MOLECULAR MODELLING OF *STREPTOCOCCUS PNEUMONIAE* CARBOHYDRATE ANTIGENS FOR OPTIMISING VACCINE DESIGN

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Introduction

Streptococcus pneumoniae is a carbohydrate encapsulated bacterium that causes invasive pneumococcal disease (IPD). The capsular polysaccharide (CPS) is a key virulence factor. When infected, the host produces antibodies to bind to these CPS (antigens)[1]. While conjugate vaccines decrease the burden of disease, it shows an increase in non-vaccine serotypes, underscoring the need for broader coverage. Cross-protection is when one antibody produced elicits a response to a related (non-vaccine) strain.

Pneumococcal serotype 33F is in the 3rd generation vaccines, however, remains persistent. Recently, it was discovered that serotype 33E emerged from 33F and shows weak cross-protection. 33A has a similar structural to both 33F and 33E yet shows weak cross-reactivity against 33F (Fig. 1). We use molecular dynamics simulations to uncover the structural and antigenic differences between these serotypes, in order to rationalise the lack of cross-protection.

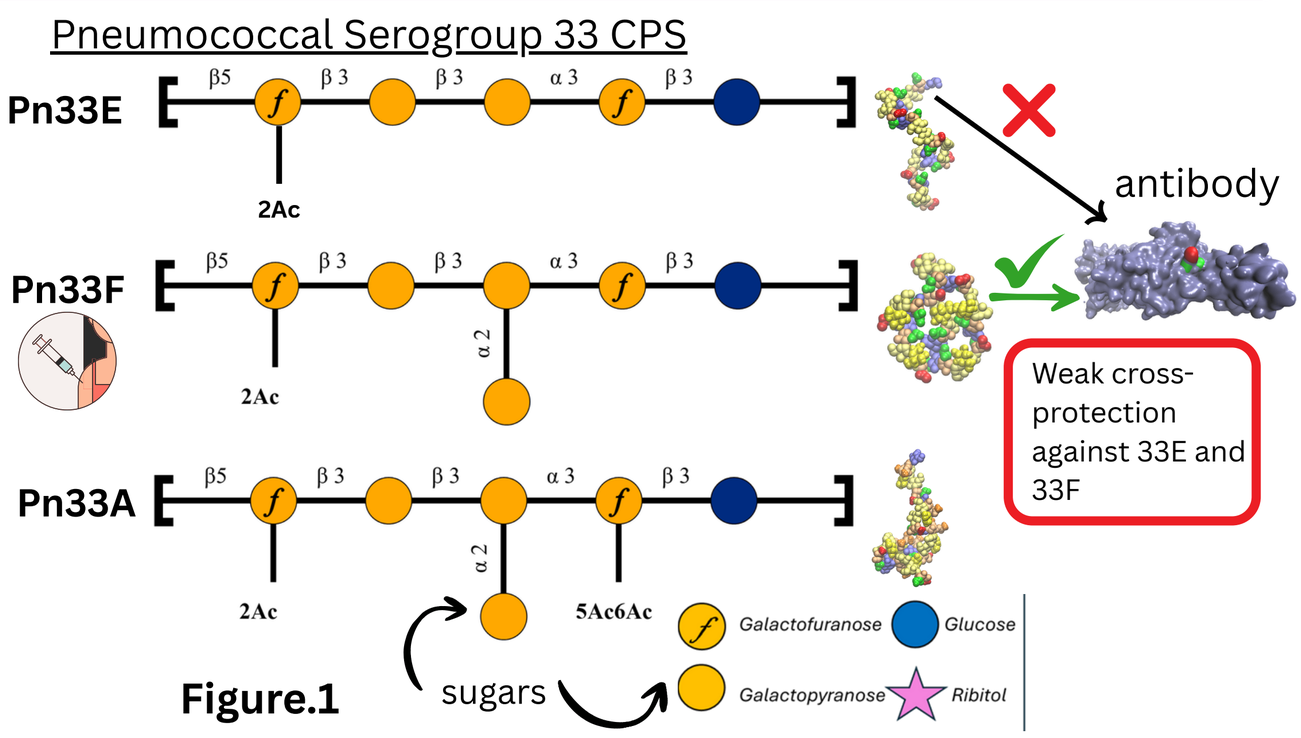
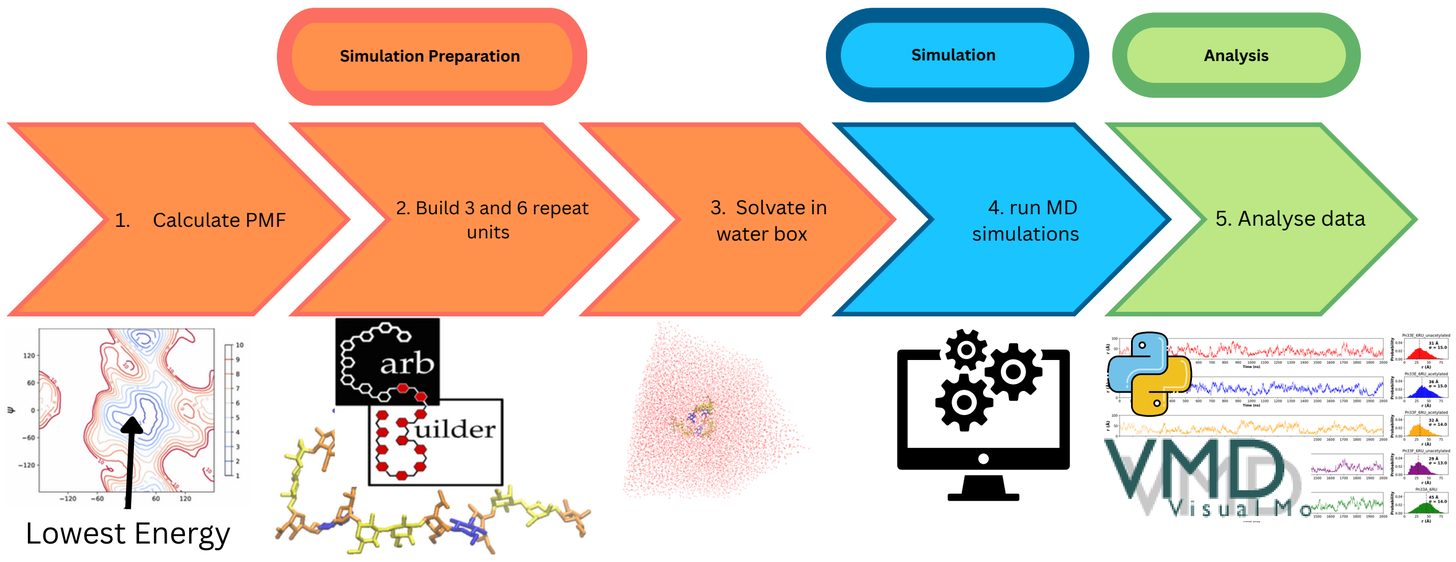


Figure.1

Metholdolgy



Molecular Dynamics Simulations are run using **NAMD software** on the High-Performance Computing (HPC) cluster. A **CHARMM force field** is used to ensure an accurate representation of the movement of carbohydrate atoms over time. We aim to investigate the effect of structural differences on the conformation of the molecules, which might then rationalise the lack of cross-protection or reactivity.

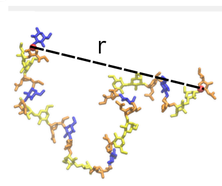
Data Visualisation: VMD software with in-house tcl and python scripts.

Results

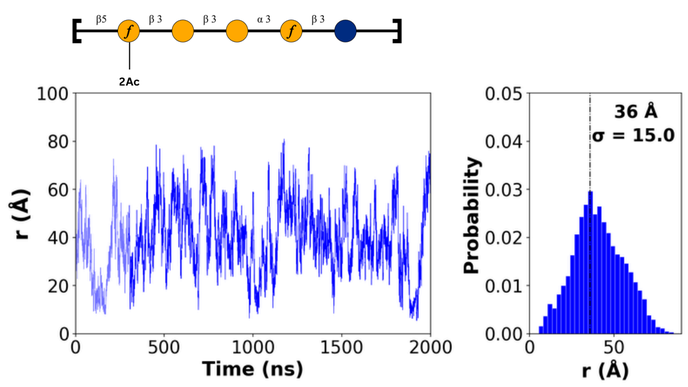
End-to-End Distance

Measures distance from one end of the molecule to the other over time.

Gives insight into **flexibility** of molecules .

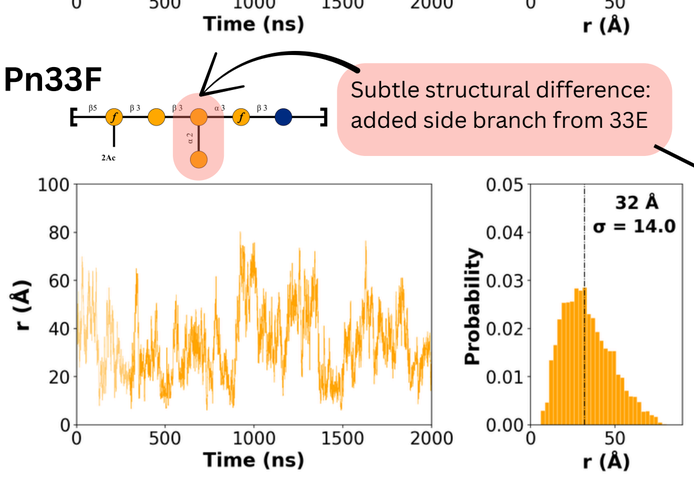


Pn33E



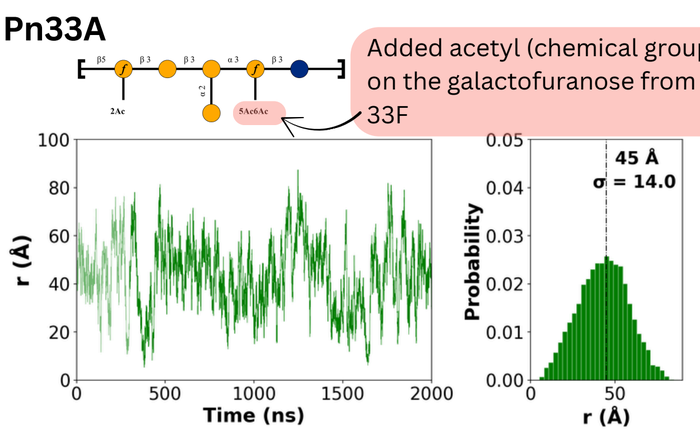
Pn33F

Subtle structural difference: added side branch from 33E



Pn33A

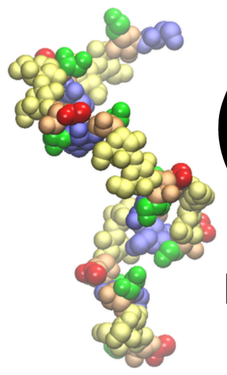
Added acetyl (chemical group) on the galactofuranose from 33F



Clustering

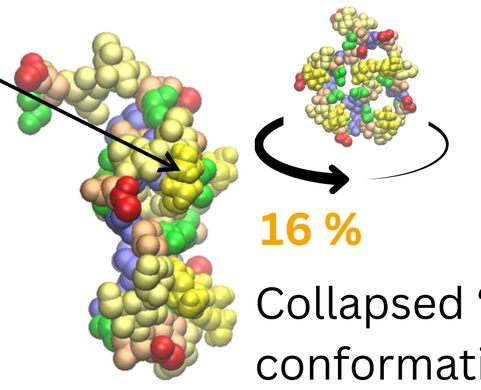
Shows preferred conformation of the molecules throughout the simulation i.e. what "shape" it is in most frequently.

How often the CPS is in this conformation. The primary cluster is the "most frequent" shape.



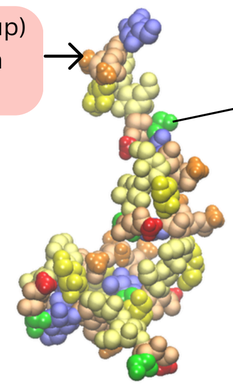
12 %

Helical "spiral" shape



16 %

Collapsed "ring" conformation



Exocylcic diol on the galactofuranose is a target for anitbodies

13 %

Extended with a loop at the bottom

Analysis

Serotype 33E, 33F and 33A have similar repeating unit structures, they differ by the addition of a galactose side branch on 33F, and an addition of a chemical group (acetyl group) on 33A.

The **End-to-end (e2e)** distance analysis revealed that all three molecules are **extremely flexible**, as seen by the large standard deviation.

The **primary cluster** indicates the most frequent conformation of the molecule over time. For all three, this cluster was **less than 20%**, further supporting the claim of **extreme flexibility**, as **rigid molecules** tend to have a **dominant conformation**.

Further analysis is needed to identify **epitopes** - small regions where the antibody is most likely to bind. From experimental data, 33F and 33E are not cross-protected. We aim to use Molecular Dynamics to understand how structural features affect the molecule's behaviour, as well as rationalise the lack of cross-reactivity/protection.

References

Ganaie, F. A. et al. Update on the evolving landscape of pneumococcal capsule types: new discoveries and way forward. Clin. Microbiol. Rev. e00175-24 (2025) doi:10.1128/cmr.00175-24

Information

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Acknowledgements

Computations were performed using facilities provided by the University of Cape Town's ICTS High Performance Computing (HPC) team: hex.uct.ac.za