The clear and present danger of carbapenemase-producing Enterobacteriaceae (CPE) in New Zealand: time for a national response plan

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ABSTRACT

Antimicrobial resistance (AMR) in general poses a threat to the sustainability of modern healthcare, but a particularly urgent and serious threat is posed by a specific group of antibiotic-resistant bacteria known as carbapenemase-producing Enterobacteriaceae (CPE). CPE are resistant to nearly all antibiotics and include common pathogens such as Escherichia coli and Klebsiella pneumoniae. In New Zealand, the incidence of CPE has increased from three isolates in 2012 to 45 in 2016. The current epidemiology of CPE in New Zealand has similarities with the extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-PE) epidemic in the early 2000s (just before ESBL-PE underwent a non-linear increase in incidence). Although to date in New Zealand, nearly all CPE have been imported from overseas, this situation appears to be changing, with evidence of secondary spread in both households and healthcare facilities over the last year. In this article, we argue that CPE should be regarded as the foremost AMR threat currently facing New Zealand, and highlight the need for a comprehensive national response plan, analogous to plans for other emerging transmissible infections, such as pandemic influenza and Ebola. We also make recommendations about the components of such a plan and advocate that CPE should be recognised as a key priority in New Zealand’s national AMR strategy, due to be published in May 2017.

Glossary

Enterobacteriaceae A family of gram-negative bacteria that are commensals of the human bowel but also cause opportunistic infections (includes Escherichia coli and Klebsiella pneumoniae)

β-lactam antibiotics A broad class of antibiotics based on a common chemical structure that includes all cephalosporins, penicillin-like antibiotics and carbapenems

Carbapenems An extremely broad spectrum subgroup of β-lactam antibiotics

Carbapenemase Enzymes that deactivate carbapenems

CPE Carbapenemase-producing Enterobacteriaceae

NDM New Delhi metallo-β-lactamase; a particular type of carbapenemase

OXA-48-like A particular group of carbapenemases

NDM-PE Enterobacteriaceae that produce NDM carbapenemase

OXA-48-like-PE Enterobacteriaceae that produce OXA-48-like carbapenemase

ESBL Extended-spectrum β-lactamase—enzymes that deactivate broad spectrum cephalosporins but not carbapenems

ESBL-PE Enterobacteriaceae that produce ESBL

CTX-M A particular molecular group of ESBLs that have become predominant globally since the early 2000s

CTX-M-15 A specific CTX-M ESBL subtype that have become particularly widespread globally since the early 2000s

LTCF Long-term care facility
Antimicrobial resistance (AMR) is recognised as a serious and urgent threat to modern healthcare. Contemporary medical interventions, such as bone marrow and solid organ transplantation, complex surgical procedures and immune-suppressive therapies all rely heavily on the availability of effective antibiotics. Although AMR affects nearly all bacteria that cause human infections, specific bacteria such as methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE), extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-PE) and carbapenemase-producing Enterobacteriaceae (CPE) are particularly important threats. Among these, CPE arguably pose the most serious and immediate threat because Enterobacteriaceae (including Escherichia coli and Klebsiella pneumoniae) are leading causes of hospital- and community-acquired infections, and CPE are resistant to nearly all antibiotics, leaving treatment options extremely limited or non-existent. Moreover, the prevalence of CPE is increasing rapidly in many countries, and the prospects of new antibiotics becoming available to treat CPE over the short- to medium-term are poor.

Carbapenemases are enzymes that deactivate carbapenems—the most broad-spectrum β-lactam agents available—which are relied on for the treatment of infections caused by ESBL-PE and other resistant gram-negative organisms. Carbapenemase genes are usually carried on extrachromosomal genetic elements known as plasmids. These plasmids tend to carry multiple resistance genes that collectively confer resistance to nearly all antibiotics. Plasmids transmit between different species and strains of the Enterobacteriaceae family, further facilitating resistance spread.

Although a variety of carbapenemases have been described, the focus of this article is on the New Delhi metallo-β-lactamase (NDM) and OXA-48-like carbapenemases because these have been the most common in New Zealand to date. In this article we describe the evolving epidemiology of CPE in New Zealand, drawing parallels with the emergence of the ESBL-PE epidemic, and argue that a nationally coordinated response plan for CPE is needed. Finally, we propose a set of high-level strategic measures we believe should be included as core components of such a plan.

Current epidemiology of CPE in New Zealand

NDM-producing Enterobacteriaceae (NDM-PE) and OXA-48-like-producing Enterobacteriaceae (OXA-48-like-PE) were first reported in New Zealand in 2009 and 2011 respectively, with a sharp increase in 2015 (Figure 1). In New Zealand to date, the majority patients have acquired CPE while receiving healthcare in high-prevalence countries, particularly the Indian Subcontinent. Of patients with available information between 2009 and 2016, 72% (49 of 68) of those with NDM-PE and 61% (19 of 31) of those with OXA-48-like-PE likely acquired the organism in the Indian Subcontinent. Furthermore, among isolates from travellers to the Indian Subcontinent in 2016, 41% (11 of 27) were recovered from travellers who did not appear to have had any contact with healthcare during their trip. Similar findings among healthy travellers returning from the Indian Subcontinent and South-East (SE) Asia have been described in Europe. These observations suggest that in the Indian Subcontinent and SE Asia, NDM-PE and OXA-48-like-PE have become established in the community. This development poses major challenges, not only for the affected countries themselves, but also for low-prevalence countries such as New Zealand, because it increases the probability these organisms will be introduced into healthcare facilities by asymptomatic carriers.

Already in New Zealand, several cases of probable secondary spread of CPE in healthcare settings have occurred, including likely hospital spread of NDM-PE and transmission of OXA-48-like-PE in a long-term care facility (LTCF). Hospital transmission of another type of CPE (known as VIM) was also reported in 2015. In addition, the indirect pathways by which NDM-PE can find their way into the hospital environment is illustrated by a trauma patient admitted to an Auckland hospital who was incidentally found to be colonised with NDM-PE as a probable consequence of living with others who had recently travelled to the Indian Subcontinent. Nonetheless, to date in New Zealand, most cases of local transmission appear to be traceable to returned travellers or repatriated patients who are presumed to have been the index case.
Parallels between the emergence of CPE and ESBL-PE in New Zealand

The evolving epidemiology of CPE in New Zealand has many similarities with the evolution of the ESBL-PE epidemic in New Zealand during the early 2000s (and in particular the predominant ESBL type known as CTX-M and the most globally prevalent subtype known as CTX-M-15). Soon after 2001, when CTX-M-15 was first described in an isolate of *E. coli* from India, it underwent rapid global spread and is now endemic in most countries.

Non-linear increases in incidence

The increasing incidence of NDM-PE and OXA-48-like-PE in New Zealand is following a similar trajectory to ESBL-PE in the early 2000s. Over the six-year period 1998–2003, the number of clinical ESBL-PE isolates increased 31-fold: from seven in 1998 to 221 in 2003 (Figure 2). This increase was presumably associated with the emergence of CTX-M-15 (and to a lesser extent CTX-M-14). Since then, the incidence of ESBL-PE has continued to increase to the point where, in 2014, there were an estimated 5,748 clinical isolates, which equates to an annual incidence of 127 ESBL-PE infections per 100,000 population (H Heffernan, personal communication).

Figure 1: CPE in New Zealand, 2009–2016.

![CPE in New Zealand, 2009–2016.](image)

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Figure 2: ESBL-PE in New Zealand 1998–2014.

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Association with travel

CTX-M ESBL-PE and CPE also share a common association with international travel. In New Zealand (and Canada) during the mid-2000s, it was reported that CTX-M-15 was associated with international travel, and in particular travel to the Indian Subcontinent. A report from Auckland showed that recent travel to the Indian Subcontinent was highly associated with community-onset CTX-M-15-producing *E. coli* genitourinary tract infection. Notably, the travellers hadn't necessarily received healthcare during their trip. Since those early reports, community spread of CTX-M ESBL-PE has occurred worldwide, with low- and middle-income countries particularly affected. In India, China and Vietnam for instance, ESBL-*E. coli* have been reported to account for 40–63% of *E. coli* from community-onset intra-abdominal infection. While in rural Thailand, the prevalence of asymptomatic community carriage of CTX-M ESBL-PE has been shown to be as high as 66%. Furthermore, the current probability of healthy travellers acquiring ESBL-*E. coli* when in Southern Asia (including the Indian Subcontinent) is 75% (and 37% to 49% when in the rest of Asia or Northern Africa).

Widespread dissemination within the Indian Subcontinent

As occurred for ESBL-PE, CPE have disseminated widely within the Indian Subcontinent over a time frame measured in years rather than decades. In a Mumbai tertiary intensive care unit, for example, the prevalence of CPE in blood cultures increased from 0% to 8% between 2006 and 2009, presumably in association with the emergence of NDM-PE. A similar prevalence of NDM-PE (5–15%) has been demonstrated among clinical *Enterobacteriaceae* isolates from hospitals spread throughout India (with OXA-48-like enzymes detected in up to 8% of isolates). More recently, a nationwide study of blood stream isolates in India found carbapenem resistance in 12% of *E. coli* and 60% of *K. pneumoniae*. In Rawalpindi, Pakistan in 2010, the rate of gastrointestinal carriage of NDM-PE among inpatients was found to be 27%.

Within the Indian Subcontinent, the prevalence of asymptomatic CPE carriage is also high in the community. In New Delhi between 2011 and 2012, 7% of outpatients and 11% of previously non-hospitalised patients on admission were carriers of CPE. Among outpatients in Rawalpindi in 2010, the faecal carriage rate of NDM-PE was 14%. Widespread contamination of the environment has also been reported, with 51 of 171 seepage samples (pools of water on streets or rivulets) and two of 50 tap water samples positive for NDM in New Delhi in 2010. Similar findings have been reported in Dhaka, Bangladesh, where 36 of 58 environmental water/sewage samples were positive for NDM in 2012. Following the pattern observed for CTX-M-15 ESBL-PE, secondary reservoirs of NDM-PE have rapidly become established worldwide, in areas such as SE Asia, China, Northern-Africa, the Middle East and the Balkans.

Association with *E. coli*

CTX-M-15 ESBL-PE and NDM/OXA-48-like-PE also share a common association with *E. coli*. In New Zealand to date, *E. coli* has accounted for 59% (64/108) of all NDM-PE and OXA-48-like-PE isolates, and in 2016 all 11 NDM-PE and OXA-48-like-PE from non-hospitalised travellers to the Indian Subcontinent were *E. coli*. This is significant because *E. coli* seems to have a particularly high propensity to spread in community settings compared to other *Enterobacteriaceae* species. This raises concerns about the potential for CPE to spread in the community post importation to New Zealand, including in LTCFs. Evidence from New Zealand and overseas suggests that LTCFs have played a significant role in the spread of CTX-M-15-producing *E. coli*. Early in the CTX-M epidemic, community-onset ESBL-PE infection in Auckland was associated with LTCF residence. Phylogenetic analysis in Ireland has also suggested CTX-M-15-producing *E. coli* strains circulate between LTCFs and hospitals. Early indications suggest that NDM/OXA-48-like-producing *E. coli* may follow a similar path (with evidence suggesting that transmission of OXA-48-like-PE has already occurred within a LTCF in New Zealand).
Conclusions and recommendations

Drawing on our national experience with ESBL-PE, it seems likely that importation of NDM-PE and OXA-48-like-PE (and other CPE) will continue to increase in New Zealand. It is conceivable that in the absence of effective interventions in high-prevalence areas, rates of travel-associated CPE acquisition will eventually reach levels currently seen with ESBL-PE. This is alarming because the consequences of CPE becoming endemic in New Zealand are more serious than for ESBL-PE. CPE have far fewer treatment options, and in some cases no antibiotic treatment options are available. Moreover, it is likely in the near future that CPE will become resistant to all known antibiotics with resistance to the last-line antibiotic colistin emerging in India, and the convergence of NDM and plasmid-mediated colistin resistance (MCR-1) reported in E. coli in SE Asia. Urgent action is therefore needed to counter the threat CPE pose to our health system.

The World Health Organization (WHO) recently published its Global Action Plan on Antimicrobial Resistance, which sets out a framework of five broad strategic objectives to address AMR. New Zealand, as a signatory to the WHO, is currently using this framework to develop its own national AMR strategy, due to be published in May 2017. Within this strategy, we contend it is imperative that the issue of CPE be addressed specifically. Moreover, because of the seriousness and complexity of the CPE threat, New Zealand’s strategy must go further than recommending the development of national CPE guidelines. Rather, the strategy should highlight the need for a coordinated national response plan, analogous to response plans developed for other transmissible infectious disease threats such as pandemic influenza and Ebola. The value of having a coordinated national response to CPE is demonstrated by experience in Israel, where a particular CPE known as KPC was controlled effectively through coordinated and targeted national efforts.

We also argue that parallels between the CPE and ESBL-PE epidemics in New Zealand provide opportunities to learn from experience. With this in mind, we propose a set of broad national-level interventions to mitigate the CPE threat. These measures are based on the understanding that CPE, like ESBL-PE, are transmissible pathogens that move between patients and across international borders, and that emergence of CPE in response to local antibiotic use in a country like New Zealand is extremely unlikely. The implication of this understanding is that national programmes to reduce total antibiotic use—while much needed—will be fundamentally inadequate to address the CPE threat in the absence of targeted infection control measures to reduce transmission.

We therefore propose the following high-level recommendations for action, to be included as core components of any coordinated national preparedness and response plan for CPE:

1. Raise awareness about the threat of CPE to the New Zealand health sector.
2. Develop a minimum set of national ‘healthcare biosecurity’ measures for New Zealand hospitals to identify CPE carriers and ensure they are managed with appropriate precautions during their hospital stay. These measures would include a set of minimum standards for laboratory testing for CPE and minimum criteria for actively screening at-risk patients for CPE colonisation when they are admitted to hospital. Currently at-risk patients would likely include all patients who have been hospitalised overseas or have travelled to high-prevalence areas within the preceding 6–12 months. Prioritisation and optimisation of general and routine transmission prevention measures, such as hand hygiene and environmental cleaning, should also occur concurrently. There should be a level of confidence that all New Zealand hospitals have reliable processes and systems in place to identify and respond to the introduction of CPE and prevent subsequent transmission.
3. Ensure that every district health board (DHB) has policies and plans in place, with clear roles and responsibilities for decision making and management, to deal effectively with the introduction and spread of CPE. This is a framework analogous to DHB preparedness for the
arrival of patients with Ebola or other exotic transmissible pathogens. The development and accurate implementation of any plan will require that, at DHB organisation level, there are appropriate resourcing, staffing and structural accountability arrangements to ensure that infection prevention services are optimised. The cost of investment in preventive efforts should be considered relative to the high expenditure and opportunity costs that would occur in association with a CPE outbreak. \(^\text{35}^\)

4. Establish appropriate processes and mechanisms to ensure that, in the event of secondary spread of CPE in healthcare settings, an adequately resourced public health investigation can be carried out. The goal of this investigation would be to maximise chances of containment and to identify human sources and/or environmental reservoirs of ongoing transmission. If there are insufficient resources or expertise within the affected healthcare facility, there should be mechanisms in place for mobilising appropriate external expertise and resources. One possible approach would be to make clusters of CPE and suspected secondary transmission of CPE notifiable to the Medical Officer of Health. Mandatory notification and investigation of CPE may also help raise the profile of CPE in healthcare organisations and encourage appropriate prioritisation.

5. Ensure that LTCFs in New Zealand are prepared and equipped to appropriately identify and manage patients colonised with CPE so that the risk of secondary spread is minimised. In parallel, an adequately resourced and tailored antimicrobial stewardship (AMS) programme that targets LTCFs should be developed. Structural factors, such as staffing levels and availability of expert infection prevention support, should also be considered as interventions that would reduce transmission risk. If changes to the Infection Control Standard are required to achieve this, then such changes should be made. The association between LTCFs and multidrug-resistant \textit{Enterobacteriaceae}, and the frequent movement of patients between LTCFs and hospitals, support the need for a co-ordinated cross-organisational response plan to CPE.

6. Ensure that every New Zealand hospital has processes and systems in place to secure rapid access to last-line antibiotics required to treat CPE, such as colistin and tigecycline. Because healthcare-associated infections (HAI) with CPE carry such a high risk of harm, national guidance should also be in place (and locally prioritised) to minimise the risk of HAI developing among patients found to carry CPE. This could include more intensive infection prevention interventions in carriers to minimise the risk of HAI.

7. Ensure that, within a broader community AMS programme, there are focused initiatives aiming to discourage the use of antibiotics for travellers’ diarrhoea. The receipt of antibiotics, especially quinolones, for travellers’ diarrhoea is a significant avoidable risk factor for travellers becoming colonised with multidrug-resistant \textit{Enterobacteriaceae}. \(^\text{17}^\)

Developing and implementing a national plan to mitigate the risk of CPE will require collaboration and coordination between a range of healthcare providers and a commitment of resources at both DHB and national level. Nonetheless, such efforts and investment should be regarded as essential in the face of such a serious and urgent public health threat. While ultimately these measures may only succeed in delaying CPE from becoming endemic in New Zealand, every year free of CPE ensures a safer healthcare system for our patients and buys a little more time for new treatment options and prevention technologies to become available.
Competing interests:
Nil.

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