**Group B Streptococcal disease in England (1998 – 2017): a population based observational study**

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Article’s main point

The burden of neonatal GBS has remained unchanged over the last 19 years despite national antenatal and postnatal initiatives. The significant decline in mortality is likely due to rapid advances on the NICU, including administering antibiotics and identifying infected cases earlier.

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**Abstract**

**Background and Objectives**

Group B Streptococcus (GBS) is the leading cause of sepsis and meningitis in infants <90 days. In this study, the burden of GBS disease and mortality in young infants in England was assessed.

**Methods**

Using linked hospitalisation records from every National Health Service (NHS) hospital from 1 April 1998 to 31 March 2017, we calculated annual GBS incidence in infants aged <90 days and, using regression models, compared their perinatal factors, rates of hospital-recorded disease outcomes and all-cause infant mortality rates with those of the general infant population.

**Results**

15,429 infants aged <90 days had a hospital-recorded diagnosis of GBS, giving an average annual incidence of 1.28 per 1000 live births (95% CI 1.26-1.30) with no significant trend over time. GBS-attributable mortality declined significantly from 0.044 (95%CI 0.029–0.065) per 1000 live births in 2001 to 0.014 (95%CI 0.010–0.026) in 2017 (annual percentage change -6.6, 95%CI -9.1 to -4.0). Infants with GBS had higher relative rates of visual impairment (HR 7.0 95% CI 4.1-12.1), cerebral palsy (HR 9.3 95% CI 6.6-13.3), hydrocephalus (HR 17.3 95% CI 13.8-21.6) and NEC (HR 18.8 95% CI 16.7-21.2) compared with those without GBS.

**Conclusions**

Annual rates of GBS disease in infants have not changed over 19 years. The reduction in mortality is likely multifactorial and due to widespread implementation of antibiotics in at-risk mothers and babies as well as advances in managing acutely unwell infants. New methods for prevention, such as maternal vaccination, must be prioritised.

Abbreviations:

EoD Early onset disease

LoD Late onset disease

GBS Group B Streptococcus

HES Hospital Episode Statistics

NHS National Health Service

NICE National Institute for Health and Care Excellence

PROM Premature rupture of membranes

RCOG Royal College of Obstetricians and Gynaecologists

**Introduction**

Approximately 20–35% of pregnant women are colonised with *Streptococcus agalactiae* (Group B Streptococcus; GBS) (1). Vertical transmission occurs in around half of these cases and invasive bacterial disease develops in approximately 1% of neonates born to colonised mothers (2). GBS is a common cause of serious bacterial infection (sepsis and pneumonia) in the first week of life and is the leading cause of meningitis in infants aged >90 days (3,4).

In the UK, GBS accounts for 50% of bacterial meningitis cases in young infants (5). An enhanced surveillance study conducted by the British Paediatric Surveillance Unit (BPSU) showed that the incidence of GBS disease in the UK and Republic of Ireland was 0.94 per 1000 livebirths (95% CI 0.88 – 1.00) in 2014-15 with a 28-day case fatality rate of 6.2% (6). Furthermore, GBS accounted for a third of deaths caused by bacteria and 11% of all infection-related deaths in neonates in England and Wales (7). Sequelae after GBS disease include cerebral palsy, visual impairment, hearing loss and epilepsy and one study has described an association between early onset GBS disease and necrotising enterocolitis (NEC) (8,9). Maternal GBS colonisation may also be a risk factor for premature birth but the mechanism for this is unclear (10,11). A global meta-analysis, which included 45 studies, demonstrated an odds ratio of 1.85 (95% CI, 1.24-2.77; p=0.03) for preterm birth <37 weeks and maternal GBS colonisation (12).

In the UK in 2003, the Royal College of Obstetricians and Gynaecologists (RCOG) proposed a risk-based approach to prevent early-onset (in the first 6 days of life) neonatal GBS disease . These guidelines were updated in 2017 to extend intrapartum antibiotic prophylaxis (IAP) to women in established preterm labour or where GBS was detected in the previous pregnancy (13). In 2012, the National Institute for Health and Care Excellence (NICE) published guidelines on the prevention and treatment of early-onset sepsis in neonates (<https://www.nice.org.uk/guidance/cg149>). An update in 2017 included consideration of IAP for women in preterm labour with premature rupture of membranes (PROM) or intrapartum rupture of membranes lasting longer than 18 hours.

The objective of this study was to measure the annual incidence of neonatal GBS over the last two decades in England, and to compare infants with and without GBS with respect to perinatal characteristics and their relative rates of specified morbidity and mortality outcomes. A secondary objective was to evaluate the effect of the NICE and RCOG guidelines on rates of neonatal GBS diagnoses and GBS-related outcomes in England.

**Methods**

Data sources

We analysed record-linked English National Hospital Episode Statistics (HES) covering all Finished Consultant Episodes (FCEs) relating to inpatient and day case care (including deliveries) in England between 1 April 1998 and 31 March 2017 (14)[[1]](#footnote-1). Each FCE record contains demographic and clinical information; diagnoses are coded by International Classification of Diseases (ICD). Multiple FCEs from the same individual were linked by NHS Digital. We also analysed a separate dataset comprising mortality certifications from 1Jan 2001 to 31 Dec 2017.

HES data were supplied by NHS Digital. Mortality records were collected by the Office for National Statistics and supplied by NHS Digital. Ethical approval to study the record-linked datasets was obtained from the Central and South Bristol Multi-Centre Research Ethics Committee (04/Q2006/176). All patient records were pseudonymized by the data providers through encryption of personal identifiers.

Incidence and mortality trends

We ascertained the numbers of infants with a hospital record of GBS (ICD10 P36.0 coded in any diagnostic field) in each year from 1 Apr 1998 to 31 Mar 2017, expressed as annual rates per 1,000 live births. We confined the analyses to those recorded as being aged <90 days at the end of their FCE. Since exact date of diagnosis is not recorded , we could not distinguish early- and late-onset disease. Only the earliest-dated GBS record per individual was counted if, for example, following transfer or re-admission, there was more than one. , We similarly ascertained annual rates of GBS mortality per 1,000 live births (where GBS was coded anywhere on the death certificate, irrespective of underlying cause) for the period 1 Jan 2001 to 31 Dec 2017 (ICD10 was not implemented on death records before 2001). Time trends and annual percentage changes were modelled using Poisson regression, assuming a constant rate of change, with scaling adjustment to correct for overdispersion. We ran interrupted time-series analyses to identify any step changes in GBS incidence and mortality rates that might have occurred after publication of RCOG guidelines ( 2003) or NICE guidelines (2012).

Perinatal and maternal factors

Every HES record relating to a mother’s delivery episode or an infants’ birth episode contains an additional ‘maternity tail’, that documents the characteristics of the mother and the child at birth as described in the HES Data Dictionary [<https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics/hospital-episode-statistics-data-dictionary>]. Between 1 April 1998 to 31 March 2012, mother-infant pairs were linked by the Unit of Health-Care Epidemiology, University of Oxford, as described elsewhere (15). This linkage enabled pooling of all available information for both the mother and the child. Using multivariable logistic regression, we compared neonates with and without recorded GBS in relation to: infant’s sex, gestational age at birth (weeks), birthweight (grams), mother’s reported ethnicity, mode of delivery, maternal age, mother’s deprivation level (using the Index of Multiple Deprivation,), number of previous deliveries, premature rupture of membranes (PROM), chorioamnionitis, and maternal septicaemia (clinical diagnosis). To assess any effect of the RCOG guidelines on the strength of associations with gestational age at birth, PROM, chorioamnionitis and maternal septicaemia, adjusted odds ratios for these factors were also calculated separately for the periods 1998-2003 and 2004-2012, by fitting interaction terms between GBS and these periods.

Rates of sequelae

Using the linked HES dataset (1 April 1998 to 31 March 2017), hazard ratios, adjusted for year, were calculated using Cox’s proportional hazards models to compare neonates with and without GBS for subsequent diagnoses of epilepsy, cerebral palsy, visual impairment, hearing loss, hydrocephalus or necrotising enterocolitis before 1 year of age (identified using ICD codes in **Table 1** and censored for death), and hospital-recorded infant mortality (i.e. where the ‘discharge method’ indicated that the patient had died [*dismeth=4*]). To assess any effect of the NICE and RCOG guidelines on the relative incidence of these outcomes in infants with and without GBS, hazard ratios were also calculated separately for the periods 1998-2003, 2004-2012, 2013-2017, by fitting interaction terms between GBS status and these periods.

Stillbirths

Stillbirths were identified through the following codes:(i) birth status (*birstat = 2 or 3 or 4*); (ii) hospital discharge method (*dismeth = 5*); (iii) ICD10 diagnosis code (P95, Z37.1, Z37.3, Z37.4, Z37.6, Z37.7). These were excluded from all analyses, but the number of stillbirths with a GBS-related ICD code was noted.

**Results**

Overall, 15,429 infants aged < 90 days in England with a GBS diagnosis were identified between 1 April 1998 to 31 March 2017, giving an average annual incidence rate of 1.28 infants (95% CI 1.26-1.30) per 1,000 live births. The annual incidence rates ranged from 1.13 (1.04-1.21) to 1.47 (1.39-1.57) per 1000 live births (**Figure 1**), with no significant trend over time (p=0.370). Between 2001 and 2017, 267 deaths were registered in England with GBS recorded as a cause. Annual GBS-related mortality rates declined significantly (**Figure 2**) from 0.044 (95%CI 0.029–0.065) per 1000 live births in 2001 to 0.014 (95%CI 0.010–0.026) in 2017. This represented a modelled annual percentage change of -6.6% (95% CI -9.1 to -4.0, p<0.0001) over the 19-year period.

Analysis of the linked mother-infant pairs dataset (6,063,962 pairs) from 1 Apr 1998 to 31 Mar 2012, showed that, after adjustment for year of birth, maternal age, maternal deprivation and gestational age at birth, significant risk factors included mothers with chorioamnionitis, mother septic at delivery, and PROM. (**Table 2**). The association between PROM and GBS was stronger in 1998-2003 than 2004-2012: respectively, OR 3.3, 95% CI 3.2-3.9 and OR 2.3, 95% CI 2.2-2.5 (LR heterogeneity test, p<0.0001). The same was true of the strength of association with maternal septicaemia: respectively, OR 8.0, 95% CI 6.8-9.4 and OR 6.1, 95% CI 5.5-6.9, (LR heterogeneity test, p=0.0099). The association with chorioamnionitis remained relatively consistent: respectively, OR 6.7, 95% CI 4.7-9.5 and 6.2, 95% CI 4.9-7.8 (LR heterogeneity test, p=0.69).

Gestational age at birth of <26 weeks (compared with >=37 weeks) was associated with 22-times higher odds of GBS diagnosis (95% CI 17.6–27.3, p<0.0001), at 26-31 weeks with 16.6-times higher odds (95% CI 15.1–18.3, p<0.0001) and at 32-36 weeks with 5.2-times higher odds (95% CI 4.8–5.5, p<0.0001). The associations with <26 weeks and 26-31 weeks gestation were significantly stronger in later years: respectively, OR 26.5 (20.6-34.1) and OR 19.4 (17.3-21.7) in 2004-2012, compared with OR 13.9 (8.8-21.9) and 12.01 (10.0-14.4) in 1998-2003. Notably, babies born <32 weeks gestation represented a larger proportion of GBS cases in the later period (12.1% in 2004-2012, *versus* 8.7% in 1998-2003), whereas the overall distribution by gestational age of babies not diagnosed with GBS remained relatively unchanged. Vaginal delivery (OR 3.5, 2.9–4.1, p<0.0001) and emergency caesarean delivery (8.8, 7.5–10.4, p<0.0001) were strongly associated with GBS compared with elective caesarean delivery. GBS was around 30% less common in infants of mothers who had given birth previously and nearly 20% less common in female babies (**Table 2**). GBS was more common in babies of mothers whose reported ethnicity was Black (OR 1.3, 1.2–1.5) compared with White, and more common in infants of younger mothers (≥24 years) compared with those aged 30-34 years. There was no observable association between GBS disease and deprivation. (**Table 2**)

Infants diagnosed with GBS were significantly more likely than the general infant population to be diagnosed with specified sequelae within the first year of life: (**Table 3**). The margins of increased incidence of epilepsy/seizures, hydrocephalus and NEC relative to the general population were significantly greater in later periods (**Table 3**).

Absolute rates of in-hospital infant mortality after GBS diagnosis declined over time (**Table 3**), corroborating the findings from death certifications. Nevertheless, neonates with GBS disease were, overall, 9 times more likely to die in infancy than those without GBS (95% CI 8.2–10.0, p<0.0001); this ratio remained largely unchanged throughout the study. Only 35 cases of stillbirth in conjunction with GBS diagnosis were recorded in HES in England between 1998 and 2017.

**Discussion**

The hospital-recorded incidence of GBS disease in England over the last two decades has remained broadly unchanged despite the introduction of different national initiatives to prevent infection. However, during the same period we have observed a significant reduction in GBS mortality rates. Our findings indicate that the 2003 RCOG guidelines, which stated that clinicians should consider giving intrapartum antibiotic prophylaxis to a mother in the presence of certain risk factors including PROM or maternal temperature >38oC, may have had a modest effect in reducing the relatively high rates of GBS in babies born to mothers with these risk factors.

Our findings on GBS incidence are broadly consistent with other studies. The incidence of both EoD and LoD in the 2014-2015 British Paediatric Surveillance Unit (BPSU) study (6) was higher than in a 2000-2001 study which used the same methodology (16). A laboratory surveillance study in England and Wales also showed an increase in EoD (0.28 per 1000 live births in 2000 vs 0.41 per 1000 live births in 2010) and LoD (0.11 per 1000 live births in 1991 vs 0.29 per 1000 live births in 2010) (17). The apparently stable trend in hospital diagnosis rates could be influenced by several factors, such as the absence of a universal maternal screening programme, implementation of RCOG guidelines and more recently improved surveillance.

According to death certifications, the GBS-attributable mortality rate more than halved between 2001-2017. Hospital-recorded all-cause infant mortality after GBS diagnosis also declined significantly. Similarly, in the 2014-15 BPSU study, the 28-day case fatality rate was lower than in the 2000-2001 study (6.2% vs 9.6%, respectively). The reasons for this are likely multifactorial. The RCOG 2003 and NICE 2012 guidelines, which advocate early use of antibiotics in at-risk mothers and infants, may have contributed to more GBS-infected infants surviving. The administration of early antibiotics may conceivably reduce bacterial load in the infected foetus/infant and thus prevent stillbirth or neonatal death but lead to a greater number of extremely preterm babies surviving. This may explain why extremely preterm births represented an increasingly large proportion of GBS cases later in our study. A prospective study of 6075 deaths in extremely preterm infants in the USA reported a reduction in infection-related deaths from 55 (95% CI 50-61) per 1000 livebirths in 2000–2003 to 45 (95% CI 41- 50) per 1000 livebirths in 2008-2011 (18). This supports the argument that guidelines to empirically commence antibiotics in at-risk and extremely preterm babies may increase survival rates. Reduced GBS mortality could also be due to general improvements in care of premature babies, including wider use of high frequency ventilation, surfactant and transferring acutely unwell and extremely preterm babies to tertiary units via established regional networks (19). Data from a large prospective UK cohort study of 22–25 week gestation neonates showed an increase in survival from 39% in 1995 to 52% in 2006 of babies admitted to NICU (Neonatal Intensive Care unit) (20). However, the relative (around 9-fold higher) infant mortality rate of GBS-infected babies compared with that of the general infant population remained consistently high throughout the 19 year study period, suggesting that there have been no additional improvements made in babies with GBS.

Our findings emphasise the importance of chorioamnionitis, maternal sepsis at delivery and premature rupture of membranes as risk factors for infant GBS disease, all now recognised in UK prevention guidelines. That babies born <32 weeks gestation represent a significantly larger proportion of GBS cases in the later study period study provides further rationale for recent national initiatives to reduce prematurity. Similarly, that GBS was more common in babies of mothers reporting Black ethnicity suggests that public health initiatives to reduce racial inequality are also required; this does not seem to be explained by deprivation.

It is difficult to disentangle the causative pathway of preterm birth, GBS and sequelae. Our study did not control for gestational age when investigating sequelae, so comparisons are with the general infant population. All of the sequelae studied were significantly more common in GBS-diagnosed infants than in the general infant population but are also more common in preterm infants. We also found that the rates of epilepsy/seizures, hydrocephalus and necrotising enterocolitis in GBS-infected infants have increased significantly over the last two decades in England, which may be explained by more extremely preterm babies with GBS surviving.

NEC is a gastrointestinal emergency, affecting up to 5% of premature infants and carries mortality rates up to 30% (21). The pathogenesis of NEC is poorly understood but defects in the host–microbiome commensalism are likely to contribute (22). Our study, which included nearly 300 infants with both GBS disease and NEC, showed the risk of NEC to be 19-times higher in infants with GBS disease. One possible explanation is that infants with GBS will have received prolonged antibiotic courses which may have caused intestinal dysbiosis, in turn leading to NEC. A systematic review of five observational studies in over 5000 infants showed an association between prolonged antibiotic exposure and the development of NEC in the neonatal period (23). These data should remind clinicians to use antibiotics judiciously and follow evidence-based guidelines to manage infants with suspected sepsis (24). Clinicians should have a heightened awareness that GBS infected infants may develop NEC and follow feeding guidelines and other medical strategies to prevent NEC in this cohort (25).

To our knowledge, this is the largest continuous study evaluating epidemiological trends and features of neonatal GBS disease. Nevertheless, there are some important limitations. The reliability of HES data depends on the ability to appropriately code information collected from clinical notes. This is particularly relevant when making comparisons over time, as completeness and accuracy of routinely collected data and surveillance may vary from one year to the next. ICD codes rely on clinical information and may include cases who do not have positive blood or CSF cultures. The limitations of the perinatal dataset are discussed elsewhere (15); in brief, there were quite high numbers of missing values for variables such as birth status, parity, birthweight, gestational age, and ethnicity (Appendix). These missing data are unlikely to have caused bias in relation to GBS diagnosis providing that the shortfall was random, but it does reduce statistical power. Additionally, knowledge of maternal GBS colonisation status or awareness of a baby’s GBS colonisation status may have led to GBS-related ICD codes being used when these facts may not have been relevant to the condition of the baby. We were not able to distinguish between early and late onset disease and thus cannot further elucidate the impact of different preventive strategies in relation to timing of disease. We also do not have data pertaining to the age of onset of GBS disease where associated mortality and sequelae are likely to be variable. This study contains no laboratory (serotyping or antimicrobial susceptibility) data..

Epidemiological data from the 2014-15 BPSU study suggest that a pentavalent GBS conjugate vaccine could cover 94% of all isolates in young infants with GBS disease in the UK (6). Several vaccine candidates planned for use in pregnant women are currently being trialled (37) and these offer the potential for long-term reduction in the burden of GBS disease.

In conclusion, theannual incidence of hospital-diagnosed GBS in infants <90 days old remained steady in England during the 19-year study period, despite the implementation of national risk-based intra-partum antibiotic guidelines. GBS mortality rates, however, have declined steadily over the last 19 years, yet the relative rates of sequelae and overall mortality in neonates with GBS disease remain substantial in comparison with the general infant population. The unchanged incidence, significant burden in preterm infants, high rates of long-term sequelae and early death suggest that further initiatives are warranted to prevent/ control GBS disease.

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**References**

1. Jones N, Oliver K, Jones Y, Haines A, Crook D. Carriage of group B streptococcus in pregnant women from Oxford, UK. J Clin Pathol. 2006;59(4):363–6.

2. Russell NJ, Seale AC, O’Sullivan C, Le Doare K, Heath PT, Lawn JE, et al. Risk of Early-Onset Neonatal Group B Streptococcal Disease with Maternal Colonization Worldwide: Systematic Review and Meta-analyses. Clin Infect Dis. 2017;15(65 (suppl 2)):S152–S159.

3. Okike IO, Ladhani SN, Johnson AP, Henderson KL, Blackburn RM, Muller-Pebody B, et al. Clinical Characteristics and Risk Factors for Poor Outcome in Infants Less Than 90 Days of Age With Bacterial Meningitis in the United Kingdom and Ireland. Pediatr Infect Dis J. 2018;37(9):837–43.

4. Le Doare K, Heath PT. An overview of global GBS epidemiology. Vaccine. 2013;31(4):7–12.

5. Okike IO, Johnson AP, Henderson KL, Blackburn RM, Muller-Pebody B, Ladhani SN, et al. Incidence, etiology, and outcome of bacterial meningitis in infants aged. Clin Infect Dis [Internet]. 2014;59(10):e150-7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24997051

6. O’Sullivan CP, Lamagni T, Patel D, Efstratiou A, Cunney R, Meehan M, et al. Group B streptococcal disease in UK and Irish infants younger than 90 days, 2014–15: a prospective surveillance study. Lancet Infect Dis. 2019;19(1):83–90.

7. Depani SJ, Ladhani S, Heath PT, Lamagni TL, Johnson AP, Pebody RG, et al. The contribution of infections to neonatal deaths in England and Wales. Pediatr Infect Dis J. 2011;30(4):345–7.

8. Bedford H, de Louvois J, Halket S, Peckham C, Hurley R, Harvey D. Meningitis in infancy in England and Wales: Follow up at age 5 years. BMJ. 2001;323(533).

9. Stafford IA, Rodrigue E, Berra A, Adams W, Heard AJ, Hagan JL, et al. The strong correlation between neonatal early-onset Group B Streptococcal disease and necrotizing enterocolitis. Eur J Obstet Gynecol Reprod Biol. 2018;223:93–7.

10. Lin FC, Weisman LE, Troendle J, Adams K. Prematurity Is the Major Risk Factor for Late‐Onset Group B Streptococcus Disease. J Infect Dis. 2003;188:267–71.

11. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75–84.

12. Bianchi-Jassir F, Seale AC, Kohli-Lynch M, Lawn JE, Baker CJ, Bartlett L, et al. Preterm Birth Associated with Group B Streptococcus Maternal Colonization Worldwide: Systematic Review and Meta-analyses. Clin Infect Dis. 2017;65:S133–42.

13. Prevention of Early-onset Neonatal Group B Streptococcal Disease: Green-top Guideline No. 36. BJOG An Int J Obstet Gynaecol. 2017;124(12):280–305.

14. Centre. NH and SCI. NHS Maternity Statistics—England.

15. Goldacre RR. Associations between birthweight, gestational age at birth and subsequent type 1 diabetes in children under 12: a retrospective cohort study in England, 1998–2012. Diabetologia. 2018;616–25.

16. Heath PT, Balfour G, Weisner AM, Efstratiou A, Lamagni TL, Tighe H, et al. Group B streptococcal disease in UK and Irish infants younger than 90 days. Lancet. 2004;363(9405):292–4.

17. Lamagni TL, Keshishian C, Efstratiou A, Guy R, Henderson KL, Broughton K, et al. Emerging Trends in the Epidemiology of Invasive Group B Streptococcal Disease in. 2013;57:682–8.

18. Patel RM, Kandefer S, Walsh MC, Bell EF, Carlo WA, Laptook AR, et al. Causes and timing of death in extremely premature infants from 2000 through 2011. N Engl J Med. 2015;372(4):331–40.

19. Marlow N, Bennett C, Draper ES, Hennessy EM, Morgan AS, Costeloe KL. Perinatal outcomes for extremely preterm babies in relation to place of birth in England: The EPICure 2 study. Arch Dis Child Fetal Neonatal Ed. 2014;99(3):F181-8.

20. Moore T, Hennessy EM, Myles J, Johnson SJ, Draper ES, Costeloe KL MN. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies. BMJ. 2012;345.

21. Horbar JD, Carpenter JH, Badger GJ, Kenny MJ, Soll RF, Morrow KA, et al. Mortality and neonatal morbidity among infants 501 to 1500 grams from 2000 to 2009. Pediatrics. 2012;129(6):1019–26.

22. Mai V, Young CM, Ukhanova M, Wang X, Sun Y, Casella G, et al. Fecal microbiota in premature infants prior to necrotizing enterocolitis. PLoS One. 2011;6(6):e20647.

23. Esaiassen E, Fjalstad JW, Juvet LK, van den Anker JN, Klingenberg C. Antibiotic exposure in neonates and early adverse outcomes: A systematic review and meta-analysis. J Antimicrob Chemother. 2017;72(7):1858–70.

24. NICE. Neonatal infection (early onset): antibiotics for prevention and treatment [Internet]. 2012 [cited 2019 Dec 2]. Available from: https://www.nice.org.uk/guidance/cg149

25. Manzoni P, Tissières P, Helder O BA. Prevention of necrotising enterocolitis (NEC) [Internet]. European standards of care for newborn health. 2018 [cited 2019 Dec 17]. Available from: https://newborn-health-standards.org/nec/

|  |  |
| --- | --- |
| **Condition** | **ICD10** |
| Epilepsy/seizures | G40-G41; R56; P90 |
| Cerebral palsy | G80-G83 |
| Visual impairment | H54 |
| Hearing loss | H90.3-H90.8 |
| Hydrocephalus | G91 |
| Necrotising enterocolitis | P77 |

**Table 1:** ICD codes for potential sequelae of GBS disease

**Fig 1:** Annual number of infants in England aged <90 days diagnosed in hospital with GBS (ICD10 P36.0), per 1,000 live births, Apr 1998 – Mar 2017

**Fig 2:** Annual number of infants in England aged <90 days who died with GBS (ICD10 P36.0) as a certified cause, per 1,000 live births, Jan 2001 – Dec 2017

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Study population (% of total)** | **GBS patients (n)** | **Absolute rates per 10,000** | **Adjusted odds ratios** |
| **Sex** |  |  |  |  |
| Males | 3,103,959 (51.3) | 4,032 | 13.0 | Reference |
| Females | 2,952,063 (48.7) | 3,168 | 10.7 | 0.83 (0.79-0.87) |
| *Missing* | *7,940* |  |  |  |
|  |  |  |  |  |
| **Ethnic group** |  |  |  |  |
| White | 4,236,188 (80.2) | 5,150 | 12.2 | Reference |
| Black | 273,234 (5.2) | 437 | 16.0 | 1.34 (1.21-1.49) |
| S.Asian | 478,153 (9.1) | 528 | 11.0 | 0.92 (0.84-1.01) |
| Other\* | 293,764 (5.6) | 352 | 12.0 | 1.01 (0.9-1.12) |
| *Missing* | *782,623* |  |  |  |
|  |  |  |  |  |
| **Mode of delivery** |  |  |  |  |
| Vaginal | 3,848,353 (73.3) | 3,913 | 10.2 | 3.5 (2.97-4.13) |
| Elective | 534,348 (10.2) | 163 | 3.1 | Reference |
| Emergency | 869,700 (16.6) | 2,229 | 25.6 | 8.71 (7.37-10.28) |
| *Missing* | *811,561* |  |  |  |
|  |  |  |  |  |
| **Gestational age (weeks)** |  |  |  |  |
| <26 | 4,616 (0.1) | 90 | 195.0 | 21.94 (17.61-27.33) |
| 26-31 | 35,077 (0.8) | 525 | 149.7 | 16.63 (15.11-18.29) |
| 32-36 | 232,765 (5.1) | 1,079 | 46.4 | 5.14 (4.8-5.5) |
| 37+ | 4,312,533 (94.1) | 3,936 | 9.1 | Reference |
| *Missing* | *1,478,971* |  |  |  |
|  |  |  |  |  |
| **Birthweight (grams)** |  |  |  |  |
| 2500+ | 18,714 (0.4) | 260 | 138.9 | Reference |
| 500-999 | 25,425 (0.5) | 348 | 136.9 | 14.32 (12.54-16.35) |
| 1000-1499 | 203,449 (4) | 909 | 44.7 | 14.27 (12.73-15.99) |
| 1500-2499 | 4,867,093 (95.2) | 4,757 | 9.8 | 4.64 (4.32-4.99) |
| *Missing* | *949,281* |  |  |  |
|  |  |  |  |  |
| **Maternal age (years)** |  |  |  |  |
| 30-34 | 400,474 (6.8) | 537 | 13.4 | Reference |
| <20 | 1,129,869 (19.1) | 1,397 | 12.4 | 1.17 (1.06-1.29) |
| 20-24 | 1,610,621 (27.2) | 1,884 | 11.7 | 1.08 (1.01-1.16) |
| 25-29 | 1,688,513 (28.5) | 1,942 | 11.5 | 1.02 (0.96-1.09) |
| 35-39 | 897,760 (15.2) | 1,050 | 11.7 | 1.02 (0.95-1.11) |
| 40+ | 190,587 (3.2) | 219 | 11.5 | 1.01 (0.87-1.16) |
| *Missing* | *146,138* |  |  |  |
|  |  |  |  |  |
| **IMD quintile** |  |  |  |  |
| 1 (least deprived) | 1,707,732 (28.3) | 2,004 | 11.7 | Reference |
| 2 | 1,285,649 (21.3) | 1,505 | 11.7 | 1 (0.93-1.07) |
| 3 | 1,085,245 (18) | 1,359 | 12.5 | 1.09 (1.01-1.17) |
| 4 | 979,192 (16.2) | 1,177 | 12.0 | 1.04 (0.96-1.12) |
| 5 (most deprived) | 976,347 (16.2) | 1,109 | 11.4 | 0.98 (0.9-1.06) |
| *Missing* | *29,797* |  |  |  |
|  |  |  |  |  |
| **Number of previous children** |  |  |  |  |
| 0 | 1,612,930 (39.5) | 2,293 | 14.2 | Reference |
| 1 | 1,274,837 (31.2) | 1,199 | 9.4 | 0.65 (0.61-0.7) |
| 2+ | 1,200,673 (29.4) | 1,213 | 10.1 | 0.7 (0.65-0.75) |
| *Missing* | *1,975,522* |  |  |  |
|  |  |  |  |  |
| **PROM (ICD O42)** |  |  |  |  |
| No | 5,538,715 (91.3) | 5,501 | 9.9 | Reference |
| Yes | 525,247 (8.7) | 1,741 | 33.1 | 2.63 (2.46-2.8) |
| *Missing* | *0* |  |  |  |
|  |  |  |  |  |
| **Chorioamnionitis (ICD O41.1)** |  |  |  |  |
| No | 6,058,167 (99.9) | 7,076 | 11.7 | Reference |
| Yes | 5,795 (0.1) | 166 | 286.5 | 6.32 (5.2-7.67) |
| *Missing* | *0* |  |  |  |
|  |  |  |  |  |
| **Maternal septicaemia (ICD O75.1-O75.3; O85; A40.1; A40.8; A40.9)** | |  |  |  |
| No | 5,975,591 (98.5) | 6,560 | 11.0 | Reference |
| Yes | 88,371 (1.5) | 682 | 77.2 | 6.68 (6.09-7.33) |
| *Missing* | *0* |  |  |  |

**Table 2:** Linked mother-infant pairs dataset (6,063,962 pairs), England, Apr 1998 to Mar 2012. Study population characteristics and perinatal associations with GBS. All ORs were adjusted for year of birth, maternal age and deprivation. Associations with PROM, chorioamnionitis and maternal septicaemia were additionally adjusted for gestational age.

\*Footnote: “Other” ethnic group comprised the following relatively uncommon codes, none of which were found to be associated with GBS when considered individually: White and Black Caribbean (Mixed), White and Black African (Mixed), White and Asian (Mixed), Any other Mixed background, Any other Asian background, Chinese (other ethnic group), Any other ethnic group. [source: ‘Ethnos’ in HES]

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Study population** | |  | **Rates of sequelae per 10,000** | |  |  |  |  |
| **Sequelae condition** | **Calendar period** | **non-GBS** | **GBS** |  | **non-GBS** | **GBS** |  | **HR (95%CI)** | **p value** | **heterogeneity across calendar periods, p-value** |
| Epilepsy | 1998-2003 | 2,370,076 | 3,473 |  | 58.1 | 270.7 |  | 4.88 (4.05-5.88) | <0.0001 | <0.0001 |
| 2004-2012 | 4,850,584 | 6,044 |  | 70.4 | 471.5 |  | 7.19 (6.38-8.11) | <0.0001 |
| 2013-2017 | 2,351,626 | 3,016 |  | 60.1 | 567.0 |  | 9.97 (8.57-11.59) | <0.0001 |
| All years | 9,572,286 | 12,533 |  | 64.8 | 438.8 |  | 7.13 (6.55-7.75) | <0.0001 |  |
|  |  |  |  |  |  |  |  |  |  |  |
| Cerebral palsy | 1998-2003 | 2,370,076 | 3,473 |  | 2.7 | 31.7 |  | 11.5 (6.5-20.34) | <0.0001 | 0.673 |
| 2004-2012 | 4,850,584 | 6,044 |  | 3.0 | 24.8 |  | 8.66 (5.12-14.67) | <0.0001 |
| 2013-2017 | 2,351,626 | 3,016 |  | 2.3 | 16.6 |  | 7.57 (3.14-18.27) | <0.0001 |
| All years | 9,572,286 | 12,533 |  | 2.7 | 24.7 |  | 9.34 (6.55-13.3) | <0.0001 |  |
|  |  |  |  |  |  |  |  |  |  |  |
| Visual impairment | 1998-2003 | 2,370,076 | 3,473 |  | 0.9 | 11.5 |  | 12.96 (5.35-31.38) | <0.0001 | 0.3561 |
| 2004-2012 | 4,850,584 | 6,044 |  | 1.7 | 9.9 |  | 5.49 (2.28-13.24) | 0.0001 |
| 2013-2017 | 2,351,626 | 3,016 |  | 1.9 | 9.9 |  | 5.43 (1.75-16.91) | 0.0035 |
| All years | 9,572,286 | 12,533 |  | 1.5 | 10.4 |  | 7.03 (4.07-12.14) | <0.0001 |  |
|  |  |  |  |  |  |  |  |  |  |  |
| Hearing loss | 1998-2003 | 2,370,076 | 3,473 |  | 2.2 | 8.6 |  | 4.13 (1.55-11.04) | 0.0047 | 0.2297 |
| 2004-2012 | 4,850,584 | 6,044 |  | 5.4 | 43.0 |  | 8.46 (5.7-12.54) | <0.0001 |
| 2013-2017 | 2,351,626 | 3,016 |  | 5.9 | 29.8 |  | 5.22 (2.71-10.06) | <0.0001 |
| All years | 9,572,286 | 12,533 |  | 4.7 | 30.3 |  | 6.73 (4.89-9.26) | <0.0001 |  |
|  |  |  |  |  |  |  |  |  |  |  |
| Hydrocephalus | 1998-2003 | 2,370,076 | 3,473 |  | 3.1 | 25.9 |  | 9.02 (4.98-16.35) | <0.0001 | 0.0036 |
| 2004-2012 | 4,850,584 | 6,044 |  | 4.0 | 89.3 |  | 23.76 (18.03-31.3) | <0.0001 |
| 2013-2017 | 2,351,626 | 3,016 |  | 4.0 | 53.1 |  | 13.71 (8.37-22.48) | <0.0001 |
| All years | 9,572,286 | 12,533 |  | 3.8 | 63.0 |  | 17.27 (13.82-21.59) | <0.0001 |  |
|  |  |  |  |  |  |  |  |  |  |  |
| Necrotising enterocolitis | 1998-2003 | 2,370,076 | 3,473 |  | 7.7 | 92.1 |  | 12.62 (9.19-17.32) | <0.0001 | 0.0036 |
| 2004-2012 | 4,850,584 | 6,044 |  | 12.7 | 274.7 |  | 22.18 (18.94-25.96) | <0.0001 |
| 2013-2017 | 2,351,626 | 3,016 |  | 14.8 | 258.6 |  | 17.71 (14.15-22.16) | <0.0001 |
| All years | 9,572,286 | 12,533 |  | 12.0 | 220.2 |  | 18.82 (16.7-21.21) | <0.0001 |  |
|  |  |  |  |  |  |  |  |  |  |  |
| All-cause mortality | 1998-2003 | 2,370,076 | 3,473 |  | 38.6 | 319.6 |  | 8.65 (7.28-10.3) | <0.0001 | 0.823 |
| 2004-2012 | 4,850,584 | 6,044 |  | 32.1 | 301.1 |  | 9.31 (7.98-10.86) | <0.0001 |
| 2013-2017 | 2,351,626 | 3,016 |  | 27.0 | 245.4 |  | 9.14 (7.27-11.5) | <0.0001 |
| All years | 9,572,286 | 12,533 |  | 32.5 | 292.8 |  | 9.03 (8.15-10.01) | <0.0001 |  |

**Table 3:** Sequelae associated with GBS, by calendar period, England, Apr 1998 – Mar 2017

1. An FCE represents a discrete episode of care under one consultant in an NHS hospital, which can result in either transfer to another consultant, transfer to another hospital, discharge from hospital, or death. [↑](#footnote-ref-1)