Reflections on a national public health emergency response to carbapenemase-producing Enterobacterales (CPE)

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Abstract

Carbapenemase-producing Enterobacterales (CPE) are important globally. In 2017, Ireland declared a national public health emergency to address CPE in acute hospitals. A National Public Health Emergency Team and an expert advisory group (EAG) were established. The EAG has identified key learnings to inform future strategies. First, there is still an opportunity to prevent CPE becoming endemic. Second, damp environmental reservoirs in hospitals are inadequately controlled. Third, antibiotic stewardship remains important in control. Finally, there is no current requirement to extend screening to detect CPE outside of acute hospitals. These conclusions and their implications may also be relevant in other countries.

Background

The Enterobacterales include bacteria such as Escherichia coli and Klebsiella pneumoniae. They are normal inhabitants of the gastrointestinal tract, but can cause serious infections, including bloodstream infection (BSI). Carbapenems are broad-spectrum beta-lactam antimicrobials used to treat Enterobacterales infections, resistant to third-generation cephalosporins and beta-lactam-beta-lactamase inhibitor combinations. Carbapenem-resistant Enterobacterales (CRE) are increasingly important, especially those mediated by carbapenemases (i.e. carbapenemase-producing Enterobacterales (CPE)) because these enzymes are encoded on mobile genetic elements that spread amongst different Enterobacterales [1]. These carbapenemases include K. pneumoniae carbapenemase (KPC), oxacillinase 48 (OXA-48) and the metallo-beta-lactamases, such as New Delhi metallo-beta-lactamase (NDM), with potential for widespread dissemination [2].

Because of delays in detection and starting appropriate treatment, those infected with CPE may be adversely affected. In an intensive care unit study, colonisation independently predicted CRE infection [3]. A multi-centre study found that carbapenem resistance was associated with an increased length of hospital stay and in-hospital mortality [4].

Key infection prevention and control (IPC) strategies include building core skills (e.g. behavioural changes, hand hygiene and cleaning), capacity and resources (e.g. staffing), the investigation of outbreaks, isolation/cohorting of positive patients and antimicrobial stewardship [5]. Strengthening laboratory diagnostics and increasing screening volumes are important as CPE detection is more challenging than for other multi-drug-resistant microorganisms, such as methicillin-resistant Staphylococcus aureus (MRSA). There is increasing emphasis on environmental reservoirs, e.g. hospital sinks, showers, previously well recognised for other Gram-negative bacilli such as Pseudomonas aeruginosa [6].

In Ireland, the Minister for Health declared a National Public Health Emergency (NPHE) on CPE in October 2017, as Ireland’s first National Action Plan on Antimicrobial Resistance (iNAP) was being launched [7]. A NPHE Team (NPHET) was convened to focus efforts on improving resource provision (national and local), surveillance, enhancing communication, increased testing and the development of policies and guidance to limit dissemination. A CPE expert advisory group (EAG) was convened to provide evidence-based guidance to the NPHET. This EAG first met in December 2017 and reviewed surveillance data, responded to enquiries on preventative aspects and reviewed draft clinical guidelines, i.e. for acute hospitals and specific services, such as haemodialysis. It has also supported the NPHET in securing additional funding (€24.4 million with 301 whole time equivalents posts in 2018–2021). It has also reviewed the evolving epidemiology to inform national strategy and ensure alignment with
the publicly funded healthcare service, the Health Service Executive’s (HSE) antimicrobial resistance and infection control (AMRIC) implementation plan. An interim analysis of the effectiveness of that NPHE process has been recently reported [8]. Governance structures were established within the HSE to oversee and direct the establishment of a CPE Implementation Team (later incorporated into AMRIC Oversight and Implementation Teams) who were tasked with the implementation of guidance agreed by the CPE NPNET and EAG (e.g. implementation of CPE screening programme).

Epidemiology of CPE in Ireland

In 2011, CRE was made a notifiable infection in Ireland. In 2012, the National Carbapenemase-Producing Enterobacteriales Reference Laboratory (NCAPERL) was established. These decisions assisted in assessing the true extent of CPE. The declaration of an NPHE has given greater impetus to more widespread surveillance and improved IPC. Surveillance resulted in increased reporting of clusters and outbreaks. Although one of the best-characterised outbreaks was caused by NDM carbapenemase, CPE mediated by OXA-48 has been more common [9]. In one prevalence survey, 1.38% of in-patients were colonised, all with OXA-48 [10]. While 65% of CPE in Ireland in 2018 was from hospital inpatients and 87% from screening specimens, CPE has also been detected from patients attending general practitioners. In addition, CPE has been detected in aquatic environments, including hospital effluent, a potential route for wider dissemination [11].

The latest annual summary data to the end of 2020 is outlined in Figure 1. Active surveillance maintained through the coronavirus disease 2019 (COVID-19) pandemic demonstrates a low prevalence. Monthly updates to the end of September 2021 are available at https://www.hpsc.ie/a-z/microbiologyantimicrobialresistance/strategyforthecontrolofantimicrobialresistanceinireland/ncaperslcarbapenem-resistant-enterobacteriaeeaeu/surveillanceofcpeinireland/cpemonthlysurveillancereports/AMRIC%20September%202021%20CPE%20monthly%20report-MC-Agreed.pdf. The data show a stable level of acquisition of CPE colonisation and ongoing detection from hospital environments where sampling is performed. Reference laboratory data show that the CPE genotype detected in hospital environments generally corresponds to that genotype acquired in that hospital (data not shown).

Ongoing IPC issues

Here, we reflect on a series of questions considered by the EAG to address ongoing issues and what needed to be done next (Table 1).

Is CPE endemic in Ireland?

No. The declaration of an NPHE led to a structured programme of increased testing on acute hospital admission, based on national guidelines (https://www.hpsc.ie/a-z/microbiologyantimicrobialresistance/strategyforthecontrolofantimicrobialresistanceinireland/cpe/ncaperslcarbapenem-resistant-enterobacteriaeeaeu/guidanceandpublications/Control%20of%CPE%20in%20the%20acute%20hospital%20setting.pdf), monthly reporting of CPE and an assessment of laboratory capacity. All new CPE are submitted to the NCAPERL for characterisation.

The term ‘endemic’ is classically applied to an infection. Here, it is appropriate to include CPE infection and colonisation. An endemic state implies that the condition persists at a baseline level in an area in the absence of continued new introduction. The rate of new detections for CPE appears to have reached a relatively stable plateau (approximately 15 per 100 000 population per year for 2019 and 2020, with 709 and 705 new detections, respectively, in a population of 4.9 million). The great majority has been in people with no history of travel outside Ireland, e.g. the index case in the first report of NDM CPE was admitted to hospital from the community [9]. Particular carbapenemases, such as KPC or OXA-48 and specific OXA-48 plasmids have persisted in some hospitals for over a decade [12].
most do not show this pattern. Although outbreaks in community
long-term care facilities have occurred, there are no reports of per-
sistent foci of acquisition. Therefore, it is not currently endemic in
the community and hence there may be an opportunity to prevent
it becoming endemic throughout the healthcare system.

**Is CPE acquisition still primarily associated with acute hospitals?**
Yes. CPE acquisition without associated in-patient hospital stay is
relatively uncommon in Ireland. However, CPE has been detected
in the partners of people with CPE, suggesting that the household
transmission of CPE can occur.

CPE has been detected in hospital effluent, sewage and seawater,
emphasising the risk that CPE could disseminate into the wider
environment from hospitals. However, in contrast to extended
spectrum beta lactamase (ESBL)-producing Enterobacterales, CPE
is currently not as frequently detected in water outlets and sewage
[13, 14]. This suggests that effective control or eradication may still
be possible, as the main challenge is in hospitals.

**What is the contribution of persistent hospital environmental
reservoirs?**
The enhanced focus on screening for asymptomatic carriage of CPE
and contact precautions is likely to have limited person-to-person
transmission. It is difficult to quantify the proportion of CPE
acquired from person-to-person transmission, compared with per-
sistent environmental reservoirs. However, based on isolates submit-
ted to the NCPERL, the detection in damp areas (e.g. showers,
sinks) is common in hospitals with persistent acquisition. The
extent of this was not apparent until the widespread adoption of
national guidance on sampling. Based on the match between environ-
mental and patient isolates, we consider that acquisition from
persistent environmental reservoirs is now a key factor in hospital
acquisition. Therefore, an effective approach to manage the risk
from persistent environmental reservoirs is needed.

**Should we increase the emphasis on reducing the risk from
persistent reservoirs?**
Yes. In Ireland and elsewhere, CPE has been detected from
showers, sinks and patient toilets in hospitals [6, 11]. Managing
this requires the optimisation of infrastructure, including the
installation of modern sanitary ware that is more appropriate
for hospital settings, and effective cleaning/decontamination.
Hospitals with ongoing transmission need to identify transmis-
sion hot spots with appropriate environmental testing. Our
experience is that detection in the environment is critically
dependent on sampling and testing methods. Sampling the hos-
pital environment with a standard diagnostic swab fails to detect
contamination that is revealed with more rigorous methods recom-
manded by the CPE EAG (https://www.hse.ie/eng/about/who/health
wellbeing/our-priority-programmes/hcai/resources/cpe/environment-
testing-for-carbapenemase-producing-enterobacterales.pdf). In
the absence of suitable sampling methods, the extent of environ-
mental contamination is likely to be underestimated. New
approaches to reduce the level of CPE in drains and/or back wash
down and to touched surfaces, may also be required.

**What is the role of antimicrobial stewardship in controlling
CPE acquisition?**
Exposure to broad-spectrum antimicrobial agents is a risk factor
for CPE acquisition [15]. Antimicrobials probably select for
CPE colonisation if a patient is exposed to CPE, and are likely
to increase shedding of CPE in the faeces of colonised patients.
Antimicrobials in urine and faeces may contribute to sustaining
CPE in hospital drainage systems. Avoiding unnecessary antimi-
crobials and minimising the use of broad-spectrum agents are
likely to be important in controlling CPE, and may reduce the
risk of CPE gaining access to and persisting in hospitals.

**Does community acquisition and spread justify extending
screening to the community?**
No. The greatest risk of transmission with adverse consequences, e.g.
BSI, occurs in acute hospitals. Hence, this is where testing for carriage
is most important. While there may be CPE carriers in the commu-
nity, the risks of transmission and infection there are probably low.
Furthermore, increasing the numbers tested on hospital admission
will detect such patients. Therefore, currently there is no requirement
to extend screening for CPE carriage outside of acute hospitals in
Ireland, e.g. in nursing homes and other residential care units.

**Next steps**
Guidelines on CPE/CRE understandably focus on acute care
[5, 16]. National priorities on controlling multi-drug-resistant
bacteria will vary by country, epidemiology and the political
priority it is accorded (https://www.gov.uk/government/publications/g7-health-ministers-meeting-june-2021-communique/g7-health-ministers-meeting-communique-oxford-4-june-2021).

In Israel in the mid-2000s, a national strategy was implemented to control CPE in response to large numbers of cases [17]. This addressed testing, specific nursing staff assigned to CPE positive patients. A reduction in new acquisitions followed, prompting reform of national infrastructure for IPC, surveillance of healthcare-associated infections (HCAIs), the strengthening of reference laboratories, a national programme for antibiotic stewardship and a focus on antimicrobial agents in agriculture.

Most measures to contain CRE/CPE are generic, and apply to other HCAIs. Furthermore, as in Ireland, the declaration of an NPHE around CPE has supported and will continue to help co-ordinate investment in building IPC capacity and infrastructure, especially in hospitals with older buildings and outdated physical infrastructure.

Failure to control CPE has significant financial consequences. An economic evaluation of a CPE outbreak in London in 2014–2015 estimated costs at £1.33 million, the largest cost being reduced capacity for elective procedures due to bed closures [18]. A simulation of a toolkit from the US Centers for Disease Control and Prevention found that cost savings were greatest if all hospitals implemented a regional coordinated approach [19]. Hence, such an approach across hospitals and applied nationally where possible, is most likely to be effective, and is a prudent use of resources.

The declaration of the CPE NPHE, reflecting a strong policy commitment in Ireland, has seen a greater emphasis on the prevention of HCAIs and enhanced IPC measures. This national approach with associated governance arrangements, performance measurements, management systems and structures has supported and informed the establishment of an NPNET to address the COVID-19 pandemic in Ireland. This has resulted in a coordinated and multi-agency approach, with many positive consequences. This was not the case in Ireland when MRSA or ESBL-producing Enterobacteriaceae emerged some decades ago, with both becoming irreversibly endemic in the country.

Following the NPHE response, CPE acquisitions have stabilised [8] (and Fig. 1). This reflects progress in reducing person-to-person acquisition through the detection of colonised individuals and the implementation of transmission-based precautions. However, surveillance for acquisition, environmental sampling and molecular characterisation of isolates has suggested a key role for persistent environmental reservoirs in hospitals. These have likely contributed to failures to eradicate CPE acquisition in some hospitals, notwithstanding rigorous measures to reduce person-to-person transmission. Therefore, measures to manage person-to-person transmission, must be accompanied by a focus on environmental monitoring and control, to drive the transition from stable levels to progressive reduction and even eradication.

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Ethical standards. The data described were collected as part of a national surveillance strategy and all patient data were anonymised, hence, no ethical issues arise.

Data availability statement. Much if not most of the data described is publicly available. However, we are happy to facilitate researchers, healthcare professionals and others in accessing other data and information on enquiry with reasonable requests.

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