Is *Clostridium difficile* a threat to Australia's biosecurity?

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Australia can benefit from lessons learned in the epidemic of C. difficile infection in Europe and North America

It is 30 years since *Clostridium difficile* was shown to be the cause of pseudomembranous colitis and many cases of antibiotic-associated diarrhoea in humans. In the interim, *C. difficile* has risen from relative obscurity to become a major hospital pathogen. Two factors were particularly important in its emergence during the 1980s. First, increased and inappropriate use of some broad-spectrum antibiotics, particularly cephalosporins, predisposed more patients to infection with *C. difficile*. Second, contamination of the hospital environment with *C. difficile* spores was, and remains, a significant problem, as the spore is likely to be the infective particle. The epidemiology of *C. difficile* infection continues to evolve, and developments overseas in the past decade threaten not only parts of Australia's vast agricultural sector but also the country's health care system.

Since 2002, rates of *C. difficile* infection have escalated, with outbreaks of severe infection in North America and Europe caused by an epidemic strain — polymerase chain reaction (PCR) ribotype 027 (also known as North American pulsed-field type 1 [NAP1]). This strain is characterised by the production of greater amounts of toxins A and B and an additional, binary toxin, as well as resistance to fluoroquinolone antimicrobials.[1] When this editorial was submitted for publication in January 2009, there was no evidence that this epidemic strain was present in Australia. However, *C. difficile* PCR ribotype 027 has now been isolated for the first time in Australia, as reported in this issue of the Journal[2] (*page 706*). Although the patient most probably acquired the organism while travelling in North America, this case illustrates the ease with which it could be introduced into Australia.

Thought to be driving the epidemic in humans in North America and Europe are the overuse of fluoroquinolones and fluoroquinolone resistance, but the ageing population and improved case ascertainment may also be contributing to the dramatic increase in cases. Other factors may also be important, such as the increase in prescription of proton-pump inhibitors, which coincided with the emergence of epidemic *C. difficile*.[3]

Several recent observations from overseas have broad relevance for Australia. First, there has been an apparent increase in community-acquired *C. difficile* infection in the absence of classic risk factors such as antibiotic exposure, leading to suggestions that all patients with community-acquired diarrhoea should be tested for *C. difficile*.[4] Assertions that community-acquired *C. difficile* infection is a new disease[4] are not correct — it has been recognised in Australia for over 15 years but is underdiagnosed.[5] Therefore, it is difficult to determine whether this increase is a true increase or rather reflects better case ascertainment. Nonetheless, the suggestion that *C. difficile* infection should be considered more than just a hospital problem is valid, and general practitioners need to be aware of this change in epidemiology. The prevalence of binary toxin-producing *C. difficile* in human disease is also increasing, and there is an association between binary toxin-producing isolates and community acquisition.[6]

Second, it is speculated that *C. difficile* is part of a zoonosis, and that transmission of infection via spores may be foodborne.[7] There is compelling evidence for the former, but none for the latter. *C. difficile* is known to colonise many animals.[8] Indeed, as in humans, it probably colonises the gastrointestinal tracts of most infant animals until weaning. There was alarm at a report that 20% of a small sample ($n = 60$) of retail beef in Canada contained *C. difficile*.[9] Equally disturbing are reports that many pig herds in the United States are infected with *C. difficile*. The overall prevalence of *C. difficile* in piglets from 10 herds in North Carolina was 48%, and ranged from 0 to 97% across the herds. Mortality for piglets with *C. difficile* infection is 15%, and animals that survive are 10% underweight when they go to market.[10]

Most animal isolates of *C. difficile* produce binary toxin, and both pigs and cattle harbour PCR ribotype 078 — a strain that, like ribotype 027, produces increased amounts of toxins A and B, in addition to binary toxin. In the Netherlands, the prevalence of human *C. difficile* infection with ribotype 078 strains has increased since 2005; these infections were in a younger population and more frequently community-acquired than infections with ribotype 027 strains. In the eastern Netherlands, where more than 90% of the country's pig farms are located, over 20% of human isolates are now ribotype 078, and human and pig strains of *C. difficile* are highly genetically related.[11] In Australia, little is known about the prevalence of *C. difficile* in pigs. A small study in 2007 found *C. difficile* in 10 of 37 samples (27%) from piglets with diarrhoea, but none of the isolates were ribotype 078 (unpublished data).

Why is *C. difficile* infection increasing in pigs in Europe, and what are the implications for Australia? The use of antimicrobials for growth promotion was banned from 2006 in Europe, and even earlier in Denmark, starting in 1995. However, since 2000, the use of therapeutic antimicrobials in production animals has increased in Europe in general, and specifically in Denmark, a big producer of pork. Of real concern is evidence of greater use of cephalosporins in animals. While the number of pigs in Denmark increased by 50% in the past 15 years, the amount of penicillinase-susceptible penicillins used increased by 400%, and cephalosporins by 1000%. Most of this increase was in piglets and sows.[12] Although the total amount of cephalosporins used remains small, this is a worrying trend. If the situation is similar in the Netherlands, and anecdotal evidence suggests that it is, then this may be analogous to the situation in humans in the 1980s when there was a dramatic increase in *C. difficile* in many hospitals, driven by cephalosporin use.[13]

The overlap between the location of pig farms in the Netherlands and the occurrence of human ribotype 078 infections suggests a common source.[11] This is likely to be the environment. The Netherlands has one of the highest population densities in the world. If infection rates in pig farms in the Netherlands are as high as those in the US,[10] then it is likely that a large proportion of the Dutch population comes into contact with *C. difficile* spores every day. Individuals are at risk of infection if they are taking antimicrobials or any other medication that perturbs the gut flora. The good news for Australia is that, with our very low population density, a similar risk to humans is unlikely to develop. However, this is no

reason for complacency. 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.

Even before the first isolation of *C. difficile* PCR ribotype 027 in a patient in Australia, health care practitioners were becoming justifiably concerned. A proposal for *C. difficile* to be made notifiable in all states and territories of Australia was approved at the Australian Health Ministers' Advisory Council meeting in November 2008. Australia's conservative policies on fluoroquinolone use in humans and animals may offer some protection. 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.

The solution to these problems continues to lie in surveillance for the emergence of virulent strains of *C. difficile*, promotion of judicious use of antimicrobials in both human and veterinary medicine, and environmental cleanliness, the latter perhaps easier said than done outside health care facilities.

Competing interests

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