Emergence, molecular mechanisms and global spread of carbapenem-resistant Acinetobacter baumannii

Mohammad Hamidian1,* and Steven J. Nigro2

Abstract
Acinetobacter baumannii is a nosocomial pathogen that has emerged as a global threat because of high levels of resistance to many antibiotics, particularly those considered to be last-resort antibiotics, such as carbapenems. Although alterations in the efflux pump and outer membrane proteins can cause carbapenem resistance, the main mechanism is the acquisition of carbapenem-hydrolyzing oxacillinase-encoding genes. Of these, oxa23 is by far the most widespread in most countries, while oxa24 and oxa58 appear to be dominant in specific regions. Historically, much of the global spread of carbapenem resistance has been due to the dissemination of two major clones, known as global clones 1 and 2, although new lineages are now common in some parts of the world. The analysis of all publicly available genome sequences performed here indicates that ST2, ST1, ST79 and ST25 account for over 71% of all genomes sequenced to date, with ST2 by far the most dominant type and oxa23 the most widespread carbapenem resistance determinant globally, regardless of clonal type. Whilst this highlights the global spread of ST1 and ST2, and the dominance of oxa23 in both clones, it could also be a result of preferential selection of carbapenem-resistant strains, which mainly belong to the two major clones. Furthermore, ~70% of the sequenced strains have been isolated from five countries, namely the USA, PR China, Australia, Thailand and Pakistan, with only a limited number from other countries. These genomes are a vital resource, but it is currently difficult to draw an accurate global picture of this important superbug, highlighting the need for more comprehensive genome sequence data and genomic analysis.

DATA SUMMARY
1. Three thousand five hundred and seventy-five A. baumannii genomes were retrieved from the GenBank non-redundant and Whole Genome Shotgun (WGS) databases and analysed here. The full strain list and the ftp addresses used to retrieve the genomes are publicly available at https://www.ncbi.nlm.nih.gov/genome/?term=Acinetobacter+baumannii.
2. Variants of the beta-lactam resistance genes used for analyses were retrieved from the NCBI Antimicrobial Resistance Reference Gene database, which is publicly available at https://www.ncbi.nlm.nih.gov/pathogens/isolates#/refgene/.

INTRODUCTION
Antibiotic resistance has increased to dangerously high levels in bacterial strains recovered in all parts of the world, threatening our ability to treat common infectious diseases [1]. Acinetobacter baumannii is one such organism and a member of the ESKAPE group of six bacterial pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter species) that are major causes of antibiotic-resistant infections [2]. A. baumannii is a Gram-negative opportunistic nosocomial pathogen that is most notably responsible for pneumonia, along with infections of burns and other wounds [3–5]. It can survive harsh environmental pressures, such as desiccation and pH extremes, making management of these infections particularly challenging in the intensive care and burns units of hospitals [6].
A. baumannii has been recognized as a threat since the 1970s [4, 7] due to the rapid development of resistance to a wide range of antibiotics, including last-resort treatments such as carbapenems [8–11]. Often, there are very limited or no remaining options to treat A. baumannii infections [3, 12]. In 2017, this prompted the World Health Organization (WHO) to recognize carbapenem-resistant A. baumannii (CRAB) as the critical, number 1 priority among a published list of 12 antibiotic-resistant bacteria that pose the greatest threat to modern medicine, underlining the clinical significance and global burden of infections caused by CRAB [13].

Here, we discuss the emergence, molecular mechanisms and global spread of CRAB. To develop a snapshot of the geographical distribution of genomes sequenced so far and their carbapenem resistance gene (CRG) repertoire, we explore over 3500 A. baumannii genomes deposited in the GenBank non-redundant and Whole Genome Shotgun (WGS) databases. We also examine the genomic context of CRGs in all 128 complete genomes to further understand the role of mobile genetic elements in the spread of CRGs in A. baumannii.

GLOBAL SPREAD OF CARBAPENEM-RESISTANT ACINETOBACTER BAUMANNII

Carbapenem antibiotics such as meropenem and imipenem belong to the β-lactam family and remain active against most β-lactamase-producing organisms, including those with extended spectrum β-lactamase enzymes [14]. Carbapenems are considered to be a front-line treatment for infections caused by multiply resistant bacteria [15], but carbapenem resistance is increasingly common in A. baumannii, imposing huge financial and healthcare burdens [8, 16–18].

The number of studies in PubMed reporting CRAB increased from a single report [19] in 2000 to over 266 in 2018, highlighting its global dissemination [20, 21]. This has been largely due to inter- and intra-hospital transfer of resistant strains over the last two decades [21–23]. One classic example involving both intra-hospital and international transfer was the dramatic increase in A. baumannii infections in soldiers injured in war zones in Iraq and Afghanistan between 2006–2008 [24–28]. These infections often were resistant to multiple antibiotics and one study showed that 37% of isolates recovered from injured deployed military personnel were also resistant to carbapenems [29]. A subsequent study found that isolates recovered from injured soldiers were genetically related to those recovered on field hospital surfaces rather than pre-injury colonization or introduction at the time of injury [28]. It has been suggested that the return of soldiers from combat zones was an important factor that contributed to the epidemiology of A. baumannii infections in the USA [21].

Outbreaks caused by CRAB have been reported from civilian hospitals in the USA, Canada, South America, Europe, Africa, the Middle East, Southeast Asia, Australia and many more countries [11, 18, 23, 30–72]. Generally, these CRAB outbreaks have been caused by the spread of a few specific clones that were already resistant to a wide range of antibiotics [22, 41, 73]. Although it was initially thought that these clones were limited to Europe [43, 74], they have now been reported in different countries of all inhabited continents [16, 18, 75–86], raising widespread clinical concerns [9, 16, 56, 59, 78, 79, 83–90]. The two major clones responsible for most of these outbreaks are now commonly referred to as global clone 1 (GC1) and global clone 2 (GC2), but have also been referred to as international clones 1 and 2 [8, 16, 75, 78, 90, 91].

As of early April 2019, there were 3609 A. baumannii genomes available in the GenBank non-redundant and WGS databases (https://www.ncbi.nlm.nih.gov/genome/?term=Acinetobacter+baumannii). Here, these genomes were downloaded, and MLST types were determined in silico using MLST v2.16.1 (https://github.com/tseemann/mlst) followed by screening for antibiotic resistance genes using Abricate v0.8.10 (https://github.com/tseemann/abricate). These data were combined with the metadata available for each genome using R v3.5.2. Thirty-four duplicate, or passaged, isolates were removed from the analysis. Of the 3575 remaining genomes analysed here, 2364 (66%) were members of GC1 (173 genomes) and GC2 (2191 genomes). These clones are defined here as ST1, representing GC1s according to the Institut Pasteur MLST scheme [92], and ST2, representing GC2s, along with their single-locus variants (ST1, SLV1, ST2 and SLV2 in Fig. 1a). However, ST2 itself is by far the dominant type, with 2105 genomes (59%) among the available complete and draft genomes (Fig. 1a). This is also consistent with a large number of previous publications that continue to report outbreaks due to these two global clones, with GC2s accounting for the bulk of CRAB outbreaks.
Fig. 1. Distribution of carbapenem resistance genes and trend of A. baumannii genomes released. (a) Distribution of carbapenem resistance genes in the 15 most prevalent sequence types (STs; according to the Institut Pasteur MLST scheme). Numbers coloured turquoise indicate carbapenem resistance genes and black numbers show STs. SLV1 and SLV2 indicate single-locus variants of ST1 and ST2, respectively. All STs are based on the Institut Pasteur MLST scheme. (b) Geographical distribution of CRGs in A. baumannii genomes publicly available in the GenBank non-redundant and WGS databases (only countries with ≥1 CRG-containing genome are shown). Countries are shown on the y-axis and the numbers on the x-axis indicate the number of CRGs. (c) Acinetobacter genomes released between 2008 and early April 2019. Black indicates total genome releases, red shows genomes with a carbapenem resistance gene and dark purple indicates genomes carrying the oxa23 gene. These figures were drawn using the ggplot2 package in R v3.5.2.
of

It has been suggested that strains with an ISAba1 upstream
ated with members of GC1 and GC2, respectively [78, 89, 90].
most common variants are
ova6
just overexpression of
ovaAb
is needed for significant levels
upstream IS, which enhances expression by providing a
their expression is often enhanced by the insertion of an
relevant levels of resistance on their own [108]. However,
often poorly expressed, hence they cannot cause clinically
[107]. Generally,
oxaAb
is the most frequently described
distribution, but
Reports of the prevalence of these genes vary by geographical

carbaPENeM RESIS TaNcE IN A. bAuMMAnII

Many carbapenem resistance mechanisms have been described in A. baumannii, including alterations or loss of outer
membrane proteins such as CarO [97, 98] and modifications of the AdeABC resistance nodulation division (RND) efflux
pump [99, 100]. Although efflux modifications contribute to carbapenem resistance in A. baumannii, on their own they are
are not sufficient to cause clinically relevant resistance [100].
Carbapenem resistance in A. baumannii is largely due to the
horizontal acquisition of genes that encode carbapenem-
hydrolyzing enzymes belonging to either Ambler class D
(oxacillinases) or class B (metallo-ß-lactamases) [101–103].

Oxacillinases

Oxacillinase enzymes (OXAs) are a heterogeneous family
[104] and, to date, several groups of carbapenem-hydrolyzing
oxacillinases have been described in A. baumannii, most
notably OXA-23, OXA-24, OXA-58, OXA-143, OXA-235
and an intrinsic OXA [105, 106], designated OXA-Ab
for simplicity [89]. Genes encoding these acquired
 carbapenem-hydrolyzing enzymes are the main cause of
 carbapenem resistance in A. baumannii [107].
Generally, oxacillinases only hydrolyze carbapenems weakly and are
often poorly expressed, hence they cannot cause clinically
relevant levels of resistance on their own [108]. However,
their expression is often enhanced by the insertion of an
upstream IS, which enhances expression by providing a
strong promoter, causing high resistance levels [109–111].
Reports of the prevalence of these genes vary by geographical
distribution, but oxa23 is the most frequently described
[34, 35, 47, 49, 50, 55, 58, 63, 66, 67, 75, 77, 106, 112, 113].

The intrinsic oxaAb

The oxaAb gene (also known as blaOXA48-lik) occurs naturally in A. baumannii and is used as a marker for speciation [114]. So
far, over 180 oxaAb variants (https://www.lahey.org/studies/)
have been identified in A. baumannii strains [115–117]. The
most common variants are oxa69 and oxa66, which are associ-
ated with members of GC1 and GC2, respectively [78, 89, 90].
It has been suggested that strains with an ISAb1 upstream
of oxaAb can be carbapenem-resistant [109], but more than
just overexpression of oxaAb is needed for significant levels
of carbapenem resistance [118]. However, further work is
required to understand the contribution of oxaAb overexpres-
sion in different genetic backgrounds and whether specific
amino acid alterations in OXA-Ab also play a significant role.
became more affordable and accessible, the number of genomes sequenced exponentially increased from 2014 onwards, and by early April 2019, over 3500 A. baumannii genomes were available (Fig. 1c).

Amongst the 3575 non-redundant genome sequences studied here, 2345 (66%) contained at least one CRG and of these, 1918 genomes (82%) carry at least 1 copy of oxa23 (Fig. 1b), consistent with worldwide reports that oxa23 is overwhelmingly predominant in A. baumannii [34, 47, 49, 50, 55, 58, 63, 66, 77]. However, these sequences have a skewed geographical distribution, with 69% (2481/3575) of all sequenced strains isolated from only five countries, namely the USA, PR China, Thailand, Australia and now Pakistan (Fig. 2). Notably, a total of 57% (838/1466), 89% (387/436), 84% (224/266), 70% (159/226) and 93% (81/87) of genomes sequenced from the USA, PR China, Thailand, Australia and Pakistan, respectively, carry a CRG of one kind (Fig. 1b). However, it is unclear to what extent these CRG proportions reflect true population trends in these countries or whether they are a result of preferential selection of CRAB isolates for large-scale WGS projects, highlighting the need to sequence all A. baumannii that cause infection, regardless of their resistance phenotype. Hence, it is difficult to draw a clear picture of the true global A. baumannii population, including CRAB, unless more representative strains from Europe, the Middle East, Russia and Africa are sequenced and made publicly available.

Furthermore, whilst GC1 and GC2 are the most common clones in many countries, this may not always be true. For instance, GC1 and GC2 strains do not seem to be the dominant types in South American countries (n=10/70), Tunisia (n=1/13), Tanzania (n=5/14), Poland (n=0/10) and Japan (n=7/26) (Fig. 2), although more genomes are needed to confirm this. Although GC2 appears to be the dominant type in some countries, for example Spain, the genomes show that oxa24 and oxa58 are the dominant CRGs rather than oxa23 (Fig. 2). However, given the relative paucity of genome data from these countries, caution needs to be exercised when drawing such conclusions.

Studying the genetic environment of antibiotic resistance genes, including CRGs, often provides valuable information on the origin, emergence, evolution and spread of resistance throughout bacterial populations [141]. Most of the currently available A. baumannii genomes have been sequenced using short-read technologies such as Illumina HiSeq or MiSeq. Although the data produced by these methods are sufficient to identify antibiotic resistance genes or draw phylogenetic trees,
they lack the power to resolve complex resistance regions, which are often made up of numerous repeated elements [8, 142]. These regions tend to compromise assembly and can only be resolved manually via PCR and Sanger sequencing or by using long-read sequencing technologies such as Oxford Nanopore Technology (ONT) or Pacific Biosciences (PacBio) [143, 144]. Indeed, only 128 (4%) genomes have been fully assembled and the majority of these were sequenced with PacBio (data not shown).

**GENOMIC CONTEXTS AND THE ROLE OF MOBILE GENETIC ELEMENTS IN THE SPREAD OF CARBAPENEM RESISTANCE GENES**

The oxa23 gene has moved into chromosomes and plasmids, on multiple occasions, via the transposons Tn2006, Tn2007, Tn2008, Tn2008B, Tn2009 and AbaR4 (Fig. 3a) [8, 9, 18, 112, 113, 145–148]. The oxa23-containing Tn2006 is the most commonly found transposon, and hence the most

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**Fig. 3.** Structure of transposons carrying the oxa23 gene. (a) Genes and open reading frames are shown using arrows.Filled boxes are insertion sequences (ISs) with ISAb1 coloured green, ISAb33 coloured dark orange and ISAb2 coloured dark purple. Arrows inside the boxes indicate the direction of transposition gene expression. The oxa23 gene is shown in dark blue and open reading frames encoding hypothetical proteins are shown in white. (b) Vertical bars marked as IR indicate inverted repeats of AbaR4. (c) DRs indicates direct repeats. Arrows located in the central segments of Tn2006, Tn2008 and Tn6549, coloured grey, yellow and pink, respectively, indicate open reading frames that encode unrelated hypothetical proteins.
important in CRAB [110, 112]. It is a 4.8 kb class I transposon that consists of a central 2445 bp segment bounded by two inversely oriented copies of ISAba1 and generates a 9 bp target site duplication (TSD) upon insertion [110], characteristic of ISAba1 transposition [111]. Tn2006 can move independently and is found in many different chromosomal and plasmid contexts in distantly related A. baumannii strains [113]. In members of a distinct clade within GC1 lineage 1, Tn2006 has been found in a specific chromosomal location [8, 9, 18]. Tn2006 within AbaR4 is also located in the chromosomal comM gene in another in a GC1 lineage, lineage 2 [70], where the A. baumannii Resistance Island (AbaR) is often present [149]. In GC2 isolates, oxa23 is often found in Tn2006 alone or in derivatives of AbaR4 as components of A. baumannii Genomic Resistance Island (AbGRI), which resides in the same location in comM as AbaR does in GC1s [11, 112]. Tn2008, Tn2008B and Tn2009 (Fig. 3 and Table S1, available in the online version of this article) are also seen in several chromosomal positions and are not associated with genomic islands [112].

Plasmids also play a crucial role in the spread of multiple carbapenem resistance genes in A. baumannii [45, 112, 130, 150]. For instance, large conjugative plasmids (80–130 kbp) encoding the RepAci6 replication initiation protein [71] are implicated in the spread of oxa23 in GC1 and GC2, as well as strains that do not belong to these clones [71, 91, 151]. To date, several oxa23 transposons have been found in different locations of related RepAci6 plasmids [71, 91, 146]. Moreover, oxa23 in Tn2006 was recently found in a RepAci6 plasmid where it was shown to be mobilized by a RepAci6 plasmid [152], further emphasizing the role of plasmids encoding RepAci6 in spreading and now in the mobilization of carbapenem resistance between disparate strains.

Currently, there are 128 completed A. baumannii genomes in GenBank, of which 91 carry at least one CRG. Examining these 91 genomes shows that 9 of the 11 oxa23-containing GC1s (Table S1) carry oxa23, either in Tn2006 in the chromosome or, in one case, Tn2006 in AbaR4 in comM [70]. In several strains, AbaR4 is found in a RepAci6 plasmid (Table S1). Members of GC2 often carry Tn2006 in the chromosome as part of AbGRI variants, with several strains carrying two oxa23 copies in this island (Table S1). Four strains, two from the Republic of Korea and two from Pakistan (Table S1), carried Tn2008B (Fig. 3a) in different chromosomal positions flanked by different TSDs. This suggests that Tn2008B is still quite active, as it was chromosomally incorporated on multiple occasions. Other GC2s carry either Tn2006 or Tn2008 in variants of RepAci6 plasmids (Table S1). Tn2009 appears most commonly in GC2 isolates from PR China (n=17) and the Republic of Korea (n=19), some with multiple chromosomal copies in tandem (Table S1). In non-GC1 or GC2 strains, chromosomal Tn2006 appears most often. Interestingly, 39 complete genomes harbour more than 1 copy of oxa23. Most often, there are multiple copies in the chromosome, although some also have oxa23 on a plasmid. This raises the question of whether these isolates, or those that harbour multiple families of CRG, have a selective advantage compared to those with fewer copies of oxa23, and warrants further investigation.

New oxa23-containing structures are still being identified, such as an ISAb1- and ISAb33-flanked transposon (Fig. 3c) described in 2016 [153]. Indeed, during the course of this work we found oxa23 in yet another novel structure with the features of a composite transposon, in the chromosome of a Canadian strain (BA30 in Fig. 3c). This 3902 bp transposon contains oxa23 flanked by directly oriented copies of ISAb1. Two copies of this transposon were found at different chromosomal locations (bases 3303155–3307056 and 4295797–4299698 in CP009257), with each copy flanked by novel 9 bp TSDs, providing evidence that it moves independently. Hence, we named this transposon Tn6549 (Fig. 3c). Tn6549 appears to be a derivative of Tn2008, rather than Tn2008B, as there is 27 bp between the start of the oxa23 gene and the ISAb1 sequence, which is indicative of Tn2008 [112]. The central segment of Tn6549 contains oxa23 and an open reading frame of unknown function (orf in Fig. 3c). A sequence identical to this open reading frame was found in the chromosome of Acinetobacter sp. strain ACNI1H1 (GenBank accession no. CP026420) and fragments of this open reading frame are in several Acinetobacter lwaffii and Acinetobacter haemolyticus plasmids (e.g. GenBank accession nos CP038010 and CP032112).

The oxa58 gene is often embedded in the ISAb3-::ISAb2-oxa58-ISAb3 structure, and carried on non-conjugative plasmids encoding both RepAc1 and RepAc10 [107, 140, 154]. This entire structure is now known to be surrounded by short inversely oriented inverted repeats similar to chromosomal dif sites, now referred to as df, targeted by XerC–XerD site-specific recombinases [154–156]. This df module containing oxa58 is found in different plasmid backgrounds, indicating that it is a discrete mobile element that is responsible for the movement of oxa58, rather than the ISs that surround it [154–156]. Analysis of the completed genomes also indicated that oxa58 is mainly associated with df modules often carried by similar small plasmids encoding RepAc1 and RepAc10 (Table S1).

The oxa24 gene is commonly seen in 8–12 kb plasmids that encode RepAc1 or RepAc2, as part of discrete df modules flanked by df sites [155, 157–159]. This was also the case in all complete genomes with oxa24, (Table S1), adding further evidence that small plasmids, particularly those encoding RepAc1 and RepAc2, are a major force behind the global spread of oxa58 and oxa24.

The oxa253 gene, a variant of oxa143, may also occur in df modules, as it has been found near a single df site in a context similar to oxa24 in a RepAc2 plasmid [160]. The oxa235 gene, and its variants oxa236 and oxa237, are often found in single-nucleotide variants of a 5.2 kb ISAb1-bounded composite transposon called Tn6252, which has been found in chromosomess and plasmids [161–163].
Conclusions
Antibiotic resistance is on the rise and we are already running out of antibiotics to treat CRAB, which are unfortunately most commonly resistant to a wide range of additional antibiotics. Members of GC1 and GC2 are responsible for the bulk of globally disseminated multi-resistant A. baumannii, including CRAB. Although the current publicly available genomes provide an invaluable snapshot of the evolution and spread of CRAB throughout much of the world, the paucity of publicly available genome sequence data from regions such as Europe, the Middle East, Russia, Africa and South America has made it difficult to draw an accurate global picture of the spread of A. baumannii clones, CRGs and their phylogeny. Notably, whilst oxa23 is predominant globally, this is not always the case, particularly in countries such as Spain, Germany or Tunisia (Fig. 1b), further emphasizing the need for more sequencing coverage to understand why these different CRGs dominate in different regions. Sequencing strains from diverse regions is vital in understanding the evolutionary trajectory of the two major global clones, as well as other emerging clones, such as ST79 or ST25.

Expanding the use of long-read sequencing will facilitate a better understanding of the mobile elements responsible for moving CRGs and their broader contexts, while also enabling the characterization of further novel transposons and conjugative and mobilizable plasmids. It is now clear that alternative methods of horizontal gene transfer, such as dif modules and homologous recombination, play a larger role in the dissemination of CRGs than previously thought. Completing genome and plasmid assemblies will provide further knowledge regarding how widespread and important these mechanisms truly are. Indeed, this understanding will be vital in curtailing the future spread of CRGs in A. baumannii, as the issues of CRG spread via successful strains or clones and the spread of CRGs to susceptible strains via HGT are distinct problems that require different solutions. This will be crucial to identify molecular and epidemiological diagnostic markers to help identify resistant clones and track their spread. A more geographically uniform distribution of genome sequence data is also needed to further monitor plasmid movement and identify the true proportion of A. baumannii harbouring conjugative plasmids carrying bla_{NPM} and other CRGs that are common in other species. With the lack of new antibiotics to treat CRAB, and the uncertainty about whether new drugs would even be effective, infection control policy and practice built upon the framework of these phylogenetic and epidemiological analyses are vital in stopping the spread of CRAB. Without such interventions, we will enter an era where common infections and minor injuries caused by CRAB can once again kill.

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Conflicts of interest
The authors declare that there are no conflicts of interest.

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