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Background. Few cross-population studies examining the epidemiology of invasive group B streptococcal (GBS) disease have been undertaken. To identify longitudinal trends in the burden and characteristics of infections, national surveillance data on diagnoses in England and Wales from 1991 to 2010 were analyzed.

Methods. A parallel review of laboratory-confirmed invasive GBS infection surveillance reports and isolates submitted to the national reference laboratory was undertaken. Cases were defined as GBS isolated from a normally sterile site.

Results. A total of 21 386 reports of invasive GBS infection were made between 1991 and 2010. The annual rate of reports doubled over the 20 years from 1.48 to 2.99 per 100 000 population. Significant increases were seen in all age groups but most pronounced in adults. Rates of early-onset (0–6 days) infant disease fluctuated but showed a general rise between 2000 and 2010 from 0.28 to 0.41 per 1000 live births. Rates of late-onset (7–90 days) disease increased steadily between 1991 and 2010 from 0.11 to 0.29 per 1000 live births. Resistance to erythromycin increased markedly from 2.5% in 1991 to 15% in 2010. The distribution of serotypes varied according to patient age and over time with type III increasing among early-onset cases and decreasing in adults.

Conclusions. Although risk of invasive GBS infection remains highest within the first few days of life, the relative burden of disease is shifting toward adults. The rise in incidence and antibiotic resistance makes development of an effective and safe vaccine all the more pressing.

Keywords. Streptococcus agalactiae; streptococcal infections; epidemiology; drug resistance; United Kingdom.

Following the success of immunization programs targeting many of the leading causes of sepsis, attention is shifting towards ß-hemolytic streptococci. Group B streptococci (GBS; Streptococcus agalactiae) are currently the most frequent cause of sepsis and infectious death in neonates in England [1, 2]. Risk of GBS infection is highest during the first few days of life through intrapartum contamination of the neonate from maternal flora. Antibiotic prophylaxis offers a means of reducing risk of transmission during childbirth and as such, a number of countries have implemented preventive strategies based on obstetric risk factors and/or maternal carriage [3].

GBS also cause disease in adults, including septicemia, pneumonia, and bone/joint and skin/soft tissue infections, primarily in individuals with serious underlying disease but also importantly in pregnant women [4]. Case fatality rates as high as 8%–24% have been observed in nonpregnant adults with invasive GBS disease [4, 5]. Between 12% and 24% of adult cases are thought to be healthcare associated, including cases arising within nursing home settings [5–8].

Changes in the epidemiology of adult GBS disease have been reported in the United States, notably,
increases in non-pregnancy-related disease [5]. As a result of these documented changes, a longitudinal assessment of population-based surveillance of invasive GBS infection in England and Wales between 1991 and 2010 was undertaken to assess changes in the epidemiology of disease.

METHODS

Routine laboratory reports of invasive GBS disease submitted by microbiology laboratories across England and Wales to the Health Protection Agency (HPA) were reviewed for the period 1 January 1991 to 31 December 2010, alongside serotype results from isolates submitted to the national reference laboratory (HPA Streptococcus and Diphtheria Reference Unit [SDRU]) between 1 January 1995 and 31 December 2010. Routine laboratory reporting and submission of isolates is undertaken on a voluntary basis, although all laboratories are expected to follow national guidelines, which request the reporting/submission of GBS identified from normally sterile sites [9,10]. Laboratory surveillance is subject to weekly audits of participation and data quality.

An invasive infection was defined as GBS cultured from blood or other normally sterile sites. Also included were non-sterile-site GBS isolates from patients clinically diagnosed with meningitis. Records were considered to relate to the same episode if specimens were taken within 7 days of each other and merged accordingly to form a single record. Recurrent episodes could not be identified due to a lack of unique patient identifiers across the study period. For this same reason, the 2 datasets were not joined but were analyzed separately.

Isolates submitted to SDRU were characterized according to their capsular polysaccharide serotype by Lancefield acid extraction followed by gel immunoprecipitation using specific antisera from January 1995 to April 2007. A more cost-effective and rapid serotyping method with equivalent discriminatory power was introduced after this time using a modified version of the Statens Serum Institut GBS latex test [11]. Antibiotic sensitivity of GBS isolates was determined by local hospital laboratories according to their own methods, primarily by disc diffusion, interpreted against British Society for Antimicrobial Chemotherapy breakpoints (http://bsac.org.uk/susceptibility/guidelines-standardized-disc-susceptibility-testing-method). Antibiotic susceptibility results were submitted through the routine HPA laboratory reporting system.

Population denominators for calculation of rates were derived from Office for National Statistics census–based midyear resident population estimates (www.ons.gov.uk). Live birth registrations for the respective years in which cases were diagnosed were used as denominators for calculating rates in infants. A multivariable logistic regression model was used to examine the independent association between year of diagnosis, patient age and sex, and seasonality (calendar month) on erythromycin resistance. Confidence intervals (CIs), $\chi^2$ tests, Poisson regression for trends over time, and logistic regression analysis were calculated using Stata statistical software, version 12.0 (StataCorp, College Station, Texas). The Simpson index of diversity was used to compare biodiversity of capsular serotypes between age groups [12].

RESULTS

Microbiology laboratories in England and Wales reported 21,386 cases of invasive GBS infections between 1991 and 2010. GBS was isolated from blood culture in 96% (20,637) of cases, cerebrospinal fluid (CSF) in 4% (919), and joints in 1% (206) (Table 1). GBS was cultured from 2 or more clinical specimens in 664 (3%) patients, 554 of which were paired blood and CSF isolates. Age-specific differences in site of isolation were evident with a higher proportion of late-onset neonatal cases isolating GBS from CSF than other age groups (Table 1). A total of 996 (5%) reports indicated a clinical diagnosis of meningitis, 22% among late-onset cases, significantly higher than for early-onset (6%) cases or any other age group (1%) ($\chi^2[1 df] = 1900, P < .001$). Of the 996 meningitis cases, 883 had CSF isolates and of the remaining cases, 112 had positive blood cultures and 1 case had no specimen site given.

The number of invasive GBS cases reported rose steadily after 1996, from 700–800 per annum to 1652 in 2010. This represented an increase in overall population rate from 1.48 per 100,000 resident population in 1991 to 2.99 per 100,000 in 2010 (Figure 1), an average increase of 5% per year (rate ratio $[RR] = 1.05$; 95% CI, 1.04–1.05).

Numbers of invasive GBS infections showed some seasonal variation with lower numbers of cases in the winter and/or spring than in the summer, although not consistently so in each year (Figure 2). Peak weekly reports occurred between...
weeks 23 and 43 (June to mid-October). No differences in seasonal patterns were discernible between different age groups.

Demographic Characteristics of Cases
The age distribution of invasive GBS cases showed a gradual shift toward relatively more disease in adults. Approximately half of all cases reported between 1991 and 1995 were infants (48%), with this proportion dropping steadily in the second half of the 1990s, staying between 29%–33% from 2000 onward. Although population rates increased significantly in all age groups between 1991 and 2010 (Figure 1), the most pronounced increases were in adults (>15 years), whose rates increased from 0.92 to 2.39 per 100,000 population, an average of 6% per annum (RR = 1.06, 95% CI, 1.06–1.07). Age-specific trends in rates were broadly similar for male and female cases, although for men, highest year-on-year increases were in those aged 15–44 years, averaging 8% per year (RR = 1.08, 95% CI, 1.07–1.09) compared to 6% for women aged 15–44 years (RR = 1.06, 95% CI, 1.05–1.07). The most pronounced rises for women were in those aged ≥75 years (females: RR = 1.07; 95% CI, 1.06–1.07; males; RR = 1.06; 95% CI, 1.05–1.07).

Disease in Infants
There were 7029 cases of infant (aged ≤90 days) invasive GBS disease reported between 1991 and 2010. Between 1991 and 2005, the annual number of cases fluctuated between 265

![Figure 2](https://academic.oup.com/cid/article-abstract/57/5/682/311537/5768215.png)

**Figure 2.** Seasonal pattern of invasive group B streptococcal (GBS) infection, England and Wales, 2001–2010.

![Figure 3](https://academic.oup.com/cid/article-abstract/57/5/682/311537/5768215.png)

**Figure 3.** Rates of early- and late-onset invasive group B streptococcal (GBS) infection, England and Wales, 1991–2010.

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Table 1. Specimen Source of *Streptococcus agalactiae* Isolates in Patients With Invasive Infection, England and Wales, 1991–2010

<table>
<thead>
<tr>
<th>Specimen Sourcea</th>
<th>All Cases</th>
<th>Early Onset (0 to 6 d)</th>
<th>Late Onset (7 to 90 d)</th>
<th>Pediatric (91 d to 14 y)</th>
<th>Adult Disease (≥15 y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>20,637</td>
<td>4436 (96.5)</td>
<td>2254 (90.2)</td>
<td>353 (91.9)</td>
<td>13,021 (97.3)</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td>919</td>
<td>261 (5.8)</td>
<td>520 (20.8)</td>
<td>36 (9.4)</td>
<td>79 (0.6)</td>
</tr>
<tr>
<td>Joint</td>
<td>206</td>
<td>0 (0.0)</td>
<td>12 (0.5)</td>
<td>2 (0.5)</td>
<td>191 (1.4)</td>
</tr>
<tr>
<td>Peritoneum/diaryse</td>
<td>50</td>
<td>0 (0.0)</td>
<td>1 (0.0)</td>
<td>2 (0.5)</td>
<td>47 (0.4)</td>
</tr>
<tr>
<td>Pericardium</td>
<td>32</td>
<td>0 (0.0)</td>
<td>1 (0.0)</td>
<td>0 (0.0)</td>
<td>31 (0.2)</td>
</tr>
<tr>
<td>Intravascular line</td>
<td>43</td>
<td>3 (0.1)</td>
<td>2 (0.1)</td>
<td>5 (1.3)</td>
<td>32 (0.2)</td>
</tr>
<tr>
<td>Pleura</td>
<td>27</td>
<td>0 (0.0)</td>
<td>1 (0.0)</td>
<td>0 (0.0)</td>
<td>26 (0.2)</td>
</tr>
<tr>
<td>Bone</td>
<td>31</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>28 (0.2)</td>
</tr>
<tr>
<td>Brain/spinal cord</td>
<td>20</td>
<td>5 (0.1)</td>
<td>7 (0.3)</td>
<td>1 (0.3)</td>
<td>5 (0.0)</td>
</tr>
<tr>
<td>Lower respiratory tract</td>
<td>36</td>
<td>14 (0.3)</td>
<td>6 (0.2)</td>
<td>5 (1.3)</td>
<td>6 (0.0)</td>
</tr>
<tr>
<td>Liver/bile</td>
<td>12</td>
<td>5 (0.1)</td>
<td>4 (0.2)</td>
<td>0 (0.0)</td>
<td>1 (0.0)</td>
</tr>
<tr>
<td>Otherb</td>
<td>79</td>
<td>28 (0.6)</td>
<td>14 (0.6)</td>
<td>2 (0.5)</td>
<td>30 (0.2)</td>
</tr>
<tr>
<td>Total No. cases</td>
<td>21,386</td>
<td>4531 (100)</td>
<td>2498 (100)</td>
<td>384 (100)</td>
<td>13,376 (100)</td>
</tr>
</tbody>
</table>

*a* *Streptococcus agalactiae* may have been isolated from >1 source in each patient.  

*b* Other sites include aspirate, biopsy, bone marrow, bone pin/plate, eye, gastrointestinal tract, heart/heart valve/pacemaker, intervertebral disc, kidney, lymph nodes, skin/wound, spleen, umbilicus, and upper respiratory tract.

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(0.44/1000 live births) in 2000 and 364 (0.57/1000 live births) in 1997. From 2006 onward, numbers of cases rose steadily from 404 (0.61/1000 live births) to 508 cases in 2010 (0.70/1000 live births). The ratio of early- (0–6 days of age) to late-onset (7–90 days) infant disease changed between 1991 and 2010, with a gradual proportional increase in late-onset disease (Figure 3). Rates of early-onset disease rose between 1991 and 1997 before dropping to reach a low in 2000 of 0.28 per 1000 live births. Subsequent to this, a clearer pattern of increased early-onset disease incidence emerged reaching 0.41 per 1000 births in 2010. Across the 2 decades, a slight increase averaging at 1% per year could be seen in cases of early-onset disease (RR = 1.01, 95% CI, 1.00–1.01), whereas rates increased by 5% per annum between 2005 and 2010 (RR = 1.05, 95% CI, 1.02–1.08). In contrast to early-onset infection, a stronger pattern of increase in late-onset disease was seen over the 2 decades from 0.11 (1991) to 0.29 (2010) per 1000 live births, an average of 5% per year (RR = 1.05, 95% CI, 1.04–1.06). With inclusion of cases in all infants up to 1 year, between 2% and 9% of invasive GBS cases in infants each year were in infants >90 days of age, with no suggestion of an increase in the relative proportion of these cases over the 2 decades.

### Antimicrobial Resistance

Of the 21,386 reports of invasive GBS infection received between 1991 and 2010, 70% (14,998) included information on susceptibility to erythromycin or clindamycin, with no clear trend in overall reporting completeness. Substantial increases in reports of erythromycin-resistant GBS isolates were observed, from <3% during the first half of the 1990s rising to 15% in 2010 (Figure 4). With adjustment for age, sex, and month of diagnosis, rates of erythromycin resistance increased by an average of 13% per annum (odds ratio [OR] = 1.13; 95% CI, 1.11–1.14). A similar pattern was seen across different age groups, although increases in resistant isolates causing infant disease began later (Figure 4). As such, overall rates of erythromycin resistance across 1991–2010 were higher in adults than infants, particularly for patients aged >75 years, whose adjusted rates of resistance were close to double those in infants (OR = 1.76; 95% CI, 1.49–2.10). Erythromycin resistance in isolates causing infant disease rose markedly from 2000 onward, reaching 15% for isolates causing early-onset disease by 2010 and 13% for late-onset isolates. No significant differences were identified between resistance rates in males and females or according to calendar month of disease onset.

Clindamycin susceptibility was reported for only 13% (2778) of isolates between 1991 and 2010, with an increasing proportion of cases including this information over time. Small sample sizes (<50 per annum) precluded meaningful analysis of clindamycin resistance trends prior to 1998. After this period, resistance was reported with increasing frequency, from 3% (2/74) in 1998 to 9% (41/463) in 2010. Of the 418 reports containing susceptibility information for both erythromycin and clindamycin in 2010, 9% (36) reported resistance to both. Of the erythromycin-resistant isolates, 67% (36/54) were also resistant to clindamycin.

### Serotype Distribution

GBS serotypes from sterile site isolates submitted to the national reference laboratory between 1995 and 2010 (n = 4878) were examined. Isolates were submitted from patients of all ages but with a moderate overrepresentation of infant cases (55%) compared to national surveillance data (33%) from this period ($\chi^2[2 df] = 740.4, P < .001$). Six percent of isolates were nontypeable (4% of early-onset cases, 1% of late-onset cases, and 11% of adults); further analyses were undertaken on the remaining isolates (n = 4583). In rank order of frequency, the overall serotype distribution over this period was: type III (40%), Ia (24%), V (14%), II (10%), Ib (9%), IV (1.7%), VI (0.5%), VII (0.4%), VIII (0.4%), and IX (0.3%). Serotype distributions varied significantly with age (Kruskal-Wallis $\chi^2[9 df] = 297.0, P < .001$) with a higher proportion of infant disease (51%) caused by type III than adult disease (25%). Among early-onset infant cases (n = 1215), type distributions were as follows: III (41%), Ia (26%), V (12%), II (9%), Ib (8%), and IV (1%), with type III showing a steady increase in relative distribution from 1997–1998 onward (Figure 5A). Types II and Ib appeared to mirror each other in their relative frequency over this period. Serotype III was particularly dominant among late-onset infant cases (n = 958), responsible for 67% of disease over the combined time period (Figure 5B). The distribution of other serotypes causing late-onset disease was as follows: Ia 18%, Ib 4%, V 5%, II 3%, and IV 1%.

The ranking of serotypes implicated in adult invasive GBS disease (n = 1775) was as follows: III (25%), Ia (25%), II (14%), V (20%), Ib (12%), IV (2%), VI (1%), VIII (1%), VII (<1%), and IX (<1%). The relative frequency of type V among adults increased markedly from 1995 onward, from 9% in 1995–1996
to 24% in 2009–2010, whereas type III fell from 30% to 22% (Figure 5C). Serotype diversity was higher among adult (Simpson index of diversity = 0.197) and early-onset cases (0.271) than late-onset infant cases (0.490).

**DISCUSSION**

Our study has identified a number of longitudinal changes in the epidemiology of invasive GBS infections in England and Wales. A marked increase in overall rates of infection reported over the 20-year period (1991–2010) was seen, from 1.48 to 2.99 per 100 000 population, driven largely by increases in adult disease. By 2010, adults contributed 66% of all invasive GBS reports compared with 51% in 1991. Increases in adult disease have also been noted in the United States and Norway [4, 5, 13]. The reasons for the observed increase in adults are not fully understood, but may be explained in part by an aging UK population and the rising number of patients with chronic disease such as diabetes [14], as observed in GBS studies in the United States [5].

Few national studies have reported rates of invasive GBS disease across the entire population, instead focusing on specific age groups. Of the studies reporting an overall population rate contemporaneous with our study, estimates from Canada, Denmark, Finland, Norway, and Sweden were broadly similar to our study, within the range of 1–4 per 100 000 population [13, 15–18]. In stark contrast, rates from the United States were estimated at more than double, approximately 7 per 100 000 in 2005 [4]. Although differences in case ascertainment methods may explain some of this variation, there appear to be geographical differences not readily explainable by methodological differences [19]. International collaborations should be fostered to explore and better understand these differences.

Rates of infant disease (0–90 days) increased between 1991 and 2010, from 0.42 per 1000 live births to 0.70, largely accounted for by marked increases in late-onset disease, from 0.11 to 0.29. The increases may relate to increased numbers of premature infants, a key risk group for late-onset infection [4, 20]. Our observed rates of late-onset disease were similar to those reported in Finland, the Netherlands, Norway, and the United States [4, 17, 21, 22]. Rates of early onset disease vary considerably across developed countries, in part a reflection of different prevention strategies [19]. UK guidelines for prevention of early-onset GBS disease, based on identification of obstetric risk factors, were introduced in November 2003 [23]. Rates of early-onset disease fell slightly between 2003 and 2005, from 0.35 to 0.31 per 1000 live births, but subsequently increased back to the same rate by 2006. Although it is tempting to look to these data to assess the impact of the UK guidelines, this has to be undertaken with caution, for 2 reasons. First, one cannot determine what the incidence of early-onset disease would have been had the guidelines not been introduced. The rate of late-onset GBS disease may provide a proxy for this; both early- and late-onset disease rose in parallel by 5% per annum from 2005.
to 2010, suggesting a limited impact of the guidelines. Second, as our study was based on culture-positive diagnoses, rates of disease may appear artificially lower owing to failure to culture the organism in the presence of systemic antibiotics given during labor. Assessing the true rate of early-onset disease clearly requires a broader case definition to include culture-negative neonatal sepsis.

Our study identified a slight seasonal variation in disease incidence with rates of infection tending to be higher in the summer and early autumn, similar to patterns reported in the United States [4]. This may in part relate to seasonal variations in numbers of births, being highest in the United Kingdom during July through September, although alternative hypotheses including seasonal effects on carriage of GBS ought to be explored given that the seasonal patterns did not appear to be restricted to infants in our study.

There have been no confirmed cases of penicillin-resistant GBS isolates in the United Kingdom to date, and our data were compatible with this. However, worrying reports from the Far East and United States describing the emergence of clinical GBS isolates with reduced susceptibility to penicillin have been made [24–27]. Resistance to clindamycin, an alternative first-line agent for penicillin-allergic patients, [23] and erythromycin increased substantially during our study period, reaching 9% and 15%, respectively, in 2010, although remaining below levels reported in the United States [28]. The high level of clindamycin resistance has severe implications for treatment options for penicillin-allergic patients, in particular where treatment is given empirically.

Changes in the distribution of serotypes responsible for infant disease were seen over the study period, although serotype III remained dominant, particularly for late-onset disease, consistent with studies in other European countries [22, 29]. Serotype III, in particular the “hypervirulent” clonal complex ST17, has been strongly associated with development of meningitis [29, 30], also reflected in our study, with a higher proportion of meningitis in late-onset cases than any other age group. Given the clinical severity associated with serotype III, our observed increase in the proportion of early-onset disease caused by this serotype is of concern. Of the serotypes Ia, Ib, and III included in the trivalent GBS vaccine currently under clinical trial (ClinicalTrials.gov identifier NCT01193920), these represented 76% of early-onset and 90% of late-onset infant disease over our study period, suggesting a reasonable coverage in this population.

The distribution of serotypes causing adult disease was broadly similar to recent data from France, but at slight variance with data from the United States and Sweden, with relatively less type V in the United Kingdom, although steady rises were noted during our study period [5, 31, 32]. This relatively lower prevalence of type V may in part explain the lower levels of erythromycin resistance in our study compared to the United States given the association of this serotype and resistance [28]. Our confidence in the serotype distributions observed is dependent on complete or representative submission of isolates from diagnostic laboratories, and as such, efforts to improve submission of sterile sites GBS isolates should be made.

In considering our data, the potential underestimation of disease incidence should be borne in mind. Although all microbiology laboratories in England and Wales are active in reporting surveillance data, the quality and quantity of data have fluctuated spatially and temporally. Comparison of routine surveillance data with mandatory returns made as part of the Department of Health’s healthcare-associated infection program suggests reporting completeness of 75% in 2003, rising thereafter to reach 83% in 2010 [33]. As such, approximately 8% of the increases noted during the second decade of the study are likely to be due to improved reporting completeness.

Our data have shown that the epidemiology of invasive GBS disease in England and Wales has changed over the past 2 decades. Although still an important cause of infant infection and death, the relative burden of cases in adults is increasing. Augmenting routine surveillance data with information on risk factors and disease outcome will be essential to the assessment of impact of future prevention strategies in the United Kingdom.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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