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 post-vaccine immunogenicity levels, using data from the Sanofi vaccine program, and to propose study design improvements.

Methods: Data from two clinical trials (Phase II and Phase III) were pooled to analyze participants who met the study criteria for immunogenicity assessments. Potential baseline predictors of high immunogenicity, measured 30 days after the third vaccine dose, included age, sex, study region, CDI risk exposure group, baseline immunoglobulins-IgG, comorbidity index, and treatment arm. High immunogenicity was categorized based on four different cut-off points (two-fold, four-fold, median, and 75% quantile increase), stratified by toxin type (Toxin A, Toxin B) and assay method (Enzyme-linked immunosorbent assay-ELISA, Toxin neutralization assay). For the analyses we used multiple statistical models such as logistic regression, mixed-effect models, classification and regression trees, and boosting models.

Results: The pooled dataset consisted of 1,096 participants. Expectedly, the treatment arms showed the strongest associations with immunogenicity, across all outcomes and different models. Both the lower comorbidity index and future CDI risk exposures (e.g., hospital/nursing care admission, or antibiotic use) showed comparable importance for both Toxin A and Toxin B immunogenicity. Higher baseline IgG levels, study region (particularly North America), and female sex demonstrated higher likelihood for increased Toxin B immunogenicity.

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 is needed to better understand the complex relationship between the host immunity, CDI, and vaccine effectiveness.

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