Epidemiology of carbapenem-resistant Gram-negative infections globally

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Purpose of review
The spread of carbapenem-resistant Gram-negative bacteria (GNB) with changes in institutional epidemiology continues to evolve worldwide. The purpose of this review is to evaluate new data with regard to the epidemiology, mechanisms of resistance and the impact of carbapenem resistance on mortality.

Recent findings
The rapid expansion of acquired carbapenem resistance is increasingly propagated by mobile genetic elements such as epidemic plasmids that transfer carbapenemase genes within and between GNB. The risk of acquisition of carbapenem-resistant Acinetobacter baumannii increases four-fold with carbapenem exposure and new meta-analyses have confirmed excess mortality associated with carbapenem-resistant Pseudomonas aeruginosa. Carbapenemase-producing Klebsiella pneumoniae, the most commonly encountered carbapenemase-producing Enterobacterales (CPE) and a major cause of high-mortality hospital-related infections, represents the most rapidly growing global threat. Carbapenem use in patients colonized with such genotypes, leads to an increase in CPE abundance in the gastrointestinal tract, which in turn increases the risk of blood-stream infections four-fold.

Summary
High-resistance rates in carbapenem-resistant GNB in many countries will inevitably complicate treatment of serious infections in vulnerable patient groups and should accelerate global attempts to overcome the impediments we face with regard to effective antimicrobial stewardship and infection prevention and control programs.

Keywords
carbapenemase-producing Klebsiella pneumoniae, carbapenem-resistant Acinetobacter baumannii, carbapenem-resistant Pseudomonas aeruginosa, epidemiology

INTRODUCTION
The spread of carbapenem-resistant Gram-negative bacteria (GNB) with the consequent change in institutional epidemiology continues to evolve rapidly worldwide despite the considerable effort put into infection prevention and control (IPC) programmes and targeted antimicrobial stewardship (AMS) interventions [1,2].

Carbapenem-resistant Pseudomonas aeruginosa (CRPA), Acinetobacter baumannii (CRAB) and Enterobacterales (CRE) remain important causes of hospital-acquired infections (HAI)s and are prioritized by the WHO as critical pathogens requiring urgent drug research and the development [3]. In fact, Klebsiella pneumoniae, the most commonly encountered carbapenemase-producing Enterobacterales (CPE), and a major cause of high-mortality HAI,s, represents the fastest growing threat to antibiotic resistance in terms of human morbidity and mortality in Europe [4**].

Carbapenem resistance in GNB results from the expression of antibiotic-inactivating enzymes and/or nonenzymatic mechanisms [5]. These may occur from mutations in chromosomal genes, but most frequently from horizontal transfer of mobile genetic element-mediated carbapenemase genes via plasmids or transposons. In this regard, since the first descriptions of a metallo-β-lactamase (MBL) IMP-1 in P. aeruginosa in 1991, OXA-23 in A. baumannii in 1993, and KPC-1 in K. pneumoniae in 2001...
KEY POINTS
- Carbapenem-resistant *P. aeruginosa* remain a major cause of high-mortality hospital-acquired infections.
- Carbapenemase encoding genes are rapidly expanding globally and are proliferating at an unprecedented rate among GNB.
- Carbapenemase-producing *K. pneumoniae* represents the fastest growing antibiotic resistance threat.
- Use of carbapenems in CPE gut colonized patients increases the risk of blood-stream infections 4× fold.
- A few international high-risk CPE clones are propagating nosocomial acquisition.

[6], carbapenemase-encoding genes have undergone exponential expansion and proliferation worldwide [7].

Up to 40% of ICU-acquired infections are caused by these three WHO priority pathogens [8] and recognition of the rapid expansion of carbapenem resistance as a consequence of the transfer of these promiscuous genetic elements within and between GNB, has changed the perspective of the magnitude of the problem and necessitated a re-evaluation of the immediate and future challenges we face (Fig. 1).

CARBAPENEM-RESISTANT PSEUDOMONAS AERUGINOSA

The capacity of *P. aeruginosa* to survive in an extraordinary variety of environmental niches, to acquire and concurrently express an astonishing array of resistance determinants and, despite these genetic transformations to maintain its virulence, endows it with all the properties necessary to have evolved into a formidable pathogen of paramount importance in HAI. To date, the global epidemiology of CRPA has not been systematically evaluated and this is contributed to by a lack of global surveillance data and the myriad mechanisms by which *P. aeruginosa* develops resistance [9*].

Resistance rates

The geographic and temporal antibiotic resistance patterns over 20 years (1997–2016) from the SENTRY surveillance program which included carbapenem resistance rates (*n* = 52,022 isolates) globally but excluding Africa and the Middle-East, have recently been published [10]. Utilising the Clinical and Laboratory Standards Institute and European Committee on Antimicrobial Susceptibility Testing standards, carbapenem resistance rates were 17.4 and 10.9%, respectively. Multidrug resistant (MDR) phenotypes were most frequently isolated in Latin America (41.1%), followed by Europe (28.4%), North America (18.9%) and the Asia-Pacific region (18.8%).

The most common infections from which *P. aeruginosa* was isolated were pneumonia in hospitalized patients (44.6%) followed by bloodstream infections (BSIs) (27.9%). In data extracted from a large US hospital database (*N* = 358 hospitals) respiratory samples were also the most frequent source of carbapenem nonsusceptible isolates (35.2%) [11].

It is important to note that MDR rates in the SENTRY program were highest in 2005–2008 and have subsequently decreased [10]. Similarly, in data from Europe in 2017, despite large intercountry variation and high carbapenem-resistance rates in Southern and Eastern Europe (25–60%, with up to 10–50% classified as MDR), a small but significant decrease in carbapenem resistance was recorded [12].

Irrespective of this, the high-resistance rates in *P. aeruginosa* in many countries will inevitably complicate treatment of serious infections and should accelerate attempts to overcome the impediments we face with regard to effective AMS and IPC interventions.

Mechanisms of resistance

In *P. aeruginosa*, carbapenem resistance may emerge following sequential chromosomal mutations, which have the effect of altering permeability and simultaneously resulting in hyperexpression of MDR efflux (MEX) pumps [5,9*] (Table 1). *P. aeruginosa* has the dubious distinction of potentially harbouring the most efflux pump genes (*n* = 39) of all GNB, and the best studied carbapenem efflux determinants are MexAB-OprM and MexEF-OprN [13,14].

A critical feature of these is that different antibiotic classes may be substrates for a single MEX pump [14] and that concurrent with hyperexpression of these MEX pumps, OprD mutants which cause in-vivo carbapenem resistance may be selected [5,9*,14]. Spontaneous mutation with expression of resistance occurs at frequency of one in 10⁶–7 wild type organisms. This process may be accelerated by overuse of antibiotics with antipseudomonal activity such as the carbapenems, particularly if therapy is prolonged [15]. It is therefore not surprising, that prior carbapenem exposure has consistently been shown on multivariate analysis to be a significant risk factor for CRPA infections in the ICU [16,17].

An equally important mechanism of resistance, and a cause of multiple outbreaks globally, is the
P. aeruginosa demonstrates substantial genomic variability [9], although the more resistant strains including CRPA belong to a few widely distributed, disease causing, dominant clones. Ninety percent of all antibiotic-resistant P. aeruginosa strains belong to one of three ‘high-risk’ clones viz. ST111, ST175 or ST235 [9*].

Impact on outcome

The clinical and economic consequences of P. aeruginosa resistance were highlighted in a meta-analysis that demonstrated a more than two-fold increased risk of mortality with MDR, and a 24% increased risk with any resistant P. aeruginosa [19]. Subsequent meta-analyses specifically comparing carbapenem-resistant and carbapenem-susceptible P. aeruginosa BSIs, confirmed a significant excess in mortality with the former [11,20]. Similarly, in neutropaenic patients, the global prevalence of carbapenem resistance and the substantial increase in mortality in association with resistant relative to susceptible strains [odds ratio (OR) 4.89] was recently described [21].

CARBAPENEM-RESISTANT ACINETOBACTER BAUMANNII

A. baumannii primarily affects compromised long-term patients and is an important cause of HAs with major outbreaks occurring globally. It is almost exclusively isolated from hospital environments where it persists for long periods and thus is notoriously difficult to eradicate once inveterated [22]. Infections are mostly acquired in ICU but are increasingly seen in the general wards and in long-term care facilities [23,24].

The organism is also known for its capacity to acquire resistance genes rapidly and for most to be extremely drug resistant (XDR). Prior colonization with CRAB and carbapenem use are significant risk factors for CRAB infections [23] with the risk for acquisition increasing four-fold following carbapenem exposure [24]. A. baumannii is accountable for more than 12% of hospital-acquired BSI in ICU [25], but wide geographic variations exist.

Resistance rates

Globally, resistance rates are increasing, with 40–70% of the isolates responsible for ICU-acquired infections, carbapenem resistant [5]. In the United States, the CRAB rates in central line-associated BSI and catheter-associated urinary tract infections are 47 and 64%, respectively [9,26]. In Europe in 2017, the mean CRAB and MDR rates in BSI were 33.4 and 28.4%, respectively [12], and in some countries, particularly those in Southern and Eastern Europe, carbapenem resistance and MDR is in excess of 80%. The prevalence of CRAB is similarly high in other parts of the world including South America (40–80%) and Asia (40–60%) [9*].

Mechanisms of resistance

Similar to CRPA, A. baumannii possesses innate resistance mechanisms against multiple antibiotics and readily acquires more resistance mechanisms [5,8,9*,25]. The most prevalent mechanism of carbapenem resistance is through carbapenem inactivation by carbapenemases, namely, the MBL and OXA-types [5,6,8,9*]. Several of these occur, some with close geographic associations (Table 2).

Equally pertinent, A. baumannii also encodes for a high number of MEX genes [13] but only expression of the adeABC efflux pump system which is present in more than 80% of clinical isolates [27],
and the combination with decreased permeability or with carbapenemases, leads to carbapenem resistance. The coexpression and synergy between resistance mechanisms is a common cause of high-level carbapenem, MDR and XDR \[5,8,9\&25\].

Compared with \textit{P. aeruginosa}, the \textit{A. baumannii} population structure is clonal in nature, with eight international lineages (IC I–VIII) having been described \[28\]. The spread of most antibiotic resistant organisms has been shown to be associated with distinct epidemic clones that belong to these clonal lineages \[22,28,29\]. The dominance of these specific lineages is determined by the capacity of the \textit{A. baumannii} pangenome to incorporate resistance determinants that support their ongoing adaptation to the hospital environment and to antibiotic pressure.

**Impact on outcome**

In a study of nosocomial pneumonia in 27 European ICUs, bacteremia (primarily due to methicillin-resistant \textit{Staphylococcus aureus} and \textit{A. baumannii}) occurred in 14.6\% of cases and was associated with prolonged ICU stay and increased mortality \[30\]. However, the attributable mortality due to CRAB remains controversial due to residual confounding factors (such as the severity of the underlying illness, the administration of inappropriate empirical antibiotics and inadequate sample sizes) \[31\]. Nevertheless, in a systematic review, patients with CRAB had a significantly higher risk of mortality and despite heterogeneity, the association remained significant in the pooled adjusted OR of 10 studies (OR 2.22) \[31\].

Furthermore, in a case–controlled study incorporating molecular techniques, infection with a specific CRAB clone may determine the prognosis of patients with BSI \[32\]. In a secondary analysis of a randomized controlled trial of patients with carbapenem-resistant, GNB infections treated with colistin or a colistin–meropenem combination, the lower mortality rates that occurred among patients with colistin resistant isolates (OR 0.285) may be explained by a loss of ‘fitness’ and virulence relative to the colistin susceptible strains \[33\].

**CARBAPENEM-RESISTANT ENTEROBACTERIALES**

\textit{K. pneumoniae} the most commonly encountered CPE is responsible for a dramatic increase in disease burden worldwide \[4**\]. One of the challenges among hospitalized patients is the asymptomatic gastrointestinal carriage of CPE which precedes, and significantly increases, the risk of developing infections caused by these pathogens \[34–36\].

This is especially so, as was recently demonstrated, if patients concurrently receive an antibiotic \[37*\]. In a long-term acute-care hospital (LTACH), colonized patients that received a carbapenem had an increased risk for a high relative abundance of KPC-producing \textit{K. pneumoniae} in the gastrointestinal tract, which in turn was associated with an increased risk of KPC bacteremia (relative risk 4.2) \[37*\]. Complicating the impending CPE crisis, colonization is protracted, and may persist in more than 40\% of patients for at least 1 year \[35\].

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**Table 2. Major mechanisms of carbapenem resistance in \textit{Acinetobacter baumannii}**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Acquisition</th>
<th>Determinant</th>
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<tr>
<td>B-lactamase:</td>
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<tr>
<td>Class A. Serine carbapenemases</td>
<td>MGE</td>
<td>KPC(^a)</td>
</tr>
<tr>
<td>Class B. Metallo-(\beta)-lactamases</td>
<td>MGE</td>
<td>VIM (-1, -2, -3, -4, -11)</td>
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<td></td>
<td></td>
<td>SIM-1</td>
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<tr>
<td></td>
<td></td>
<td>IMP (-1, -2, -4, -5, -6, -8, -10, -11, and -19)</td>
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<tr>
<td></td>
<td></td>
<td>NDM (-1, -2)</td>
</tr>
<tr>
<td>Class D. Oxacillinase-type</td>
<td>MGE</td>
<td>OXA-23 cluster: (OXA-23, -27 and -49)</td>
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<td></td>
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<td>OXA-24/40 cluster (OXA-25, -26, -40 and -72)</td>
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<td>OXA-58</td>
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<td></td>
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<td>OXA-51 cluster (n = 14 variants)</td>
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<td></td>
<td></td>
<td>OXA-48(^a)</td>
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<td></td>
<td></td>
<td>OXA-235</td>
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<tr>
<td>Impermeability</td>
<td>CM</td>
<td>High-level OXA-51</td>
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<tr>
<td>Efflux pumps</td>
<td>CM</td>
<td>Variable binding</td>
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<tr>
<td>Altered penicillin-binding proteins</td>
<td>CM</td>
<td>AdeABC</td>
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</tbody>
</table>

CM, chromosomal mutation; KPC, \textit{Klebsiella pneumoniae} carbapenemase; MGE, mobile genetic element; NDM, New Delhi metallo-\(\beta\)-lactamase; OXA, oxacillinase; VIM, Verona-integrated metalloprotease.

\(^a\)Rare.
A recent systematic review to identify risk factors for CRE acquisition, showed that use of medical devices generated the highest pooled estimate (OR 5.09) followed by carbapenem use (OR 4.71) [38]. While this may direct and inform a bundled approach to prevention [38], another unexplored risk for CPE is disturbance of the gastrointestinal microbiome [2,37,39,40]. In this regard, innovative strategies that are required to ameliorate and restore colonization resistance, needed to be explored urgently [2,37]. One option is targeted bacteriophage therapy which has recently been shown to eradicate long-term CPE colonization safely [2,35].

Prevalence rates

The global epidemiology of CRE and CPE has not been systematically evaluated. The most comprehensive continental survey to date is the European Survey of Carbapenemase-Producing Enterobacteriaceae initiative [41]. The infection prevalence of CPE was shown to be 1.3 per 10,000 hospital admissions. Subsequent genomic analysis of carbapenemase-producing *K. pneumoniae* established that the epidemic of carbapenem nonsusceptible *K. pneumoniae* in Europe is driven by the expansion of a small number of high-risk clones [42]. Of paramount importance, most were nosocomially acquired, intrahospital and interhospital spread was far more frequent within, rather than between, countries and that antibiotic use served as a major effect modifier.

In the United States, a reported incidence of 0.3–2.93 infections per 100,000 person-years with the highest rates occurring in LTACH, has been reported [43]. CRE pose a serious threat to immunocompromised hosts where, in endemic areas, carbapenem-resistant *K. pneumoniae* infections occur in 1–18% of solid organ transplant recipients, and similarly patients with hematologic malignancies represent 16–24% of all patients with CRE bacteremia [44].

The prevalence of CRE infections in the community is largely unknown [45], but a recent review found that percentages range from 0.04 to 29.5% [46]. From a One Health perspective the occurrence of CRE also poses a risk for public health. Notably, a prevalence of less than 1% among livestock and companion animals in Europe, but 2–26% in Africa, and 1–15% in Asia [47], has been documented.

A system-wide molecular ecological study from Algeria confirmed that clonal expansion of *K. pneumoniae* occurred in different niches (e.g. human gastrointestinal tract, animal farms, food products and in wastewater treatment plants) due mainly to the spread of an epidemic plasmid [48]. The survey highlighted that *K. pneumoniae* and commensal *Escherichia coli* are potential reservoirs of carbapenemases, contributing to their dissemination and transfer to diverse bacteria among different sources.

**Mechanisms of resistance**

The most important mechanism of carbapenem resistance in the *Enterobacteriales* order is the acquisition of plasmid-mediated carbapenemases, specifically three of the four Ambler classes (Table 3). These are rapidly expanding globally (Fig. 1), are proliferating at an unprecedented rate, are distributed in many species of *Enterobacteriales* but are dominated by *K. pneumoniae* [42].

While the different carbapenemases were previously typically associated with specific regions or countries [49] the geographical distributions are increasingly converging [50]. This evolving epidemiology may progressively complicate management and choice of new beta-lactam/beta-lactamase inhibitors, as an optimal antibiotic regimen might be difficult to attain in the presence of coproduction

<table>
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<tr>
<th>Mechanism</th>
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<td>β-lactamases:</td>
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<tr>
<td>Class A.</td>
<td>MGE</td>
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<tr>
<td>Serine carbapenemases</td>
<td>KPC&lt;sup&gt;a&lt;/sup&gt; (n = 22 variants)</td>
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<td>IMI-1, -2</td>
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<td>SME&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>GES&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>NMC-A&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>FRI-1&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>IMI-1&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>SFC&lt;sup&gt;c&lt;/sup&gt;</td>
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<td></td>
<td>SHV-38&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Class B.</td>
<td>MGE</td>
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<tr>
<td>Metallo-beta-lactamases</td>
<td>VIM&lt;sup&gt;a&lt;/sup&gt; (n = 46 variants)</td>
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<td></td>
<td>NDM&lt;sup&gt;b&lt;/sup&gt; (n = 16 variants)</td>
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<td></td>
<td>IMP (n = 52 variants)</td>
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<td>GIM-1&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>SIM&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>SPM&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Class C.</td>
<td>MGE</td>
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<tr>
<td>Cephalosporinase</td>
<td>CMY-10&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Class D.</td>
<td>MGE</td>
</tr>
<tr>
<td>Oxacillinase-type</td>
<td>OXA-48-like&lt;sup&gt;a&lt;/sup&gt; (n = 13 variants)</td>
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<tr>
<td>Impermeability (porin lesions)</td>
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<tr>
<td>CM</td>
<td>ompK35</td>
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<td>ompK37</td>
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*CM, chromosomal mutation; KPC, Klebsiella pneumoniae carbapenemase; MGE, mobile genetic element; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; VIM, Verona-integrated metalloprotease.*

<sup>a</sup>Most common.

<sup>b</sup>Geographically variable but less common or rare and sporadic.

<sup>c</sup>Low-level carbapenem hydrolysis.
of multiple resistance determinants [51,52]. The major epidemic high-risk international clones vary but mostly belong to ST11, ST15, ST101, ST147 and ST258, as well as their derivatives with ST258 the most global distribution [6,9*,39,42**].

Carbapenem resistance may also emerge in vivo in extended-spectrum-β-lactamase or AmpC hyperproducing *Enterobacteriales* spp. concurrent with mutation-derived outer-membrane porin lesions or loss [5].

**Impact on outcome**

The magnitude of the CBE burden is exemplified in recent data from the United States where it is estimated that CRE infections result in 26% mortality and cost hospitals $275 million annually [11]. In addition, a meta-analysis that compared serious CPE infections with those due to carbapenem-susceptible organisms, showed that there was a significant risk of excess mortality (OR 3.39) [53*].

A study on effect of carbapenem resistance on outcome of *Enterobacteriales* BSIs in low and middle-income countries (PANORAMA) was recently published [54**,55]. In this analysis, CRE BSI was associated with a 75% increased probability of in-hospital mortality, an almost 40% decreased probability of being discharged alive, and an increased length of hospital stay of 3.7 days.

**CONCLUSION**

Carbapenem-resistant GNB is increasing globally at an unimaginable rate and to an alarming extent. Collective efforts at the highest level have to be directed at the systematic evaluation of the global epidemiology across a One Health platform.

To inform a public health response, it has to include prevalence and incidence rates in addition to identifying reservoirs, transmission dynamics and antibiotic selection determinants. It will require unparalleled funding for global surveillance and molecular laboratory standardization including system-wide whole-genome sequencing.

To reduce the substantial excess mortality associated with carbapenem-resistant pathogens such as CPE, more than new antibiotics are required. Novel IPC management and decolonization strategies are essential if we are to avert ‘our worst nightmare’.

**Acknowledgements**

None.

**Financial support and sponsorship**

None.
Gram-negative infections


32. Most comprehensive, prospective continental CRE survey to date representing a model for other country-wide or continental surveillance programs.


