TITLE PAGE

***Full title*:** Serotype association with neonatal invasive potential, disease manifestation, and clinical outcome in group B Streptococcus: A Bayesian analysis

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***Running title*:** Role of serotype in neonatal GBS

***Keywords*:** Group B Streptococcus; *Streptococcus agalactiae*; serotype replacement; vaccine

***Main point*:** Group B Streptococcus serotypes targeted by the hexavalent vaccine formulation include those with the greatest invasive neonatal invasive potential and likelihood of presenting as meningitis. These circumstances reduce the risk that vaccine-driven serotype replacement in carriage would offset vaccine impact.

ABSTRACT

Background: Polyvalent vaccines targeting group B Streptococcus (GBS) serotypes are under development to reduce perinatal disease burden. To understand potential impacts of vaccination on GBS epidemiology, we assessed serotype associations with invasiveness, clinical manifestation, and case-fatality ratio in neonates.

Methods: Via a systematic review, we obtained data from 15 paired sets of serotyped GBS isolates from intrapartum recto-vaginal colonization (*n*=3403) and neonatal invasive disease (*n*=1088), 16 sets from blood (*n*=2352) and cerebrospinal fluid (*n*=780) in neonatal invasive disease, and 3 sets from fatal (*n*=173) and non-fatal (*n*=1684) neonatal invasive disease. We compared serotype-specific invasive potential, risk for meningitis presentation, and case-fatality ratio in a Bayesian random-effects framework.

Results: Serotype III was associated with the greatest neonatal invasive potential, followed by serotype Ia with a 75.3% (95%CI: 43.7-93.8%) lower estimate. While non–hexavalent-vaccine serotypes had lower invasive potential than serotype III, we estimated the invasive potential of serotypes VI and Ia to be equivalent. Serotype III infections were more likely than other infections to present as meningitis. Enhanced serotype III invasiveness and meningitis risk were more pronounced in late-onset than early-onset disease. Infections caused by serotypes Ia and V showed weak evidence of elevated case-fatality.

Conclusions: GBS serotypes targeted by the hexavalent vaccine formulation include those with the greatest invasive potential, clinical severity, and risk of death in neonates. While these findings suggest serotype replacement may have limited potential to offset vaccine impact, high rates of recombination in GBS underscore the need for molecular surveillance.

INTRODUCTION

Group B Streptococcus (GBS; *Streptococcus agalactiae*) is the leading cause of neonatal invasive infections, with 0.53 cases per 1000 live-births globally [1] and 2.03 cases per 1000 live-births in sub-saharan Africa [2]. While intrapartum antimicrobial prophylaxis prevents early-onset GBS disease (EOD; occurring 0-6 days after birth) [3], additional preventive strategies are needed to combat late-onset disease (LOD; 7-90 days), and to serve populations with limited access to antenatal care. There are ten recognized serotypes of GBS defined by distinct polysaccharide capsular antigens (Ia, Ib, II-IX) as well as non-typeable strains (NT-GBS). Anticapsular conjugate vaccines intended for pregnant women are currently under development. A trivalent conjugate vaccine (GlaxoSmithKline) targeting serotypes Ia, Ib, and III has completed phase-2 trials [4,5], and a hexavalent vaccine (Pfizer) against serotypes Ia-V is entering phase-1 studies.

Considerations around vaccine compositions have centered around serotype frequencies in neonatal invasive disease, with serotypes Ia, Ib, and III alone comprising 85% of cases worldwide [6]. However, concerns surround the possibility that vaccine-derived immunity against targeted GBS serotypes may exert selective pressure on the circulating GBS population, enabling non-vaccine serotypes that are currently rare to expand in prevalence [7,8]. Such “serotype replacement” in *Streptococcus pneumoniae*—whereby serotypes not targeted by pneumococcal conjugate vaccines (PCVs) have overtaken the ecological niche formerly inhabited by vaccine-targeted serotypes [9]—has offset the impact of PCVs against invasive pneumococcal disease [10].

Whether routine maternal vaccination will drive serotype replacement in GBS is difficult to predict given limited understanding of GBS transmission dynamics. However, estimates of the relative capacity of GBS serotypes to cause disease, and of the relative severity of disease caused by distinct serotypes, provide a basis for forecasting the impact of vaccines on GBS epidemiology. Experience with PCVs has illustrated that such estimates can inform more optimal vaccine compositions than those defined by serotype-specific prevalence [11,12], and provide a baseline for monitoring post-vaccination epidemiological changes [13]. While historical data demonstrate enhanced invasiveness of GBS serotype III [14,15], these studies predate the emergence or discovery of serotypes IV-IX, and are of limited size and geographic scope. We therefore undertook a systematic review and Bayesian meta-analysis of epidemiological studies to compare GBS serotypes in terms of invasive potential, clinical presentation, and risk of death among neonates.

METHODS

Outcome definition

We sought to determine the association of serotype with the following natural history features of neonatal invasive GBS:

1. Risk of causing invasive disease given maternal colonization: We defined invasive disease as GBS isolation from an ordinarily sterile site (e.g., blood or cerebrospinal fluid), and distinguished between EOD and LOD;
2. Risk for meningitis during neonatal invasive infection: We defined cases with GBS isolation from cerebrospinal fluid as meningitis; and
3. Risk for fatal outcome: We defined fatal cases as deaths attributable to invasive GBS among liveborn infants (thus excluding stillbirths).

For our analyses of invasive potential, we compared serotype frequencies in neonatal disease against serotype frequencies in recto-vaginal colonization among pregnant women; we did not restrict colonization samples according to time of sampling within pregnancy due to limited metadata on when swabs were obtained.

Study identification

We updated three previously-undertaken systematic literature reviews [1,6,16] and extracted serotype-stratified data on maternal carriage, disease timing (EOD/LOD), disease manifestation (meningitis or

other), and outcome (fatal or non-fatal). For analyses of serotype associations with neonatal invasive potential, we aimed to include all studies monitoring both carriage and disease serotype distributions within a single source population or setting; for analyses of serotype associations with meningeal invasion and fatal outcome, we sought all studies presenting serotype frequencies in neonatal meningitis and sepsis, and in fatal and non-fatal neonatal invasive disease. We examined full texts of all studies included in the previous reviews to determine eligibility, and conducted a PubMed search as well as citation tracking of these reviews and two other relevant studies [17,18] to identify new articles for screening. We detail the search strategy and inclusion/exclusion criteria in the **Supplementary information**.

Statistical analyses

Included studies presented paired frequencies of GBS serotypes in carriage and disease, meningitis and other invasive disease, and fatal and nonfatal cases. We pooled estimates of serotype frequencies and their association with these conditions under a Bayesian random effects framework, applying Dirichlet distributions to serotype frequencies in order to sample parameters in the presence of sparse (including zero-valued) counts within studies. We assumed flat (uninformative) priors for all parameters and hyperparameters. We describe the full methods in the **Supplementary information**.

From each study with paired carriage and disease data, we pooled estimates of the odds ratio for a serotype to be isolated from neonatal invasive disease (all neonatal invasive disease, EOD, LOD) versus maternal colonization. For studies reporting GBS isolation from blood or CSF, we pooled estimates of the relative risk that invasive disease caused by each serotype would manifest as meningitis, again stratifying for EOD and LOD. Last, for studies reporting fatal and non-fatal outcome, we pooled estimates of the relative case-fatality ratio (CFR) of invasive disease caused by each serotype. For all analyses, we report relative measures (odds ratios and relative risks) using the serotype with the greatest absolute odds or risk of the endpoint as the reference.

RESULTS

Data abstraction

We assessed full texts of 599 studies covered in previous systematic reviews [1,6,16], and screened abstracts of 50 articles identified via a PubMed search and 529 articles citing the previous reviews and two other relevant articles [17,18], not exclusive of duplicates (**Figure 1**). From these, we identified 15 paired datasets of GBS serotype distributions in carriage and neonatal invasive disease (3403 and 1088 isolates, respectively; **Table 1**); 16 datasets presenting serotype distributions in meningitis and other neonatal invasive disease (3132 isolates; **Table 2**); and 3 datasets presenting serotypes isolated from fatal and non-fatal neonatal invasive disease cases (1684 isolates; **Table 2**).

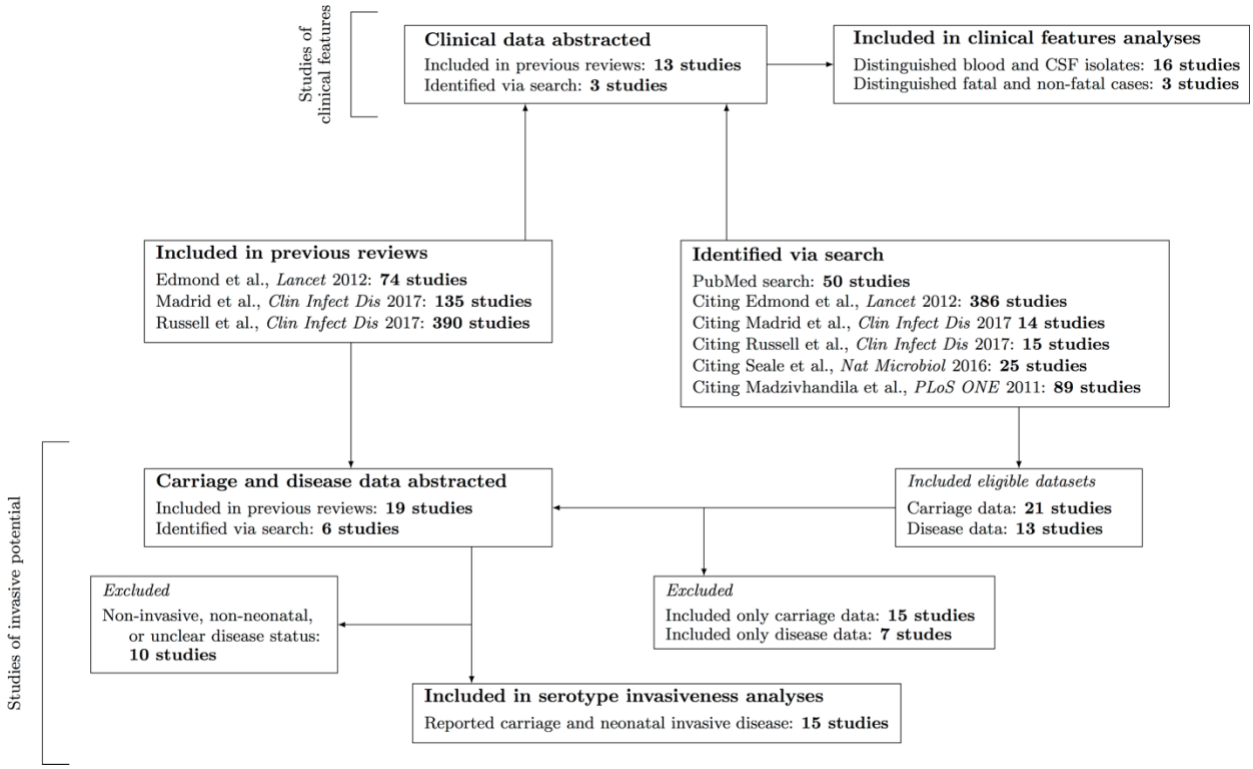


Figure 1: Systematic review flowchart. We detail the identification and inclusion/exclusion of articles from three previous systematic reviews [1,6,16] and their citations, as well as citations of two additional relevant studies [17,18], and a PubMed search for articles published after January 1, 2016. Tabulations do not exclude duplicate results.

Table 1: Included studies indicating serotype association with invasive potential.

Study	Reference (Supplement)	Setting	Basis for pairing	Isolates obtained			
				Carriage	Neonatal disease	EOD	LOD
Ko et al., 2015	41	Australia	Geography, date	408	108	60	48
Seale et al., 2016	42	Kenya	Mother-infant dyads	915	70	30	40
van Elzakker et al., 2009	43	Taiwan	Geography, date	58	43	– ––	– ––
van Elzakker et al., 2009	43	Netherlands	Geography, date	92	44	– ––	– ––
Madzivhandila et al., 2011	44	South Africa	Mother-infant dyads	541	245	137	108
Martins et al., 2007	45	Portugal	Geography, date	269	64	42	22
Bisharat et al., 2005	46	Israel	Geography, date	104	50	– ––	– ––
Berg et al., 2000	47	Sweden	Geography, date	114	128	40	10
Moraleda et al., 2018	48	Morocco	Geography, date	67	5	– ––	– ––
Lopez et al., 2018	49	Spain	Facility, date	242	79	– ––	– ––
Figueira-Coelho et al., 2004	50	Portugal	Facility, date	108	17	– ––	– ––

Davies et al., 2001	51	Canada	Geography, date	118	– ––	75	– ––
Teatero et al., 2014	52	Canada	Facility, date	102	93	34	59
Martinez et al., 2004	53	Chile	Geography, date	65	10	– ––	– ––
Hayes et al., 2017	54	Ireland	Geography, date	200	7	– ––	– ––

Table 2: Included studies indicating serotype association with disease manifestation and fatal outcome.

Study	Reference (Supplement)	Setting	Isolates obtained		
			Meningitis	Non-meningitis	Fatal outcome
Davies et al., 2001	51	Canada	17	74	91
Ekelund et al., 2004	55	Denmark	107	405	– –
Gray et al., 2007	56	Malawi	21	25	– –
Zhao et al., 2008	57	Australia, New Zealand	20	73	– –
Martins et al., 2007	45	Portugal	4	55	– –
Trijbels-Smeulders et al., 2006	58	Netherlands	63	135	– –
Fluegge et al., 2005	59	Germany	67	225	– –
Chang et al., 2014	60	Japan	37	21	– –
Liu et al., 2015	61	Chiu	3	5	– –
Morozumi et al., 2014	62	Japan	81	48	– –
Six et al., 2016	63	France	4	12	– –
Teatero et al., 2014	52	Canada	9	80	– –
Yoon et al., 2015	64	Republic of Korea	25	24	– –
Siguaque et al., 2018	65	Mozambique	14	21	– –
Dangor et al., 2016	66	South Africa	172	424	596
Phares et al., 2008	67	United States	156	841	997

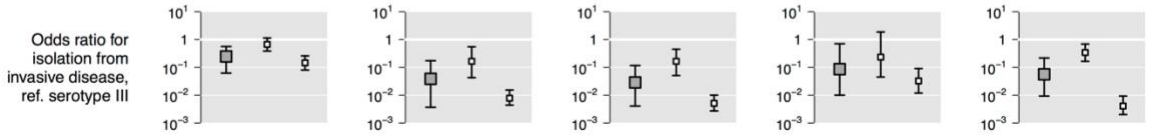
Of the paired maternal carriage and neonatal disease datasets, two were obtained from maternal-newborn dyads [17,18]; all others were from geographically- and temporally-matched samples of maternal colonization and neonatal invasive disease isolates. Latin American (1 study, 75 isolates), East Asian (1 study, 101 isolates), and South/Southeast Asian (0 studies) populations were under-represented; nine datasets were from North America, Europe, and Oceania. Studies reporting disease manifestation and fatal outcome were from North America, Europe, Oceania, East Asia, and sub-Saharan Africa; no data from Latin America or South/Southeast Asia were available.

Neonatal invasive potential

Serotype III caused between 48-95% of neonatal invasive disease cases across the included studies,

followed by serotype Ia (1-28 %), serotype V (0-15%), and serotype II (0-10%). However, this hierarchy of serotype frequencies was less evident in colonization (**Figure 2**). Serotypes Ia-VII and IX/NT-GBS were each associated with lower neonatal invasive potential in comparison to serotype III; we did not generate pooled estimates for serotype VIII due to sparse data availability. Relative to serotype III, we estimated serotypes Ia and V were 24.7% (6.2-56.3%) and 5.6% (0.9%-21.8%) as likely, respectively, to cause neonatal invasive disease given maternal carriage. These pooled estimates were consistent with findings of individual studies; nine and eleven studies, respectively, provided evidence of lower neonatal invasive potential of serotypes Ia and V (relative to serotype III) at the 97.5% confidence threshold. We estimated the neonatal invasive potential for serotypes Ib, II, and IV—the remaining serotypes included in the candidate hexavalent vaccine—to be 3.9% (0.4-17.4%), 2.9% (0.4-11.6%), and 8.6% (1.0-70.5%) that of serotype III, respectively, and 12.2% (1.6-70.5%), 16.1% (1.5-97.5%), and 36.8% (3.7–459.5%) that of serotype Ia.

Study	Serotype Ia				Serotype Ib				Serotype II				Serotype IV				Serotype V			
	Car.	Dis.	EOD	LOD	Car.	Dis.	EOD	LOD	Car.	Dis.	EOD	LOD	Car.	Dis.	EOD	LOD	Car.	Dis.	EOD	LOD
Hayes et al., 2017	59	1			20	0			31	1			8	0			23	1		
Martinez et al., 2004	20	3			3	0			14	0			0	0			1	0		
Teatero et al., 2017	24	13	5	8	12	6	5	1	13	4	3	1	6	1	0	1	20	8	5	3
Davies et al., 2001	24		20		10		4		10		6		0		0		33		13	
Figueira–Coelho et al., 2004	21	5			5	0			14	1			1	2			26	3		
Lopez et al., 2018	36	18			20	9			55	10			21	2			26	9		
Moraleda et al., 2018	6	0			0	0			17	2			5	1			24	1		
Bergal et al., 2000	15	19	5	0	15	4	1	1	13	5	1	0	3	3	0	1	25	18	9	2
Misharat et al., 2005	12	10			9	2			23	4			0	0			18	9		
Martins et al., 2000	42	18	13	5	14	2	1	1	46	8	8	0	6	2	1	1	59	7	7	0
Madzivhandila et al., 2011	163	46	31	15	36	7	7	0	61	7	7	0	20	5	5	0	55	10	8	2
van Elzakker et al., 2009	24	6			6	0			12	0			7	0			14	4		
van Elzakker et al., 2009	13	5			5	2			2	0			0	0			15	2		
Seale et al., 2016	194	10	7	3	114	4	3	1	80	1	1	0	18	1	1	0	156	0	0	0
Ko et al., 2015	107	26	18	8	31	6	4	2	40	5	4	1	5	2	2	0	68	18	12	6



Study	Serotype VI				Serotype VII				Serotype VIII				Serotype IX/NT				Serotype III (ref.)			
	Car.	Dis.	EOD	LOD	Car.	Dis.	EOD	LOD	Car.	Dis.	EOD	LOD	Car.	Dis.	EOD	LOD	Car.	Dis.	EOD	LOD
Hayes et al., 2017	2	1			4	0			1	0			1	0			51	3		
Martinez et al., 2004		0				0				0				0			24	7		
Teatero et al., 2017	1	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	26	59	15	44
Davies et al., 2001	0				0				0				23				18		28	
Figueira–Coelho et al., 2004	0	0			1	0			1	0			11	0			28	6		
Lopez et al., 2018	0	0			2	0			0	0			0	0			82	31		
Moraleda et al., 2018	0	0			0	0			0	0			3	0			12	1		
Bergal et al., 2000	0	0	0	0	0	0	0	0	0	0	0	0	7	1	0	0	36	78	24	6
Misharat et al., 2005	0	1			0	0			0	0			16	5			26	19		
Martins et al., 2000	0	0	0	0	5	0	0	0	0	0	0	0	38	1	0	1	59	26	12	14
Madzivhandila et al., 2011	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	202	170	79	91
van Elzakker et al., 2009	2	0			0				0				2				20	33		
van Elzakker et al., 2009	2	0			0	0			0	0			2	0			19	34		
Seale et al., 2016	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	350	54	18	36
Ko et al., 2015	3	4	4	0	3	1	1	0	0	0	0	0	9	0	0	0	142	46	15	31

Figure 2: Association of serotype with neonatal invasive potential. For each study, we indicate serotype frequencies in intrapartum recto-vaginal colonization ("car.") and neonatal invasive disease ("Dis."), as well as EOD and LOD, as permitted by reporting within original studies. We plot pooled estimates of serotype-specific relative invasive potential beneath serotype frequencies for all disease (grey points) as well as EOD and LOD (white points), measured from the odds ratio that an isolate came from invasive disease versus colonization, relative to serotype III (lower right corner). Our derivation of this measure is provided in the **Supporting information**. Pooled estimates include data from studies reporting only partial selections of serotypes, where total numbers of included isolates provide a basis for sampling from proportions attributable to each serotype. Bars signify 95% credible intervals around pooled estimates.

Serotype VI caused only 0-2% of neonatal invasive disease within studies. We identified 87.9% posterior probability that serotype VI was associated with reduced serotype potential relative to serotype III, but found its invasiveness to be statistically indistinguishable from that of serotype Ia at levels of statistical power afforded by our meta-analysis; we identified ≥80% probability that serotype VI invasiveness exceeded that of vaccine-targeted serotypes Ib and II. We estimated the neonatal invasive potential of serotype VII to be 4.5% (0.3-105.1%) that of serotype III. Serotype IX/NT-GBS was associated with the lowest neonatal invasive potential, at 1.3% (<0.1-18.3%) that of serotype III; we moreover identified ≥80% posterior probability that this reflected lower neonatal invasive potential than each serotype except Ib, II, and VII.

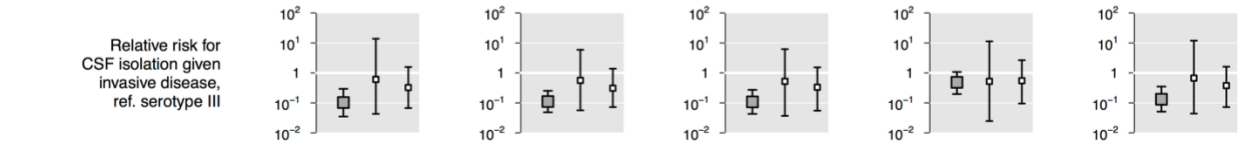
Serotype differences in invasive potential were less apparent in EOD than in LOD. Point estimates of EOD potential again suggested exceptional invasiveness for serotype III; we estimated the EOD potential of serotypes Ia and IV to be 67.0% (38.7-113.3%) and 23.5% (4.5-186.8%) that of serotype III, respectively, whereas these serotypes showed 14.6% (9.0-25.9%) and 3.3% (1.2-9.1%) the LOD potential of serotype III. For serotypes Ib, II, and V, we estimated EOD potentials to be 16.5% (4.3-54.9%), 16.5% (5.1-44.9%), and 34.1% (16.5-68.7%) as high as serotype III, respectively, whereas the LOD potentials of these serotypes were 0.8% (0.4-1.5%), 0.5% (0.3-1.0%), and 0.4% (0.2-0.9%) that of serotype III.

For serotype IX/NT-GBS, we estimated the EOD and LOD potentials to be 11.1% (0.9-278.7%) and 6.4% (0.5-228.2%) as high as the same measures for serotype III; although consistent with our finding of low serotype IX/NT-GBS invasive potential, median estimates of EOD and LOD potential exceeded our estimates of overall neonatal invasive potential due to imprecision and the availability of EOD and LOD frequencies from only a subset of studies. Low serotype-specific frequencies in both carriage and disease prohibited us from distinguishing EOD and LOD potentials for other non-vaccine serotypes.

Clinical manifestation and outcome

Meningitis occurred in 10–77% of serotype III neonatal infections across the included studies; as compared to serotype III, serotypes Ia, Ib, II, and V showed 10-13% as high a risk of meningeal invasion, given invasive disease (**Figure 3**). Serotypes IV, VI, and IX/NT-GBS were isolated in a lower proportion of studies, and caused meningitis in 0-100% of invasive disease episodes within these studies. Pooled estimates suggested they were each less likely than serotype III to manifest as meningitis in invasive disease cases, albeit with weaker precision as compared to estimates for serotypes Ia, Ib, II and V. In stratified analyses, the excess meningitis risk associated with serotype III appeared more pronounced in LOD than EOD, although analyses were underpowered to distinguish serotype-specific risk within either state.

Study	Serotype Ia						Serotype Ib						Serotype II						Serotype IV						Serotype V					
	All inv. dis.			Meningitis			All inv. dis.			Meningitis			All inv. dis.			Meningitis			All inv. dis.			Meningitis			All inv. dis.			Meningitis		
	All	EOD	LOD	All	EOD	LOD	All	EOD	LOD	All	EOD	LOD	All	EOD	LOD	All	EOD	LOD	All	EOD	LOD	All	EOD	LOD	All	EOD	LOD	All	EOD	LOD
Phares et al., 2008	268	157	111	41	12	29	68	37	31	9	2	7	78	69	9	3	1	2					0		158	93	65	13	3	10
Dangor et al., 2016	172	123	49	34	8	26	21	16	5	1	0	1	21	19	2	1	1	0	5	5	0	0	0	0	47	39	8	2	1	1
Sigauque et al., 2018	1			0			0			0			0			0			0			0			1			0		
Yoon et al., 2015	6			4			6			3			0			0			0			0			13			5		
Teatero et al., 2014	12	5	7	2	0	2	6	5	1	0	0	0	4	3	1	0	0	0	1	0	1	0	0	0	6	3	3	0	0	0
Six et al., 2016	1	0	1	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0
Morozumi et al., 2014	29	8	21	12	3	9	12	4	8	7	1	6	5	3	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Liu et al., 2015	2	1	1	0			3	1	2	1			0	0	0	0			0	0	0	0			1	0	1	1		
Chang et al., 2014	18	4	14	12	3	9	5	1	4	4	1	3	2	1	1	1	1	0	2	1	1	1	0	1	1	1	0	0	0	0
Fluegge et al., 2005	43	29	14	5	1	4	13	8	5	1	0	1	16	13	3	1	0	1	2	2	0	0	0	0	22	15	7	4	1	3
Trijbels–Smeulders et al., 2006	37	30	7	10	6	4	6	5	1	0	0	0	16	15	1	0	0	0					0		14	13	1	2	1	1
Martins et al., 2007	18			1			2			0			8			1			2			0			7			0		
Zhao et al., 2008			25			2			14			3			1			0			1			0			3			1
Gray et al., 2007	10	7	3	4	2	2	3	2	1	1	1	0	2	2	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Ekelund et al., 2004	95	70	25	20	10	10	37	29	8	5	2	3	29	26	3	0	0	0	5	3	2	2	1	1	21	19	2	3	3	0
Davies et al., 2001	14	13	1	2	2	0	4	2	2	0	0	0	2	2	0	0	0	0			0	0	0	0	13	9	4	1	1	0



Study	Serotype VI						Serotype VII						Serotype VIII						Serotype IX/NT						Serotype III (ref.)					
	All inv. dis.			Meningitis			All inv. dis.			Meningitis			All inv. dis.			Meningitis			All inv. dis.			Meningitis			All inv. dis.			Meningitis		
	All	EOD	LOD	All	EOD	LOD	All	EOD	LOD	All	EOD	LOD	All	EOD	LOD	All	EOD	LOD	All	EOD	LOD	All	EOD	LOD	All	EOD	LOD	All	EOD	LOD
Phares et al., 2008					0						0						0						0		385	146	239	85	17	68
Dangor et al., 2016	1	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	329	139	190	133	20	113
Sigauque et al., 2018	0			0			0			0			0			0			0			0			33			14		
Yoon et al., 2015	1			0			0			0			0			0			0			0			23			13		
Teatero et al., 2014	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	59	15	44	7	1	6
Six et al., 2016	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	12	3	9	4	1	3
Morozumi et al., 2014	4	3	1	2	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	78	5	73	60	4	56
Liu et al., 2015	0	0	0	0			0	0	0	0			0	0	0	0			0	0	0	0			2	0	2	1		
Chang et al., 2014	1	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	28	5	23	19	3	16
Fluegge et al., 2005			0	0	0	0			0	0	0	0			0	0	0	0			0	0	0	0	193	98	95	56	9	47
Trijbels–Smeulders et al., 2006					0						0						0		14	10	4	1	0	1	109	68	41	49	22	27
Martins et al., 2007	0			0			0			0			0			0			1			0			21			2		
Zhao et al., 2008			0			0			0			0			0			0			0			0			49			14
Gray et al., 2007	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	0	1	30	13	17	14	5	9
Ekelund et al., 2004	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	31	28	3	0	0	0	294	184	110	77	38	39
Davies et al., 2001			0	0	0	0			0	0	0	0			0	0	0	0			1	0	0	0	55	20	35	14	5	9

Figure 3: Association of serotype with meningeal invasion. For each study, we indicate serotype frequencies in all neonatal disease and in meningitis (signified by isolation from CSF), including all neonatal disease as well as EOD and LOD, as permitted by reporting within original studies. We plot pooled estimates of serotype-specific relative risk of meningitis beneath serotype frequencies for all disease (grey points) as well as EOD and LOD (white points), measured from the relative risk that an isolate came from CSF, measured against serotype III (lower right corner). Our derivation of this measure is provided in the **Supporting information**. Pooled estimates include data from studies reporting only partial selections of serotypes, where total numbers of included isolates provide a basis for sampling from proportions attributable to each serotype. Bars signify 95% credible intervals around pooled estimates.

Risk of death showed lower degrees of variation among serotypes, and no estimated differences met conventional thresholds of statistical significance (**Figure 4**). Point estimates suggested the highest CFR for neonatal invasive disease caused by serotype Ia, followed by serotype V and VI with relative risks of 90.5% (15.7-376.2%) and 77.9% (5.0-902.5%), respectively. We estimated the CFR for disease caused by serotype III to be 46.1% (5.6-271.8%) that of serotype Ia; point estimates for the relative risk of death given invasive infection were in the range of 31-59% for the remaining vaccine-targeted serotypes. No fatal cases of disease caused by serotypes VII, VIII, and IX/NT-GBS were reported in the original studies.

	Davies et al. (2001)		Dangor et al. (2016)		Phares et al. (2008)	
	All	Fatal	All	Fatal	All	Fatal
Serotype Ia (ref.)						
All dis.	14	6	172	31	268	18
EOD	13	1	123	21	157	10
LOD	1	0	49	10	111	8
Serotype Ib						
All dis.	4	3	21	2	68	3
EOD	2	1	16	1	37	2
LOD	2	0	5	1	31	1
Serotype II						
All dis.	2	1	21	4	78	3
EOD	2	0	19	3	69	3
LOD	0	0	2	1	9	0
Serotype III						
All dis.	55	5	329	56	385	11
EOD	20	2	139	28	146	6
LOD	35	0	190	28	239	5
Serotype IV						
All dis.	--	0	5	1	--	--
EOD	--	0	5	1	--	--
LOD	0	0	0	0	--	0
Serotype V						
All dis.	13	4	47	10	158	13
EOD	9	1	39	9	93	8
LOD	4	1	8	1	65	5
Serotype VI						
All dis.	--	0	1	1	--	--
EOD	--	0	0	0	--	--
LOD	0	0	1	1	--	0
Serotype VII						
All dis.	--	0	0	0	--	--
EOD	--	0	0	0	--	--
LOD	0	0	0	0	--	0
Serotype VIII						
All dis.	--	0	0	0	--	--
EOD	--	0	0	0	--	--
LOD	0	0	0	0	--	0
Serotype IX/NT						
All dis.	--	0	0	0	--	--
EOD	--	0	0	0	--	--
LOD	1	0	0	0	--	0

Relative risk of fatal outcome, ref. serotype Ia

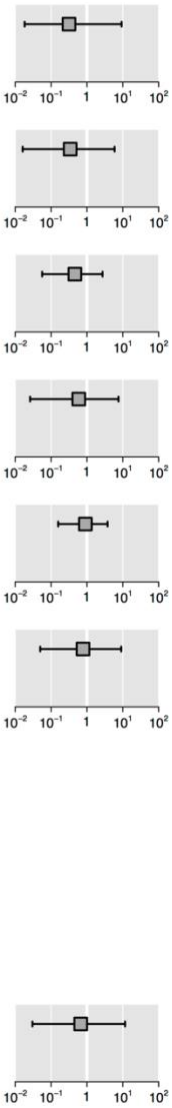


Figure 4: Association of serotype with risk of fatal outcome. For each study, we indicate serotype frequencies in all neonatal invasive disease and in fatal cases, including totals as well as EOD and LOD. We plot pooled estimates of serotype-specific relative risk of death given invasive infection, measured against serotype Ia, without disaggregating by EOD/LOD due to sparse counts. Pooled estimates include data from studies reporting only partial selections of serotypes, where total numbers of included isolates provide a basis for sampling from proportions attributable to each serotype. Bars signify 95% credible intervals around pooled estimates.

DISCUSSION

The persistence or expansion of pathogenic non-vaccine lineages may undermine the impact of vaccines against antigenically-diverse pathogens. Extending the evidence from historical studies to encompass data from all GBS serotypes and non-US settings [14,15], our analysis confirms that GBS serotypes III

and Ia pose the greatest risk of neonatal disease risk when carried by mothers. While disease caused by serotype III is the most likely to manifest as meningitis, serotypes do not appear to differ substantially in risk of death. Although serotype VI has not historically been a prevalent cause of disease, we found invasiveness of serotype VI to be roughly equal to that of serotype Ia at levels of statistical power afforded by our meta-analysis. Serotype VI was also suggested to be more invasive than vaccine-targeted serotypes such as Ib and II, whereas other non-vaccine serotypes including VII and NT-GBS were associated with low neonatal invasive potential. Inclusion of serotype IV in the hexavalent vaccine formulation is likely to mitigate replacement risks that may have been present with earlier vaccine candidates; our analysis characterizes serotype IV as equally or more invasive in comparison to serotypes Ib, II, and V. Taken together, our findings suggest non-vaccine types are unlikely to offset the vaccine-preventable disease burden associated with serotype III, but identifies serotype VI as a potential source of replacement disease that should be monitored in surveillance.

Whereas screening-based intrapartum antimicrobial prophylaxis is effective against early-onset GBS disease, maternal vaccination has been sought as a means of protecting against GBS in the later neonatal period. Relative to serotypes Ib, II, IV, V, and IX/NT-GBS, we estimated serotypes III and Ia to be associated, respectively, with 15.6-244.7-fold and 2.2-34.8-fold higher frequencies of LOD per maternal carrier. The association of serotypes III and Ia with invasive potential in the later neonatal period underscores the potential for vaccination to reduce the burden of LOD. In contrast, serotypes III and Ia were associated, respectively, with only 2.9-9.0-fold and 1.9-5.9-fold greater EOD potential than the same comparator serotypes. Similarly, our analyses suggested the association of serotype III with meningeal invasion is more pronounced in LOD than EOD. Determining the EOD and LOD potential of non-vaccine serotypes such as VI, VII, and VIII remains a priority and will require further observational studies to facilitate comparison of the relative advantages of alternative vaccine formulations [11].

Although the type III capsule has long been recognized as a virulence factor in GBS [19], the basis for invasiveness in this and other serotypes remains incompletely understood. Relationships such as we identify between polysaccharide capsular type and virulence have been well-studied in pneumococcus as well as other commensal bacterial pathogens such as *Neisseria meningitides* [20], and *Haemophilus influenzae* [21]. Importantly, associations of serotype with invasiveness may owe to lineage-linked pathogenicity factors other than the capsule. In epidemiologic studies, serotype III invasiveness may be associated with the “hypervirulent” clonal complex (CC) CC17; in addition, CC23 and CC24 are prevalent among invasive serotype Ia isolates [22–24], suggesting a role of non-capsular genomic features. Large-scale studies based on whole-genome sequencing data from carriage and invasive isolates have recently yielded insight into pneumococcal virulence factors [25,26], and are warranted in GBS to understand invasiveness and pre-vaccination population structure. Such studies can also yield insights into the ability of different lineages to expand in the context of vaccine-induced population immunity.

Beyond serotype replacement, the emergence of virulent vaccine-escape lineages by recombination constitutes an important threat foreshadowed by evolutionary responses of *S. pneumoniae* to PCVs [27,28]. A majority of recombination events in GBS has involved genes encoding surface protein antigens and capsular biosynthesis proteins, suggesting immune escape via horizontal gene transfer [29]. The acquisition of serotype IV capsule by historically serotype III CC17 lineages illustrates the capacity for invasive lineages to escape immunity via capsular switching [30–32]. Expression of ≥7 distinct serotypes in CC1 isolates obtained from surveillance in Toronto underscores the frequency of serotype-switching events in GBS, raising concerns about the role of recombination in the emergence of rare serotypes such as VI-IX [32]. While such events are presumed to result from epidemiologic factors such as population immunity, our ability to predict recombination nonetheless remains poor, highlighting the need for molecular surveillance to monitor bacterial evolution in response to vaccination [33]. Beyond transfers of large genomic segments [34], smaller core genome changes within clonal lineages have also been recognized to influence GBS phenotype [35].

Associations of anticapsular antibody and cell-mediated with homotypic protection against acquisition of serotypes Ia, III, and V [36–38] support the possibility that immunization may reduce the prevalence of vaccine-serotype colonization. However, given limited understanding of interactions among GBS serotypes, and between GBS serotypes and other vaginal microbiota [39], it remains unclear whether

reducing vaccine-serotype colonization may expand the niche for non-vaccine serotypes. Fundamental aspects of transmission dynamics—including modes of GBS acquisition, anatomical reservoirs, and the duration of colonization—remain poorly understood [40]. Observational and modeling studies provide a basis for inferring the extent to which vaccination programs may alter the carriage and disease profile of GBS, including potential indirect effects of vaccination. Carriage or serological studies in populations other than pregnant women, including studies of colonization at non-genitourinary sites, may offer insight into the age and mode of GBS acquisition, immune correlates of protection, and transmission dynamics. Such studies can also clarify the association of serotype with invasive potential in adult disease.

Our analysis has several limitations. The under-representation of populous world regions, notably including East, South, and Southeast Asia, demonstrates the need for epidemiological surveillance in such settings. While longitudinal studies of mother-infant dyads provide the most direct assessment of GBS neonatal invasive potential, only two studies of this design were available in our review [17,18]; invasive potential estimates based on geographically-matched samples of isolates are less ideal given the potential for differences in the population screened for carriage and the population experiencing disease. The rare occurrence of carriage and disease associated with certain serotypes limited statistical precision and hindered estimation of EOD and LOD potential associated with serotypes VI-VIII, as well as our ability to distinguish the role of serotype in meningeal invasion and fatal outcome. In addition, studies did not provide adequate disaggregation to assess serotype associations with other risk factors for neonatal infection, such as preterm birth and low birthweight. Last, associations of serotype with invasiveness and clinical aspects of invasive GBS disease may not be causally attributable to the capsule. Distinguishing lineage-specific virulence, for instance among CCs, will provide further insight into determinants of pathogenicity and potential outcomes of recombination.

Our analysis points to lower vaccine-driven serotype replacement risks in GBS disease than were seen in pneumococcus, but suggests a need to monitor serotype VI as a potential source of replacement disease. Molecular characterization of surveillance isolates should be undertaken to monitor emergence and expansion of lineages, recombination events, and changes in clinical properties such as antimicrobial resistance [33]. Including carriage isolates in active surveillance programs affords a picture of the broader GBS population, and enables identification of pathogenicity determinants. Our estimates provide a basis for determining statistical power of serotype-specific endpoints in GBS vaccine trials. While neonatal invasive disease is a rare outcome for such trials, serotype-specific maternal carriage endpoints can illustrate the potential for indirect effects and serotype replacement.

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SEARCH STRATEGY

We searched the following string in titles and abstracts of articles indexed in PubMed between 1 January, 2016 and 22 April, 2018 to identify relevant studies not included in previous reviews:

(("group b streptococc") OR ("streptococcus agalactiae")) AND ((coloni* OR carria* OR carrie* OR carry*) AND (diseas* OR infect* OR invas* OR mening* OR sepsis OR septic*)) AND (serotyp* OR capsul* OR cps*)*

We included studies that:

1. Were written in English, Spanish, German, or French.

2. Conducted serotyping by molecular or phenotypic assays for, at minimum, serotypes Ia, Ib, II, III, IV, and V, and reported the total number of isolates tested; this led to the exclusion of studies before 1999. We recorded the total number of isolates tested and the numbers identified as serotypes Ia, Ib, II, III, IV, V, VI, VII, VIII, and IX or NT-GBS; we pooled serotype IX and NT-GBS to accommodate data from studies undertaken before identification of serotype IX.

3. Described the population, setting, and study design: We excluded studies selecting patients based on microbiological findings post-hoc (e.g. studies limited to disease caused by a pre-defined sets clones or serotypes), and studies within which it was not possible to associate isolates with the specific colonization or disease outcomes under consideration (e.g. studies that did not specify whether patients were symptomatic or asymptomatic).

For analyses of neonatal invasive potential of serotypes, we included studies presenting "paired" sets of carriage and disease isolates, defined as isolates obtained from epidemiologically-linked individuals (i.e., mother-newborn dyads), or from geographically- and temporally-matched samples of neonatal disease cases and asymptomatically-colonized pregnant women. For analyses of serotype associations with disease manifestation and clinical outcome, we included studies presenting frequencies of individual serotypes in samples of all neonatal sepsis and meningitis cases, and in samples of all fatal and non-fatal neonatal invasive disease cases.

When studies presented data from multiple settings or populations, we abstracted data at the finest demographic and geographic resolution permitted by available metadata. We excluded articles presenting duplicate data from the same original study.

MEASUREMENT OF SEROTYPE ATTRIBUTES

Statistical approach to analyses of invasive potential

The invasive potential of serotype *j*, measured relative to serotype *k*, from serotype frequencies in carriage and disease ($\mathbf{x}^C$and $\mathbf{x}^D$, respectively), is

$$IP(j,k) = \frac{x^D(j)x^C(k)}{x^D(k)x^C(j)} = \frac{\left(\frac{x^D(j)}{x^C(j)}\right)}{\left(\frac{x^D(k)}{x^C(k)}\right)}.$$

We aimed to pool log odds ratio estimates from individual studies meta-analytically; however, despite offering meaningful information about serotype prevalence, zero-valued frequencies of serotypes in carriage or disease prohibit such analyses. We used a Bayesian estimation strategy to overcome this problem. Within the ℓth study, observed serotype-specific frequencies in carriage and disease (vectors $\mathbf{x}_\ell^C$ and $\mathbf{x}_\ell^D$, respectively) were taken to be random draws from a multinomial distribution, specified in full by the number of carriage and disease isolates obtained (n_ℓ^C and n_ℓ^D, respectively) and the true underlying

proportions of carriage and disease (vectors $\mathbf{p}_{\boldsymbol{\ell}}^{C}$ and $\mathbf{p}_{\boldsymbol{\ell}}^{D}$, respectively) attributable to each serotype within the populations from which cases and carriers were sampled:

$$\mathbf{x}_{\ell}^{C} \sim \mathrm{Multinom}\left(n_{\ell}^{C}, \mathbf{p}_{\boldsymbol{\ell}}^{C}\right)$$

and

$$\mathbf{x}_{\ell}^{D} \sim \mathrm{Multinom}(n_{\ell}^{D}, \mathbf{p}_{\boldsymbol{\ell}}^{D}).$$

We used the Dirichlet conjugate prior for the population proportion parameters $\mathbf{p}_{\boldsymbol{\ell}}^{C}$ and $\mathbf{p}_{\boldsymbol{\ell}}^{D}$, defining the study-level proportions as random deviates of global serotype distributions with parameters $\boldsymbol{\alpha}^{C}$ and $\boldsymbol{\alpha}^{D}$:

$$\mathbf{p}_{\ell}^{C} \sim \mathrm{Dir}(\boldsymbol{\alpha}^{C})$$

and

$$\mathbf{p}_{\ell}^{D} \sim \mathrm{Dir}(\boldsymbol{\alpha}^{D}).$$

This strategy ensured nonzero maximum *a posteriori* estimates of $\mathbf{p}_{\ell}^{C}$ and $\mathbf{p}_{\ell}^{D}$ across the included studies. We sampled from the joint distributions $f(\boldsymbol{\alpha}^{C}, \mathbf{p}_{1}^{C}, \mathbf{p}_{2}^{C}, \ldots, \mathbf{p}_{g}^{C} | \mathbf{x}_{1}^{C}, \mathbf{x}_{2}^{C}, \ldots \mathbf{x}_{g}^{C})$ and $f(\boldsymbol{\alpha}^{D}, \mathbf{p}_{1}^{D}, \ldots, \mathbf{p}_{g}^{D} | \mathbf{x}_{1}^{D}, \ldots \mathbf{x}_{g}^{D})$ via Markov Chain Monte Carlo (MCMC) using a Metropolis-Hastings updating procedure. We ran chains for 600,000 iterations after the burn-in period, saving the state of the chain at every 500th sample to reduce autocorrelation.

We defined study-level estimates of neonatal invasive potential using the inferred population proportions of carriage and disease attributable to each serotype. Within the ℓth study,

$$IP_{\ell}(j,k) = \frac{p_{\ell}^{D}(j) p_{\ell}^{C}(k)}{p_{\ell}^{D}(k) p_{\ell}^{C}(j)},$$

thus recovering the expected relative incidence of disease cases per exposed neonate (see below). We calculated invasive potential relative to serotype III (*k*).

Invasive potential measures from each study were taken to be deviates from a global serotype-specific value, $\theta(j,k)$, with associated variance across studies $\sigma^2(j,k)$:

$$\log IP_{\ell}(j,k) \sim \mathrm{N}\left(\log \theta(j,k), \sigma^2(j,k)\right).$$

We estimated these global invasiveness parameters using non-informative prior distributions:

$$\log \theta(j,k) \sim \mathrm{N}(0, 10^6)$$

and

$$\log \sigma(j,k) \sim \mathrm{N}(0, 10^6).$$

For each serotype, we calculated posterior densities over the intervals $-10 \leq \log \theta(j,k) \leq 10$ and $-10 \leq \log \sigma(j,k) \leq 10$ according to

$$\Pr\left(\theta(j,k), \sigma(j,k) | \mathbf{IP}(j,k)\right) \propto \pi\left(\theta(j,k)\right) \pi\left(\sigma(j,k)\right) \prod_{\ell} f(\log IP_{\ell}(j,k) | \theta(j,k), \sigma^2(j,k)),$$

which provided a basis for sampling from the joint distribution of $\{\theta(j,k), \sigma^2(j,k)\}$ for each serotype *j*, relative to serotype III (*k*).

Deriving the odds ratio as an estimator of neonatal invasive potential

Define the neonatal invasive potential of serotype *j* relative to serotype *k* as the ratio

$$IP(j,k) = \frac{\pi(j)}{\pi(k)}$$

of the probabilities $\pi(j)$ and $\pi(k)$ for neonates exposed to serotypes *j* and *k*, respectively, to experience invasive disease, such that

$$p^D(j) = \pi(j)p^C(j)$$
$$p^D(k) = \pi(k)p^C(k)$$

for the variables $\mathbf{p}^D$ and $\mathbf{p}^C$ defined above. We note that π represents the joint probability of both GBS transmission from mother (or other source) to neonate and of disease progression given transmission. Thus,

$$IP(j,k) = \frac{x^D(j)x^C(k)}{x^C(j)x^D(k)} = \frac{\left(\frac{x^D(j)}{x^C(j)}\right)}{\left(\frac{x^D(k)}{x^C(k)}\right)} = \frac{\left(\frac{p^D(j)N^D}{p^C(j)N^C}\right)}{\left(\frac{p^D(k)N^D}{p^C(k)N^C}\right)} = \frac{\pi(j)}{\pi(k)}.$$

Serotype-specific relative risks of meningitis and fatal outcome

The relative risk for invasive disease cause by serotype *j* to manifest as meningitis, as compared to invasive disease caused by serotype *k*, is

$$RR^M(j,k) = \frac{x^M(j)x^D(k)}{x^D(j)x^M(k)} = \frac{\left(\frac{x^M(j)}{x^D(j)}\right)}{\left(\frac{x^M(k)}{x^D(k)}\right)}$$

for the vectors of serotype frequencies in meningitis ($\mathbf{x}^M$), here specifying that $\mathbf{x}^D$ includes cases with known clinical manifestations. Similarly, the relative risk for invasive disease caused by serotype *j* to result in fatality, as compared to invasive disease caused by serotype *k*, is

$$RR^F(j,k) = \frac{x^F(j)x^D(k)}{x^D(j)x^F(k)} = \frac{\left(\frac{x^F(j)}{x^D(j)}\right)}{\left(\frac{x^F(k)}{x^D(k)}\right)}$$

where $\mathbf{x}^F$ indicates serotype frequencies in fatal cases of illness, while $\mathbf{x}^D$ includes cases with known clinical outcomes (fatal or nonfatal). As in the previous analysis, we sampled from the distributions of serotype-specific proportions in all meningitis cases ($\mathbf{p}_\ell^M$) and fatal invasive disease cases ($\mathbf{p}_\ell^F$) via

$$\mathbf{x}_\ell^M \sim \mathrm{Multinom}(n_\ell^M, \mathbf{p}_\ell^M)$$

$$\mathbf{x}_\ell^F \sim \mathrm{Multinom}(n_\ell^F, \mathbf{p}_\ell^F)$$

$$\mathbf{p}_\ell^M \sim \mathrm{Dir}(\boldsymbol{\alpha}^M)$$

$$\mathbf{p}_\ell^F \sim \mathrm{Dir}(\boldsymbol{\alpha}^F),$$

where n_ℓ^M and n_ℓ^F indicate the total number of meningitis isolates and fatal case isolates, respectively, in the ℓth study, and $\boldsymbol{\alpha}^M$ and $\boldsymbol{\alpha}^F$ serve as hyperparameters for the underlying distributions. We defined global estimates for serotype-specific relative risks from the normal distribution of log-transformed estimates from each study as above:

$$RR_\ell^M(j,k) = \frac{p_\ell^M(j)p_\ell^D(k)}{p_\ell^M(k)p_\ell^D(j)}$$

$$RR_\ell^F(j,k) = \frac{p_\ell^F(j)p_\ell^D(k)}{p_\ell^F(k)p_\ell^D(j)},$$

again assuming flat priors for the mean and variance across studies.

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