

Carbapenemase-producing Enterobacterales: a profound threat to Australian public health

The spread of carbapenemase-producing Enterobacterales (CPE) is a major threat to health care systems worldwide.¹ In regions where CPE has become endemic, its impact on health outcomes has been catastrophic. The timely implementation of coordinated national responses is key to minimising these risks in Australia.

Effective antibiotic treatment of infections is fundamental to modern medicine. Without it, the risks associated with routine activities, including surgery, cancer therapy and childbirth, are unacceptably high. Worryingly, the number of bacterial pathogens that are associated with antibiotic treatment failure due to acquired resistance is growing rapidly. Among these, CPE is arguably the most concerning.¹ Enterobacterales is an order of Gram-negative bacilli that includes pathogenic genera, such as *Escherichia*, *Klebsiella* and *Salmonella*. While these bacteria can colonise the gastrointestinal tract asymptotically, they can also spread beyond the gut to cause life-threatening infections, even in otherwise healthy individuals.

CPE results from the acquisition of genes that encode carbapenemase enzymes by Enterobacterales bacteria. Carbapenemases allow bacteria to hydrolyse carbapenem antibiotics, as well as other β -lactams, such as penicillins and cephalosporins. Carbapenemase genes can be of several different types, of which *Klebsiella pneumoniae* carbapenemase (KPC) and New Delhi metallo- β -lactamase (NDM) are among the most widely recognised. They are capable of spreading rapidly, both within and between bacterial populations, through highly transmissible mobile genetic elements. Plasmids encoding carbapenemase genes also commonly carry other resistance genes, such as those conferring resistance to aminoglycoside and fluoroquinolone antibiotics, resulting in multidrug resistance in bacteria that acquire them. For such multidrug-resistant bacteria, the remaining treatment options are often more costly, less efficacious, and may have less desirable adverse effect profiles. Worryingly, pan-resistant CPE bacteria, against which no effective antibiotic treatments are available, are being reported with increasing frequency.² Despite the World Health Organization (WHO) listing CPE as a critical priority for antibiotic research and development,³ there are marked insufficiencies in the clinical development pipeline of new agents for CPE treatment.

Carriage of CPE in the gut can be prolonged and symptomless. Within health care settings, colonised individuals can spread CPE to other patients through person-to-person contact or indirectly via shared equipment or contaminating environmental reservoirs. Of those carrying CPE, it is estimated that 10–30% will develop a CPE infection.⁴ The first such infection to be described was an *Enterobacter cloacae* isolate from a patient treated for a subcutaneous abscess in a French hospital in 1990.⁵ Since then, the rapid spread of CPE has been clearly evident. In Greece, KPC-positive

K. pneumoniae reached epidemic proportions within about two years of initial detection.⁴ Similarly, after reporting its first KPC-positive *K. pneumoniae* isolate in 2008, active surveillance in two Italian hospitals identified almost 200 cases in the three years following.⁶ By 2011, close to 30% of *K. pneumoniae* isolates in Italy were resistant to carbapenems.⁶ CPE is also endemic in many countries outside Europe.⁶ For example, 31% of *Escherichia coli* isolates and 40% of *K. pneumoniae* isolates in India harbour an NDM gene.⁷ Emerging evidence suggests that indiscriminate use of antibacterials during the first two years of the COVID-19 pandemic has had a further exacerbatory effect.⁸

The clinical impact of the spread of CPE is also becoming evident in antibiotic treatment outcomes, particularly those relating to sepsis. Bacterial bloodstream infection and the associated development of sepsis is a serious clinical problem and is far more lethal when caused by virulent bacteria with antibiotic resistance, such as CPE. For a bacterial infection resulting in septic shock, every hour of ineffective antibiotic therapy results in a 7.6% relative reduction in survival.⁹ In practice, current empirical antibiotic regimens are not tailored to cover CPE, a factor contributing to high mortality rates for CPE infections.¹⁰

Beyond the human cost, the economic burden of CPE outbreaks is considerable. A recent 40-case outbreak in the United Kingdom is estimated to have cost the National Health Service the equivalent of AU\$1.7 million.¹¹ In France, a 19-month outbreak involving only 16 patients with CPE infection was estimated to have cost an individual hospital the equivalent of AU\$2 million.¹² These costs, resulting from increased lengths of stay and restricted admissions, highlight the considerable impact that a small CPE outbreak can have on the wider health care system.¹² Australia's only published economic estimate of the financial cost associated with asymptomatic CPE colonisation found that affected individuals had, on average, six times higher health care costs (\$155 784) compared with non-colonised individuals (\$25 964) of a similar age and clinical presentation.¹³ A recent WHO report projected a cumulative total of 5.2 million antimicrobial resistance-related deaths in the Western Pacific region from 2020 to 2030, with economic costs forecast to reach US\$148 billion, indicating the enormity of the problem in our region.¹⁴

Surveillance is fundamental to the control of communicable diseases.¹⁵ For CPE infection, this is underpinned by the work of diagnostic and public health laboratories to identify and report CPE carriage and spread. This work includes identifying resistance through phenotypic testing, confirming the presence of specific CPE genes through molecular assays, and further characterising complex resistance genetics of individual pathogens and the phylogenetic links

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between pathogens through genomic methods such as whole genome sequencing.

Data from laboratories have been critical in informing our current estimates of the CPE burden across Australia. These are based on data from individual studies,¹⁶⁻¹⁸ state surveillance programs,¹⁹ and the National Alert System for Critical Antimicrobial Resistances (CARAlert), a voluntary reporting mechanism for bacterial isolates with critical antimicrobial resistance.

In 2022, CARAlert reported a 37.8% increase in the number of CPE cases from 2021 and received reports from all states and territories.²⁰ CPE was detected across all age groups, with the majority in people aged 50 years and older.²⁰ Over 5% of CPE reports were in children aged up to 4 years.²⁰ CPE accounted for over 50% of all critical antimicrobial resistance reports confirmed from blood specimens, and over 80% of urine specimens, highlighting the clinical significance of CPE.²⁰ The highest proportion of CPE was detected in hospitals.²⁰ In April 2023, there had been a 43% year-to-date increase in CPE CARAlert reports compared with 2022, with over 50% detected from clinical isolates.²¹

Although CPE is frequently associated with protracted, widespread hospital outbreaks,^{4,16,17,19} thinking of CPE as solely a hospital infection control problem may impair our ability to respond effectively.^{22,23} CPE is increasingly reported from residential aged care and community settings,²⁰ despite the fact that targeted screening for CPE colonisation does not occur in these settings. The potential for CPE transmission in the wider community, particularly among vulnerable older people in aged care facilities, is of concern.^{20,23}

The value of taking a systematic approach to addressing the risks posed by CPE has been described in an Australian context and abroad,^{19,24} yet opportunities for improvement exist. Currently, CPE infection is only notifiable in five of the eight states and territories, and consequently, CPE burden is likely underestimated. Furthermore, there is no national linkage of epidemiological data to the CARAlert surveillance system. Therefore, the proportion of CPE infections that are acquired overseas, linked to outbreaks, associated with specific settings or patient cohorts, and the infection-to-colonisation ratio are not comprehensively monitored. There is also no coordinated approach to comparative genomic analysis fundamental to detecting hypervirulent strains, and clonal and plasmid-borne outbreaks. For these reasons, our understanding of CPE epidemiology, the risks posed, and the effectiveness of prevention and control measures are limited. Central to achieving a systematic response to CPE is the establishment of nationally consistent and coordinated CPE surveillance. (Box 1).

In the global context, current estimates suggest Australia's CPE burden is still low,¹ and adverse impacts of CPE on the Australian population, health care system and economy can be mitigated. The threats posed by CPE, and the diminishing time left for action, have been highlighted before.²⁵⁻²⁷ Although

Actions to enhance effective carbapenemase-producing Enterobacterales (CPE) surveillance in Australia

- Nationally consistent notification of CPE, incorporating case definitions for colonisation and infection, across all states and territories.
- Funding mechanisms established to support laboratory detection of CPE, pathogen genomics and public health surveillance to ensure equitable resources are available across jurisdictions.
- Structures to enable sharing and linkage of epidemiological, clinical, and genomic data across jurisdictions.
- Incorporation of surveillance data from animals and the environment using a One Health framework.

progress has been made in recent years,^{19,20,23} these efforts are not nationally consistent or coordinated. In 2023, the process of establishing an Australian Centre for Disease Control has begun.²⁸ One of the stated aims of this federally funded body is to work to prevent and control communicable (infectious) diseases.²⁸ As such, the Australian Centre for Disease Control is ideally placed as a national coordinating body to guide a systematic, evidence-based and harmonised approach to CPE surveillance and public health action. Australia now has a unique opportunity to take coordinated national action to prevent the spread of CPE.

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