The Quest for a *Clostridium difficile* Vaccine, Where are we Now?

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**Abstract**

*Clostridium difficile* infection is the most common acquired health care infection with significant morbidity, mortality and health care costs. Although therapy is available, recurrences are common, and vaccination would be a cost effective strategy for prevention. Three toxin based vaccine candidates are the most advanced in clinical trials for primary prevention in high risk individuals.

**Clostridium difficile** is an anaerobic, gram-positive, spore-forming, toxin-producing bacillus acquired through ingestion of spores after disruption of normal gut flora. The virulence factors in *C. difficile* are Toxin A and Toxin B encoded by the genes TcdA and TcdB. *C. difficile* infection (CDI) is currently the leading nosocomial infection in the US. According to the Centers for Disease Control and Prevention estimates, the yearly incidence is 453,000 cases, leading to 29,300 deaths [1]. CDI results in $4.8 billion in excess cost in US acute care facilities annually [2]. Recent data suggest that *C. difficile* has replaced methicillin resistant *Staphylococcus aureus* as the most common healthcare-associated infection in some hospitals [3]. CDI was thought to be the hallmark of prolonged hospital stay and antibiotic exposure, but is now frequently seen in populations considered previously to be at low risk for infection, such as young and healthy non hospitalized individuals [4,5]. Also severe cases of CDI have been reported in peripartum women [6,7]. According to studies conducted across the United States, Canada, and the United Kingdom community-acquired cases of CDI account for 20%-27% of all CDI cases [8-10].

While CDI can be mild, it can also progress to a severe disease with pseudomembranous colitis and toxic megacolon requiring ICU stay, colectomy [11] and potential death. Most initial episodes respond to treatment with fidaxomicin [12], vancomycin [13], or metronidazole [14,15]. A decreased clinical response of *C. difficile* treated with metronidazole has been observed, but is not attributed to drug resistance [16]. Among patients with severe CDI, vancomycin is superior [13] and fidaxomicin use is associated with a lower rate of recurrences.

Approximately 15%-30% of patients experience a recurrence in symptoms after successful initial therapy, usually occurring in the first few weeks after treatment discontinuation [17]. Fecal transplants have been shown to be effective for treating recurrent CDI. However, the optimal route of administration and long-term effects remain unknown [18]. Prevention of CDI includes hand washing, personal protective equipment for healthcare workers, and strategic antibiotic prescribing. New methods for CDI prevention such as vaccination are needed. Early animal studies showed that administration of TcdA/B protected animal models from CDI [19]. Adequate humoral immune responses to CDI through production of sufficient quantity of IgG against TcdA/B has been shown to correlate with decreased likelihood of developing disease [20] and subsequent episodes [21]. Since then strategies using both passive and active immunization have been studied for the prevention and treatment of CDI. Human monoclonal antibodies CDA-1 and CDB-2 have been tested in CDI and demonstrated a decreased risk of recurrence from 25% to 7% when compared to placebo [22-24]. However considering the cost and inconvenience of this form of therapy, it is unlikely to be used as primary prophylaxis except in very high-risk patients [25]. On the other hand, vaccines against *C. difficile*, if and when they are available, will be a cost-effective method to limit the spread of CDI [26].

The first vaccination approach was the use of the toxoid-based vaccine building on the success against other important pathogens such as *Clostridium tetani* and *Corynebacterium diphtheria*. More recent studies provided important information about the nature and localization of toxin-neutralizing epitopes and led to the use of recombinant engineered toxin fragments as vaccine candidates. While many candidates are being evaluated, only 3 are currently undergoing testing in clinical trial (Table 1).

The first vaccine, developed by Acambis and used in humans, contained formalin inactivated partially purified TcdA and TcdB adjuvanted with alum (ACAM-CDIFFTM) [27]. In a phase 1 trial, the vaccine was safe and immunogenic in 30 subjects with 90% of them developing a serum antibody response measured by ELISA and toxin neutralization assay. The immunogenicity was increased when higher and adjuvanted doses were used. The vaccine was subsequently studied in 3 cases with recurrent CDI receiving long-term vancomycin (7-22 months). The study had a small number of subjects and was not placebo controlled but showed that the vaccine was able to induce neutralizing antibody in 2 out of the 3 vaccine recipients, none of whom had recurrent disease [28].

This vaccine candidate has undergone further purification, and was tested later by Sanofi Pasteur using highly purified formalin-inactivated alum-absorbed preparations of TcdA and B [29]. In healthy...
adults and elderly, the vaccine was shown to be safe and well tolerated. The Sanofi Pasteur vaccine induced a complete seroconversion for TcdA that was achieved at all doses in adults, and at the highest vaccine dose in the elderly. The TcdB seroconversion was lower, both in adults and elderly groups reaching 75%. The antibody response appeared persistent only for TcdA in adult groups, whereas the TcdB response declined 6 months after vaccination [30] suggesting the need for a boost. Phase 2 trials that test the immunogenicity in adults for primary prevention (NCT01230957) and infected adults for prevention of recurrent disease (NCT00772343) have been completed, and currently a phase 3 trial is recruiting 15,000 adults ≥50 years at risk for CDI to assess the efficacy of the vaccine (NCT01887912), 10,000 will receive the vaccine, and 5,000 will receive placebo.

Newer vaccine candidates use recombinant toxin based epitopes. The advantages of this technique are that the vaccine contains specific epitopes that enhance neutralizing antibodies, and overcomes the potential risk of incomplete inactivation of the toxins by formalin. Pfizer uses ClosTron mutagenesis procedure and a specific shuttle vector system to produce genetically modified full length TcdA and TcdB toxoid based vaccine from a toxin deficient C. difficile strain [31,32]. Phase 1 trials with and without alum as an adjuvant have been completed (NCT01706367 & NCT02052726), and phase 2 trials are currently ongoing (NCT02117570 & NCT02561195). The last vaccine candidate currently in clinical trials was developed by Valneva using a recombinant fusion protein containing cell binding domains from truncated forms of TcdA and TcdB [32,33]. This recombinant fusion protein was first named IC84 then VLA84 [34]. A phase 1 clinical trial (NCT01296386), and demonstrated favorable safety and tolerability in a press release by the company. IgG Toxin A/B were induced at similar levels in adults and elderly but neutralizing antibody responses were less common in elderly when compared to adults. Enrollment for 10,000 will receive the vaccine, and 5,000 will receive placebo.

These last three vaccine candidates are being tested for primary prevention in high-risk subjects 50 years and above. The vaccine schedule is typically 3 doses by intramuscular route with the second and third doses given 1 and 4 weeks after the initial dose.

One of the main challenges in the development of an effective vaccine against CDI, is its ability to elicit a protective immune response in the highest risk population [34]. The use of adjuvants will likely play an important role in optimizing the immune response in elderly and immunocompromised patients who are at the highest risk for disease complications [33]. Another challenge is identifying the target population for the vaccines and the need for boosting. The hope is that the next few years will witness the licensure of a safe and effective vaccine against CDI, the leading nosocomial infection in the US.

Conflict of Interest
RM and NR receive funds from Sanofi Cdiffense trial.

References


