Group B streptococcal disease in UK and Irish infants younger than 90 days, 2014–15: a prospective surveillance study

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Summary

Background **Group B streptococcus is a leading cause of serious infection in young infants in many countries worldwide. We aimed to define the burden and clinical features of invasive group B streptococcal disease in infants younger than 90 days in the UK and Ireland, together with the characteristics of disease-causing isolates.**

Methods **Prospective, active national surveillance of invasive group B streptococcal disease in infants younger than 90 days was done from April 1, 2014, to April 30, 2015, through the British Paediatric Surveillance Unit, microbiology reference laboratories, and national public health agencies in the UK and Ireland. Early onset was defined as disease in the first 6 days of life and late onset was defined as 7–89 days of life. Incidence was calculated using livebirths in 2014 (after adjustment for the 13-month surveillance period). Isolates were characterised by serotyping, multilocus sequence typing, and antimicrobial susceptibility testing.**

Findings **856 cases of group B streptococcus were identified in 2014–15, an incidence of 0·94 per 1000 livebirths (95% CI 0·88–1·00). Incidence for early-onset disease (n=517) was 0·57 per 1000 livebirths (95% CI 0·52–0·62), and for late-onset disease (n=339) was 0·37 per 1000 livebirths (0·33–0·41). 53 infants died (case fatality rate 6·2%), of whom 27 had early-onset disease (case fatality rate 5·2%) and 26 had late-onset disease (case fatality rate 7·7%). The predominant serotypes were III (241 [60%] of 402 serotyped isolates) and Ia (69 [17%]); five serotypes (Ia, Ib, II, III, V) accounted for 377 (94%) of all serotyped isolates.**

Interpretation **The incidence of invasive infant group B streptococcal disease in the UK and Ireland has increased since a comparable study done in 2000–01. The burden of early-onset disease has not declined despite the introduction of national prevention guidelines. New strategies for prevention are required.**

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Introduction

Streptococcus agalactiae (group B streptococcus) 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 3 months of life in many countries worldwide.[1,2] Group B streptococcal meningitis is associated with substantial long-term neurological disability.[3] In a systematic review and meta-analysis, the mean case fatality ratio for invasive group B streptococcal disease in infants was 9·6%, and almost three times higher in low-income countries (12·6%) than in high-income countries (4·6%).[4]

Group B streptococcus colonises the gastrointestinal and genital tracts of around 20% of pregnant women.[5] Transmission from colonised mothers to their infants can occur before or during birth, and can result in early-onset disease (in the first 6 days of life). Late-onset disease (7–89 days of age) can result from vertical transmission but also from nosocomial or community transmission. Intravenous antibiotics given to the mother during labour can prevent early-onset disease and intrapartum antibiotic prophylaxis has 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.[9,10] However, intrapartum antibiotic prophylaxis does not prevent late-onset disease.[11]

In 2000–01, we did the first enhanced national surveillance of group B streptococcus in the UK and Ireland.[12] We identified 568 cases (incidence 0·72 per 1000 livebirths) in the first 3 months of life, including 377 cases of early-onset disease (incidence 0·48 per 1000 livebirths). Several initiatives have subsequently been implemented in the UK and Ireland that might 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 early-onset group B streptococcal disease (updated in 2012).[6] 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

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Research in context

Evidence before this study

We searched PubMed with the terms "streptococcal infections", "*Streptococcus agalactiae*", "group B streptococcus", "epidemiology", and "prevention", with no language or date restrictions. We restricted the search to studies in humans and in infants aged 0–23 months. The date of our last search was May 12, 2017. We identified one published systematic review and meta-analysis, which estimated a mean incidence of group B streptococcus in infants aged 0–89 days of 0·53 per 1000 livebirths (95% CI 0·44–0·62) with a mean case fatality ratio of 9·6% (95% CI 7·5–11·8). For high-income countries, the incidence estimate was 0·56 (95% CI 0·47–0·65) and for countries with an intrapartum antibiotic prophylaxis policy it was 0·55 (0·46–0·64). A more recent study from the Netherlands reported increasing incidence of early-onset group B streptococcus in infants younger than 3 months from 0·20 per 1000 livebirths in 1987 to 0·32 per 1000 livebirths in 2011, despite the presence of a national risk-based intrapartum antibiotic policy.

Added value of this study

Our study provides comprehensive data on the burden of group B streptococcal disease in young infants in the UK and Ireland with a combined annual birth cohort of 914 132. The incidence of group B streptococcal disease in infants aged 0–89 days (0·94 per 1000 livebirths, 95% CI 0·88–1·00) is substantially higher than estimates in the global systematic review and, in keeping with the recent experience in the Netherlands, has substantially increased during the past decade, despite the presence of national intrapartum antibiotic prophylaxis guidelines for prevention of early-onset disease.

Implications of all the available evidence

The burden of early-onset group B streptococcal disease has not declined in the UK and Ireland, despite national guidelines that target women in labour to receive antibiotics on the basis of the presence of risk factors. Furthermore, the burden of late-onset group B streptococcal disease has increased over time. Our data provide a strong rationale for the development and implementation of an effective antenatal group B streptococcal vaccine. A pentavalent conjugate vaccine (containing serotypes Ia, Ib, II, III, V) would cover around 95% of disease-causing isolates in young infants.

membranes and premature rupture of membranes lasting more than 18 h.[13]

Vaccines against group B streptococcus are being tested in clinical trials in pregnant women.[14] Knowledge of the burden of group B streptococcal disease and the responsible serotypes is crucial for assessing the success of current guidelines as well as the potential impact of a group B streptococcus vaccination programme in pregnancy.

We did a prospective, population-based, enhanced surveillance study of group B streptococcus in young infants in the UK and Ireland. Because the same methods were used for the 2000–01 surveillance, we directly compared results between the two time periods.[12]

Methods

Study design and patients

Enhanced national surveillance of invasive group B streptococcal disease in infants younger than 90 days was done between April 1, 2014, and April 30, 2015, through the British Paediatric Surveillance Unit (BPSU),[15,16] in collaboration with microbiology reference laboratories, microbiology laboratory surveillance, and public health agencies in England, Wales, Scotland, Northern Ireland, and Ireland.

BPSU reports were made using the orange card system, in which an email or card was sent on a monthly basis to all consultant paediatricians in the UK and Ireland, asking them to notify any case with a positive culture for group B streptococcus from a normally sterile site in an infant younger than 3 months of age. Laboratory-confirmed cases were also identified by interrogation of the Public Health England national electronic surveillance database routinely used by hospital laboratories in England, Wales, and Northern Ireland. Cases were also identified through reference laboratories of Public Health England,[17] Health Protection Scotland,[18] Public Health Agency Northern Ireland,[19] and the Irish Meningitis and Sepsis Reference Laboratory,[20] which receive group B streptococcus isolates for confirmation and serotyping. All hospital laboratories were encouraged to submit isolates to their respective reference laboratories during the surveillance period. 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, Northern Ireland, and Ireland. Invasive group B streptococcal disease has been a notifiable condition in Ireland since 2012 and in Northern Ireland since 2013.

The study was approved by the South East Coast–Brighton and Sussex Research Ethics Committee. The public health agencies in the UK and Ireland have legal permission to collect laboratory data for infectious disease surveillance and control. Parental consent was not required.

Procedures

Serotyping and multilocus sequence typing of group B streptococcal isolates was done by Public Health England and the Irish Meningitis and Sepsis Reference Laboratory. 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 done using latex agglutination according to the manufacturer's instructions (Statens Serum Institut, Copenhagen, Denmark). Bacterial cells were resuspended 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 1 h at 80°C. DNA was then extracted using the QIAsymphony SP system and the QIAsymphony 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 multilocus sequence types of isolates were determined from processed sequencing reads using in-house bioinformatics pipelines developed by Public Health England and an external database.[21]

To test for antimicrobial susceptibility, minimum inhibitory concentrations of erythromycin, clindamycin, and penicillin were determined at Public Health England via agar dilution. For erythromycin and clindamycin, a 0·06–128 µg/mL range of antibiotic concentrations was tested, and for penicillin a range of 0·015–0·5 µg/mL was tested. Iso-Sensitest agar containing 5% horse blood (Oxoid) was inoculated with $1·5\times10^8$ colony-forming units per spot of sample using a multipoint inoculator and incubated aerobically overnight at 37°C. British Society of Antimicrobial Chemotherapy criteria were used to determine whether isolates were resistant or susceptible to erythromycin (susceptibility ≤0·25 µg/mL; resistance >0·5 µg/mL), clindamycin (susceptibility ≤0·5 µg/mL; resistance >0·5 µg/mL), and penicillin (susceptibility ≤0·25 µg/mL; resistance >0·25 µg/mL).[22]

Data from all sources were entered into a single Excel database and duplicates removed 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 age, birthweight, demographics, antenatal and intra partum risk factors (in cases of early-onset disease), disease presentation and management, and outcomes at hospital discharge. Clinical presentation was defined as meningitis if cerebrospinal fluid culture was positive or if the paediatrician indicated treatment for meningitis; bacteraemic pneumonia if blood culture was positive and chest radiograph changes were compatible with pneumonia; focal infection if blood culture was positive and clinical features of a focal infection were present (typically, septic arthritis or osteomyelitis); and septicaemia if 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 for which 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. UKOSS has a nominated reporter in each National Health Service Trust who has access to maternity and perinatal data.

For more on **UKOSS** see https://www.npeu.ox.ac.uk/ukoss

Risk factors that were sought in cases of early-onset disease were those specified in the RCOG guideline for prevention of early-onset group B streptococcal disease (maternal fever during labour, known maternal group B streptococcal carriage, previous baby with invasive group B streptococcal disease, group B streptococcal bacteriuria, and suspected chorioamnionitis),[6] the NICE guideline on antibiotics for early-onset neonatal infection (as for the RCOG guideline plus premature pre-labour rupture of membranes, premature rupture of membranes >18 h),[13] and the US Centers for Disease Control and Prevention (CDC) guidelines for the prevention of perinatal group B streptococcal disease (as for the RCOG guideline plus rupture of membranes ≥18 h and prematurity <37 weeks).[9]

For the ***Streptococcus agalactiae* multilocus sequence typing database** see https://pubmlst.org/sagalactiae

Data analysis

Cases were classified as early onset (age 0–6 days) or late onset (age 7–89 days) and term (≥37 weeks) or premature (<37 weeks). Incidence was calculated using livebirths in 2014 (after adjustment for the 13-month surveillance period). Livebirth data were obtained from the Office for National Statistics (ONS),[23] National Records of Scotland,[24] Central Statistics Office of Ireland,[25] and Northern Ireland Statistics and Research Agency.[26] Incidence by birthweight was calculated for England and Wales, using ONS data. The binomial method was used to calculate 95% CIs. 7-day and 28-day case fatality rates based on the date of diagnosis were calculated. Continuous data that were non-normally distributed were described as medians with IQRs. Data were analysed using Stata version 13.1.

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

During the 13-month surveillance period, 856 cases of invasive group B streptococcus were identified in infants younger than 3 months (462 [54%] male). Information was available from both paediatricians and microbiology laboratories for 657 (77%) infants, from microbiology laboratories alone for 140 (16%) infants, and from paediatricians alone for 59 (7%) infants. 41 cases were from twin pregnancies, including six infant pairs.

Positive group B streptococcal cultures were obtained from blood in 756 (88%) cases, cerebrospinal fluid in 94 (11%) cases, and from joint fluid and blood in six (<1%) cases.

	Estimated number of livebirths in 2014*	Total cases (n)	Early-onset cases (n)	Late-onset cases (n)	Incidence per 1000 livebirths (95% CI)		
					Total	Early-onset	Late-onset
England	716 830	686	420	266	0·97 (0·89–1·03)	0·59 (0·53–0·65)	0·37 (0·33–0·42)
Ireland	73 084	54	33	21	0·75 (0·56–0·96)	0·45 (0·31–0·63)	0·29 (0·18–0·44)
Northern Ireland	26 427	26	17	9	0·98 (0·64–1·44)	0·64 (0·38–1·03)	0·34 (0·16–0·65)
Scotland	61 452	56	30	26	0·91 (0·69–1·18)	0·49 (0·33–0·70)	0·42 (0·28–0·62)
Wales	36 339	34	17	17	0·96 (0·65–1·31)	0·47 (0·27–0·75)	0·47 (0·27–0·75)
Total	914 132	856	517	339	0·94 (0·88–1·00)	0·57 (0·52–0·62)	0·37 (0·33–0·41)

*Adjusted for 13-month study period.

Table 1: **Incidence of invasive group B streptococcal disease in young infants in the UK and Ireland, 2014–2015**

	Estimated number of livebirths in 2014*	Total cases (n)	Early-onset cases (n)	Late-onset cases (n)	Incidence per 1000 livebirths (95% CI)		
					Total	Early-onset	Late-onset
<1500 g	7569	64	17	47	8·44 (6·51–10·8)	2·24 (1·31–3·59)	6·20 (4·56–8·23)
1500–2499 g	42 531	81	50	31	1·90 (1·51–2·36)	1·17 (0·87–1·55)	0·73 (0·50–1·03)
≥2500 g	655 259	385	284	101	0·59 (0·53–0·65)	0·43 (0·38–0·49)	0·15 (0·13–0·19)
All	705 359	530	351	179	0·75 (0·69–0·82)	0·50 (0·45–0·55)	0·25 (0·22–0·29)

*Adjusted for 13-month study period.

Table 2: **Incidence of invasive group B streptococcal disease in young infants in England by birthweight, 2014–15**

See Online for appendix

More than half the cases (517 [60%]) presented at 0–6 days (early-onset disease), and 339 (40%) presented at 7–89 days (late-onset disease). 193 (57%) cases of late-onset disease presented at 7–28 days and 130 (38%) presented at 29–89 days (the specific day was not reported for 16 cases of late-onset disease; appendix). The median age at presentation for infants with late-onset disease was 23 days (IQR 15–38); infants born at term presented at a median age of 20 days (14–30) and those born prematurely (<37 weeks' gestation; 107 [39%] of 323) presented at a median of 35 days (21–55).

The incidence of group B streptococcus in infants younger than 90 days was 0·94 per 1000 livebirths (95% CI 0·88–1·00; table 1). Incidence of early-onset disease was 0·57 per 1000 livebirths and incidence of late-onset disease was 0·37 per 1000 livebirths. The incidence was similar across the five countries, with the lowest incidence in Ireland. When categorised by birthweight, babies born weighing less than 1500 g had the highest incidence of group B streptococcus, approximately 14 times higher than that of babies weighing 2500 g or more (table 2, appendix). A similar trend was observed for gestational age, with incidence highest in babies born before 28 weeks' gestation (appendix).

The most common clinical syndrome was septicaemia (449 [62%] of 719 infants), followed by meningitis (155 [22%]), bacteraemic pneumonia (107 [15%]), and focal infections (six [<1%]). A lumbar puncture was done in 600 (84%) of 716 infants; of the remaining 116 (16%), either the procedure was unsuccessful or the baby was deemed too ill for lumbar puncture. Infants with late-onset disease were more likely to present with meningitis than those with early-onset disease (98 [29%] of 339 *vs* 57 [11%] of 517, respectively). The overall incidence of meningitis was 0·17 per 1000 livebirths.

94 (22%) of 423 infants with early-onset disease and 107 (39%) of 276 with late-onset disease were born prematurely, and 62 (15%) infants with early-onset disease were born at less than 35 weeks' gestation (appendix). Notably, 55 (19%) of 290 infants with late-onset disease were on a neonatal unit at the time of onset and 52 (95%) of these babies had been born prematurely. Of the 217 late-onset cases presenting from home, 55 (25%) were born prematurely. The median gestational age of infants with late-onset disease who were resident on neonatal units at the time of presentation was 28 weeks (IQR 25–31) and their median age at disease onset was 34 days (19–55).

Among 517 infants with early-onset disease, 429 (83%) had available clinical information. Of these, 152 (35%) had at least one reported RCOG risk factor (table 3); 67 (44%) of those with risk factors had received intrapartum antibiotic prophylaxis at a median time of 2 h before delivery (IQR 1–4). 177 (41%) of 429 infants with available data had at least one reported NICE risk factor and 253 (59%) had at least one reported CDC risk factor.

Isolates were received from 402 (47%) cases. The only notable difference between cases with and without submitted isolates was a higher prevalence of meningitis in cases with submitted isolates (89 [22%] of 402 *vs* 66 [15%] of 454). The predominant serotypes were III (241 [60%]) and Ia (69 [17%]); five serotypes (Ia, Ib, II, III, V) accounted for 377 (94%) of all serotyped isolates (figure, appendix). The proportions of serotype III and Ia isolates differed between cases of early-onset and late-onset disease; 116 (51%) of 229 isolates from infants with early-onset disease were serotype III compared with 125 (72%) of 173 isolates from infants with late-onset disease. 46 (20%) isolates from patients with early-onset disease were serotype Ia, compared with 23 (13%) from infants with late-onset disease. The proportion of serotype III isolates also differed according to disease presentation, accounting for 45 (78%) of 60 meningitis isolates, 107 (53%) of 201 sepsis isolates, and 25 (47%) of 53 bacteraemic pneumonia isolates.

Multilocus sequence typing analysis revealed 57 sequence types (appendix). 21 of the sequence types were novel, of which seven were single locus variants of ST17. The prevalent sequence types were ST17 (185 [46%] of 402 isolates) and ST23 (55 [13%]). Most serotype III (177 [74%] of 241) and Ia isolates (51 [74%] of 69) belonged to ST17 and ST23, respectively. The majority of meningitis cases were attributable to serotype III/ST17 isolates (56 [64%] of 88), of which 18 (32%) were attributed to early-onset disease and 38 (68%) to late-onset disease. A greater diversity of sequence types was identified among isolates from early-onset disease (48 sequence types) than late-onset disease (30 sequence types) and most (≥91%) ST12 and ST28 isolates were associated with cases of early-onset disease.

None of the isolates were resistant to penicillin, whereas resistance to clindamycin was identified in 72 (17%) of 402 isolates and to erythromycin in 101 (25%) isolates. Of the 31 isolates that were resistant to erythromycin but sensitive to clindamycin, 15 (48%) showed inducible clindamycin resistance. A large proportion of serotype II (six [33%] of 18) and serotype V (12 [43%] of 28) isolates were resistant to erythromycin and clindamycin. 70 (17%) isolates were resistant to both clindamycin and erythromycin. Only 28 (6%) isolates were susceptible to tetracycline; 389 (91%) were fully resistant and 12 (3%) had intermediate resistance.

There were 53 deaths (case fatality rate 6·2%; table 4); 41 infants died within 7 days of disease onset (7-day case fatality rate 4·9%). 52 infants died within 28 days of disease onset. 11 (21%) deaths were in infants with meningitis; three (5·3%) of 57 infants with early-onset meningitis and eight (8·2%) of 98 infants with lateonset meningitis. Just over half (24/46) the deaths were in premature infants. The highest case fatality rate was in very preterm infants (≤33 weeks' gestation) with early-onset disease (12 [26·7%] of 45 cases), ten times higher than that of infants born at term (nine [2·7%] of 330 cases; table 4). Of the 27 infants with early-onset disease who died, ten (37%) had one or more RCOG risk factors and only one had received intrapartum antibiotic prophylaxis.

Of 631 infants who survived and whose discharge status was known, 572 (91%) were clinically well, including 361 (93%) of 390 cases with early-onset disease and 211 (88%) of 241 cases with late-onset disease.

	2000–01	2014–15 (n=429)
Risk factors in RCOG, NICE, and CDC guidelines[6,9,13]		
Known carriage	13 (4%)	39 (9%)
Previous baby with invasive disease	..	2 (<1%)
Group B streptococcal bacteriuria	..	18 (4%)
Maternal fever during labour	..	83 (19%)
Suspected chorioamnionitis	..	133 (31%)
Risk factors in NICE guidelines[13]		
Premature pre-labour rupture of membranes	..	49 (11%)
Premature rupture of membranes >18 h	..	41 (10%)
Risk factors in CDC guidelines[9]		
Prematurity <37 weeks	131 (37%)	94 (22%)
Rupture of membranes >18 h	140 (44%)	136 (32%)

Data are number of infants with risk factor (%). RCOG=Royal College of Obstetricians and Gynaecologists. NICE=National Institute for Health and Care Excellence. CDC=Centers for Disease Control and Prevention.

Table 3: **Risk factors in cases of early-onset group B streptococcus in 2014–15 and 2000–01**

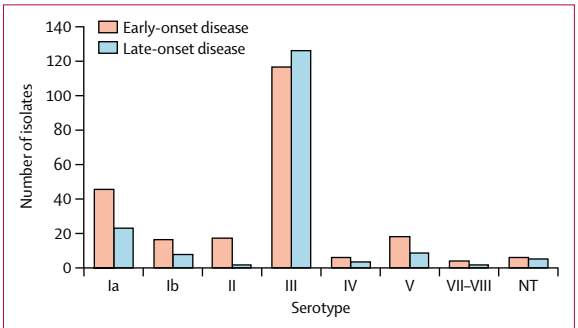

Figure: **Serotypes of group B streptococcus associated with cases of invasive disease, 2014–15**
Total number of serotyped isolates: early-onset disease, n=229; late-onset disease, n=173. NT=non-typeable.

	Overall	Early-onset disease	Late-onset disease
Total	53/856 (6·2%)	27/517 (5·2%)	26/339 (7·7%)
Gestational age*			
≤33 weeks	19/117 (16·2%)	12/45 (26·7%)	7/72 (9·7%)
34–36 weeks	4/79 (5·1%)	3/49 (6·1%)	1/30 (3·3%)
≥37 weeks	20/492 (4·0%)	9/330 (2·7%)	11/165 (6·7%)

Data are number of deaths/number of cases (case fatality rate, %). *Ten deaths were not recorded in the gestational age chart as their gestational ages were unavailable.

Table 4: **Case fatality rate of invasive group B streptococcal disease in young infants in the UK and Ireland overall and by gestational age, 2014–15**

Discussion

Our study defines the burden of invasive group B streptococcal disease in infants younger than 90 days in the UK and Ireland. It provides information on risk factors and changes in disease incidence since the previous national surveillance 15 years ago.[12] We have defined the continuing burden of group B streptococcus in a highly vulnerable age group despite national initiatives for prevention, with increased incidence of both early-onset and late-onset disease across all five countries of the British Isles.

Approximately 18% of all infants with group B streptococcus (30% of cases of late-onset disease) presented with meningitis, a condition associated with poor outcomes as well as long-term neurodevelopmental impairment among survivors.[27] The incidence of group B streptococcal meningitis in 2014–15 (0·17 per 1000 livebirths) was similar to that found in our national meningitis surveillance study in 2010–11 (0·16 per 1000 livebirths)[28] and in the previous group B streptococcus surveillance in 2000–01 (0·15 per 1000 livebirths).[12] Therefore, the burden of group B streptococcal meningitis in young infants has changed little over the past 15 years.

The relative increase in incidence of early-onset disease between the two surveillance periods (0·57 per 1000 livebirths in 2014–15 *vs* 0·48 per 1000 in 2000–01; 1·2-fold increase) is lower than the relative increase in incidence of late-onset disease (0·37 per 1000 *vs* 0·24 per 1000; 1·5-fold increase). One hypothesis for this observation could be an increased use of intrapartum antibiotic prophylaxis between the two surveillance periods, as a result of implementation of national guidelines,[6] because this would reduce the relative contribution of early-onset disease to the overall burden.

The case fatality rate was lower in 2014–15 than in 2000–01 (6·2% *vs* 9·6%), primarily among cases of early-onset disease (10·6% *vs* 5·2%) but not late-onset disease (8·2% *vs* 7·7%). These findings might reflect the implementation of new guidelines for the management of early-onset infection in 2012, which promoted earlier and more appropriate use of antibiotics and supportive care.[6]

It is difficult to compare frequency of risk factors for group B streptococcus 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 incidence of early-onset disease in infants of low birthweight (<2·5 kg) in 2014–15 was much higher than that observed in 2000–01 (1·34 per 1000 livebirths and 1·81 per 1000 livebirths). These findings might suggest that clinicians have particularly targeted intrapartum antibiotic prophylaxis efforts towards women in preterm labour, and also reflect the introduction of 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 intrapartum antibiotic prophylaxis.[13]

Despite this tentative evidence of an impact of national guidelines on subgroups of infants, it is clear that overall the burden of group B streptococcus in young infants in the UK and Ireland has not declined. The current guidelines target only cases of early-onset disease, identified by the presence of risk factors, yet we have shown that half to two-thirds of cases of early-onset disease do not have such risk factors and are, therefore, not preventable. Since this surveillance was done, the UK national guidelines have been updated again (in 2017) with premature labour added as an additional risk factor for the receipt of intrapartum antibiotic prophylaxis.[29] This addition could potentially add up to 12% more cases to the proportion who might be offered intrapartum antibiotic prophylaxis.

Most countries with intrapartum antibiotic prophylaxis guidelines to prevent early-onset group B streptococcal disease do so on the basis of culture-based screening at 35–37 weeks' gestation.[30] Experience from the USA provides most support for this approach with notable reductions in early-onset disease from 1·7 per 1000 livebirths in the 1990s to 0·21 per 1000 livebirths in 2015.[31] A smaller number of countries have maintained risk-based guidelines, with reductions in early-onset disease also noted in some (New Zealand[7] and Denmark[32]), but not all, countries. An increasing incidence of early-onset group B streptococcal disease has been described in the Netherlands (from 0·11 to 0·19 per 1000 livebirths between 1987 and 2011), another country with risk-based prevention guidelines.[33]

For the UK and the Netherlands, this increase in incidence might reflect natural secular trends; for example, the serotypes responsible for both early-onset and late-onset 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 associated with a particularly high risk of invasive neonatal disease and meningitis.[34,35] We do not have multilocus sequence typing data from the previous UK national surveillance study for comparison; 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.

As with any surveillance, our estimates of disease burden should be considered a minimum incidence. Although we attempted to maximise our ascertainment using multiple sources, we recognise that there will inevitably be under-reporting of cases. We have only reported the burden of culture-confirmed cases. Infants with probable (culture-negative) invasive group B streptococcus, stillbirths and early pregnancy losses due to maternal group B streptococcus, and the potential contribution of group B streptococcus to premature births, should all be considered when assessing the burden of this disease.[36]

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

An additional limitation is that the comprehensive surveillance studies were done at two fixed 13-month timepoints (2000–01 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 2000–10, in keeping with our findings.[37]

Finally, although invasive group B streptococcal disease became a notifiable condition in Ireland and Northern Ireland 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 Ireland and Northern Ireland was similar to that of the other countries. We also cannot comment on the impact of the risk-based intrapartum antibiotic prophylaxis recommendations because we do not have information on total deliveries with risk factors that did and did not receive intrapartum antibiotic prophylaxis. Clinical or microbiological changes in culture practices might 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 group B streptococcal 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 prevention of early-onset disease, provide a strong rationale for an effective antenatal group B streptococcus vaccine. This conclusion is particularly relevant when considering prevention of late-onset disease because, irrespective of the strategy used to identify infants at high risk of early-onset disease, intrapartum antibiotic prophylaxis will have no effect on the incidence of late-onset disease. 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.[14]

Contributors

CPO'S, TL, AE, and PTH conceived the idea and designed the study; TL oversaw the development of the web-based survey application with design input from CPO'S, PTH, and AE. CPO'S, TL, DP, RCu, MM, AJR, RCa, LD, MB, GK, VC, DL, AS, and ED provided laboratory surveillance data and all authors interpreted data. CPO'S, SL, TL, and PTH analysed the data. CPO'S, SL, CEJ, and PTH drafted the manuscript and all authors reviewed and approved the final manuscript.

Declaration of interests

PTH is a scientific advisory group member to the WHO project Developing a Value Proposition for Vaccines Against Group B Streptococcal Disease and a member of the UK RCOG Prevention of Early-onset Neonatal Group B Streptococcal Disease Guideline. TL and DP have received grants from Meningitis Now. All other authors declare no competing interests.

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