# Predicting Antibody Responses to Type V GBS-TT Conjugate Vaccine Using Computational Modelling


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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 and a major cause of neonatal infections.
- The innate immune system acts as the first line of defense, involving cells such as neutrophils and macrophages.
- The adaptive immune system produces specific antibodies against GBS antigens, primarily targeting the polysaccharide capsule.
- Vaccines mimic natural infection to elicit memory immune responses without causing disease.
- The 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 inducing greater production of 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

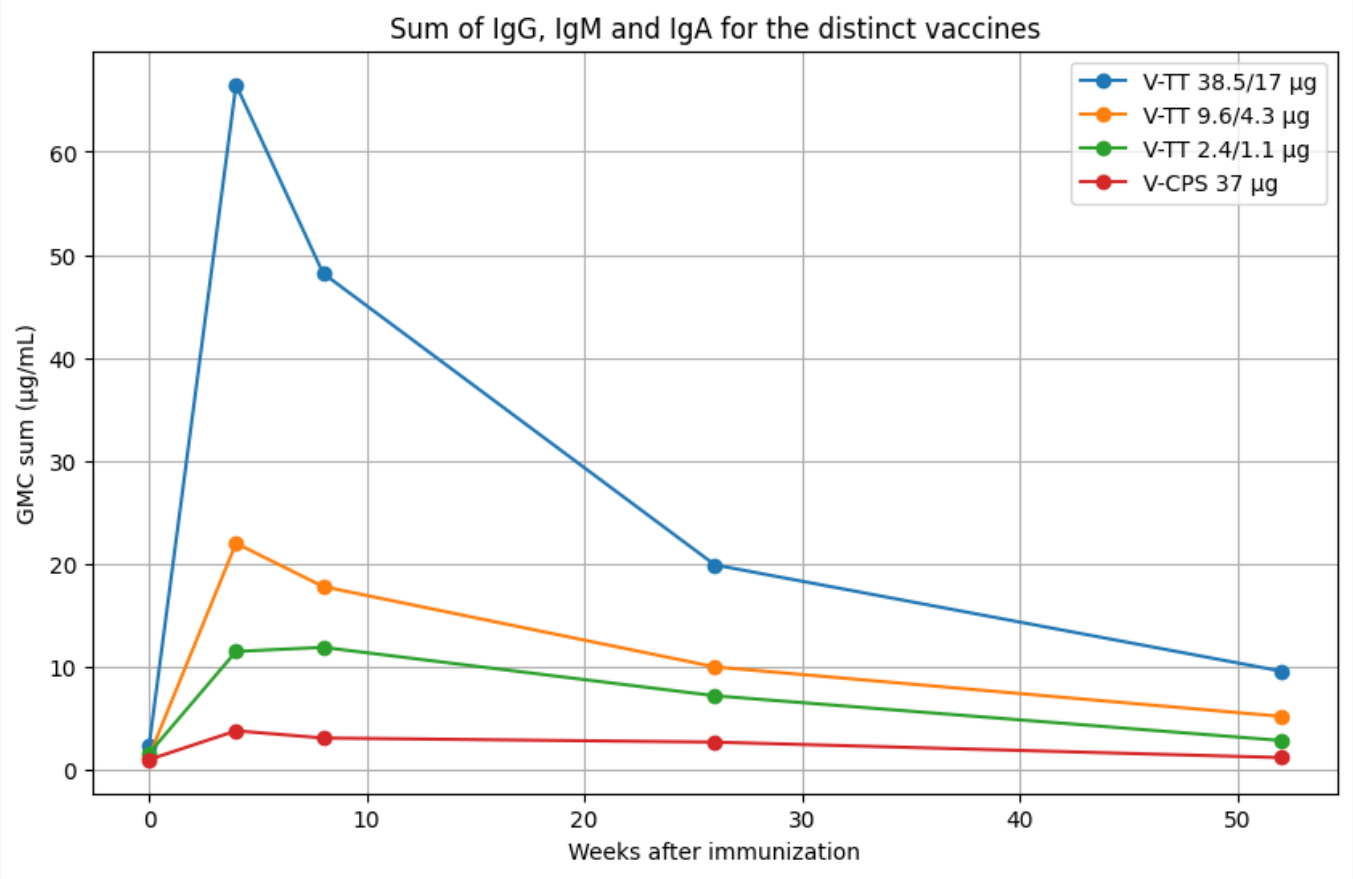



**Figure 1:** Sum of IgG, IgM and IgA for the distinct vaccines. Cohort data from Baker *et al.*

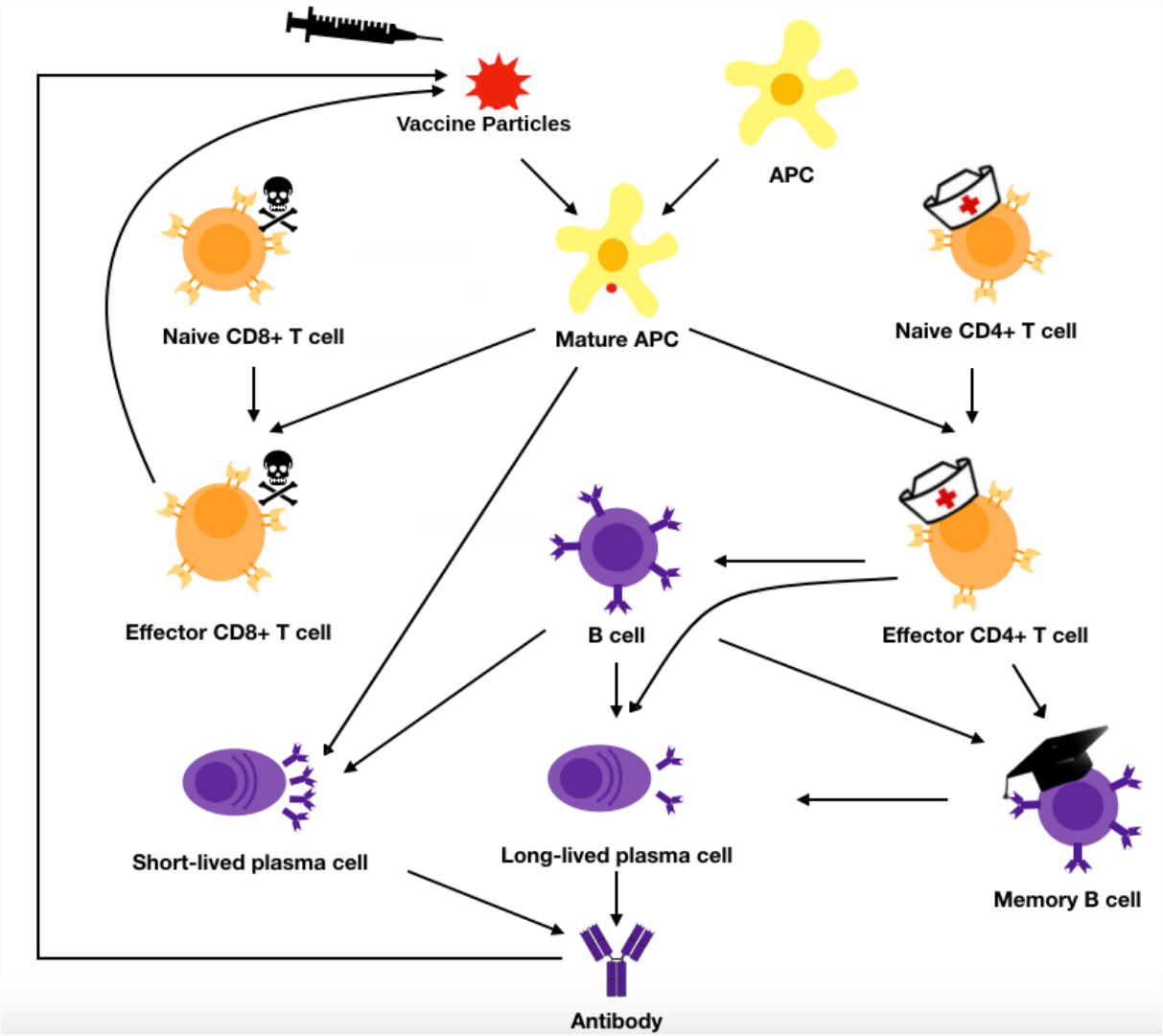
# Methods

# 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



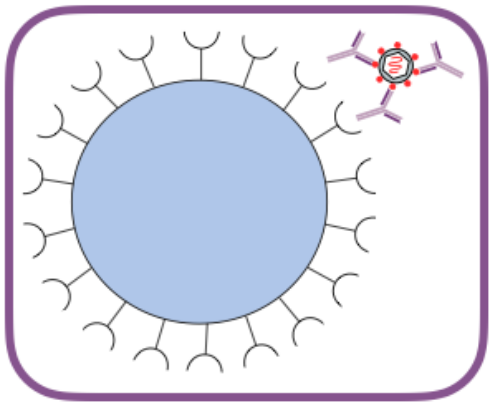
# Mathematical Model - Virus

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

Innate system action

# Mathematical Model - Virus

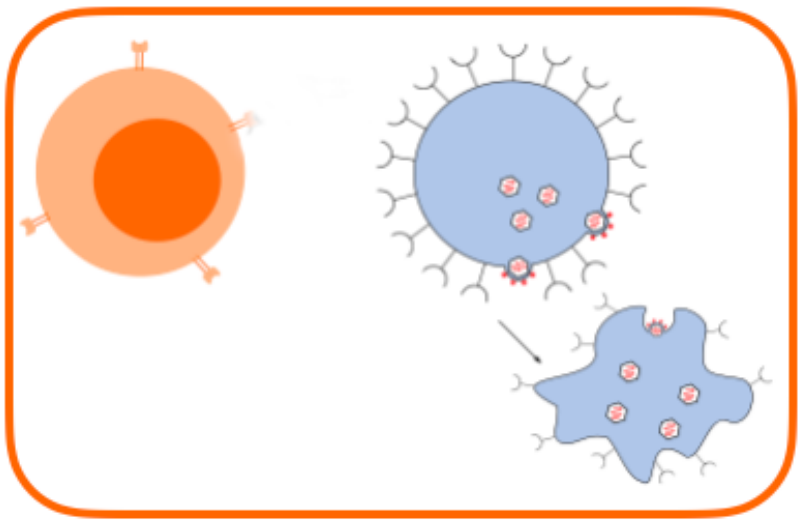
$$\frac{d}{dt}V_p = -\frac{c_{v1}V_p}{c_{v2}+V_p} - k_{v1}V_pA - k_{v2}V_pT_E$$



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 ...

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

# ... Calibration

- Type V CPS-specific antibodies (IgG, IgA, and IgM) were quantified using ELISA.
- Differential Evolution (DE) was employed to calibrate seven key model parameters.
- The objective function minimized the $L_2$ norm of the relative error between observed and simulated antibody levels.

# Results and Discussion

# Model Accuracy Across Vaccine Doses

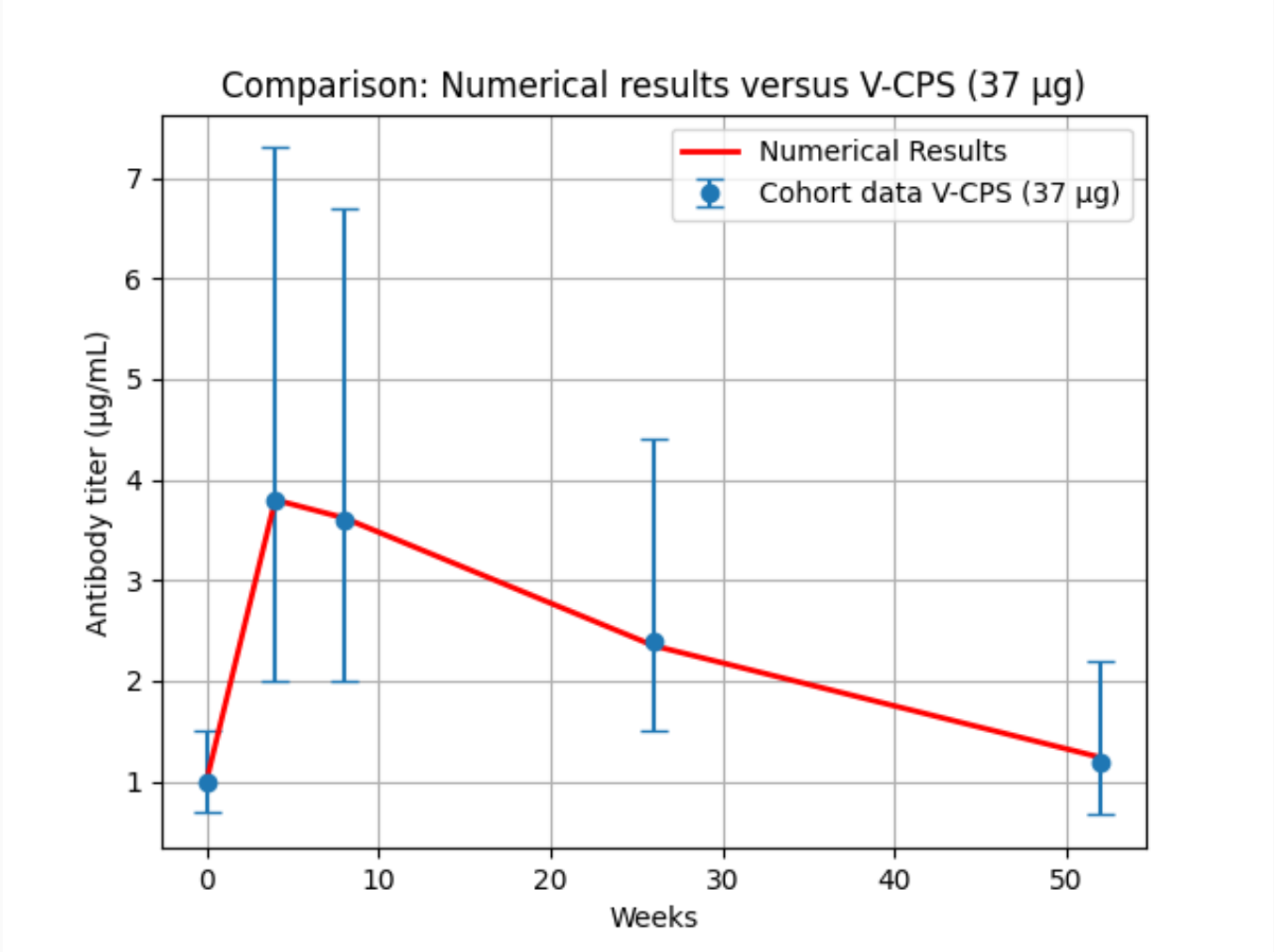



**Figure 2:** Unconjugated CPS: 37$\mu$g

# Model Accuracy Across Vaccine Doses (Cont.)

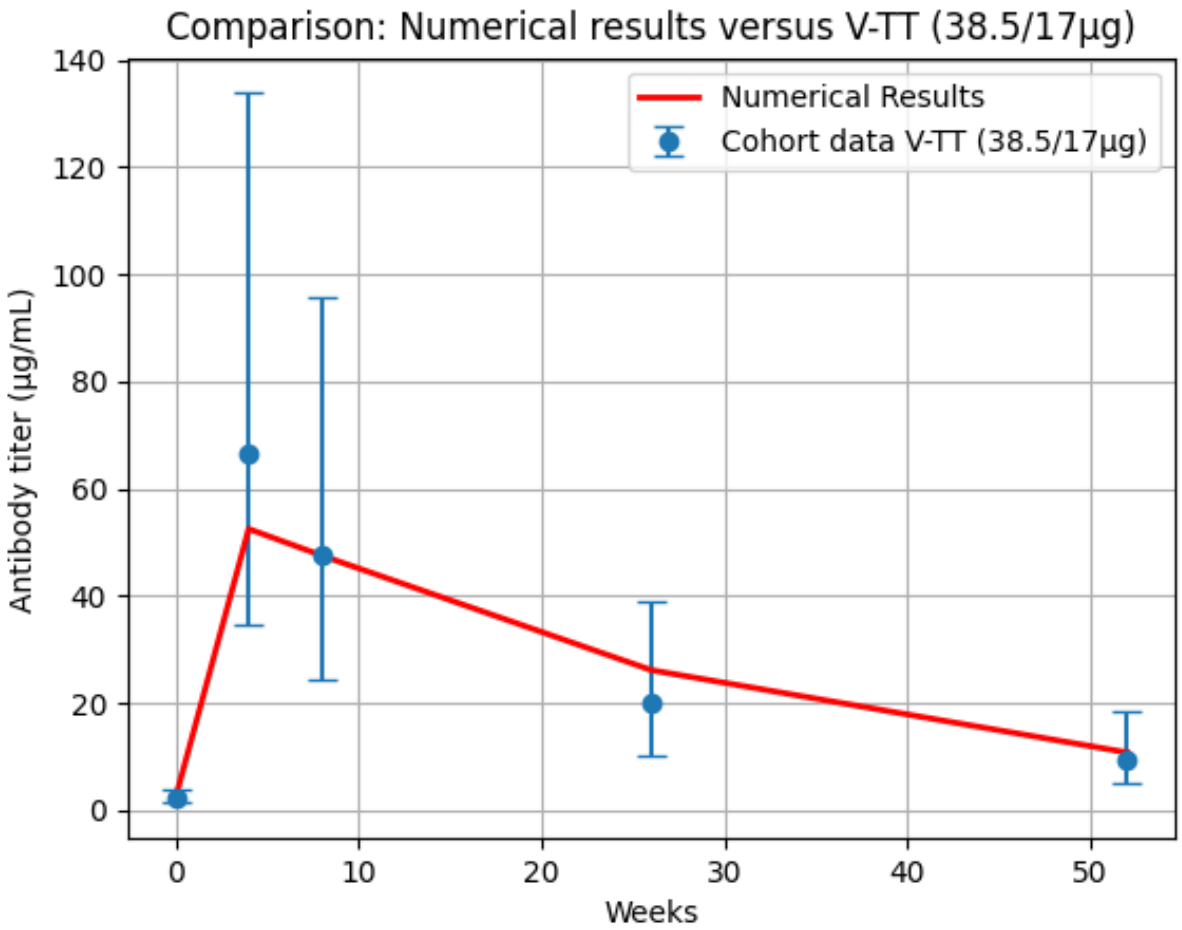



**Figure 3:** V-TT: 38.5$\mu$g CPS/17.0$\mu$g TT

# Model Accuracy Across Vaccine Doses (Cont.)

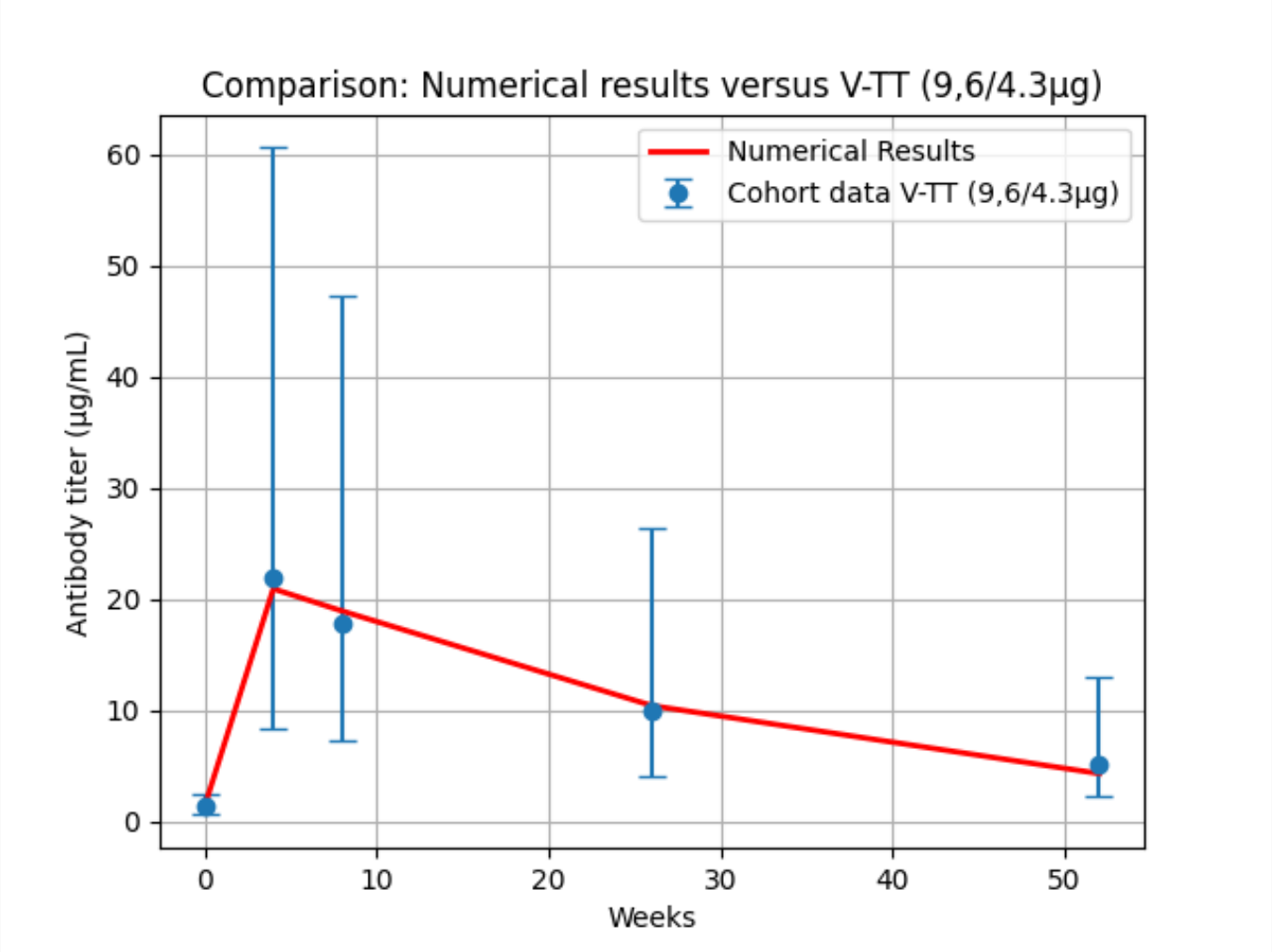



**Figure 4:** V-TT: 9.6$\mu$g CPS/4.3$\mu$g TT

# Model Accuracy Across Vaccine Doses (Cont.)

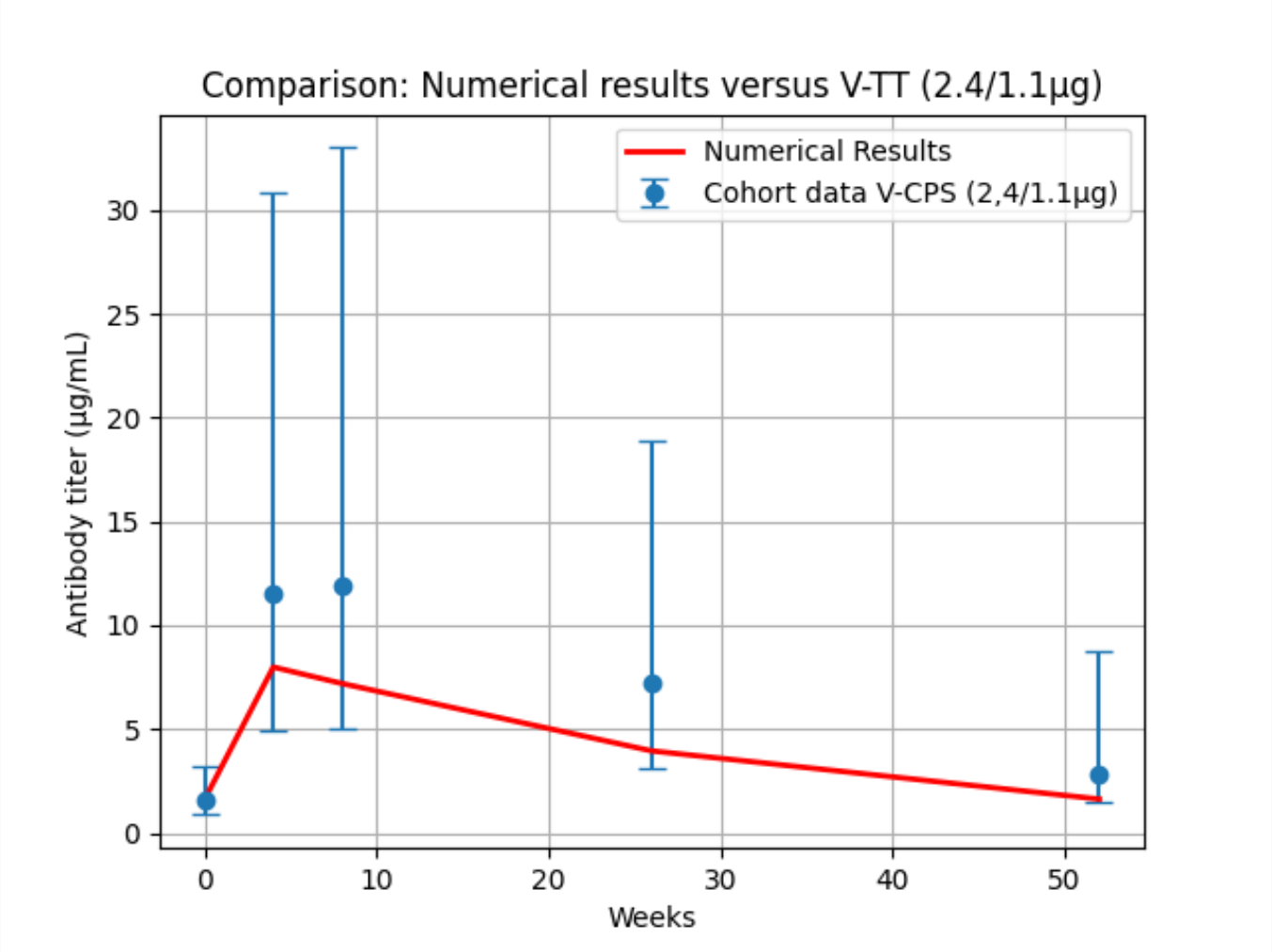



**Figure 5:** V-TT: 2.4$\mu$g CPS/1.1$\mu$g TT

# Model Accuracy Across Vaccine Doses

- The model accurately reproduced the dose-dependent antibody response observed in the clinical trial.
- Higher CPS doses elicited stronger and more sustained antibody levels.
- The highest V-TT dose (38.5 $\mu$g CPS / 17.0 $\mu$g TT) showed near-perfect alignment with cohort data.
- Lower doses (2.4 $\mu$g CPS / 1.1 $\mu$g TT) exhibited greater discrepancies, with simulated titers consistently falling below the geometric mean titer (GMT).
- These deviations suggest opportunities for model 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 ($\beta_{ap}$) 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, suggesting more effective neutralization of vaccine particles.
- The short-lived plasmocyte decay rate ($\delta_{ps}$) remained consistent across formulations.
- The antibody decay rate ($\delta_A$) was slightly higher for the V-TT conjugate vaccine.

# Conclusion and Future Work

# Conclusions

- Developed a computational model to simulate the immune response to the Type V GBS-TT conjugate vaccine.
- Successfully reproduced clinical trial data across multiple dosage groups.
- Calibration using Differential Evolution provided mechanistic insights into dose-dependent efficacy.
- The conjugated V-TT vaccine elicited a more robust and sustained antibody response than the unconjugated CPS formulation.
- Enhanced APC maturation and accelerated antibody-mediated clearance emerged as key contributors to the superior immune response.

# Future Work

- Incorporate additional parameters into the calibration process to improve model precision.
- Explore uncertainty quantification to assess confidence in model predictions.
- Integrate patient-specific immune profiles to enable personalized dosing strategies, especially for high-risk populations.

# Acknowledgements

Obrigado!

Thanks!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