



Review

# Control of carbapenemase-producing Enterobacteriaceae outbreaks in acute settings: an evidence review

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## SUMMARY

**Background:** In recent years, infections with carbapenemase-producing Enterobacteriaceae (CPE) have been increasing globally and present a major public health challenge. **Aim:** To review the international literature: (i) to describe CPE outbreaks in acute hospital settings globally; and (ii) to identify the control measures used during these outbreaks and report on their effectiveness.

**Methods:** A systematic search of MEDLINE and EMBASE databases, abstract lists for key conferences and reference lists of key reviews was undertaken, and information on unpublished outbreaks was sought for 2000–2015. Where relevant, risk of bias was assessed using the Newcastle–Ottawa scale. A narrative synthesis of the evidence was conducted.

**Findings:** Ninety-eight outbreaks were eligible. These occurred worldwide, with 53 reports from Europe. The number of cases (CPE infection or colonization) involved in outbreaks varied widely, from two to 803. In the vast majority of outbreaks, multi-component infection control measures were used, commonly including: patient screening; contact precautions (e.g. gowns, gloves); handwashing interventions; staff education or monitoring; enhanced environmental cleaning/decontamination; cohorting of patients and/or staff; and patient isolation. Seven studies were identified as providing the best-available evidence on the effectiveness of control measures. These demonstrated that CPE outbreaks can be controlled successfully using a range of appropriate, commonly used, infection control measures. However, risk of bias was considered relatively high for these studies.

**Conclusion:** The findings indicate that CPE outbreaks can be controlled using combinations of existing measures. However, the quality of the evidence base is weak and further high-quality research is needed, particularly on the effectiveness of individual infection control measures.

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## Introduction

In recent years, infections with carbapenemase-producing Enterobacteriaceae (CPE) have been increasing globally.<sup>1–3</sup> Carbapenem antibiotics are usually reserved for treating serious drug-resistant infections;<sup>4</sup> as such, the emergence of resistance to carbapenems is a major public health concern. Patients infected with CPE have limited treatment options and high mortality rates (26–44%, based on a recently published review).<sup>5</sup> CPE transmission may occur in both healthcare and community settings.<sup>1,6,7</sup> Hospitalized patients may be particularly susceptible to infections; CPE is associated with increased risks of morbidity and mortality, prolonged hospital stay and increased healthcare costs.<sup>8,9</sup> A number of risk factors for CPE acquisition have been identified, including previous hospitalization (particularly abroad, e.g. in an endemic country), prolonged hospitalization, previous exposure to antibiotics, surgery, organ or stem cell transplantation, critical illness/residency in an intensive care unit, transfer between units, and exposure to invasive/indwelling devices (e.g. catheters).<sup>8,10–14</sup> Outbreaks associated with contaminated endoscopic equipment have also been documented.<sup>15–18</sup>

The control of CPE in hospital settings is not only costly<sup>19</sup> but presents a significant challenge. Reliable laboratory detection of CPE is an essential first step but may be hampered as a range of different mechanisms can cause resistance, and this may occur to varying degrees; not all laboratories are equipped to detect all types of CPE.<sup>20–22</sup> Meanwhile, asymptomatic CPE-colonized patients may be an important source of infection, spreading the bacteria to other patients before they are identified as carriers.<sup>22</sup> These difficulties in the detection of cases, combined with the challenges in treating the infection once it is diagnosed, may allow for the rapid dissemination of CPE. Various agencies, societies and countries have developed guidelines on CPE control.<sup>23</sup> These recommend a range of control measures including early detection of cases, isolation of patients, patient/staff cohorting and enhanced hygiene measures.<sup>24</sup> However, evidence on the effectiveness of such measures is lacking, as highlighted in a review of measures to prevent the transmission of CPE through cross-border transfer of patients conducted by the European Centres for Disease Control (ECDC).<sup>25</sup>

CPE outbreaks occur in acute settings with worrying frequency, and there is a need to identify the most effective methods of control. As such, a comprehensive evidence review was undertaken with two main objectives: (i) to describe CPE outbreaks in acute hospital settings globally; and (ii) to identify the control measures used during these outbreaks and report on their effectiveness.

## Methods

### Study conduct

This review was conducted based on the Cochrane Handbook for Systematic Reviews of Interventions,<sup>26</sup> and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).<sup>27</sup>

### Search strategy

MEDLINE and EMBASE were searched for papers published in the English language between 2000 and 2015 on 5<sup>th</sup> May 2015

(Appendix 1). Searches combined MeSH terms and free-text key words. Search terms for 'CPE' were based on those used in the ECDC review.<sup>25</sup> The Cochrane Library was also searched, together with reference lists of relevant reviews. Abstract lists for conferences of the following organizations were searched: Public Health England; the Healthcare Infection Society and Infection Prevention Society; the European Society of Clinical Microbiology and Infectious Diseases; the Centers for Disease Control and Prevention Epidemic Intelligence Service; and the Federation of Infection Societies. To obtain information on unpublished outbreaks, the outbreaks database of Public Health England was searched, and information on European outbreaks was requested from ECDC. All records were imported into an Endnote database.

### Study selection

To be eligible for inclusion in the review as a whole, studies had to: (i) report on a CPE outbreak in an acute setting; and (ii) report on the control measures used during the outbreak. Once the final list of eligible studies had been selected, a subset of studies providing the best-available evidence on the effectiveness of control measures was identified. The PICO for the substudy was as follows:

- Patients: patients in an acute care setting at potential risk of CPE infection or colonization in the context of an outbreak;
- Intervention: introduction of (any type of) specific infection control measures;
- Comparator: no introduction of these specific infection control measures (or introduction of less rigorous measures); and
- Outcome: measure of the occurrence of CPE colonization and/or infection (e.g. number, rate).

To be eligible for inclusion in the subset, studies had to: (i) utilize a comparator group (e.g. phased introduction of control measures enabling comparisons); (b) provide sufficient detail on the type and timing of infection control measures; and (c) quantitatively report on the outcome in the intervention and comparator groups.

For the purpose of this review, an outbreak was defined as two or more cases of CPE infection epidemiologically linked in time and place. However, once this definition had been met, to assist in differentiating between an outbreak and prevalence data, if the authors described the situation as an outbreak or cluster then this was accepted. Studies reporting on CPE infections and/or colonizations were eligible, and no restriction was placed on the type of infection control measures used. In selecting studies for inclusion in the review as a whole, all types of primary studies (e.g. descriptive studies, cohort studies and trials) were included. Literature reviews, expert opinion and guidance documents were not eligible for inclusion, but the reference lists were used to identify any additional eligible primary studies. Although conference abstracts were eligible for inclusion in the review as a whole, they were not considered for inclusion in the subset of best-available evidence studies due to limited information.

Records were screened independently for eligibility by two reviewers, with disagreements resolved by discussion. Where multiple studies on the same outbreak were identified, the

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