

Epidemic *Clostridium difficile*

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We need to know if and when this organism arrives in Australia

There is world-wide concern about a new infectious diseases threat following the recent emergence, in Canada,¹ the United States,² and now Europe,³ of a highly virulent strain of *Clostridium difficile* (called PCR ribotype 027/NAP1 in Europe and NAP1 in the US). Rates of detection of *C. difficile* have risen dramatically: at the Centre Hospitalier Universitaire de Sherbrooke in Quebec Province (population, 7.5 million in 2003) in Canada, the incidence among patients aged ≥ 65 years increased from 102 per 100 000 population in 1991 to 867 per 100 000 in 2003.⁴ *C. difficile* disease has been more severe, with the proportion of complicated cases in Sherbrooke increasing from 7.1% (12/169) in 1991–92 to 18.2% (71/390) in 2003,⁴ suggesting a more virulent strain of the organism is emerging. The Quebec Health Ministry reported a total of 7004 cases of *C. difficile* infection between 1 April 2003 and 31 March 2004, with 1270 deaths (a crude mortality rate of 18%).⁵ Loo and colleagues¹ reported an attributable mortality of greater than 10% in those aged over 60 years — a remarkably high figure.

C. difficile is the most commonly diagnosed cause of infectious hospital-acquired diarrhoea in developed countries. Most patients with *C. difficile*-associated diarrhoea have been exposed to antimicrobials that reduce “colonisation resistance” of the large intestine, allowing subsequent infection with *C. difficile*. Acquisition of *C. difficile* is facilitated by its ability to form spores that are resistant to many disinfectants, so that it remains viable in the hospital environment for long periods of time. Toxigenic isolates of *C. difficile* usually produce two toxins, toxin A (tcdA, an enterotoxin) and toxin B (tcdB, a cytotoxin), which are considered the major virulence factors.⁶

Some strains of *C. difficile* produce an additional toxin called binary toxin (CDT). This was first reported in 1988 but not considered important until now.^{1,2,7} Binary toxin producers make up the majority of the *C. difficile* strains isolated in the recent large outbreaks of the disease overseas.^{1,2} A correlation between binary toxin production and severity of diarrhoea has been demonstrated,⁷ and more community-acquired *C. difficile*-associated diarrhoea was found to be caused by binary toxin producers. To determine the effects of binary toxin alone, researchers have characterised *C. difficile* strains that only produce binary toxin (ie, tcdA⁻ tcdB⁻ CDT⁺ strains). Although supernatants from tcdA⁻ tcdB⁻ CDT⁺ strains of *C. difficile* caused fluid accumulation in a rabbit ileal loop after concentration and trypsinisation, challenge of clindamycin-treated hamsters with these strains resulted in colonisation but not diarrhoea or death, suggesting that binary toxin by itself may not cause disease.⁸ The significance of binary toxin clearly needs further investigation.

A second important feature of this “new” organism is that it produces more toxin A and B than other strains. Production of these toxins in *C. difficile* is encoded by the *tcdA* and *tcdB* genes, respectively. These two genes form part of a highly stable pathogenicity locus (PaLoc), a region of the chromosome that also includes the genes *tcdC*, *tcdR* and *tcdE*. Toxin A variant strains fail

to produce toxin A detectable by enzyme immunoassay because of a deletion in the *tcdA* gene. The *tcdC* gene is a down-regulator of toxin A and B production. The PCR ribotype 027/NAP1 strain has a deletion in the *tcdC* gene resulting in it no longer down-regulating, and strains produce toxin throughout the log phase of growth instead of just in the stationary phase.⁹ Non-toxigenic strains lack the PaLoc.

The third important feature of these strains is that they are resistant to fluoroquinolone antibiotics, and excessive fluoroquinolone use appears to be a contributing factor in the recent outbreaks.¹⁰ *C. difficile* develops resistance to quinolones soon after exposure.¹¹ Both the newer fluoroquinolones, such as gatifloxacin and levofloxacin, and, somewhat surprisingly, the older one, ciprofloxacin, have been implicated.¹⁰ Ciprofloxacin has always been thought of as a low-risk antimicrobial for inciting *C. difficile*-associated diarrhoea.¹² However, once *C. difficile* becomes resistant to the later fluoroquinolones, it is also resistant to ciprofloxacin, and the resistance trait may become more important for initiation of disease.

Another significant finding from the outbreaks reported overseas is the marked variation in *C. difficile*-associated diarrhoea rates among different age groups. While older people have always been at increased risk, due primarily to decreased host defences, rates in those ≥ 65 years of age have increased dramatically since 2000.¹³ One possible novel risk factor is exposure to gastric acid suppressants, such as histamine-2 receptor inhibitors or proton pump inhibitors. These agents have been more commonly prescribed in recent years and may be linked with the increased rates of *C. difficile*-associated diarrhoea in the community,¹⁴ although some case-control studies with hospital patients show no association.^{1,10} The importance of community onset *C. difficile*-associated diarrhoea was highlighted recently by a report of severe cases in previously healthy people and peripartum women.¹⁵

Is this organism in Australia yet? We do not really know because molecular typing is required to distinguish the outbreak strain from others, and this is rarely done. However, it is probably not here — there have been no reports of more severe *C. difficile* disease, and Australia uses less of the most incriminated fluoroquinolones than other parts of the world. A major problem is that many laboratories in Australia have moved away from culturing for *C. difficile*, and to save money and time are using enzyme immunoassay kits. *C. difficile* toxin A enzyme immunoassay kits will not detect strains that don't produce toxin A, and toxin A + B kits will not detect binary toxin producers. This diagnostic problem is compounded by the fact that laboratories servicing general practitioners often do not examine faecal samples for *C. difficile* because of the continuing misconception that *C. difficile*-associated diarrhoea is a hospital problem only.

Given the high mortality rate in recent *C. difficile*-associated diarrhoea cases overseas, it is important that we know if and when this organism arrives in Australia. How could this be achieved? Should *C. difficile*-associated diarrhoea become a notifiable disease

in Australia, as happened in Canada in response to the outbreak there? This is unlikely to be particularly helpful without molecular typing to distinguish the outbreak strain. Targeted surveillance, with one or two laboratories being funded periodically to type a representative sample of isolates of *C. difficile* from a variety of Australian hospitals, would seem a more reasonable approach.

Finally, the value of sensible policies regarding antibiotic use, and good infection control staff and procedures, cannot be over-emphasised. Antibiotic restriction can be effective in reducing *C. difficile*-associated diarrhoea.¹⁶ In response to the outbreak in Canada, the Quebec government recently provided CA\$20 million to hospitals in the province to buy additional equipment and hire infection control staff.¹⁷ In the long term, such initiatives are likely to have an impact not only on *C. difficile*-associated diarrhoea but also on other infection control problem organisms, such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* spp.

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