Association between anti-capsular IgG levels at birth and risk of invasive group B streptococcus disease in Finnish newborns: a retrospective case–control study

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Summary

Background Group B streptococcus is a major cause of neonatal disease. Natural history studies have linked maternally transferred anti-group B streptococcus capsular polysaccharide antibodies with protection against infant group B streptococcus disease. Previous studies of capsular polysaccharide antibody concentration in European populations have used maternal (not infant) sera and a non-standardised assay. This study aimed to evaluate anti-capsular polysaccharide IgG concentrations associated with protection against invasive group B streptococcus disease in Finnish infants.

Methods In this retrospective case–control study, we used cord sera from the Finnish DIPP study repository, which was obtained between Jan 1, 1995, and Dec 31, 2017. We included infants aged 6 months or younger with group B streptococcus infection (cases) and healthy infants (controls). We enrolled infants with invasive neonatal group B streptococcus (55 cases) and matched controls (229 controls) aged 6 months or younger after identification from Finnish health registers. We measured anti-capsular polysaccharide IgG (serotypes Ia–V) concentration using a standardised immunoassay and we estimated its relationship to disease risk using a Bayesian model. We used the derived risk–concentration curve to predict potential efficacy of six-valent group B streptococcus capsular polysaccharide vaccine (GBS6) based on previously reported immunogenicity data.

Findings Most (32 [58%] of 55 cases) group B streptococcus cases were due to serotype III and anti-serotype III streptococcus capsular IgG concentrations were higher in serotype III-matched controls than in cases ($p<0·001$). 0·120–0·266 µg/mL serotype III-specific IgG was estimated to confer 75–90% risk reduction against serotype III disease. A universal risk–concentration curve, aggregating results across all six serotypes, yielded similar results. Application of this curve to GBS6 immunogenicity data predicted maternal immunisation to be more than 80% efficacious for prevention of infant group B streptococcus disease.

Interpretation Higher neonatal anti-capsular polysaccharide serum IgG concentration at birth correlated with reduced risk of infant group B streptococcus disease in Finland. Based on these results, a maternal group B streptococcus capsular conjugate vaccine currently in development is predicted to be efficacious.

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Introduction

Streptococcus agalactiae, or group B streptococcus, is an important cause of invasive bacterial disease in young infants until age 3 months. Group B streptococcus causes sepsis, meningitis, and pneumonia in neonates and can lead to debilitating late-term sequelae, including neurological impairment, hearing loss, and cognitive disabilities.[1] The main risk factor for the development of early-onset disease, which manifests within the first 6 days of life, is the presence of group B streptococcus bacteria in the rectovaginal tract of the mother. Bacteria can be transferred from the mother to the fetus during delivery or via ascending infection before delivery, which can lead to stillbirth or premature labour.[1] Late-onset disease occurs between 7 days and 89 days of life and might be acquired perinatally or via community sources.[1]

Several countries use microbiological or risk-based screening methods to identify pregnant individuals at risk of transmitting group B streptococcus to their infant. These pregnant individuals who are identified as group B streptococcus positive are administered intrapartum antibiotic prophylaxis (IAP) during labour. Universal microbiological screening paired with IAP has been up to 91% effective in preventing early-onset disease group B streptococcus infections in the USA.[2] However, there has been no effect on late-onset disease or prenatal sequelae, and IAP is not frequently available in low-resource settings. Thus, a substantial burden of neonatal early-onset and late-onset group B streptococcus disease remains worldwide, with an estimated 162 200 cases occurring annually.[2,3] Infant group B streptococcus disease has been monitored in Finland

Research in context

Evidence before this study

Numerous seroepidemiology studies (also known as natural history studies) have identified thresholds for anti-capsular polysaccharide IgG concentrations associated with a reduced risk of invasive group B streptococcus disease in newborns. These studies have documented a wide range of protective anti-capsular polysaccharide IgG thresholds (eg, 0·5–6 µg/mL); however, due to inherent confounding variables, such as differing serum sources (infant or maternal) and fundamentally different serological assays, these values cannot be compared across studies. We searched PubMed and the medRxiv preprint servers for articles published from Jan 1, 1970, to Dec 12, 2023, using the keywords "neonatal GBS disease" or "infant GBS disease" or "Group B streptococcus" and "correlates of protection" or "correlation" or "association" and "antibody" or "capsular polysaccharide". We used no language restrictions. We identified a total of nine studies, of which, one study had evaluated antibody concentrations in cases and controls in a European population and used maternal sera. Three studies evaluated the relationship between antibody concentration and risk of disease in case–control studies using infant sera, but not in European populations.

Added value of this study

To our knowledge, this is the first retrospective case–control study to evaluate infant (cord blood) protective concentrations of anti-capsular polysaccharide antibody taken at delivery in Europe. In addition, apart from our recently reported study in South Africa, previous studies have used various assays to quantify anti-capsular polysaccharide IgG concentrations in sera and, therefore, were not comparable to one another or our study. Our study uses a standardised, validated serological assay that has been adopted by an international consortium for the measurement of anti-capsular polysaccharide IgG concentrations against the six group B streptococcus disease serotypes of epidemiological significance (Ia to V). Use of this assay enabled a direct comparison of naturally acquired anti-capsular polysaccharide IgG titres and vaccine-induced anti-capsular polysaccharide IgG titres from an ongoing clinical trial of a conjugate group B streptococcus vaccine. Our study demonstrates that such comparisons can be made across studies using the same standardised assay.

Implications of all the available evidence

Data from our retrospective Finnish cohort corroborates previous seroepidemiological studies supporting an association between infant anti-capsular polysaccharide IgG concentrations at birth and risk of invasive neonatal group B streptococcus disease in early life. Our findings highlight the use of Bayesian-modelled risk–concentration curves as a practical statistical approach to assess absolute group B streptococcus disease risk in a relevant population and to assess the efficacy of candidate capsular polysaccharide-based group B streptococcus vaccines.

since the 1990s, with a reported annual incidence of early-onset disease of 0·6–0·7 per 1000 livebirths (32–38 cases per year) and late-onset disease between 0·1 and 0·3 per 1000 livebirths (6–16 cases per year) between 1995 and 2000.[4] Universal microbiological screening and IAP policies were introduced in Finland in 2011.

The capsular polysaccharide of group B streptococcus is a crucial virulence factor. Of the ten capsular polysaccharide serotypes that have been identified, at least 98% of cases of invasive group B streptococcus disease are caused by serotypes Ia, Ib, II, III, IV, and V.[5] A link between maternal anti-capsular polysaccharide antibodies and the risk of invasive disease in neonates was first established in the 1970s.[6] Studies have confirmed the relationship between the risk of disease and concentration of maternal antibodies or maternally transferred antibodies in infant serum in various populations and settings. These studies have identified protective antibody concentrations at birth associated with a reduced risk of invasive disease in young infants.[6–14] However, due to variations in sample source (infant and maternal) and the use of different serological assays to measure IgG concentration, comparisons across these studies cannot be made. The absence of a standardised serological assay to measure anti-capsular polysaccharide IgG concentrations has been a major challenge to the field. Consequently, there is no consensus on the protective antibody thresholds for invasive group B streptococcus disease.

Pfizer has developed and validated a Luminex-based assay to measure anti-capsular polysaccharide IgG concentrations in human sera, which is standardised across serotypes, enabling cross-serotype IgG titre comparisons.[15] This assay is being used to quantify immune responses to six-valent group B streptococcus polysaccharide-cross-reacting material 197 conjugate vaccine (GBS6) currently in clinical development by Pfizer.[16] The assay has further been adopted as the standardised assay for analysis of serum anti-group B streptococcus capsular polysaccharide IgG serocorrelates by the GASTON international consortium.[17] The assay was also used to determine protective anti-capsular polysaccharide IgG concentrations in an observational non-interventional study in a South African population, which was done in parallel with the clinical trial evaluating GBS6.[16] In this study, infants born to mothers given GBS6 had robust anti-capsular polysaccharide IgG titres and, based on protective thresholds determined from the South African population, 57·1–97·1% of infants born to mothers who were immunised with the optimal dose and formulation (20 µg without aluminium phosphate) had, or had exceeded, the anti-capsular polysaccharide IgG concentrations associated with a 75% reduction in disease risk.[16] However, a limitation of this natural history study was that it only evaluated protective thresholds among the South African population,

which has a high burden of infant invasive group B streptococcus disease.

A large longitudinal birth cohort study in Finland to assess risk factors for the development of type 1 diabetes (Type 1 Diabetes Prediction and Prevention study; DIPP[18]) has been ongoing since Nov 7, 1994, and has collected cord serum at delivery. To evaluate potential protective antibody concentration based on anti-capsular IgG in a setting of lower disease burden than in South Africa, we conducted a retrospective case–control study in Finland based on identification of cases of invasive group B streptococcus disease and their controls from participants in the DIPP study in the first 90 days of life. The aim of this study was to determine the threshold of infant anti-capsular polysaccharide IgG concentrations that correlate with a reduced risk of invasive group B streptococcus disease up to the first 89 days of life. Application of these thresholds to the reported immunogenicity stage 2 data[16] from the ongoing phase 1/2 study of GBS6 (C1091002) in pregnant women enabled a prediction of potential vaccine efficacy based on anti-capsular polysaccharide IgG concentrations in cord blood, measured using the same standardised assay.

Methods

Study population and participants

This was a retrospective case–control study of infants aged 6 months or younger with group B streptococcus infection (cases) and healthy infants (controls) within the DIPP study repository.[18] The source population included infants born in the University Hospitals of Oulu, Tampere, and Turku, Finland, who were enrolled in the DIPP study from Jan 1, 1995, to Dec 31, 2017, and for whom cord serum was available (roughly 209 000 infants).

Details on inclusion criteria (appendix p 4), eligible cases for study enrolment, relevant ICD-10 codes (appendix p 5), and parental informed written consent are provided in the appendix. Ethics approval was obtained from the ethics committee of the Northern Ostrobothnia Hospital District.

Procedures

DIPP cord serum samples were stored at –20°C or –80°C at the three DIPP study centres. An aliquot of the DIPP study cord serum sample of each of the consenting participants was selected and sent frozen to the Finnish Institute for Health and Welfare for recoding with study-specific sample identification numbers before sending to Pfizer (Pearl River, NY, USA) for analysis. The IgG concentration present in each undiluted sample was analysed by a six-plex direct Luminex immunoassay (dLIA; Pfizer, Pearl River, NY, USA), described previously.[15,16] Laboratory staff were masked to the disease status. Median fluorescence intensities were recorded and IgG concentrations (µg/mL) were interpolated from the reference standard, as described by Esadze and colleagues.[15]

Statistical analysis

For exploratory comparisons, we created a control group that comprised a healthy population based on data obtained from the Finnish Medical Birth Register by randomly selecting 10% of the liveborn infants born in the Oulu, Tampere, and Turku University Hospitals between Jan 1, 2004, and Dec 31, 2017. Infants in the control group had no group B streptococcus episodes recorded in the Finnish National Infectious Diseases Register and were selected from a cohort that included 58 037 infants born in Oulu University Hospital, 72 339 infants born in Tampere University Hospital, and 57 086 infants born in Turku University Hospital.

For serological analyses, we used a Bayesian method[16,19] to estimate absolute risk of invasive group B streptococcus disease as a function of anti-capsular polysaccharide IgG concentrations across cases (infants aged ≤89 days) and controls, for serotype III or all serotypes combined using a universal risk–concentration curve. No adjustment for confounding variables was made. A sensitivity analysis of the Bayesian model was repeated in which values less than the lower limit of quantification were treated as left censored (see appendix p 12). Case numbers required to power different levels of risk are shown in the appendix (p 6). Details on our statistical analyses are provided in the appendix (pp 2–3).

C1091002 was the first study to assess the maternal transfer of antibodies induced by GBS6 vaccination.[16] We previously reported interim safety and immunogenicity results from stage 2 of C1091002 that was conducted in a cohort of 360 women who were pregnant from South Africa at three different vaccine doses (5 µg, 10 µg, and 20 µg with and without aluminium phosphate).[16] As the clinical study samples were tested with the same standardised immunoassay as the samples from the natural history study described,[16] the results could be compared. To predict the vaccine efficacy of GBS6 in infants of vaccinated mothers in C1091002,[16] the universal risk–concentration curve from the present study was used to translate the serotype-specific IgG concentration of every individual from cord sera into a predicted risk of invasive group B streptococcus disease due to that serotype. Average risk of disease was calculated for each GBS6 vaccine group and placebo group. Vaccine efficacy was calculated as:

See Online for appendix

$$\textit{Vaccine efficacy} = 100\% \times \left(1 - \frac{\textit{average disease risk in vaccine group}}{\textit{average disease risk in placebo group}}\right)$$

Vaccine efficacy across all six serotypes was a weighted average of the six serotype-specific efficacies using global relative serotype prevalence.[5] 95% CIs were derived from bootstrap resampling of the C1091002 dataset, treating the risk–concentration curve as fixed. Analyses were done in R (R2Jags package, 0.6–1) and SAS (9.4).

	Early-onset disease (age 0–6 days)	Late-onset disease (age 7–89 days)	All disease (proportion of total cases; %)	Matched controls
Ia	6	3	9 (16%)	40
Ib	3	0	3 (5%)	13
II	3	1	4 (7%)	16
III	15	17	32 (58%)	133
IV	3	0	3 (5%)	11
V	3	1	4 (7%)	16
Total	33	22	55	229

Table 1: **Serotype distribution of group B streptococcus invasive disease cases**

Role of the funding source

Pfizer was involved in the study concept and design; the collection, analysis, and interpretation of the data; the drafting of the manuscript; and the decision to submit the manuscript for publication.

Results

Early-onset group B streptococcus disease incidence remained stable in Finland between 1998 and 2010 (average annual incidence of roughly 0·54 cases per 1000 livebirths) except for 2005, when a spike in cases was recorded (appendix p 12). A decline in early-onset disease began in 2011, which coincided with the implementation of universal microbiological screening and IAP policies in Finland. After 2011, early-onset disease incidence declined to about 0·16 cases per 1000 livebirths annually at the end of the study in 2017. By comparison, late-onset group B streptococcus disease incidence remained stable over the full study period, with an average of about 0·26 cases per 1000 livebirths annually (appendix pp 7, 12).

For the serological analyses, infant invasive group B streptococcus cases and controls were identified as detailed in the consort diagram (appendix p 13). 55 cases (33 early-onset disease and 22 late-onset disease) of invasive neonatal group B streptococcus disease were enrolled and matched to 229 control infants. Of the group B streptococcus cases, 32 (58%) were serotype III, nine (16%) were serotype Ia, four (7%) were serotype II, four (7%) were serotype V, three (5%) were serotype Ib, and three (5%) were serotype IV (table 1). Serotype III was identified in 15 (45%) early-onset disease cases and 17 (77%) late-onset disease cases.

The background characteristics of the analysed cases and their matched controls and a pool of randomly selected healthy controls are shown in the appendix (p 8). Overall, cases (53% male and 47% female) and controls (50% male and 50% female) had similar ratios of males and females. There was a lower median birthweight and a higher proportion of preterm births in cases than in controls, as might be expected given that premature birth is a known risk factor for neonatal group B streptococcus disease and a potential consequence of ascending group B streptococcus infection in pregnant individuals.[20] There was a lower number of elective (but not emergency or urgent) caesarean sections for mothers of infants who developed group B streptococcus disease than in healthy controls.

For analysis of serological correlates, anti-capsular polysaccharide antibody concentrations in cord serum were compared between the 55 cases and 229 controls matched by year of birth and hospital district (roughly 4:1 control-to-case ratio). Generally, anti-capsular polysaccharide IgG concentrations were higher in controls compared with in cases, although there was a wide variation in the individual antibody concentrations. The number of cases was too low to provide sufficient precision for most serotypes (figure, table 2). For serotype III, for which the largest number of cases were available, the anti-capsular polysaccharide IgG geometric mean concentration in cases was 0·008 μg/mL (95% CI 0·005–0·013) and 0·022 μg/mL (0·015–0·033) in controls. Furthermore, for serotype III, anti-capsular polysaccharide IgG concentrations were higher in controls than in cases in both early-onset disease and late-onset disease. These findings were similar after adjustment for matching variables (appendix p 9).

For serotype-specific analyses, only serotype III had a sufficient number of cases in this study to deduce risk–concentration associations with adequate statistical power. Since the serological assay uses a serum reference standard with weight-based assignments for anti-capsular

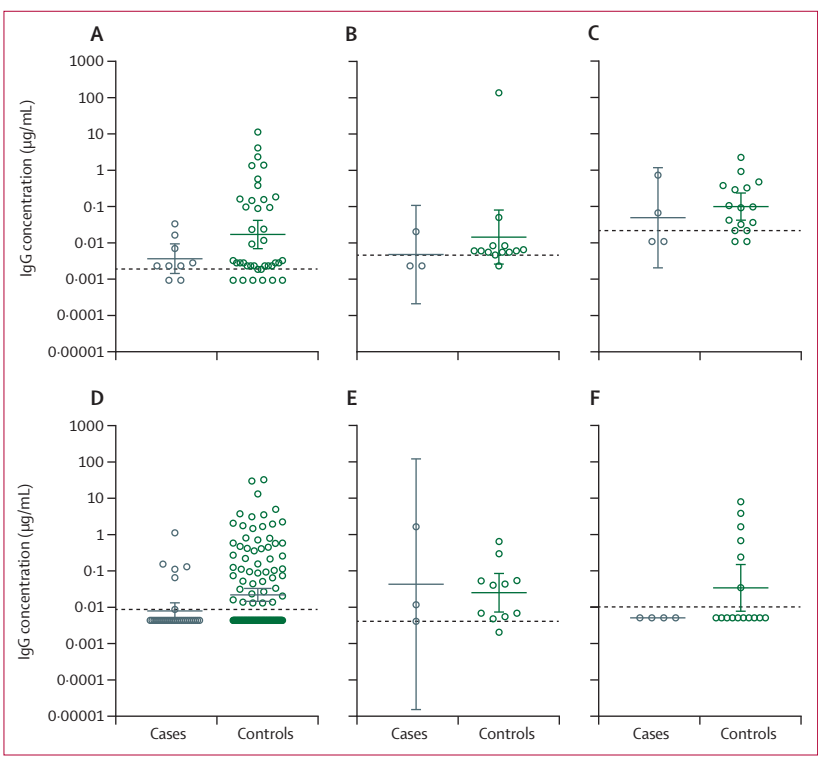

Figure: **Group B streptococcus anti-capsular polysaccharide IgG titres for cases and matched controls**
Serotype-specific IgG titres are shown for serotype Ia (A), serotype Ib (B), serotype II (C), serotype III (D), serotype IV (E), serotype V (F). Each point represents an individual cord serum sample. Geometric mean concentrations and the 95% CI are shown. Dashed line represents the assay lower limit of quantitation.

	Cases (n=55)		Controls (n=229)		Geometric mean ratio (95% CI)‡
	Participants, n*	Geometric mean concentration (95% CI), µg/mL†	Participants, n*	Geometric mean concentration (95% CI), µg/mL†	
Serotype Ia					
All	9	0·004 (0·001–0·009)	39	0·017 (0·007–0·042)	4·646 (1·354–15·942)
Early-onset disease	6	0·004 (0·001–0·022)	26	0·013 (0·005–0·034)	2·820 (0·519–15·322)
Late-onset disease	3	0·002 (0·002–0·003)	13	0·031 (0·004–0·242)	12·610 (1·625–97·826)
Serotype Ib					
All	3	0·005 (0·000–0·108)	13	0·014 (0·003–0·080)	3·030 (0·253–36·271)
Serotype II					
All	4	0·049 (0·002–1·172)	16	0·099 (0·042–0·235)	2·028 (0·104–39·715)
Serotype III					
All	32	0·008 (0·005–0·013)	133	0·022 (0·015–0·033)	2·756 (1·446–5·252)
Early-onset disease	15	0·010 (0·004–0·027)	65	0·020 (0·011–0·037)	1·973 (0·656–5·932)
Late-onset disease	17	0·006 (0·004–0·011)	68	0·023 (0·013–0·042)	3·721 (1·717–8·065)
Serotype IV					
All	3	0·043 (0·000–120·396)	11	0·025 (0·007–0·085)	0·585 (0·000–764·129)
Serotype V					
All	4	0·005 (0·005–0·005)	16	0·034 (0·008–0·150)	6·688 (1·520–29·423)

The timing for blood sample (ie, for early-onset or late-onset disease cases) collection was specified at delivery. CIs were back transformations of a CI based on the student *t* distribution for the mean logarithm of the concentrations. *Number of individuals with valid and determinate assay results for the specific serotype at the specified timepoint. †Geometric mean concentrations (µg/mL) were calculated using all individuals with available data at either birth or time of infection; geometric mean concentrations were included for early-onset disease and long-onset disease only for serotypes for which there were sufficient cases (Ia, III). ‡The geometric mean ratio was calculated as the group mean difference (control–case) of logarithmically transformed antibody concentration and back transformed to the original units.

Table 2: **Geometric mean IgG concentrations in cord serum of cases and controls**

	Type III only (32 cases; 133 controls)	All types combined (55 cases; 228 controls)
Protective IgG concentrations, µg/mL		
Target risk reductions*		
70%	0·097	0·132
75%	0·120	0·168
80%	0·151	0·217
90%	0·266	0·404
Parameter estimates (95% CI) of Bayesian posterior disease risk†		
Parameter		
λ_1	0·020 (0·008–0·036)	0·022 (0·011–0·036)
ν_1	0·516 (0·405–0·635)	0·474 (0·393–0·556)
λ_0	0·085 (0·046–0·131)	0·092 (0·058–0·13)
ν_0	0·354 (0·315–0·397)	0·346 (0·318–0·378)
π	0·001 (0·001–0·001)	0·001 (0·001–0·001)

*Protective concentrations are derived as the IgG concentration at which the probability of disease is reduced by the stated percentage relative to the assumed population probability of disease, for any individual with IgG concentration at or above the cutoff. †ν_1 and ν_0 are estimated shape parameter of Weibull distribution in case and control groups, respectively; λ_1 and λ_0 are the corresponding scale parameters; and π is the group B streptococcus disease prevalence in the population.

Table 3: **Estimated anti-capsular polysaccharide IgG thresholds for selected risk reduction levels**

polysaccharide IgG[15] and is standardised across serotypes, analysis of a universal risk–concentration curve with data from all six serotypes combined was feasible (appendix p 14). The appendix (p 14) displays risk–concentration curves for serotype III individually and all serotypes combined, with 95% CIs. The estimated anti-capsular polysaccharide IgG thresholds associated with specific risk reductions (RR) for invasive disease are shown in table 3. The discrete protective threshold values for serotype III and all serotypes combined were similar between these two analyses. For example, for 80% RR, the serotype III IgG concentration threshold was 0·151 µg/mL, and when all serotypes were included, the value was 0·217 µg/mL (table 3).

To assess model fit, empirical and fitted reverse cumulative distribution functions in cases and controls for serotype III and all serotypes combined are shown in the appendix (p 15). To evaluate the accuracy of these predicted thresholds, we compared the odds of disease in cases and controls based on the discrete protective threshold values for serotype III or all serotypes combined (appendix p 10). Overall, fewer cases had titres that reached protective thresholds compared with controls, using either approach. As an example, two (6·3%) of 32 cases had concentrations above the serotype III-specific threshold for 80% RR (0·151 µg/mL) compared with 29 (21·8%) of 133 controls. For all serotypes combined, three (5·5%) of 55 cases had levels above the threshold associated with 80% RR (0·217 µg/mL) compared with 48 (21·0%) of 229 controls.

A sensitivity analysis was done in which values less than the lower limit of quantification were treated as left censored. With the left censoring, thresholds could still be estimated, although they were higher than for the main analysis (appendix p 11).

For the optimal vaccine formulation (20 µg per serotype, no aluminium phosphate) in the C1091002 study,[16]

	GBS6 5 µg		GBS6 10 µg		GBS6 20 µg	
	With aluminium phosphate	Without aluminium phosphate	With aluminium phosphate	Without aluminium phosphate	With aluminium phosphate	Without aluminium phosphate
Serotype Ia	79·0% (59·7–93·1)	94·3% (88·1–99·1)	93·0% (77·6–99·8)	84·8% (67·2–96·3)	74·8% (54·5–90·2)	96·0% (86·8–100·0)
Serotype Ib	42·1% (23·8–59·2)	50·0% (29·8–68·4)	47·9% (28·4–66·4)	55·4% (36·6–72·9)	55·1% (37·6–70·7)	63·5% (47·0–78·5)
Serotype II	96·5% (93·0–98·7)	93·7% (85·4–98·3)	95·3% (88·3–99·1)	91·4% (76·9–99·2)	88·3% (75·3–97·0)	96·0% (89·5–99·9)
Serotype III	69·9% (53·8–83·8)	76·5% (61·0–89·6)	78·5% (65·8–89·3)	80·9% (67·5–91·5)	65·3% (48·7–80·4)	82·3% (70·1–92·1)
Serotype IV	82·1% (71·9–90·5)	71·5% (58·7–82·2)	84·8% (76·7–91·0)	73·9% (61·7–84·7)	79·5% (69·3–88·3)	90·7% (85·3–95·2)
Serotype V	36·4% (22·4–50·3)	41·7% (23·5–60·0)	58·1% (42·8–72·6)	69·0% (51·1–85·1)	55·0% (40·6–68·6)	59·2% (45·3–72·6)
All serotypes*	68·7% (58·2–78·2)	76·6% (66·7–85·1)	78·7% (70·1–86·1)	79·5% (70·3–87·0)	66·7% (55·6–76·9)	82·8% (74·9–89·4)

Data are median predicted vaccine efficacy (95% CI) derived from 10 000 bootstrap samples. Predicted vaccine efficacy is the mean estimated risk from the risk-concentration curve in the vaccine group as a percentage reduction from the mean estimated risk on placebo. Total GBS6 dose was 30 µg (5 µg capsular polysaccharide per serotype per dose); 60 µg (10 µg capsular polysaccharide per serotype per dose); 120 µg (20 µg capsular polysaccharide per serotype per dose). *Aggregate predicted vaccine efficacy for all six serotypes (Ia–V) was a weighted average of serotype-specific predicted efficacy using the relative global prevalence of each serotype for all associated disease cases (early-onset plus late-onset disease).

Table 4: **Predicted GBS6 vaccine efficacy in C1091002 study infants for all formulations and serotypes using the risk-concentration curve from the Finnish cohort study**

predicted vaccine efficacy against all six serotypes was 82·8% (95% CI 74·9–89·4) and was 82·3% (70·1–92·1) for serotype III (table 4). This prediction indicated that infants born to GBS6-vaccinated mothers might be more than 80% less likely to develop invasive group B streptococcus disease than infants born to unvaccinated mothers.

Discussion

In the USA, incidence of early-onset group B streptococcus disease has gradually declined from 1·4 per 1000 livebirths in 1990 to 0·19 per 1000 livebirths in 2019, mostly due to the introduction of universal microbiological-based screening with IAP. The incidence of late-onset group B streptococcus disease has remained unchanged at 0·3–0·4 per 1000 livebirths annually.[21] A similar trend was observed in Finland,[22] with the exception of an unusual spike in early-onset disease cases in 2005.[23] This spike in cases was previously attributed to the introduction of an ineffective risk-based screening protocol for group B streptococcus culture that led to false-negative results, thus leading to administration of IAP to less than 5% of parturient individuals.[24] Changing to the use of a simple risk-based interview screening without group B streptococcus culture in the next year resulted in six-fold higher IAP administration and a subsequent reduction in disease incidence.[24] Nevertheless, the limitations of IAP are evident by the measurable residual burden of early-onset disease and unchanged incidence of late-onset disease. In addition, IAP might have an effect on the developing infant microbiome.[25]

The serological analyses in this Article, which assessed cord blood samples from Finland, align with the results of a multitude of previous studies that have documented an association between anti-capsular polysaccharide IgG concentrations at birth and risk of invasive group B streptococcus disease until 90 days of life, a period that includes both early-onset and late-onset disease.[6–14] Cord blood anti-capsular polysaccharide IgG concentrations in control participants tended to be higher than in group B streptococcus-positive cases. This difference was particularly evident for the most common serotypes, Ia and III, thus corroborating the association between the risk of the disease and antibody concentration shown in previous studies.[6–14] The identification of antibody concentrations that are protective for group B streptococcus disease is crucial for the evaluation of vaccines under development. An efficacious group B streptococcus vaccine administered to pregnant individuals has the potential to address prepartum sequelae of invasive group B streptococcus disease as well as early-onset and late-onset disease through maternally transferred antibodies. Licensure of a GBS vaccine might be enabled by determination of protective anti-capsular polysaccharide IgG thresholds in the infant that could be used as an immunological endpoint.[26]

Although several seroepidemiological studies have documented an association between anti-capsular polysaccharide IgG concentrations and reduced risk of group B streptococcus disease, the only two European studies that evaluated this relationship used maternal sera.[7,13] There have been no studies that have evaluated protective infant serum anti-capsular polysaccharide IgG concentrations in a European population. Maternal sera might be suboptimal for these analyses as the disease occurs in the infant and maternal antibody concentrations might not reflect IgG concentrations in the infant due to variability in transfer rates, gestational age, and placental health.[27,28] In the present study, we used umbilical cord sera as it reflects the antibody concentrations that the infant receives from the mother. Determination of protective thresholds based on circulating antibody concentrations in the infant may more accurately reflect the concentrations required for protection.

The anti-capsular IgG assay used in this Article was also used by Madhi and colleagues to quantify protective IgG concentrations in infant cord sera from a prospective case–control seroepidemiological study in South Africa.[16] The anti-capsular IgG concentrations observed in cases and controls in our study were very similar to those reported by Madhi and colleagues,[16] despite differences in the standard of care and national IAP policy. The anti-capsular polysaccharide IgG protective threshold values from the Finnish study were similar for serotype III (the most common serotype globally[5]) and all serotypes combined, which is an

important finding that was also observed in the South African study.[16] These data suggest that similar amounts of anti-capsular polysaccharide antibody might be required for equivalent protection against group B streptococcus disease caused by different serotypes. The similarity in thresholds for serotype III and all serotypes combined could be explained by the role of capsular polysaccharide in evading the alternative complement pathway and similar mechanisms of action of anti-capsular polysaccharide antibodies regardless of serotype. The similarities between the thresholds derived from Finland and South Africa suggest that protective antibody thresholds might be similar in both high-income and low-to-middle-income countries.

The strengths of this study include that the serotype of the causative isolate and the timing of disease were known, and that infant cord serum was used. Although controls were infants who did not have invasive group B streptococcus disease, the group B streptococcus colonisation status of the mother was unknown for these infants. A limitation of the study is that, in general, measured and unmeasured confounders were not adjusted for and maternal colonisation information was not available. However, colonisation is transient and status at the time of screening might not reflect the status at the time of delivery.[2] Since 2013, there has been a national recommendation in Finland for universal microbiological screening and to administer IAP to pregnant individuals who are positive for group B streptococcus.[29] Therefore, more pregnant individuals in the study cohort would have been given IAP after 2013. This increase in the use of IAP might have decreased the relative risk of invasive group B streptococcus disease for some control infants who could have developed the disease without screening and IAP due to sub-protective anti-capsular polysaccharide antibody concentrations. In addition, the number of cases of serotypes other than serotype III was low.

GBS6 is designed to target the six serotypes responsible for more than 98% of cases of invasive group B streptococcus disease worldwide (Ia, Ib, II, III, IV and V).[5] Application of the risk–concentration curve from Finnish infants to anti-capsular polysaccharide IgG concentrations in cord blood of infants in the C1091002 study[16] made it possible to estimate disease protection afforded by GBS6 relative to the placebo group. Comparison of serological data across studies and estimation of protective antibody thresholds were facilitated by the use of a standardised assay to quantify IgG. For optimal comparisons, the socioeconomic settings of such studies will also need to be considered. For instance, the risk–concentration curve applied to participants in C1091002 in this Article is from a high-income country (Finland), whereas the C1091002 study was conducted in a low-to-middle income country (South Africa). All participants in the Finnish study were White and all participants in the C1091002 study were Black. In addition, the median age of the mothers in the C1091002 study was lower than in the Finnish study. Despite these differences in baseline characteristics, the thresholds derived from the present study and the South Africa seroepidemiology study[16] were similar and, therefore, the predicted efficacy might be comparable in both settings. Future studies should confirm that the protective thresholds are similar in high-income countries and low and middle income countries.

The results of this study support the use of a universal risk–concentration curve based on all six serotypes that might be used to assess the potential efficacy of candidate polysaccharide-based group B streptococcus vaccines in high-income countries and low and middle income countries and across different geographical regions.

Contributors

AS, NCS, and DR contributed to data collection and analysis, figure creation, as well as writing of the manuscript. DR did statistical analyses and MT and LL did bacteriological analyses. RV, JT, and MK were investigators of the DIPP study and contributed to patient data collection. BJ, EG, ASA, AAP, and RS contributed to the conception of the work and analysis of data. All authors contributed to the manuscript development and had permission to access the raw data, reviewed the results, and approved the final manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

DR, EG, NCS, BJ, ASA, and RS are employees of Pfizer and are recipients of stock options in Pfizer. ASA is an inventor on patents related to group B streptococcus vaccines. AS, MT, LL, and AAP are employees of the Finnish Institute for Health and Welfare, which has received research funding from Pfizer.

Data sharing

The study sponsor, Pfizer, will provide aggregate data that support the findings of this study on request, subject to review. This publication includes seroepidemiology data that Pfizer is not responsible for validating or storing. Due to data confidentiality reasons, individual participant data cannot be made available. Contact the corresponding author for more information.

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