CANADIAN TASK FORCE ON PREVENTIVE HEALTH CARE

GROUPE D'ÉTUDE CANADIEN SUR LES SOINS DE SANTÉ PRÉVENTIFS

Prevention of Early-onset Group B Streptococcal (GBS)

Infection in the Newborn

Systematic Review and Recommendations

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TECHNICAL REPORT

Preventive Health Care 2001 Update:

Prevention of Early-onset Group B Streptococcal (GBS) Infection in the Newborn: Systematic Review and Recommendations

Vibhuti Shah, MD, MRCP
Staff Neonatologist, Department of Paediatrics, Mount Sinai Hospital
Assistant Professor, Department of Paediatrics, University of Toronto

Arne Ohlsson MD, MSc, FRCPC, FAAP
Director Evidence Based Neonatal Care and Outcomes Research, Department of Paediatrics, Mount Sinai Hospital
Director Canadian Cochrane Network and Centre
Professor Departments of Paediatrics, Obstetrics and Gynaecology, Health Policy, Management and Evaluation
University of Toronto.
Professor (part-time) Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton

with

Running head: *Shah & Ohlsson with CTF – Group B Strep*

Abstract

Objectives: (1) To perform a systematic review of the evidence relating to the effectiveness of intrapartum chemoprophylaxis administered to pregnant women in preventing early onset group B streptococcal infection in the newborn, and (2) to identify the best preventive strategy.

Options: The three management options available are a) universal screening of pregnant women and selective intrapartum chemoprophylaxis to colonized women with risk factors, b) universal screening of pregnant women for group B streptococcus colonization and intrapartum chemoprophylaxis to all colonized women, and c) intrapartum chemoprophylaxis based on risk factors only.

Outcomes: The effectiveness of intrapartum chemoprophylaxis on (1) neonatal colonization and (2) early onset group B streptococcal infection in the neonate.

Evidence: MEDLINE (1966 – December 2000), EMBASE (1980 – December 2000) and the Cochrane controlled trials register was searched for randomized controlled trials and cohort studies evaluating the effectiveness of intrapartum chemoprophylaxis for the prevention of early onset group B streptococcal infection in the newborn. Cited references from retrieved articles, editorials indicating expert opinions, personal files, standard neonatal and obstetric textbooks and included references were reviewed. In the synthesis of the evidence, data from randomised trials and cohort studies were pooled separately.

Benefits, harms and costs: The benefits of intrapartum chemoprophylaxis based on the three management options were evaluated in terms of reduction in neonatal colonization and early onset group B streptococcal infection in the neonate. Harms related to the potential emergence of antibiotic resistant strains are discussed.

Values: The recommendations of this report reflect the commitment of the Canadian Task Force on Preventive Health Care to provide a structured, evidence-based appraisal of whether a maneuver should be part of a periodic health examination.

Recommendations:

- There is fair evidence that universal screening for group B streptococcal colonization at 35-37 weeks' gestation followed by selective intrapartum chemoprophylaxis given to colonized women who have risk factors reduces the incidence of colonization and early onset infection in neonates. This appears to be the most efficient strategy (**B recommendation***).

- There is fair evidence that universal screening for group B streptococcal colonization at 35-37 week's gestation followed by intrapartum chemoprophylaxis of all colonized women reduces the incidence of colonization in neonates and prevents early onset neonatal infection, but this strategy is associated with a much larger proportion of women being treated (**B recommendation**).

- There is insufficient evidence to evaluate the effectiveness of intrapartum chemoprophylaxis given on the basis of risk factors alone (**C recommendation).**

Collection of antenatal cultures (swab from lower vagina and rectum) should occur at 35-37 weeks gestation. Swabs should be inoculated into selective broth medium, followed by overnight incubation and then subcultured onto solid blood agar medium. Currently adequate intrapartum chemoprophylaxis consists of at least one dose of intravenous penicillin (5 million units) given at least 4 hours prior to birth. If labour continues beyond 4 hours then penicillin (2.5 million units) should be administered every 4 hours until delivery. Clindamycin 900mg IV every 8 hours or erythromycin 500 mg IV every 6 hours until delivery are recommended for women allergic to

penicillin. Risk factors include 1) preterm labor (< 37 weeks gestation), 2) prolonged rupture of membranes ≥ 18 hours, 3) maternal fever $\geq 38.0^0$C, 4) group B streptococcal bacteriuria during pregnancy and 5) previous delivery of a newborn with group B streptococcal disease regardless of current group B streptococcus colonization.

The emerging resistance to erythromycin and clindamycin among group B streptococcal strains is of concern suggesting that the currently recommended antibiotic therapy for women with penicillin allergy may need modification. The increased use of antibiotics in the perinatal period may lead to an increased incidence of bacteria resistant to antibiotics that are currently used as initial therapy for suspected perinatal infections.

Validation: The findings of this analysis were reviewed through an iterative process by the members of the Canadian Task Force on Preventive Health Care.

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BACKGROUND

In 1964, Eickhoff et al (Eickhoff, 1964) published the first report on group B streptococcus (GBS) infections in neonates and adults. Two forms of GBS disease in infants are well recognized. Early-onset disease (EOD) is defined as isolation of GBS from a normally sterile site (i.e., blood and/or cerebrospinal fluid) in an infant less than 7 days of age with clinical symptoms and signs compatible with a systemic infection. It accounts for 80% to 85% of neonatal infections, has a higher mortality rate and is acquired through vertical transmission from colonized mothers. Exposure of the neonate to the organism occurs either by an ascending route in utero through ruptured or intact membranes or by acquisition during passage through the birth canal. The three most common clinical presentations include sepsis, pneumonia, and meningitis. Late-onset disease (LOD) usually occurs in infants between one week and up to 3 months of age with meningitis being the most common clinical presentation (85% of cases) (Baker, 1995). Late-onset disease is acquired either by vertical transmission (delayed infection after early colonization in 50% of the cases) (Dillon, 1987) or by horizontal transmission (due to cross infection in the hospital from healthcare workers or in the community) (Noya, 1987). GBS also causes chorioamnionitis, endometritis, urinary tract infection, and puerperal wound infection (CDC, 1996; Baker, 1997) (see Table 1).

The rapidity in the onset of postnatal disease and its associated high mortality has led to numerous strategies to prevent EOD. These include antenatal, intrapartum, and postnatal (neonatal) chemoprophylaxis, active and passive immunoprophylaxis and vaginal antisepsis. Ablow et al (Ablow, 1976) in 1976 were the first to suggest intrapartum chemoprophylaxis (IPC) for prevention of EOD. Since 1992 a variety of recommendations have been made for preventing EOD (CDC, 1996; AAP, 1992; AAP, 1997; SOGC, 1994; ACOG, 1993; SOGC, 1997). Despite the apparent effectiveness of IPC in preventing EOD**,** uncertainty exists regarding the best preventive strategy. The potential effect of IPC on LOD has not been evaluated.

Burden of Suffering

<u>Incidence</u>

In the U.S., the incidence of EOD ranged from 1-3/1000 live births, although there are substantial geographical and racial differences (Regan, 1996; Zangwill, 1992). Estimates of disease were based on occurrence in a single hospital or from multistate, population based

surveillance (CDC, 1997; Schuchat, 1994). The introduction of consensus guidelines has been followed by a sharp decline in the incidence of EOD to 0.6/1000 live births in the active surveillance areas in the U.S (Scharg, 2000). Similarly, in Australia the incidence of EOD fell from 2.0/1000 live births in 1991-93 to 0.5/1000 live births in 1995-97. This decline was associated with an increased use of intrapartum chemoprophylaxis (Isaacs, 1999). In Canada, The Toronto GBS study group has reported an incidence of 1.21/1000 live births in Metropolitan Toronto/Peel region in 1995 and 0.77/1000 live births in 1997 (Goldenberg, 1998). In the UK, the reported incidence of EOD for Oxford was 0.5/1000 live births for the years 1985-1996 (Moses, 1998) compared to the incidence of 1.15/1000 live births (95% CI 0.64 to 1.66) in South Bedfordshire for the years 1993-98 (Beardsall, 2000). The reported incidence of EOD for Taiwan (Ho, 1999), Saudi Arabia (Almuneef, 2000) and India (Kuruvilla, 1999) have been 0.11, 1.39, 0.8 and 0.17/1000 live births respectively.

Colonization

The reservoir for GBS in the human species is the gastrointestinal tract; with the genitourinary loci (vagina and urethra) being the major additional sites of colonization in women. GBS colonizes the genitourinary tract of 10-40% of all pregnant women (Baker, 1995; Gordon, 1976; Anthony, 1981). Colonization rates vary among ethnic groups, geographic locations, age, and with sexual habits; however these rates are similar for pregnant and non pregnant women and do not vary from trimester to trimester during pregnancy (Yow, 1980). A significant geographic variation in the prevalence of GBS colonization have been reported, especially in non-US localities: Australia, 12% (Jeffery, 1994); Brazil, 26% (Baker, 1995); Italy, 7% (Citernesi, 1996); India, 6% (Baker, 1995); and Israel, 2-3% (Schimmel, 1994). Stoll and Schuchat in their review have reported the prevalence of GBS colonization based on geographic regions as follows: Middle East/North Africa, 22%; Asia/Pacific, 19%; Sub-Saharan Africa, 18%; India/Pakistan, 12% and Americas, 14% (Stoll, 1998). However, it should be noted that specimen collection and microbiologic methods play an important role in identification of colonized women and may contribute to the differing rates observed in various countries.

Individual mother colonization varies throughout pregnancy with results obtained at 35-37 weeks' gestation correlating best with the culture status at birth (Boyer, Gadzala, Burd, 1983; Boyer, Gadzala, Kelly, 1983; Gotoff, 1997). In a study conducted by Yancey et al, (Yancey,

1996) swabs were obtained both from the vagina and rectum from 826 women during prenatal visits at approximately 35-36 weeks gestation and again at the time of delivery and inoculated into broth media. The sensitivity and specificity in predicting colonization status at term were 87% and 96%. Test performance was similar from 1-5 weeks before delivery but declined when 6 or more weeks elapsed between the time of culture and delivery, i.e. sensitivity fell to 43% and specificity was 85% in patients cultured 6 or more weeks before delivery. In fact this study substantiated the higher sensitivity and specificity of screening carried out within 1-5 weeks of delivery and supports the recommendations from Centers for Disease Control and Prevention (CDC) to perform antenatal GBS cultures at 35-37 weeks' gestation (CDC, 1996).

The isolation rate of GBS from clinical specimens depends on several factors. As bacteria colonize the genital tract from the lower digestive tract intermittently, culture specimens taken both from the anorectal region and vagina increased GBS isolation from 5% to 27% over vaginal cultures alone (Boyer, Gadzala, Kelly, 1983; Dillon, 1982; Badri, 1977; Philipson, 1995). The use of selective media (i.e. broth containing antimicrobial agents to inhibit competing organisms) increases the yield by as much as 50% (Philipson, 1995; Baker, 1977; Ferrieri, 1977; Baker, 1973; Altaie, 1994; Silver, 1996). Selective medium cultures have become the standard for detection of maternal colonization, but take 24 to 48 hours before the final result is available.

Efforts have been made to create a sensitive and rapid test for detection of maternal colonization. Rapid antigen detection test methods include coagglutination, latex particle agglutination and enzyme immunoassay. These tests have a wide range of sensitivity (30%-80%) with specificity ranging from 95% to 100% (Yancey, 1992; Greenspoon, 1991). However, due to potentially low sensitivity of these tests, the US Food and Drug Administration have cautioned that they not be considered substitutes for selective broth cultures (FDA, 1997).

In a recent study, Bergeron et al (Bergeron, 2000) compared the accuracy of two polymerase-chain-reaction (PCR) assays to combined vaginal and rectal swabs inoculated into selective broth medium. The PCR assays had a sensitivity of 97% and a specificity of 100%. The time required to obtain results varied from 30 to 45 minutes and 100 minutes for the two PCR assays suggesting that it is a rapid and reliable method to identify colonized women.

Various risk factors for maternal GBS colonization such as maternal age, parity, ethnicity, marital status, education, socioeconomic status and smoking may influence the prevalence of colonization, however there have been marked inconsistencies in studies that

report the relationship among these factors and GBS colonization (Schuchat, 1994; Schuchat, 1990; Hickman, 1999; Terry, 1999). Currently a shift in the prevalence of serotypes among isolates from neonates have been identified with Ia as the predominant serotype followed by serotypes II, III and V (Hickman, 1999).

Risk factors for EOD

Based on univariate analyses, several maternal factors increase the risk of neonatal GBS disease including GBS bacteriuria during pregnancy, gestational age < 37 weeks, prolonged rupture of membranes (> 18 hours), and maternal intrapartum pyrexia (temperature > 38^0 C) (CDC, 1996; Schuchat, 1994; Bramer, 1997). Additional risk factors, such as risk of neonatal GBS disease complicating subsequent pregnancies, were derived from anecdotal reports (Carstensen, 1988; Faxelius, 1988).

Burden of illness

GBS case-fatality rates are now much lower than they were in the 1970s (>50%) and 1980s (15-25%). This reduction is attributed to the prompt recognition and initiation of antibiotic therapy as well as improvements in neonatal intensive care. The mortality rate in a large multi-state population was reported to be 6%, with higher rates in preterm infants, which account for about 25% of all infections (Zangwill, 1992). Once age- and race- adjustments were made for the entire U.S. population in 1990, 7600 cases of neonatal GBS sepsis (1.8/1000 live births) and 310 deaths (Dillon, 1987) were projected to occur. In the era of IPC the case fatality rate was 4.7% for EOD and 2.8% for LOD in selected counties in the US between the years 1993-8 (Scharg, 2000). In Canada, the case fatality rate was 9% for EOD and 2% for LOD (Davies, 2001).

Objectives

This paper: (1) systematically reviews the evidence relating to the effectiveness of IPC on neonatal colonization (NC) and EOD based on three different strategies: A) universal screening of pregnant women and selective IPC of colonized women with risk factors; B) universal screening of pregnant women for GBS and IPC to all colonized women; and C) IPC based on risk factors only, and (2) identifies the best preventive strategy.

It should be noted that there is no direct evidence regarding the effectiveness of screening as no study to date has compared the outcomes for screened and unscreened women.

METHODS

Extraction of Evidence

MEDLINE (1966 – December 2000), EMBASE (1980 – December 2000) and the Cochrane controlled trials register were searched using the following key words: *Streptococcus agalactiae, streptococcal infections*, *infant-newborn, intrapartum chemoprophylaxis, risk-based strategy, screening*. No language restrictions were applied. All comparative and descriptive studies evaluating the effectiveness of IPC based on three different strategies were selected. Cited references from retrieved articles were searched for additional studies. Standard neonatal and obstetric textbooks and included reference lists were examined. Abstracts and letters to the editor were excluded. Editorials, indicating expert opinion were reviewed to identify and ensure that no key studies were missed for inclusion in this review.

Critical Appraisal and Consensus Development

The evidence was systematically reviewed using the methodology of the Canadian Task Force (CTF) on Preventive Health Care. The Task Force of expert clinician/methodologists from a variety of medical specialties used a standardized evidence-based method for evaluating the effectiveness of this intervention. The two lead authors prepared a manuscript providing critical appraisal of the evidence. This included identification and critical appraisal of the key studies, and ratings of the quality of the evidence using the task force's established methodological hierarchy (Appendix 1), resulting in a summary of proposed conclusions and recommendations for consideration by the task force. This manuscript was pre-circulated to the members in May 1999 and evidence for this topic was presented by the lead author and deliberated upon in 3 meetings at which the review was presented to CTF in October 1998 and January 1999.

At the meetings, the expert panelists addressed critical issues, clarified ambiguous concepts and analyzed the synthesis of the evidence. At the end of the process, the specific clinical recommendations proposed by the lead authors were discussed, as were issues related to clarification of the recommendations for clinical application, and any gaps in evidence. The results of this process are reflected in the description of the decision criteria presented with

specific recommendations. The final decisions on recommendations were arrived at unanimously by the group and the two lead authors.

Subsequent to the meetings, the two lead authors revised the manuscript accordingly. After final revision, the manuscript was sent by the task force to 2 experts in the field (identified by the task force members at the meeting). Feedback from these experts was incorporated into a subsequent draft of the manuscript. The Task Force reviewed a more final draft of the manuscript in February 2001.

Procedures to achieve adequate documentation, consistency, comprehensiveness, objectivity and adherence to the task force methodology were maintained at all stages during review development, the consensus process, and beyond. These were managed by the task force office, under the supervision of the Chair, and ensured uniformity and impartiality in the analytic process. The full methodology is described in the paper by Woolf, Battista et al (Woolf, 1990). For each trial, information was sought regarding the method of randomization, blinding and reporting of all outcomes for all women and infants enrolled in the trials. Retrieved articles were assessed and data abstracted independently by two reviewers (VS, AO).

Quantitative Evidence Synthesis

Data from individual RCTs or cohort studies were pooled separately using Review Manager 4.1 (Update Software Ltd, Oxford) to assess the effectiveness of IPC for various strategies on NC and EOD. Due to different study designs, the patient populations, and antibiotic regimens the results of RCTs and cohort studies were not pooled. The statistical methods used were relative risk (RR), risk difference (RD), and numbers needed to treat (NNTs), which were derived from the calculated risk difference. Based on the strategy evaluated, the results are expressed either as (a) all colonized women with risk factors who received IPC or did not receive IPC or (b) as all colonized women who received IPC or did not receive IPC.

RESULTS

(A) Universal screening of pregnant women and selective IPC of colonized women with risk factors (selective IPC)

Two publications regarding one RCT were identified (Boyer, Gotoff, 1986; Boyer, Gadzala, Kelly, Gotoff, 1983). One publication was excluded, as the patient population was a subset in a subsequent publication (Boyer, Gadzala, Kelly, Gotoff, 1983). Four cohort studies were identified (Morales, 1987; Pylipow, 1994; Gibbs, 1994; Poulain, 1997). One prospective study was excluded, as data of interest could not be extracted (Poulain, 1997).

a) <u>Randomized controlled trials:</u>

Boyer et al. (Boyer, Gotoff, 1986) conducted a randomised controlled trial of selective IPC. Pregnant GBS colonized women who presented with either preterm labor (< 37 weeks of gestation) or prolonged rupture of membranes for >12 hours, were randomized to receive either no antibiotics or ampicillin (2 grams IV initially followed by one gram every four hours until delivery). It was not possible to identify in the article the median or mean gestational age at which women were screened with regard to GBS colonization status. Participants were excluded if there was a history of penicillin allergy. Women who developed an elevated temperature intrapartum were excluded from the study and treated with ampicillin. Surface swabs and blood cultures were obtained from all newborns at birth. Healthy infants whose mothers had received ampicillin were treated with four doses of intramuscular ampicillin until the culture results were available. Healthy infants born to untreated mothers were given antibiotics only if symptomatic. One hundred and eighty high-risk women and their 185 newborns provided results. Thirteen women with intrapartum fever and seven who had randomization errors or incomplete data were excluded. Thus, eighty-three women (85 newborns) remained in the treatment group and 77 women (79 newborns) remained in the control group. A statistically significant decrease was observed in NC (8/85 vs. 40/79; p<0.001) but not EOD (0/85 vs. 4/79; p=0.052) after IPC.

b) <u>Cohort studies:</u>

Morales et al (Morales, 1987) evaluated 260 women at preterm gestation ($\leq$ 34 weeks) and prelabour rupture of membranes > 12 hours before onset of labor. Women who were in labor, those with foul-smelling liquor, ultrasonographic evidence of intrauterine growth

retardation and neonates with congenital anomalies were excluded. A rapid screen based on a coagglutination method was performed. Women found positive for GBS were treated with ampicillin and managed expectantly. Those allergic to penicillin were treated with cephalosporin. Eighty-four of the 260 women were positive for GBS. Thirty-six women received IPC (one-gram ampicillin IV every 6 hours until delivery) while 48 women were not treated due to a short latency period or delay in processing the screens. There was no case of EOD in the treatment group as compared to thirteen in the untreated group (p<0.01).

Pylipow et al. (Pylipow, 1994) assessed the effectiveness of selective IPC strategy over a 20-month period. Screening was performed some time in the third trimester and again at delivery. GBS positive women with a risk factor at the time of delivery received IPC (2 grams of ampicillin IV followed by one gram IV every 4 hours until delivery). Risk factors included fever and/or amnionitis, preterm labor and prolonged prelabour rupture of membranes. In the first 14 months of the study, prolonged prelabour rupture of membranes was defined as > 6 hours due to their previous experience with clustered EOD (Adams, 1993). During the last 6 months of the study, prolonged prelabour rupture of membranes was defined as > 12 hours. Screening laboratory tests were performed on all newborns whose mothers received IPC. These included a blood culture, two surface swabs and two complete blood cell and differential counts. Antibiotics were administered to asymptomatic infants with an abnormal screening test and those with symptoms. During this period the maternal colonization rate was 16.3%. Of the 122 mothers (124 newborns) colonized with GBS and with at least one risk factor, IPC was administered to 70 women (70 newborns). No case of EOD was noted in the treatment group as compared to 5 in the control group. Despite the initiation of this protocol, fifty-four mothers failed to receive IPC. The reasons for this were: failure to follow protocol, no prenatal care, negative prenatal cultures but were positive at the time of delivery, and arrival in labor one hour or less before delivery.

Gibbs et al. (Gibbs, 1994) tested a similar protocol of screening at 26-28 weeks and administered antibiotics (ampicillin 2 grams IV, then one gram IV every 4 hours until delivery) to women with risk factors. Erythromycin was used to treat women allergic to penicillin. During a 2-year period, the maternal colonization rate was 18.5%, of which 35% developed risk factors. IPC was administered to 80.3% of the 142 women who gave birth and who were GBS positive at screening and had risk factors. Twenty-eight women did not receive IPC and this was considered to be due to protocol violations. Five cases of EOD were noted in infants born to mothers who

did not receive IPC due to protocol violation or failure. The EOD rate was 1.5/1000 births preceding the protocol implementation. During the first year of the protocol, the rate was 1.6/1000 and during the second year it was 0.5/1000 births.

Neonatal colonization is reduced by universal screening and selective IPC of women with risk factors as demonstrated in the RCT by Boyer and Gotoff (Boyer, Gotoff, 1986) [RR, 95%CI; 0.19 (0.09, 0.37)] (Table 2) with a RD of – 0.41 (95% CI; - 0.54, - 0.29), however the study was unable to demonstrate a significant reduction in EOD [RR, 95%CI; 0.10 (0.01,1.89)] (Table 3). A pooled result based on cohort studies was obtained to assess the effectiveness of universal screening and selective IPC based on risk factors on EOD. There was a significant reduction in EOD with the use of IPC (RR, 95%CI; 0.05, 0.01,0.24) (Table 4) with a RD of - 0.17 (95% CI; - 0.24, -0.10).

(B) Effectiveness of universal screening of pregnant women and IPC to all colonized women

Six publications (Tuppurainen, 1989; Matorras, 1991; Easmon, 1983; Morales, 1986; Lim, 1986; Tuppurainen, 1986) regarding four RCTs were identified. Three publications were excluded, one due to violation of the randomization process (Morales, 1986) and two where the patient populations were subsets of subsequent publications (Lim, 1986; Tuppurainen, 1986). Four cohort studies (Yow, 1979; Allardice, 1982; Garland, 1991; Jeffery, 1998) were identified. One was excluded because it used a before-after study design (Jeffery, 1998).

<u>a) Randomized controlled trials:</u>

Tuppurainen et al (Tuppurainen, 1989) used a rapid latex agglutination test (streptolatex test) to identify GBS colonization status for women admitted in labor. The streptolatex test had a sensitivity of 84.2% and a specificity of 95.9%. Randomization to the treatment or control group was performed using sequential sealed envelopes. Eighty-eight women were enrolled in the treatment group and 111 women in the control group. Women with a history of penicillin allergy and women who underwent a cesarean section without labor or rupture of fetal membranes were excluded. Penicillin (5 million units) was used intravenously (IV) every 6 hours during labor for IPC. If delivery did not occur within 18 hours, penicillin prophylaxis was continued by administering 1 million units penicillin V orally every 8 hours until parturition. All newborns of GBS positive mothers were studied prospectively. Surface swabs were obtained within 30

minutes of birth and a blood culture within 2 hours of birth from all newborns. EOD was noted in one neonate in the treatment group as compared to five neonates in the control group (1/88 vs. 5/111; p=0.231). One hundred and fifty-seven women with a positive streptolatex test delivered precipitously before the test results were available and could not participate in the trial. There are several limitations to this study. No details regarding the baseline characteristics of the study group were provided. Women with penicillin allergy were excluded from the study and not treated with antibiotics as the investigators felt it was unethical to subject them to broad-spectrum antibiotics or painful erythromycin injections. A rapid screening test was used rather than culture, which may fail to identify women with light or intermittent colonization. Nevertheless, this trial does support a benefit of antibiotic prophylaxis.

Matorras et al (Matorras, 1991) randomized 121 women with a positive culture obtained between 17-42 weeks (mean gestational age 33 weeks) during labor. Fifty-seven women (60 newborns) received IPC with ampicillin (500 mg IV every 6 hours during delivery), while 64 women (65 newborns) in the control group did not receive any prophylaxis. An identical dose of erythromycin was used in women with allergy to penicillin. Surface swabs were obtained from the newborn infants in the delivery room. A blood culture was only obtained if infection was suspected. IPC led to a reduction in NC (2/54 vs. 24/56; p <0.0001). Three cases of EOD were noted in the control group as compared to none in the treatment group, the difference was not statistically significant (p=0.137). The study included both low and high-risk pregnancies.

Easmon et al (Easmon, 1983) evaluated the effect of IPC on NC in a RCT of 87 women who were colonized with GBS at 36 weeks. Forty-nine women were included in the control group and 38 in the IPC group received benzylpenicillin (600 mg intramuscularly) or erythromycin (100 mg intramuscularly) every 8 hrs in women with a history of possible penicillin allergy. No infant in the treatment group was colonized as compared to 17 in the control group (p<0.001).

In summary, NC is significantly reduced by IPC as shown by a pooled result of RCTs [relative risk (RR), 95% confidence interval (CI); 0.07 (0.02, 0.23)] (Table 5) with a risk difference (RD) of – 0.37 and 95% CI (- 0.47, - 0.27). A pooled result of two RCTs of universal screening of pregnant women and IPC to all colonized women vs. no IPC demonstrated a reduction of EOD (RR: 0.21; 95% CI: 0.04, 1.17) (Table 6). However, this difference did not reach statistical significance as the upper confidence limit for RR is greater than 1.

b) Cohort studies:

Yow et al (Yow, 1979) demonstrated that ampicillin administered to women during labor significantly reduced the NC rate (0/34 vs. 14/24; p<0.001). Similarly, Allardice et al (Allardice, 1982) showed a significant reduction in NC (4/57 vs. 62/136; p=0.0001) and a non-significant reduction in EOD (0/57 vs. 9/136; p=0.06) in women treated with IPC.

In a study by Garland and Fliegner (Garland, 1991) women were screened at 32 weeks to identify carrier status. Women with a positive result received IPC during labor. IPC consisted of penicillin (1 million units IV) every 6 hours until delivery. Women with a history of penicillin allergy were treated with erythromycin 500 mg every 6 hours. There was a significant reduction in EOD (16/30,197 vs. 27/26,915; p=0.046). Of the 16 cases of EOD that occurred in the treatment group, eight were born between 29 to 32 weeks' gestation and of the remaining eight infants, five resulted from failure to follow the protocol.

Neonatal colonization is significantly reduced by IPC as shown by pooled analyses of cohort studies [RR, 95% CI; 0.11 (0.05, 0.27)] (Table 7) with a RD of – 0.44 (95% CI; - 0.53, - 0.34).

In view of statistically significant in between study heterogeneity (p = 0.0062) for risk difference the results of the studies by Allardice at al (Allardice, 1982) and Garland and Fliegner (Garland, 1991) were not combined. For the study by Allardice et al (Allardice, 1982) the RR was 0.12 (95% CI; 0.01, 2.1) with a RD of -0.060722 (95% CI; -0.10946, - 0.011982). Based on this RD the NNT would be 16 (95% CI; 9,84). It is of note that the RR was not statistically significant but the RD was. The results should therefore be interpreted with caution. For the study by Garland and Fliegner (Garland, 1991) the RR was 0.52 (95% CI; 0.28, 0.96) with a RD of -0.000486 (95% CI; -0.00094, - 0.00003). Based on this RD the NNT would be 2059 (95% CI; 1062, 32968).

Intrapartum prophylaxis (IPC) based on risk factors only

There have been no prospective studies to date evaluating the effectiveness of using the risk-based strategy to reduce early onset neonatal disease.

Timing of Screening

The study by Yancey et al (Yancey, 1996) determined that vaginal and rectal cultures in broth media obtained during the late antenatal period (35-36) weeks were significantly (p< 0.01) more sensitive and specific in predicting group B streptococcal colonization status at delivery than cultures obtained 6 or more weeks before delivery.

Potential Harms and Costs of Screening & Treatment

Antibiotic resistant strains

Several investigators have recently reported an increase in the incidence of GBS strains resistant to erythromycin and clindamycin (Berkowitz 1990; Fernandez, 1998; Pearlman, 1998; Morales, 1999). Berkowitz et al (Berkowitz, 1990) tested 159 GBS isolates from the genital tract of pregnant women for antibiotic resistance. While none of the isolates were resistant to penicillin G or ampicillin, 3.2% and 2.5% of the isolates exhibited resistance to erythromycin and clindamycin respectively. In a study by Fernandez et al (Fernandez 1998) 229 GBS isolates identified in the blood or cerebrospinal fluid of hospitalized patients between 1992-1996 were tested in vitro to determine the frequency of resistance to 11 antibiotics including penicillin G, erythromycin, clindamycin, and cephalosporins. All isolates were sensitive to penicillin G, while 17 isolates (7.4%) were resistant to erythromycin and 8 isolates (3.4%) were resistant to clindamycin. Similarly, Pearlman et al (Pearlman, 1998) have reported a resistance rate of 15% to clindamycin and 16% to erythromycin among 100 GBS isolates tested in vitro. Morales et al (Morales, 1999) compared the sensitivity of 100 GBS isolates retrieved during the period 1997 – 1998 to 85 GBS isolates retrieved from 1980 – 1993. All isolates were sensitive to penicillin and ampicillin. However, for the period of 1997-1998, 18 isolates were noted to be resistant to erythromycin of which 5 were also resistant to clindamycin as compared to only one isolate resistant to erythromycin for the period of 1980-1993 (p < 0.001). All 18 resistant strains for the years 1997 – 1998 were sensitive to cephalothin. The increase in resistance to the two alternative antibiotics (erythromycin and clindamycin) recommended for women allergic to penicillin is of concern. Women allergic to penicillin and GBS colonized should have their GBS isolates tested for sensitivity to the alternative antibiotics prior to giving birth (Morales, 1999).

Several studies have reported an increase in early-onset neonatal sepsis due to organisms other than GBS that are resistant to ampicillin and possibly related to widespread use of

antepartum and intrapartum antibiotics (Towers, 1998; Mercer, 1999). The most commonly reported non-GBS organism is *E. coli* (Towers, 1998; Mercer, 1999). In a prospective cohort study 42 cases of early–onset neonatal sepsis were reported among 29,897 neonates delivered during a 6-year period (Towers, 1998). Fifteen cases of sepsis were due to GBS while 27 were due to other organisms. Among these 27 cases, 15 mothers had received antenatal ampicillin. Thirteen of the 15 (87%) bacterial isolates from these neonates were resistant to ampicillin as compared to 2 (17%) ampicillin-resistant isolates among the 12 cases in which no antenatal antibiotics were administered (p = 0.0004). During this period there was an increase in the proportion of women who received antenatal antibiotics. A decrease in the incidence of EOD due to GBS was noted, whereas the incidence of EOD with other organisms, especially *Escherichia coli* increased. Among 96 neonates with confirmed sepsis/meningitis identified from a cohort of 8474 pregnancies (8593 live births) 45% of the pathogens were resistant to ampicillin. Variables associated with ampicillin resistance included preterm birth, ante- and intrapartum antibiotics and any prenatal exposure to antibiotics (Mercer, 1999).

Antibiotic reactions in the mother and newborn

There are also concerns about the development of maternal anaphylactic reactions. Any allergy to penicillin has been reported with a frequency of 0.7-10%, anaphylactic reactions at 0.015 – 0.04% and deaths at 0.0015 – 0.002% (Idsoe, 1969).

Cost-effectiveness

More than a dozen approaches to selection for prophylaxis have been evaluated using decision analysis (Yancey, 1994; Strickland, 1990; Mohle-Beotani, 1993; Rouse, 1994), although most are based on theoretical decision analyses and have not been tested in clinical studies.

In their analysis Yancey et al (Yancey, 1994) concluded that universal screening using vaginal-rectal cultures and treatment of all GBS positive mothers is cost-effective. However, Strickland et al (Strickland, 1990) calculated that universal screening programs are not cost efficient when the colonization rate is <10%. Mohle-Boetani et al (Mohle-Boetani, 1993) suggested that implementation of a risk factor strategy is not cost-effective unless the incidence is greater than 0.6/1000 live births and universal screening with selective IPC of colonized

women with risk factors is not cost-effective unless the incidence is 1.2/1000 live births. Rouse et al (Rouse, 1994) analyzed 19 different preventive strategies and concluded that universal intrapartum maternal treatment, treatment based on risk factors and antenatal screening at 36 weeks and intrapartum treatment of all GBS positive mothers and all preterm deliveries were the optimal strategies. Fargason et al (Fargason, 1997) noted that for the risk-based strategy the CDC pediatric algorithm increased the cost of averting one case by 94-112% as compared to 51% for the screening based strategy. Similarly Mohle-Boetani et al (Mohle-Boetani, 1999) in their analysis of the risk-based strategy suggested that cost savings occurred only if the hospital stay of the neonate is not extended beyond 24 hours. Thus, the pediatric costs of longer hospital stays and therapies may have a major impact on the cost-effectiveness analysis of these strategies. Differences in conclusions across the cost-effectiveness studies may due to variability in maternal colonization rates, the frequency of EOD and management practices of neonates born to mothers treated with antibiotics.

Thus, within a given health care system the choice of a preventive strategy depends on the incidence of the EOD, the patient characteristics, available clinical resources and possibly maternal colonization rates. In Canada, the information to enable us to assess cost-effectiveness of any preventive strategy is lacking. Ongoing surveillance of all cases of early onset bacterial infections is important for timely detection of increase in the rate of sepsis from other causes or an increase in infections with antibiotic-resistant pathogens.

INTERPRETATION

Summary of Key Evidence

Randomized controlled trials provide the most valid data on which to base measures of benefits and risks of particular therapies. None of the RCTs evaluating the effectiveness of universal screening and selective IPC of colonized women with risk factors (Boyer, Gotoff, 1986) or universal screening of pregnant women for group B colonization and IPC to all colonized women (Tuppurainen, 1989; Matorras, 1991) have shown a statistically significant reduction in EOD. Although they show a trend towards reduction in EOD, none of these studies has enough power to demonstrate a significant difference in EOD between the treatment and control group (Type II error). There is evidence that both strategies reduce NC.

There is evidence from cohort studies that universal screening and selective IPC of colonized women with risk factors (Morales, 1987; Pylipow, 1994; Gibbs, 1994) or universal screening of pregnant women for GBS and IPC to all colonized women (Allardice, 1982; Garland, 1991) is effective in preventing EOD. The rates of early onset infection in the control groups were 7% and 0.1% in the study by Allardice et al (Allardice, 1982) and Garland and Fliegner (Garland, 1991) respectively. It is also of note that for the study by Allardice et al (Allardice, 1982) the RR was not statistically significantly decreased with treatment but it was for the RD. The results should therefore be interpreted with caution. The efficacy of IPC based on risk factors only has not been tested.

The effectiveness of a therapeutic maneuver can be assessed by the number of patients requiring treatment - the number needed to screen (NNS) and/or to treat to prevent one adverse event (Laupacis, 1988). We could not calculate the NNS as no study to date has compared the outcomes for screened and unscreened pregnant women. The NNT for the different strategies are presented below.

Based on our pooled analyses of the data from RCTs and cohort studies (Tables 2, 4, 5, and 7, estimates of NNT were calculated (Table 8). Two to three women need to be treated with IPC to prevent one infant from colonization in both universal and selective IPC strategies. To prevent one case of EOD 6 colonized women with risk factors (95% CI; 4, 10) need to be treated with selective IPC. In comparison, evidence from two studies indicates that 16 colonized women (95% CI; 9, 84) (Allardice, 1982) and 2059 colonized women (95% CI; 1062, 32968) (Garland, 1991) need to be treated to prevent one case of EOD if IPC is administered to all colonized women (the rates of early onset infection in the control groups were 7% and 0.1% respectively). In view of statistically significant heterogeneity (p = 0.0062) the results of the two studies were not combined. Thus, a much larger proportion of women will receive antibiotics if universal screening of pregnant women for GBS and IPC is adopted as a preventive strategy compared to universal screening and selective IPC based on risk factors. The results of these analyses favor universal screening of pregnant women and selective IPC of colonized women with risk factors over universal screening of pregnant women and IPC to all colonized women.

In the absence of IPC, approximately 40 – 50% of infants of screen positive mothers are colonized (Tables 2, 5 and 7). IPC is effective in reducing colonization (80 –90%). In the absence of treatment, a small but important proportion of infants of colonized mothers develop

EOD. The proportion of EOD in the RCTs was approximately 5% (Tables 3 and 6). IPC also appears effective at reducing the risk of EOD in births to colonized women. Although the low rate of EOD has made it difficult to demonstrate significance in individual trials, evidence from this systematic review suggest reduction for colonized women, regardless of risk factors.

To summarize, IPC is effective in reducing both neonatal colonization and EOD. The most efficient preventive strategy appears to be universal screening of all pregnant women and selective IPC of colonized women with risk factors. Universal screening of all pregnant women and IPC to all colonized women is also found to be effective. The benefits of either strategy must be weighed against the number of women who need to be treated with IPC. In view of the concerns raised about the quality and heterogeneity of the studies, it is likely that the point estimates for effectiveness for the different strategies have been overestimated (Ohlsson & Myhr, 1994, Shah & Ohlsson, 2000). The emerging resistance to erythromycin and clindamycin among GBS strains is of concern suggesting that the currently recommended antibiotic therapy for women with penicillin allergy may need modification. The increased use of antibiotics in the perinatal period may lead to an increased incidence of bacteria resistant to antibiotics that are currently used as initial therapy for suspected perinatal infections.

Canadian Task Force Recommendations (Table 9)
Universal screening of pregnant women for GBS colonization and selective IPC to colonized women with risk factors

There is fair evidence (level II-1, II-2) to recommend universal screening of pregnant women for GBS colonization and selective IPC to colonized women with risk factors to reduce neonatal colonization and early onset neonatal disease (B recommendation). Risk factors include preterm labour (<37 weeks gestation), prolonged rupture of membranes ≥ 18 hours, maternal fever ≥ 38.0C, group B streptococcus bacteriuria during pregnancy, and previous delivery of a infant with neonatal group B streptococcus disease regardless of current group B streptococcus colonization. Antenatal cultures (swab from lower vagina and rectum) obtained between 35-37 weeks gestation correlate best with maternal colonization status at delivery. Swabs should be inoculated into selective broth medium, followed by overnight incubation and then subcultured onto solid blood agar medium. Currently adequate IPC consists of at least one dose of intravenous penicillin (5 million units) given at least 4 hours prior to birth and if labour persists

beyond 4 hours penicillin (2.5 million units) should be administered every 4 hours until delivery (CDC, 1996). Clindamycin 900 mg IV every 8 hours or erythromycin 500 mg IV every 6 hours until delivery are recommended for women allergic to penicillin (CDC, 1996). Intravenous ampicillin is an acceptable alternative to penicillin, but penicillin is the antibiotic of choice due to its narrow spectrum. It is therefore less likely to cause antibiotic resistant organisms (CDC, 1996).

Universal screening of pregnant women for GBS colonization and intrapartum chemoprophylaxis to all colonized women

There is fair evidence (level II-2) to recommend universal screening of pregnant women for GBS colonization and intrapartum chemoprophylaxis to all colonized women, to reduce neonatal colonization and early onset neonatal disease (B recommendation).

Intrapartum prophylaxis based on presence of risk factors

There is insufficient evidence to recommend for or against the risk factor strategy to reduce early onset neonatal disease (C recommendation).

Recommendations of Others

The Society of Obstetricians and Gynecologists of Canada, the Centers for Disease Control and the American Academy of Pediatrics have published guidelines regarding prevention of perinatal group B streptococcal disease. They recommend either of two strategies: universal screening at 35-37 weeks and offer IPC to colonized women, or IPC based on maternal risk factors. (CDC, 1996; AAP, 1992; AAP, 1997; SOGC, 1994; ACOG, 1993; SOGC, 1997). Since the 1996 CDC guidelines, AAP withdrew its initial recommendations for 28-week screening and selective IPC and endorsed the CDC guidelines. The ACOG and CDC recommend that individual obstetric practices should choose one of the two alternative protocols published in 1996 to establish consistent management of patients (CDC, 1996).

Research Agenda

Clinicians continue to face the challenge of choosing between preventive strategies to reduce EOD. Controversy exists regarding the ideal preventive strategy. There is an urgent need to carry out comparative studies of various preventive strategies to determine the optimal strategy. The effectiveness of IPC based on a risk factor approach needs to be evaluated. There is a need for ongoing surveillance of perinatal GBS infections as well as perinatal infections due to other bacteria. The effectiveness of the currently recommended algorithm for treatment of the neonate born to mothers who received IPC needs to be evaluated. In addition a study evaluating the cost-effectiveness of GBS screening in Canada is needed.

The development of an effective vaccine would be ideal as it has the potential of preventing GBS infections occurring in term pregnancies. It also has the potential of preventing GBS infection outside of the perinatal population.

References:

Ablow RC, Driscoll SG, Effmann EL Gross I, Jolles CJ, Uauy R, Warshaw JB. A comparison of early-onset group B streptococcal neonatal infection and the respiratory-distress syndrome of the newborn. N Engl J Med 1976;294:65-70.

Adams WG, Kinney JS, Schuchat A, Collier CL, Papasian CJ et al. Outbreak of early onset group B streptococcal sepsis. Pediatr Infect Dis J 1993;12:565-70.

Allardice JG, Baskett TF, Seshia MM, Bowman N, Malazdrewicz R. Perinatal group B streptococcal colonization and infection. Am J Obstet Gynecol 1982;142:617-20.

Almuneef M, Alalola S, Ahmed S, Memish Z, Khan MY, Alshaalan M. The changing pattern of group B streptococcal (GBS) infection in infants of Saudi Arabia. J Chemother 2000;12:48-52.

Altaie SS, Dryja D. Detection of group B Streptococcus. Comparison of solid and liquid culture medium with and without selective antibiotics. Diagn Microbiol Infect Dis 1994;18:141-4.

American Academy of Pediatrics, Committee on Infectious Diseases and Committee on Fetus and Newborn. Guidelines for prevention of group B streptococcal infection by chemoprophylaxis. Pediatrics 1992;90:775-8.

American Academy of Pediatrics, Committee on Infectious Diseases and Committee on Fetus and Newborn. Revised guidelines for prevention of early-onset group B streptococcal (GBS) infection. Pediatrics 1997;99:489-96.

American College of Obstetricians and Gynecologists. Group B streptococcal infections in pregnancy: ACOG's recommendations. ACOG Newsletter 1993;37:1.

Anthony BF, Eisenstadt R, Carter J, Kim KS, Hobel CJ. Genital and intestinal carriage of group B streptococci during pregnancy. J Infect Dis 1981;143:761-6.

Badri MS, Zawaneh S, Cruz AC, Mantilla G, Baer H, Spellacy WN, Ayoub EM. Rectal colonization with group B streptococcus: relation to vaginal colonization in pregnant women. J Infect Dis 1977;135:308-12.

Baker CJ, Clark DJ, Barrett FF. Selective broth medium for isolation of group B streptococci. Appl Microbiol 1973;26:884-5.

Baker CJ, Edwards MS. Group B streptococcal infections. In: Remington J, Klein JO, eds. Infectious Disease of the Fetus and Newborn Infant. 4th ed. Philadelphia:WB Saunders. 1995:980-1054.

Baker CJ, Goroff DK, Alpert S et al. Vaginal colonization with group B streptococcus: a study of college women. J Infect Dis 1977;135:392-7.

Baker CJ. Group B streptococcal infections. Clin Perinatol 1997;24:59-70.

Beardsall K, Thompson MH, Mulla RJ. Neonatal group B streptococcal infection in South Bedfordshire, 1993-1998. Arch Dis Child 2000:82:205-7.

Bergeron MG, Danding KE, Menard C, Picard FJ, Gagnon M, Bernier M et al. Rapid detection of group B streptococci in pregnant women at delivery. N Engl J Med 2000;343:175-9.

Berkowitz K, Regan JA, Greenberg E. Antibioitic resistance patterns of group B streptococci in pregnant women. J Clin Microbiol 1990;28:5-7.

Boyer KM, Gadzala CA, Burd LI, Fisher DE, Paton JB, Gotoff SP. Selective intrapartum chemoprophylaxis of neonatal group B streptococcal and early- onset disease. I. Epidemiologic Rationale. J Infect Dis 1983;148:795-801.

Boyer KM, Gadzala CA, Kelly PD, Burd LI, Gotoff SP. Selective intrapartum chemoprophylaxis of neonatal group B streptococcal early-onset disease. II. Predictive value of prenatal cultures. J Infect Dis 1983;148:802-9.

Boyer KM, Gadzala CA, Kelly PD, Gotoff SP. Selective intrapartum chemoprophylaxis of neonatal group B streptococcal early-onset disease. III. Interruption of mother-to-infant transmission. J Infect Dis 1983;148:810-6.

Boyer KM, Gotoff SP. Prevention of early-onset neonatal group B streptococcus disease with selective intrapartum chemoprophylaxis. N Engl J Med 1986;314:1665-9.

Bramer S, van Wijk FH, Mol BW, Adriaanse AH. Risk indicators for neonatal early-onset GBS-related disease. A case-control study. J Perinat Med 1997;25:469-75.

Carstensen H, Christensen KK, Grennet L, Persson K, Polberger S. Early-onset neonatal group B septicemia in siblings. J Infect 1988;17:201-4.

Centers for Disease Control and Prevention. Decreasing the incidence of perinatal group B streptococcal disease-United States, 1993-95. MMWR 1997;46:473-7.

Centers for Disease Control and Prevention: Prevention of perinatal group B streptococcal disease: A public health perspective. MMWR 1996;45:1-24.

Citernesi A, Formica G, Caruso S, Curiel P. Vaginal colonization of streptococcus B in pregnancy. Minerva Ginecol 1996;48:227-33.

Davies HD, Raj S, Adair C, Robinson J, McGeer A, Group TA. Population-based active surveillance for neoantal group B streptococcal infections in Alberta: implications for vaccine formulation. Pediatr Infect Dis J 2001;20:879-84.

Dillon HC Jr, Gray E, Pass MA, Gray BM. Anorectal and vaginal carriage of group B streptococci during pregnancy. J Infect Dis 1982;145:794-9.

Dillon HC Jr, Khare S, Gray BM. Group B streptococcal carriage and disease: a 6-year prospective study. J Pediatr 1987;110:31-6.

Easmon CS, Hastings MJ, Deeley J, Bloxham B, Rivers RP, Marwood R. The effect of intrapartum chemoprophylaxis on the vertical transmissiom of group B streptococci. Br J Obstet Gynecol 1983;90:633-5.

Eickhoff TC, Klein JO, Daly K, et al. Neonatal sepsis and other infections due to group B beta-hemolytic streptococci. N Engl J Med 1964;271:1221-8.

Fargason CA Jr, Peralta-Carcelen M, Rouse DJ, Cutter GR, Goldenberg RL. The pediatric costs of strategies for minimizing the risk of early-onset group B streptococcal disease. Obstet Gynecol 1997;90:347-52.

Faxelius G, Bremme K, Kvist-Christensen K, Christensen P, Ringertz S. Neonatal septicemia due to group B streptococci- perinatal risk factors and outcome of subsequent pregnancies. J Perinat Med 1988;16:423-30.

Fernandez M, Hickman ME, Baker CJ. Antimicrobial susceptibilies of group B streptococci isolated between 1992 and 1996 from patients with bacteremia or meningitis. Antimicrob Agents Chemother 1998;42:1517-9.

Ferrieri P, Blair LL. Pharyngeal carriage of group B streptococci: detection by three methods. J Clin Microbiol 1977;6:136-9.

Food and Drug Administration (US). FDA safety alert: risks of devices for direct detection of group B streptococcal antigen. Rockville (MD): Dept. of Health and Human Services (US); 1997.

Garland SM, Fliegner JR. Group B streptococcus (GBS) and neonatal infections: the case for intrapartum chemoprophylaxis. Aust NZ J Obstet Gynecol 1991;31:119-22.

Gibbs RS, McDuffie RS Jr, McNabb F, Fryer GE, Miyoshi T, Merenstein G. Neonatal group B streptococcal sepsis during 2 years of a universal screening program. Obstet Gynecol 1994;84:496-500.

Goldenberg E, Davies HD, Landry L, The Toronto GBS study group. Hospital prevention policies and the incidence of early onset neonatal group B streptococcal disease. Abstract presented at the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, 1998;No.1879.

Gordon JS, Sbarra AJ. Incidence, technique of isolation, and treatment of group B streptococci in obstetric patients. Am J Obstet Gynecol 1976;126:1023-6.

Gotoff SP, Boyer KM. Prevention of early-onset neonatal group B streptococcal disease. Pediatrics 1997;99:866-9.

Greenspoon JS, Fishman A, Wilcox JG, Greenspoon RL, Lewis W. Comparison of culture for group B streptococcus.versus enzyme immunoassay and latex agglutination rapid tests: results in 250 patients during labor. Obstet Gynecol 1991;77:97-100.

Hickman ME, Rench MA, Ferrieri P, Baker CJ. Changing epidemiology of group B streptococcal colonization. Pediatrics 1999;104:203-9.

Ho MY, Wu CT, Ku YT, Huang FY, Peng CC. Group B streptococcal infection in neonates: an 11-year review. Taiwan Erh Ko I Hsueh Hui Tsa Chih 1999;40:83-6.

Idsoe O, Guthe T, Willcox RR, de Weck AL. Nature and scope of adverse effects of penicillin with special reference to 151 deaths following anaphylactic shock. Schweiz Med Wochenschr 1969;99:1221-9.

Isaacs D, Royle JA. Intrapartum antibiotics and early onset neonatal sepsis caused by group B streptococcus and by other organisms in Australia. Australasian Study Group for Neonatal Infections. Pediatr Infect Dis J 1999;18:524-8

Jeffery HE, Lahra MM. Eight-year outcome of universal screening and intrapartum antibiotics for maternal group B streptococcal carriers. Pediatrics 1998;101:E2. URL: http://www.pediatrics.org/cgi/content/full/101/1e2.

Jeffery HE, McIntosh ED. Antepartum screening and non- selective intrapartum chemoprophylaxis for group B streptococcus. Aus N Z J Obstet Gynaecol 1994;34:14-9.

Kuruvilla KA, Thomas N, Jesudasan MV, Jana AK. Neonatal group B streptococcal bacteraemia in India: ten years' experience. Acta Paediatr 1999;88:1031-2.

Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. N Engl J Med 1988;318:1728-33.

Lim DV, Morales WJ, Walsh AF, Kazanis D. Reduction of morbidity and mortality rates for neonatal group B streptococcal disease through early diagnosis and chemoprophylaxis. J Clin Microbiol 1986;23:489-92.

Matorras R, Garcia-Perea A, Omenaca F, Diez-Enciso M, Madero R, Usandizaga JA. Intrapartum chemoprophylaxis of early-onset group B streptococcal disease. Eur J Obstet Gynecol Reprod Biol 1991;40:57-62.

Mercer BM, Carr TL, Beazley DD, Crouse DT, Sibai BM. Antibiotic use in pregnancy and drug-resistant infant sepsis. Am J Obstet Gynecol 1999;181:816-21.

Mohle-Boetani JC, Lieu TA, Ray GT, Escobar G. Preventing neonatal group B streptococcal disease: cost-effectiveness in a health maintenance organization and the impact of delayed hospital discharge for newborns who received intrapartum antibiotics. Pediatrics 1999;103;703-10.

Mohle-Boetani JC, Schuchat A, Plikaytis BD, Smith JD, Broome CV. Comparison of preventive strategies for neonatal group B streptococcal infection. A population-based economic analysis. JAMA 1993;270:1442-8.

Morales WJ, Dickey SS, Bornick P, Lim DV. Change in antibiotic resistance of group B streptococcus: impact on intrapartum management. Am J Obstet Gynecol 1999;181:310-4.

Morales WJ, Lim D. Reduction of group B streptococcal maternal and neonatal infections in preterm pregnancies with premature rupture of membranes through a rapid identification test. Am J Obstet Gynecol 1987;157:13-6.

Morales WJ, Lim DV, Walsh AF. Prevention of neonatal group B streptococcal sepsis by the use of a rapid screening test and selective intrapartum chemoprophylaxis. Am J Obstet Gynecol 1986;155:979-83.

Moses LM, Heath PT, Wilkinson AR, Jeffery HE, Isaacs D. Early onset group B streptococcal neonatal infection in Oxford 1985-96. Arch Dis Child 1998;79:148-9.

Noya FJ, Rench MA, Metzger TG, Colman G et al. Unusual occurrence of an epidemic of type Ib/c group B streptococcal sepsis in a neonatal intensive care unit. J Infect Dis 1987;155:1135-44.

Ohlsson A, Myhr TL. Intrapartum chemoprophylaxis of perinatal group B streptococcal infections: A critical review of randomized controlled trials. Am J Obstet Gynecol 1994;170:910-7.

Pearlman MD, Pierson CL, Faix RG. Frequent resistance of clinical group B streptococci isolates to clindamycin and erythromycin. Obstet Gynecol 1998;92:258-61.

Philipson EH, Palermino DA, Robinson A. Enhanced antenatal detection of group B streptococcus colonization. Obstet Gynecol 1995;85:437-9.

Poulain P, Betremieux P, Donnio PY, Proudhon JF, Karege G, Giraud JR. Selective intrapartum anti-bioprohylaxy of group B streptococci infection of neonates: a prospective study in 2454 subsequent deliveries. Eur J Obstet Gynecol Reprod Biol 1997;72:137-40.

Pylipow M, Gaddis M, Kinney JS. Selective intrapartum prophylaxis for group B streptococcus colonization: management and outcomes of newborns. Pediatrics 1994;93:631-5.

Regan JA, Klebanoff MA, Nugent RP et al. Colonization with group B streptococci in pregnancy and adverse outcome. VIP Study Group. Am J Obstet Gynecol 1996;174:1354-60.

Rouse DJ, Goldenberg RL, Cliver SP, Cutter GR, Mennemeyer ST, Fargason CA Jr. Strategies for the prevention of early-onset neonatal group B streptococcal sepsis: a decision analysis. Obstet Gynecol 1994;83:483-94.

Scharg SJ, Zywicki S, Farley MM, Reingold AL, Harrison LH, Lefkowitz LB et al. Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis. N Engl J Med 2000;342:15-20.

Schimmel MS, Eidelman AI, Rudensky B, Tadmor OP, Isacsohn M et al. Epidemiology of group B streptococcal colonization and infection in Jerusalem, 1989-1991. Isr J Med Sci 1994;30:349-51.

Schuchat A, Deaver-Robinson K, Plikaytis BD, Zangwill KM, Mohle-Boetani J, Wenger JD. Multistate case-control study of maternal risk factors for group B streptococcal disease. The Active Surveillance Study Group. Pediatr Infect Dis J 1994;13:623-9.

Schuchat A, Oxtoby M, Cochi S, Sikes RK, Hightower A, Plikaytis B, Broome CV. Population-based risk factors for neonatal group B streptococcal disease: Results of a cohort study in metropolitan Atlanta. J Infect Dis 1990;162:672-7.

Shah V, Ohlsson A. Perinatal group B streptococcal infections. In: Newell M-L, McIntyre J. Congenital and perinatal infections. Prevention, diagnosis and treatment. Cambridge University Press, Cambridge, 2000. Pp. 96-121.

Silver HM, Struminsky J. A comparison of the yield of positive antenatal group B streptococcus cultures with direct inoculation in selective growth medium versus primary inoculation in transport medium followed by delayed inoculation in selective growth medium. Am J Obstet Gynecol 1996;175:155-7.

Society of Obstetricians and Gynaecologists of Canada, Canadian Pediatric Society. National consensus statement on the prevention of early-onset group B streptococcal infections in the newborn. J Soc Obstet Gynaecol Can 1994;16:2271-8.

Society of Obstetricians and Gynecologists. Statement on the prevention of early-onset group B streptococcal infections in the newborn. J Soc Obstet Gynaecol 1997;19:751-8.

Stoll BJ, Schuchat A. Maternal carriage of group B streptococci in developing countries. Pediatr Infect Dis J 1998;17:499-503.

Strickland DM, Yeomans ER, Hankins GD. Cost-effectiveness of intrapartum screening and treatment for maternal group B streptococci colonization. Am J Obstet Gynecol 1990;163:4-8.

Terry RR, Kelly FW, Gauzer C, Jeitler M. Risk factors for maternal colonization with group B beta-hemolytic streptococci. J Am Osteopath Assoc 1999;99:571-3.

Towers CV, Carr MH, Padilla G, Asrat T. Potential consequences of widespread antepartal use of ampicillin. Am J Obstet Gynecol 1998;179:879-83.

Tuppurainen N, Hallman M. Prevention of neonatal group B streptococcal disease: intrapartum detection and chemoprophylaxis of heavily colonized parturients. Obstet Gynecol 1989;73:583-7.

Tuppurainen N, Osterlund K, Hallman M. Selective intrapartum penicillin prophylaxis of early onset group B streptococcal disease. Pediatr Res 1986;20:403A.

Woolf SH, Battista RN, Anderson GM, Logan AG, Wang E and other members of the Canadian Task Force on the Periodic Health Examination. Assessing the clinical effectiveness of preventive maneuvers: Analytic principles and systematic methods in reviewing evidence and developing clinical practice recommendations. J Clin Epidemiol 1990;43:891-905.

Yancey MK, Armer T, Clark P, Duff P. Assessment of rapid identification tests for genital carriage of group B streptococci. Obstet Gynecol 1992;80:1038-47.

Yancey MK, Duff P. An analysis of the cost-effectiveness of selected protocols for the prevention of neonatal group B streptococcal infection. Obstet Gynecol 1994;83:367-71.

Yancey MK, Schuchat A, Brown LK, Ventura VL, Markenson GR. The accuracy of late antenatal screening cultures in predicting genital group B streptococcal colonization at delivery. Obstet Gynecol 1996;88:811-5.

Yow MD, Leeds LJ, Thompson PK, Mason EO Jr, Clark DJ, Beachler CW. The natural history of group B streptococcal colonization in the pregnant women and her offspring. I. Colonization studies. Am J Obstet Gynecol 1980;137:34-8.

Yow MD, Mason EO, Leeds LJ, Thompson PK, Clark DJ, Gardner SE. Ampicillin prevents intrapartum transmission of group B streptococcus. JAMA 1979;241:1245-7.

Zangwill KM, Schuchat A, Wenger JD. Group B streptococcal disease in the United States,1990: report from a multistate active surveillance system. Mor Mortal Wkly Rep CDC Surveill Summ 1992;41;25-32.

Table 1: Description of group B streptococcal (GBS) infection in newborns by age at onset

Onset	Definition and signs at presentation	Incidence	Death rate, %
Early	• Occurs in infants < 1 wk old • Acquired through vertical transmission from colonized mothers • Clinical presentations include sepsis, pneumonia and meningitis (Baker, 1995; Davies, 2001)	1–3 per 1000 live births (declined to 0.6 per 1000 live births in active surveillance areas in the United States) (Regan, 1996; Zangwill, 1992; Goldenburg, 1998; Scharg, 2000) 0.42 per 1000 total births in Alberta during 1995–1999 (Davies, 2001)	4.7 (Scharg, 2000) 9.0 (Davies, 2001)
Late	• Occurs in infants older than 1 wk • Acquired either by vertical transmission (delayed infection after early colonization in 50% of cases) (Dillon, 1987) or by horizontal transmission (in hospital or in the community) (Noya, 1987) • Meningitis is most common presentation (in 85% of cases) (Baker, 1995)	0.22 per 1000 total births in Alberta during 1995–1999 (Davies, 2001)	2.8 (Dillon, 1987) 2.0 (Davies, 2001)

Table 2: Effectiveness of selective IPC treatment on neonatal colonization for colonized women with risk factors identified by screening (RCT)

Comparison:	Effectiveness of Selective IPC					
Outcome:	Neonatal colonization					
Study	Expt n/N	Ctrl n/N	Relative Risk (95%CI Fixed)		Weight %	RR (95%CI Fixed)
Boyer 1986	8 / 85	40 / 79			100.0	0.19 [0.09,0.37]
Total (95%CI)	8 / 85	40 / 79			100.0	0.19 [0.09,0.37]
Chi-square 0.00 (df=0) Z=4.75						

.1   .2   1   5   10
Favours Treatment   Favours Control
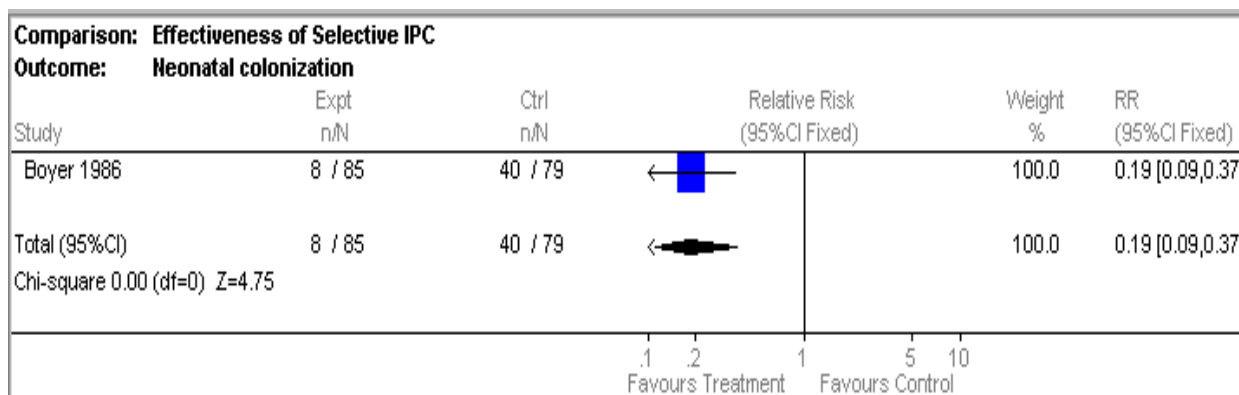
Table 3: Effectiveness of selective IPC treatment on EOD for colonized women with risk factors identified by screening (RCT)

Comparison:	Effectiveness of Selective IPC					
Outcome:	Early onset GBS disease					
Study	Expt n/N	Ctrl n/N	Relative Risk (95%CI Fixed)		Weight %	RR (95%CI Fixed)
Boyer 1986	0 / 85	4 / 79			100.0	0.10 [0.01,1.89]
Total (95%CI)	0 / 85	4 / 79			100.0	0.10 [0.01,1.89]
Chi-square 0.00 (df=0) Z=1.53						

.1   .2   1   5   10
Favours Treatment   Favours Control
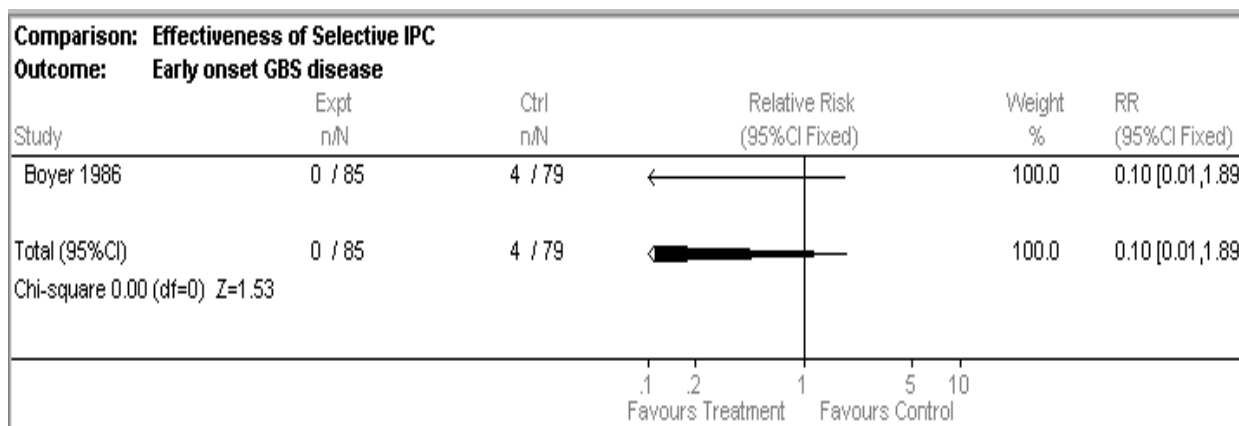
Table 4: Effectiveness of selective IPC treatment on EOD for colonized women with risk factors identified by screening (Cohort studies)

Comparison:	Effectiveness of Selective IPC					
Outcome:	Early onset GBS disease					
Study	Expt n/N	Ctrl n/N	Relative Risk (95%CI Fixed)		Weight %	RR (95%CI Fixed)
Gibbs 1994	0 / 114	5 / 28			33.0	0.02 [0.00,0.40]
Morales 1987	0 / 36	13 / 48			43.7	0.05 [0.00,0.80]
Pylipow 1994	0 / 70	5 / 54			23.3	0.07 [0.00,1.25]
Total (95%CI)	0 / 220	23 / 130			100.0	0.05 [0.01,0.24]
Chi-square 0.31 (df=2) Z=3.65						

.1   .2   1   5   10
Favours Treatment   Favours Control

Table 5: Effectiveness of IPC treatment on neonatal colonization in populations identified by screening (RCTs)

Comparison:	Effectiveness of Universal screening and IPC					
Outcome:	Neonatal colonization					
Study	Expt n/N	Ctrl n/N	Relative Risk (95%CI Fixed)	Weight %	RR (95%CI Fixed)	
Easmon 1983	0 / 38	17 / 49		39.4	0.04 [0.00,0.59]	
Matorras 1991	2 / 54	24 / 56		60.6	0.09 [0.02,0.35]	
Total (95%CI)	2 / 92	41 / 105		100.0	0.07 [0.02,0.23]	
Chi-square 0.31 (df=1) Z=4.22						

.1 .2 1 5 10
Favours Treatment   Favours Control

Table 6: Effectiveness of IPC treatment on EOD in populations identified by screening (RCTs)

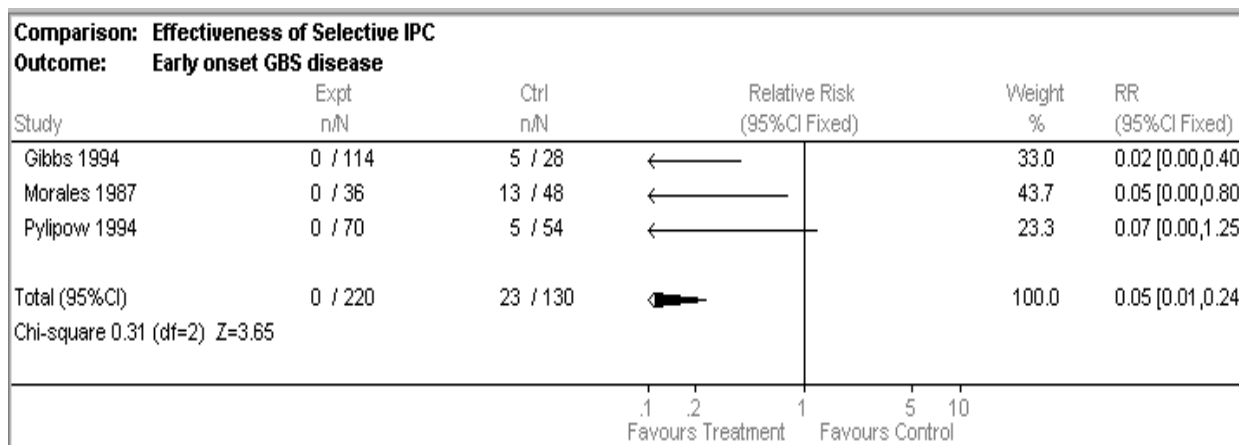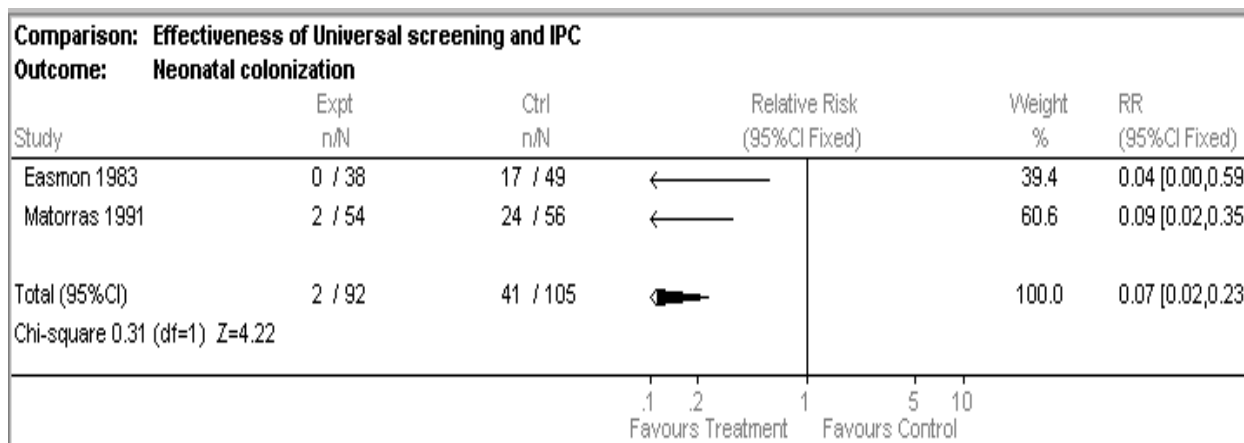| Comparison:	Effectiveness of Universal screening and IPC					
Outcome:	Early onset GBS disease					
Study	Expt n/N	Ctrl n/N	Relative Risk (95%CI Fixed)	Weight %	RR (95%CI Fixed)	
Matorras 1991	0 / 60	3 / 65		43.2	0.15 [0.01,2.93]	
Tuppurainen 1989	1 / 88	5 / 111		56.8	0.25 [0.03,2.12]	
Total (95%CI)	1 / 148	8 / 176		100.0	0.21 [0.04,1.17]	
Chi-square 0.07 (df=1) Z=1.78						

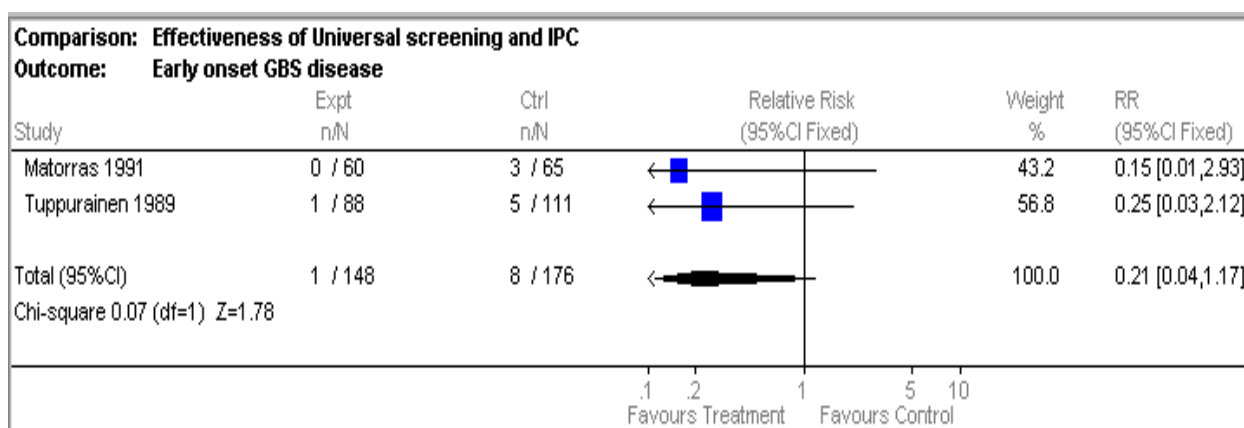.1 .2 1 5 10
Favours Treatment   Favours Control

Table 7: Effectiveness of IPC treatment on neonatal colonization in populations identified by screening (Cohort studies)

Comparison:	Effectiveness of Universal screening and IPC					
Outcome:	Neonatal colonization					
Study	Treatment n/N	Control n/N	RR (95%CI Fixed)	Weight %	RR (95%CI Fixed)	
Allardice 1982	4 / 57	62 / 136		68.4	0.15[0.06,0.40]	
Yow 1979	0 / 34	14 / 24		31.6	0.02[0.00,0.39]	
Total(95%CI)	4 / 91	76 / 160		100.0	0.11[0.05,0.27]	
Test for heterogeneity chi-square=1.56 df=1 p=0.21						
Test for overall effect z=-4.91 p<0.00001						

.1 .2 1 5 10
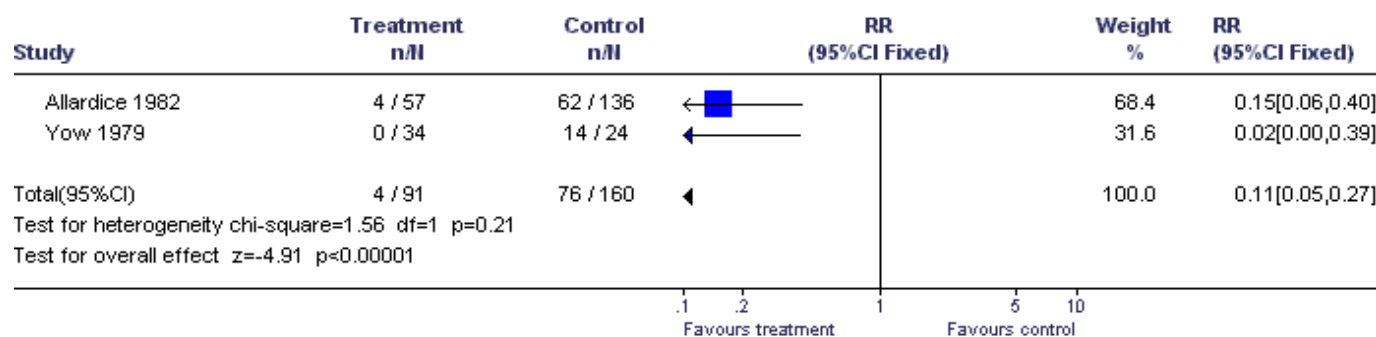Favours treatment   Favours control

Table 8: Number (women) needed to treat with antibiotics based on preventive strategies [point estimate, 95% confidence interval (CI)]

Outcomes (Study design)	Universal screening of pregnant women and selective IPC of colonized women with risk factors	Universal screening of pregnant women and IPC to all colonized women
Neonatal colonization (RCT)	2.4 (2, 4)	3 (2, 4)
Neonatal colonization (Cohort studies)	Not available	2.3 (1.9, 3)
EOD (Cohort studies)	6 (4, 10)	16 (9, 84) (Allardice, 1982) 2059 (1062, 32968) (Garland, 1991)

Table 9. Summary of recommendations: Prevention of early-onset group B streptococcal (GBS) infection in the newborn

Maneuver	Effectiveness	Level of Evidence <Refs>	Recommendation
Universal screening* of pregnant women for GBS colonization and selective IPC** to colonized women with risk factors***	Clinical effectiveness is proven for reduction in neonatal colonization and early onset neonatal disease. Associated with low level of antibiotic use. Dependent on compliance with screening and availability of adequate laboratory resources. Use of penicillin may lead to selection of antibiotic resistant bacteria and increases the risk of allergic reactions in women. Not effective for women who do not receive prenatal care.	Small cohort studies (II-1, II-2), <Morales, 1987; Pylipow, 1994; Gibbs, 1994>.	The CTFPHC concludes that there is fair evidence to recommend this strategy in reducing neonatal colonization and early onset neonatal disease. (**B Recommendation**) *Most efficient strategy based on number needed to treat.*
Universal screening* of pregnant women for GBS colonization and intrapartum chemoprophylaxis (IPC**) to all colonized women	Clinical effectiveness is proven for reduction in neonatal colonization and early onset neonatal disease. Associated with high level of antibiotic use. Dependent on compliance with screening and availability of adequate laboratory resources. Increased use of penicillin may lead to selection of antibiotic resistant bacteria and increases the risk of allergic reactions in women. Not effective for women who do not receive prenatal care.	Based on cohort studies (II-2), <Allardice , 1982; Garland, 1991>.	The CTFPHC concludes that there is fair evidence to recommend this strategy in reducing neonatal colonization and early onset neonatal disease (**B Recommendation**).
IPC** based on risk factors only	The effectiveness of a risk factors based strategy has not been evaluated.	Insufficient evidence available	The CTFPHC concludes that there is insufficient evidence to recommend for or against risk factor based strategy to reduce early onset neonatal disease (**C Recommendation**).

*Collection of antenatal cultures (swab from lower vagina and rectum) should occur at 35-37 weeks gestation. Swabs should be inoculated into selective broth medium, followed by overnight incubation and then subcultured onto solid blood agar medium.

**Currently adequate IPC consists of at least one dose of intravenous penicillin (5 million units) given at least 4 hours prior to birth. If labour continues beyond 4 hours penicillin (2.5 million units) should be administered every 4 hours until delivery (CDC, 1996). Clindamycin 900 mg IV every 8 hours or erythromycin 500 mg IV every 6 hours until delivery are recommended for women allergic to penicillin (CDC, 1996).

***Risk factors include 1) preterm labor (< 37 weeks gestation), 2) prolonged rupture of membranes ≥ 18 hours, 3) maternal fever ≥ 38.0^0C, 4) group B streptococcus bacteriuria during pregnancy and 5) previous delivery of a newborn with group B streptococcus disease regardless of current group B streptococcus colonization

<u>**Cautionary note**</u>**: The emerging resistance to erythromycin and clindamycin among GBS strains is of concern.**

Appendix 1:
Levels of Evidence and Grades of Recommendations
of the Canadian Task Force on Preventive Health Care

Levels of evidence

I   Evidence from at least one well-designed randomized controlled trial

II-1   Evidence from well-designed controlled trials without randomization

II-2   Evidence from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group

II-3   Evidence from comparisons between times or places with or without the intervention; dramatic results from uncontrolled studies could be included here

III   Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert Committees

Grades of recommendations

A   Good evidence to support the recommendation that the condition or manoeuvre be specifically considered in a periodic health examination (PHE)

B   Fair evidence to support the recommendation that the condition or manoeuvre be specifically considered in a PHE

C   Insufficient evidence regarding inclusion or exclusion of the condition or manoeuvre in a PHE, but recommendations may be made on other grounds

D   Fair evidence to support the recommendation that the condition or manoeuvre be specifically excluded from a PHE

E   Good evidence to support the recommendation that the condition or manoeuvre be specifically excluded from a PHE