A Computational Immune Approach for Modeling Different Levels of Severity in COVID-19 Infections

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Overview

Introduction

The Challenge of GBS

- Group B Streptococcus (GBS) is a leading cause of neonatal mortality and morbidity.
  - 410,000 cases worldwide, leading to 147,000 stillbirths and infant deaths
- It can cause severe infections like sepsis, pneumonia, and meningitis in newborns.
- Current prevention relies on maternal screening and intrapartum antimicrobial prophylaxis (IAP).
- Maternal vaccination is a promising strategy, offering transplacental transfer of antibodies for protection.
- The Type V GBS-TT conjugate vaccine is a significant development.

The Role of Computational Models

- Computational models are valuable tools in vaccine research.
- They simulate disease dynamics, immune responses, and vaccine effects within a controlled virtual environment.
- Such models enable rapid exploration of scenarios, including variations in vaccine dosage and administration schedules.
- Ordinary differential equation (ODE) models offer a balance between interpretability and computational efficiency.
- In this study, we extend an established ODE model to evaluate the Type V GBS-TT conjugate vaccine.

Background

GBS and Immune Response

- GBS (*Streptococcus agalactiae*) is a common bacterium.
- The innate immune system is the first line of defense, involving cells like neutrophils and macrophages.
- The adaptive immune system produces specific antibodies against GBS antigens, primarily targeting the polysaccharide capsule.
- Vaccines mimic natural infection to stimulate memory responses without causing disease.
- Type V GBS-TT conjugate vaccine uses capsular polysaccharides (CPS) conjugated with tetanus toxoid (TT) to enhance immunogenicity.

Vaccine Dosages and Antibody Production

- A study by Baker *et al.* [1] evaluated the Type V GBS-TT conjugate vaccine at different dosages in healthy adults.
- The vaccine elicited a dose-dependent immune response, with higher doses leading to increased specific antibodies.

[1] Baker *et al.*, Dose–response to type V group B streptococcal polysaccharide–tetanus toxoid conjugate vaccine in healthy adults, Vaccine 25(1), pp 55-63, (Jan 2007).

Vaccine Dosages and Antibody Production

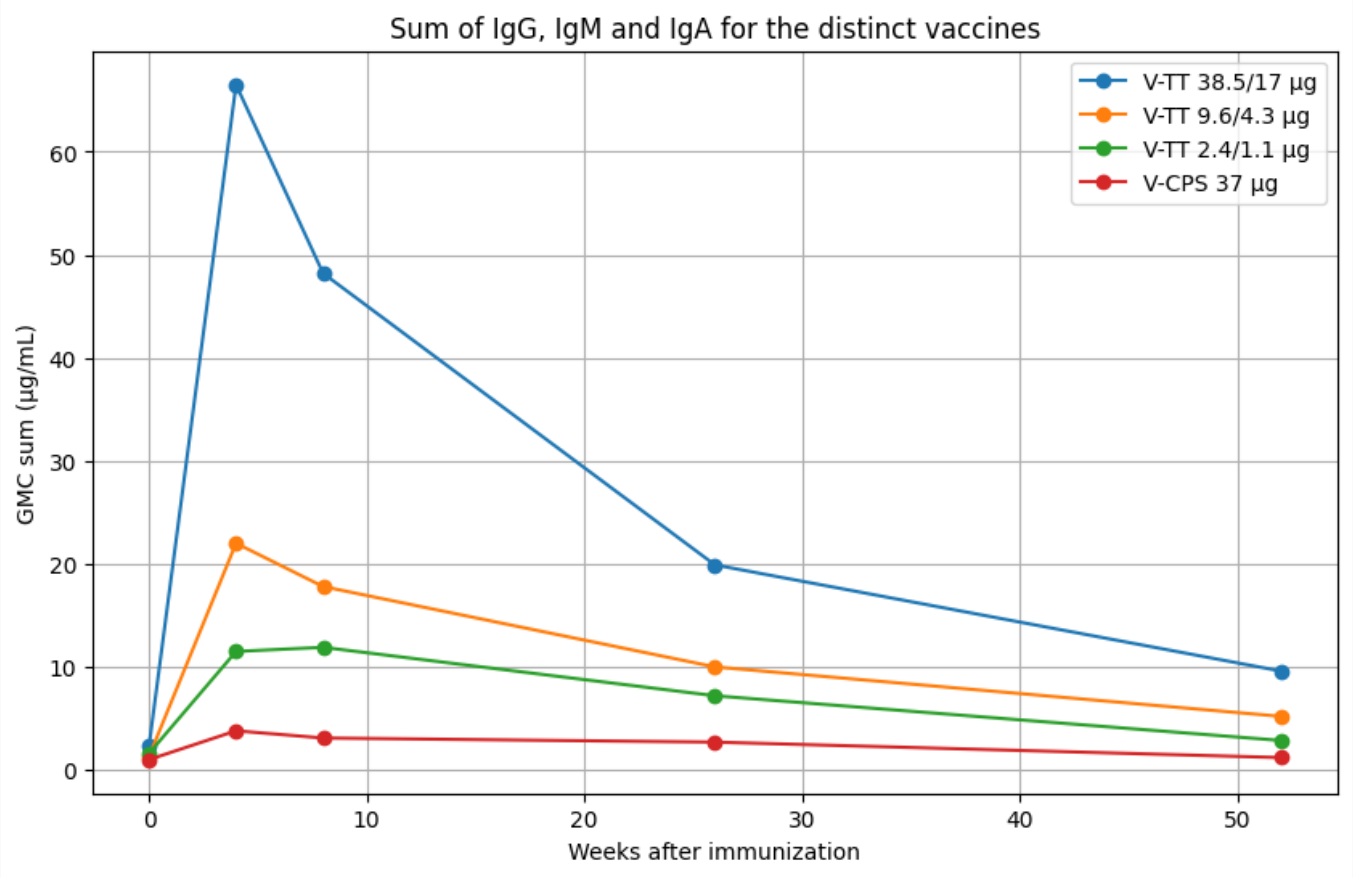


Figure 1: Sum of IgG, IgM and IgA for the distinct vaccines

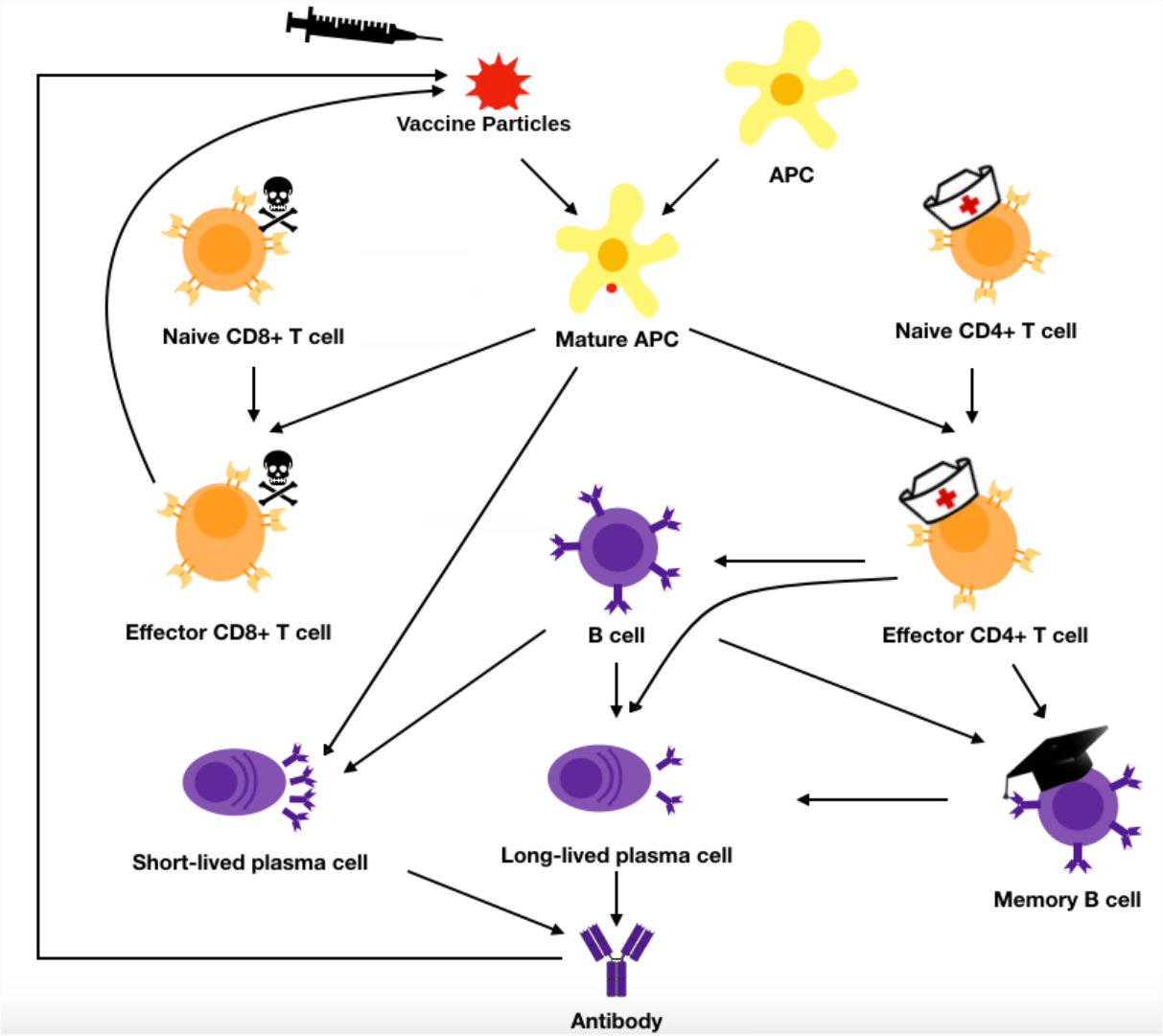
Methods

Mathematical Model for Immune Response

- The model is a system of Ordinary Differential Equations (ODEs) adapted from Bonin *et al.* [2].
- It describes interactions among:
  - Vaccine particles (Vp)
  - Antigen-presenting cells (naive Ap, mature Apm)
  - Lymphocytes (Thn, The, Tkn, Tke, B, Bm, Ps, Pl)
  - Antibodies (A)
- The model includes terms for vaccine elimination, cell maturation, activation, replication, differentiation, and decay.

[2] Bonin *et al.*, Validation of a yellow fever vaccine model using data from primary vaccination in children and adults, revaccination and dose-response in adults and studies with immunocompromised individuals. BMC Bioinformatics 21(S17) (Dec 2020)

Model scheme



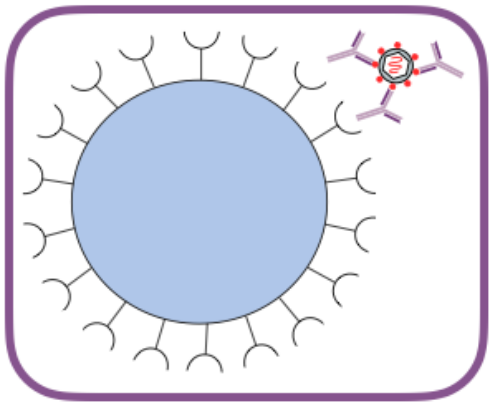
Mathematical Model - Virus

$$\frac{d}{dt}V_p = -\frac{c_{v1}V_p}{c_{v2}+V_p} - k_{v1}V_pA - k_{v2}V_pT_E$$

Innate system action

Mathematical Model - Virus

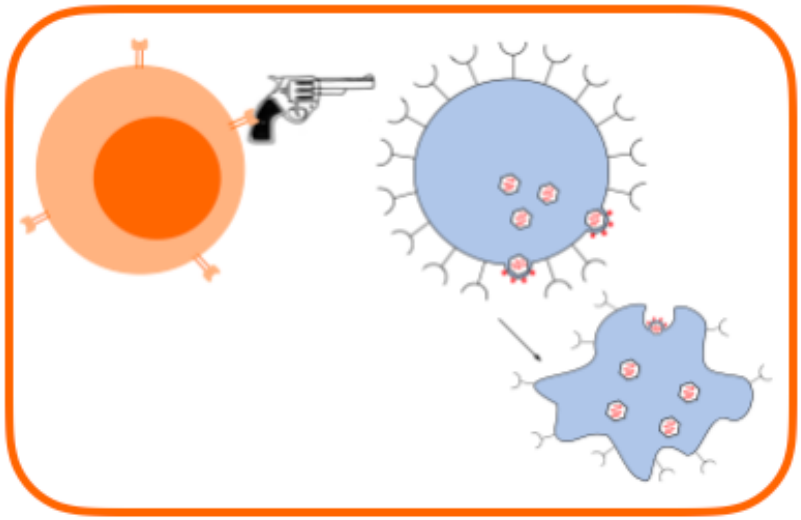
$$\frac{d}{dt}V_p = -\frac{c_{v1}V_p}{c_{v2}+V_p} - k_{v1}V_pA - k_{v2}V_pT_E$$



Neutralization by antibodies

Mathematical Model - Virus

$$\frac{d}{dt}V_p = -\frac{c_{v1}V_p}{c_{v2}+V_p} - k_{v1}V_pA - k_{v2}V_pT_E$$



Elimination by T killer cells

Cohort Data and Calibration

- Cohort data was extracted from a phase 1 trial on Type V GBS-TT conjugate vaccine (V-TT) versus an unconjugated Type V capsular polysaccharide (V CPS) vaccine.
- Healthy adults (18-50 years) were assigned to four vaccine groups.
- Blood samples were collected at baseline, 4, 8, 26, and 52 weeks post-vaccination.

Cohort Data and Calibration

- Type V CPS-specific antibodies (IgG, IgA, and IgM) were quantified by ELISA.
- Differential Evolution (DE) was used to calibrate seven key parameters.
- The objective function minimized the L2 norm of the relative error between observed and numerical antibody levels.

Results and Discussion

Model Accuracy Across Vaccine Doses

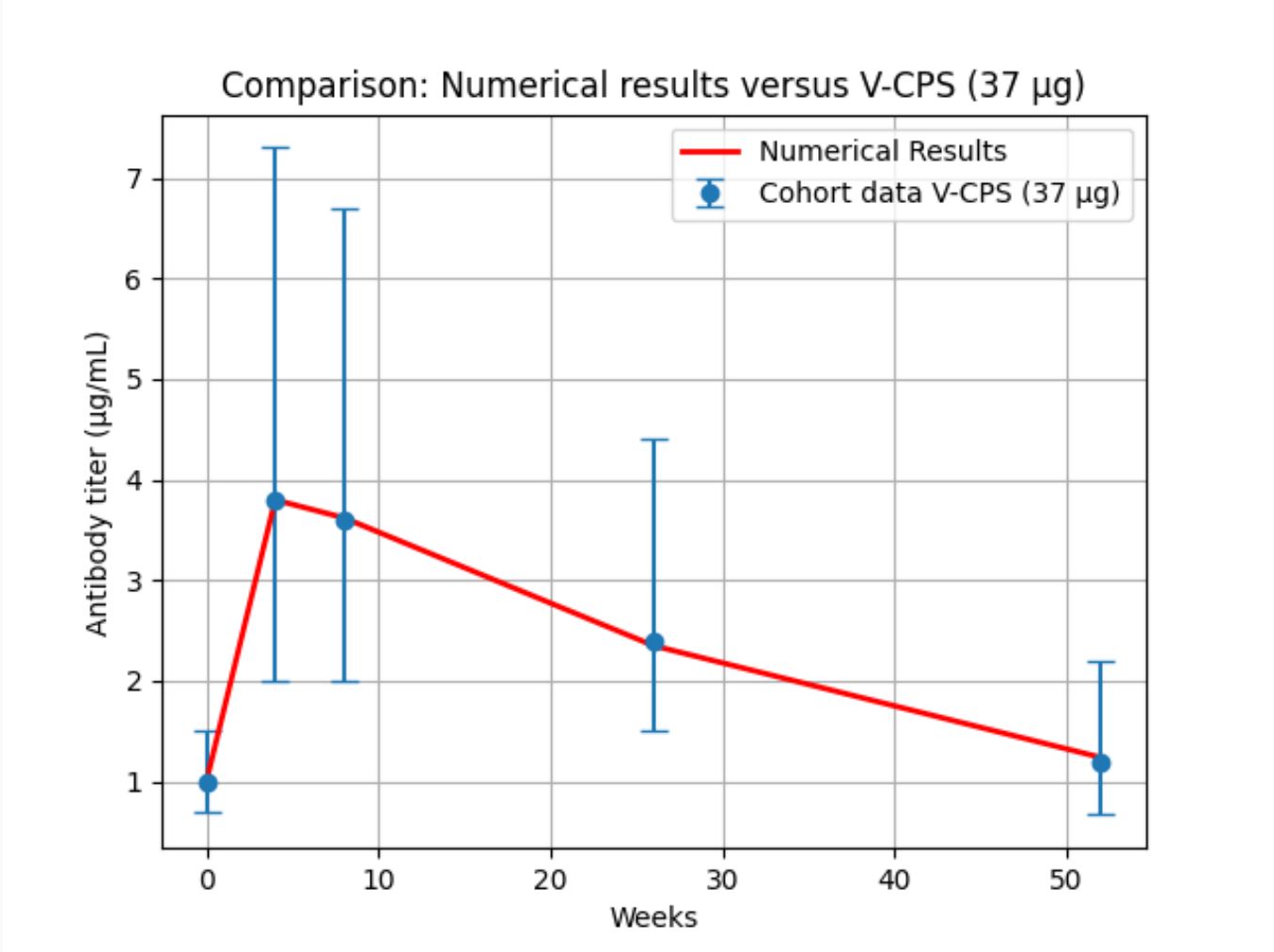


Figure 2: Unconjugated CPS: 37μg

Model Accuracy Across Vaccine Doses (Cont.)

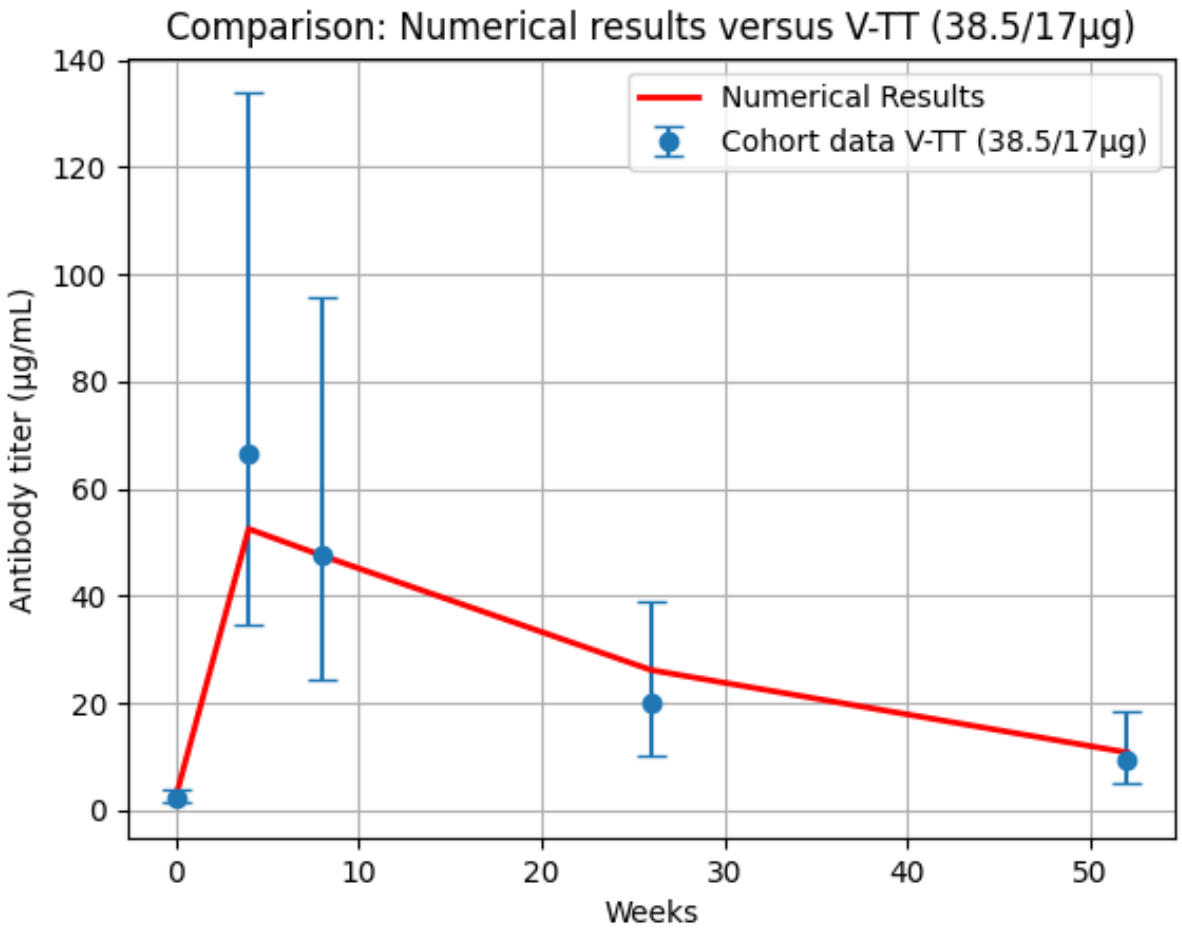


Figure 3: V-TT: 38.5μg CPS/17.0μg TT

Model Accuracy Across Vaccine Doses (Cont.)

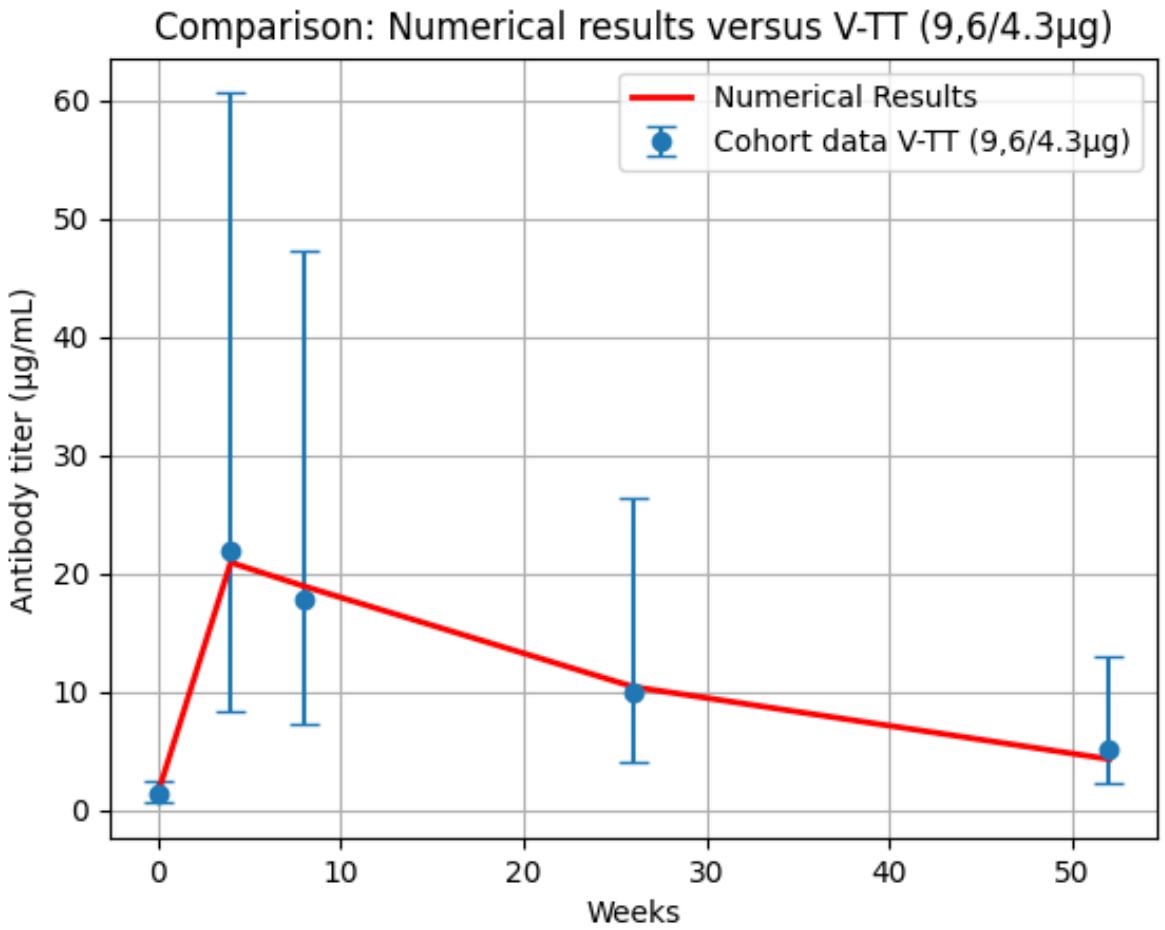


Figure 4: V-TT: 9.6μg CPS/4.3μg TT

Model Accuracy Across Vaccine Doses (Cont.)

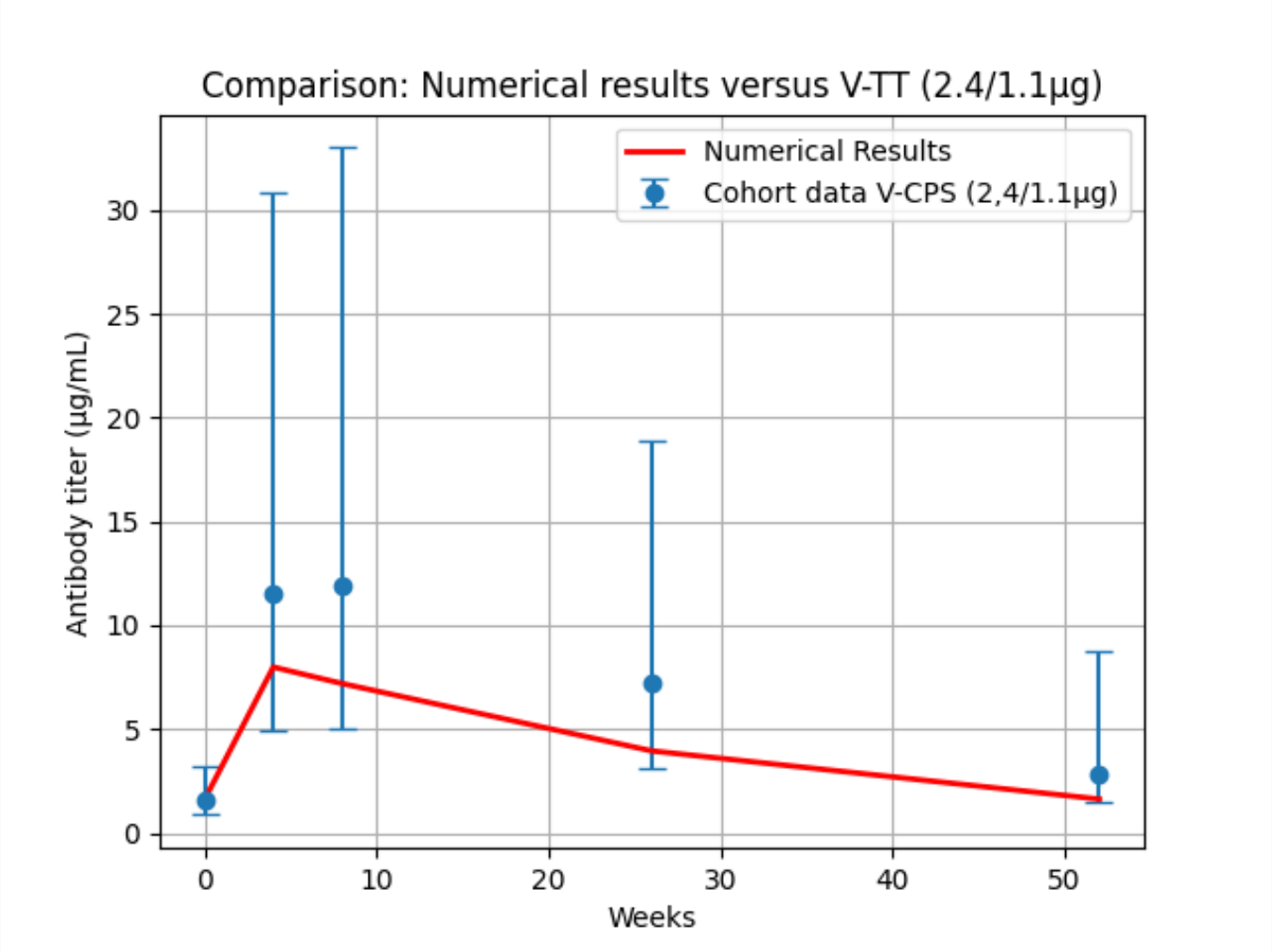


Figure 5: V-TT: 2.4μg CPS/1.1μg TT

Model Accuracy Across Vaccine Doses

- The model accurately reproduced the dose-dependent response observed in the clinical trial.
- Higher CPS doses elicited stronger and more sustained antibody levels.
- The highest V-TT dose (38.5μg CPS/17.0μg TT) showed near-perfect alignment with cohort data.
- Lower doses (2.4μg CPS/1.1μg TT) exhibited greater discrepancies, with simulated titers consistently falling below the GMT.
    - These deviations suggest opportunities for refinement.

Calibration Success and Parameter Differences

- The DE algorithm successfully calibrated seven key parameters to fit the model to cohort data for both unconjugated CPS and conjugated V-TT vaccines.
- Significant differences were observed between the two vaccine formulations, reflecting distinct immunological mechanisms.
- For the V-TT vaccine, the antigen-presenting cell maturation rate (β_{ap}) was 93 times higher than for the unconjugated vaccine.
    - This supports the adjuvant effect of tetanus toxoid.

Calibration Success and Parameter Differences

- The antibody-mediated vaccine clearance rate (k_{v1}) was approximately 1,700 times higher for the conjugated vaccine.
  - Suggests more effective neutralization of vaccine particles.
- Short-lived plasmocyte decay rate (δ_{ps}) remained consistent, but antibody decay rate (δ_A) was slightly higher for V-TT.

Conclusion and Future Work

Conclusions

- Developed a computational model to simulate immune response to Type V GBS-TT conjugate vaccine.
- Successfully reproduced clinical trial data across multiple dosages.
- Calibration with Differential Evolution provided mechanistic insights into dose-dependent efficacy.
- Conjugated V-TT vaccine elicited a more robust and sustained antibody response than unconjugated CPS.
- Enhanced APC maturation and accelerated antibody-mediated clearance are critical factors for the superior immune response.

Future Work

- Incorporate additional parameters into the calibration process for improved precision.
- Explore uncertainty quantification.
- Integrate patient-specific immune profiles to enable personalized dosing recommendations.
    - Especially for high-risk populations.

Acknowledgements

Obrigado!

Thanks!

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