Published in final edited form as:

Microb Drug Resist. 2022 June ; 28(6): 645–653. doi:10.1089/mdr.2021.0352.

Molecular Epidemiology of Carbapenem-Resistant *Acinetobacter baumannii* in the United States, 2013–2017

Susannah L. McKay[1], **Nicholas Vlachos**[1], **Jonathan B. Daniels**[1], **Valerie S. Albrecht**[1], **Valerie A. Stevens**[1], **J. Kamile Rasheed**[1], **J. Kristie Johnson**[2,3], **Joseph D. Lutgring**[1], **Maria Sjölund-Karlsson**[1], **Alison Laufer Halpin**[1]

[1]Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA.

[2]Department of Pathology, University of Maryland School of Medicine, Baltimore, Maryland, USA.

[3]Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, Maryland, USA.

Abstract

Healthcare-associated carbapenem-resistant *Acinetobacter baumannii* (CRAB) infections are a serious threat associated with global epidemic clones and a variety of carbapenemase gene classes. In this study, we describe the molecular epidemiology, including whole-genome sequencing analysis and antimicrobial susceptibility profiles of 92 selected, nonredundant CRAB collected through public health efforts in the United States from 2013 to 2017. Among the 92 isolates, the Oxford (OX) multilocus sequence typing scheme identified 30 sequence types (STs); the majority of isolates (n = 59, 64%) represented STs belonging to the international clonal complex 92 ($CC92_{OX}$). Among these, $ST208_{OX}$ (n = 21) and $ST281_{OX}$ (n = 20) were the most common. All isolates carried an OXA-type carbapenemase gene, comprising 20 alleles. Ninety isolates (98%) encoded an intrinsic OXA-51-like enzyme; 67 (73%) harbored an additional acquired bla_{OXA} gene, most commonly bla_{OXA-23} (n = 45; 49%).

Compared with isolates harboring only intrinsic oxacillinase genes, acquired bla_{OXA} gene presence was associated with higher prevalence of resistance and a higher median minimum inhibitory concentration to the carbapenem imipenem (64 μg/mL vs. 8 μg/mL), and antibiotics from other drug classes, including penicillin, aminoglycosides, cephalosporins, and polymyxins.

Address correspondence to: Susannah L. McKay, PhD, MPH, Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS H17-4, Atlanta, GA 30329, USA, smckay@cdc.gov.

Disclosure Statement

No competing financial interests exist.

Supplementary Material

Supplementary Table S1

Supplementary Figure S1

Supplementary Figure S2

These data illustrate the wide distribution of $CC92_{OX}$ and high prevalence of acquired bla_{OXA} carbapenemase genes among CRAB in the United States.

Keywords

healthcare-associated infections; WGS; *Acinetobacter baumannii* ; carbapenem resistance; molecular epidemiology; MLST

Introduction

Acinetobacter, an opportunistic healthcare-associated pathogen, inflicts significant morbidity and mortality in the most vulnerable patient populations.[1–3] *Acinetobacter* infections often occur in intensive care settings and can cause pneumonia, bacteremia, and urinary tract infections. While carbapenems remain the drugs of choice for treating multidrug-resistant *Acinetobacter* infections, carbapenem-resistant strains caused one-third of healthcare-associated *Acinetobacter* infections in 2019.[4] In 2019, the U.S. Centers for Disease Control and Prevention (CDC) designated carbapenem-resistant *Acinetobacter* an urgent threat to public health.[5]

Acinetobacter baumannii is generally considered the most medically significant *Acinetobacter* spp. and carbapenem-resistant *A. baumannii* (CRAB) emergence is of major concern. Carbapenem resistance in *A. baumannii* often occurs through upregulation of an intrinsic $bla_{OXA51\text{-}like}$ gene or by acquiring a gene encoding an OXA-type carbapenemase (OXA-23-like, −24/40-like, and −58-like variants).[6] Acquired OXA enzymes are some of the most epidemiologically relevant as they are commonly carried on mobile genetic elements that can spread horizontally between bacteria.[7] In addition to carbapenems, *A. baumannii* strains often display broad antimicrobial resistance to other drug classes, leading to significant treatment challenges.[8]

Resistance to carbapenems has increased globally in the last decade due to the successful expansion of a few international epidemic lineages producing carbapenemase enzymes. One of the most successful clonal lineages, international clone II (IC II), corresponds to clonal complex 92 (CC92), according to the multilocus sequence typing (MLST) Oxford scheme developed by Bartual *et al.*,[9] and to clonal complex 2 (CC2) comprising sequence type 2 (ST2) of the alternative Pasteur MLST scheme.[10] In the United States, $CC92_{OX}$ carbapenemase-producing strains are increasingly prevalent and implicated in driving the epidemic spread of CRAB.[11–13]

Although overall rates of hospital-associated CRAB infections in the United States have been declining since 2012, the prevalence of *A. baumannii* that produce carbapenemases, a capacity that can be transferred to other organisms through mobile genetic elements, appears to be increasing.[5] Despite this, the molecular epidemiology, including prevalence of particular clonal types and carriage of specific carbapenemase genes by CRAB isolates in the United States, is not well defined. In this study, we describe the molecular characteristics and antibiotic susceptibility profiles for CRAB isolates collected through public health efforts in the United States from 2013 to 2017.

Materials and Methods

Isolates

From October 2013 to December 2017, nine Sentinel sites forwarded to CDC a convenience sample of up to 32 *Acinetobacter* spp. isolates per quarter collected prospectively from sterile body sites.[14] Submitted isolates underwent species identification confirmation by matrix-assisted laser desorption ionization–time-of-flight (MALDI-TOF) mass spectrometry using a Biotyper 3.1 MALDI-TOF system (Bruker Daltonics, Billerica, MA) and antimicrobial susceptibility testing (AST) according to guidelines from the Clinical and Laboratory Standards Institute (CLSI).

The case definition for CRAB was *A. baumannii* isolates resistant to meropenem, doripenem, or imipenem based on current CLSI Standards. Of the 450 *Acinetobacter* spp. submitted through Sentinel, 79 were confirmed as CRAB and were submitted for whole genome sequencing (WGS). To bolster this convenience sample, the CDC laboratory information management system was queried for nonredundant isolates submitted and confirmed as CRAB during this same time frame, yielding an additional 13 isolates for WGS. The collection described here comprised these 92 *A. baumannii* isolates, from sites representing five of seven U.S. Association of Public Health Laboratories geographic regions (Supplementary Fig. S1).

Whole-genome sequencing and bioinformatics

WGS was completed using the Illumina MiSeq platform (San Diego, CA) as previously described.[15] WGS data were analyzed using our in-house bioinformatics pipeline (QuAISAR-H; https://github.com/DHQP/QuAISAR_singu larity) to determine quality, antimicrobial resistance genes, and MLST and confirm species identity. Antimicrobial resistance genes had to meet 98% identity across 90% length to be considered. STs were determined using PubMLST (https://pubmlst.org/), accessed on May 2, 2018.[16] Applying BURST plugin, STs were grouped into clonal complexes using the traditional standard of ≤1 allelic mismatch.[17,18] Whole-genome MLST (wgMLST) was assigned using Bio-Numerics (version 7.2) and visualized using Microreact.[19]

Antibiotic susceptibility testing

We performed reference broth microdilution AST on all isolates using in-house prepared frozen panels according to CLSI guidance.[20] Panels included amikacin, ampicillin–sulbactam, cefepime, cefotaxime, ceftazidime, ceftriaxone, ciprofloxacin, colistin, doripenem, gentamicin, imipenem, levofloxacin, meropenem, minocycline, piperacillin–tazobactam, tetracycline, tobramycin, and trimethoprim–sulfamethoxazole. Results were interpreted according to contemporary CLSI guidance.[21] This surveillance protocol was reviewed by the CDC institutional review board (IRB) and at all participating sites and was deemed non-research or received IRB approval with a waiver of informed consent.

Results

From October 2013 to December 2017, CDC received 292 isolates meeting the CRAB case definition; among the 105 isolates that underwent WGS at CDC, 92 nonredundant isolates (64 Sentinel; 28 reference testing) are characterized herein.

Among the 92 isolates, the Institut Pasteur (IP) MLST scheme identified 17 STs, including 4 novel STs; 59 (64%) isolates were classified as $ST2_{IP}$. $ST2_{IP}$ isolates were more prevalent by an order of magnitude over the next-most prevalent type, $ST406_{IP}$ (n = 7, 7.6%) (Supplementary Table S1). The Oxford (OX) scheme identified 31 STs, including 5 novel STs. Among the 59 $ST2_{IP}$ isolates, the Oxford scheme classified 12 STs with the most prevalent being $ST208_{OX}$ (n = 21, 36%) and $ST281_{OX}$ (n = 20, 34%). These 59 $ST2_{IP}$ isolates are members of the IC II lineage, which corresponds to $CC2_{IP}$ and $CC92_{OX}$. Because the Oxford scheme provides higher resolution on the underlying diversity of these isolates, in the remainder of the article we will follow the Oxford designations.

All five regions with isolate data available submitted $CC92_{OX}$ isolates with the majority from the Northeast (n = 21; 36%) and Mid-Atlantic (n = 20; 34%) regions, followed by the Mountain (n = 8; 14%), West (n = 6; 10%), and Midwest (n = 4; 7%) regions (Fig. 1). While $ST208_{OX}$ was identified in all regions, the majority of $ST281_{OX}$ isolates (n = 15, 75%) were submitted from the Mid-Atlantic region.

Sequencing analysis identified 20 bla_{OXA} carbapenemase alleles among the 92 isolates (Table 1). All bla_{OXA} alleles detected had ≥99% identity across the full length of the gene. We identified at least one intrinsic OXA-51-like enzyme in 90 isolates (98%), including 1 isolate that harbored two intrinsic variants. Among the 90 OXA-51-like-positive isolates, 15 different OXA-51-like variants were identified, with the most prevalent being OXA-82 (n = 28, 31%), followed by OXA-66 (22, 24%). Among the 25 isolates carrying only an intrinsic OXA variant, the most common variants were OXA-82 (9, 36%) and OXA-71 (9, 36%). All the OXA-71-encoding isolates were collected in the Northeast region.

Sixty-seven (73%) isolates harbored at least one acquired bla_{OXA} gene; one isolate harbored two acquired OXA-type carbapenemase variants. We identified five unique acquired OXA-type enzyme variants; the most common was OXA-23 (n = 45, 49%). Among the 65 isolates identified as harboring both intrinsic and acquired bla_{OXA} genes, the most common combination was $bla_{OXA\text{-}82}$ and $bla_{OXA\text{-}23}$ (n = 19, 29%).

One isolate encoded three OXA-type enzymes, including the intrinsic OXA-223 variant, and the acquired OXA-23 and OXA-237 variants. No isolate was found to encode class A (KPC) or class B (IMP, NDM, VIM) carbapenem-hydrolyzing β-lactamases previously associated with CRAB.[22,23] Among the 59 $CC92_{OX}$ isolates, nearly half harbored the OXA-23 variant (n = 29; 49%). OXA-23-positive $CC92_{OX}$ isolates were submitted from all regions, with the greatest number from the Northeast (n = 12) followed by the Mid-Atlantic (n = 9), Mountain (n = 3), West (n = 3), and Midwest regions (n = 2). $ST281_{OX}$ was the most common ST harboring the OXA-23 variant (n = 13, 29%), with most (n = 8) coming from the Mid-Atlantic region.

All 92 isolates (100%) met the definition for multidrug-resistant (MDR; nonsusceptible to ≥1 drug in ≥3 drug classes), 81 (88%) were extensively drug-resistant (XDR; nonsusceptible to ≥1 drug in all but ≤2 drug classes), and 3 isolates (3%) were pan drug-resistant (nonsusceptible to all drugs tested, including colistin) (Fig. 2).[24]

AST results are presented in Table 2 with the minimum inhibitory concentration (MIC) frequency distributions presented in Supplementary Fig. S2. Most isolates displayed resistance to the carbapenems meropenem (n = 92, 100%), doripenem (n = 91, 99%), or imipenem (n = 86, 93%); 86 (93%) were resistant to all 3 drugs. In addition, a majority of isolates displayed resistance to at least one drug of each drug class, except for the polymyxin colistin for which only a minority were resistant (n = 19, 21%). The mobilized colistin resistance (*mcr*) gene was not identified in any isolates tested.

Carbapenem resistance differed among isolates carrying an acquired OXA-type carbapenemase compared with those without (Table 2 and Supplementary Fig. S2); all 67 isolates harboring an acquired bla_{OXA} carbapenemase gene were resistant to all 3 carbapenem drugs tested compared with 19 (76%) of the 25 isolates harboring only intrinsic bla_{OXA} genes. The imipenem MIC_{50} and MIC_{90} varied according to whether isolates harbored an acquired OXA-type carbapenemase or not (64 μg/mL vs. 8 μg/mL and >64 μg/mL vs. 64 μg/mL, respectively). Among resistant isolates, the median imipenem MIC was 64 and 16 μg/mL for isolates with and without an acquired OXA-type carbapenemase, respectively. Among isolates harboring an acquired OXA-type carbapenemase, the median imipenem MIC was 16 μg/mL for isolates encoding $bla_{\text{OXA-235}}$ or $bla_{\text{OXA-237}}$, whereas the median MIC for the three other acquired bla_{OXA} alleles was 64 μg/mL.

The median MIC for the other two carbapenems, doripenem, and meropenem (>8 μg/mL) remained the same regardless of enzyme variant. However, the MIC of 95% of these isolates exceeded the maximum concentration tested (8 μg/mL) and the standard method for these drugs[20] lacks the dynamic range necessary to reveal a difference if one exists. Isolates harboring an acquired bla_{OXA} gene had a higher resistance prevalence and median MIC than those with only an intrinsic bla_{OXA} to aminoglycosides (amikacin, gentamicin, and tobramycin), cefepime, ampicillin/sulbactam, and colistin. Conversely, resistance prevalence was higher among isolates harboring only intrinsic than those with acquired OXA-type carbapenemase for tetracycline, minocycline, cefotaxime, and ceftazidime; median MIC was higher for tetracycline (>32 μg/mL vs. 32 μg/mL).

Given the highly clonal nature of CRAB, we wanted to determine the clonal relatedness of these isolates and evaluate genetic commonalities. BURST analysis of the Oxford STs identified 4 clonal complexes, including CC92_{OX} and 19 singleton isolates. We applied wgMLST to determine the population structure and gain additional information on the genetic diversity than is provided by traditional MLST (Fig. 2). The isolates separate into two subsets with the CC92_{OX} isolates clustered together (yellow circles) and the non-CC92_{OX} isolates in the other.

Discussion

The epidemic spread of successful *A. baumannii* lineages was recognized over 20 years ago.[25] Our MLST and whole-genome analyses underscore the role of $CC92_{OX}$ in driving this epidemic spread of *A. baumannii*, including CRAB in the United States. Over 60% of the isolates included in this report belonged to $CC92_{OX}$ and were found in all U.S. regions with data available. Previous epidemiology of CRAB similarly demonstrated preponderance of $CC92_{OX}$ CRAB in the United States.[11,13] However, aside from $ST208_{OX}$, we did not detect any of the $CC92_{OX}$ STs previously identified in the United States. More data are needed to determine if these differences in ST distribution are due to sampling or true shifts in CRAB epidemiology.

The Oxford and IP MLST schemes are based on seven genes each, three of which are shared between the schemes.[9,10] In our analysis, the Oxford scheme had more discriminatory power and further distinguished 12 STs within the 59 $ST2_{IP}$ isolates, including 5 isolates belonging to $ST348_{OX}$ and $ST1578_{OX}$ classified as singletons outside of CC92.

Phylogenetic classification by wgMLST supported the Oxford scheme distinctions and illustrated that $ST281_{OX}$ and $ST208_{OX}$ isolates cluster according to their respective Oxford ST designation, residing on separate branches of the $ST2_{IP}$ clade. The presence of singletons within the CC92 clade is indicative of the continued diversification of this epidemic lineage. While both MLST schemes have their unique limitations,[26,27] they complement each other in grouping (IP) and subdividing (OX) the isolates. Reporting STs from both schemes will facilitate making connections with historical isolates where only one MLST scheme was reported.[26,28]

The two most common STs in our study each displayed unique epidemiology. $ST208_{OX}$ was spread across all five geographic regions and associated with several OXA variants. $ST208_{OX}$ is common worldwide and previous studies have likewise found a variety of associated OXAs.[13,29,30] Conversely, in this study, $ST281_{OX}$ was largely restricted to the Mid-Atlantic region and all isolates harbored the same intrinsic OXA-82 variant, with or without OXA-23. Of concern, antimicrobial testing indicated that $ST281_{OX}$ comprised over 1/3rd of the colistin-resistant isolates in the collection. These data suggest that local transmission (*i.e.,* endemic) of this clone may be occurring, perhaps through patient transfers among healthcare facilities as has been previously implicated.[13,31] We also detected STs not previously reported in the United States, including $ST195_{OX}$ belonging to $CC92_{OX}$, which has previously been reported only in Asia.[32,33]

Taken together, these data suggest both importations and transmissions contribute to the preponderance of $CC92_{OX}$ in this collection. The molecular mechanisms of how $CC92_{OX}$ has become predominant in clinical settings remain unknown. However, our results complement other studies demonstrating $CC92_{OX}$'s diverse resistome, which may have contributed the overall success of $CC92_{OX}$ in clinical settings where antibiotic pressures are prevalent.[34–36]

In our *A. baumannii* collection, nearly 3/4 of isolates harbored an acquired bla_{OXA} carbapenemase gene with the majority (67%) of these carrying an OXA-23 variant. OXA-23

is the most common acquired oxacillinase across the globe[37] and in our dataset. We found that OXA-235 and −237 were rare in this data set and only identified in the Western United States. Reports of these acquired OXA-type carbapenemases are rare, including isolates reported in Canada,[30] one isolate reported in Mexico,[38] and two reports in the United States; an outbreak of CRAB harboring OXA-237 was previously reported in Oregon (2012–2014)[31,39] and in a single isolate collected in California.[38]

Three regions reported a total of seven isolates encoding an OXA-72 enzyme, an OXA-24/40-like variant. Although less common than OXA-23, CRAB harboring OXA-72 has been reported from countries in eastern Asia, Latin America, and southern Europe.[40–46] Before this work, there has only been one report of OXA-72 in the United States.[47]

While acquired OXA-type carbapenemases merit height-ened attention, our data suggest that CRAB lacking acquired OXA carbapenemase genes are also of significant concern. The presence of carbapenem resistance without an acquired OXA-type carbapenemase suggests resistance mediated through upregulation of an intrinsic bla_{OXA} gene; this occurred in a minority of isolates in our collection. Among isolates with only intrinsic OXA-type enzyme variants, AST results demonstrated that the meropenem and doripenem MICs were comparable to those of isolates carrying acquired OXA-type carbapenemases. Given the limited range of standard dilutions for these carbapenems, further studies at higher drug concentrations will be necessary to determine if any true MIC differences exist between isolates producing acquired or intrinsic OXA variants.

Finally, although the standard analysis executed here identified two isolates that appeared to be missing the intrinsic OXA enzyme, the root cause of this is likely that the genes were split across multiple contigs and could have posed a challenge for detection by the standard workflow.

A. baumannii is particularly challenging healthcare-associated pathogen because of its ability to develop resistance to most available antimicrobial agents.[8] The prevalence of MDR and XDR among CRAB isolates in this collection merit special mention as these isolates remain susceptible only to older, more toxic drugs like colistin. Patients harboring MDR *Acinetobacter* are more likely to receive inappropriate empiric therapy, which has been shown, in turn, to be associated with increased mortality.[48] Thus, the spread of these highly resistant, successful clones is concerning and underscores the importance of antibiotic stewardship to preserve the remaining options for serious CRAB infections.

There were limitations to this analysis. Cefiderocol, a drug shown to be effective against XDR *A. baumannii*,[49] was not yet available when this study was conducted and the sensitivity of these CRAB isolates to this drug is not known. The isolates described in this study were selected and may not represent the overall epidemiology of CRAB in the United States. In addition, data on the volume of isolates being reported by each site were not available, limiting our ability to make conclusions about differences in prevalence or calculate rates. Finally, these isolates were collected through clinical laboratories, some for surveillance, and lacked accompanying demographic and clinical information necessary to comprehensively understand patient outcomes and the clinical significance of these strains.

In summary, this is the first study using WGS data to elucidate the molecular epidemiology of highly resistant CRAB in the United States. Our findings underscore the successful dissemination of $CC92_{OX}$ clones in the United States, particularly those harboring the acquired $bla_{OXA\text{-}23}$ β-lactamase gene. Taken together, these data emphasize the propensity for this organism to acquire antibiotic resistance and the importance of further public health detection and containment activities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

The authors thank Sarah Gilbert for her help pulling data from CDC's reference isolate database.

Funding Information

This work was made possible, in part, through support from CDC's investments in the National Strategy for Combating Antibiotic-Resistant Bacteria (CARB) initiative, the Advanced Molecular Detection (AMD) program at CDC, and SHEPheRD funding awarded to J.K.J. (contract 200-2011-42064).

Data Availability

Whole-genome sequencing raw reads for this collection were deposited in the Sequence Read Archive (SRA). Assembly and SRA data are available at NCBI under Bio-Project number PRJNA288601 and includes SRA numbers SRR15845918 to SRR15846009.

References

1. Bergogne-Berezin E, and Towner KJ. 1996. *Acinetobacter* spp. as nosocomial pathogens: microbiological, clinical, and epidemiological features. Clin. Microbiol. Rev 9:148–165. [PubMed: 8964033]
2. Karageorgopoulos DE, and Falagas ME. 2008. Current control and treatment of multidrug-resistant *Acinetobacter baumannii* infections. Lancet. Infect. Dis 8:751–762. [PubMed: 19022191]
3. Theaker C, Azadian B, and Soni N. 2003. The impact of *Acinetobacter baumannii* in the intensive care unit. Anaesthesia 58:271–274. [PubMed: 12638567]
4. CDC. 2021. Antibiotic resistance & patient safety portal: Carbapenem-resistant *Acinetobacter*. Available at https://arpsp.cdc.gov/profile/antibiotic-resistance/carbapenem-resistant-acinetobacter (accessed October 4, 2021).
5. CDC. 2019. Antibiotic resistance threats in the United States, 2019 Available at https://www.cdc.gov/drugresistance/biggest-threats.html (accessed October 4, 2021).
6. Evans BA, and Amyes SGB. 2014. OXA β-lactamases. Clin. Microbiol. Rev 27:241–263. [PubMed: 24696435]
7. Queenan AM, and Bush K. 2007. Carbapenemases: the versatile beta-lactamases. Clin. Microbiol. Rev 20:440–458. [PubMed: 17630334]
8. Bulens SN, Yi SH, Walters MS, et al. 2018. Carbapenem-nonsusceptible *Acinetobacter baumannii*, 8 US Metropolitan Areas, 2012–2015. Emerg. Infect. Dis 24: 727–734. [PubMed: 29553339]
9. Bartual SG, Seifert H, Hippler C, D Luzon MA, Wisplinghoff H, and Rodríguez-Valera F. 2005. Development of a multilocus sequence typing scheme for characterization of clinical isolates of *Acinetobacter baumannii*. J. Clin. Microbiol 43:4382–4390. [PubMed: 16145081]

10. Diancourt L, Passet V, Nemec A, Dijkshoorn L, and Brisse S. 2010. The population structure of *Acinetobacter baumannii*: expanding multiresistant clones from an ancestral susceptible genetic pool. PLoS One 5: e10034. [PubMed: 20383326]
11. Higgins PG, Dammhayn C, Hackel M, and Seifert H. 2010. Global spread of carbapenem-resistant *Acinetobacter baumannii*. J. Antimicrob. Chemother 65: 233–238. [PubMed: 19996144]
12. Zarrilli R, Pournaras S, Giannouli M, and Tsakris A. 2013. Global evolution of multidrug-resistant *Acinetobacter baumannii* clonal lineages. Int. J. Antimicrob. Agents 41:11–19. [PubMed: 23127486]
13. Adams-Haduch JM, Onuoha EO, Bogdanovich T, et al. 2011. Molecular epidemiology of carbapenem-nonsusceptible *Acinetobacter baumannii* in the United States. J. Clin. Microbiol 49:3849–3854. [PubMed: 21918019]
14. Halpin AL, McDonald LC, and Elkins CA. 2021. Framing bacterial genomics for public health(care). J. Clin. Microbiol 59:e0013521. [PubMed: 34076468]
15. Stanton RA, McAllister G, Daniels JB, et al. 2020. Development and application of a core genome multilocus sequence typing scheme for the health care-associated pathogen *Pseudomonas aeruginosa*. J. Clin. Microbiol 58: e00214–20. [PubMed: 32493782]
16. Jolley KA, and Maiden MC. 2010. BIGSdb: scalable analysis of bacterial genome variation at the population level. BMC Bioinformatics 11:595. [PubMed: 21143983]
17. Francisco AP, Bugalho M, Ramirez M, and Carrico JA. 2009. Global optimal eBURST analysis of multilocus typing data using a graphic matroid approach. BMC Bioinformatics 10:152. [PubMed: 19450271]
18. Jolley KA 2018. BURST algorithm plugin Available at https://pubmlst.org/bigsdb?db=pubmlst_abaumannii_seqdef&page=plugin&name=BURST (accessed October 4, 2021).
19. Argimón S, Abudahab K, Goater RJE, et al. 2016. Microreact: visualizing and sharing data for genomic epidemiology and phylogeography. Microb. Genom 2: e000093. [PubMed: 28348833]
20. Clinical and Laboratory Standards Institute. 2018. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically 11th ed. Wayne, PA.
21. Clinical and Laboratory Standards Institute. 2019. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Ninth Informational Supplement Wayne, PA.
22. Codjoe FS, and Donkor ES. 2018. Carbapenem resistance: a review. Med. Sci 6:1.
23. Lima WG, Silva Alves GC, Sanches C, Antunes Fernandes SO, and de Paiva MC. 2019. Carbapenem-resistant *Acinetobacter baumannii* in patients with burn injury: a systematic review and meta-analysis. Burns 45:1495–1508. [PubMed: 31351820]
24. Magiorakos AP, Srinivasan A, Carey RB, et al. 2012. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin. Microbiol. Infect 18:268–281. [PubMed: 21793988]
25. Nemec A, Janda L, Melter O, and Dijkshoorn L. 1999. Genotypic and phenotypic similarity of multiresistant *Acinetobacter baumannii* isolates in the Czech Republic. J. Med. Microbiol 48:287–296. [PubMed: 10334596]
26. Gaiarsa S, Batisti Biffignandi G, Esposito EP, et al. 2019. Comparative analysis of the two *Acinetobacter baumannii* multilocus sequence typing (MLST) schemes. Front. Microbiol 10:930. [PubMed: 31130931]
27. Hamidian M, Nigro SJ, and Hall RM. 2017. Problems with the oxford multilocus sequence typing scheme for *Acinetobacter baumannii*: do sequence type 92 (ST92) and ST109 exist? J. Clin. Microbiol 55:2287–2289. [PubMed: 28490493]
28. Tomaschek F, Higgins PG, Stefanik D, Wisplinghoff H, and Seifert H. 2016. Head-to-head comparison of two multi-locus sequence typing (MLST) schemes for characterization of *Acinetobacter baumannii* outbreak and sporadic isolates. PLoS One 11:e0153014. [PubMed: 27071077]
29. Alcántar-Curiel MD, Rosales-Reyes R, Jarillo-Quijada MD, et al. 2019. Carbapenem-resistant *Acinetobacter baumannii* in three tertiary care hospitals in Mexico: virulence profiles, innate immune response and clonal dissemination. Front. Microbiol 10:2116. [PubMed: 31616391]

30. Boyd DA, Mataseje LF, Pelude L, et al. 2018. Results from the Canadian Nosocomial Infection Surveillance Program for detection of carbapenemase-producing Acinetobacter spp. in Canadian hospitals, 2010–16. J. Antimicrob. Chemother 74:315–320.
31. Buser GL, Cassidy PM, Cunningham MC, et al. 2017. Failure to communicate: transmission of extensively drug-resistant bla OXA-237-containing *Acinetobacter baumannii*-multiple facilities in Oregon, 2012–2014. Infect. Control Hosp. Epidemiol 38:1335–1341. [PubMed: 28870269]
32. Kim DH, Choi J-Y, Kim HW, et al. 2013. Spread of carbapenem-resistant *Acinetobacter baumannii* global clone 2 in Asia and AbaR-type resistance islands. Antimicrob. Agents Chemother 57:5239–5246. [PubMed: 23939892]
33. Qu J, Du Y, Yu R, and Lü X. 2016. The first outbreak caused by *Acinetobacter baumannii* ST208 and ST195 in China. BioMed Res. Int 2016:9254907. [PubMed: 27144176]
34. Lee Y, Bae IK, Kim J, Jeong SH, and Lee K. 2012. Dissemination of ceftazidime-resistant *Acinetobacter baumannii* clonal complex 92 in Korea. J. Appl. Microbiol 112:1207–1211. [PubMed: 22404202]
35. Nemec A, Křížová L, Maixnerová M, et al. 2008. Emergence of carbapenem resistance in *Acinetobacter baumannii* in the Czech Republic is associated with the spread of multidrug-resistant strains of European clone II. J. Antimicrob. Chemother 62:484–489. [PubMed: 18477708]
36. Wu W, He Y, Lu J, Lu Y, Wu J, and Liu Y. 2015. Transition of blaOXA-58-like to blaOXA-23-like in *Acinetobacter baumannii* Clinical Isolates in Southern China: an 8-year study. PLoS One 10:e0137174. [PubMed: 26340666]
37. Mugnier PD, Poirel L, Naas T, and Nordmann P. 2010. Worldwide dissemination of the blaOXA-23 carbapenemase gene of *Acinetobacter baumannii*. Emerg. Infect. Dis 16:35–40. [PubMed: 20031040]
38. Higgins PG, Pérez-Llarena FJ, Zander E, Fernández A, Bou G, and Seifert H. 2013. OXA-235, a novel class D β-lactamase involved in resistance to carbapenems in *Acinetobacter baumannii*. Antimicrob. Agents Chemother 57: 2121–2126. [PubMed: 23439638]
39. Hujer AM, Higgins PG, Rudin SD, et al. 2017. Nosocomial outbreak of extensively drug-resistant *Acinetobacter baumannii* isolates containing bla(OXA-237) carried on a plasmid. Antimicrob. Agents Chemother 61: e00797–17. [PubMed: 28893775]
40. de Sá Cavalcanti FL, Almeida ACS, Vilela MA, de Morais MA Junior, de Morais MMC, and Leal-Balbino TC. 2013. Emergence of extensively drug-resistant OXA-72–producing *Acinetobacter baumannii* in Recife, Brazil: risk of clonal dissemination? Diagn. Microbiol. Infect. Dis 77:250–251. [PubMed: 24055437]
41. Dortet L, Bonnin RA, Bernabeu S, et al. 2016. First occurrence of OXA-72-producing *Acinetobacter baumannii* in Serbia. Antimicrob. Agents Chemother 60:5724–5730. [PubMed: 27431216]
42. Franolić-Kukina I, Bedenić B, Budimir A, Herljević Z, Vraneš J, and Higgins PG. 2011. Clonal spread of carbapenem-resistant OXA-72-positive *Acinetobacter baumannii* in a Croatian university hospital. Int. J. Infect. Dis 15:e706–e709. [PubMed: 21798787]
43. Georgescu M, Gheorghe I, Dudu A, et al. 2016. First report of OXA-72 producing *Acinetobacter baumannii* in Romania. N. Microb. N. Infect 13:87–88.
44. Kuo SC, Yang S-P, Lee Y-T, et al. 2013. Dissemination of imipenem-resistant *Acinetobacter baumannii* with new plasmid-borne blaOXA-72 in Taiwan. BMC Infect. Dis 13:319. [PubMed: 23849336]
45. Montealegre MC, Maya JJ, Correa A, et al. 2012. First identification of OXA-72 carbapenemase from Acinetobacter pittii in Colombia. Antimicrob. Agents Chemother 56:3996–3998. [PubMed: 22508295]
46. Saavedra SY, Cayô R, Gales AC, Leal AL, and Saavedra CH. Early dissemination of OXA-72-producing *Acinetobacter baumannii* strain in Colombia: a case report. Braz. J. Infect. Dis 18:678–680.
47. Tian GB, Adams-Haduch JM, Bogdanovich T, et al. 2011. Identification of diverse OXA-40 group carbapenemases, including a novel variant, OXA-160, from *Acinetobacter baumannii* in Pennsylvania. Antimicrob. Agents Chemother 55:429–432. [PubMed: 21041501]

48. Zilberberg MD, Nathanson BH, Sulham K, Fan W, and Shorr AF. 2016. Multidrug resistance, inappropriate empiric therapy, and hospital mortality in *Acinetobacter baumannii* pneumonia and sepsis. Crit. Care 20:221. [PubMed: 27417949]

49. Oliva A, Ceccarelli G, De Angelis M, et al. 2020. Cefiderocol for compassionate use in the treatment of complicated infections caused by extensively and pan-resistant *Acinetobacter baumannii*. J. Glob. Antimicrob. Resist 23:292–296. [PubMed: 33065329]

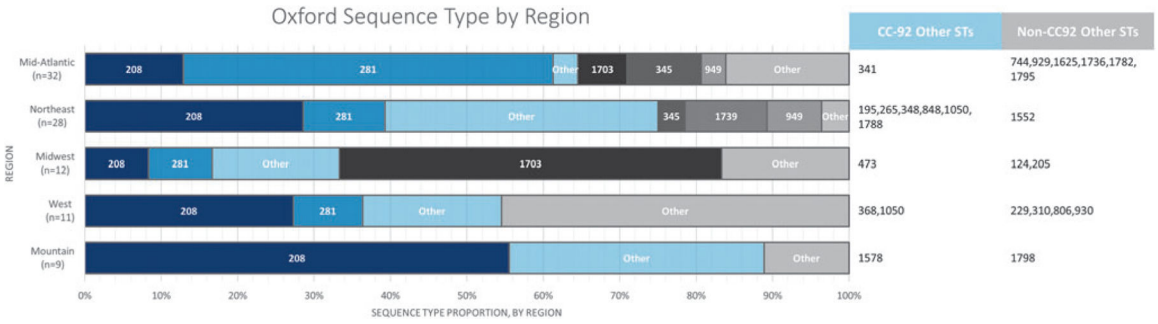

FIG. 1.

Oxford MLST for CRAB isolates by geographic region. ST belonging to $CC92_{OX}$ are in *blue*. Non-$CC92_{OX}$ STs in *gray*. STs reported as the proportion of total isolates from that region. Total number of isolates for each region indicated in parentheses. "Other" category comprises STs with ≤3 total isolates and are listed, by CC, to the *right* of the graph. CC92, clonal complex 92; CRAB, carbapenem-resistant *Acinetobacter baumannii*; MLST, multilocus sequence typing; ST, sequence type.

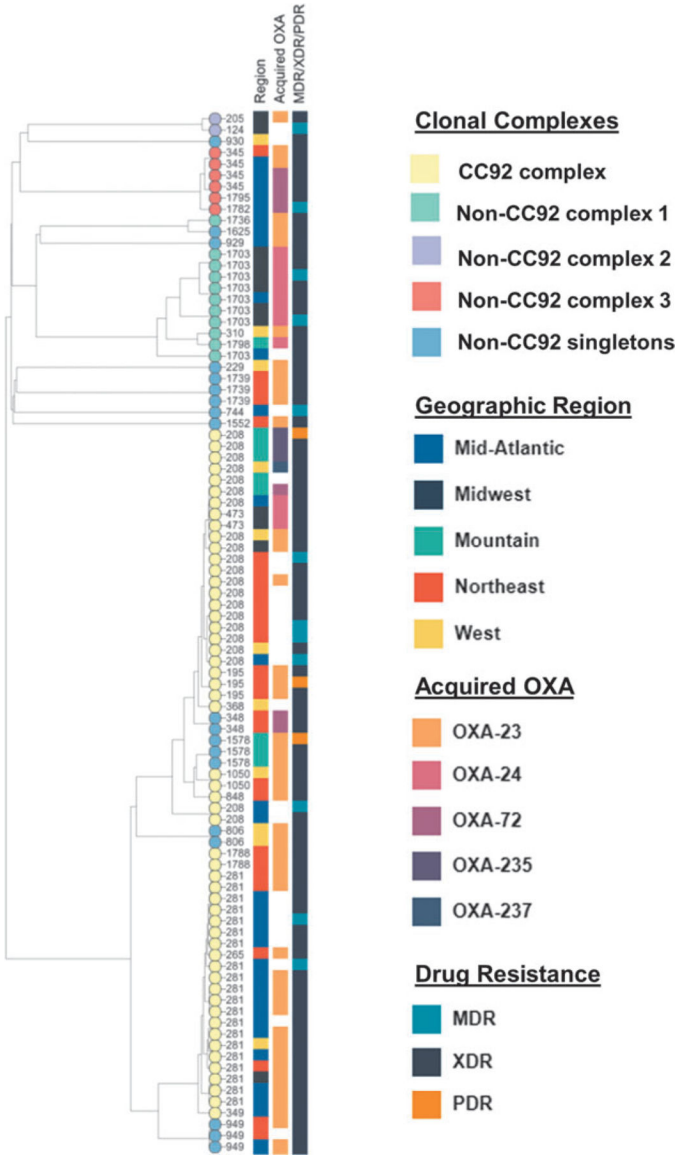

FIG. 2.

Phylogenetic classification of 92 CRAB isolates based on whole-genome MLST reveals genetic diversity within $CC92_{OX}$. Clonal complexes defined by BURST are indicated by colored *circles*. Numbers indicate Oxford MLST designations. Geographic region, acquired OXA, and drug resistance patterns are indicated by colored blocks. MDR, multidrug-resistant; PDR, pan drug-resistant; XDR, extensively drug-resistant.

Table 1.

Distribution of OXA Variants by Type and Region

	OXA VARIANT	FREQUENCY[a]	% OF ISOLATES (N=92)	REGION[b]				
				Mid-Atlantic n=32	Northeast n=28	Midwest n=12	West n=11	Mountain n=9
ACQUIRED	OXA-23	45	49	■	■	■	■	
	OXA-24/40	11	12	■		■		■
	OXA-72	7	8	■	■			■
	OXA-235	3	3					■
	OXA-237	2	2				■	
INTRINSIC	OXA-82	28	30	■	■	■	■	
	OXA-66	22	24	■	■	■	■	■
	OXA-71	11	12	■	■			
	OXA-95	6	7	■	■			
	OXA-51	5	5	■	■			
	OXA-83	5	5	■		■		
	OXA-65	2	2			■		
	OXA-69	2	2	■				
	OXA-113	2	2		■		■	
	OXA-173	2	2			■		
	OXA-223	2	2				■	■
	OXA-64	1	1				■	
	OXA-100	1	1				■	
	OXA-109	1	1				■	
	OXA-172	1	1	■				

[a] Total number of OXA variants; some isolates carried >1 variant

[b] Detected OXA variants are indicated with colored blocks, by geographic region

Table 2.

Antimicrobial Susceptibility of 92 Carbapenem-Resistant Acinetobacter baumannii Isolates by OXA Variant Present

	Total (n = *92*)				*Acquired OXA* (n = *67*)				*Intrinsic OXA*[a] (n = *25*)			
	MIC[b] *μg/mL*				*MIC*[b] *μg/mL*				*MIC*[b] *μg/mL*			
Antimicrobial agent	***Resistant* n (%)**	***Range***	***MIC*** $_{50}$	***MIC*** $_{90}$	***Resistant* n (%)**	***Range***	***MIC*** $_{50}$	***MIC*** $_{90}$	***Resistant* n (%)**	***Range***	***MIC*** $_{50}$	***MIC*** $_{90}$
Carbapenem												
Doripenem	91 (99)	4 to >8	>8	>8	67 (100)	>8	>8	>8	24 (96)	4 to >8	>8	>8
Imipenem	86 (94)	<0.5 to >64	64	>64	67 (100)	8 to >64	64	>64	19 (76)	<0.5 to 64	8	64
Meropenem	92 (100)	8 to >8	>8	>8	67 (100)	>8	>8	>8	25 (100)	8 to >8	>8	>8
Penicillin/beta-lactamase inhibitor												
Piperacillin/tazobactam	88 (96)	<4 to >128	>128	>128	67 (100)	>128	>128	>128	21 (84)	<4 to >128	>128	>128
Ampicillin/sulbactam	67 (73)	4 to >32	32	>32	59 (88)	8 to >32	>32	>32	8 (32)	4 to >32	16	>32
Cephalosporins												
Cefepime	81 (88)	1 to >32	>32	>32	64 (96)	8 to >32	>32	>32	17 (68)	1 to >32	32	>32
Ceftriaxone	83 (90)	8 to >32	>32	>32	61 (91)	8 to >32	>32	>32	22 (88)	32 to >32	>32	>32
Cefotaxime	85 (92)	8 to >64	>64	>64	60 (90)	8 to >64	>64	>64	25 (100)	64 to >64	>64	>64
Ceftazidime	82 (89)	4 to >128	>128	>128	58 (87)	4 to >128	>128	>128	24 (96)	16 to >128	>128	>128
Quinolones												
Ciprofloxacin	90 (98)	0.5 to >8	>8	>8	67 (100)	>8	>8	>8	23 (92)	0.5 to >8	>8	>8
Levofloxacin	87 (95)	<0.12 to >8	>8	>8	66 (99)	4 to >8	>8	>8	17 (68)	<0.12 to >8	>8	>8
Tetracyclines												
Tetracycline	73 (79)	<2 to >32	32	>32	53 (79)	4 to >32	32	>32	20 (80)	<2 to >32	>32	>32
Minocycline	12 (13)	<4 to 16	<4	16	7 (10)	<4 to 16	<4	16	5 (20)	<4 to 16	<4	16
Aminoglycosides												
Gentamicin	55 (60)	<0.25 to >16	>16	>16	48 (72)	<0.25 to >16	>16	>16	7 (28)	<0.25 to >16	4	>16
Amikacin	41 (45)	<1 to >64	32	>64	37 (55)	<1 to >64	64	>64	4 (16)	<1 to >64	4	64
Tobramycin	42 (46)	<0.5 to >16	4	>16	37 (55)	<0.5 to >16	16	>16	5 (20)	<0.5 to >16	1	16
Polymyxins												
Colistin	19 (21)	<0.25 to >8	1	>8	18 (27)	<0.25 to >8	1	>8	1 (4)	0.5 to >8	1	2

[a]Isolates that solely harbored an intrinsic-type OXA.

[b] MIC values less than or greater than the lowest or highest antimicrobial concentration tested are indicated by < or >, respectively.

MIC, minimum inhibitory concentration.