UPDATE: Vaccine Candidate Against *C. difficile*

Shon Anthony Remich, MD  
Senior Director,  
Vaccine Clinical Research & Development

*Shon Anthony Remich, MD, is employed by Pfizer and owns stock in the company*
**If Nothing Else, You Should Remember…**

*Clostridium (Clostridioides) difficile*: A Significant Unmet Medical Need

1. *C. difficile* bacteria express toxins, causing severe diarrhea<sup>1</sup>

2. Antibiotic use causes CDI<sup>1</sup>

3. CDI cases and deaths/year in US<sup>2</sup>

4. 1 in 5 recurrence<sup>2</sup>

5. *C. difficile* at “Hazard Level – Urgent” (CDC)<sup>3</sup>

Currently, there is **no vaccine** to prevent initial or recurrent CDI

---

CDI—*Clostridium difficile* infection.


A Nationwide Surveillance Program by the CDC Demonstrates That the Incidence of *C. difficile* Increases With Age

**CDI Incidence in the US by Age Group (2011)**

- **All Ages**
  - 147 CDI Incidence per 100,000 persons
- **1-17 yr**
  - 24 CDI Incidence per 100,000 persons
- **18-44 yr**
  - 47 CDI Incidence per 100,000 persons
- **45-64 yr**
  - 149 CDI Incidence per 100,000 persons
- **≥65 yr**
  - 628 CDI Incidence per 100,000 persons

1 in 11 patients aged ≥65 years died of healthcare-related CDI within 1 month of diagnosis.

CDC Emerging Infections Program *C. difficile*

Reported Crude Incidence of Community-Associated and Healthcare-Associated CDI Among the 10 Emerging Infections Program Sites, 2011-2016


In 2011: 453,000 cases, 29,000 deaths

Overall 3% decrease in CDI from 2011 to 2016

19% decrease
in healthcare-associated CDI from 2011-2016

39% increase
in community-associated CDI from 2011-2016
Pfizer’s Bivalent Toxoid Vaccine Preserves Important Antigenic Epitopes

Key Advantages:

- **Safety**: Genetically detoxified toxin
- **Efficacy**: Preservation of neutralizing epitopes
- **Implementation**: Ease of manufacturing

**Toxin A**

- NH₂
- Glucosyl Transferase
- Auto Protease
- Cell Entry
- Binding
- COOH

**Toxin B**

- NH₂
- Glucosyl Transferase
- Auto Protease
- Cell Entry
- Binding
- COOH

**Expression in C. difficile**

**Recipient VPI 11186**

SPO-A and Toxin minus

**Toxoid Antigenicity**

- Max Binding (Rmax)
- Neut mAb

**APD**= autoprotease domain; **GTD**= glucosyl transferase domain.

**C. difficile Vaccine Clinical Development Program**

- **2012-2013**
  - **Phase 1, n=192 (US)**
    - First-in-human study at three dose levels, with or without adjuvant, to assess safety and tolerability in adults aged 50 to 85 years.

- **2015**
  - **Phase 1, n=100 (Japan)**
    - First-in-Japan study of the safety, tolerability, and immunogenicity of 2 dose levels over 2 vaccination schedules of CDI vaccine in adults aged 65 to 85 years.

- **2016**
  - **Phase 2, n=855 (US)**
    - Evaluation of the safety, tolerability, and immunogenicity of CDI vaccine in adults aged 65 to 85 years on two vaccination schedules, with or without an additional dose 1 year after third dose.

- **2017**
  - **Clover, Phase 3, n~17.5k (Global)**
    - Safety, tolerability, and efficacy of CDI vaccine in adults aged ≥50 years.

- **2018**
  - **Phase 3, n=1316 (US)**
    - Study to evaluate the lot consistency, safety, tolerability, and immunogenicity of CDI vaccine in adults aged 65 to 85 years.

- **2019**
  - **Phase 3, n=500 (US)**
    - Study to evaluate the immunogenicity, safety, and tolerability of a 2-dose CDI vaccine regimen compared to a 3-dose regimen in adults aged ≥50 years.

Proof of Concept Phase 2 Study to Evaluate the Safety, Tolerability, and Immunogenicity of CDI Vaccine in Adults Aged 65 to 85 Years (NCT02561195)

Randomization

Vaccination period

CDI vaccine 100 µg (n=183)

CDI vaccine 200 µg (n=183)

Placebo (n=61)

Follow-up period

Extension stage

Month 0, 1, 6 Schedule:

Patient Demographics | (200 µg – Month 0, 1, 6)

Sex Ratio

97 : 86

Age (y)

Range: 65-85
Mean: 71.3

3.3

9.8

67.2

Sero-Status

Sero-negative

Sero-positive

65 ➔ 85

Remich S, et al. A phase-2, placebo-controlled, randomized, observer-blinded study to evaluate the safety, tolerability and immunogenicity of two 3-dose regimens of a Clostridium difficile vaccine in healthy adults 65 to 85 years of age. Poster presented at: ECCMID; April 21-24, 2018; Madrid, Spain.
Month Regimen Geometric Mean Concentration (GMC) Levels (200 μg vs Placebo)

GMC levels - Month Regimen (Toxin A)

GMC levels - Month Regimen (Toxin B)

Month 0, 1, 6 Schedule:

Remich S, et al. A phase-2, placebo-controlled, randomized, observer-blinded study to evaluate the safety, tolerability and immunogenicity of two 3-dose regimens of a Clostridium difficile vaccine in healthy adults 65 to 85 years of age. Poster presented at: ECCMID; April 21-24, 2018; Madrid, Spain.
E-diary Reported Events: Month 0, 1, 6 Regimen
(Follow-up 14 Days After Each Dose)

Remich S, et al. A phase-2, placebo-controlled, randomized, observer-blinded study to evaluate the safety, tolerability and immunogenicity of two 3-dose regimens of a *Clostridium difficile* vaccine in healthy adults 65 to 85 years of age. Poster presented at: ECCMID; April 21-24, 2018; Madrid, Spain.
E-diary Reported Fever: Month 0, 1, 6 Regimen
(Follow-up 14 Days After Each Dose)

Remich S, et al. A phase-2, placebo-controlled, randomized, observer-blinded study to evaluate the safety, tolerability and immunogenicity of two 3-dose regimens of a \textit{Clostridium difficile} vaccine in healthy adults 65 to 85 years of age. Poster presented at: ECCMID; April 21-24, 2018; Madrid, Spain.
E-diary Reported Events: Month 0, 1, 6 Regimen (Follow-up 14 Days After Each Dose)

Diarrhea and vomiting

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>200 μg</th>
<th>Placebo</th>
<th>200 μg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Muscle pain and joint pain

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>200 μg</th>
<th>Placebo</th>
<th>200 μg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle pain</td>
<td></td>
<td></td>
<td>Joint pain</td>
<td></td>
</tr>
<tr>
<td>Joint pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Grade 1 (mild)  Grade 2 (moderate)  Grade 3 (severe)  Grade 4

Remich S, et al. A phase-2, placebo-controlled, randomized, observer-blinded study to evaluate the safety, tolerability and immunogenicity of two 3-dose regimens of a Clostridium difficile vaccine in healthy adults 65 to 85 years of age. Poster presented at: ECCMID; April 21-24, 2018; Madrid, Spain.
Safety Profile: Adverse Events and Serious Adverse Events

Safety profile of 200 μg dose at 0, 1, and 6 months in this phase 2 study is consistent with previous studies.

AE=adverse event; SAE=serious adverse event.

Remich S, et al. A phase-2, placebo-controlled, randomized, observer-blinded study to evaluate the safety, tolerability and immunogenicity of two 3-dose regimens of a Clostridium difficile vaccine in healthy adults 65 to 85 years of age. Poster presented at: ECCMID; April 21-24, 2018; Madrid, Spain.
**Clostridium Difficile Vaccine Efficacy Trial (Clover)**

- **Enrollment**: ~17.5k subjects
  - Subjects meeting all inclusion and no exclusion criteria

- **Vaccination Period**
  - Month 0, 1, 6

- **Follow-up Period**
  - Up to 3 years
  - 3 or more unformed stools (Bristol stool chart types 5-7) within 24 hours
  - Interim analysis: 63 cases
  - Final analysis: 106 cases

- **PPD**
  - Diagnostic Assays
  - Sites: Kentucky, Brussels, Singapore

- **Diagnostic Assays**
  - 382 sites in 23 countries
Two-Step Testing Algorithm
Endorsed by KOLs, ESCMID, ISDA, SHEA, CHMP, and the FDA

≥3 diarrheal episodes in 24 hrs

Stool Collection:
Home, Nursing Home, Clinic / Urgent Care, Hospital

NanoCool Shipper
2-10 °C 96 hrs

PPD Processing Lab
Kentucky
Belgium
Singapore

Central Testing Lab
Pearl River, NY

Stool Sample

PCR
Xpert® C. difficile/Epi

Diagnostic Testing

STEP 1

No Case

Positive Case

Perform CCNA

STEP 2

No Case

Positive Case
Conclusions

• CDI causes **significant disease in adults >50 years of age** in community and hospital settings

• Pfizer’s vaccine was produced using a **novel detoxification process that preserves critical epitopes maximizing production of neutralizing antibodies**

• The vaccine induces polyclonal antibodies that **neutralize diverse toxins** and shows protection in preclinical models

• Vaccine program has progressed through proof of concept to phase 3 demonstrating **robust immune responses with a strong safety profile**

• Status: phase 3 Clover trial is fully enrolled and awaiting case accrual
Acknowledgments

We thank all of the study participants and the investigators for their substantial contributions to the enrollment of subjects and collection of data.

Pfizer Contributors

Chris Webber       Ping Li
Nick Kitchin       Stephen Lockhart
Shon Remich        Bill Gruber
Catia Ferreira     Michael Pride
Jody Lawrence      Kathrin Jansen