7**	0.00072 (95% CI, 0.19-0.67)
Neonatal sepsis rate (/1000)	**0.2**	**0.8**	<0.01, OR=4.26 (95% CI 0.13-0.39)
Most prevalent serotype	**I**	**V**	NA

- After this started to recommend culture screening

Recommendation from study

When maternal colonization rate exceeds 10%, the risk for neonatal disease increases significantly and a culture based protocol should be considered.

Even in countries with low maternal GBS colonization rates the local rate should be constantly monitored.

In a low colonization rate population (<10%), a 'high risk approach" might be sufficient

Strickland DM et al. Cost-effectiveness of intrapartum screening and treatment for maternal GBS colonization. Am J Obstet Gynecol 1990;163:4.

Southern Israel

- Carriers: overall 12.3%
  - Israeli origin – 11.4%
  - Abroad - 18.7% (NS)
- Most common serotypes Ia/C, II/C, III/R
- V – 7.1%
- Attack rate 0.1/1000 LB
- Low attack rate may be associated with less pathogenic serotypes?

Northern Israel

- German et al, Nahariya
- 700 women in 2 groups:
  - **High risk group** – 414 – PMC, UTI, PET (24-37 gestational weeks)– carriers **15.2%**
  - **Low risk group** – 286 – induction after 37 gestational weeks – carriers **18.2% (NS)**
  - Overall **16.4%** carrier rate
- Origin:
  - Jewish women – 342 – 13.7% carrier rate
  - Arabic women – 358 – 19% carrier rate (p=0.038)
- No serotype testing

Northern Israel

- Efrat et al, 2006-2007, Carmel, Hadera, Nahariya, TAU epidemiol

- Prospective screening study, 35 gestational weeks
- Questionnaire, vaginorectal cultures, GBS blood antibodies, urinary culture chlamydia

- 732 (Carmel – 189, Hadera – 495, Nahariya – 48)
- Jewish – 48.9%, Arabic – 51.1%
- Colonization rate 14.3% (Jewish 11.7%, Arabic 17.8%, 0=0.02)
- Most common serotypes: II and III (approx 20% each), Ia 17%, V 12.4%

Policy of the ministry of health in Israel

מדינת ישראל – משרד הבריאות

החטיבה לעניני בריאות

מנהל רפואה

חוזר מס': 22/2005

ירושלים, ה' תמוז, תשס"ה
12 יולי, 2005

תיק מס': 4/1/14

הנדון: בדיקת GROUP B STREPTOCOCCUS (GBS) בנשים הרות

בהתאם להמלצת המועצה הלאומית לרפואת נשים, נאוטולוגיה וגנטיקה ובאישור מנכ"ל משרד הבריאות, להלן ההנחיות הקליניות לבדיקת חיידק סטרפטוקוקוס מקבוצה B (GBS) בנשים הרות:

1. **אין מקום לבצע סקר לנוכחות חיידק GBS בשבוע 35-37 באופן שגרתי (סקר) לנשים הרות.**

2. בדיקת חיידק GBS תבוצע בנשים הרות הנמצאות באחת מקבוצות הסיכון הבאות:

2.1. אישה שילדה בלידה קודמת ילוד אשר חלה ב- GBS.
2.2. ירידת מים לפני שבוע 37.
2.3. צירים לפני שבוע 37 הגורמים שינויים ברורים בצוואר הרחם.
2.4. ירידת מים מעל 18 שעות.
2.5. בקטריאוריה עם GBS בכל ריכוז בהריון הנוכחי.
2.6. חום מעל 38 ° C במהלך הלידה.

3. קיימת חשיבות רבה לטכניקה של לקיחת התרביות, המפורטות להלן:

3.1. יש לקחת את התרבית ע"י מטוש רגיל לתרביות.
3.2. את הדגימה יש לקחת מהשליש החיצוני של הנרתיק, אחר כך מהאזור הפריאנלי והחדרה לחלל הרקטום – הכל עם אותו מטוש.

3.3. בטופס הנלווה לבדיקה יש לרשום בכתב גדול ואותיות ברורות: "תרבית ל-GBS".
3.4. במעבדה הבקטריולוגית יש לזרוע את הדגימה על קרקע מזון מיוחד ל- GBS.

הואילו להעביר תוכן חוזר זה לידיעת כל הנוגעים בדבר במוסדכם.

בברכה,

ד"ר יצחק בוגלוביץ
המשנה למנב"ל
וראש מינהל רפואה

העתק: המנהל הכללי

טבלה: שיעורי היארעות* של early onset iGBS ל-1,000 לידות חי, 2006-2007 ICDC

שנה	מספר לידות חי	סה"כ מקרי iGBS	שיעור היארעות גולמי (CI 95%)	מספר מקרי iGBS עם גורמי סיכון	שיעור היארעות עם גורמי סיכון (CI 95%)	מספר מקרי iGBS ללא גורמי סיכון	שיעור היארעות ללא גורמי סיכון (CI 95%)
2006	132,817	47	0.35 (0.27-0.47)	20	0.86 (0.56-1.32)	21	0.23 (0.15-0.34)
2007	136,565	47	0.34 (0.26-0.46)	14	0.64 (0.38-1.07)	25	0.28 (0.19-0.42)
2006-2007	269,382	94	**0.35** (0.29-0.43)	34	0.75 (0.54-1.05)	46	0.25 (0.19-0.34)

- איסוף נתונים ארצי של מקרי EOGBS בשנים 2006-2007 בארץ, 23 בתי חולים
- בהנחה כי ל-20% מהנשים ההרות יש גורמי סיכון ול- 80% אין
- לרב השיעורים הם פחות מ – 0.5/1000 (הסף שנקבע לצורך ביצוע בדיקות סקר לנשאות)
- לא ידוע האם התחלואה בקרב הילודים בסיכון גבוה היא "כתוצאה מכשל בביצוע הפרוטוקול על פי חוזר מינהל הרפואה או של כשל ביעילות הפרוטוקול במניעת תחלואה"
- מכאן המלצתם שאין צורך בשינוי המדיניות הקיימת לפיה יש לסקור רק את הנשים ההרות הנמצאות בקבוצות הסיכון שהוגדרו
- החל מ – 01/01/2008 – חובת דיווח של כל מקרי ה – EOGBS

Decision and cost analysis

Cost

- Estimated cost of culture screening in Israel (MOH) – 3-4 million shekels/year (150,000 deliveries, cost of culture 20 shekels)
- Approximately 60 EOGBS cases/year at an estimated cost ranging between 15,000-60,000 $ (3.15 mill – 12.6 mill)

Round table debate, Israeli OB/GYN journal, December 2007

Cost - Netherlands

- 31% home deliveries, 200,000 deliveries per year
- Guidelines 1999 based on risk factors:
  - IAP given to:
    - Intrapartum fever > 37.8º
    - Previous GBS child
    - GBS bacteriuria during pregnancy
    - Other risk factors receive IAP if intrapartum culture is positive
- Screening based strategy showed the highest reduction in EOGBS for the highest cost
- PCR test for women at risk had the lowest costs

- Epidemiology: (TS)
- Risk factors were absent in 46% of cases
- Incidence of EOGBS decreased from 0.54 to 0.36/1000 LB ($P<0.05$), but no change in meningitis and mortality, or late-onset GBS
- RECOMMEND CHANGING THE GUIDELINES

Van den Akker-van Marle, BJOG, 2005;112:820-26, Trijbels-Smeulders et al, Pediatr Perinat Epidemiol 2002;16:334-341

Decision analysis

- Culture testing of low risk term women, combined with Rx without testing for all high risk term and preterm women, would be the most cost-effective strategy
- Vaccination and Rx of all preterm and high risk term women is more cost-effective with less AB exposure

Colbourn et al, BMJ 2007;335:665-671

Decision analysis

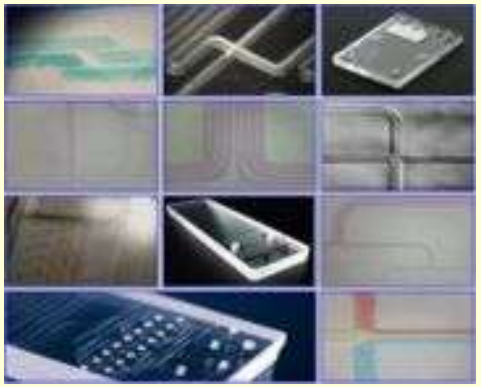
- Screening reduces incidence of EOGBS more than 5 fold (Rosenstein et al, Obstet Gynecol 1997;90:901-6)
- 45-50% of infected term infants would be missed by the risk-factor strategy (Schrag NEJM 2002;347:233-9)
- Screening is associated with lowest estimated probability of EOGBS but highest total cost (Brozanski et al, Obstet Gynecol 2000;95:496-501)
- Screening is associated with 27% maternal Rx rate, reduces attack rate by 86% (Rouse et al, Obstet Gynecol 1994;83:483-94)
- If the carrier rate in a population is higher than 10% screening becomes cost-effective (Strickland et al, AJOG 1990;163:4-8)
- **Studies in Israel have targeted unique groups (NA, USSR, etc.) which together constitute a significant proportion of the Israeli population**

Intervention	Cost	Reference
Screening culture	20$	Benitz 1999, Strickland 1990, Moehle-Boetani 1993, Yancey 1994
Maternal intrapartum antibiotics	29$	Benitz 1999, Rouse 1994
Neonatal antibiotic prophylaxis	13$	Benitz 1999
Treatment of GBS case	15,200$	Benitz 1999 estimate 15,200-67,229$ (Strickland, Moehle,
Cost per case prevented (CDC)	11,925$	Benitz 1999, CDC 1996
Cost of maternal screening Israel	20$	Macabbi Health Services
Current screening cost	20 shekels	MOH

- Antibiotics Anaphylaxis – 0.4-4/10000
- 47% of GBS infants – did not receive prophylactic antibiotics because there were no risk factors (Main 2000)
- Only in 89.9% of women was culture result available (Main 2000)
- 26.3% women received prophylactic antibiotics (Main 2000)
- Screening culture decreases morbidity by 50% (RR 0.48) (Schrag 2002)

Future prospects

Rapid detection



- 1) Testing aliquots from samples grown on enriched selective medium
  - Efficient mainly in high colonization rates
- 2) PCR – rapid < 1 hr without culture
  - Sensitivity – 94-97%, Specificity – 95.9%-100% for GBS*cfb* gene
  - Goal – answer within 15 min by microfluidic devices that speed up hybridization
  - No susceptibility data, problem for Penicillin sensitive
  - **Probably more applicable for preterm GBS negative women who are treated empirically until culture results arrive**
  - **May decrease costs overall but shift payment issues to the hospital**

Bergeron et al, NEJM 2000;343:175-179; Davies et al, CID 2004;39:1129-35; Schrag, Clin Infect Dis 2004;39:1136-8; Larsen, AJOG 2008;April:440-450

Vaccine

- Maternal antibody deficiency to GBS is associated with increased neonatal susceptibility
  - Combining the GBS polysaccharide with tetanus toxoid yields an excellent immune response
  - Produces IgG antibodies that cross the placenta (limitation for premies, poor placental transfer at less than 32 weeks)
  - Multivalent
- Immunogenic pilli on surface of bacterium in phase I clinical trial, recombinant pilus protein
  - If succeeds can be given intranasally
- Presently unavailable (maybe in 5 years)
  - Possibly more beneficial for late onset disease
  - There may be non-responders

Shuchat et al, Lancet, 1999;353:51-56; Baker et al, Vaccine, 2003;21:3468-72; Maione et al, Science 2005;309:148-50

Conclusion

- The consequences of EOGBS are significant
- Morbidity and mortality are lower with a culture based approach
- The overall colonization rates in Israel are increasing and are approaching 15%
- The EOGBS incidence varies among populations
- Several high risk groups have been targeted
- A vaccine is currently unavailable and rapid testing is not rapid enough
- Is it time to re-evaluate the current standard of care in Israel in view of the available data?

Thank you