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Title: Group B streptococcal (GBS) disease in UK and Irish infants younger than 90 days, 2014-2015. A national surveillance study.

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Background:

Group B *Streptococcus* (GBS) is a leading cause of serious infection in young infants. We aimed to define the current burden and clinical features of invasive GBS disease in infants younger than 90 days in the UK and the Republic of Ireland (ROI), together with the characteristics of disease-causing isolates.

Methods:

Prospective, active national surveillance was undertaken from April 2014 to May 2015 through the British Paediatric Surveillance Unit (BPSU), microbiology reference laboratories and national public health agencies. Results were compared with those obtained from surveillance undertaken using the same methodology in 2000-2001. Isolates were characterised by serotyping, multi-locus sequence typing, and antimicrobial susceptibility testing.

Findings:

Eight hundred and fifty-six cases were identified, an incidence rate of 0.94/1000 live-births. Early onset disease (EOD) represented 60% of cases (0.57/1000) and was higher than in 2000-2001 (0.48/1000). The incidence of late onset disease (LOD) was also higher (0.37/1000 vs. 0.24/1000). The overall case fatality rate (CFR) was 6.2% (n=53), a decline since 2000-2001 (9.7%), reflecting a reduction in EOD CFR (10.6% to 5.2%) but not LOD CFR (8.0% to 7.7%).

The predominant serotypes were III (n=258, 60%) and Ia (n=73, 17%); five serotypes (Ia, Ib, II, III, V) comprised 94% (n=377) of serotyped isolates (n=402).

Interpretation:

The incidence of invasive infant GBS disease in the UK and Ireland has increased since 2000-2001. The burden of EOD incidence has not declined despite the introduction of national prevention guidelines. New strategies for prevention are required.

Funding:

Meningitis Now

Introduction

Streptococcus agalactiae (group B *Streptococcus*, GBS) is an important cause of disease in neonates and young infants. It is the most common cause of serious bacterial infections (septicaemia, pneumonia) in the first week of life and of meningitis in the first three months of life.¹⁻² GBS meningitis is associated with significant long-term neurodisability.³ In a recent systematic review and meta-analysis, the mean case fatality ratio for invasive GBS disease in infants was 9.6%, three times higher in low-income countries (12.6%) than in high-income countries (4.6%).⁴

GBS colonises the gastrointestinal and genital tracts of around 20% of pregnant women.⁵ Transmission from colonised mothers to their infants can occur prior to or during birth, and this may result in early onset disease (in the first 6 days of life, EOD). Late onset disease (LOD) (7-89 days of age) can also result from vertical transmission but also from nosocomial or community transmission. Intravenous antibiotics given to the mother during labour may prevent EOD and intrapartum antibiotic prophylaxis (IAP) strategies have been adopted in many countries.⁶⁻⁸ Such strategies are based either on identifying at-risk women using swab-based screening or on the presence of clinical risk factors.⁹ IAP-based strategies, however, do not prevent LOD.

In 2000-2001, we conducted the first enhanced national surveillance of GBS in the UK and Ireland.¹⁰ We identified 568 cases (incidence, 0.72/1,000 live-births) in the first three months of life, including 377 EOD cases (incidence 0.48/1,000 live-births).

Several initiatives have subsequently been implemented in the UK and Ireland which may have had an impact on the burden of disease in young infants. In 2003, the Royal College of Obstetricians and Gynaecologists (RCOG) published risk-based guidelines for the prevention of EO-GBS (updated in 2012).⁷ In 2012, the National Institute for Health and Care Excellence (NICE)

published guidelines on the prevention and treatment of early onset neonatal infection, which extended the risk factor-based approach to include premature pre-labour rupture of membranes and premature rupture of membranes >18 hours.¹¹

Vaccines against GBS are currently undergoing clinical trials in pregnant women.¹² Knowledge of the current burden of GBS disease and the responsible serotypes is critical for evaluating both the success of current guidelines as well as the potential impact of a GBS vaccination programme in pregnancy.

We undertook an enhanced, prospective, population-based surveillance study of GBS in young infants in the UK and ROI. As the same methodology was used for the 2000-2001 surveillance, we directly compared results between the two time-periods.¹⁰

Methods

Enhanced national surveillance of invasive GBS disease in infants younger than 90 days was undertaken between 1st April 2014 and 30th April 2015 through the British Paediatric Surveillance Unit (BPSU),^{13,14} in collaboration with microbiology reference laboratories, microbiology laboratory surveillance and Public Health agencies in England, Wales, Scotland, Northern Ireland (NI), and ROI.

BPSU reports were made using the “orange card” system, in which an email and/or card was sent on a monthly basis to all consultant paediatricians in the British Isles, asking them to notify any case with a positive sterile site culture for GBS in an infant younger than three months of age. Laboratory-confirmed cases were also identified by interrogation of the Public Health England (PHE) national electronic surveillance database routinely used by hospital laboratories in England, Wales, and NI. Cases were also identified through reference laboratories of PHE,¹⁵ Health Protection Scotland,¹⁶ Public Health Agency NI,¹⁷ and the Irish Meningitis and Sepsis Reference Laboratory (IMSRL),¹⁸ which receive GBS isolates for confirmation and serotyping. All hospital laboratories were encouraged to submit isolates to their respective reference laboratories during the surveillance. At the end of the surveillance period, all hospital laboratories were individually contacted to confirm the completeness of their surveillance.

Finally, cases were ascertained directly from the public health agencies of Scotland, NI, and ROI. In ROI and NI invasive GBS disease has been a notifiable condition since 2012 and 2013 respectively.

Serotyping and multi-locus sequence typing (MLST) of GBS isolates was performed by PHE and IMSRL. Briefly, isolates were cultured onto Columbia agar plates supplemented with horse blood (Oxoid, Thermo Scientific, UK) and incubated aerobically at 37°C for 24 h. Serological classification based on capsular polysaccharide types Ia, Ib and II to IX was performed using latex agglutination according to the manufacturer’s instructions (Statens Serum

Institut, Copenhagen, Denmark). Bacterial cells were re-suspended in a pre-lysis buffer composed of 2 mg lysozyme (Sigma-Aldrich, UK), 120 U mutanolysin (Sigma-Aldrich, UK), 400 µg RNase A (Qiagen, Germany) and 20 µl proteinase K (>600 mAU/mL) and incubated for 1 h at 37°C, 2 h at 56°C followed by 1h at 80°C. DNA was then extracted using the QIAAsymphony SP system and the QIAAsymphony DSP mini kit (Qiagen, Germany) according to the manufacturers' instructions. The sequencing reads were trimmed for quality by removing end nucleotides of Phred quality score of less than 30. The MLST sequence types of isolates were determined from processed sequencing reads using in-house bioinformatics pipelines developed in PHE and an external database (<http://pubmlst.org/sagalactiae/>).¹⁹

To test for antimicrobial susceptibility minimum inhibitory concentrations to erythromycin, clindamycin and penicillin were determined at PHE via agar dilution. For erythromycin and clindamycin, a 0.06 to 128 µg/mL range of antibiotic concentrations were tested and for penicillin a range of 0.015 to 0.5 µg/mL were tested. Iso-Sensitest agar containing 5% horse blood (Oxoid, Thermo Scientific, UK) was inoculated with 1.5x10⁸ CFU/spot of sample using a multipoint inoculator and incubated aerobically overnight at 37°C. British Society of Antimicrobial Chemotherapy (BSAC) criteria were used to determine whether isolates were resistant or susceptible to erythromycin (susceptibility and resistance, ≤0.25 µg/mL and >0.5 µg/mL), clindamycin (susceptibility, ≤0.5 µg/mL) and penicillin (susceptibility, ≤0.25 µg/mL).²⁰

Data from all sources were entered into a single Excel database and de-duplicated at regular intervals. The responsible paediatricians were sent a link to a secure web-based electronic questionnaire, or a paper version of the same questionnaire, which requested information on demographics, antenatal and intrapartum risk factors (in EOD cases), disease presentation and management, and outcomes at hospital discharge. Clinical presentation was defined as meningitis, if the CSF culture was positive and / or if the paediatrician indicated it was treated as meningitis; bacteraemic pneumonia, if the blood culture was positive and there were chest x-ray changes compatible with pneumonia; focal infection, if the blood culture was positive and there were clinical features of a focal infection (typically, septic arthritis or osteomyelitis); and septicaemia, if the blood culture was positive and there were no clinical features of a focal infection. Poor outcome was defined as any major or minor disability identified by the clinician at hospital discharge. For cases where antenatal and intrapartum information was not available, with the named paediatrician's permission, we sought the assistance of the UK Obstetric Surveillance System (UKOSS) to obtain the information.²¹ UKOSS has a nominated reporter in each NHS Trust who has access to maternity and perinatal data.

Risk factors that were sought in EOD cases were those specified in the RCOG guideline for prevention of early-onset GBS disease (maternal fever during labour, known maternal GBS carriage, previous baby with invasive GBS, GBS bacteriuria, suspected chorioamnionitis),⁶ the NICE antibiotics for early onset infection guideline (as above plus premature pre-labour rupture of

membranes, premature rupture of membranes >18 hours), ¹¹ and the CDC Guidelines for the Prevention of Perinatal Group B Streptococcal (GBS) Disease (as above plus rupture of membranes \geq 18 hours and prematurity < 37 weeks). ⁹

Data were analysed using Stata version 13.1 (StataCorp, College Station, Texas). Cases were classified as early or late onset and term (\geq 37 weeks) or premature (<37 weeks). Incidence was calculated using live-births in 2014 (after adjustment for the 13-month surveillance period). Live-births data were obtained from the Office for National Statistics (ONS), ²² National Records of Scotland, ²³ Republic of Ireland Central Statistics Office, ²⁴ and Northern Ireland Statistics and Research Agency. ²⁵ Incidence by birth-weight was calculated for England and Wales, using ONS data. The binomial method was used to calculate 95% confidence intervals (CI). Seven-day and 28-day case fatality rates (CFR) based on the date of diagnosis were calculated.

Continuous data that were non-normally distributed were described as median with interquartile ranges (IQRs).

The study was approved by the South East Coast – Brighton and Sussex Research Ethics Committee (REC Reference: 13/LO/19112). The public health agencies in the UK and Ireland have legal permission to collect laboratory data for infectious disease surveillance and control.

Role of the funding source.

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

There were 856 cases of invasive GBS in infants <3 months of age over the 13-month surveillance period (54.2% male). Information from both paediatricians and microbiology laboratories was available for 657 (76.8%) infants, from microbiology laboratories alone for 142 (16.6%) and from paediatricians alone for 59 (6.9%). Forty-one cases were from twin pregnancies, including six infant pairs.

Positive GBS cultures were obtained from blood in 90% (n=769) of cases, CSF in 9.5% (n=81; CSF alone in 28 [3.3%] cases, CSF and blood in 53 [6.2%] cases) and from joint fluid and blood (n=2) in <1%.

Age at presentation:

More than half the cases (n=517, 60.4%) presented at 0-6 days (EOD), 39.5% presented at 7-89 days (n=339, LOD); 193 (56.9%) of LOD cases presented at 7-28 days and 130 (38.3%) at 29-89 days (specific day not reported for 16 LOD cases) (Supplementary Figure 1). The median age at presentation for LOD disease was 23 days (IQR 15-38); infants born at term presented at a median age of 20 days (IQR 14-30) and those born

prematurely (<37 weeks gestation, representing 38.8% (n=107) of LOD cases), presented at 35 days (IQR 21-55).

Incidence:

The GBS incidence in <90 day-old infants was 0.94/1,000 live-births; EOD incidence 0.57/ 1,000 live births and LOD incidence 0.37/ 1,000 live-births (Table 1). The incidence was similar across the five countries; the lowest incidence was in the Republic of Ireland. When categorized by birth-weight, babies born at <1500g had the highest incidence, approximately 14-fold higher than that of babies >2500g (Table 2, Supplementary Table 1). A similar trend was observed for gestational age (Supplementary Table 2).

Clinical presentation:

The most common clinical syndrome was septicaemia (n=449, 52.5%), followed by meningitis (n=155, 18.1%), bacteraemic pneumonia (n=107, 12.5%) and focal infections (n=6, 0.7%). A lumbar puncture was performed in 86% (n=600) of cases; of the remaining 14%, either the procedure was unsuccessful or the baby deemed too ill for lumbar puncture. Infants with LOD were more likely to present with meningitis than those with EOD (98 [28.9%] vs. 57 [11%]). The overall meningitis incidence was 0.17 per 1,000 live births.

Risk factors:

Overall, 22.2% (n=94) of EOD cases and 38.8% (n=107) of LOD cases were born prematurely and 14.6% (n=62) of EOD cases were born at <35 weeks gestation (Table 3). Notably, 19% (n=55) of LOD cases were on a neonatal

unit at the time of onset and 95% of these babies had been born prematurely. Of the LOD cases presenting from home, 24% were born prematurely. The median gestational age of LOD babies who were resident on neonatal units at the time of presentation was 28 weeks and their median age at disease onset was 34 days.

Among 517 EOD cases, 429 (83%) had available clinical information. Of these, 152 (35.4%) had ≥ 1 RCOG risk factor reported (Table 3); 44% of those with risk factors had received IAP at a median time of 2 hours before delivery (IQR 1-4 hours). For risk factors based on NICE and CDC guidelines, the corresponding figures were 41.3% (n=177) and 59% (n=253).

Isolates:

Isolates were received from 402 (47%) cases. The only significant difference between cases with and without submitted isolates was a higher prevalence of meningitis (22% vs. 14%). The predominant serotypes were III (n=258, 60%) and Ia (n=73, 17%); five serotypes (Ia, Ib, II, III, V) comprised 94% of all isolates (Figure 1, supplementary Table 3). The proportion of serotype III and Ia isolates differed between EOD and LOD cases; 50.7% (n=116) of EOD isolates were serotype III and 20.1% (n=46) were Ia, compared with 72.3% (n=125) and 13.3% (n=23) of LOD isolates respectively. The proportion of serotype III isolates also differed according to disease presentation comprising 78% (n=45) of meningitis isolates, 53% (n=107) of sepsis isolates and 47% (n=25) of bacteraemic pneumonia isolates.

MLST analysis revealed 57 sequence types (ST) (Supplementary Table 4). Twenty-one of the STs were novel, of which seven were single locus variants of ST17. The prevalent STs were ST17 (n=185, 43%) and ST23 (n=55, 13%). The majority of serotype III (n=197, 76%) and Ia isolates (n=55, 75%) belonged to ST17 and ST23 respectively. The majority of meningitis cases were attributable to serotype III / ST17 isolates (n=56, 62%), of these 32.7% (n=18) were attributed to EOD and 67.3% (n=37) to LOD. A greater diversity of STs were identified amongst isolates from EOD (48 STs) than LOD (30 STs) and the majority ($\geq 91\%$) of ST12 and ST28 isolates were associated with EOD cases.

None of the isolates were resistant to penicillin while resistance to clindamycin and erythromycin was identified in 17% (n=72) and 24% (n=101) of isolates respectively. Of the 31 isolates which were resistant to erythromycin but sensitive to clindamycin 15 (48.4%) showed inducible clindamycin resistance. A large proportion of serotype II (n=6, 33%) and V (n=12, 43%) isolates were resistant to erythromycin and clindamycin. Sixteen percent (n=70) of isolates were resistant to both clindamycin and erythromycin. Only 6% (n=28) of isolates were susceptible to tetracycline; 91% (n=389) were fully resistant while 3% (n=12) had intermediate resistance.

Outcomes:

There were 53 deaths (CFR, 6.2%), 41 died within seven days of disease onset (7-day CFR; 4.9%). 21% of the deaths were in infants with meningitis; 3/57 [5.3%] with EOD meningitis and 8/98 [8.2%] with LOD meningitis. Half

the deaths were in premature infants. The highest CFR was in very preterm infants (≤ 33 weeks gestation) with EOD (12/45 cases, 27%), 10-fold higher than that of infants born at term (9/330 cases, 2.7%) (Table 4). Among the 27 EOD deaths, 37% (n=10) had ≥ 1 RCOG risk factors and only one had received IAP.

Of the infants who survived and whose discharge status was known (n=631), 90.6% were clinically well, including 92.6% of EOD and 87.6% of LOD cases.

Discussion

Our study defines the current burden of invasive GBS disease in infants aged <90 days in the UK and Republic of Ireland. It provides information on the risk factors and the changes in disease incidence since the previous national surveillance 15 years ago.¹⁰ We have defined the on-going burden of GBS in a highly vulnerable age group despite national initiatives for prevention, with increased incidence of both EO and LO disease across all five countries of the British Isles.

Approximately 18% of all GBS cases (30% of LOD cases) presented with meningitis, a condition associated with poor outcomes as well as long-term neurodevelopmental impairment among survivors.²⁶ The incidence of GBS meningitis in 2014-2015 (0.17/1000) is similar to that found in our national meningitis surveillance study conducted in 2010-2011 (0.16/1000) and in the previous GBS surveillance in 2000-2001 (0.15/1000).^{27, 10} The burden of GBS meningitis in young infants, therefore, has not changed over the last 15 years.

The relative increase in EOD incidence between the two surveillance periods (0.57/1000 vs. 0.48/1000, 1.2-fold) is lower than the relative increase in LOD incidence (0.37/1000 vs. 0.24/1000, 1.5-fold). One hypothesis for this observation could be an increased use of IAP between the two surveillance periods, as a result of implementation of national guidelines⁶, as this will reduce the relative contribution of EOD to the overall burden.

The CFR was lower than that recorded in 2000-2001 (6.2% vs. 9.7%), primarily among EOD cases (10.6% vs. 5.3%) but not LOD cases (8.2% vs. 7.7%). It is possible that this reflects the implementation of new guidelines for the management of early onset infection in 2012 which promote earlier and more appropriate use of antibiotics and supportive care.⁶

It is difficult to compare risk factors for GBS between the two surveillance studies because not all risk factor data were collected in the first period. We did, however, observe a lower proportion of cases with two of the three risk factors collected in both studies, especially prematurity. Notably, the EOD incidence in infants of low birth weight (<2.5kg) in 2014-15 was nearly half that observed in 2000-01. It is possible, therefore, that clinicians have particularly targeted IAP efforts towards women in preterm labour, and may also reflect the introduction of the new guidelines for the management of early onset infection in 2012 which added pre-labour or prolonged rupture of membranes in premature labour as risk factors for the receipt of IAP.¹¹

Despite this tentative evidence of an impact of national guidelines on subgroups of infants, it is clear that overall the burden of GBS in young infants in the UK and Ireland has not declined. The current guidelines target only EOD cases, identified by the presence of risk factors, yet we have shown that one half to two-thirds of EOD cases do not have such risk factors and are, therefore, not preventable. Since this surveillance was undertaken, the UK national guidelines have been updated again (in 2017) and premature labour added as an additional risk factor for the receipt of IAP.²⁸ This could

potentially add up to 12% more cases to the proportion who might be offered IAP.

Most countries with IAP guidelines to prevent EO GBS disease do so based on culture-based screening at 35-37 weeks gestation.²⁹ The USA experience provides most support for this approach with notable reductions in EO disease from 1.7 per 1000 live-births in the 1990s to 0.21 per 1000 live-births in 2015.³⁰ A smaller number of countries have maintained risk-based guidelines, with reductions in EOD also noted in some (New Zealand⁸ and Denmark³¹), but not in all countries. Most recently, an increasing incidence of EO GBS disease has been described in the Netherlands (from 0.11 to 0.19 per 1000 live births between 1987 and 2011), another country with risk-based prevention guidelines.³²

For both the UK and the Netherlands, this increase in incidence may reflect natural secular trends; for example, the serotypes responsible for both EOD and LOD disease have changed over time in both countries. A particular concern in this regard is the large number of isolates identified as ST17, a clone known to be particularly associated with a high risk of invasive neonatal disease and with meningitis.^{33,34} We do not have MLST data from the previous UK national surveillance study with which to compare; however, there has been an increase in the proportion of cases caused by serotype III between the two surveillance studies and many of these will belong to ST17.

Limitations.

As with any surveillance, our estimates of disease burden should be considered a minimum incidence. Although we attempted to maximize our ascertainment using multiple sources, we recognise that there will inevitably be underreporting of cases. It is also important to emphasize that we have only reported the burden of culture-confirmed cases. Infants with probable (culture-negative) invasive GBS, stillbirths and early pregnancy losses due to maternal GBS, and the potential contribution of GBS to premature births, should all be considered when assessing the burden of this disease.³⁹

We recognise that, in 53% of cases, isolates were not submitted to their respective reference laboratories for analysis and, therefore, the microbiological data are not complete. We note that isolates from cases of meningitis were more likely to have been submitted for confirmation and characterisation could impact the serotype and sequence type profiles that we have reported.

An additional limitation is that the comprehensive surveillance studies were performed at two fixed 13-month time points (2000-1 and 2014-15) and not as part of a continuous surveillance over this 15 year interval. However, national passive surveillance for England and Wales is continuous and has shown that rates of disease have been consistent and slowly risen over the period 2000-2010, in keeping with our findings.⁴⁰

Finally, although invasive GBS disease became notifiable in ROI and NI since the previous surveillance, this is likely to have had only a minimal effect on overall estimates because the proportion of cases notified by non-clinical sources in ROI and NI was similar to that of the other countries. We also cannot comment on the impact of the risk-based IAP recommendations because we do not have information on total deliveries with risk factors who did and did not receive IAP. Clinical and/or microbiological changes in culturing practices may also have changed during the two surveillance periods, but we do not have any evidence to support or refute this.

In conclusion the data from our study, particularly in relation to the increased incidence of invasive GBS disease in 2014-15 compared with 2000-01, together with a rising background incidence ascertained through passive surveillance, and despite the presence of national guidelines for EOD prevention, provide a strong rationale for an effective antenatal GBS vaccine. This is particularly so when considering prevention of LOD because, regardless of the strategy used to identify infants at high risk of EOD, IAP will have no impact on LOD. The leading candidates are capsular polysaccharide-protein conjugate vaccines and our data suggest that a pentavalent conjugate vaccine (containing serotypes Ia, Ib, II, III, V) could cover around 94% of disease-causing isolates in young infants. ¹²

Contributors

C.P.O'S, TL, AE and PTH conceived the idea and designed the study; CPOS, TL, DP, RC, MM, AJR, RC, LD, MB, GK, VC, DL, AS, ED provided epidemiological data and all authors interpreted data. C.P.O'S, SL, TL and PTH analysed the data; C.P.O'S, SL and PTH drafted the manuscript and all authors reviewed and approved the final manuscript.

We declare that we have no conflicts of interest.

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