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Prevention of group B streptococcal neonatal disease revisited. The DEVANI European project

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Abstract The purpose of this paper was to present the current knowledge on the prevention of group B streptococcus (GBS) neonatal infections and the status of prevention policies in European countries and to present the DEVANI pan-European program, launched in 2008. The aim of this program was to assess the GBS neonatal infection burden in Europe, to design a new vaccine to immunize neonates against GBS infections, to improve the laboratory performance for the diagnosis of GBS colonization and infection, and to improve the methods for the typing of GBS strains. The current guidelines for GBS prevention in different countries were ascertained and a picture of the burden before and after the instauration of prevention policies has been drawn. After the issue of the Centers for Disease Control and Prevention (CDC) guidelines, many European countries have adopted universal screening for the GBS colonization of pregnant women and intrapartum

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prophylaxis to colonized mothers. Nevertheless, some European countries continue advocating the risk factor approach to GBS prevention. Most European countries have implemented policies to prevent GBS neonatal infections and the burden of the disease has decreased during the last several years. Nevertheless, further steps are necessary in order to develop new strategies of prevention, to improve microbiological techniques to detect GBS colonization and infection, and to coordinate the prevention policies in the EU.

Background

Streptococcus agalactiae, also known as group B streptococcus (GBS), is a commensal bacterium that asymptomatically colonizes the gastrointestinal and genitourinary tract of up to 30% of healthy adults [1, 2].

The reported rate of GBS colonization in European countries among pregnant women ranges from 4% to 36%, with most studies reporting rates higher than 20% [3], with important variations from country to country and even from hospital to hospital in the same country [3, 4]. The variations in the reported prevalence of asymptomatic GBS colonization could be related to the sample sites, methods used for the detection of the organism, and demographic differences in populations [3–5].

GBS is also a leading cause of sepsis and meningitis in newborns (NBs) during the first seven days of life (early-onset GBS disease, EO-GBSD). The vast majority of cases present during the first 24 h of life and the most common EO-GBSD infection is bacteremia (non-focal), also pneumonia or meningitis, and, less commonly, joint and bone involvement [1, 2, 6–8]. Infants with GBS infections after the first week of life (late-onset GBS disease, LO-GBSD) commonly present with bacteremia and frequently develop meningitis [1, 2, 6, 7, 9, 10].

Overall, the case–fatality rates from EO-GBSD have declined, from 20–50% observed in studies from the 1970s to 4–6% in recent years, as a consequence of improvements in therapy and management [1, 2, 7, 9, 11–15]. EO-GBSD is also associated with significant morbidity and GBS meningitis leaves half of the infected NBs with long-term neurodevelopmental defects [2, 16].

GBS can also cause endometritis, chorioamnionitis, and bacteremia in pregnant women, and significant morbidity and mortality in nonpregnant adults, mainly amongst immunocompromised individuals [1]. Vertical transmission from mother to the NB occurs at delivery in about 50% of neonates whose mothers are colonized with GBS [1, 2, 17]. In the absence of any intervention, 1–2% of NBs born to GBS-colonized mothers may develop EO-GBSD [18].

There are well-defined maternal risk factors that favor the development of EO-GBSD in an exposed infant; these include premature birth, maternal chorioamnionitis, prolonged membrane rupture (>18 h), intrapartum fever (≥38°C), a previous sibling with EO-GBSD, and GBS bacteriuria during the current pregnancy [2, 18, 19]. Another risk factor is exposure to a high maternal inoculum of a virulent GBS strain [2, 20, 21]. Nevertheless, the majority of the neonates developing EO-GBSD are born to mothers who do not present with any risk factors [19].

GBS are bacteria encapsulated by a rich sialic acid capsular exopolysaccharide (CPS). There are ten antigenically and structurally distinct capsular polysaccharide serotypes (Ia, Ib, II–IX) [1, 2, 22]. CPS is, among many others, a major virulence factor that helps GBS to evade the host's defense mechanisms and prevents phagocytosis of GBS by the host's immune system [2, 23]. Another important risk factor for EO-GBSD is a low concentration of maternal antibodies to the type-specific CPS antigens of the colonizing strain at delivery [24].

In the US, the incidence of EO-GBSD remained almost constant, between 1 and 3 per 1,000 live births before preventive intervention [11, 19, 25, 26]. In Europe, prior to 2000, the reported incidence (per 1,000 live births) of EO-GBSD varied between 0.2 and 0.3 of early reports from Denmark [27] to 0.76 in Finland [28], 0.69 to 4.5 in France [29, 30], 3.25 in the Czech Republic [31], and 2.4 in Spain [32].

Intrapartum antibiotic prophylaxis and prevention of GBS neonatal infection

The current era of intrapartum antibiotic prophylaxis (IAP) for EO-GBSD prevention dates from 1986 [33], when it was demonstrated that the administration of intravenous penicillin

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or ampicillin to GBS-colonized pregnant women during delivery prevents the mother-to-NB transmission of GBS; therefore, this is an effective way of preventing EO-GBSD. The efficacy of IAP to prevent EO-GBSD is estimated at around 80% [34, 35], but, unfortunately, in contrast, there are no preventative strategies for LO-GBSD; IAP is ineffective upon LO-GBSD incidence [10, 36]. The administration of antibiotics to women trying to eradicate GBS colonization before delivery is not efficacious [37].

The first Centers for Disease Control and Prevention (CDC) guidelines for GBS prevention were issued in 1996 in the US [11] following the seminal paper from Gibbs et al. [38]. These guidelines recommended the use of either a screening-based or a risk-based approach to identify mothers who are candidates for IAP. The risk-based approach provided IAP to women who had any of the above-mentioned risk factors. The screening-based approach proposed routine prenatal GBS screening between 35 and 37 weeks gestation, and recommended IAP for all women who are either colonized, or who presented in labor before 37 weeks of gestation, or whose colonization status was unknown, and those with risk factors. It has been documented that the risk-based strategy which targets women with one or more risk factors can prevent approximately 50% of all EO-GBSD cases and IAP given to women with two or more risk factors might prevent only approximately 30% of cases [34, 35]. In 2002, updated guidelines were published by the CDC that shifted away from the risk-based approach and recommended the universal screening approach [19]. More recently, the CDC guidelines were again updated, but there were no major changes regarding IAP [12].

In the US, upon recommendation of IAP, the incidence of EO-GBSD declined to 0.5 per 1,000 live births, with a further reduction to 0.3 to 0.4 per 1,000 live births following the recommendation for universal screening [36, 39].

After the first CDC guidelines were issued in 1996 and then updated in 2002, most European countries launched national guidelines for GBS prevention. Guidelines based upon a preventative approach with screening and IAP for all GBS carriers were developed in Italy in 1996 [40], Spain in 1998 and 2003 [41, 42], France in 2001 [43], Germany in 1996 and 2008 [44], Switzerland in 2007 [45], the Czech Republic in 2008 [46], Belgium in 2003 [47], and Poland in 2008 [48]. In contrast, risk factor-based guidelines were issued in the Netherlands in 1999 (revised in 2008) [49] and in the UK [50]. Similar guidelines based also on the risk factor approach were also issued in New Zealand [51]. In developed countries, a significant decrease in EO-GBSD occurred when a prevention policy had been established, e.g., in Australia, the incidence fell from 1.43 per 1,000 live births in 1993 to 0.25 in 2001 [52], and in Spain, the incidence declined from 2.4/1,000 live births in 1996 to 0.33 in 2008 [32].

Even after the implementation of EO-GBSD prevention policies, GBS continues to be an important cause of neonatal sepsis and meningitis in the US [8, 53] and in Europe. The current reported incidence (per 1,000 live births) varies in different European countries between 0.23 reported in France and 1.22 in the Czech Republic [14, 30–32, 54–62].

In marked contrast with the decreasing incidence of EO-GBSD, the incidence of LO-GBSD remained the same even after the implementation of maternal IAP for GBS neonatal disease prevention [10, 60, 63].

Immunoprophylaxis

More than 70 years after Rebecca Lancefield [64] demonstrated that it was possible to protect mice against GBS infection using a specific antiserum raised in rabbits against GBS CPS, all GBS clinicians and researchers would agree that (if it were feasible) the best strategy to fight GBS infections would be the development of an effective vaccine [2, 9, 10, 12, 65, 66], especially in view of the fact that current prevention strategies are not useful for the prevention of LO-GBSD [10, 12, 67] and that the burden of invasive GBS disease beyond the neonatal period is constantly increasing [1, 9, 68].

Antibodies against GBS CPS provide serotype-specific protection and maternal immunization against GBS to increase the level of protective CPS type-specific antibodies is an appealing approach for the prevention of both EO-GBSD and LO-GBSD. Polysaccharide conjugate vaccines are currently the most promising, with GBS protein vaccines also under development [2, 10, 69, 70].

The main difficulty in developing a globally effective GBS vaccine based on protein-conjugated CPS is the existence of different serotypes with heterogeneous geographical distributions. And knowledge of the serotype distribution is essential for the selection and development of serotype-based vaccines in a given geographic area [70–72].

Meanwhile, the problem is being resolved by a potential new generation of GBS vaccines which incorporate, in addition to conjugated CPS, immunogenic surface proteins from GBS and also pili [73]. The administration of a GBS vaccine to pregnant women is problematic because of fears of risks of birth defects and the potential for subsequent liability [74]. In addition, there is considerable discussion among experts regarding the most appropriate target population for immunization; nonpregnant adolescents or pregnant women in the third trimester [72]. Moreover, given the current use of IAP, it would be difficult to design a controlled clinical trial to determine the efficacy of a GBS vaccine [73, 74]. The real impact and usefulness of any vaccine against the GBS disease burden will, however, not

be known until the development of such a vaccine is completed by the pharmaceutical industry.

The DEVANI program

To assess the current GBS burden in Europe and to facilitate the design of a new vaccine to immunize neonates against GBS infections, a pan-European program (European Commission Seventh Framework Programme [FP7]) known as DEVANI (*De*sign of a *V*accine *A*gainst *N*eonatal *I*nfections) was launched in 2008. Eight European countries participate within the program (Belgium, Bulgaria, Czech Republic, Denmark, Germany, Italy, Spain, and the UK), together with Novartis Vaccines [70].

The reported differences of GBS carriage between the prenatal and labor periods and the fact that the majority of recent cases of EO-GBSD occur in NBs to prenatally GBS-negative mothers [5, 12, 61] emphasizes the need for a reliable and rapid procedure for the detection of GBS carriers at delivery to guide the administration of IAP. Because of that, it is necessary to improve laboratory microbial methods for the accurate detection of GBS in pregnant women [12].

The DEVANI consortium is working towards the standardization and improvement of laboratory performance for the diagnosis of maternal GBS colonization and neonatal infections in the EU. The consortium is also working on improvements of the methods used for the serotyping and molecular typing of European GBS strains [75]. Existing policies and recommendations for the prevention of EO-GBSD disease among various European countries have also been reviewed under the auspices of the DEVANI program. The project provides a unique opportunity to address all these issues on a pan-European scale [75]. The overall aim of the DEVANI project is to assess European GBS epidemiology in order to facilitate the design of a new vaccine to immunize neonates against GBS infections through a durable maternal immune response.

For these reasons, the DEVANI consortium has collected GBS strains from cases of neonatal disease from across Europe to understand the distribution of GBS types and to select the most appropriate for inclusion in a future vaccine.

The project is also monitoring the level of maternal antibodies of both healthy GBS carriers and GBS-infected children. The project includes also studies in vitro and in vivo in mice to identify appropriate adjuvant and delivery systems capable of inducing strong, long-lasting protective response in the mothers. Sera and strains have been collected by all the participating countries. Strains are being typed and studied to determine the presence of specific antigens to be included in a future vaccine. In parallel, the level of maternal antibodies required for protection is being assessed.

Remaining questions

Even when a prevention policy is in place, missed opportunities for GBS prevention—mainly the lack of compliance with the recommendations and the failure of the laboratory to detect GBS in pregnant women accurately—still accounts for a consistent proportion of EO-GBSD cases [8, 12, 35, 63, 76].

The definition of EO-GBSD cases based upon the isolation of GBS from a normally sterile site (such as blood and cerebrospinal fluid) is likely to underestimate the real burden of the disease. The low yield of isolation of GBS from blood drawn from sick babies could be due to the antibiotics administered to mothers before delivery that would hamper the growth of GBS in neonatal cultures; limitations of the blood volume from neonates inoculated for culture would also potentially affect the bacterial recovery rate. Several studies have suggested that the real incidence of EO-GBSD could be 1–3-fold higher than that defined by positive sterile site cultures alone [35, 77, 78].

It has also been documented that prevention protocols greatly increase the proportion of women who receive antibiotics during labor [12, 14] and delivery, and this could increase the risk of neonatal sepsis caused by resistant *Enterobacteriaceae*. Though some alarming reports on this matter have been published [79, 80] in the early days of GBS prevention by IAP, an increase in Gram-negative neonatal infections related to IAP was not confirmed in later studies [32, 81, 82], and repeat cultures 6 weeks after delivery have shown that IAP is not associated with increased antibiotic resistance for *Escherichia coli* isolated from the vaginorectal tract [83]. Although neonatal sepsis caused by Gram-negative bacteria is more often a disease of prematurity, the severity of resistant *E. coli* neonatal infections suggests caution and highlights the need for surveillance regarding the widespread use of IAP [8, 12, 14, 32]. A concern that should also favor the use of penicillin G instead of ampicillin in IAP is to eliminate the potential selection of resistant Gram-negative bacteria.

It has also been advocated that universal screening and IAP medicalizes pregnancy, and more than 30% of otherwise healthy women would receive intravenous antibiotics [12, 14]. Another unsettled question is what is the best strategy to manage well-appearing NBs born to mothers who are GBS carriers, either exposed to correct IAP (more than 4 h) or not [12, 39, 84].

It has been suggested that ”when the incidence of early onset streptococcal infection is low, expensive preventive measures may not be justified”, but there is no concrete consensus recommendation as to the best strategy for the prevention of EO-GBSD today [7, 9, 15, 85, 86]. Nowadays, even the layperson is seriously concerned about GBS disease and GBS support associations and forums have been established in many countries, e.g., UK, Group B Strep Support

[87]; Netherlands, Dutch Foundation [88]; USA, Group B Strep Association [89]; Argentina [90]; and Canada [91].

Summary

More than 40 years after the dramatic emergence of the disease [92], GBS still remains a major cause of threatening infections in NBs. Thirty years after the rationale of IAP was established [33], it is evident that EO-GBSD is still a very important cause of suffering for parents and NBs that is largely preventable with currently available methods. Nevertheless, there is no currently available strategy for the prevention of LO-GBSD, which is responsible for most meningitis cases [3, 10, 36]. In this scenario, the development of a new vaccine to immunize neonates against GBS infections is a most promising possibility for the near future. Quoting an American colleague [93], we can still confirm, as we wrote ten years ago [94], "First and foremost, we must not ignore the problem. Neonatal group B streptococcal infection is more prevalent than many other conditions we screen for in pregnancy and the effect can be just as devastating." So, perhaps the time has now arrived for European obstetricians, neonatologists, infectious diseases physicians, and clinical microbiologists to look together and deeper into the issue of the prevention of GBS neonatal infection.

We now have the opportunity and the means to reach a European consensus on GBS neonatal disease prevention policies through the DEVANI program.

We, therefore, believe that we as countries should support the DEVANI project; to develop an effective GBS vaccine, to improve GBS diagnostic techniques, to constitute a European network on the epidemiology of neonatal GBS infection in Europe in order to obtain a true picture of the disease burden, to inform the medical community and health authorities as well as parents and families, and, perhaps, to develop a European policy for the prevention of devastating neonatal GBS disease.

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The researchers are not dependent on the founder.

References

1. Edwards MS, Baker CJ (2010) *Streptococcus agalactiae* (group B streptococcus). In: Mandell GL, Bennett JE, Dolin R (eds) Principles and practice of infectious diseases. Vol 2, 7th edn. Elsevier, Philadelphia, Chapter 202
2. Edwards MS, Nizet V (2011) Group B streptococcal infections. In: Remington JS, Klein JO, Wilson CB, Nizet V, Maldonado YA (eds) Diseases of the fetus and newborn infant, 7th edn. Elsevier, Philadelphia, pp 419–469
3. Barcaite E, Bartusevicius A, Tameliene R, Kliucinskas M, Maleckiene L, Nadisauskiene R (2008) Prevalence of maternal group B streptococcal colonisation in European countries. Acta Obstet Gynecol Scand 87:260–271
4. Stupak A, Kwaśniewska A, Semczuk M, Zdzienicka G, Malm A (2010) The colonization of women genital tract by *Streptococcus agalactiae*. Arch Perinatal Med 16:48–50
5. Lin FYC, Weisman LE, Azimi P, Young AE, Chang K, Cielo M, Moyer P, Troendle JF, Schneerson R, Robbins JB (2011) Assessment of intrapartum antibiotic prophylaxis for the prevention of early-onset group B streptococcal disease. Pediatr Infect Dis J 30:759–763
6. Koenig JM, Keenan WJ (2009) Group B streptococcus and early-onset sepsis in the era of maternal prophylaxis. Pediatr Clin North Am 56:689–708
7. Verani JR, Schrag SJ (2010) Group B streptococcal disease in infants: progress in prevention and continued challenges. Clin Perinatol 37:375–392
8. Stoll BJ, Hansen NI, Sánchez PJ, Faix RG, Poindexter BB, Van Meurs KP, Bizzarro MJ, Goldberg RN, Frantz ID 3rd, Hale EC, Shankaran S, Kennedy K, Carlo WA, Watterberg KL, Bell EF, Walsh MC, Schibler K, Laptook AR, Shane AL, Schrag SJ, Das A, Higgins RD; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (2011) Early onset neonatal sepsis: The burden of group B streptococcal and *E. coli* disease continues. Pediatrics 127:817–826
9. Schrag SJ, Zywicki S, Farley MM, Reingold AL, Harrison LH, Lefkowitz LB, Hadler JL, Danila R, Cieslak PR, Schuchat A (2000) Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis. N Engl J Med 342:15–20
10. Jordan HT, Farley MM, Craig A, Mohle-Boetani J, Harrison LH, Petit S, Lynfield R, Thomas A, Zansky S, Gershman K, Albanese BA, Schaffner W, Schrag SJ; Active Bacterial Core Surveillance (ABCs)/Emerging Infections Program Network, CDC (2008) Revisiting the need for vaccine prevention of late-onset neonatal group B streptococcal disease: a multistate, population-based analysis. Pediatr Infect Dis J 27:1057–1064
11. Centers for Disease Control and Prevention (CDC) (1996) Prevention of perinatal group B streptococcal disease: a public health perspective. Centers for Disease Control and Prevention. MMWR Recomm Rep 45:1–24
12. Verani JR, McGee L, Schrag SJ; Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC) (2010) Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC, 2010. MMWR Recomm Rep 59:1–32
13. Gibbs RS, Schrag S, Schuchat A (2004) Perinatal Infections due to group B streptococci. Obstet Gynecol 104:1062–1076
14. Heath PT, Schuchat A (2007) Perinatal group B streptococcal disease. Best Pract Res Clin Obstet Gynaecol 21:411–424
15. Ohlsson A, Shah VS (2009) Intrapartum antibiotics for known maternal Group B streptococcal colonization. Cochrane Database Syst Rev (3):CD007467
16. Bedford H, de Louvois J, Halket S, Peckham C, Hurley R, Harvey D (2001) Meningitis in infancy in England and Wales: follow up at age 5 years. BMJ 323:533–536
17. Baker CJ, Barrett FF (1973) Transmission of group B streptococci among parturient women and their neonates. J Pediatr 83:919–925
18. Boyer KM, Gotoff SP (1985) Strategies for chemoprophylaxis of GBS early-onset infections. Antibiot Chemother 35:267–280
19. Schrag S, Gorwitz R, Fultz-Butts K, Schuchat A (2002) Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC. MMWR Recomm Rep 51:1–22
20. Ancona RJ, Ferrieri P, Williams PP (1980) Maternal factors that enhance the acquisition of group-B streptococci by newborn infants. J Med Microbiol 13:273–280

21. Boyer KM, Gadzala CA, Kelly PD, Burd LI, Gotoff SP (1983) Selective intrapartum chemoprophylaxis of neonatal group B streptococcal early-onset disease. II. Predictive value of prenatal cultures. J Infect Dis 148:802–809
22. Slotved HC, Kong F, Lambertsen L, Sauer S, Gilbert GL (2007) Serotype IX, a proposed new *Streptococcus agalactiae* serotype. J Clin Micobiol 45:2929–2936
23. Rajagopal L (2009) Understanding the regulation of group B streptococcal virulence factors. Future Microbiol 4:201–221
24. Baker CJ, Kasper DL (1976) Correlation of maternal antibody deficiency with susceptibility to neonatal group B streptococcal infection. N Engl J Med 294:753–756
25. Zangwill KM, Schuchat A, Wenger JD (1992) Group B streptococcal disease in the United States, 1990: report from a multistate active surveillance system. MMWR CDC Surveill Summ 41:25–32
26. Centers for Disease Control and Prevention (CDC) (1997) Decreasing Incidence of perinatal group B streptococcal disease—United States, 1993–1995. MMWR Morb Mortal Wkly Rep 46:473–477
27. Mayon-White RT (1985) The Incidence of GBS disease in neonates in different countries. Antibiot Chemother 35:17–27
28. Kalliola S, Vuopio-Varkila J, Takala AK, Eskola J (1999) Neonatal group B streptococcal disease in Finland: a ten-year nationwide study. Pediatr Infect Dis J 18:806–810
29. Poulain P, Betremieux P, Donnio PY, Proudhon JF, Karege G, Giraud JR (1997) Selective intrapartum anti-bioprophylaxy of group B streptococci infection of neonates: a prospective study in 2454 subsequent deliveries. Eur J Obstet Gynecol Reprod Biol 72:137–140
30. Jourdan-Da Silva N, Antona D, Six C, Georges S, Goulet V, Judlin P, Lévy-Bruhl D (2008) Neonatal group B streptococcus infections in France: incidence from 1997 to 2006 and current prevention practices in maternity wards. Bull Epidemiol Hebd 14:110–113
31. Simetka O, Petros M, Podesvová H (2010) Prevention of early-onset neonatal group B streptococcal infection: neonatal outcome after introduction of national screening guideline. Ceska Gynekol 75:41–46
32. López Sastre JB, Coto Cotallo GD, Fernández Colomer B; Grupo de Hospitales Castrillo (2009) Neonatal sepsis of vertical transmission: an epidemiological study from the "Grupo de Hospitales Castrillo". J Perinat Med 28:309–315
33. Boyer KM, Gotoff SP (1986) Prevention of early-onset neonatal Group B streptococcal disease with selective intrapartum chemoprophylaxis. N Engl J Med 314:1665–1669
34. Benitz WE, Gould JB, Druzin ML (1999) Antimicrobial prevention of early-onset group B streptococcal sepsis: estimates of risk reduction based on a critical literature review. Pediatrics 103: e78
35. Vergnano S, Embleton N, Collinson A, Menson E, Russell AB, Heath P (2010) Missed opportunities for preventing group B streptococcus infection. Arch Dis Child Fetal Neonatal Ed 95: F72–F73
36. Centers for Disease Control and Prevention (CDC) (2009) Trends in perinatal group B streptococcal disease—United States, 2000–2006. MMWR Morb Mortal Wkly Rep 58:109–112
37. Gardner SE, Yow MD, Leeds LJ, Thompson PK, Mason EO Jr, Clark DJ (1979) Failure of penicillin to eradicate group B streptococcal colonization in the pregnant woman. A couple study. Am J Obstet Gynecol 135:1062–1065
38. Gibbs RS, Hall RT, Yow MD, McCracken GH Jr, Nelson JD (1992) Consensus: perinatal prophylaxis for group B streptococcal infection. Pediatr Infect Dis J 11:179–183
39. Phares CR, Lynfield R, Farley MM, Mohle-Boetani J, Harrison LH, Petit S, Craig AS, Schaffner W, Zansky SM, Gershman K, Stefonek KR, Albanese BA, Zell ER, Schuchat A, Schrag SJ; Active Bacterial Core surveillance/Emerging Infections Program Network (2008) Epidemiology of invasive group B streptococcal disease in the United States, 1999–2005. JAMA 299:2056–2065
40. Società Italiana di Medicina Perinatale (1996) Proposta: linee-guida per la prevenzione delle infezioni perinatali da streptococco β-emolitico di gruppo B. Boll Soc Ital Med Perinatale 1:21–24
41. Sociedad Española de Obstetricia y Ginecología (1998) Recomendaciones para la prevención de la infección perinatal por estreptococo del grupo B. Prog Obstet Gynecol 41:431–435
42. Sociedades Españolas de Obstetricia y Ginecología, Neonatología, Enfermedades Infecciosas y Microbiología Clínica, Quimioterapia, Medicina Familiar y Comunitaria (2003) Prevención de la infección perinatal por estreptococo del grupo B. Recomendaciones españolas revisadas. Enferm Infecc Microbiol Clin 21:417–423
43. Agence Nationale d'Accreditation et d'Evaluation en Santé (2001) Prévention anténatale du risque infectieux bactérien néonatal précoce. Available online at: http://www.has-sante.fr/portail/jcms/c_272118/prevention-antenatale-du-risque-infectieux-bacterien-neonatal-precoce Accessed 29 December 2011
44. Leitlinien der Gesellschaft für Neonatologie und Pädiatrische Intensivmedizin (GNPI), Deutschen Gesellschaft für Gynäkologie und Geburtshilfe, Deutschen Gesellschaft für Pädiatrische Infektiologie (DGPI), und Deutsche Gesellschaft für Perinatale Medizin (DGPM) (2008) Prophylaxe der neugeborenensepsis (frühe form) durch streptokokken der gruppe B. Available online at: http://www.uni-duesseldorf.de/AWMF/ll/024-020.htm. Accessed 28 December 2011
45. Kommission für Qualitätssicherung der Schweizerischen Gesellschaft für Gynäkologie und Geburtshilfe (2007) Prophylaxe der frühen neugeborenensepsis durch streptokokken der gruppe B. Gynäkol Geburtshilfliche Rundsch 47:103–104
46. Měchurová A, Unzeitig V, Vlk R (2008) Doporučené postupy V perinatologii 3. Doporučený postup při diagnostice a léčbě streptokoků skupiny B v těhotenství a za porodu. Moderní Gynekologii Porodnictví 16:45–48
47. Belgium Health Council (2003) Prevention of perinatal streptococcal infections. Guidelines from the Belgian Health Council. Available online at: https://portal.health.fgov.be/pls/portal/docs/PAGE/INTERNET_PG/HOMEPAGE_MENU/ABOUTUS1_MENU/INSTITUTIONSAPPARENTEES1_MENU/HOGEGEZONDHEIDSRAAD1_MENU/ADVIEZENENAANBEVELINGEN1_MENU/ADVIEZENENAANBEVELINGEN1_DOCS/7721%20GBS_EN%202003.PDF. Accessed 28 December 2011
48. Kotarski J, Heczko PB, Lauterbach R, Niemiec T, Leszczyńska-Gorzelak B (2008) Rekomendacje polskiego towarzystwa ginekologicznego dotyczące wykrywania nosicielstwa paciorkowców grupy B (GBS) u kobiet w ciąży i zapobiegania zakażeniom u noworodków. Ginekol Pol 79:221–223
49. Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG) (2008) Preventie van neonatale groep-B-streptokokkenziekte (GBS-Ziekte). Versie 2.0. Available online at: http://www.nvog-documenten.nl/richtlijn/item/pagina.php?id=26959&richtlijn_id=827. Accessed 28 December 2011
50. Royal College of Obstetricians and Gynaecologists (2003) RCOG Guideline No. 36. Prevention of early onset neonatal group B streptococcal disease. Available online at: http://www.rcog.org.uk/files/rcog-corp/uploaded-files/GT36GroupBStrep2003.pdf. Accessed 28 December 2011
51. Campbell N, Eddy A, Darlow B, Stone P, Grimwood K; New Zealand GBS Consensus Working Party (2004) The prevention of early-onset neonatal group B streptococcus infection: technical report from the New Zealand GBS Consensus Working Party. N Z Med J 117(1200):U1023
52. Daley AJ, Isaacs D; Australasian Study Group for Neonatal Infections (2004) Ten-year study on the effect of intrapartum antibiotic prophylaxis on early onset group B streptococcal and *Escherichia*

coli neonatal sepsis in Australasia. Pediatr Infect Dis J 23:630–634
53. Weston EJ, Pondo T, Lewis MM, Martell-Cleary P, Morin C, Jewell B, Daily P, Apostol M, Petit S, Farley M, Lynfield R, Reingold A, Hansen NI, Stoll BJ, Shane AJ, Zell E, Schrag SJ (2011) The burden of invasive early-onset neonatal sepsis in the United States, 2005–2008. Pediatr Infect Dis J 30:937–941
54. Dahl MS, Tessin I, Trollfors B (2003) Invasive group B streptococcal infections in Sweden: incidence, predisposing factors and prognosis. Int J Infect Dis 7:113–119
55. Lyytikäinen O, Nuorti JP, Halmesmäki E, Carlson P, Uotila J, Vuento R, Ranta T, Sarkkinen H, Ámmälä M, Kostiala A, Järvenpää AL (2003) Invasive group B streptococcal infections in Finland: a population-based study. Emerg Infect Dis 9:469–473
56. Andersen J, Christensen R, Hertel J (2004) Clinical features and epidemiology of septicaemia and meningitis in neonates due to *Streptococcus agalactiae* in Copenhagen county, Denmark: a 10 year survey from 1992 to 2001. Acta Paediatr 93:1334–1339
57. Fluegge K, Siedler A, Heinrich B, Schulte-Moenting J, Moennig MJ, Bartels DB, Dammann O, Von Kries R, Berner R; German Pediatric Surveillance Unit Study Group (2006) Incidence and clinical presentation of invasive neonatal group B streptococcal infections in Germany. Pediatrics 117:e1139–e1145
58. Neto MT (2008) Group B streptococcal disease in Portuguese infants younger than 90 days. Arch Dis Child Fetal Neonatal Ed 93:F90–F93
59. Poyart C, Réglier-Poupet H, Tazi A, Billoët A, Dmytruk N, Bidet P, Bingen E, Raymond J, Trieu-Cuot P (2008) Invasive group B streptococcal infections in infants, France. Emerg Infect Dis 14:1647–1649
60. Bergseng H, Rygg M, Bevanger L, Bergh K (2008) Invasive group B streptococcus (GBS) disease in Norway 1996–2006. Eur J Clin Microbiol Infect Dis 27:1193–1199
61. Berardi A, Lugli L, Baronciani D, Rossi C, Ciccia M, Creti R, Gambini L, Mariani S, Papa I, Tridapalli E, Vagnarelli F, Ferrari F; GBS Prevention Working Group of Emilia-Romagna (2010) Group B streptococcus early-onset disease in Emilia-Romagna: review after Introduction of a screening-based approach. Pediatr Infect Dis J 29:115–121
62. Doit C, Mariani-Kurkdjian P, Mahjoub-Messai F, Bidet P, Bonacorsi S, Carol A, Varon E, Bingen E (2010) Epidemiology of pediatric community-acquired bloodstream infections in a children hospital in Paris, France, 2001 to 2008. Diagn Microbiol Infect Dis 66:332–335
63. Berardi A, Lugli L, Baronciani D, Creti R, Rossi K, Ciccia M, Gambini L, Mariani S, Papa I, Serra L, Tridapalli E, Ferrari F; GBS Prevention Working Group of Emilia-Romagna (2007) Group B streptococcal infections in a northern region of Italy. Pediatrics 120:e487–e493
64. Lancefield RC (1938) Two serological types of group B hemolytic streptococci with related, but not identical, type-specific substances. J Exp Med 67:25–40
65. Baker CJ, Edwards MS, Kasper DL (1981) Role of antibody to native type III polysaccharide of group B streptococcus in infant infection. Pediatrics 68:544–549
66. Baker CJ (1990) Immunization to prevent group B streptococcal disease: victories and vexations. J Infect Dis 161:917–921
67. Prieto Tato LM, Gimeno Díaz de Atauri A, Aracil Santos J, Omeñaca Teres F, del Castillo MF, de José Gómez MI (2008) Infección tardía por estreptococo del grupo B: experiencia en un hospital de tercer nivel (2000–2006). An Pediatr (Barc) 68:239–243
68. Farley MM (2001) Group B streptococcal disease in nonpregnant adults. Clin Infect Dis 33:556–561
69. Lin FY, Weisman LE, Azimi PH, Philips JB 3rd, Clark P, Regan J, Rhoads GG, Frasch CE, Gray BM, Troendle J, Brenner RA, Moyer P, Clemens JD (2004) Level of maternal IgG anti-group B streptococcus type III antibody correlated with protection of neonates against early-onset disease caused by this pathogen. J Infect Dis 190:928–934
70. DEVANI. Vaccine against neonatal infections. Home page at: http://www.devaniproject.org/. Accessed 28 December 2011
71. Heath PT (2011) An update on vaccination against group B streptococcus. Expert Rev Vaccines 10:685–694
72. Melin P (2011) Neonatal group B streptococcal disease: from pathogenesis to preventive strategies. Clin Microbiol Infect 17:1294–1303
73. Johri AK, Paoletti LC, Glaser P, Dua M, Sharma PK, Grandi G, Rappuoli R (2006) Group B streptococcus: global incidence and vaccine development. Nat Rev Microbiol 4:932–942
74. World Health Organization (WHO) (2005) State of the art of vaccine research and development: initiative for vaccine research. Available online at: http://www.who.int/vaccine_research/documents/Dip%20814.pdf. Accessed 28 December 2011
75. Afshar B, Broughton K, Creti R, Decheva A, Hufnagel M, Kriz P, Lambertsen L, Lovgren M, Melin P, Orefici G, Poyart C, Radtke A, Rodriguez-Granger J, Sørensen UB, Telford J, Valinsky L, Zachariadou L; Members of the DEVANI Study Group, Efstratiou A (2011) International external quality assurance for laboratory identification and typing of *Streptococcus agalactiae* (group B streptococci). J Clin Microbiol 49:1475–1482
76. Berardi A, Di Fazzio G, Gavioli S, Di Grande E, Groppi A, Papa I, Piccinini G, Simoni A, Tridapalli E, Volta A, Facchinetti F, Ferrari F; GBS Prevention Working Group, Emilia-Romagna (2011) Universal antenatal screening for group B streptococcus in Emilia-Romagna. J Med Screen 18:60–64
77. Bedford Russell AR, Breathnach A, Sender P (2001) Confirmed group B streptococcus infection: the tip of the iceberg. Arch Dis Child Fetal Neonatal Ed 84:F140
78. Carbonell-Estrany X, Figueras-Aloy J, Salcedo-Abizanda S, de la Rosa-Fraile M; Castrillo Study Group (2008) Probable early-onset group B streptococcal neonatal sepsis: a serious clinical condition related to intrauterine infection. Arch Dis Child Fetal Neonatal Ed 93:F85–F89
79. Terrone DA, Rinehart BK, Einstein MH, Britt LB, Martin JN Jr, Perry KG (1999) Neonatal sepsis and death caused by resistant *Escherichia coli:* possible consequences of extended maternal ampicillin administration. Am J Obstet Gynecol 180:1345–1348
80. Moore MR, Schrag SJ, Schuchat A (2003) Effects of intrapartum antimicrobial prophylaxis for prevention of group-B-streptococcal disease on the incidence and ecology of early-onset neonatal sepsis. Lancet Infect Dis 3:201–213
81. Schrag SJ, Hadler JL, Arnold KE, Martell-Cleary P, Reingold A, Schuchat A (2006) Risk factors for invasive, early-onset *Escherichia coli* infections in the era of widespread intrapartum antibiotic use. Pediatrics 118:570–6
82. Schrag SJ, Stoll BJ (2006) Early-onset neonatal sepsis in the era of widespread intrapartum chemoprophylaxis. Pediatr Infect Dis J 25:939–940
83. Spaetgens R, DeBella K, Ma D, Robertson S, Mucenski M, Davies HD (2002) Perinatal antibiotic usage and changes in colonization and resistance rates of group B streptococcus and other pathogens. Obstet Gynecol 100:525–533
84. Betreuung der Neugeborenen von Müttern, die mit Streptokokken der Gruppe B kolonisiert sind. Empfehlungen der Schweizerischen

Gesellschaft für Neonatologie (2007) Available online at: http://www.gfmer.ch/Guidelines/Neonatologie_d/Neonatologie_mt.htm. Accessed 28 December 2011
85. Isaacs D (1998) Prevention of early onset group B streptococcal infection: screen, treat, or observe? Arch Dis Child Fetal Neonatal Ed 79:F81–F82
86. Colbourn TE, Asseburg C, Bojke L, Philips Z, Welton NJ, Claxton K, Ades AE, Gilbert RE (2007) Preventive strategies for group B streptococcal and other bacterial infections in early infancy: cost effectiveness and value of information analyses. BMJ 335:655
87. UK, Group B Strep Support. Home page at: http://www.gbss.org.uk/. Accessed 28 December 2011
88. Netherlands, Dutch Foundation GBS. Home page at: http://www.ogbs.nl/. Accessed 28 December 2011
89. USA, Group B Strep Association. Home page at: http://GroupBStrep.org/. Accessed 28 December 2011
90. Argentina, Prevencionegb. Home page at: http://www.pacienteson-line.org/medicina/protagonistas/prevencionegb.php. Accessed 28 December 2011
91. Canada, Strep B Foundation. Home page at: http://www.strepb.ca/. Accessed 24 May 2011
92. Eickhoff TC, Klein JO, Daly AK, Ingall D, Finland M (1964) Neonatal sepsis and other infections due to group B β-hemolytic streptococci. N Engl J Med 271:1221–1228
93. Deutchman M (1998) Thoughts on the prevention of neonatal group B streptococcal infection. Am Fam Physician 57:2602–2606
94. de la Rosa Fraile M, Cabero L, Andreu A, Rao GG (2001) Prevention of group B streptococcal neonatal disease: a plea for a European consensus. Clin Microbiol Infect 7:25–27