Distribution of surface proteins among Group B Streptococcus infant invasive and maternal colonizing isolates from South Africa

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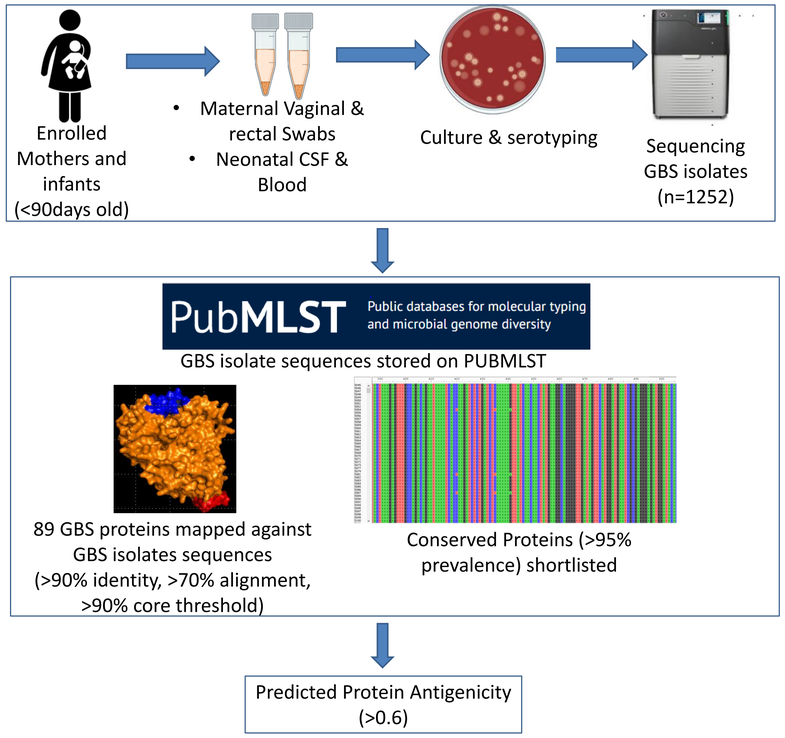
Introduction

Group B Streptococcus (GBS) is a gram positive bacteria that exists as 10 serotypes (Ia, Ib, II-IX) the leading cause of neonatal infections. These neonatal infections are categorized as Early on-set disease (EOD) - which occurs within the first 7 days of birth- and Late on-set disease (LOD) which occurs within 7 to 90 days after birth[1]. GBS is also associated with preterm deliveries and still-births. Due to its high mortality rate and challenges with current prophylactic measures, maternal vaccination provides a more promising preventative strategy against neonatal GBS disease. Yet there is still no licensed vaccine available. The publication of the complete genome sequences of the GBS serotypes has enabled the identification of highly immunogenic surface proteins with potential as vaccine targets. Unfortunately, many of these proteins are not present in all clinical isolates. Highly conserved surface proteins, especially those that are necessary for GBS virulence, would be an ideal vaccine target as variation would be less likely as change could be detrimental to GBS survival[4]. A vaccine that targets highly conserved surface proteins could provide broad coverage of protection against the different GBS serotypes and this would be beneficial in reducing the burden of GBS disease.

Methodology



Acknowledgements

Boston Children's PATH University of the Witwatersrand, Johannesburg WITS VIDA University of the Witwatersrand Vaccines & Infectious Diseases Analytics

Results

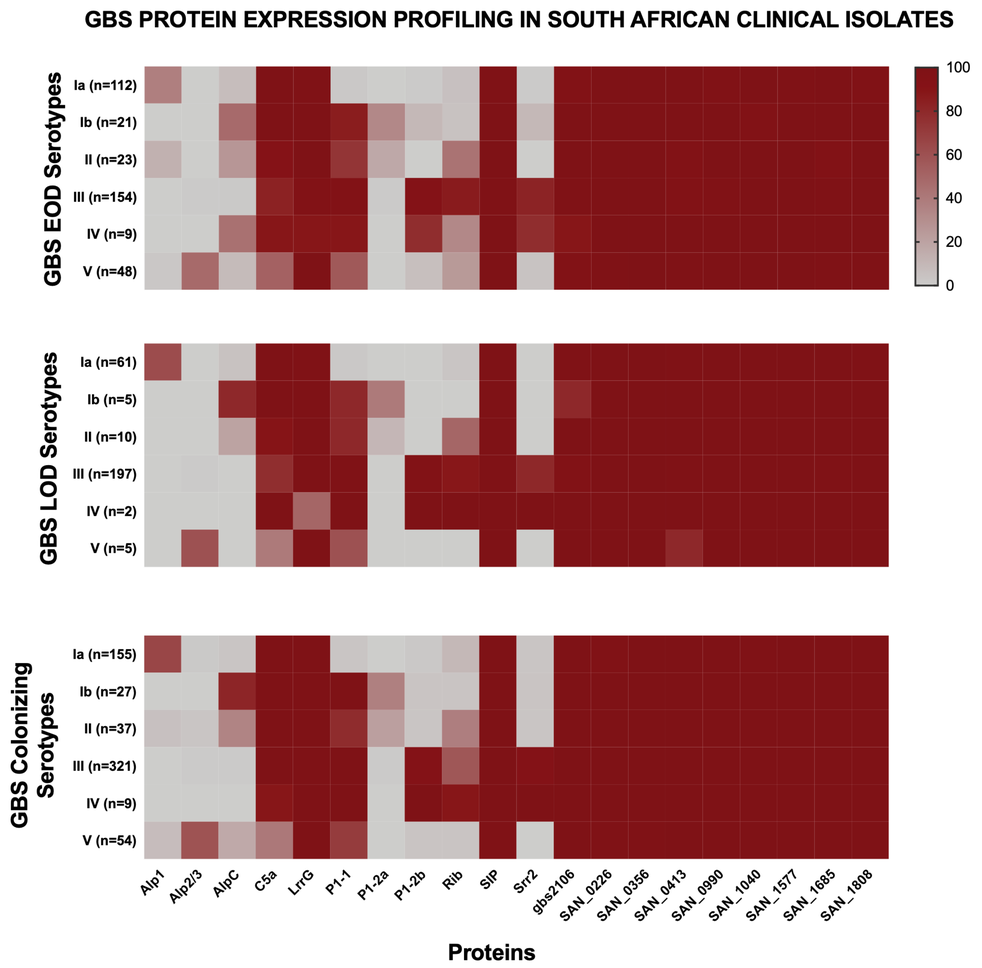


Figure 1: Heatmaps illustrating the prevalence of GBS surface proteins present in South African GBS clinical isolates and stratified according to disease phenotype: invasive (EOD, LOD) and non-invasive (colonization isolates).

Nine bioinformatically inferred proteins predicted to be surface proteins and highly antigenic (gbs2106, SAN_0226, SAN_0356, SAN_0413, SAN_0990, SAN_1040, SAN_1577 SAN_1685 and SAN_1808) were present in majority of the serotypes of invasive and colonization isolates (>95%). Surface proteins such as Alp1, Alp2/3, AlpC. PI-2a, PI-2b, rib and Srr2 are less prevalent in all serotypes. Analysis of Serotype III isolates which is highly prevalent in South Africa, shows differential distribution of Rib protein. It shows that it is highly prevalent in invasive isolates compared to colonizing isolates. The highly prevalent proteins present in all invasive and colonizing isolates would be good vaccine candidates as they could potentially provide broad coverage of protection.

Moreover, our data shows that the Alp1, Alp2/3, AlpC and C5a proteins are less prevalent in our isolates and they are less antigenic, as predicted by the VaxiJen tool. Although LrrG is prevalent in most of the serotypes, it is predicted to be a non-antigen, hence would be a poor vaccine candidate.

Table 1:Antigenic potential of candidate proteins predicted using VaxiJen tool. Fifteen proteins had high predictive antigenic scores (>0.6) although only 10 of these proteins were highly prevalent the GBS isolates (>95%).This implies that these proteins could have the potential of stimulating robust immune responses in a larger population.

Protein	Antigenic potential Model: Bacteria Threshold: 0.6	
	Predictive score	Remarks
Alp1	0.4449	Probable Antigen
Alp2/3	0.5202	Probable Antigen
AlpC	0.5438	Probable Antigen
C5a	0.5173	Probable Antigen
LrrG	0.3120	Non Antigen
PI-1	0.7022	Antigen
PI-2a	0.6108	Antigen
PI-2b	0.6967	Antigen
Rib	0.6205	Antigen
SIP	0.6498	Antigen
Srr2	0.7272	Antigen
gbs2106	0.8361	Antigen
SAN_0226	0.6604	Antigen
SAN_0356	0.7674	Antigen
SAN_0413	0.7142	Antigen
SAN_0990	0.6904	Antigen
SAN_1040	0.6757	Antigen
SAN_1577	1.1756	Antigen
SAN_1685	0.7336	Antigen
SAN_1808	0.7453	Antigen

Conclusion

- Out of the 89 candidate proteins screened, 61 proteins were present in ≥95% of infant invasive and maternal colonizing GBS clinical isolates.
- Of the 61 proteins, 10 proteins; SAN_1577, gbs2106, SAN_0356, SAN_1808, SAN_1685, SAN_0413, SAN_0990, SAN_1040, SAN_0226 and SIP, showed to be highly antigenic.
- The proteins identified in this study have the potential of eliciting protective immune responses targeting most of the GBS serotypes in a South African population.
- Further experimental studies to evaluate the immunological response of these proteins using animal models is underway.

References

1. Le Doare, K., Jarju, S., Darboe, S., Warburton, F., Gorringe, A., Heath, P. T., & Kampmann, B. (2016). Risk factors for Group B Streptococcus colonisation and disease in Gambian women and their infants. *Journal of Infection*, *72*(3), 283–294. https://doi.org/10.1016/j.jinf.2015.12.014
2. Dangor, Z., Kwatra, G., Izu, A., Adrian, P., Cutland, C. L., Velaphi, S., Ballot, D., Reubenson, G., Zell, E. R., Lala, S. G., & Madhi, S. A. (2015). Association between maternal Group B Streptococcus surface-protein antibody concentrations and invasive disease in their infants. *Expert Review of Vaccines*, *14*(12), 1651–1660. https://doi.org/10.1586/14760584.2015.1085307
3. Ku, L., Boggess, K., & Cohen-Wolkowiez, M. (2015). Bacterial Meningitis in the infant. *Clinics in Perinatology*, *42*(1), 29–45. https://doi.org/10.1016/j.clp.2014.10.004.Bacterial
4. Nuccitelli, A., Rinaudo, C. D., & Maione, D. (2015). Group B Streptococcus vaccine: state of the art. *Therapeutic Advances in Vaccines*, *3*(3), 76–90. https://doi.org/10.1177/2051013615579869