Group B Streptococci

Declining Incidence in Infants in Germany

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Abstract: Group B streptococcus (GBS) is a leading cause of morbidity and mortality in newborns worldwide. From 2000 to 2008, national guidelines in Germany recommended intrapartum antibiotic prophylaxis for pregnant women displaying risk factors (eg, perinatal anogenital GBS colonization, rupture of the membranes ≥18 hours before birth) for the vertical transmission of GBS to their children. In 2008, these guidelines were revised to advocate universal, culture-based screening for GBS colonization among all pregnant women between 35 and 37 weeks of gestation. For the period 2009–2010, our prospective active surveillance study assessed the incidence of invasive GBS infections in infants 0–90 days of age in Germany. We did this by means of a capture–recapture analysis of 2 separate, independent systems (pediatric reporting versus laboratory reporting). We compared our results with those from a previous study by employing an equivalent design (2001–2003). We detected a 32% reduction in GBS incidence, from 0.47 per 1000 live births (n = 679) in 2001–2003 to 0.34 per 1000 live births (n = 450) in 2009–2010. This decline primarily is tied to a reduced number of GBS cases in children under 1 week of age. In 2009–2010, the ratio of early-onset disease to late-onset disease reversed from 1.52 (206:136), as determined in 2001–2003, to 0.75 (92:122). This study is the first to assess changes in the incidence of invasive GBS in Germany after the implementation of the guidelines for intrapartum prophylaxis for pregnant women colonized with GBS.

Key Words: invasive streptococcal infections, streptococcus agalactiae, incidence, neonatal, infant, Germany, capture–recapture method

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Group B streptococcus (GBS), also known as *Streptococcus agalactiae*, is a common commensal of the gastrointestinal tract and can be isolated from the vagino-rectal tract in approximately 1-quarter of pregnant women.[1]

With a global mean incidence in infants 0–89 days of age of 0.53 per 1000 live births (95% confidence interval 0.44–0.62), GBS is recognized as the leading cause of neonatal sepsis.[2] Infant GBS infection is usually subdivided in 2 groups: early-onset disease (EOD) occurring at 0–6 days of age and late-onset disease (LOD) occurring at 7–90 days of age. The major risk factor for EOD is maternal colonization with GBS in the genitourinary or gastrointestinal tracts.[1,3] In approximately 50% of cases, GBS is likely to have been transferred to the fetus from aspiration of amniotic fluid infected with ascending bacteria.[4]

A prospective active surveillance study based on capture–recapture analysis—a study involving laboratories and pediatric hospitals from across Germany from 2001 to 2003—calculated an incidence of 0.47 infant invasive GBS (iGBS) infections per 1000 live births.[5] Along with reports from the Netherlands (EOD 0.36 and LOD 0.14 per 1000 live births in 1999/2001 and in total 0.56 per 1000 live births in 1997–2001) and England (EOD 0.48, LOD 0.24 and total 0.72 per 1000 live births in 2000/2001) that related to the same time period, this German study published nationwide data on the incidence of infant GBS sepsis in Europe.[6,7] Intrapartum antibiotic prophylaxis (IAP) has been shown to significantly reduce the incidence of EOD.[3] Pregnant women at risk for vertically transmitting GBS and who are eligible for IAP can be identified by either clinical risk factors or by detection of GBS colonization via culture-based screening.[3] In Germany, from 2000 to 2008, guidelines recommended 2 alternative strategies: (a) screening-based intrapartum antimicrobial prophylaxis and (b) a risk factor–based approach.

Risk factors are perinatal anogenital GBS colonization, bacteriuria, rupture of the membranes ≥18 hours before birth, fever ≥38°C during delivery, premature birth <37 weeks gestation and previous delivery of a child suffering from GBS infection.[8]

In the United States, new guidelines recommending a universal, culture-based GBS screening were introduced in 2002, resulting in significant decrease of neonatal iGBS.[9,10] This decrease was the main reason for the implementation of revised guidelines in Germany in 2008. The most important change was the recommendation of a universal, culture-based screening for all pregnant women between 35 and 37 weeks of gestation, along with the restriction of the risk factor approach for women whose screening results were not available.[11] Since 2008, however, there have not been any continuous surveillance systems put in place in Germany that would allow for the assessment of the impact of these revised guidelines.[12,13]

Therefore, the objective of our follow-up study was to detect and analyze potential changes in the incidence of invasive infant GBS infections before (2001–2003) versus after (2009–2010) the implementation of the revised guidelines for prevention of infant GBS disease in Germany.

METHODS

Case Definition

A case of invasive GBS infections was defined as an isolation of GBS in any sample obtained from a normally sterile body site (eg, blood, cerebrospinal fluid) in infants ≤90 days of age during the period January 1, 2009, to December 31, 2010, in Germany.

Study Design

In the current, prospective active surveillance study, we applied the same study design and methods as had been used in the

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preceding 2001–2003 study. We collected and matched data regarding invasive GBS infections from 2 separate, independent sources.

German Pediatric Surveillance Unit/Survey of Rare Diseases

The first data source was the German Pediatric Surveillance Survey of rare diseases. For this, monthly reporting forms were sent to the staff coordinators at pediatric departments across Germany (pediatric reporting). Pediatric hospitals either provided notification of new cases of invasive GBS infection or else they opted for zero reporting.

Robert Koch Institute

Microbiology laboratories across Germany provided the second source of data on invasive infant GBS infections. These labs were identified through (a) laboratory directories at the Robert Koch Institute (RKI; the German National Public Health Institute), (b) the laboratory directory from the preceding study (2001–2003) and (c) a systematic search of the German national digital Yellow Pages (DeTeMedien GmbH, Frankfurt; http://www.gelbeseiten.de).

Once we had identified a list of laboratories, we sent them a description of our surveillance project and invited them to submit monthly reports of infant GBS infections, including zero reports (laboratory reporting). Before submitting data, laboratories undertook a pseudonymization of patient identities—a procedure approved by the RKI's data confidentiality officer.

We did not apply any selection procedure with respect to geography or other eligibility criteria for reporting institutions.

Data Analysis

Before merging the data from our 2 independent sources, we examined the inclusion criteria and eliminated double reports and false-positive reports (ie, false age, obtained outside the study period, isolation of GBS from no sterile body site). If a case returned more than 2 cultures as positive for GBS in under 30 days, only the first report was counted. We manually matched the reports based on the following criteria: first/second initials of patient's name; date of birth (month and year); sex; first 3 digits of the patient's postal code (home address); and the date of illness onset (day, month, year).

Statistical Methods

We applied a two-sample, capture–recapture method (CRM) to account for incomplete case collection within both sources, as well as to predict the number of unobserved individuals.[14,15] Our method assumed that "captured" cases in one data set of the underlying population were "recaptured" by appearing in one (or more) other data sets. Conditions we considered to be mandatory were (a) the cases had to be true cases and be marked by unique personal identifiers so that we could match cases from different sources; (b) the sources had to be independent; (c) the probability of being captured had to be the same for all cases. Our study design complied with all three of these conditions.

After completing stratification by age and sex, we applied a Bayesian approach for the capture–recapture–based estimation of the overall number of GBS cases during the study period.[16,17] We calculated incidence rates in relation to the total number of 1,343,073 recorded live births that occurred during the 24-month period, as documented by the German Federal Statistics Office.

A separate computation of either EOD- or LOD-specific incidence by means of the CRC analysis was not possible because RKI only was allowed to receive pseudonymized data. Unfortunately, these data did not include the exact age at onset of infection.

RESULTS

During the study period, an estimated 470 pediatric in-patient departments and units were active in Germany. Of these, 445 participated in the German Pediatric Surveillance Survey of Rare Diseases survey, (ie, a 95% participation rate). The return rate for the reporting forms was >95% over the course of the entire study period.

From the list of laboratories we identified (as described above), the laboratories who had agreed to perform GBS tests in Germany (n = 129) were invited to join our study. Of these, 111 agreed to participate in our study (ie, a 86% participation rate). Over the course of the full study period, the return rate for the reporting forms was >95% (Table 1).

Pediatric in-patient departments and units, as well as the laboratories providing data for the study, were distributed across all 16 German states. In total, there were 226 infant GBS cases detected by the pediatric reporting system, 169 cases by laboratory reporting and 76 cases detected by both (Table 1).

Taking only pediatric reporting into account, the incidence was 0.17 (95% confidence interval [CI], 0.13–0.15) per 1000 live births, with 48.9% of patients being male (110/224, with sex being unknown in 2 cases). Through the laboratory reporting, 169 cases were detected, which corresponded to an incidence of 0.13 (95% CI, 0.11–0.15) per 1000 live births. Here, 55.7% of patients were male (93/167, with sex being unknown in 2 cases; Table 2). Data from the laboratory reporting did not allow us to distinguish between EOD and LOD cases. Via pediatric reporting, however, data regarding age at disease onset was available for 214 out of 226 cases (94.7%). Among those, 92 (43%) patients were below 7 days of age and 122 (57%) patients were 7–90 days old. The ratio of EOD to LOD was 0.75 (92:122).

Calculation by CRM estimated 450 cases (95% CI, 403–510) of infant GBS in Germany during the 2-year study period (Table 2). This was equivalent to an overall incidence of 0.34 (95% CI, 0.30–0.38) per 1000 live births for invasive GBS infections with onset ≤3 month of age in Germany. Calculation based on the pediatric reporting gives an incidence of 0.15 for EOD and 0.19 for LOD per 1000 live births, respectively. From this, we estimate detection sensitivity to be 50% for pediatric reporting (95% CI, 43%–58%) and 38% for laboratory reporting (95% CI, 32%–44%).

DISCUSSION

In 2009–2010, the overall incidence of invasive infant GBS infection in Germany—estimated from our nationwide surveillance study—was 0.34 per 1000 live births. This represented a significant

TABLE 1. Participation Numbers and Rates, Case Numbers and Sensitivity Arranged by the 2 Data Sources (ESPED, RKI)

	Pediatric Reporting System (ESPED)	Laboratory Reporting System (RKI)
Total number of potential participants in the study	470	129
Total number of participants (%)	445 (95)	111 (86)
Total number of case reports	226	169
Female	114	74
Male	110	93
Incidence	0.17	0.13
Sensitivity [CI] (%)	50 [43–58]	38 [32–44]

CI indicates confidence interval; ESPED, German Paediatric Surveillance Unit/Survey of rare diseases; RKI, Robert Koch-Institute

TABLE 2. Number of Recorded Neonatal Invasive GBS Cases in Germany From 2009 to 2010, as Reported by the Laboratory Reporting System (RKI) and the Pediatric Reporting System (ESPED), in Addition to the Estimated Total Number of Neonatal GBS Infection After the CRM

No. of RKI Cases (%)			No. of ESPED Cases (%)			CRM	
Total	Female*	Male*	Total	Female*	Male*	No. of Matched Cases	No. of Estimated Cases (95% CI)
169	74 (44, 3)	93 (55, 7)	226	115 (51, 3)	109 (48, 7)	76	450 (403–510)

*Two cases from each data system (RKI, ESPED) needed to be excluded from this analysis because of missing data on sex.

CI indicates credibility interval; CRM, capture–recapture method; ESPED, German Pediatric Surveillance Unit/ Survey of rare diseases; RKI, Robert Koch-Institute.

32% decline in incidence as compared with the period 2001–2003 (0.47 per 1000 live births). According to the pediatric reporting system, the absolute numbers of GBS cases with LOD was stable (n = 136 in 2001–2003; n = 122 in 2009–2010), whereas the number of EOD cases decreased considerably (n = 206 in 2001–2003 to n = 92 in 2009–2010). In 2009–2010, the ratio of EOD to LOD reversed from 1.52 (206:136), as determined in 2001–2003, to 0.75 (92:122). Based on this analysis, we conclude that the reduced incidence of infant invasive GBS disease mainly can be attributed to the decline in EOD cases.

In the United States, GBS guidelines first issued in 1996 implemented a risk-based approach. They were revised in 2002 to a screening-based IAP approach.

Implementing these guidelines resulted in a decrease in the incidence of EOD from 1.7 per 1000 live births in 1990 to 0.25 by 2010 (1999–2001: 0.47 and 2003: 0.32 per 1000 live births).[3]

Some European countries have supported a risk factor–based IAP approach that has received differing results: in England, for example, when a risk factor approach was introduced in November 2003, a slight increase of the incidence of infant GBS infections was detected (0.35 per 1000 live births in 2003 to 0.41 in 2010).[18] In the Netherlands, where a risk factor approach also was applied, a 60% increase in the incidence of infant GBS infections resulted (1987: 0.20 and 2011: 0.32 per 1000 live births).[19]

In New Zealand, by contrast, the incidence of EOD GBS disease was reduced by more than half after the implementation of a single, risk-based approach (0.5 per 1000 live births in 1998–1999 to 0.23 in 2009–2011).[20] This New Zealand example demonstrates that the increase of EOD GBS disease may not be the result of a single measure (ie, risk factor–based vs. screening-based approach) but rather the consequence of bundling prevention and treatment. Here, the reduced incidence primarily was the outcome of having promoted a universally accepted guideline—one that reduced both confusion and treatment errors.

When considering the decline in infant GBS infections in Germany in relation to the newly implemented, culture-based universal screening approach, several additional factors should be taken into account. First, in Germany, GBS screening is optional. It is not reimbursed by either public or private health insurance. This may significantly limit adherence to recommended guidelines. In 2011–2012, a cohort study revealed participation rates for prenatal GBS screening in the southwest of Germany to be 68.1%. This rate was considerably lower than that reported in the United States during 2003–2004 (85%).[21] However, Kunze et al[21] have found an increase of IAP among GBS-positive pregnant women in their German cohort—one that increased from 39% in 2003–2004 to 89% in 2011–2012. This indicates a significant change in intrapartum management and supports the assumption that Germany's new GBS screening policy has played a role in the declining incidence.[21,22]

As a second point, changes in the sensitivity of the 2 assessment procedures may have occurred between the time periods 2001–2003 and 2009–2010. However, major changes in this respect seem unlikely because the data collection procedures, as well as the relevant variables in the assessment forms, were identical during both periods. Nevertheless, to account for any under-detection or varying sensitivity of single data sources, we purposefully used a capture–recapture-based estimation.

Third, the validity of the CRM relies upon the independence of our 2 data sources. In our setting, this was fairly guaranteed because one source was from pediatric hospitals and the other from microbiologic laboratories. According to our case definition (culture-proven cases), the probability of being captured should be the same for all cases. Furthermore, participants from both data sources were fairly evenly distributed across all 16 German states. The total number of participants on the laboratory-based reporting system is lower than the number of participants on the hospital-based reporting system. The reason is that not every hospital in Germany has its own laboratory. There are rather big central laboratories serving several hospitals. The lower sensitivity of the laboratory reporting system is likely because of the lower participation rates among laboratories in our study.

Fourth, given our multisided approach to identifying and recruiting laboratories across Germany, we believe our laboratory list to have been sufficiently comprehensive, with laboratories from the preceding study also likely to have been participants in the current study. At a minimum, wide disparities in participation appear unlikely, as the laboratories' 85% participation rate speaks for their representativeness.

Several limitations of our study may be outlined. Because laboratory reporting does not provide clinical information, data on EOD and LOD are only available by means of the pediatric reporting system. For this reason, it was not possible to estimate the overall incidence of EOD and LOD for GBS via the CRM. However, assuming the sensitivity of the pediatric reporting to be equal for both EOD and LOD cases, the analysis would yield an estimated incidence of iGBS at 0.15 for EOD and 0.19 for LOD per 1000 live births, respectively. Finally, survey data was available only from a restricted, 2-year time span and not continuously from 2003 to 2012. Nevertheless, short-term fluctuations in GBS incidence were not witnessed during the 2-year observation period, a fact suggesting that the 2 measurements represent a true difference. Because our findings were based on culture-confirmed cases, theoretically, the observed decline could be the consequence of a decrease in culture-positive rates—one related to increased numbers of infants becoming exposed to antibiotics as a result of the new screening approach.

In conclusion, our analysis indicates a 32% decline in cases of infant-invasive GBS infection between the years 2003 and 2010

in Germany—a change due primarily to a decline in EOD cases. This suggests that the recommendation for universal GBS screening for all pregnant women between 35 and 37 weeks gestation has contributed to this decline. Given the lack of both contradictory evidence and alternative explanations, we argue that the guideline for universal GBS screening should continue to be maintained.

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