Systematic review and meta-analyses of Group B Streptococcus serotypes:
Worldwide distribution, sequence types and virulence to inform vaccine development

Fiorella Bianchi-Jassir[1], Proma Paul[1], Kay To[2],Clare Carreras Abad[2], Shabir A Madhi[3], Neal Russell[2], Jenny Hall[4], Lola Madrid[1], Quique Bassat[5,6], Anna C Seale[1], Kirsty Le Doare[2], Joy E Lawn[1]

1 Maternal, Adolescent, Reproductive & Child Health (MARCH) Centre, London School of Hygiene & Tropical Medicine, London, UK; 2 St George's University of London, UK; 3 Respiratory and Meningeal Pathogens Research Unit, South Africa; 4 University College London Institute for Women's Health, London, UK; 5 Centro de Investigação em Saúde de Manhiça, Maputo, Mozambique; 6 ISGlobal, Barcelona Center for International Health Research, and Hospital Clinic-Universitat de Barcelona, Barcelona, Spain

Background and Aim

- Group B Streptococcus (GBS) invasive disease is a leading cause of mortality and morbidity in neonates and young infants
- Intrapartum antibiotic chemoprophylaxis (IAP) aims to prevent vertical transmission and early-onset disease
- Vaccines can control infection and reduce antibiotic usage and thereby reduce AMR
- GBS serotypes plays a central role in vaccine development
- ***We aimed to synthesise data on GBS serotypes and strains worldwide, characterised by serotyping, multilocus sequence typing, and whole-genome sequencing, in order to inform vaccine development.***
- ***We also reviewed available data on antibiotic resistance among GBS isolates.***

Methods

- Systematic review serotyping, multilocus sequence typing (ST), and whole-genome sequencing (WGS) data for various outcomes:
  - Maternal colonisation (n=128)
  - Maternal invasive disease (n=6)
  - Invasive infant disease (n=53)
  - Stillbirths (n=3)
  - Invasive disease in elderly population (n=11)
- Systematic review of antibiotic resistance to first line and other common antibiotics
- Meta-analyses conducted in Stata 14.0 to estimate:
  - Serotype prevalence for each outcome
  - ST-17 prevalence
  - Antibiotic resistance prevalence for GBS maternal colonisation and infant invasive disease
- Pooled estimates for each serotype were then transformed to percentages and adjusted (scaled up or down) to obtain 100% of the total of all serotypes.

Results: Data availability

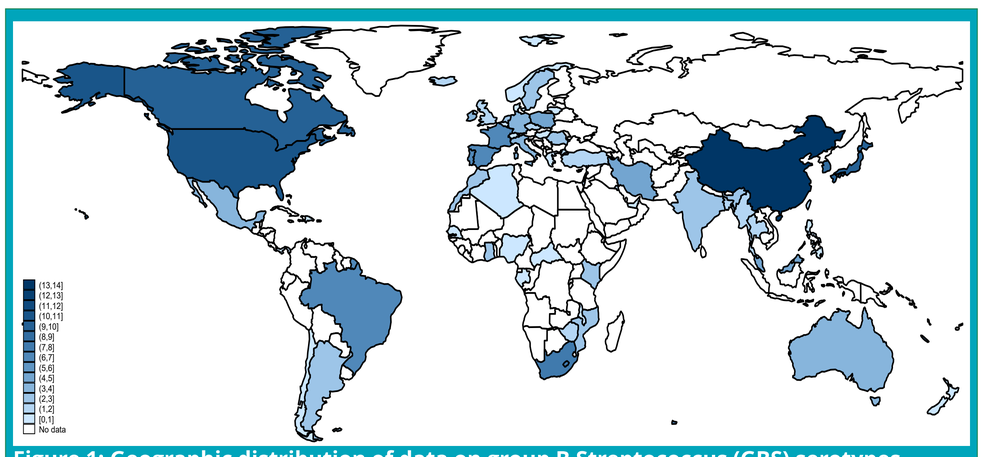

Figure 1: Geographic distribution of data on group B Streptococcus (GBS) serotypes.
Borders of countries/territories in map do not imply any political statement

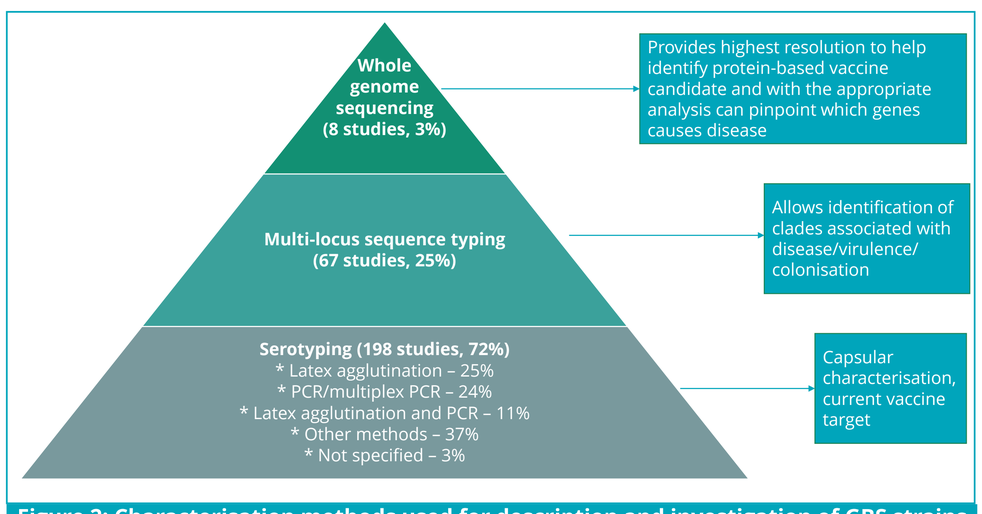

Figure 2: Characterisation methods used for description and investigation of GBS strains

Table 1: Regional distribution on antibiotic resistance

	Number of studies (% total)	
	Maternal colonization	Infant invasive disease
Developed	25 (39.7)	10 (50.0)
Africa	10 (15.9)	2 (10.0)
Asia	21 (33.3)	5 (25.0)
Latin America and Caribbean	7 (11.1)	3 (15.0)
Total	**63**	**20**

This work was funded by the Bill & Melinda Gates Foundation, Seattle, WA (OPP1180644 and OPP1157270).

Results: Serotype prevalence

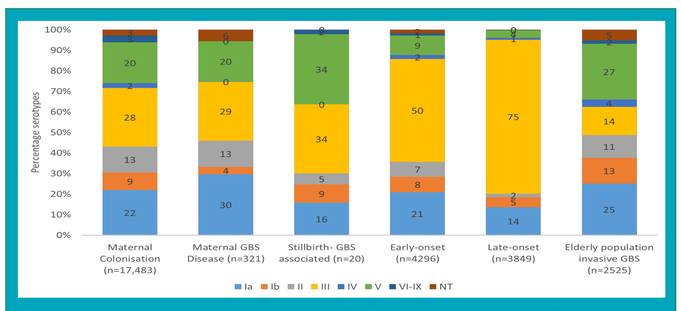

Figure 3: Global distribution of GBS serotypes by clinical outcome (adjusted proportions)
n= total number of isolates

- Serotype III is among the dominate serotypes for maternal colonisation and invasive disease, early and late onset infant disease, and stillbirths
- Serotype Ia and V are the dominate serotypes for invasive disease in elderly populations

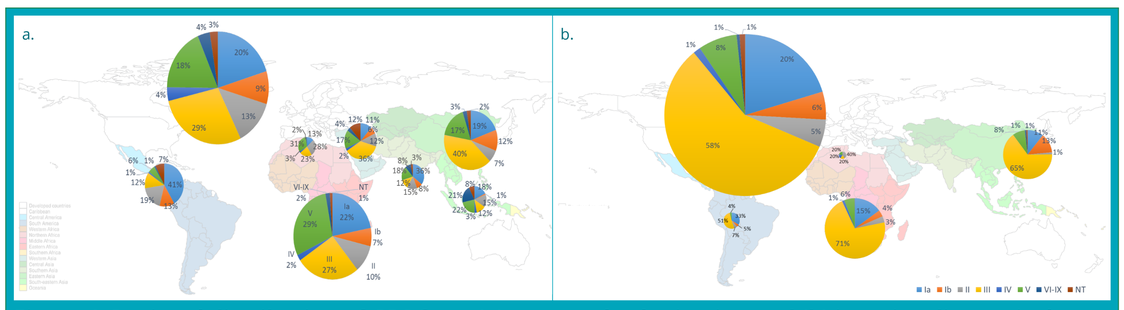

Figure 4: Regional distribution of GBS from (a) maternal colonisation and (b) invasive disease isolates from pregnant/postpartum women, stillbirth, and infants (adjusted proportions)

Results: GBS MLST and whole genome sequencing

- Pooled proportion of hyprevirulent strain ST17 was :
  - 8% (5%-13%) maternal colonisation
  - 40% (33% - 49%) infant invasive disease
- Surface protein associated with infant disease:
  - HvgA belonging to ST-17 stains
  - Rib belonging to serotype III

Results: Antibiotic resistance

Table 2: GBS maternal colonisation global antibiotic resistance

	Number of studies	Susceptible (n)	Resistance (n)	Meta-analysis for proportion of antibiotic resistance (95% CI)
Penicillin	57	7644	4	0% (0% – 0%)
Gentamicin	10	477	369	42% (11% - 77%)
Erythromycin	53	6015	1792	18% (12% – 24%)
Clindamycin	44	5540	1450	17% (12% – 24%)
Vancomycin	30	3951	2	0% (0% – 0%)
3rd generation cephalosporins	23	2783	2	0% (0% – 0%)
Chloramphenicol	12	1429	102	5% (2% - 9%)
Tetracycline	21	484	2307	88% (88% - 93%)

Table 3: GBS infant invasive disease global antibiotic resistance

	Number of studies	Susceptible (n)	Resistance (n)	Meta-analysis for proportion of antibiotic resistance (95% CI)
Penicillin	20	8414	9	0.0% (0% – 0%)
Gentamicin	2	654	2	0.3% (0.0% - 1.0%)
Erythromycin	20	5766	2654	26.7% (20.2% – 22.7%)
Clindamycin	20	6857	1566	20.8% (14.8% – 27.5%)
Vancomycin	10	7549	0	0.0% (0.0% – 0.0%)
3rd generation cephalosporins	5	304	0	0.0% (0.0% – 0.0%)
Chloramphenicol	4	2238	54	3.8% (0.0% - 15/2%)
Tetracycline	12	175	1216	90.6% (85.9% - 94.5)

Conclusions

- Our results show that a hexavalent protein-conjugate vaccine could cover around 94% of worldwide colonising isolates, 94% of maternal GBS disease, 98% of GBS-associated stillbirth, 97% of early onset GBS, 98% of late onset GBS, and 93% of elderly population.
- ST 17 is associated with infant invasive disease and with serotype III (the most common serotype in infant disease).
- Good susceptibility to first-line (penicillin) and second-line (clindamycin, 3rd gen cephalosporins) antibiotics used for GBS prevention and treatment.
- Concerning resistance to other commonly used antibiotics gentamicin (given in combination with penicillin)and erythromycin (given in combination with clindamycin).

1. Seale AC, Blencowe H, Bianchi-Jassir F, Embleton N, Bassat Q, Ordi J, et al. Stillbirth With Group B Streptococcus Disease Worldwide: Systematic Review and Meta-analyses. Clin Infect Dis. 2017;65(suppl_2):S125-s32. 2. Russell NJ, Seale AC, O'Driscoll M, O'Sullivan C, Bianchi-Jassir F, Gonzalez-Guarin J, et al. Maternal Colonization With Group B Streptococcus and Serotype Distribution Worldwide: Systematic Review and Meta-analyses. Clin Infect Dis. 2017;65(suppl_2):S100-s11. 3. Clift C, Salisbury DM. Enhancing the role of vaccines in combatting antimicrobial resistance. Vaccine, 2017: 6591-6593.