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Development of a Pentavalent Group B Streptococcus (GBS) Glycoconjugate Vaccine in Africa

Outline

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1. Group B Streptococcus Disease and Prevention
2. Serotype and Antigen Selection
3. CPS Process Development
4. Glycoconjugate Process Development
5. Pre-Clinical Data

Group B Streptococcus Disease

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- Group B Streptococcus (GBS) disease is caused by the gram-positive bacterium *S.agalactiae*.
- The disease remains the leading cause of neonatal sepsis and meningitis in newborns and estimated to be responsible for **150,000** stillborn & infant deaths annually.
- There are two forms of GBS disease:
  - **Early-onset disease** which occurs within the first **7 days** after birth.
  - **Late-onset disease** which occurs **8 to 90 days** after birth.
- A recent meta-analysis report found that for every 10000 live births there are:
  - **5.3** incidences of GBS with a mean case fatality ratio of **9.3 %**, globally.
  - **12.1** incidences of GBS with a mean case fatality ratio of **22.0 %**, in Africa.
- More than **20 %** of GBS survivors have moderate to severe deficits - deafness, cerebral palsy & GDD

Current GBS Disease Prevention

- Nearly **20 %** of woman carry GBS which can be passed onto newborns during delivery.
- National guidelines in some developed countries recommend screening pregnant women for GBS and providing IAP treatment:
  - Significantly reduces **early-onset disease**
  - Does not prevent **late-onset disease** and unlikely impact on **preterm birth** or **stillbirth**
- Currently there is no licensed vaccine
- Vaccination of newborns is not an effective option
  - Immature immune system
  - Ineffective in preventing **early-onset disease**

Maternal Immunisation

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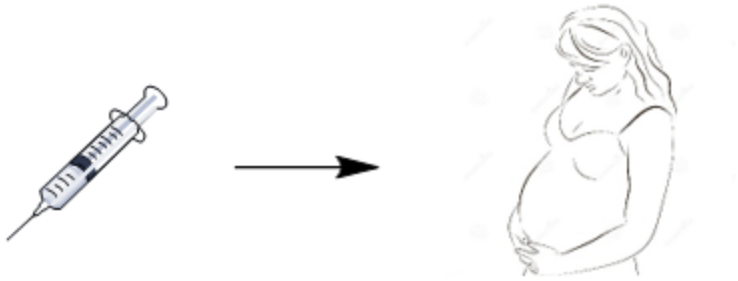
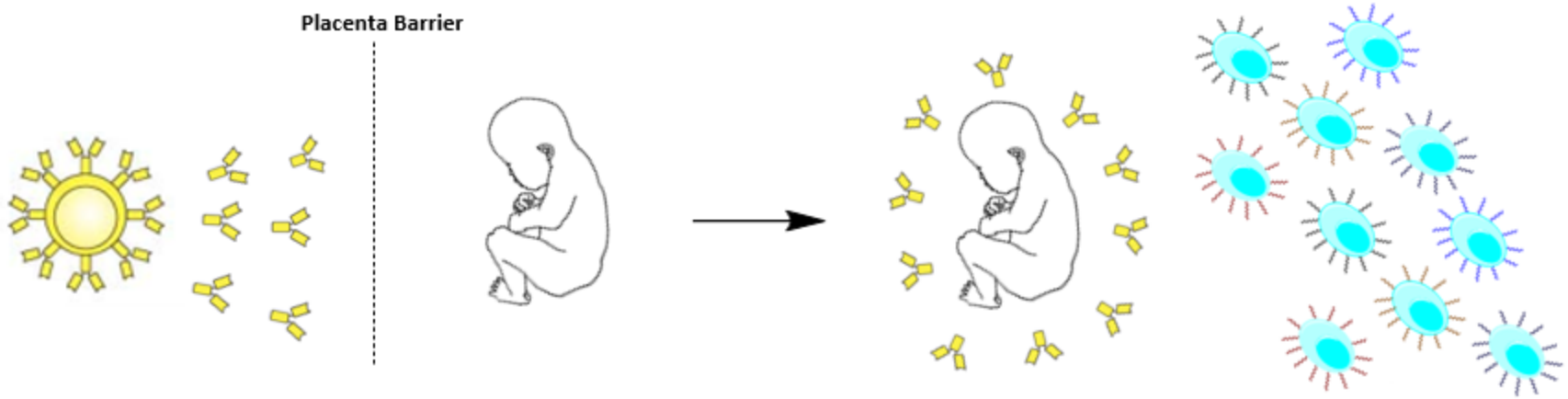
Influenza



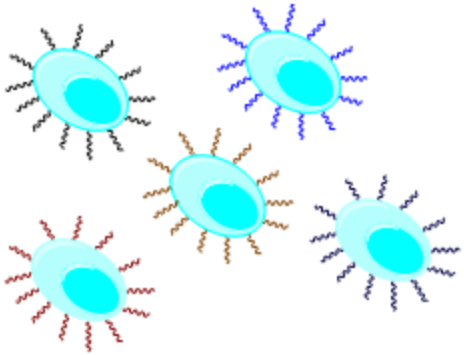
Tdap

Vaccination of pregnant woman with a GBS vaccine



Maternal Antibodies generated by the mother are transferred to unborn child - PASSIVE IMMUNITY

Serotype Selection



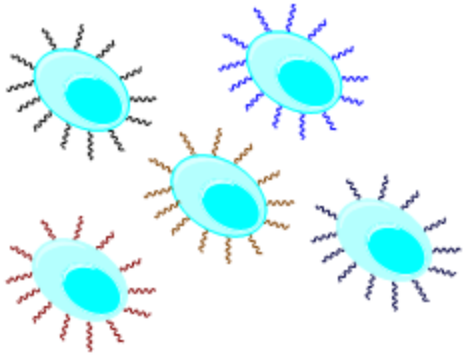
Ia, Ib, II, III & V

98 %

Global

92 %

Africa



IV, VI, VII, VIII & IX

2 %

Global

8 %

Africa

GBS Antigen Target

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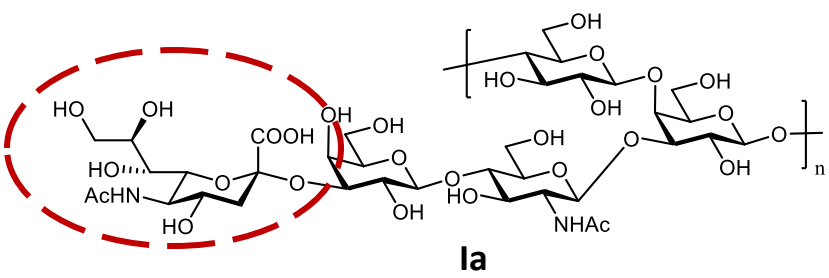
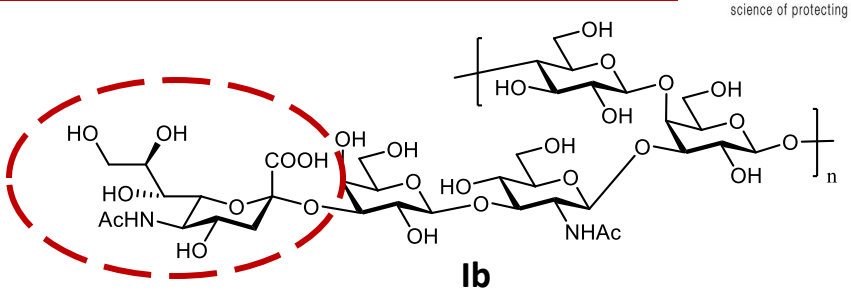


Ia



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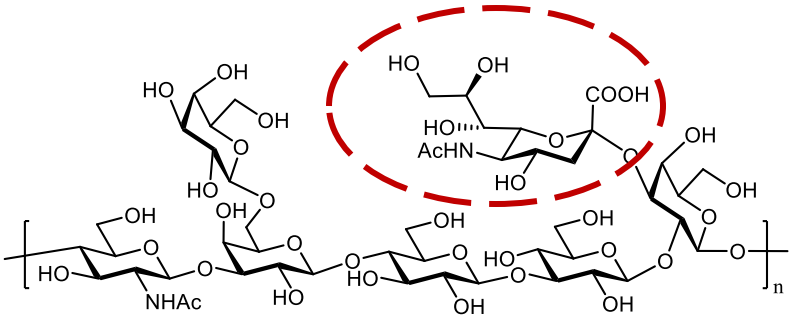

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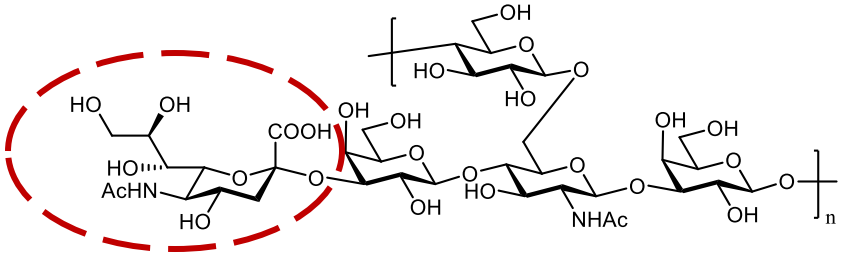
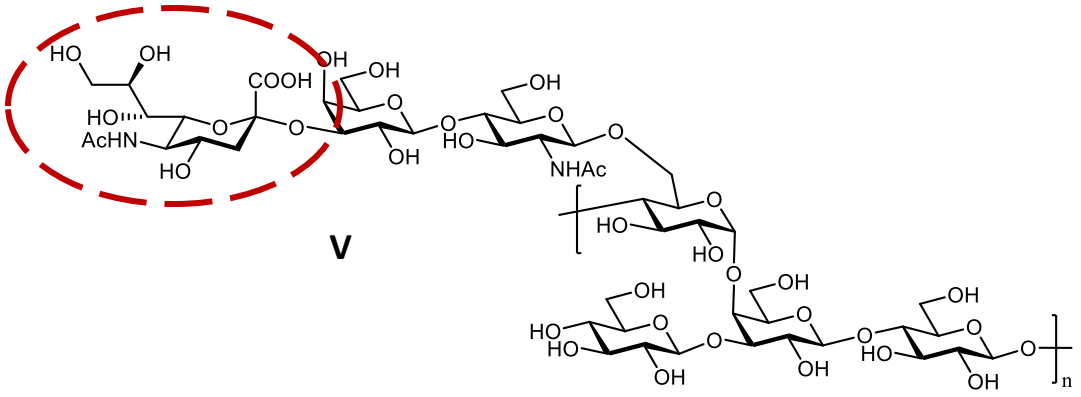


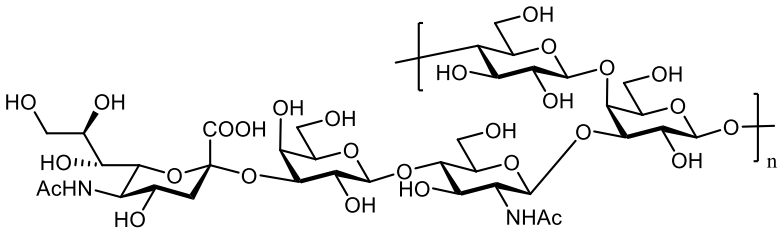
III

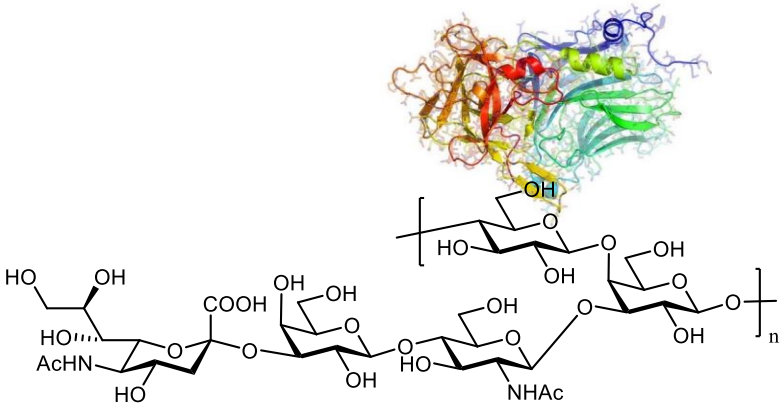


V

CPS versus Glycoconjugate

Effect on immune system	Polysaccharide vaccine	Conjugate Vaccine
Immunogenicity (< 5 years)	Low	High
Immunogenicity (> 5 years)	High	High
Response to Booster	Low	High
Induction of memory	Low	High
Production of IgG	Moderate	High

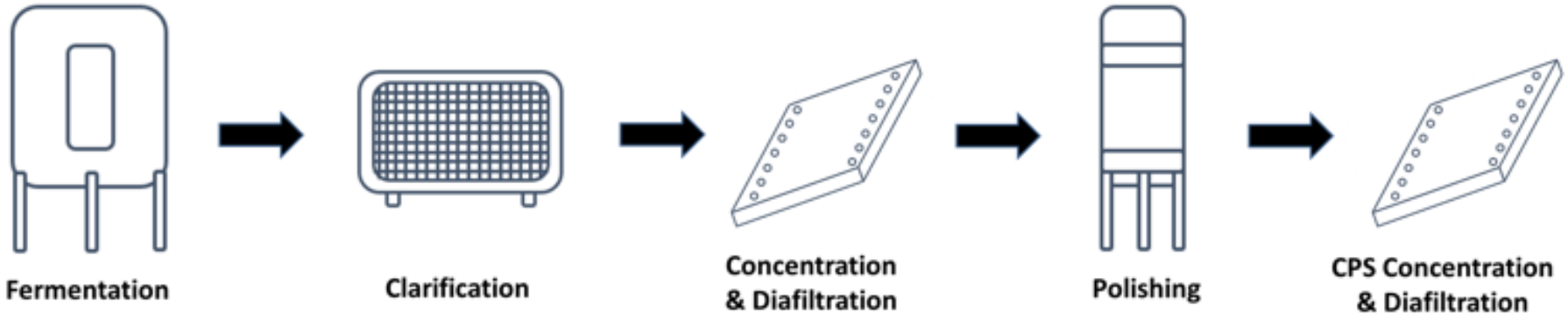




GBS Program Overview

- Development of a robust process to produce GBS capsular polysaccharide (CPS) for serotypes Ia, Ib, II, III and V.
- Development of a conjugation process, which involves covalently linking the capsular polysaccharide to a carrier protein and purifying the resulting glycoconjugate.
- Evaluation of the pentavalent glycoconjugate vaccine in a pre-clinical mice study.

CPS Process Development

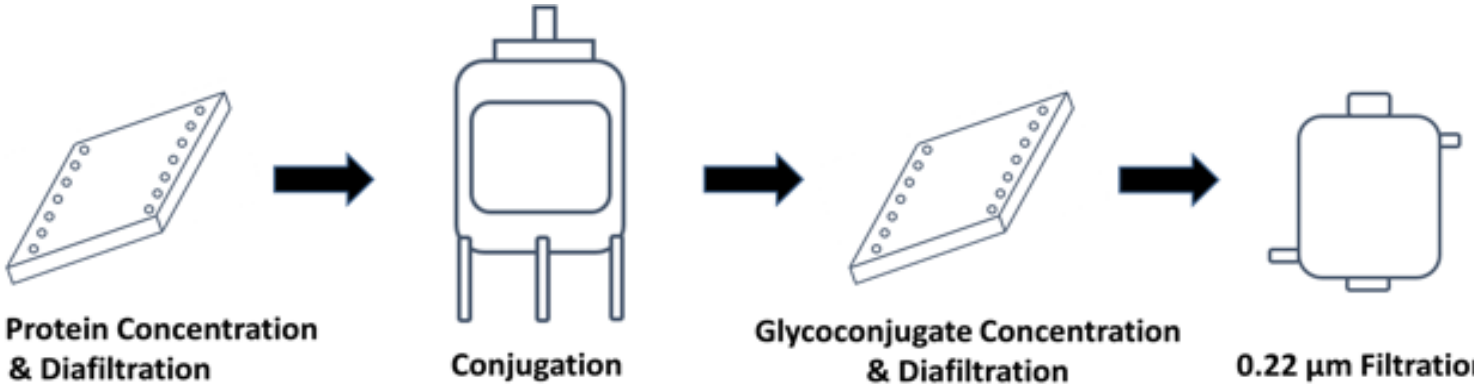


Scale:	Fermentation:	Purification:	Titer:
20 - 30 L	6-hour fed-batch followed by chemical inactivation	3-day process incorporating single use technology	120 - 180 mg/L

Product Quality Attributes

Bound sialic acid: > 90 % / O-Acetylation: < 5 % / N-Acetylation: > 95 % / Residual nucleic acid: ≤ 3 % / Residual protein: ≤ 2 % / Endotoxin: < 0.1 EU/ug / Relative molecular weight: ≥ 100 kDa

Conjugate Process Development



Scale:	Conjugation:	Purification:	Efficiency:
0.5 - 1.0 g	Direct coupling using cyanylation chemistry	1-day single TFF step	20 - 40 %

Product Quality Attributes

CPS/Protein ratio: 0.5 - 1.5 / Free CPS: < 20 % / Free protein: < 1 % /
Endotoxin: < 0.1 EU/ug / Relative molecular weight: 200 - 600 kDa

Pre-Clinical Study Design

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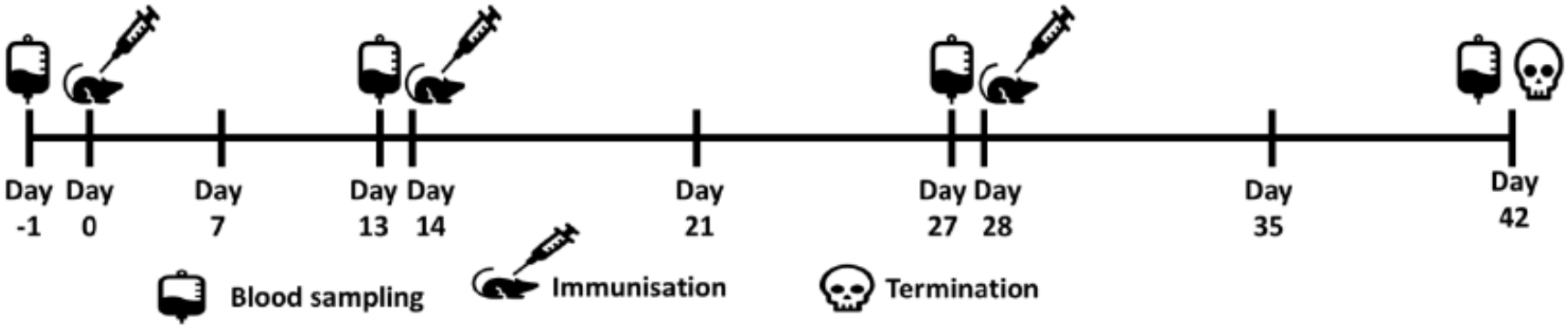
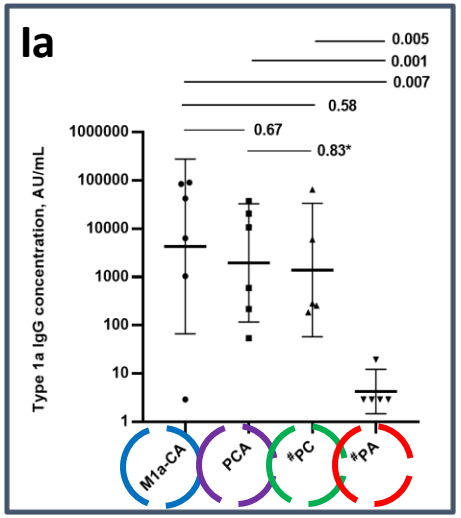
Study Group	Purpose	Formulation	Conjugated	Adjuvanted
1	Negative Control	Placebo	N/A	+
2	Monovalent EG	Ia conjugate	+	+
3	Monovalent EG	Ib conjugate	+	+
4	Monovalent EG	II conjugate	+	+
5	Monovalent EG	III conjugate	+	+
6	Monovalent EG	V conjugate	+	+
7	Pentavalent EG	Ia, Ib, II, III & V conjugates	+	+
8	Control Group	Ia, Ib, II, III & V conjugates	+	-
9	Control Group	TT + Ia, Ib, II, III & V CPS	-	+

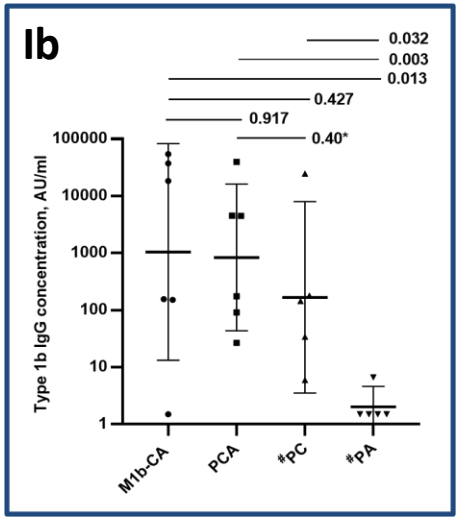
Planned Treatment Regime

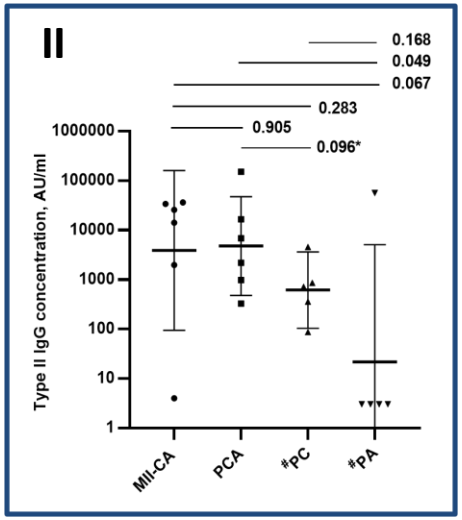


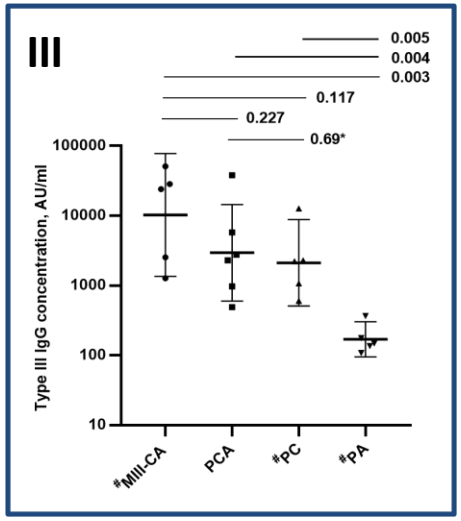
1. IgG Titres - Luminex Based Method
2. OPA Titres - Opsonophagocytic Killing Assay

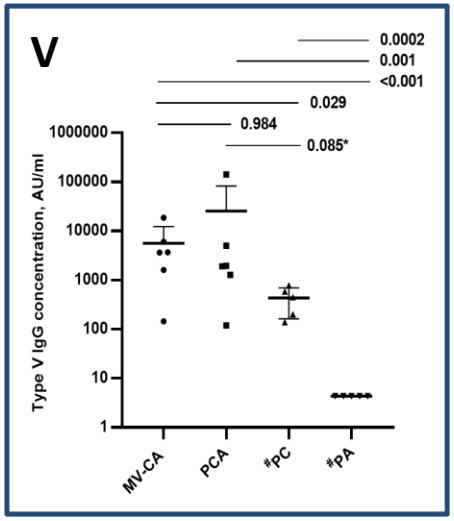
Serotype Specific IgG Titers











IgG Titres - Day 42

Lane 1: Monovalent EG - adjuvanted

Lane 2: Pentavalent EG - adjuvanted

Lane 3: Pentavalent EG

Lane 4: Unconjugated CG - adjuvanted

Serotype Specific OPA Titers

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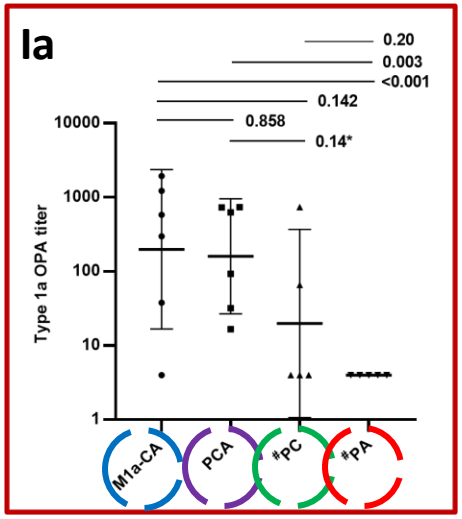

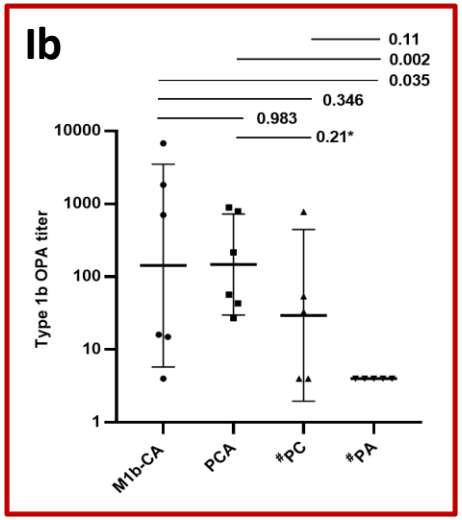

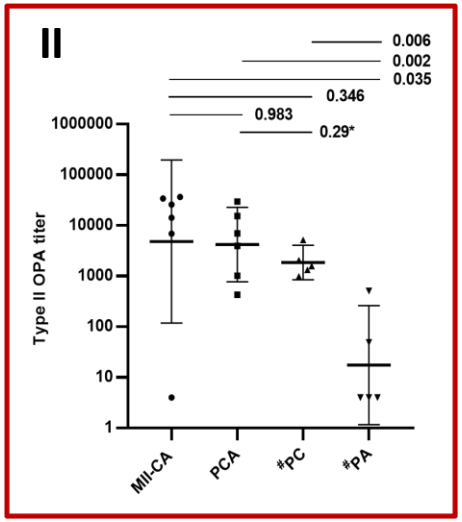

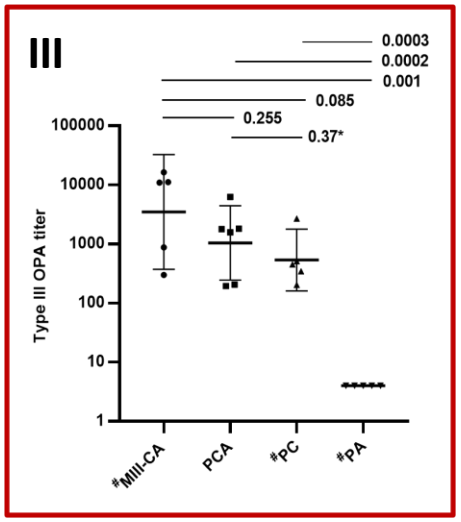

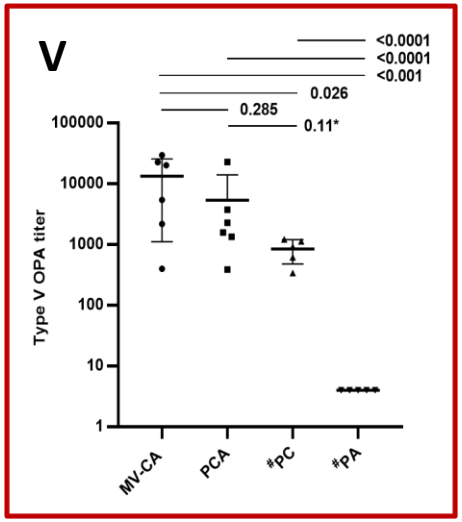

OPA Titres - Day 42

Lane 1: Monovalent EG - adjuvanted
Lane 2: Pentavalent EG - adjuvanted
Lane 3: Pentavalent EG
Lane 4: Unconjugated CG - adjuvanted

Conclusions

- A robust process to produce capsular polysaccharide and their subsequent glycoconjugates has been developed for serotypes Ia, Ib, II, III and V.
- All five glycoconjugates were immunogenic in both their monovalent and pentavalent formulations
- There was good correlation between serotype specific IgG responses and opsonophagocytic titers

Future Work

- Toxicology study and First in Human Phase I clinical trial
- Optimisation and scale-up of the process to achieve high yields without impacting product quality
- The production of a maternal GBS vaccines at a commercial scale

Acknowledgements

WITS VIDA
UNIVERSITY OF THE WITWATERSRAND
VACCINES & INFECTIOUS DISEASES ANALYTICS