C. difficile infection

- Most common cause of infectious diarrhoea in hospital patients
- 2 major virulence factors:
  - toxin A (an enterotoxin)
  - toxin B (a cytotoxin)
- 3rd “binary” toxin

Bartlett JG Clin Infect Dis 1994,18:S265-72
Toxin A & toxin B

- Large structurally and functionally related proteins
- Genes are contained on a 19.6-kB Pathogenicity Locus (PaLoc) which is absent in non-toxigenic strains
- Majority of pathogenic strains produce both toxins which affect actin cytoskeleton
- Polymorphisms in the PaLoc can affect toxin production - toxin A-negative, toxin B-positive strains

Toxin phenotypes:
- $A^+B^+$
- $A^-B^+$
- $A^-B^-$

Diagram:
- $tcdR$ (positive regulator)
- $tcdB$ (toxin B)
- $tcdE$ (holin-like protein)
- $tcdA$ (toxin A)
- $tcdC$ (negative regulator)
Binary toxin

- Additional toxin produced by 2-5% of isolates
- Consists of two component proteins, the genes for which are contained within the CDT locus on the chromosome
- Actin-specific ADP-ribosyltransferase
- Unknown significance in disease, but associated with increased severity of diarrhoea
Risk factors for getting *C. difficile*?

- Exposure to the organism – how much?
- Exposure to antibiotics – clindamycin, then cephalosporins, now fluoroquinolones
- Maybe others now?
A Predominantly Clonal Multi-Institutional Outbreak of *Clostridium difficile*–Associated Diarrhea with High Morbidity and Mortality

Vivian G. Loo, M.D., Louise Poirier, M.D., Mark A. Miller, M.D., Matthew Oughton, M.D., Michael D. Libman, M.D., Sophie Michaud, M.D., M.P.H., Anne-Marie Bourgault, M.D., Tuyen Nguyen, M.D., Charles Frenette, M.D., Mirabelle Kelly, M.D., Anne Vibien, M.D., Paul Brassard, M.D., Susan Fenn, M.L.T., Ken Dewar, Ph.D., Thomas J. Hudson, M.D., Ruth Horn, M.D., Pierre René, M.D., Yury Monczak, Ph.D., and André Dascal, M.D.
Investigation into outbreaks of *Clostridium difficile* at Stoke Mandeville Hospital, Buckinghamshire Hospitals NHS Trust

July 2006
Superbug kills war hero who survived three years as a PoW

By Luke Salkeld

THE family of a distinguished war veteran have criticised the hospital where he was infected by a killer bug.

Major Sam Weller – who survived three years as a prisoner of war – died after catching Clostridium difficile following an operation on his hip. Yesterday, his relatives said he had been let down by the country he fought for.

Major Weller, 88, had surgery at Gloucestershire Royal Hospital but he developed an infection and was given a course of antibiotics.

Weeks later he died and an inquest was told the medicine had left him more vulnerable to catching the superbug.

Yesterday, his family criticised the hospital treatment he received and standards of care.

Almost 56,000 vulnerable and elderly patients have been infected with C. Diff in the past year.

Between January and March alone, 15,992 caught the bug – an astonishing 22 per cent rise on the previous three months.

C. Diff, which is spread by dirty hands and bedding, is a bigger killer than MRSA. It claimed 2,247 lives in 2005 – a 69 per cent rise on the previous year.

It exists naturally in the stomachs of many healthy adults, where it is kept under control by ‘friendly’ bacteria.

Problems start if the balance of bacteria is disturbed, perhaps as a result of taking antibiotics for another infection.

Once the ‘friendly’ bacteria are killed off, the C. Diff is able to multiply and produce the toxins which cause diarrhoea and, in the worst cases, a fatal infection of the abdomen.

Fearless officer: Major Sam Weller, left, who was decorated for his bravery, is pictured with his brother Tony in 1947.
CDI in Australia

- Not a notifiable infection

- But mandatory reporting by hospitals since 2010

- Reporting of “hospital identified” cases of CDI
Aggregate *Clostridium difficile* Infection Rates

Western Australia

![Graph](image-url)
Reasons for increase

- Changes in test numbers
  - Greater awareness
  - Some evidence of this - 25%
- Changes in testing methods
  - Yes – when and what impact?
- If a real increase then why?
  - Healthcare associated vs community-associated
  - Changes in risk factors???????
Community acquired CDI

☐ This is not new!
☐ Very much under-diagnosed for years
☐ *C. difficile* is ubiquitous – but low numbers
☐ Many sources in the community
☐ All animals get colonised at birth incl. humans
☐ But – generally requires exposure to an infectious dose **AND** prior gut insult
☐ Risk factors need further investigation
CDI CASES IDENTIFIED AT METRO NON-TERTIARY HOSPITALS 2010-2011

45% CAI
25% in tertiary hospitals
CA-C DI CASES - MNT HOSPITALS - PATIENT DEMOGRAPHICS

AGE

NUMBER OF CASES

0-9 10-19 20-29 30-39 40-49 50-59 60-69 70-79 80+

80+
C. difficile PCR ribotype 244

- More severe disease – attributable mortality 30% (Dr Rhonda Stuart)
- Currently community acquired
- Produces more toxins A and B
- Produces binary toxin
- Fluoroquinolone susceptible
- Sept-Oct 2010 ACSQHC snapshot – one isolate
- Was 3\textsuperscript{rd} most common ribotype in Australia \(~5\%\)
Early this century outbreaks of CDI in 5d old piglets in USA - high mortality (16%)

Since 2000, *C. difficile* the major & most common cause of enteritis in neonatal piglets in USA

Economic losses

Pig ribotype 078

078 now infecting people in Europe and USA, 3rd most common

? Food source or environment
**Methods** We set up a network of 106 laboratories in 34 European countries.

### Microbiological characteristics

<table>
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<th>Most frequent PCR-ribotypes of toxigenic isolates</th>
<th>( \text{Number of isolates} )</th>
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<td>014/020</td>
<td>( 61/389 ) (16%)</td>
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<td>001</td>
<td>( 37/389 ) (10%)</td>
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<td>( 14/389 ) (4%)</td>
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Total 209

Prevalence in adult cattle: 2%, prevalence in calves <7 days old 60%
Relative evolutionary relatedness of five main subgroups and demonstration of microdiversity of subgroups.


Branch colouring: black = clade 1, red = clade 2 (inc ST-1/RT027), blue = clade 3 (inc ST-22/RT023), orange = clade 4 (inc ST-37/RT017), green = clade 5 (inc ST-11/RT078).
Contaminated vegetables


- MUSHROOMS!
1a: J01: AUS vs NLD

Generic prescribing indicators

DID/1000/day

01 Jan 00 01 Jan 02 01 Jan 04 01 Jan 06 01 Jan 08 01 Jan 10
dt

DUSC data: July 2000 - June 2010, GIP data January - December 2000-2010

Courtesy of John Turnidge
PathWest QEII Influenza percentage positive 2009 - 2012

Box shows when onions/garlic are imported from the USA/Mexico
To summarise the issues

- Significant new human health problem in Australia – community acquired CDI
- Need to find the source/reservoir
- Need to prevent establishment of RT 244/251 in hospitals
- Now a major animal health problem (pigs/horses)
- Gross contamination of the environment OUTSIDE hospitals
- Probable contamination of food
- CDI is a zoonosis
- Will require a One Health approach to resolve
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