Immunogenicity, Safety and Tolerability of a Booster Dose of *Clostridium difficile* Vaccine and 4 Year Antibody Persistence

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BACKGROUND

- *C difficile*, a gram-positive anaerobic, spore-forming bacillus, is the main cause of nosocomial infectious diarrhea in industrialized countries,[2] accounting for 20% to 30% of cases of antibiotic-associated diarrhea, and is the most commonly recognized cause of infectious diarrhea in healthcare settings[3]
- *C difficile* can produce 3 toxins, toxin A (TcdA), toxin B (TcdB), and binary toxin. TcdA and TcdB are the principal virulence factors for *C difficile* infection (CDI).[8] The spectrum of clinical CDI ranges from mild symptomatic colonization to serious complications, such as severe diarrhea, pseudomembranous colitis, toxic megacolon, intestinal perforation, and death[4]
- The primary risk factors for an initial episode of CDI are antibiotic therapy, prolonged hospitalization, and medical comorbidities. Older adults (>65 years of age) are at an increased risk for CDI, particularly when exposed to healthcare settings[5]
- Increased incidence and severity of CDI with associated complications, colectomy rates, and mortality have been observed over the past 10 to 20 years, including community-associated disease and among younger adults[6]
- To date, there are limited options to prevent CDI. These include appropriate use of antimicrobials, contact precautions, disinfection of equipment, and the environment. There is no licensed vaccine to prevent CDI[7]

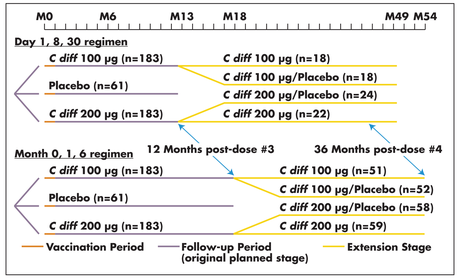
OBJECTIVE

- Immunogenicity objective:
  - Describe the immunogenicity of each study group of C difficile vaccination in 2 antigen dose levels at days 8 and 30, and at months 6, 12, 24, 30, and 36
- Safety objective:
  - Assess the safety and tolerability of a fourth dose of *C difficile* vaccine in 2 antigen dose levels 7 days post-dose 4

METHODS

- 300 healthy, immunocompetent participants having received three doses of *C difficile* vaccine in one of two regimens (Day regimen; days 1, 8, and 30 or Month regimen; months 0, 1, and 6) and two dose groups (100 µg or 200 µg) were rerandomized to receive either a fourth *C difficile* vaccine or placebo in a 1:1 ratio 12 months following their third dose. Participants were rerandomized to the same dose group as they received in the first stage **(Figure 1)**

Figure 1. Study Schematic



- Immunogenicity testing was conducted on blood samples obtained at each of 8 visits (day 8 and 30, and at months 6, 12, 18, 24, 30, and 36) following a fourth dose
- Toxin A- and toxin B-specific neutralizing immunoglobulin G (IgG) concentrations (neutralization units/mL) were measured at each scheduled study visit. Geometric mean concentrations (GMC) were calculated for toxin A and toxin B
- Local reactions and systemic events were collected by e-diary for 7 days after vaccination
- Adverse event reporting occurred from signing of informed consent through 1 month post-dose 4. Serious adverse event (SAE) reporting occurred through 6 months post-dose 4

RESULTS

- Immune response to a fourth dose of *C difficile* vaccine was observed for all regimens, dose groups, and toxins, with peak antibody levels higher post-dose 4 compared to post-dose 3 **(Figures 2 & 3)**
- GMCs 36 months post-dose 4 were similar for the month and day regimens **(Figures 2 & 3)**
- At 48 months post-dose 3, overall GMC levels were higher in the month regimen compared to the day regimen for participants who only received 3 doses of *C difficile* vaccine **(Figures 2 & 3)**

Figure 2. Immune Response to Month Regimen

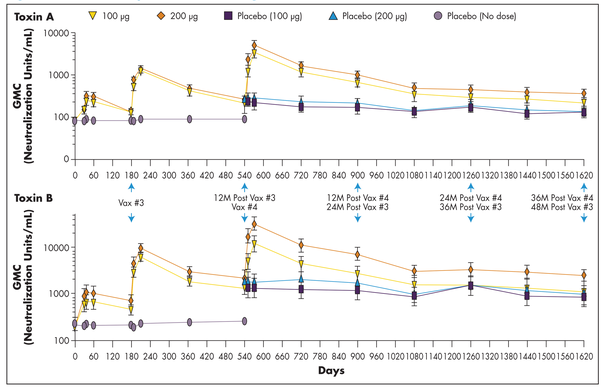
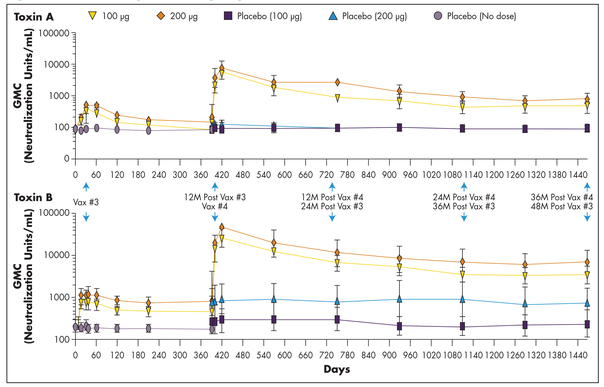


Figure 3. Immune Response to Day Regimen



- Pain was the most common local reaction reported, while fatigue was the most common systemic event reported **(Figure 4)**
- No Grade 4 local or systemic reactogenicity were reported during the study **(Figure 4)**
- There were no SAEs related to *C difficile* vaccination reported during the trial for any regimen or dose group **(Figure 5)**

Figure 4. Reactogenicity in the Extension Stage (Post-dose 4)

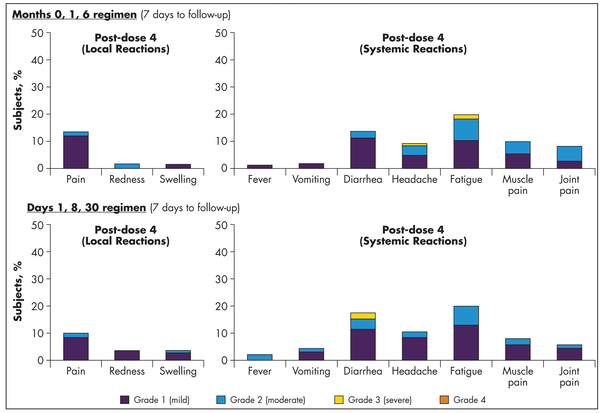
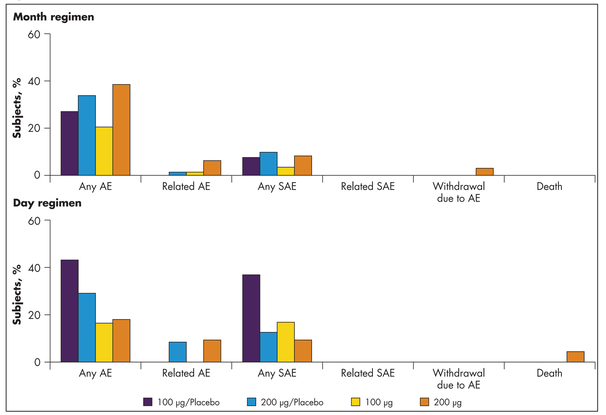


Figure 5. Overview of Adverse Events



DISCUSSION

- A fourth dose of *C difficile* vaccination was highly immunogenic, demonstrating a robust anamnestic response 12 months following dose 3 irrespective of dose regimen and was well tolerated and demonstrated an acceptable safety profile
- The durability of a three-dose series 4 years post-dose 3 demonstrated the month regimen was superior to the day regimen, especially for toxin B
- Overall adverse events were similar numerically between dose groups and placebo, with no vaccine-related SAEs reported

CONCLUSIONS

- **A fourth dose of *C difficile* vaccine was well tolerated, highly immunogenic, and demonstrated an acceptable safety profile**
- **Among participants in the 200 µg Month regimen, durability persisted up to 4 years post-dose 3 in those who received only 3 doses**

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