Clostridium difficile infection: the Australian experience

Tom Riley

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Microbiology & Immunology, The University of Western Australia, Nedlands, WA, Australia.
“serious colitis” following administration of clindamycin is in the range of one in 50,000 to one in 100,000. This information is in striking contrast with a prospective study\(^7\) of 200 patients in hospitals who were given clindamycin for various reasons. In that study, diarrhea (21 percent) and pseudomembranous colitis (10 percent) were frequently found. Since all symptoms disappeared on
The Association of Viral Activation with Penicillin Toxicity in Guinea Pigs and Hamsters

ROBERT H. GREEN

Departments of Pathology and Internal Medicine, Yale University School of Medicine, and the West Haven Veterans Administration Hospital, New Haven, Connecticut 06510
CLOSTRIDIUM DIFFICILE: ISOLATION AND CHARACTERISTICS

S. HAFIZ* AND THE LATE C. L. OAKLEY

Department of Microbiology, Medical School, University of Leeds, LS2 9NL
**Historical background**

- *Clostridium difficile* – an anaerobic Gram +ve bacillus
- Specific anti-anaerobe drugs developed in 70s, e.g. clindamycin
- Clindamycin-associated diarrhoea became a real problem in some hospitals in the USA
- Outbreaks of pseudomembranous colitis
- Cause elucidated in 1978
- Largely ignored until 2000s
- Bit of diarrhoea in the elderly
- Not too many people died!
**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

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

<table>
<thead>
<tr>
<th>tcdR (positive regulator)</th>
<th>tcdB (toxin B)</th>
<th>tcdE (holin-like protein)</th>
<th>tcdA (toxin A)</th>
<th>tcdC (negative regulator)</th>
</tr>
</thead>
</table>
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

**BINDING COMPONENT**

- **cdtB**

**ENZYMATIC COMPONENT**

- **cdtA**
Cytopathic effects

**Cellular Morphology**
- Cell-rounding
- Detachment from extracellular matrix

**Cellular Processes**
- Activation of caspases → apoptosis
- Decrease in integrity of tight-cell junctions
- Inflammatory response
  - Release of cytokines & chemokines
  - Production of reactive oxygen intermediates

Infect Immun 2001; 69:5487-93
Histological effects

- Massive inflammatory response
- Recruitment of polymorphonuclear neutrophils to area
- Increase in epithelial permeability

Risk factors for getting *C. difficile*?

- Exposure to the organism – how much?
- Exposure to antibiotics – clindamycin, then cephalosporins, now fluoroquinolones
- Maybe others now?
Effect of antibiotics on normal flora

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

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—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 "2,247"

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 diarrhea 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.
C. difficile PCR ribotype 027

- More severe disease
- Produces more toxins A and B
- Produces binary toxin
- Fluoroquinolone resistant
- Epidemic spread across North America and UK/Europe from early 2000s
- Numbers dropping in UK/Europe
- Still major issue in USA
- Three clusters in Australia since 2009
England distribution of PCR ribotypes 2005/6 to 2007/8 as percentages

2005-6 (n=881)

2007-8* (n=677)

Study done 04/05.

Similar overall rate as earlier study but attributable mortality increased about 4 fold.

Rates in England 2008-11

Trust apportioned reports (per 100,000 bed-days)
Comparison of the Burdens of Hospital-Onset, Healthcare Facility–Associated \textit{Clostridium difficile} Infection and of Healthcare-Associated Infection due to Methicillin-Resistant \textit{Staphylococcus aureus} in Community Hospitals

Becky A. Miller, MD;\textsuperscript{1} Luke F. Chen, MD, MPH;\textsuperscript{1} Daniel J. Sexton, MD;\textsuperscript{1} Deverick J. Anderson, MD, MPH\textsuperscript{1}

We sought to determine the burden of nosocomial \textit{Clostridium difficile} infection in comparison to other healthcare-associated infections (HAIs) in community hospitals participating in an infection control network. Our data suggest that \textit{C. difficile} has replaced MRSA as the most common etiology of HAI in community hospitals in the southeastern United States.

CDI in Australia

- Not a notifiable infection

- But mandatory reporting by hospitals since 2010

- Reporting of “hospital identified” cases of CDI
Fig. 2 Incidence of *Clostridium difficile*-associated diarrhoea at SCGH 1983-92

Cephalosporin use SCGH, 1983-92

Growth (g x 1000) by year:
- 1983: Low
- 1984: Low
- 1985: Moderate
- 1986: Moderate
- 1987: High
- 1988: High
- 1989: Highest
- 1990: Highest
- 1991: Highest
- 1992: Highest
C. difficile: monthly episodes 1993-2000

[Graph showing monthly episodes of C. difficile from 1993 to 2000, with lines indicating CDAD study hospital, CDAD control hospital, and 3GC use study hospital.]
<table>
<thead>
<tr>
<th>Ribotype</th>
<th>State/Territory*</th>
<th>Australia</th>
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<tr>
<td></td>
<td>NSW</td>
<td>Qld</td>
</tr>
<tr>
<td>014/020</td>
<td>39 (25)</td>
<td>13 (17)</td>
</tr>
<tr>
<td>002</td>
<td>24 (16)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>112</td>
<td>5 (3)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>010</td>
<td>6 (4)</td>
<td>-</td>
</tr>
<tr>
<td>027</td>
<td>3 (2)</td>
<td>-</td>
</tr>
<tr>
<td>001</td>
<td>-</td>
<td>1 (1)</td>
</tr>
<tr>
<td>012</td>
<td>-</td>
<td>1 (1)</td>
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<tr>
<td>078</td>
<td>2 (1)</td>
<td>-</td>
</tr>
<tr>
<td>005</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>026</td>
<td>1 (&lt;1)</td>
<td>-</td>
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<tr>
<td>Other</td>
<td>74 (48)</td>
<td>50 (66)</td>
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<tr>
<td>UTR#</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Totals</td>
<td>154 (47)</td>
<td>76 (23)</td>
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</tbody>
</table>

ACSQH snap-shot October-November 2010
Reasons for increase

- Changes in test numbers
  - Some evidence of this
  - Greater awareness

- Changes in testing methods
  - Yes – when and what impact?

- If a real increase then why?
  - Healthcare associated vs community-associated
  - Changes in risk factors???????
The Epidemiology of Community-Acquired *Clostridium difficile* Infection: A Population-Based Study

Sahil Khanna, MBBS¹, Darrell S. Pardi, MD, MS, FACG¹, Scott L. Aronson, MD¹,², Patricia P. Kammer, CCRP¹, Robert Orenstein, DO³, Jennifer L. St Sauver, PhD⁴, W. Scott Harmsen, MS⁵ and Alan R. Zinsmeister, PhD⁵

Study highlights

What is current knowledge?

- *Clostridium difficile infection* is increasing worldwide with hospitalization and antibiotic exposure as the most common risk factors.
- The epidemiology and characteristics of community-acquired *Clostridium difficile* infection are not well defined.

What is new here?

- A major proportion of *Clostridium difficile* infection patients is community-acquired.
- These patients are younger, often lack traditional risk factors, and have less severe disease than patients with hospital-acquired infection.

Community acquired CDI

- This is not new!
- Very much under-diagnosed for years
- *C. difficile* is ubiquitous
- 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
Contact with infants <2 years old significantly associated with CDI

Figure 1. Comparative antibiotic usage in randomly selected community-associated CDI cases and controls. *P < 0.05; **P < 0.01; ***P < 0.001.
CDI CASES IDENTIFIED AT METRO NON-TERTIARY HOSPITALS 2010-2011

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

NUMBER OF CASES

AGE

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

0 | 0 | 10 | 3 | 3 | 6 | 11 | 7 | 13
Clostridium difficile infection rates - South Australia

- Total hospital identified
- Onset >2 days post admission

Rate per 10,000 patient days

<table>
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<tr>
<th>Quarter</th>
<th>2009/10</th>
<th>2010/11</th>
<th>2011/12</th>
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<tr>
<td>Q4</td>
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</table>
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
- Putative 027 with GeneXpert
- Sept-Oct 2010 ACSQHC snapshot – one isolate
- Now 3rd most common ribotype in Australia ~5%
Case control study – Dr Rhonda Stuart

- 10 cases – July - December 2011
  - Mean age 74 years (range 38 – 92)
  - 80% > 65 years
  - Comorbidities
    - Diabetes 30%
    - Malignancy 20%
    - IHD 50%
    - No comorbidities 10%
  - Onset
    - Community onset = 80%
    - Community acquired = 40%

- 20 Controls
  - Matched to site and time (within 4 weeks) of isolate
<table>
<thead>
<tr>
<th></th>
<th>MDU - 064</th>
<th>Non- 064</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td><strong>Disease Severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Creat &gt; 200 or &gt; 50% baseline</td>
<td>6/10 (60)</td>
<td>1/20 (5)</td>
<td><strong>0.002</strong></td>
<td>28 (2 – 306)</td>
</tr>
<tr>
<td>Albumin &lt; 25</td>
<td>8/10 (80)</td>
<td>3/17 (18)</td>
<td><strong>0.003</strong></td>
<td>18 (2 – 136)</td>
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<tr>
<td>Fever &gt; 38</td>
<td>3/10 (30)</td>
<td>5/20 (25)</td>
<td>NS</td>
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<tr>
<td>WCC &gt; 15</td>
<td>4/10 (40)</td>
<td>4/20 (20)</td>
<td>NS</td>
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<tr>
<td><strong>Total June – Dec 11</strong></td>
<td>10</td>
<td>246</td>
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<tr>
<td><strong>In Hospital Deaths</strong></td>
<td>2</td>
<td>2</td>
<td><strong>0.008</strong></td>
<td>30 (4 – 244)</td>
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<td><strong>Severe disease (ESCMID)</strong></td>
<td>10/10 (100)</td>
<td>14/20 (70)</td>
<td>0.074</td>
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<tr>
<td><strong>Severe disease (Zar)</strong></td>
<td>8/10 (80)</td>
<td>7/20 (35)</td>
<td><strong>0.006</strong></td>
<td>7 (1 – 84)</td>
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<tr>
<td><strong>Treatment</strong></td>
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<tr>
<td>Vancomycin</td>
<td>8/10 (80)</td>
<td>2/20 (10)</td>
<td>&lt; <strong>0.001</strong></td>
<td>36 (3 – 495)</td>
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<tr>
<td><strong>Outcome</strong></td>
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<tr>
<td>Response</td>
<td>7/10 (70)</td>
<td>18/20 (90)</td>
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<tr>
<td>Death within 30 days</td>
<td>4/10 (40)</td>
<td>0/20 (0)</td>
<td><strong>0.007</strong></td>
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<tr>
<td>Attributable mortality</td>
<td>3/10 (30)</td>
<td>0/13 (0)</td>
<td><strong>0.029</strong></td>
<td></td>
</tr>
</tbody>
</table>
Is *Clostridium difficile* a threat to Australia’s biosecurity?

Thomas V Riley

Australia can benefit from lessons learned in the epidemic of *C. difficile* infection in Europe and North America. Every effort should be made to stop epidemic *C. difficile* from becoming established in our production animals. Unfortunately, the mere perception of *C. difficile* infection as a foodborne disease will damage the industry. However, if cephalosporin use is driving *C. difficile* infection in animals overseas, then additional efforts to target cephalosporin use in veterinary medicine may be needed in Australia.
<table>
<thead>
<tr>
<th>Meat product</th>
<th>No. samples cultured</th>
<th>Total no. (%) positive</th>
<th>Ribotype</th>
<th>Toxinotype</th>
<th>ΔtdcC, bp†</th>
<th>PFGE type</th>
<th>No. (%) pos</th>
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<tr>
<td>Ground beef (uncooked)</td>
<td>26</td>
<td>13 (50)</td>
<td>027</td>
<td>III</td>
<td>18</td>
<td>NAP1</td>
<td>1 (3.8)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>078</td>
<td>V</td>
<td>39</td>
<td>NAP1-related</td>
<td>2 (7.7)</td>
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<td>078</td>
<td>V</td>
<td>39</td>
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<td>III</td>
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*All samples were positive for cdhB, which encodes the binding component of binary toxin. PFGE, pulsed-field gel electrophoresis.
†Deletions in tdcC regulatory gene.
Molecular and epidemiologic information of selected study *C. difficile* isolates.

<table>
<thead>
<tr>
<th>Cluster</th>
<th>No.</th>
<th>Source</th>
<th>Location</th>
<th>CDR4</th>
<th>CDR5</th>
<th>CDR6</th>
<th>CDR9</th>
<th>CDR48</th>
<th>CDR49</th>
<th>CDR60</th>
<th>tcdC</th>
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<td>1</td>
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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
**Clostridium difficile** infection in Europe: a hospital-based survey

Martijn P Bauer, Daan W Notermans, Birgit H B van Bentheim, Jon S Brazier, Mark H Wilcox, Maja Rupnik, Dominique L Monnet, Jaap T van Dissel, Ed J Kuijper, for the ECDIS Study Group*

Methods We set up a network of 106 laboratories in 34 European countries.

<table>
<thead>
<tr>
<th>Microbiological characteristics</th>
<th>Most frequent PCR-ribotypes of toxigenic isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>014/020                         61/389 (16%)</td>
</tr>
<tr>
<td></td>
<td>001                             37/389 (10%)</td>
</tr>
<tr>
<td></td>
<td>078                             31/389 (8%)</td>
</tr>
<tr>
<td></td>
<td>018                             23/389 (6%)</td>
</tr>
<tr>
<td></td>
<td>106                             20/389 (5%)</td>
</tr>
<tr>
<td></td>
<td>027                             19/389 (5%)</td>
</tr>
<tr>
<td></td>
<td>002                             18/389 (5%)</td>
</tr>
<tr>
<td></td>
<td>012                             17/389 (4%)</td>
</tr>
<tr>
<td></td>
<td>017                             14/389 (4%)</td>
</tr>
</tbody>
</table>
Rates of detection of *C. difficile* in Australian sheep and lambs

<table>
<thead>
<tr>
<th>Faecal samples</th>
<th>Sheep</th>
<th>No. positive</th>
<th>(%) positive</th>
<th>Lambs</th>
<th>No. positive</th>
<th>(%) positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. tested</td>
<td></td>
<td></td>
<td>No. tested</td>
<td></td>
</tr>
<tr>
<td>Batch 1 (n=50)</td>
<td>1/27</td>
<td></td>
<td>3.7%</td>
<td>3/23</td>
<td></td>
<td>13%</td>
</tr>
<tr>
<td>Batch 2 (n=100)</td>
<td>0/47</td>
<td></td>
<td></td>
<td>1/53</td>
<td></td>
<td>1.8%</td>
</tr>
<tr>
<td>Batch 3 (n=50)</td>
<td>0/24</td>
<td></td>
<td></td>
<td>0/26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Batch 4 (n=100)</td>
<td>0/58</td>
<td></td>
<td></td>
<td>2/42</td>
<td></td>
<td>4.2%</td>
</tr>
<tr>
<td>Total (n=300)</td>
<td>1/156</td>
<td></td>
<td>0.6%</td>
<td>6/144*</td>
<td></td>
<td>4.2%</td>
</tr>
</tbody>
</table>

*p=0.04*
C. difficile in chickens

- No C. difficile in chickens – relatively small sample (~60)
  - 4-5 day old chicks
  - 4 weeks old
  - At slaughter – 8 weeks
C. difficile in cattle in Australia

- 2008/9: adult cattle, 151 carcass washings and 151 gut contents from WA
  - No C. difficile
- 2009/10: 280 faecal samples from adults E Australia
  - 5 positives (1.8%)
- 2012: 360 <7 day old veal calves, several abattoirs in Vic and Queensland (4% in 2-6 month old calves)
  - 56% positive
<table>
<thead>
<tr>
<th>PCR Ribotype</th>
<th>tcdA</th>
<th>tcdB</th>
<th>cdtA/ctdB</th>
<th>n (%)</th>
<th>Specimen</th>
<th>Age distribution (n)</th>
<th>Abattoir distribution (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT027*</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>1 (0.5)</td>
<td>Faeces</td>
<td>&lt;7 day old calf (1)</td>
<td>V5‡ (1)</td>
</tr>
<tr>
<td>QX022</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>1 (0.5)</td>
<td>Faeces</td>
<td>&lt;7 day old calf (1)</td>
<td></td>
</tr>
<tr>
<td>RT103</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>3 (1.4)</td>
<td>Faeces</td>
<td>&lt;7 day old calf (3)</td>
<td>V6‡ (3)</td>
</tr>
<tr>
<td>QX058</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>2 (1.0)</td>
<td>Faeces</td>
<td>&lt;7 day old calf (2)</td>
<td>V6‡ (2)</td>
</tr>
<tr>
<td>RT033*</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>16 (7.7)</td>
<td>Faeces</td>
<td>&lt;7 day old calf (15)</td>
<td>Q4 ‡ (1), V5 ‡ (14), V6α‡ (1)</td>
</tr>
<tr>
<td>RT087</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>7 (3.3)</td>
<td>Faeces</td>
<td>&lt;7 day old calf (7)</td>
<td>V5‡ (1), V6‡ (6)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>209</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Contaminated vegetables


- MUSHROOMS!
Our 1st theory

- Contaminated Australian meat or vegetables
- Driven by flu season
- But can’t find RT 244 in any animals!
- Doesn’t account for all the increase
- Briony Elliott thinks RT 244 comes from North America
Quarterly counts of *C. difficile*: comparison of mandatory and voluntary quarterly reporting

Voluntary (2-64 years)
Mandatory (2-64 years)
Voluntary (65 years and over)
Mandatory (65 years and over)

Please note that the voluntary *C. difficile* 2009 data at time of extraction may be under completed.
C. difficile voluntary data includes toxin negative reports.
Extraction date: 26.01.2009
1a: J01: AUS vs NLD
Generic prescribing indicators

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

All antibacterials

Courtesy of John Turnidge
CDI CASES 2010 - 2012

Graph showing the number of CDI cases from January 2010 to December 2012.
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).
Ribotype 251

- 2nd major new RT emerged in Australia
- Similar to RT 244
- Community acquired, severe disease
- Binary toxin positive
- Groups with 027 by PFGE
- Cluster found in USA along with a cluster of 244
Our 2\textsuperscript{nd} theory

- Contaminated food imported from North America
- 96% of Australian food local
- Possibly onions
- Exactly the same problem occurring in NZ with the same food importation patterns as Australia
- But probably endemic local food-borne disease also
PathWest QEII Influenza percentage positive 2009 - 2012

Box shows when onions/garlic are imported from the USA/Mexico
Animal/human connections

- Ribotype 126
- Ribotype 127
- Ribotype 033
- Ribotype 237 - pigs
- Ribotype ??? – horses
- Many other new ribotypes from animals: usually binary toxin positive, that are starting to appear in humans
Emerging infectious diseases

But what is driving the emergence of *C. difficile* in animals?
### Table 1. Production of food animals (including export of live animals) and the production of meat and milk, Denmark

<table>
<thead>
<tr>
<th>Year</th>
<th>Broilers</th>
<th>Turkeys a)</th>
<th>Cattle (slaughtered)</th>
<th>Dairy cows</th>
<th>Pigs</th>
<th>Farmed fish</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,000 heads</td>
<td>mill. kg</td>
<td>1,000 heads</td>
<td>mill. kg</td>
<td>1,000 heads</td>
<td>mill. kg</td>
</tr>
<tr>
<td>1990</td>
<td>94,560</td>
<td>116</td>
<td>571</td>
<td>2.5</td>
<td>789</td>
<td>219</td>
</tr>
<tr>
<td>1992</td>
<td>107,188</td>
<td>137</td>
<td>761</td>
<td>5.4</td>
<td>862</td>
<td>236</td>
</tr>
<tr>
<td>1994</td>
<td>116,036</td>
<td>152</td>
<td>1,091</td>
<td>8.6</td>
<td>813</td>
<td>210</td>
</tr>
<tr>
<td>1996</td>
<td>107,895</td>
<td>149</td>
<td>961</td>
<td>9.3</td>
<td>789</td>
<td>198</td>
</tr>
<tr>
<td>1998</td>
<td>126,063</td>
<td>168</td>
<td>1,124</td>
<td>11.6</td>
<td>732</td>
<td>179</td>
</tr>
<tr>
<td>2000</td>
<td>133,987</td>
<td>181</td>
<td>1,042</td>
<td>10.3</td>
<td>691</td>
<td>171</td>
</tr>
<tr>
<td>2001</td>
<td>136,603</td>
<td>192</td>
<td>1,038</td>
<td>12.6</td>
<td>653</td>
<td>169</td>
</tr>
<tr>
<td>2002</td>
<td>136,350</td>
<td>190</td>
<td>965</td>
<td>11.5</td>
<td>668</td>
<td>169</td>
</tr>
<tr>
<td>2003</td>
<td>129,861</td>
<td>181</td>
<td>510</td>
<td>7.4</td>
<td>625</td>
<td>161</td>
</tr>
<tr>
<td>2004</td>
<td>130,674</td>
<td>181</td>
<td>55</td>
<td>1.0</td>
<td>632</td>
<td>165</td>
</tr>
<tr>
<td>2005</td>
<td>120,498</td>
<td>180</td>
<td>158</td>
<td>0.5</td>
<td>549</td>
<td>145</td>
</tr>
<tr>
<td>2006</td>
<td>105,888</td>
<td>163</td>
<td>32</td>
<td>0.1</td>
<td>509</td>
<td>140</td>
</tr>
</tbody>
</table>

Data from Statistics Denmark (www.dst.dk) and The Danish Directorate for Fisheries
a) From 2002, the export of live turkeys for slaughter increased. By 2004, 95% of all turkeys raised in Denmark were slaughtered abroad. For turkeys, data on export of live animals is not included in the table.

Approx. 50% increase in numbers
### Table 4. Trends in the estimated total consumption (kg active compound) of prescribed antimicrobials for production animals, Denmark

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>QJ01AA</td>
<td>Tetracyclines</td>
<td>9,300</td>
<td>22,000</td>
<td>36,500</td>
<td>12,900</td>
<td>12,100</td>
<td>24,000</td>
<td>28,500</td>
<td>24,500</td>
<td>27,300</td>
<td>29,500</td>
<td>30,050</td>
<td>32,650</td>
</tr>
<tr>
<td>QJ01CE</td>
<td>Penicillins, β-lactamase sens.</td>
<td>5,000</td>
<td>6,700</td>
<td>9,400</td>
<td>7,200</td>
<td>14,300</td>
<td>15,100</td>
<td>16,400</td>
<td>17,400</td>
<td>19,000</td>
<td>20,900</td>
<td>22,250</td>
<td>22,600</td>
</tr>
<tr>
<td>QJ01C/QJ01DA</td>
<td>Other penicillins, cephalosporins</td>
<td>1,200</td>
<td>2,500</td>
<td>4,400</td>
<td>5,800</td>
<td>6,700</td>
<td>7,300</td>
<td>8,800</td>
<td>9,900</td>
<td>11,100</td>
<td>12,900</td>
<td>12,300</td>
<td>11,550</td>
</tr>
<tr>
<td>QJ01EW</td>
<td>Sulfonamides + trimethoprim</td>
<td>3,800</td>
<td>7,900</td>
<td>9,500</td>
<td>4,800</td>
<td>7,700</td>
<td>7,000</td>
<td>9,200</td>
<td>10,600</td>
<td>10,600</td>
<td>11,500</td>
<td>12,200</td>
<td>13,800</td>
</tr>
<tr>
<td>QJ01EQ</td>
<td>Sulfonamides</td>
<td>8,700</td>
<td>5,900</td>
<td>5,600</td>
<td>2,100</td>
<td>1,000</td>
<td>1,000</td>
<td>950</td>
<td>900</td>
<td>850</td>
<td>850</td>
<td>750</td>
<td>750</td>
</tr>
<tr>
<td>QJ01F/QJ01XX</td>
<td>Macrolides, lincosamides, pleuromutilins</td>
<td>10,900</td>
<td>12,900</td>
<td>11,400</td>
<td>7,600</td>
<td>7,100</td>
<td>15,600</td>
<td>18,400</td>
<td>19,200</td>
<td>20,700</td>
<td>24,200</td>
<td>22,350</td>
<td>22,050</td>
</tr>
<tr>
<td>QJ01G/QA07AA</td>
<td>Aminoglycosides</td>
<td>7,700</td>
<td>8,500</td>
<td>8,600</td>
<td>7,100</td>
<td>7,800</td>
<td>10,400</td>
<td>11,600</td>
<td>11,700</td>
<td>11,700</td>
<td>11,600</td>
<td>10,800</td>
<td>10,500</td>
</tr>
<tr>
<td>Others c)</td>
<td></td>
<td>6,700</td>
<td>6,800</td>
<td>4,400</td>
<td>600</td>
<td>650</td>
<td>300</td>
<td>900</td>
<td>1,600</td>
<td>1,500</td>
<td>1,000</td>
<td>1,950</td>
<td>1,250</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>53,400</td>
<td>73,200</td>
<td>89,900</td>
<td>48,000</td>
<td>57,300</td>
<td>80,700</td>
<td>94,700</td>
<td>95,900</td>
<td>102,500</td>
<td>112,500</td>
<td>112,650</td>
<td>115,150</td>
</tr>
</tbody>
</table>


a) Kg active compound rounded to nearest 50 or 100

b) Only the major contributing ATC$_{vet}$ groups are mentioned

c) Consumption in aquaculture was not included before 2001

---

Approx. 400% increase in penicillins, β-lactamase sens.
Other penicillins, cephalosporins 1000% increase
Figure 4: Consumption of cephalosporins in pigs given as kg active compound from 2001 to 2006, Denmark.
“This change in prescription habits suggests that the consumption of cephalosporins in pigs is changing from occasional prescription to more systematic prescription in herds producing 14-29% of the weaned pigs.”

Figure 7. Use of 3rd and 4th generation cephalosporins in pigs and cattle, 2001-2007, Denmark
To summarise the issues

- Major new human health problem in Australia (and NZ) – community CDI
- Need to find the source/reservoir
- Need to prevent establishment of RTs 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
Global Alert & Response: the need for global surveillance

Globalization of pathogens
- Global travel: people, animals, vectors
- Global trade: animal and their products, vaccines, medical products, etc.

Amplification of pathogens
- Successful H2H transmission,
- Nosocomial transmission in health care centers
- New introduction from animals
- Urbanization
- Agricultural Intensification
- Technology And Industry

Emergence of pathogens
- Encroachment introduction, “Spill over”
- At-risk behaviour
- Human encroachment, Ex situ contact, Ecological manipulation
- Translocation of wildlife

Slide courtesy of Dr Pierre Formenty, WHO
CDI control strategies

- Prevent ingestion of *C. difficile* spores from environment
  - Cleaning hospitals
  - Vaccinating animals

- Prevent development of CDI if spores are ingested
  - Antibiotic stewardship
Acknowledgments

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