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ORIGINAL ARTICLE

Mortality and neurodevelopmental outcome after invasive group B streptococcal infection in infants

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Abstract

Aim: To assess case fatality rate (CFR), infant mortality, and long-term neurodevelopmental disorders (NDDs) after invasive group B streptococcal (GBS; *Streptococcus agalactiae*) infection in infants.

Method: Children born in Norway between 1996 and 2019 were included. Data on pregnancies/deliveries, GBS infection, NDDs, and causes of death were retrieved from five national registries. The exposure was culture-confirmed invasive GBS infection during infancy. Outcomes were mortality and NDDs, the latter at a mean age of 12 years 10 months.

Results: Among 1 415 625 live-born children, 866 (87%) of 1007 infants diagnosed with GBS infection (prevalence 0.71 per 1000) were included. The CFR was 5.0% (n = 43). GBS infection was associated with higher infant mortality (relative risk 19.41; 95% confidence interval [CI] 14.79–25.36) than the general population. Among survivors, 169 (20.7%) children were diagnosed with any NDD (relative risk 3.49; 95% CI 3.05–3.98). In particular, GBS meningitis was associated with high risks of attention-deficit/hyperactivity disorder, cerebral palsy, epilepsy, hearing impairment, and pervasive and specific developmental disorder.

Interpretation: The burden of invasive GBS infection during infancy is considerable and continues to affect children beyond infancy. These findings emphasize the need for new preventive strategies for disease reduction, and the need for survivors to be directly included into early detection pathways to access early intervention if required.

Streptococcus agalactiae (group B streptococcus, GBS) is the leading cause of invasive neonatal infection worldwide.[1] Despite more than 30 years of prevention strategies,[2,3] the burden of disease remains high.[1,4] Intrapartum antibiotic prophylaxis has reduced the incidence of early-onset disease (EOD),[1,3] but there is currently no prevention strategy for late-onset disease (LOD).[6]

Annually, about 40 000 survivors of GBS infection develop moderate and/or severe neurodevelopmental impairments.[7] A meta-analysis of 453 children estimated that,

Abbreviations: CFR, case fatality rate; EOD, early-onset disease; GBS, group B streptococcus; LOD, late-onset disease; NDD, neurodevelopmental disorder; NPR, Norwegian Patient Registry; PSDD, pervasive and specific developmental disorder; VLOD, very-late-onset disease.

0.5 to 10.5 years after infant GBS meningitis, up to 50% of survivors were diagnosed with neurodevelopmental impairments.[8] The risk of such impairments following sepsis could not be estimated,[8] and the authors emphasized the need for data on long-term outcomes.[8] A more recent cohort study found that 4.6% of Danish infants surviving a GBS infection had moderate to severe neurodevelopmental impairments at age 10 years.[9]

In Norway, several compulsory national health registers collect information on pregnancy and delivery, mortality, infectious diseases, and diagnoses of patients receiving specialized health care. These registers provide robust health data on the entire Norwegian population.[10,11] Every Norwegian citizen is given a unique 11-digit personal identification number, which enables linkage of the registers.[10] This provides a unique opportunity to study short- and long-term outcomes of GBS infections in a large population.

With this background, the aim of this study was to assess case fatality rate (CFR), infant mortality, and long-term neurodevelopmental disorders (NDDs) after invasive GBS infection during infancy. Secondary aims were to assess (1) the risk associated with GBS infection for specific NDDs and (2) whether CFR and the risk of NDDs differed between infants with EOD and LOD, meningitis and sepsis, and born preterm and at term.

What this paper adds

- The burden of invasive group B streptococcal (GBS) infection in Norway is considerable.
- Of GBS infection survivors, 20.7% were diagnosed with neurodevelopmental disorders (NDDs) at mean age 12 years 10 months.
- Infants with GBS meningitis were more often diagnosed with NDDs.
- Absolute risks associated with GBS infections were highest for pervasive and specific developmental disorder, cerebral palsy, and attention-deficit/hyperactivity disorder.

METHOD

Study design and population

This prospective cohort study included children born alive in Norway between 1996 and 2019. Exposure was invasive GBS infection during infancy, documented by a positive culture from blood or cerebrospinal fluid recorded in the Norwegian National Reference Laboratory for GBS ('The Reference Lab').

Submitting GBS isolates from invasive infections to The Reference Lab has been compulsory since 2006. Before 2006, the laboratory offered typing of GBS isolates on a collegial basis. For this study, a request was sent to all laboratories to submit available isolates not previously submitted.

Additional clinical and laboratory information on GBS disease was retrieved from the Norwegian Surveillance System for Communicable Diseases, which was combined with information from the Medical Birth Registry of Norway, the Norwegian Patient Registry (NPR), and the Norwegian Cause of Death Registry.[13,14]

It has been compulsory to report invasive infections with GBS to the Norwegian Surveillance System for Communicable Diseases since 1986. The Medical Birth Registry of Norway has recorded data on all pregnancies and births since 1967. The NPR has recorded data on all patients treated by the Norwegian specialist healthcare services since 1997. However, data were not patient identifiable until 2008.[13] Data collected from the NPR included International Classification of Diseases, Tenth Revision (ICD-10) diagnosis codes as recorded by 31st August 2021. At this date, the estimated mean age of the children with invasive GBS infection was 12 years 10 months (range 1 year 8 months–25 years 7 months). The Norwegian Cause of Death Registry has recorded causes of all deaths since 1951.[14]

Children with an invasive GBS infection were identified through The Reference Lab, and their data were linked with individual-level data from the four other registries using the unique personal identification number. In addition, the NPR provided aggregated data on the prevalence of the NDDs, recorded until 31st August 2021, and the Medical Birth Registry of Norway provided aggregated information on pregnancies, deliveries, and infant mortality in the general Norwegian population born alive between 1996 and 2019.

Variables

The primary exposure variable was GBS infection in children up to 1 year of age, confirmed by a positive culture from blood or cerebrospinal fluid. Age at onset of infection was categorized as EOD when diagnosed between 0 and 6 days of age, LOD when diagnosed between 7 and 89 days, and very-late-onset disease (VLOD) when diagnosed between 90 and 365 days of age. In the main analyses, LOD and VLOD were merged into one variable ('LOD/VLOD'), owing to the low number in the latter group, and because their clinical and bacteriological characteristics were similar.[15] However, we also present the results separately as Table S1. The infection was classified as meningitis if GBS was isolated from cerebrospinal fluid, or if the patient had a clinical diagnosis of meningitis and a positive blood culture, while it was classified as sepsis if GBS was isolated from blood without evidence of meningitis.

The primary outcomes were CFR, infant mortality, and NDDs. Infant mortality was defined as death before 1 year of age. In the estimates of CFR, causes of death were included where GBS was registered as immediate, intermediate, or underlying cause of death on the death certificate. Since all cases had GBS positive cultures or cerebrospinal fluid, cases

registered with unspecified pneumonia/sepsis/meningitis as cause of death were also included as case fatalities. In addition, death was classified as case fatalities when death occurred within 8 days of diagnosis, without other more likely causes of death. Thus, cases where the primary cause of death was a severe congenital malformation such as hypoplastic left ventricle syndrome, or extreme preterm birth, and where GBS was not given as the immediate/intermediate/underlying cause of death, were, despite a positive culture, not counted as a case fatality.

The included NDDs were attention-deficit/hyperactivity disorder (ADHD), cerebral palsy (CP), epilepsy, intellectual disability, pervasive and specific developmental disorder (PSDD), binocular visual impairment/blindness ('visual impairment'), and sensorineural hearing loss ('hearing impairment') (Table S2). In addition, we coded a composite variable comprising all NDDs (named 'any NDD'), where each individual (with one or more NDDs) was counted only once.

Preterm birth was defined as a gestational age at birth of 22 to 36 weeks.

Statistical analysis

Infant death, CFR, and the prevalence of NDDs are presented as percentages with Wilson score 95% confidence intervals (CI).[16] Relative risks with Koopman asymptotic score confidence intervals were calculated by comparing outcomes in individuals with GBS infection with the general population without GBS infection, as well as in the comparisons of infants with LOD/VLOD and infants with EOD, infants with meningitis and infants with sepsis, and between infants born preterm and at term. Owing to the short follow-up of the youngest children, we performed a sensitivity analysis restricting the study population to children born between 1996 and 2014. The CI methods are recommended by Fagerland et al.[16] Available data were used, and imputation was not performed on missing data. Stata version 15 (StatCorp, College Station, TX, USA) was used for calculating the Wilson score CIs, while R 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for calculating relative risk with Koopman CIs, and SPSS version 25 (IBM Corp., Armonk, NY, USA) for all other analyses.

Ethics

The study was approved by the Regional Committee for Medical Research Ethics (REK 2019/790). A data protection impact assessment was approved by the head of the Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology. In addition, the study was legally approved by each registry according to regulations.

RESULTS

In all, 1 415 625 children were born alive in Norway. Of these, 1007 children were diagnosed with an invasive GBS infection (prevalence 0.71 per 1000), whereby 866 (86%) were identified with isolates in The Reference Lab (Figure S1). Most infants presented with EOD and sepsis (Table 1). While the incidence of EOD declined and the incidence of LOD increased slightly, the overall incidence remained stable during the study period (Figure S2).

Obstetric and perinatal complications were more common among infants diagnosed with GBS than in the general population (Tables S3 and S4). Complications were especially prevalent among infants with LOD and VLOD. Infants with EOD were more mature at birth than infants with LOD and VLOD (Table S4).

There were 43 case fatalities, resulting in a CFR of 5.0%. The CFR showed significant annual variations, but essentially did not change during the study period (Figure S3). A further seven children died during infancy, resulting in significantly higher infant mortality (5.8%) than in the general population (Table 2). Among children surviving the first year of life, 169 (20.7%) were diagnosed with any NDD, resulting in a relative risk of 3.49 (95% CI 3.05–3.98) compared with the general population. The proportion of children diagnosed with NDDs after invasive GBS infection was clearly higher among children with GBS infection than in the general population during the study period, even in the later birth cohorts (Figure S4).

Table 2 also shows high relative risks for all included NDDs among children with GBS. The highest relative risk was observed for ADHD, CP, PSDD, and visual impairment, while

TABLE 1 Clinical diagnosis and age at disease onset of invasive GBS infection during infancy.

	EOD[a]		LOD[b]		VLOD[c]		All GBS	
	n	%	*n*	%	*n*	%	*n*	%
All infants	501	100	341	100	24	100	866	100
Sepsis	453	90.4	243	71.3	15	62.5	711	82.1
Meningitis[d]	48	9.6	98	28.7	9	37.5	155	17.9

[a]Early-onset disease (EOD) diagnosed between 0 and 6 days of age.
[b]Late-onset disease (LOD) diagnosed between 7 and 89 days of age.
[c] Very-late-onset disease (VLOD) diagnosed between 90 and 365 days of age.
[d]Among infants with meningitis, 21 (48%), 64 (75%), and 8 (89%) were cerebrospinal fluid culture positive in the EOD, LOD, and VLOD groups respectively.
Abbreviation: GBS, group B streptococcus.

TABLE 2 Number of children, prevalence, and relative risk[a] of mortality or NDDs among infants with invasive GBS infection.

	Invasive GBS		General population		
	n	% (95% CI)	*n*	% (95% CI)	RR (95% CI)[b]
All children	866		1 414 759		
Infant mortality	50	5.77 (4.41–7.53)	4209	0.30 (0.29–0.31)	19.41 (14.79–25.36)
Any NDD	169	20.7 (18.1–23.6)	83 653	5.93 (5.89–5.97)	3.49 (3.05–3.98)
ADHD[c]	46	5.64 (4.25–7.44)	16 898	1.20 (1.18–1.22)	4.71 (3.55–6.21)
Cerebral palsy[d]	44	5.39 (4.04–7.16)	4691	0.33 (0.32–0.34)	16.21 (12.13–21.45)
Epilepsy[e]	38	4.66 (3.41–6.33)	19 122	1.36 (1.34–1.38)	3.44 (2.52–4.67)
Hearing impairment[f]	36	4.41 (3.20–6.05)	24 522	1.74 (1.72–1.76)	2.54 (1.84–3.48)
Intellectual disability[g]	22	2.70 (1.79–4.05)	10 213	0.72 (0.71–0.74)	3.72 (2.47–5.59)
PSDD[h]	80	9.80 (7.95–12.0)	27 979	1.98 (1.96–2.01)	4.94 (4.01–6.07)
Visual impairment[i]	7	0.86 (0.4–1.76)	2185	0.16 (0.15–0.16)	5.54 (2.68–11.39)

[a]In the calculations of prevalence and relative risk of NDDs, children who died before 1 year of age were removed.
[b]Koopman asymptotic score.
[c]Including ICD-10 diagnosis F90*.
[d]Including ICD-10 diagnosis G80*.
[e]Including ICD-10 diagnosis G40*.
[f]Including ICD-10 diagnoses H90.3, H90.4, H90.5, H90.6, H90.7, H90.8.
[g]Including ICD-10 diagnoses F70–F79*.
[h]Including ICD-10 diagnoses F80–F89*.
[i]Including ICD-10 diagnoses H54.0, H54.1, H54.2 H54.3, H54.9.
*Indicates that the whole range of the diagnosis code is included.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; GBS, group B streptococcus; ICD-10, International Classification of Diseases, 10th Revision; NDD, neurodevelopmental disorder; PSDD, pervasive and specific developmental disorder; RR, relative risk.

the highest absolute risk was observed for PSDD (Table 2). The relative risks for any NDD, as well as for specific NDDs, were practically unchanged when analyses were restricted to children born between 1996 and 2014 (Table S5).

The CFR did not differ between infants with EOD and LOD/VLOD, while the risk of being diagnosed with any NDD was higher among infants with LOD/VLOD (Table 3). In particular, LOD/VLOD was associated with a higher risk of CP, epilepsy, hearing impairment, and PSDD compared with EOD (Table 3). Results for EOD, LOD, and VLOD are presented separately in Table S1.

The CFR did not differ between infants with meningitis and sepsis (Table 4). However, meningitis was associated with a higher risk of any NDD as well as of CP, epilepsy, hearing impairment, and intellectual disability (Table 4).

Among infants with GBS infection, 30 born preterm died (CFR 10.9%), compared with 11 (CFR 1.9%) infants born at term (relative risk 5.64 [95% CI 2.97–10.96]) (Table 5). The relative risk of any NDD after GBS infection among infants born preterm compared with those born at term was 1.93 (95% CI 1.47–2.52). Infants born preterm were at especially high risk of being diagnosed with ADHD, CP, and PSDD.

DISCUSSION

We found that the burden of invasive GBS infection in Norway between 1996 and 2019 was considerable, with a CFR of 5.0%, and with 20.7% of surviving children being diagnosed with any NDD. Infants with LOD/VLOD did not have increased risk of death compared with infants with EOD but were more likely to be diagnosed with any NDD. The CFR did not differ between infants with meningitis and sepsis, while infants with meningitis were more often diagnosed with NDDs.

In addition to the higher absolute and relative risks of CP consistent with previous studies,[17,18] we found that GBS infection was associated with high absolute and relative risks for ADHD, epilepsy, hearing impairment, and PSDD, while for intellectual disability and visual impairment relative risks were high but absolute risks were low.

The strengths of the present study are the large number of individuals included and the prospective recording of robust and high-quality data from the Norwegian national health registries. Another strength is that all cases are culture confirmed and include 86% of all infants diagnosed with GBS infection during the study period. The misclassification of 141 individuals with GBS infection (recorded only in the Norwegian Surveillance System for Communicable Diseases) as part of the general population is negligible compared with the 1.4 million children constituting the latter group.

A possible limitation is the low age of some of the children by August 2021.[19] However, at this date, 75% of the included children were at least 6 years old, and the mean age of the children was 12 years 10 months (range 1 year 8 months–25 years 7 months). Thus, although in the youngest children, exposed or unexposed, NDDs may not yet have

TABLE 3 Number of infants, prevalence, and relative risk[a] of death (case fatality) and NDDs among infants with early-onset and late- and very-late-onset GBS infection.

	EOD		LOD/VLOD		
	n	% (95% CI)	*n*	% (95% CI)	RR (95% CI)[b]
All infants	501		365		
Case fatality rate	22	4.39 (2.92–6.56)	21	5.75 (3.79–8.64)	1.31 (0.74–2.33)
Any NDD	72	15.22 (12.27–18.74)	97	28.28 (23.78–33.27)	1.86 (1.42–2.44)
ADHD[c]	21	4.44 (2.92–6.69)	25	7.29 (4.99–10.54)	1.64 (0.94–2.86)
Cerebral palsy[d]	16	3.38 (2.09–5.42)	28	8.16 (5.71–11.55)	2.41 (1.34–4.35)
Epilepsy[e]	15	3.17 (1.93–5.17)	23	6.71 (4.51–9.86)	2.11 (1.13–3.95)
Hearing impairment[f]	14	2.96 (1.77–4.91)	22	6.41 (4.27–9.52)	2.17 (1.14–4.13)
Intellectual disability[g]	10	2.11 (1.15–3.85)	12	3.50 (2.01–6.02)	1.65 (0.74–3.70)
PSDD[h]	34	7.19 (5.19–9.89)	46	13.41 (10.21–17.43)	1.87 (1.23–2.83)
Visual impairment[i]	3	0.63 (0.22–1.85)	4	0.12 (0.45–2.96)	1.84 (0.46–7.30)

[a]In the calculations of prevalence and relative risk of NDDs, children who died before 1 year of age were removed (i.e. 28 infants in the group with EOD and 22 in the group with LOD/VLOD).

[b]Koopman asymptotic score.

[c]Including ICD10 diagnosis F90*.

[d]Including ICD-10 diagnosis G80*.

[e]Including ICD-10 diagnosis G40*.

[f]Including ICD-10 diagnoses H90.3, H90.4, H90.5, H90.6, H90.7, H90.8.

[g]Including ICD-10 diagnoses F70–F79*.

[h]Including ICD-10 diagnoses F80–F89*.

[i]Including ICD-10 diagnoses H54.0, H54.1, H54.2 H54.3, H54.9.

*Indicates that the whole range of the diagnosis code is included.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; EOD, early-onset disease (0–6 days); GBS, group B streptococcus; ICD-10, International Classification of Diseases, 10th Revision; NDD, neurodevelopmental disorder; PSDD, pervasive and specific developmental disorder; LOD/VLOD, late- and very-late-onset disease (0–365 days); RR, relative risk.

been diagnosed, most of the included NDDs are diagnosed before school age,[19] and we therefore consider it unlikely that our main findings are due to selection bias. Moreover, it could be possible that NDDs are diagnosed earlier in children who survived a GBS infection than in the general population. However, when the analyses were restricted to children born before 2015 (i.e. those aged 6 years 8 months and older) the results were essentially unchanged (Table S5), making the latter explanation unlikely. The comparison of the annual incidence of NDDs among children with GBS and in the general population (Figure S4) lends further support to this conclusion. Another potential limitation could be potential misclassification of the NDD diagnoses in the NPR, and that diagnoses have only been linked to the personal identification number since 2008. Two validation studies of NPR suggested that CP and epilepsy were correctly recorded in respectively 86% and 66% of the cases.[20,21] Moreover, children born before 2008 were most likely included in the NPR with their personal identification numbers because most NDDs included in this study usually require specialist follow-up into adulthood. However, while these possible misclassifications may affect the prevalence estimates, they are most likely non-differential and therefore less likely to affect the estimates of relative risks.

In line with previous studies,[3,17,18,22,23] we found that GBS infection was associated with complications of pregnancy and delivery that are also associated with increased risk of NDDs. Thus, when comparing the population of infants having GBS infection with the general population, it may be considered a limitation that parts of the data were aggregated and therefore we were unable to adjust for these variables as possible confounders. However, a perinatal GBS infection could equally cause or contribute to these complications, and it is generally not appropriate to adjust for mediators in this setting.[24] In particular, this applies for preterm birth, being both a possible confounder as well as a mediator.

The clinical characteristics of early GBS infection, namely age at disease onset and meningitis versus sepsis, are broadly the same as described in other studies from high-income countries.[1,3] Our finding that preterm birth[3,25] and multiple gestation[23] was associated with LOD/VLOD has also been reported. In line with previous studies, we found that nearly 50% of infants with LOD/VLOD were born preterm,[15,26] confirming that infants born preterm are susceptible to invasive GBS infection throughout the first year of life.

The CFR observed in our study (5.0%) is in line with the average rate of 4.7% (95% CI 3.3–6.1) reported in a meta-analysis by Madrid et al.[1] The higher CFR among infants born preterm than at term[3] and the similar CFR of EOD and LOD/VLOD[1] have also been reported previously. Finally, the CFR did not differ between meningitis and sepsis, consistent with a large, recently published study from the Netherlands.[27]

TABLE 4 Number of infants, prevalence, and relative risk[a] of death (case fatality) and NDDs among children with GBS meningitis or sepsis during infancy.

	Meningitis		Sepsis		
	n	% (95% CI)	*n*	% (95% CI)	RR (95% CI)[b]
All infants	155		711		
Case fatality rate	7	4.52 (2.21–9.03)	36	5.49 (4.04–7.41)	0.89 (0.41–1.91)
Any NDD	49	33.11 (26.04–41.03)	120	17.96 (15.24–21.06)	1.84 (1.38–2.42)
ADHD[c]	9	6.09 (3.23–11.15)	37	5.54 (4.05–7.54)	1.10 (0.55–2.17)
Cerebral palsy[d]	16	10.81 (6.77–16.84)	28	4.19 (2.92–5.99)	2.58 (1.44–4.58)
Epilepsy[e]	22	14.87 (10.03–21.48)	16	2.40 (1.49–3.86)	6.21 (3.36–11.38)
Hearing impairment[f]	11	7.43 (4.20–12.82)	25	3.74 (2.55–5.47)	1.99 (1.01–3.86)
Intellectual disability[g]	14	9.55 (5.72–15.25)	8	1.20 (0.61–2.35)	7.90 (3.45–18.02)
PSDD[h]	20	13.51 (8.92–19.95)	60	8.98 (7.94–11.39)	1.51 (0.93–2.38)
Visual impairment[i]	2	0.14 (0.37–4.79)	5	0.75 (0.32–1.74)	1.81 (0.41–7.95)

[a]In the calculations of prevalence and relative risk of NDDs, children who died before 1 year of age were removed (i.e. seven infants in the group with meningitis and 43 in the group with sepsis).

[b]Koopman asymptotic score.

[c]Including ICD10 diagnosis F90*.

[d]Including ICD-10 diagnosis G80*.

[e]Including ICD-10 diagnosis G40*.

[f]Including ICD-10 diagnoses H90.3, H90.4, H90.5, H90.6, H90.7, H90.8.

[g]Including ICD-10 diagnoses F70–F79*.

[h]Including ICD-10 diagnoses F80–F89*.

[i]Including ICD-10 diagnoses H54.0, H54.1, H54.2, H54.3, H54.9.

*Indicates that the whole range of the diagnosis code is included.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; GBS, group B streptococcus; ICD-10, International Classification of Diseases, 10th Revision; NDD, neurodevelopmental disorder; PSDD, pervasive and specific developmental disorder; RR, relative risk.

Until recently, few studies have been able to assess neurodevelopmental outcome following GBS infection.[7] Moreover, because a wide range of neurodevelopmental outcomes are described, from various impairments to specific diagnoses, direct comparison of results is difficult. However, we have identified two recent studies that have assessed NDDs specifically. One of these studies, by Kadambari et al., reported higher relative risk of epilepsy and hearing loss, but lower relative risk of CP, compared with our study.[4] Some significant differences in study design may explain the different estimates, since Kadambari et al. included non-culture proven GBS cases and only recorded diagnoses reported during the first year of life. The other study was published by Horváth-Puhó et al. and included two different cohorts: one from the Netherlands and one from Denmark. While in the Dutch cohort the main outcome was special education, in the Danish cohort the outcome was any NDD at 10 years of age.[9] In the latter cohort, 10% had any NDD at 10 years of age, significantly lower than the 20.7% in our study. However, the Danish cohort comprised fewer infants born preterm (21% vs 31% in our study) and included cases not confirmed by culture.[9] Four studies from low-income countries reported that 27.9% to 50.0% of infants surviving GBS infection had any neurodevelopmental impairment.[28–31] In total, 273 children with invasive GBS infection during infancy were included in these studies, and the follow-up ranged from 1 to 18 years. Despite different estimates, the main results of these studies as well as those reported by Kadambari et al. and Horváth-Puhó et al. agree with our findings, indicating a substantial burden of NDDs following invasive GBS infection. Taken together, these results suggest that infants who survive a GBS infection should be included in long-term follow-up programmes aiming at early diagnosis and appropriate intervention.

Among infants with meningitis, 33% were later diagnosed with an NDD in our study. This finding is consistent with the 25% reported by Horváth-Puhó et al. in their cohort of Danish children.[9] The meta-analysis by Kohli-Lynch et al. published in 2017 found that 18% (95% CI 13–22) of infants with GBS meningitis had moderate to severe neurodevelopmental impairments at 18 months follow-up.[8] Again, at 18 months of age most NDDs are not yet diagnosed,[32] which may explain the lower prevalence of NDDs in the meta-analysis. The high risk of epilepsy, CP, hearing impairment, and intellectual disability following meningitis is not unexpected, as previous studies have found that epilepsy, hearing impairment, intellectual disability, and motor impairments are frequently reported sequelae of meningitis of other aetiologies.[33,34]

Infants born preterm with GBS infection were at especially high risk of ADHD, CP, and PSDD. These are all NDDs that are known to be associated with preterm birth.[35–39] Moreover, it is well established that GBS infection and preterm birth independently increase the risk of mortality and NDDs.[25,40] A recent study found that the combined

TABLE 5 Number of infants, prevalence, and relative risk[a] for death (case fatality) and NDDs following invasive GBS infection among infants born preterm and at term.[b]

	Preterm		Term		
	n	% (95% CI)	*n*	% (95% CI)	RR (95% CI)[c]
All infants	276		571		
Case fatality rate	30	10.87 (7.72–15.09)	11	1.93 (1.08–3.42)	5.64 (2.97–10.96)
Any NDD	75	30.61 (25.18–36.65)	88	15.88 (13.01–19.16)	1.93 (1.47–2.52)
ADHD[d]	20	8.16 (5.35–12.27)	24	4.33 (2.93–6.37)	1.88 (1.07–3.31)
Cerebral palsy[e]	26	10.61 (7.35–15.10)	15	2.71 (1.65–4.42)	3.32 (2.13–7.20)
Epilepsy[f]	16	6.53 (4.06–10.34)	22	3.97 (2.64–5.94)	1.64 (0.89–3.04)
Hearing impairment[g]	13	5.31 (3.13–8.87)	21	3.79 (2.49–5.73)	1.40 (0.72–2.71)
Intellectual disability[h]	10	4.08 (2.23–7.35)	12	2.17 (1.24–3.75)	1.88 (0.84–4.20)
PSDD[i]	37	15.10 (9.41–17.86)	40	7.22 (5.35–9.68)	2.09 (1.37–3.17)
Visual impairment[j]	2	0.82 (0.22–2.93)	5	0.90 (0.39–2.10)	0.90 (0.20–4.00)

[a]In the calculations of prevalence and RR of NDDs, children who died before 1 year of age were removed (i.e. 31 infants in the preterm group and 17 in the term-born group).
[b]Information on gestational age missing for 19 infants.
[c]Koopman asymptotic score.
[d]Including ICD10 diagnosis F90*.
[e]Including ICD10 diagnosis G80*.
[f]Including ICD-10 diagnosis G40*.
[g]Including ICD-10 diagnoses H90.3, H90.4, H90.5, H90.6, H90.7, H90.8.
[h]Including ICD-10 diagnoses F70–F79*.
[i]Including ICD-10 diagnoses F80–F89*.
[j]Including ICD-10 diagnoses H54.0, H54.1, H54.2 H54.3, H54.9.
*Indicates that the whole range of the diagnosis code is included.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; ICD-10, International Classification of Diseases, 10th Revision; NDD, neurodevelopmental disorder; PSDD, pervasive and specific developmental disorder; RR, relative risk.

effects of GBS infection and preterm birth lead to a worse outcome than would be expected on the basis of their individual effects.[25] Partly consistent with this, we found that infants born preterm with GBS had a higher CFR and were twice as likely as term-born infants with GBS to develop any NDD. The significant burden in infants born preterm suggests that further initiatives are warranted to prevent and control GBS disease and could imply that preventive measures should be especially targeted on how to reduce invasive GBS infection among infants born preterm.

CONCLUSION

In Norway, the burden of invasive GBS infection during infancy is considerable and continues to affect children well beyond infancy. This study adds valuable information on the burden of GBS infection in a high-income setting and emphasizes the need for improved prevention strategies and better follow-up of survivors of infant GBS infection. Future research needs to address prevention and improved treatment of early GBS infection, and survivors of infection need long-term follow-up and appropriate care.

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CONFLICT OF INTEREST
The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

The following additional material may be found online:

Figure S1: Flow chart of the study population.

Figure S2: Incidence of invasive GBS infection during 1996–2019 in Norway according to the reference laboratory.

Figure S3: Case fatality rate following invasive GBS infection during infancy in Norway, 1996–2019.
Figure S4: Annual incidence of NDDs among children with and without an invasive GBS infection during infancy.
Table S1: NDDs following an invasive GBS infection, in children born 1996–2019, with early onset disease, compared to late onset disease and very late onset disease.
Table S2: Included NDDs and the corresponding ICD-10 code.
Table S3: Maternal, pregnancy and delivery characteristics of all deliveries of liveborn children with and without an invasive GBS infection during infancy, 1996–2019.
Table S4: Infant characteristics of all liveborn children with and without an invasive GBS infection during infancy, 1996–2019.
Table S5: Sensitivity analysis.

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