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Implementation of an antimicrobial stewardship programme and reduction in carbapenemase-producing Enterobacterales in an Australian local health district

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Background: Carbapenemase-producing Enterobacterales (CPE) are increasingly seen in Australian hospitals. Antimicrobial stewardship (AMS) interventions have been shown to reduce rates of carbapenem-resistant organisms; data on their effect on CPE rates are limited.

Objectives: To explore the effect of a multi-site computer-supported AMS programme on the rates of CPE in an Australian local health district.

Methods: All laboratory CPE isolates between 2008 and 2018 were identified. Microbiological and demographic data, CPE risk factors and outcomes were collected. Monthly carbapenem use was expressed as DDD per 1000 occupied bed days (OBD). Hand hygiene compliance rates among healthcare workers were analysed. A computer-supported AMS programme was implemented district-wide in 2012. Bivariate relationships were examined using Pearson's *r* and predictors of CPE isolates using time series linear regression.

Results: We identified 120 isolates from 110 patients. Numbers of CPE isolates and carbapenem use both showed a strong downward trend during the study period; the decreases were strongly correlated ($r = 0.80$, $P = 0.006$). The positive relationship between carbapenem use and CPE isolation was maintained while adjusting for time ($b = 0.05$, $P < 0.001$). Average yearly consumption of carbapenems fell by 20%, from 18.4 to 14.7 DDD/1000 OBD following implementation of the AMS programme. Hand hygiene compliance rates remained high throughout.

Conclusions: We demonstrated a reduction of CPE isolates in conjunction with reduced carbapenem use, longitudinally consolidated by a formal AMS programme. Prospective studies are needed to validate the effect of AMS on carbapenem resistance, especially in high-prevalence settings.

Introduction

Carbapenemase-producing Enterobacterales (CPE) are being increasingly isolated in many countries worldwide.[1–4] This is concerning, since carbapenems are often 'last-line' antimicrobials for infections caused by MDR Gram-negative bacteria. In Australia, CPE are generally isolated during small outbreaks or from patients with overseas healthcare contact.[4] They have become endemic in some ICUs.[5–7] In 2017, CPE comprised 81% of all critical antimicrobial resistances (CARs) confirmed from blood culture specimens

and reported to the national alert system for CARs (CARAlert).[8] Despite this, overall CPE numbers in Australia remain low in comparison with other countries, including several in the Asia-Pacific region.[7] Between 1 October 2017 and 31 March 2018, there were 528 CPE isolates in Australia reported to the CARAlert system;[9] however, data on the exact incidence nationwide are limited by inconsistent reporting and a lack of uniform methods for detection.[4]

There is evidence of worse outcomes with CPE infections compared with those caused by susceptible Enterobacterales,[1,5,10,11] with reported mortality rates for CPE infections varying from 22.2% (attributable mortality)[12] to 71.9% for bacteraemias.[13]

Risk factors for CPE acquisition include increasing age, reduced functional status, living in a long-term care facility and invasive procedures.[3,4,14,15] Overseas travel and healthcare contact in endemic settings have been recognized as risk factors in Australia.[5,16] Carbapenem use has been associated with a high prevalence of carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.[1,17,18] Some evidence exists for the association of prior use of carbapenems[1,3,18,19] and other broad-spectrum antimicrobials with the isolation of carbapenem-resistant Enterobacterales (CRE; including CPE).[3,10,14,15] Conclusions are limited by differences in study methodologies and the definition and mechanisms of carbapenem resistance.

Antimicrobial stewardship (AMS) programmes have been shown to reduce rates of carbapenem-resistant *P. aeruginosa* and *A. baumannii*.[14,20] In Australia, AMS programmes are mandatory in all hospitals in line with Standard 3 of the National Safety and Quality Health Service (NSQHS) Standards developed by the Australian Commission on Safety and Quality in Healthcare (ACSQHC).[21] The ACSQHC also established the Antimicrobial Use and Resistance in Australia (AURA) surveillance system to provide a nationally coordinated system for monitoring antimicrobial resistance, including CPE, and antimicrobial use.[8] As part of AURA, CARAlert was established to collect data on priority organisms, including CPE.[9] A National Antimicrobial Utilisation Surveillance Program (NAUSP) has also been established for monitoring and benchmarking antimicrobial use in Australian hospitals.[22]

AMS interventions have been shown to be more successful when implemented alongside infection control measures, particularly hand hygiene interventions, as a bundle of care.[20] Data on reduced CPE rates following AMS intervention are not longitudinal and are limited to small studies in countries with high CPE prevalence.[23–26]

In this study we report a continuous reduction in the number of CPE isolates in an Australian local health district, in particular following the introduction of a multi-site computer-supported AMS programme, with an associated reduction in carbapenem use. We also examined previously reported risk factors for CPE acquisition: overseas travel, prior healthcare contact, exposure to ICU and residential aged-care facility (RACF) residence. The effect of longitudinal hand hygiene compliance among healthcare workers was also assessed.

Materials and methods

The Illawarra Shoalhaven Local Health District (ISLHD) in New South Wales (NSW), Australia extends from the Royal National Park south of Sydney for 250 km down the coast and services a population approaching 400 000. It comprises a tertiary referral hospital and two regional hospitals, as well as five smaller hospitals primarily used for rehabilitation and aged care services. All microbiological specimens from these hospitals are processed centrally at the tertiary referral hospital in Wollongong. Records of CPE isolated in the ISLHD began in 2008. In May/June 2012, an AMS programme supported by a computerized clinical decision support system (CDSS) (GuidanceMS®[17]) was uniformly implemented across the district. GuidanceMS®[17] is an intranet browser-based CDSS with integrated antimicrobial guidelines and antimicrobial restriction, which provides guidance to prescribers and generates approvals for restricted antimicrobials.[27] The AMS programme also includes daily infectious diseases physician-led post-prescription review of restricted antimicrobials flagged by GuidanceMS®[17] (mainly third-generation cephalosporins, IV β-lactam/β-lactamase inhibitors, carbapenems and fluoroquinolones) and a local 24 h AMS telephone hotline for advice on antimicrobial use.[27,28]

All CPE isolated from clinical specimens and screening swabs over an 11 year period (between 1 January 2008 and 31 December 2018) were identified by a search of the computerized laboratory information system (Integrated Software Solutions ISS Omni-Lab v11.1.23®). Where the same species was isolated from different specimens (e.g. blood and urine) from the same patient during the same admission, only one specimen was included. Data regarding the date of collection, geographical location of collection, type of specimen, bacterial species isolated and the gene(s) conferring carbapenem resistance (if available) were collected. Antimicrobial susceptibility was determined by the Calibrated Dichotomous Susceptibility (CDS) agar disc diffusion method.[29] Expression of an MBL was confirmed by demonstrating loss of enzymatic activity following the chelation of zinc ions using an EDTA disc adjacent to a carbapenem disc (Bell CDS).[29] From 2011 onwards, isolates resistant to carbapenems or suspected to be CPE based on phenotypic testing with the CDS method were routinely referred for confirmatory testing to identify the carbapenemase gene. This was performed using an in-house multiplex PCR assay (with targets for bla_{IMP}, bla_{OXA-48}, bla_{NDM}, bla_{KPC} and bla_{VIM}) at the Molecular Microbiology/CDS Reference Laboratory, NSW Health Pathology, St George Hospital, Kogarah, NSW, Australia.

CPE screening across the health district was performed according to local Infection Management and Control Service (IMACS) guidelines for contacts of known CPE cases and patients with overseas healthcare contact prior to admission.[30] Where a patient was found to be positive for CPE, they were isolated in a single room with a private bathroom, contact precautions were instituted and environmental cleaning was performed in accordance with ACSQHC recommendations for the control of CPE.[4] Methods for antimicrobial susceptibility testing, CPE detection and CPE screening policies remained unchanged throughout the study period. There were no CPE outbreaks during the study period.

Patient electronic medical records were reviewed to identify: gender; age at CPE isolation; healthcare contact within 90 days of admission (timeframe extended to 12 months if none within 90 days); overseas travel within 6 months of admission; RACF residence at the time of admission; whether the patient had admission to an ICU, high dependency unit (HDU) or neonatal unit (NNU) prior to CPE detection; and 30 day all-cause in-hospital mortality. CPE acquisition was categorized by IMACS as community, inpatient healthcare-associated, outpatient healthcare-associated or non-ISLHD healthcare-associated (i.e. out of district) based on standardized definitions.[31] Hand hygiene compliance data for medical and nursing staff were available for the years 2010–18 from routine audits performed in accordance with Hand Hygiene Australia's audit programme. This is based on the WHO's '5 moments for Hand Hygiene' methodology.[32] The audit programme stipulates three audit cycles per year and data on 200–350 hand hygiene moments per audit cycle per ward are collected (depending on facility size).[33]

Monthly antimicrobial use data for each carbapenem (ertapenem, imipenem/cilastatin and meropenem) across the study period were extracted from data previously submitted to the NAUSP.[22] Doripenem was not used during the study period. Data on the use of other broad-spectrum

antimicrobials targeted by the AMS programme (third- and fourth-generation cephalosporins, glycopeptides, fluoroquinolones, aminoglycosides and extended-spectrum penicillin/β-lactamase inhibitor combinations) were also available for the same time period. Antimicrobial usage data were derived from iPharmacy® dispensing software and patient admission data and converted into DDD per 1000 occupied bed days (OBD) as per WHO Collaborating Centre for Drug Statistics Methodology.[34]

The study was assessed by the joint University of Wollongong and ISLHD human research and ethics committee and exempted from requiring formal ethics review.

Statistical analysis

We plotted CPE isolate numbers, antimicrobial use and hand hygiene by year blocks from 2008 to 2018. To examine bivariate relationships between individual time series we computed Pearson's *r* correlation coefficients. Since positive autocorrelation and time trends of individual time series could increase type I error rates[35] we repeated the correlation analysis using first-differenced data. By replacing the time series with the difference between successive observations,[36] both trend and autocorrelation could be removed from the individual series. Carbapenem use was then examined as a predictor of CPE isolation by fitting a time series linear regression with a first-order autoregressive process. All statistical tests were two-sided and *P* values <0.05 were considered statistically significant. The statistical analyses were conducted using SAS 9.4.

Results

In total, 122 CPE isolates were identified between 1 January 2008 and 31 December 2018. After excluding two duplicate (identical, same-day) samples, 120 isolates from 110 unique patients were analysed. One hundred and thirteen (94%) isolates were from clinical specimens and 7 isolates (6%) from CPE screening rectal swabs. The majority of clinical isolates were from urine (69/113, 61%), followed by wound swabs (16/113, 14%) and blood (13/113, 12%). The remaining 15 isolates were from sputum, bone/other operative tissue, drain fluid, bile, a central venous catheter tip and a vaginal swab. Eight patients had more than one (up to three) different CPE species isolated.

Table 1 contains data on the number of CPE isolates per year, carbapenem use, CPE acquisition type and hand hygiene compliance. Carbapenem use in our district was principally meropenem (96%), with ertapenem (2%) and imipenem/cilastatin (2%) together comprising a negligible percentage, which remained stable throughout the study period. The median age of patients was 76 years (IQR 66–82) and 52% were male. The 30 day in-hospital all-cause mortality rate was 5% (6/113 patients), with 3 patients having septicaemia or infection listed as their cause of death.

Between 2008 and 2018, carbapenem use and numbers of CPE isolates showed a strong downward trend (Figure 1). At the same time, hand hygiene compliance showed a moderate upward trend

Table 1. Carbapenem use, CPE numbers, CPE acquisition type and hand hygiene compliance

		CPE isolates					
				CPE acquisition type, *n* (%)[b]		Hand hygiene[a]	
Year	Meropenem, ertapenem and imipenem/cilastatin (DDD per 1000 OBD)	total CPE isolates (*n*)	no. isolates per 10 000 OBD	healthcare associated[c]	community[d]	compliance (%)	total moments measured (*n*)
2008	25.8	16	1.29	10 (63)[e]	1 (6)	—	—
2009	23.2	16	1.08	14 (88)	2 (13)	—	—
2010	14.3	9	0.48	8 (89)	1 (11)	86	982
2011	15.2	14	0.63	9 (64)	5 (36)	77	17 418
2012[f]	13.3	10	0.45	7 (70)	2 (20)	77	20 250
2013	19.1	14	0.65	11 (79)	3 (21)	81	36 063
2014	16.6	11	0.51	6 (55)	4 (36)	84	37 658
2015	13.6	10	0.43	7 (70)	2 (20)	83	36 043
2016	11.7	9	0.38	5 (56)	4 (44)	85	35 690
2017	15.1	6	0.26	4 (67)	2 (33)	87	42 583
2018	12.3	5	0.28	2 (40)	3 (60)	87	28 654

[a]Composite hand hygiene compliance data for medical and nursing staff across ISLHD.
[b]CPE acquisition categorized as per local IMACS guidelines, which are based on standardized CDC definitions.
[c]Healthcare associated, composite of inpatient healthcare associated and outpatient healthcare associated; inpatient healthcare associated, CPE identified in a sample collected more than 48 h after ISLHD admission or within 48 h of discharge from an ISLHD facility; outpatient healthcare associated, CPE identified in a sample that relates to infection in an indwelling device inserted within an ISLHD facility or procedure undertaken within an ISLHD facility outside the 48 h window.
[d]CPE identified but no known contact with an ISLHD facility. Three patients had non-ISLHD healthcare-associated acquisition, i.e. CPE identified in a patient transferred to ISLHD from a non-ISLHD facility and sample collected within 48 h of ISLHD admission. This is not shown in the table.
[e]In 2008 there were five patients where the CPE acquisition type was unable to be categorized. These are not shown in the table.
[f]An AMS programme was implemented uniformly across the district in May/June 2012. Average yearly consumption of carbapenems in the period prior to AMS implementation was 18.4 DDD/1000 OBD. Average yearly consumption of carbapenems in the period following AMS implementation fell to 14.7 DDD/1000 OBD.

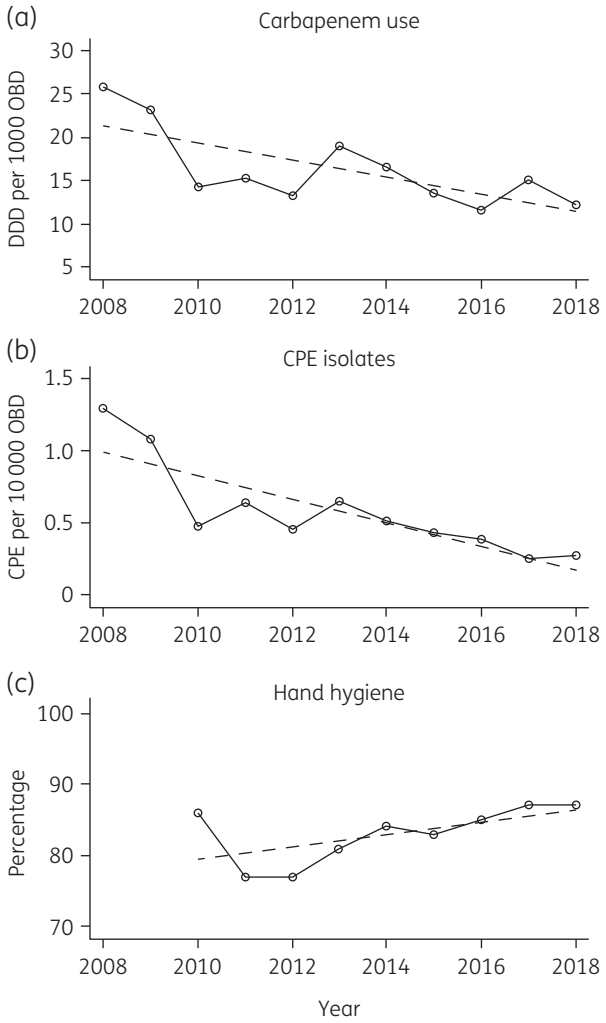

Figure 1. Trends in carbapenem use, CPE isolate numbers and hand hygiene over time. (a) Carbapenem use shown as DDD per 1000 OBD. (b) Number of CPE isolates per 10 000 OBD. (c) Percentage of hand hygiene compliance across the health district. Linear time trends are shown in dotted lines.

between 2010 and 2018 and remained at a high level throughout the study period. The decrease in the number of CPE isolates was strongly correlated with the decrease in carbapenem use ($r = 0.94$, $P < 0.001$). Numbers of CPE isolates were negatively correlated with hand hygiene compliance rates ($r = -0.70$, $P = 0.038$) (Figure 1). Using first-differenced data, the number of CPE isolates was still correlated with carbapenem use ($r = 0.80$, $P = 0.006$), but no longer related to hand hygiene compliance ($r = -0.33$, $P = 0.426$). Carbapenem use and hand hygiene were not correlated using either the original data ($r = -0.24$, $P = 0.541$) or first-differenced data ($r = 0.15$, $P = 0.725$). The time series regression analysis showed that the positive relationship between CPE isolation and carbapenem use was maintained while adjusting for time ($b = 0.05$, $P < 0.001$).

The average yearly consumption of carbapenems fell from 18.4 DDD/1000 OBD in the years prior to implementation of the AMS programme to 14.7 DDD/1000 OBD in the years following AMS introduction (Table 1). In addition to carbapenems, usage of other broad-spectrum antimicrobials (glycopeptides, fluoroquinolones, aminoglycosides and extended-spectrum penicillin/β-lactamase inhibitor combinations) across the district between January 2008 and February 2018 also showed a statistically significant downward trend, with the exception of third- and fourth-generation cephalosporins (Figure S1, available as Supplementary data at *JAC-AMR* Online).

CPE were primarily categorized as 'hospital acquired' across the study period (Table 1). The distribution of resistance genes did not change significantly across the study period and consisted of bla_{IMP} in the vast majority of samples (Figure 2). One patient had two different CPE species, one carrying bla_{NDM} and the other bla_{OXA-48}; this patient had overseas healthcare contact in India. Two patients who had had healthcare contact in other hospitals in Australia also had non-IMP CPE genes isolated: one bla_{NDM} and one bla_{VIM}. There were no isolates carrying bla_{KPC}.

From the available data on other factors previously described as being associated with CPE acquisition, 26/93 (28%) patients had a preceding ICU, HDU or NNU admission. Nine out of 94 (10%) patients were residents of an RACF at the time of admission, with 2 having community acquisition of their CPE. Only 3/93 patients (3%) had documented overseas travel within the preceding 6 months, including 1 patient to the Indian subcontinent who had two different CPE species isolated with two different CPE genes. More than two-thirds (70/101, 69%) of patients had documented healthcare contact within 90 days prior to admission, rising to 79% (80/101) when the time frame was extended to 12 months.

Discussion

We observed a strong correlation between reduction in carbapenem use and the number of CPE isolates in hospital patients within an Australian local health district. CPE rates fell from 1.29/10 000 OBD in 2008 to only 0.28/10 000 OBD in 2018, which contrasts with the overall increasing incidence in Australia.[5,6] At the same time, the average yearly consumption of carbapenems fell from 18.4 DDD/1000 OBD in the 4 years prior to implementation of the AMS programme to 14.7 DDD/1000 OBD in the 6 years following AMS introduction and showed a steady downward trend. Hand hygiene compliance remained consistently high throughout the study (from 86% in 2010 to 87% in 2018). Of note, methods of screening and laboratory detection of CPE remained unchanged during the study.

Reductions in some CPE organisms, in association with reduced carbapenem use, have been sporadically reported in different countries.[23–26] Those studies, performed with different methodologies in different hospital settings, examined the effect over a short period of time (between 12 months and 4 years). To our knowledge, this is the first study showing a sustained longitudinal reduction in CPE rates, consolidated after the implementation of a multi-site computer-supported AMS programme where carbapenem use was targeted and consistently and significantly reduced. Of note, use of several other broad-spectrum antimicrobials also reduced during the study period across the district. This highlights the effect of the local AMS programme; however, it may interfere with the interpretation of the effect of carbapenem usage alone on the reduction in CPE isolates, given that other broad-spectrum antimicrobials have been associated with CPE isolation in other settings.[3,10,14,15]

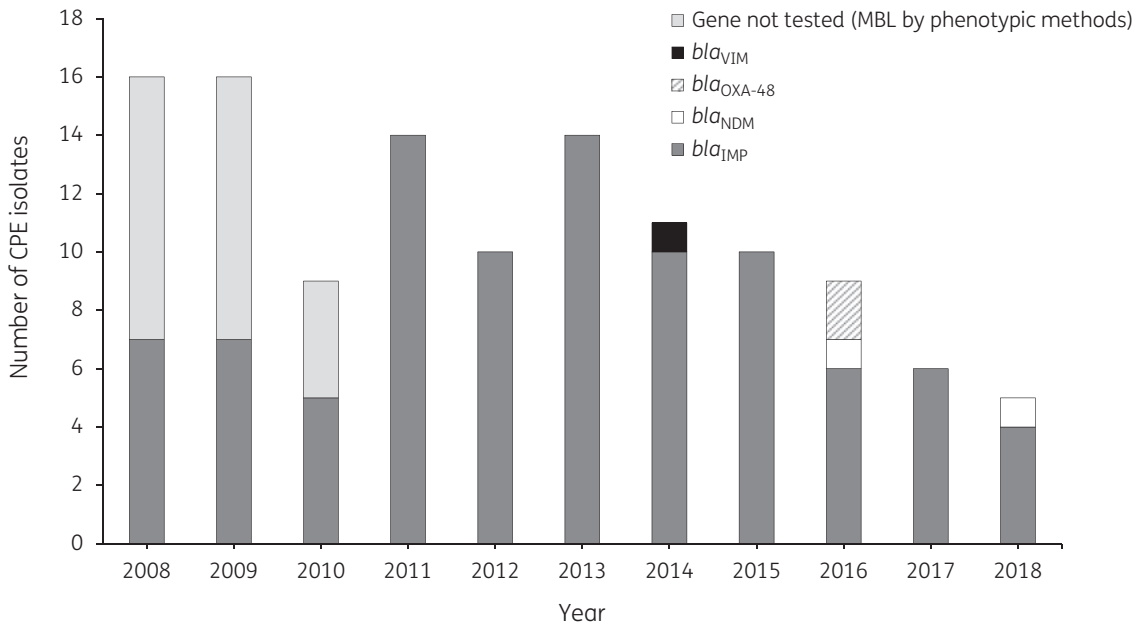

Figure 2. Distribution of CPE genes over time.

CPE acquisition type was predominantly 'healthcare' over the study period. CPE gene type was almost exclusively bla_{IMP}, unless a patient had overseas healthcare contact or contact with another health facility elsewhere in Australia. This is consistent with the literature, with bla_{IMP} (particularly bla_{IMP-4}) being the most prevalent carbapenemase gene found in NSW, Australia.[8] Given that only four patients in the study had confirmed overseas healthcare contact, this may explain why there was not more heterogeneity in the CPE gene types as higher-prevalence countries have a greater variety of carbapenemase genes (bla_{NDM}, bla_{OXA-48}, bla_{KPC} etc.).[7]

Our retrospective study has several other limitations. The study was conducted in Australia, which is a low-prevalence setting for CPE.[5–7,9] As such, we do not know whether similar results would be seen in an endemic setting. Current evidence suggests that CPE are harder to eradicate once established as endemic.[37]

Hand hygiene compliance data were only available from 2010 onwards, thus limiting our ability to analyse its full effect on CPE reduction. The auditing methodology of hand hygiene compliance was in line with Hand Hygiene Australia's guidelines and has been shown to be a valid and reliable outcome measure for assessing the effectiveness of a hand hygiene programme.[32] Hand hygiene compliance is the only measurable component of the infection control activities in our health district and thus was used as a proxy measure for the infection control bundle of care. As a result, the present study does not allow examination of the potential effect over time of other infection prevention and control actions.

Targeted, rather than universal, CPE screening was performed in our district; higher CPE rates may be expected with universal screening and the influence of an AMS programme in such settings remains unknown. The number of CPE from screening specimens in this study is low. This may be due to the fact that Australia is a low-prevalence setting or that contacts of known CPE cases did not acquire CPE; however, the possibility of missed screening opportunities cannot be excluded as we do not have data available on CPE screening policy compliance within our health district or the total number of patients screened.

We examined the effect on CPE isolation rates longitudinally for 6 years after the implementation of an AMS programme. Despite this relatively long time frame, the implications in the longer term remain unknown, as well as the potential influence of other factors that could be associated with CPE acquisition.

Carbapenem use was high at the start of the study and started declining prior to the implementation of the AMS programme. The first cases of CPE in our district were noted in 2008. This led to active monitoring by IMACS and provided impetus to commence targeted carbapenem restriction as well as educational interventions by microbiologists and infectious diseases physicians. This occurred prior to formal computer-supported AMS implementation in 2012. Following AMS implementation, carbapenem use showed a continuous downward trend, with the lowest rates seen consistently since 2015.

Thirty-day in-hospital mortality in our study was 5%, which is lower than previously reported.[12,13] Of note, the majority of our isolates (61%) were urinary, whereas other studies have focused on mortality from CPE bacteraemia.[13] Bacteraemias accounted for 13/113 (12%) of the clinical isolates in our study but, importantly, 3/13 (23%) bacteraemic patients died. Among the six patients who died from any reason while in hospital, half had CPE bacteraemia. The effect of carbapenem resistance on mortality can be confounded by the fact that CPE isolation is associated with poor host status (i.e. increased frailty, prolonged or frequent hospitalization).[3,4]

In conclusion, we demonstrated a reduction in CPE isolates in conjunction with reduced carbapenem use in an Australian setting, longitudinally consolidated by a comprehensive district-wide AMS programme. Prospective studies are needed to confirm the influence of the AMS-driven carbapenem use reduction on carbapenemase prevalence, as well as the effect in high-prevalence settings.

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Transparency declarations

None to declare.

Supplementary data

Figure S1 and Reviewer report 1 are available as Supplementary data at *JAC-AMR* Online.

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