Exploring the Association Between Study Characteristics and Post-Vaccine Immunogenicity for *C. diff*: Data-Driven Analyses of Two Vaccine Trials

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Introduction

Clostridioides difficile (C. diff) causes severe diarrhea and colitis, particularly in healthcare environments. As an opportunistic pathogen, *C. diff* primarily affects individuals with disrupted gut microbiota, often due to age-related changes, underlying health conditions, or associated healthcare exposure and treatments (particularly antibiotics).

Given the challenging management of *C. diff* infections (CDIs), developing an effective and safe vaccine has become high priority.

This study aims to analyze baseline determinants associated with different post-vaccine immunogenicity levels, using data from the Sanofi vaccine program,[1,2] and to propose study design improvements.

Methods

Data from two clinical trials (Phase II and Phase III), provided by Sanofi via the Vivli platform, were pooled and analyzed together.

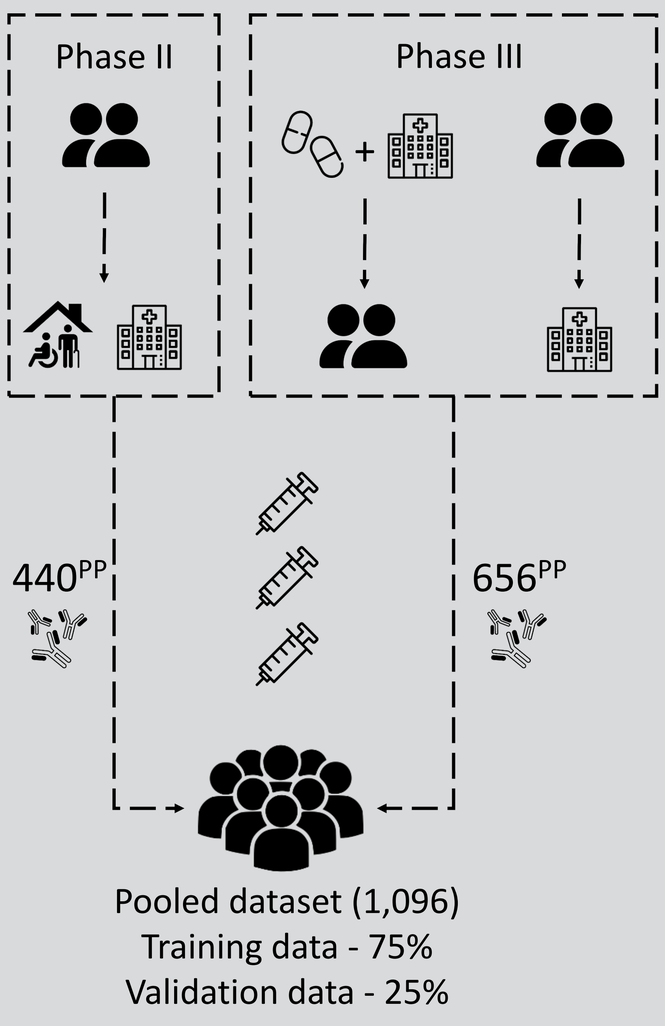
Seroresponse was defined by four different cut-off points, based on the increase from baseline (two-fold, four-fold, median, and 75th percentile), separately for each toxin type (Toxin A, Toxin B) and assay method (Enzyme-linked immunosorbent assay, ELISA; Toxin neutralization assay, TNA).

Potential baseline determinants of seroresponse, measured 30 days after the third vaccine dose, included age, sex, study region, CDI risk exposure group, baseline immunoglobulins (IgG), comorbidity index, and vaccination arm as a known determinant.

For the analyses we used multiple statistical models such as logistic regression (full & stepwise), mixed-effect models, classification and regression trees, and boosting models.

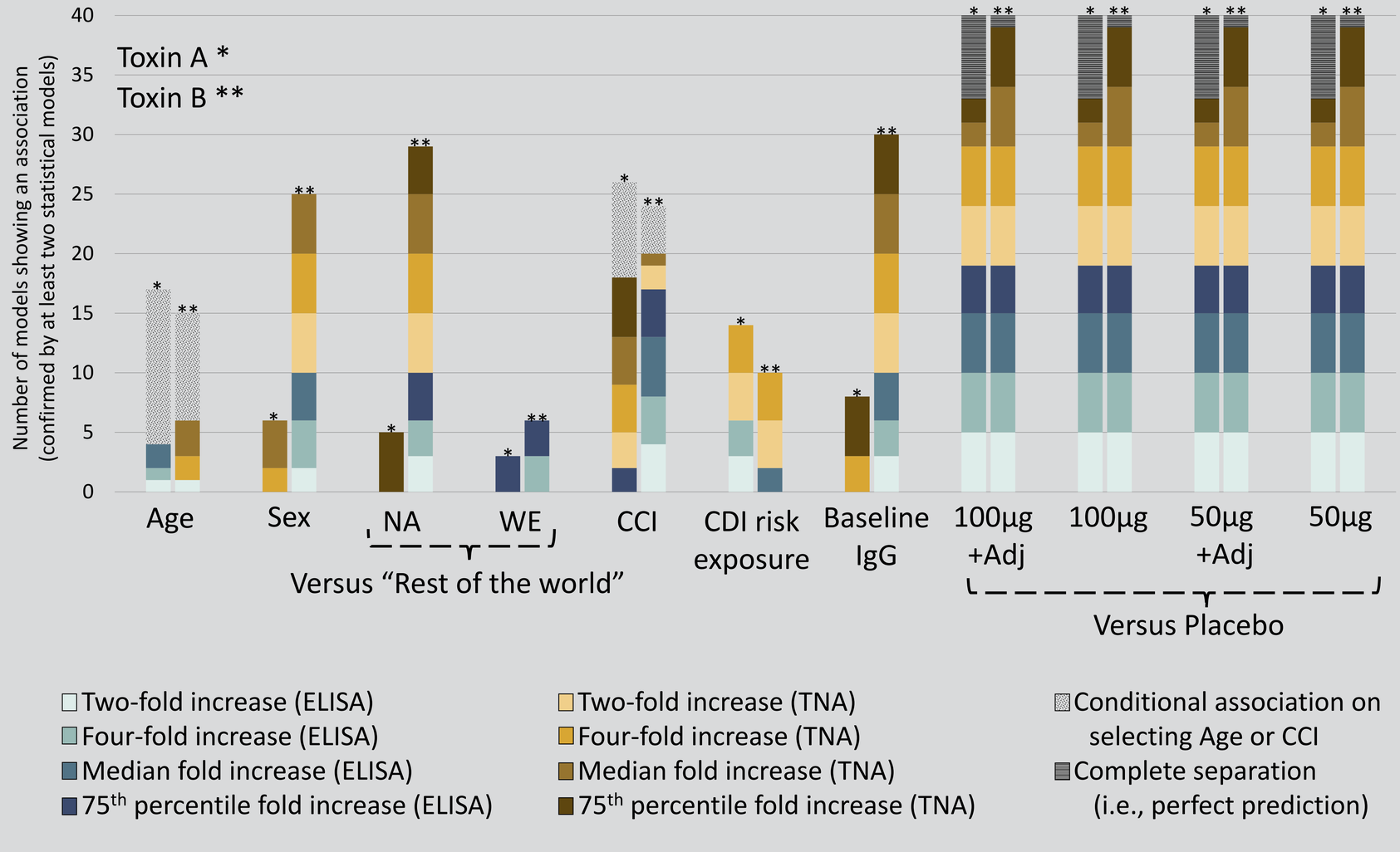
Results

The pooled dataset consisted of 1,096 participants (Figure 1). In addition to vaccination, which showed the strongest associations with seroresponse across all different models, lower comorbidity index and future CDI risk exposure (e.g., hospital/nursing care admission or antibiotic use) showed comparable importance for both Toxin A and Toxin B seroresponse. Higher baseline IgG levels, study region (particularly North America), and female sex demonstrated higher likelihood for increased Toxin B seroresponse, especially for the TNA measurements (Figure 2).



PP - Per-protocol (immunogenicity data available)

Figure 1. *C. diff* vaccine data structure (pooled dataset)



Adj - Adjuvant; CCI - Charlson Comorbidity index (modified); NA - North America; WE - Western Europe

Figure 2. Number of models with confirmed association between baseline determinants and seroresponse

Conclusion

An effective personalized approach in developing a *C. diff* vaccine could enhance immunogenicity in study participants while improving effectiveness and safety across a diverse range of individuals. This may include targeting those at risk for future CDI, adjusting vaccine dosage, schedule, or adjuvant classes according to the personal comorbidity index, or implementing study designs with stratified enrollment. Further research should focus on the complex relationship between the host immunity, CDI, and vaccine effectiveness.

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1. de Bruyn, G. et al. Defining the optimal formulation and schedule of a candidate toxoid vaccine against Clostridium difficile infection: A randomized Phase 2 clinical trial. *Vaccine*. 2016; 34(19):2170-8.
2. de Bruyn, G. et al. Safety, immunogenicity, and efficacy of a Clostridioides difficile toxoid vaccine candidate: a phase 3 multicentre, observer-blind, randomised, controlled trial. *The Lancet Infectious Diseases*. 2021; 21(2):252-62.

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