Clostridium difficile

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Prepared for the WHO`S Product Development Vaccine Advisory Committee, June 2016
The organism

A small % of strains carry a third toxin – Binary toxin

Mild to severe diarrhoeal disease/other inflammatory complications

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Disease Burden

- Recurrent infection

### Economic burden
- LOS: primary 9.5 days\(^1\)
- recurrent 20 days
- Cost: primary $16,930
- recurrent $36,683
- Drugs: primary $60
- secondary $140

Shah: Journal of hospital infection 2016

### Impact of disease
- US - 500,000 infections*
- 29,000 deaths*
- Increase in 30 day patient mortality

* Lessa N. Eng J Med 2015 372:825-34

### Risk Factors
- Increasing age
- Length of hospital stay
- Antibiotic use
- Co-morbidities
Changing epidemiology

Increased rates of infection in the UK
• About 25% of CDIs in US are due to CD027
Current interventions

• Prudent antibiotic prescribing
  – Avoid 4C antibiotics in vulnerable population
    • Fluoroquinolones
    • Clindamycin
    • Co-amox-clav,
    • 3rd generation cephalosporins
  – Narrow spectrum antibiotics
    • Fidaxomicin

• Enhanced infection control
  – Hand washing/disinfection
  – Environmental decontamination
  – Isolation/cohort nursing

• Faecal transplantation
  – Re-establish microbiome diversity
The unmet need

• No prophylactic treatment available
• Treatments effective
  – Withdrawal can initiate recurrent infection
• Changes in Transmission
  – Increased acquisition in community
    • disease reported in younger population
• Global Surveillance
  – Early warning for emergence of virulent types
Target groups for vaccination

Vaccine Development: Background

- Correlation between toxin neutralising antibody in human serum and disease protection
  - Against toxin A – acute diarrhoea
  - Against toxin B – severe, relapsing disease

- Toxins as vaccines - Complexity and size of protein/difficult to produce

Lyerly 1990 Curr Microbiol 21:29-32
Animal models of disease

- **Syrian Golden Hamster**
  - Model of acute toxin mediated disease
    - Diarrhoea
    - Pathology
    - Fatal
    - Preclinical testing

Presentation to WHO Vaccine Advisory Committee, 8-19th June 2016
Correlates of Protection – Toxin Neutralising Activity (TNA)

Combining anti-serum from vaccinated patients with toxin – capacity to limit toxin mediated damage can be quantified.
Vaccine Candidate Selection criteria

- Strong neutralising activity
- Prevention of fatal disease/symptoms/pathology in hamsters
- Protection against multiple *C. difficile* types including epidemic hypervirulent 027 strains
Vaccine Development: most advanced candidates

**Sanofi Pasteur** – toxoid vaccine (based on toxin A and B)

**Pfizer** – genetically detoxified toxins expressed in non-toxic *C. difficile*

**Valneva/SKB** – Recombinant fragment encode binding domains of both toxins

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# Clinical Data

<table>
<thead>
<tr>
<th>Vaccine type</th>
<th>Age</th>
<th>Dose</th>
<th>+/- Adjuvant</th>
<th>Schedule (days)</th>
<th>Optimal formulation</th>
<th>Readout TNA</th>
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</thead>
<tbody>
<tr>
<td>Sanofi/Pasteur(^1)</td>
<td>40-75</td>
<td>50-100ug</td>
<td>+</td>
<td>0, 7, 30</td>
<td>100ug in Al(OH3)</td>
<td>97% tox A, 64% tox B</td>
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<tr>
<td></td>
<td></td>
<td>50-100ug</td>
<td>-</td>
<td>0, 7, 30, 180</td>
<td>0, 7, 30</td>
<td></td>
</tr>
<tr>
<td>Pfizer(^2)</td>
<td>50-85</td>
<td>50, 100,</td>
<td>+</td>
<td>1, 28, 180</td>
<td>100-200ug No adjuvant</td>
<td>Ave increase 3 fold tox A, 4 fold tox B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200ug</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valneva(^3)</td>
<td>18-65</td>
<td>20, 75, 200ug</td>
<td>+</td>
<td>0, 7, 21</td>
<td>75ug No adjuvant</td>
<td>4 fold in 70% to toxin A and 80% to toxin B</td>
</tr>
<tr>
<td></td>
<td>&gt;65</td>
<td></td>
<td>-</td>
<td>0, 7, 21, 56</td>
<td>1, 7, 21, 56</td>
<td></td>
</tr>
</tbody>
</table>

1. **Reported Phase II** De Bryn 2016 Vaccine 34:2170-78, initiated phase III
2. **Reported Phase I** Sheldon 2016 Vaccine 34:2082-91, completed phase II
3. **Reported Phase I** Bezay 2016 34:2585-92, completed phase II
Most promising approaches

• All candidates successful in phase II studies
  – Healthy adults (40-85)
  – Safe/well tolerated
  – Immunogenic / Neutralising activity

• Observations
  – Slightly less efficacious elderly (65+) versus 40-65 group
  – Less requirement for adjuvant (Pfizer/Valneva vaccines)
  – No and timing of vaccinations

• Correlation of TNA to Protection?

• Additional/ alternative candidates
  • Inclusion of Binary toxins
  • Inclusion of additional toxin B neutralising epitopes

Leuzzi 2013 Infect Immun 81:2851-60
Manard-Smith 2014 Vaccine 32:700-5

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Weakness in current approach

- Vaccines limit toxin mediated symptoms
- No impact on transmission

- Vaccinated individuals - remain a silent source of infection?
- Target antigens reduce colonisation and/or sporulation

- Possible candidate antigens
  - Cwp84, 66, fli, slpA, spore proteins
Assessment

• **Current Vaccines in development**
  – Potential to be effective against symptomatic primary and recurrent CDI
    • Require confirmation efficacious in vulnerable populations

• **Further optimization work required**
  – Inclusion of
    • additional toxin neutralising epitopes and antigens to prevent transmission
      – Spore proteins, S layer, cwp84, flagella

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Potential Role for WHO

• **Improve**
  – Awareness and diagnosis of CDI worldwide

• **Encourage**
  – Adoption of National Surveillance within countries
  – Early warning of emergence of virulent types

• **Reduce incidence**
  – Set policy/guidelines to reduction/restriction of antibiotic use
    • Especially fluoroquinolone use – limit spread of epidemic 027 strains

• **Target vaccination**
  – to appropriate/vulnerable populations

• **Encourage**
  – Further development and optimisation to ensure vaccines are both easy to manufacture and efficacious
Vaccination – not the only approach?

• Passive Immunisation
  • **Merek** – iv infusion as adjunct to standard antibiotic treatment
  • Bezlotoxumab in phase III studies (toxin B)
    • Actoxumab (toxin A) - ? Prophylactic?

• Microbiome Replacement
  • **Rebiotix** - Standardised microbiota suspension/ Restoration therapy for microbiome
  • Future
    • Combination of defined bacteria that limit spore germination

• Antibiotic Binding Resin
  • **DaVolterra** – charcoal based resin
    • Bind excess antibiotics in gut
    • Minimal changes to microbiome
THANK YOU