

From obscurity to ‘superbug’ – The rise of *Clostridium difficile*

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The anaerobic bacterium *Clostridium difficile* is a major nosocomial pathogen, the most commonly diagnosed cause of infectious hospital diarrhoea.¹ *C. difficile* infection has a wide clinical spectrum, ranging from asymptomatic carriage, to mild-self limiting diarrhoea, and more severe pseudomembranous colitis (PMC). Antimicrobial exposure is the most significant risk factor for acquiring *C. difficile* and, of course, being exposed to the organism. Prior to the advent of antibiotics, PMC was a relatively rare disease, largely associated with colonic, pelvic or gastric surgery.² As the use of antimicrobial agents became more common, PMC emerged as an important complication. Although *C. difficile* was first described in 1935, it was not identified as the aetiological agent of PMC and cases of antibiotic-associated diarrhoea (AAD) until the late 1970s. The observations that the toxic activity of faecal filtrates of patients with PMC could be neutralised by *C. sordellii* antisera (due to cross-reactivity with *C. difficile* toxins), together with the failure to isolate *C. sordellii* from patients, eventually led to *C. difficile* being incriminated. Toxigenic isolates of *C. difficile* usually produce two toxins, toxin A and toxin B, and these are thought of as the major virulence factors. Some strains of *C. difficile* produce an additional toxin, binary toxin (actin-specific ADP-ribosyltransferase, CDT), first reported in 1988 but not considered important until now.³

Over the last 25 years, most patients with *C. difficile* infection have not progressed to PMC, due to increased awareness and better laboratory diagnosis. The term *C. difficile*-associated diarrhoea (CDAD) was initially a popular way of describing the disease; however, this has largely been replaced by the term ‘*C. difficile* infection’ (CDI). In hospitals, *C. difficile* has been viewed by many as more of an annoyance rather than a serious hospital-acquired infection. This has changed as a recent epidemic in North America,⁴ associated with high mortality and morbidity, has been due to the emergence of a new strain of *C. difficile*. The new strain is resistant to fluoroquinolone antimicrobials and fluoroquinolone use in humans appears to be driving the epidemic. The strain of *C. difficile* responsible for the epidemic in Canada (NAP1/BI in North America and PCR ribotype 027 in Europe) has now been linked to outbreaks in multiple countries, including Great Britain, the USA, France,

Belgium and The Netherlands, and poses a significant threat to public health in the Australasian region.³

Even non-epidemic CDI represents a major burden to the healthcare system. One study from ~15 years ago showed that *C. difficile* cost a 700-bed teaching hospital in Australia about AU\$1.25 million annually, either as a real or opportunity cost.⁵ Current conservative estimates suggest that the cost of CDI in the USA now exceeds US\$3 billion annually.⁶ The attributable mortality and morbidity between 2002 and 2003 in the Canadian epidemic has been calculated. On average, each case resulted in an additional 10.7 days in hospital and, compared with controls, patients with CDI had a significantly higher mortality of >10% in those aged 70 years or more.⁴

There has also been an apparent increase in community-acquired CDI overseas in the absence of classic risk factors, such as antibiotic exposure. Despite assertions that community-acquired CDI is a new disease,⁷ it is not new, just under-diagnosed.⁸ Therefore, it is difficult to tell whether this is a true increase or better case ascertainment. Unfortunately many laboratories servicing general practitioners often do not examine faecal samples for *C. difficile* unless asked because of the continuing misconception that CDI is a hospital problem only.

Because of the increase in community-acquired CDI there has been speculation that *C. difficile* may be part of a zoonosis and that transmission of infection via spores is food-borne.⁹ *C. difficile* is known to colonise many animals.¹⁰ Indeed, as with humans, the gastrointestinal tracts of most infant animals are probably colonised by *C. difficile* until weaning. Most animal isolates of *C. difficile* produce binary toxin, and both pigs and cattle in Europe harbour PCR ribotype 078 a strain that, like ribotype 027, also produces more toxins A and B. In The Netherlands, since 2005, there has been an increase in prevalence of human CDI with ribotype 078 strains. These infections were in a younger population and more frequently community-acquired. In the eastern part of The Netherlands where >90% of the country’s pig farms are located, 22.4% of human isolates were ribotype 078, and human and pig strains of *C. difficile* were highly genetically related.¹¹ Of great concern is the fact that ribotype 078 is now the third most common ribotype of *C. difficile* isolated from human infections across Europe.¹²

Clearly, if *C. difficile* becomes established in animal populations in Australia, as appears to be the case in The Netherlands, this may pose a risk to humans, not necessarily through consumption of food but more likely through environmental contamination. The lower population density in this country may lessen this risk. The amplification of *C. difficile* in humans and animals is driven by antimicrobial use. Australia's conservative policies thus far regarding newer fluoroquinolone use in humans and animals may offer us some protection against epidemic strains of *C. difficile* circulating in North America and Europe. However, if cephalosporins are driving *C. difficile* infection in animals, additional effort may be required to target cephalosporin use in veterinary medicine.

Until now, Australia has been spared from the epidemic ribotype 027 strain of *C. difficile*. As mentioned above, it is possible that antibiotic prescribing in Australia has not favoured the emergence of epidemic strains. It is also possible that the geographical isolation of Australia together with our strict quarantine laws is responsible for the delayed emergence of ribotype 027. However, the fluoroquinolone-resistant ribotype 027 strain has now been detected in Australia.¹³ This strain was responsible for an outbreak involving at least six patients at a Victorian hospital early this year. While the ribotype 027 epidemic strain is currently rare in Australia, this is no reason for complacency. It is likely to spread unless surveillance and infection control measures are enhanced, and antibiotic stewardship programs reinforced. How is this to be achieved?

Some insights can be gained by looking at the French response to the threat of epidemic *C. difficile*. Within 12 months of a meeting of experts convened to discuss the threat, there had been a strengthening of *C. difficile* surveillance and publication of guidelines for CDI diagnosis, surveillance and notification. A national network of five regional laboratories with *C. difficile* strain typing capability, connected with the French Anaerobe National Reference Centre at the Pasteur Institute, had been established, and Department of Health guidelines on prevention and control had been circulated to all hospitals and nursing homes. Six months later a national laboratory dedicated to *C. difficile* was created.

This contrasts starkly with the Australian situation where there has been limited government attention to CDI before the identification of cases in Victoria in 2010. A recommendation from the Australian Commission on Safety and Quality in Healthcare for hospital surveillance programs in all states and territories to monitor *C. difficile* was approved by Australian Health Ministers in November 2008. In 2009, a surveillance definition was endorsed, but by mid-2010 all states and territories have yet to enact this recommendation, there has been no collation or analysis of national surveillance data, and no government funding for laboratories to perform strain typing. In response to events in Victoria this year, the Australian Commission on Safety and Quality in Healthcare organised a national workshop inviting clinical and laboratory experts and representatives of state and federal governments,

and is supporting an initial laboratory typing survey. Most activity has arisen from two professional groups, the Australian Infectious Diseases Society (ASID) and the Australian Infection Control Association (AICA). ASID has prepared guidelines for the diagnosis and treatment of CDI, while ASID and AICA jointly have prepared infection control guidelines for patients with CDI in healthcare settings. Both sets of guidelines should be published shortly, and jurisdictions are urged to support integration of these expert recommendations into policy and practice as a matter of urgency. This includes ensuring effective routine diagnostic testing is in place in public and private hospitals, as well as appropriate infection control and surveillance strategies.

The importance of effective infection control staff and procedures in CDI prevention and control cannot be overemphasised. In response to the CDI outbreak in Canada, the Quebec government provided CA\$20 million to hospitals in the province to buy additional equipment and hire infection control staff.¹⁴ Although not yet back to baseline, there have been significant reductions in the rates of CDI in Quebec Province. There has also been a decline in *C. difficile* notifications in the United Kingdom following the introduction of a comprehensive control program, including improved surveillance, attention to early diagnosis, treatment and effective infection control. Compared with the period 2007–08, there was a 19% decrease in the prevalence of ribotype 027 in 2008–09. There had been a quadrupling in the numbers of death certificates where *C. difficile* was mentioned in England and Wales between 2004 and 2007; however, this had decreased by 29% in 2008. The successful control of ribotype 027 is likely to explain this marked reduction in CDI-related deaths.^{15,16} Ultimately, the responsibility for stopping the spread of PCR ribotype 027 *C. difficile* throughout Australia will rest with alert infection control practitioners.

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