Serotype Distribution of Invasive Group B Streptococcal Isolates in Infants: Results from a Nationwide Active Laboratory Surveillance Study over 2 Years in Germany

Kirsten Fluegge, Sven Supper, Anette Siedler, and Reinhard Berner

We report the serotype distribution of invasive group B streptococci (GBS) isolated from 296 infants in Germany. Serotype distribution was as follows: serotype Ia, 15%; Ib, 5%; II, 5%; III, 65%; IV, 1%; and V, 8%. Analysis of serotype according to the source of isolation highlighted the considerable role of serotype III in meningitis in early-onset infection (82%) and late-onset infection (84%). Use of a trivalent GBS vaccine in Germany could theoretically provide protection against 84% and 94% of invasive early-onset and late-onset infections, respectively.

Streptococcus agalactiae (group B streptococci [GBS]) is the leading cause of sepsis and meningitis in infants [1]. Neonatal GBS infection presents as early-onset disease (EOD; age at onset, 0–6 days) or late-onset disease (LOD; age at onset, 7–90 days). GBS are classified into 9 serotypes (Ia, Ib, and II–VIII). In the 1970s–1980s, serotypes Ia, Ib, and II–VIII were the most common serotypes to be associated with EOD in the United States [2, 3]. More recently, serotype V has emerged as a frequent cause of neonatal sepsis [4], and additional serotypes VI–VIII have been described [5–7]. Knowledge of serotype distribution is an important prerequisite for the formulation of serotype-based vaccines in a given country. Few data are available regarding the distribution of GBS serotypes among invasive isolates recovered from European infants [8, 9]. This is the first report, to our knowledge, to describe the distribution among GBS isolates from 296 infants with EOD and LOD during an active surveillance study performed in Germany from 1 April 2001 through 31 March 2003.

**Patients, materials, and methods.** For the active surveillance study, monthly questionnaires were sent by the Laboratory Sentinel Group at Robert-Koch-Institute (Berlin, Germany) to all microbiological laboratories serving pediatric hospitals to report any invasive GBS infections that occurred in infants up to 3 months of age. Laboratories were asked to send GBS isolates to the central study laboratory in Freiburg, Germany. The overall response rate of reporting was 95%, and 82% of the isolates were provided.

A surveillance case was defined as the isolation of GBS from a specimen of normally sterile body fluid. A total of 296 invasive neonatal isolates were analyzed. GBS serotyping was performed with antisera specific for capsular serotypes I–V using a slide agglutination test (Denka Seiken) in accordance with the manufacturer’s instructions. If no serotype designation could be made, the isolate was determined to be nontypeable. Serotype distributions were compared with the $\chi^2$ test.

**Results.** Of the 296 GBS strains recovered, 228 were isolated from blood samples, 67 were isolated from CSF samples, and 1 was isolated from a pleural effusion sample; for reasons of simplicity, the latter sample was considered part of the blood culture group. Serotypes III (65%) and Ia (15%) were the most frequent serotypes, accounting for 80% of all invasive isolates; 8% of the isolates belonged to serotype V. Five percent belonged to serotypes Ib and II each, and 1% belonged to serotype IV. Three isolates were nontypeable.

Serotypes III, Ia, and V had the same rank order of frequency irrespective of source or time of onset of infection. Serotype III was recovered significantly more often from CSF specimens (85%) than from blood cultures (60%), irrespective of the time of onset of infection ($P < .001$). Although serotype Ia remained the second most common serotype, it was recovered less than half as often from CSF cultures (7%) as from blood cultures (17%). The proportion of serotype V strains recovered from blood and CSF cultures was similar (8% vs. 6%).

For 292 of 296 isolates, the time of infection onset could be determined. One hundred sixty-eight isolates were recovered from patients with EOD isolates, and 124 were recovered from patients with LOD. LOD was more likely than EOD to be caused by serotype III ($P < .01$). EOD and LOD isolates were further classified according to the source of isolation (i.e., blood samples vs. CSF samples), thereby emphasizing the predominant role of serotype III among CSF isolates and cases of LOD.
Figure 1. Serotype distribution of isolates recovered from infants with early-onset (EOD) or late-onset (LOD) group B streptococcal disease, according to source of isolation (blood sample [top] vs. CSF sample [bottom]). In 4 infants, the time of onset of infection could not be determined. One isolate was recovered from a pleural puncture specimen, which, for reasons of simplicity, was included with the blood culture group. NT, nontypeable.
changes in serotype frequency were observed, with the percentage of cases due to serotype III increasing over time. The Swedish data allow for an overview of serotype distribution, but the study was geographically restricted, retrospective, and included small sample sizes. Therefore, the results cannot be assigned without bias to the whole population in Sweden. Until now, no valid data on serotype distribution of isolates recovered from neonates with invasive GBS disease are available for Germany. Our surveillance study presents, to our knowledge, the first representative data on neonatal isolates. We show that serotypes III, Ia, and V constituted 88% of all isolates in Germany, with serotype III (65%) clearly outnumbering others. The design of a recently published study from England [9], which includes enhanced surveillance for invasive GBS infection, is comparable to our study. Therefore, valid comparisons of serotype distributions between these 2 countries are possible.

Although the serotype distribution may appear to be identical at first glance (serotype III was the most common, followed in descending order by Ia and V), the actual share of the individual serotypes III and Ia is significantly different. In Germany, we found a higher proportion of cases due to serotype III (65% vs. 48%; \( P < .001 \)) and a lower proportion of cases due to serotype Ia (15% vs. 27%; \( P < .001 \)) than the English study.

With particular respect to EOD, different serotype distributions were found by Harrison et al. [12] in the United States, with serotype Ia and III being predominant. European data for EOD from Sweden, Finland, and England [8, 9, 16] are similar to those reported above, with the order of serotype frequency being III, followed in descending order by Ia and V. Nonetheless, there were remarkable differences between the countries concerning the actual percentage of the single serotypes. In this report and in the Swedish study [8], serotype III clearly outnumbered the other serotypes (58% and 55%, respectively), whereas the proportions of serotypes Ia and V were comparable. In Finland, less than one-half of the GBS isolates were serotype III (42%), and in England, serotypes III and Ia were found in nearly equal proportions (37% and 32%, respectively). In our study, serotype III was recovered significantly more frequently than in England (58% vs. 37%; \( P < .001 \)), and significantly lower rates of serotype Ia were recorded (17% vs. 32%; \( P < .01 \)).

The predominance of serotype III among persons with LOD and meningitis is well known. We found a significantly higher proportion of cases of LOD due to serotype III (77%) than has been found in other countries, such as the United States (59.6%), Finland (63%), and England (67%). In our study, it was found that LOD was more likely than EOD to be caused by serotype III (\( P < .01 \)), which was not the case in the study from England. Analysis of the German LOD isolates on the basis of the source of the isolate also emphasizes the predominance of serotype III, which accounted for 82% of CSF isolates recovered from patients with EOD (figure 1).

The most challenging way to prevent neonatal GBS infections is vaccination of women of childbearing age. Results from phase I and II studies are promising [17]. Knowledge of the serotype distribution of invasive isolates is a prerequisite for successful vaccine development in a given country. On the basis of our data, a trivalent vaccine containing serotypes III, Ia, and V would provide coverage against 88% of GBS infections (95% CI, 84%–92%), thereby preventing 84% of cases of EOD due to GBS (95% CI, 79%–90%) and 94% of cases of LOD due to GBS (95% CI, 89%–98%) in Germany. Addition of a fourth serotype, such as Ib or II, would increase the coverage rate to 93% of all GBS infections, 92% of cases of EOD, and 96% of cases of LOD. GBS meningitis occurred in 67 cases in this present study. A trivalent vaccine could provide coverage against 98% of GBS meningitis cases. Assuming that long-term sequelae can be expected in a large number of patients after GBS meningitis, this goal is a particularly challenging one.

In conclusion, this study presents, for the first time, valid baseline data on serotype distribution of invasive neonatal GBS disease in Germany. Serotype III plays a predominant role in invasive GBS infections, especially in cases of LOD and meningitis. Inclusion of serotypes Ia, III, and V in a GBS vaccine could provide protection against the majority of causes of invasive neonatal GBS disease.

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References


