Molecular and clinical epidemiology of carbapenem-resistant Enterobacterales in the USA (CRACKLE-2): a prospective cohort study

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Summary

Background Carbapenem-resistant Enterobacterales (CRE) are a global threat. We aimed to describe the clinical and molecular characteristics of Centers for Disease Control and Prevention (CDC)-defined CRE in the USA.

Methods CRACKLE-2 is a prospective, multicentre, cohort study. Patients hospitalised in 49 US hospitals, with clinical cultures positive for CDC-defined CRE between April 30, 2016, and Aug 31, 2017, were included. There was no age exclusion. The primary outcome was desirability of outcome ranking (DOOR) at 30 days after index culture. Clinical data and bacteria were collected, and whole genome sequencing was done. This trial is registered with ClinicalTrials.gov, number NCT03646227.

Findings 1040 patients with unique isolates were included, 449 (43%) with infection and 591 (57%) with colonisation. The CDC-defined CRE admission rate was 57 per 100 000 admissions (95% CI 45–71). Three subsets of CDC-defined CRE were identified: carbapenemase-producing Enterobacterales (618 [59%] of 1040), non-carbapenemase-producing Enterobacterales (194 [19%]), and unconfirmed CRE (228 [22%]; initially reported as CRE, but susceptible to carbapenems in two central laboratories). *Klebsiella pneumoniae* carbapenemase-producing clonal group 258 *K pneumoniae* was the most common carbapenemase-producing Enterobacterales. In 449 patients with CDC-defined CRE infections, DOOR outcomes were not significantly different in patients with carbapenemase-producing Enterobacterales, non-carbapenemase-producing Enterobacterales, and unconfirmed CRE. At 30 days 107 (24%, 95% CI 20–28) of these patients had died.

Interpretation Among patients with CDC-defined CRE, similar outcomes were observed among three subgroups, including the novel unconfirmed CRE group. CDC-defined CRE represent diverse bacteria, whose spread might not respond to interventions directed to carbapenemase-producing Enterobacterales.

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Introduction

Antimicrobial resistance is a threat to global public health.[1,2] Carbapenem-resistant Enterobacterales (CRE) rank among the top three multidrug-resistant pathogens on WHO's priority list.[3] The subset of CRE that produce carbapenemases, carbapenemase-producing Enterobacterales (CPE), are of high clinical and public health concern, because they might spread quickly in health-care systems.[4]

Globally, common carbapenemases in Enterobacterales include the *Klebsiella pneumoniae* carbapenemases (KPC), oxacillinase (OXA)-48-like β-lactamases, and metallo-β-lactamases, such as New-Delhi-metallo-β-lactamases (NDM), the active-in-imipenem family of carbapenemases, and Verona integron-encoded metallo-β-lactamases (VIM).[1] When expressed in enteric bacteria, KPC are resistant to inactivation by clavulanic acid, sulbactam, and tazobactam.[5] In the retrospective INCREMENT cohort, 43% all-cause 30-day mortality in 437 patients with CPE bloodstream infection was observed.[6] Patients in INCREMENT originated from 12 countries, including the USA.[6] KPC-producing *K pneumoniae* was the predominant species of CPE in the INCREMENT study.[6] In hospitalised patients in low-income and middle-income countries (LMICs), bloodstream infection due to CRE is associated with an adjusted hazard ratio of 1·75 (95% CI 1·04–2·94) for in-hospital mortality.[7] Of note, in LMICs, only a minority of carbapenem-resistant *K pneumoniae* were part of clonal group 258, and bla_{NDM} was the most commonly identified carbapenemase-encoding gene.[7] In a microbiological survey of 1801 CRE isolates—defined as in-vitro resistance to any carbapenem—from China, 86% of isolates were CPE. Of these CPE, KPC-producing

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Research in context

Evidence before this study

Resistance to carbapenems in Enterobacterales is a threat to global public health. We searched MEDLINE and Google Scholar from database inception to July 1, 2019, using the terms "carbapenem resistant Enterobacterales", "carbapenemase", and "mortality". Our search identified reports of surveillance studies done by the US Centers for Disease Control and Prevention (CDC). These reports indicate that a subset of CDC-defined carbapenem-resistant Enterobacterales (CRE) in the USA do not produce carbapenemases. Data from large retrospective cohorts of patients with carbapenemase-producing Enterobacterales (CPE) from Europe, the USA, and China indicate a predominance of *Klebsiella pneumoniae* carbapenemase-producing *K pneumoniae*. Retrospective multicentre data on CPE bloodstream infections show a 30-day all-cause mortality of 43%. Furthermore, in low-income and middle-income countries, carbapenem resistance is associated with a 15% absolute increase in in-hospital mortality among inpatients with a bloodstream infection due to Enterobacterales. A single-centre, retrospective study from the USA suggested that infection with CPE is associated with increased mortality compared with non-carbapenemase-producing Enterobacterales (non-CPE).

Added value of this study

In this study, we provide comprehensive clinical and whole genome sequencing data for a cohort of 1040 patients with CDC-defined CRE. In addition to CPE, and non-CPE, we identified a novel subset of CDC-defined CRE. These unconfirmed CRE met criteria for CRE at the clinical laboratory but were found to be carbapenem-susceptible in two central laboratories. Clinical outcomes in patients infected with these three subsets were similar. Analyses of whole genome sequencing data showed that clonal group 258 *K pneumoniae* remains the most common CPE. However, *K pneumoniae* belonging to clonal group 307 might be increasing in prevalence.

Implications of all the available evidence

Among US patients with CDC-defined CRE, clinical outcomes in three subgroups were similar, including the novel unconfirmed CRE group. CDC-defined CRE represent a diverse group of bacteria, whose spread might not respond to interventions directed solely to CPE.

sequence type (ST) 11 *K pneumoniae* were the most common.[8]

In 2012, the US Centers for Disease Control and Prevention (CDC) defined CRE as Enterobacterales with non-susceptibility to imipenem, meropenem, or doripenem and resistance to extended-spectrum cephalosporins (ceftriaxone, ceftazidime, ceftizoxime, and cefotaxime).[9] In 2015, the CDC definition was updated to include in-vitro resistance to one or more carbapenems, including ertapenem, without any requirement for cephalosporin resistance.[10] In the USA, a more detailed understanding of outcomes, and the effect of bacterial characteristics on those outcomes, in patients with CRE is needed, to help guide future interventional trials. Therefore, we aimed to describe in detail the clinical spectrum of patients diagnosed with CDC-defined CRE infection or colonisation in the USA, their outcomes, and the phenotypic and genotypic characterisation of their isolates. Our research question was whether carbapenemase production in CRE is associated with adverse clinical outcomes.

Methods

Study design and participants

CRACKLE-2 is a prospective, observational, multicentre study with consecutive enrolment of hospitalised patients.[11,12] Patients were eligible for inclusion if CDC-defined CRE was isolated in a clinical culture from any anatomical site during hospitalisation; surveillance cultures were not eligible. There was no age exclusion. The first qualifying culture episode during the first admission for each unique patient enrolled during the study period (April 30, 2016 to Aug 31, 2017) with an available CDC-defined CRE isolate was included. 26 study sites with 49 US hospitals in 15 states and the District of Columbia contributed patients. The 49 study hospitals are compared with 6282 US hospitals in the appendix (p 4). The final study size was derived by inclusion of all eligible patients within the study period. The study was approved by the Institutional Review Boards of all the health systems involved with a waiver of consent.

Procedures

Clinical data, including race or ethnicity (which were included to facilitate comparisons with non-study populations) were obtained from the electronic health record. Infections were defined by standard criteria (appendix p 1); otherwise, positive cultures were considered colonisation.[12] At 90 days after discharge, data on post-hospitalisation death and readmission were collected from the electronic health record. Treatment was divided into empirical antibiotics (those given before the date of the antibacterial susceptibility report) and definitive treatment (antibiotics given after susceptibility results were available).

CRE were defined according to CDC guidelines, applied in local clinical microbiology laboratories.[10] Briefly, CDC-defined CRE were Enterobacterales that tested resistant to any of the carbapenems (ie, minimum inhibitory concentration [MIC] of ≥4 μg/mL for doripenem, meropenem, or imipenem, odds ratio ≥2μg/mL for ertapenem) or were documented to harbour a gene

encoding a carbapenemase or were positive for carbapenemase production. For Enterobacterales that exhibit intrinsic imipenem non-susceptibility (ie, *Morganella morganii*, *Proteus* species, and *Providencia* species), resistance to carbapenems other than imipenem was required. Eligibility was based on antimicrobial susceptibility testing done in local contributing clinical microbiology laboratories. Bacterial identification and carbapenem susceptibility testing were done in these laboratories using MicroScan (Beckman Coulter, Atlanta, GA, USA), Vitek 2, Etest (both bioMérieux, Durham, NC, USA), BD Phoenix, BBL disks (both Becton Dickinson, Durham, NC, USA), Sensititre (Thermo Fisher, Waltham, MA, USA), disc diffusion, or in-house agar dilution. Central carbapenem susceptibility testing was done in two independent central research laboratories using Etest and Microscan (Beckman Coulter, Atlanta, GA, USA).

Sequencing of genomic DNA extracted from isolates was done at three locations: Molecular Resource Facility, Rutgers (Rutgers; Illumina NextSeq500), UTHealth (Illumina MiSeq), and Baylor College of Medicine (Illumina HiSeq X). ST was defined as an allele combination of housekeeping genes (n=7) resulting in a number that identify the genetic background of a bacterial isolate based on multilocus sequence typing. Clonal groups (CG) were defined as related STs differing only in one or two alleles. The CGs are named according to the predominant (main) ST. Due to the genetic heterogeneity of the *Enterobacter* spp, genomic clades were used to show the population structure of *Enterobacter* spp isolates. Genomic clades in *Enterobacter* spp were defined by pairwise average nucleotide identity-based distance matrix and core single nucleotide polymorphism-based phylogeny analysis. Mean average nucleotide identity values within a clade were usually at least 95%, whereas the values between clades were mainly less than 95%. The average nucleotide identity and single nucleotide polymorphism phylogeny were concordant in clustering the genomes into phylogenetic clades. A genomic cluster within highly related isolates was defined as having fewer than 20 single nucleotide polymorphisms in the core genome by phylogenetic analyses. Details of sequencing, bioinformatics, and phylogenetic analyses are available in the appendix (pp 1, 2).

Outcomes

Outcomes were evaluated 30 days after the index culture. The primary outcomes were a desirability of outcome ranking (DOOR) analysis assessing three deleterious events (absence of clinical response, unsuccessful discharge, and adverse events; appendix pp 2, 3) 30 days after the index culture.[13] The best outcome was defined as being alive without deleterious events and the worst as death. The three categories between these two extremes were alive with one, two, or three deleterious events. Because only one of 450 patients with CRE infection fell into the alive with three events category, that level was grouped post hoc with the alive with two events category for analysis, with four total categories of outcomes. DOOR is a method for comparing groups using a single ordinal patient-centric outcome. This ordinal outcome represents a global assessment of patient wellbeing, including efficacy and safety components. Analyses consist of estimating the probability of a more desirable result in one group relative to another, with a probability of 50% implying equality of groups.[11,13] A probability of greater than 50%, with a 95% CI that excludes 50%, implies superiority of one group compared with the other. Similarly, a probability of less than 50%, with a 95% CI that excludes 50%, implies inferiority of one group compared with the other. Secondary outcomes were 30-day all-cause mortality, 90-day all-cause mortality, clinical response, and 90-day readmissions in participants who were discharged alive.

Statistical analysis

Distributions of continuous variables were compared across groups using the Kruskal-Wallis test. Pearson χ^2 testing across three groups was used for categorical variables. CDC-defined CRE admission rates and robust 95% CIs were estimated using a generalised linear mixed effects model (glimmix) with hospital as a random effect (appendix p 3).

To compare outcomes between CPE, non-carbapenemase-producing Enterobacterales (non-CPE), and unconfirmed CRE, pairwise DOOR analyses were done (appendix p 3).[13] A weight was calculated for each patient using the following variables based on their clinical relevance: origin (home *vs* other), Charlson comorbidity index (>3 *vs* 3), and age at culture, resulting in a pseudo-population of weights where the three CDC-defined CRE groups were similar at baseline based on the inverse probability weighted variables. Desirability of outcome ranking probabilities and 95% bootstrap CIs were then calculated using the weighted population. Less than 1% of outcome data were missing (appendix p 3). Because of the potential for type 1 error due to multiple comparisons, findings for analyses of secondary endpoints should be interpreted as exploratory. p values of 0·05 or smaller were considered statistically significant, and all tests were two-sided. All analyses were done using SAS software version 9.4.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Three mutually exclusive subsets were identified in 1040 CDC-defined CRE isolates from the 49 participating

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See **Online** for appendix

	Carbapenemase-producing carbapenem-resistant Enterobacterales	Non-carbapenemase-producing carbapenem-resistant Enterobacterales	Unconfirmed carbapenem-resistant Enterobacterales	Total	p value*
N	618 (59%)	194 (19%)	228 (22%)	1040	..
Region†	..	..	..	..	<0·0001
Midwest	119 (19%)	31 (16%)	24 (11%)	174 (17%)	..
Northeast	316 (51%)	67 (35%)	70 (31%)	453 (44%)	..
South	136 (22%)	67 (35%)	105 (46%)	308 (30%)	..
West	47 (8%)	29 (15%)	29 (13%)	105 (10%)	..
Age, years	64 (54–75)	64 (53–75)	63 (51–74)	64 (53–75)	0·51
Sex	..	..	..	..	0·0076
Male	329 (53%)	128 (66%)	127 (56%)	584 (56%)	..
Female	289 (47%)	66 (34%)	101 (44%)	456 (44%)	..
Race	..	..	..	..	0·73
White	292 (47%)	96 (49%)	103 (45%)	491 (47%)	..
Black	201 (33%)	55 (28%)	79 (35%)	335 (32%)	..
Other‡	125 (20%)	43 (22%)	46 (20%)	214 (21%)	..
Hispanic ethnicity	74 (12%)	26 (13%)	25 (11%)	125 (12%)	0·74
Charlson comorbidity index§	3 (1–5)	3 (1–5)	2 (1–4)	3 (1–5)	0·013
Pitt bacteraemia score¶	3 (2–6)	3 (1–6)	2 (0–5)	3 (2–6)	0·011
Time to positive culture, days‖	2 (0–16)	11 (1–30)	3 (0–13)	3 (0–18)	<0·0001
Community onset**	147 (24%)	42 (22%)	63 (28%)	253 (24%)	0·38
Admitted from ††	..	..	..	..	<0·0001
Home	323 (52%)	127 (65%)	151 (66%)	601 (58%)	..
Long-term chronic care	172 (28%)	23 (12%)	35 (15%)	230 (22%)	..
Hospital transfer	79 (13%)	39 (20%)	34 (15%)	152 (15%)	..
Long term acute care	41 (7%)	3 (2%)	7 (3%)	51 (5%)	..
Transferred from foreign country	3 (<1%)	2 (1%)	0 (0%)	5 (<1%)	..
Hospice	0 (0%)	0 (0%)	1 (<1%)	1 (<1%)	..
Tertiary care centre	471 (76%)	162 (84%)	175 (77%)	808 (78%)	0·10
Hospital size	..	..	..	..	0·22
0–499 beds	147 (24%)	54 (28%)	67 (29%)	268 (26%)	..
500–999 beds	189 (31%)	64 (33%)	74 (32%)	327 (31%)	..
≥1000 beds	282 (46%)	76 (39%)	87 (38%)	445 (43%)	
Culture	..	..	..	..	<0·0001
Blood infection	75 (12%)	25 (13%)	30 (13%)	130 (13%)	..
Urine infection	84 (14%)	20 (10%)	25 (11%)	129 (12%)	..
Urine colonisation	175 (28%)	39 (20%)	61 (27%)	275 (26%)	..
Respiratory infection	41 (7%)	15 (8%)	11 (5%)	67 (6%)	..
Respiratory colonisation	129 (21%)	29 (15%)	43 (19%)	201 (19%)	..
Wound infection	32 (5%)	10 (5%)	17 (7%)	59 (6%)	..
Wound colonisation	41 (7%)	12 (6%)	18 (8%)	71 (7%)	..
Intra-abdominal infection	19 (3%)	29 (15%)	10 (4%)	58 (6%)	..
Other infection	2 (<1%)	3 (2%)	1 (<1%)	6 (1%)	..
Other colonisation	20 (3%)	12 (6%)	12 (5%)	44 (4%)	..

Data are n (%) or median (IQR). *p value comparing distributions where applicable. †US Census Bureau definitions. ‡Other races included Asian (n=40), native Hawaiian or Pacific islander (n=3), multi-racial (n=5), and patients for whom race was not specified in the medical record (n=166). §Charlson comorbidity index is a chronic comorbidity score with a range from 0 to 37, with higher scores indicating more comorbid conditions present. A patient with a score of 3 could have three level 1 comorbid conditions (eg, dementia, chronic pulmonary disease, and congestive heart failure), one level 1 (eg, dementia) and one level 2 comorbid condition (eg, leukaemia), or one level 3 condition (moderate or severe liver disease).[34] ¶Pitt bacteraemia score is an acute severity of illness score. Higher scores indicate more severe illness. A patient with a score of 3 would have one level 1 marker (eg, disoriented mental status) and one level 2 marker of acute illness (eg, hypotension).[35] ‖Time to first positive culture indicates the number of days from admission to the collection date of the index culture, with 0 indicating that the index culture was obtained on the day of admission. **Community onset defined as home origin with first positive culture date less than 3 days from date of admission. ††For analysis purposes grouped as home or transferred from foreign country, long-term acute care or hospital transfer, and long-term chronic care or hospice.

Table 1: **Baseline characteristics**

hospitals (table 1). Carbapenemase genes were present in 618 (59%, 95% CI 56–62) CRE, referred to as CPE. In 194 (19%, 95% CI 16–21), in-vitro resistance to at least one carbapenem was confirmed in the absence of any carbapenemase gene. These isolates, except for five imipenem-resistant *Proteus* species, were defined as non-CPE. Carbapenemase genes were not found in an additional 228 (22%, 95% CI 19–24) of the 1040 CDC-defined CRE. These CDC-defined CRE, although identified as carbapenem-resistant by local laboratories, were found to be susceptible or intermediate to all tested carbapenems in both central laboratories (appendix p 5). These isolates were defined as unconfirmed CRE.

The mean CDC-defined CRE admission rate was 57 per 100 000 admissions (95% CI 45–71; figure 1). 316 (70%) of 453 CDC-defined CRE were CPE in participating hospitals in the Northeast (as defined by US Census Bureau) compared with 136 (44%) of 308 in the South (difference 26%, 95% CI 19–33, p<0·0001). 601 (58%) of 1040 patients were admitted from home. Patients with CPE (213 [34%] of 618) were more likely to be admitted from long-term care settings as compared with patients with non-CPE (26 [13%] of 194; difference 21%, 95% CI 15–27) and unconfirmed CRE (42 [18%] of 228; difference 16%, 95% CI 10–22; p<0·0001). Compared with patients with unconfirmed CRE, patients with CPE had more chronic comorbid conditions (median Charlson comorbidity index 3 [IQR 1–3] *vs* 2 [IQR 1–4]) and were more acutely ill (median Pitt bacteraemia score 3 [IQR 2–6] *vs* 2 [IQR 0–5]).

The most common source of CRE isolates was urine (404 [39%] of 1040), followed by respiratory (268 [26%]), blood (130 [13%]), and wound (130 [13%]). CRE infection was present in 449 (43%) patients, with the remaining 591 (57%) classified as CRE-colonisation. Within the group of CDC-defined CRE-infected patients, those with non-CPE were less likely to have urinary tract infections (20 [20%] of 102; difference 14%; 95% CI 4–23) and more likely to have abdominal infections (29 [28%] of 102; difference 21%; 95% CI 12–30) compared with patients with CPE (urine 84 [33%] of 253; abdominal 19 [8%] of 253; p<0·0001 for overall distribution).

493 (83%) of 593 of *K pneumoniae* identified as CDC-defined CRE by local laboratories were CPE, compared with 46 (24%) of 192 for *Enterobacter* species (difference 59%, 95% CI 52–66) and 38 (31%) of 122 for *Escherichia coli* (difference 52%, 95% CI 43–61; p<0·0001; table 2; appendix pp 6, 7). For 105 (46%) of 228 of unconfirmed CRE, ertapenem was the only carbapenem with in-vitro resistance as reported by the local microbiology laboratory, compared with 27 (4%) of 618 CPE (difference 42%, 95% CI 35–48). MIC distribution, as determined CWRU-Cleveland VAMC Center for Antimicrobial Resistance and Epidemiology (Cleveland, OH), is shown in the appendix (p 12). Unconfirmed CRE and non-CPE were more susceptible to non-carbapenem antibiotics, as compared with CPE (appendix p 7). The 2012 CDC criteria for CRE would have defined 520 (84%) of 618 CPE, but only 97 (50%) of 194 non-CPE (difference 34%, 95% CI 27–42) and 65 (29%) of 228 unconfirmed CRE (difference 56%, 95% CI 49–62), as CDC-defined CRE (p<0·0001).

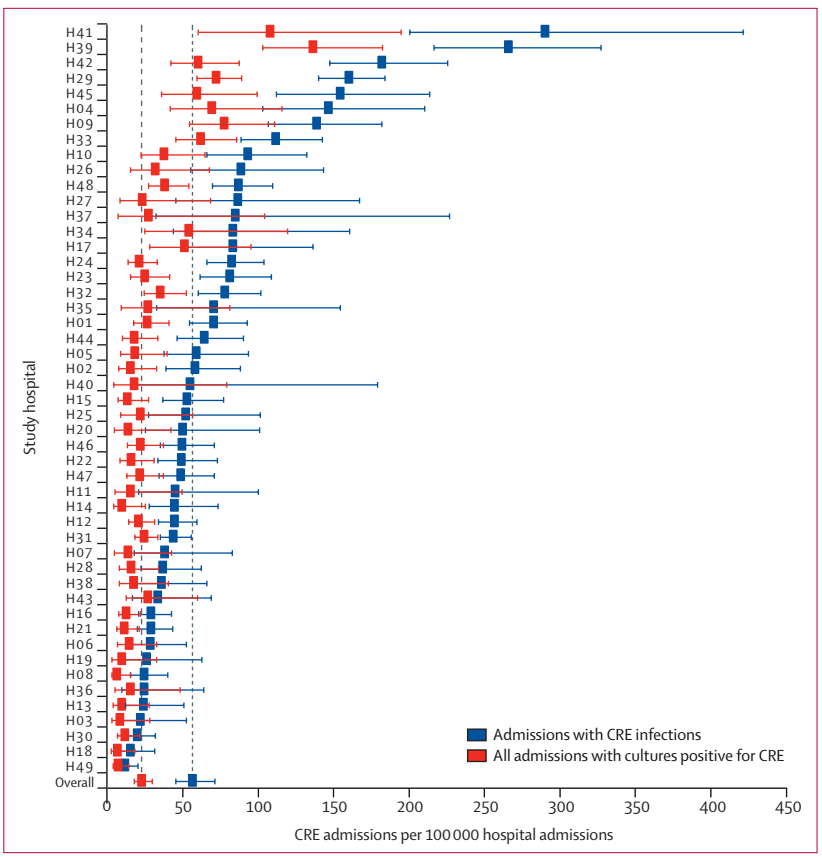

Figure 1: **CDC-defined CRE admission rates at participating hospitals**
The rates of all admissions during which CRE were identified (blue) and of admissions during which at least one CRE infection was diagnosed (red) are shown. CDC-defined CRE admission rates and robust 95% CIs were estimated using a generalised linear mixed effects model with hospital as a random effect. Error bars indicate 95% CIs. CDC=US Centers for Disease Control and Prevention. CRE=carbapenem-resistant Enterobacterales.

Observed carbapenemase genes included bla_{KPC-2} (313 [51%] of 618), bla_{KPC-3} (253 [41%]), bla_{NDM} (22 [3%]), and $bla_{OXA-48-like}$ (21 [3%]; figure 2; table 2; appendix pp 6, 8). Extended spectrum β-lactamase genes found in CPE included extended spectrum β-lactamase bla_{SHV} (217 [35%] of 618) and bla_{CTX-M} (121 [20%]). Non-CP-CRE were more likely to carry bla_{CTX-M} (59 [30%] of 194; difference 11%, 95% CI 4–18), whereas bla_{AmpC} carriage was associated with both non-CPE (112 [58%] of 194) and unconfirmed CRE (141 [62%] of 228). Mutations in either or both genes encoding outer membrane porins OmpK35 and OmpK36 were present in 120 (62%) of 194 non-CPE and 49 (21%) of 228 unconfirmed CRE.

The most common CG of *K pneumoniae* was CG258 (382 [64%] of 593), representing 364 (74%) of 493 carbapenemase-producing *K pneumoniae* (figure 2A). Of 382 CG258 *K pneumoniae*, 364 (95%) were carbapenemase-producing, harbouring primarily bla_{KPC-2}

	Carbapenemase-producing carbapenem-resistant Enterobacterales (n=618)	Non-carbapenemase-producing carbapenem-resistant Enterobacterales (n=194)	Unconfirmed carbapenem-resistant Enterobacterales (n=228)	All (n=1040)	p value
Species	..	..	..	..	<0·0001
Klebsiella pneumoniae	493 (80%)	52 (27%)	48 (21%)	593 (57%)	..
ST258 *K pneumoniae*	334 (54%)	6 (3%)	4 (2%)	344 (33%)	..
Enterobacter spp	46 (7%)	73 (38%)	73 (32%)	192 (18%)	..
Escherichia coli	38 (6%)	33 (17%)	51 (22%)	122 (12%)	..
ST131 *E coli*	22 (4%)	13 (7%)	24 (11%)	59 (6%)	..
Non-*K pneumoniae Klebsiella* spp	14 (2%)	26 (13%)	16 (7%)	56 (5%)	..
Other	27 (4%)	10 (5%)	40 (18%)	77 (7%)	..
Meets 2012 CDC criteria for CRE	520 (84%)	97 (50%)	65 (29%)	682 (66%)	<0·0001
Carbapenemases*					
bla_{KPC-2}	313 (51%)	..	..	313 (30%)	..
bla_{KPC-3}	253 (41%)	..	..	253 (24%)	..
other bla_{KPC}†	7 (1%)	..	..	7 (1%)	..
bla_{NDM-1}	15 (2%)	..	..	15 (1%)	..
Other bla_{NDM}‡	7 (1%)	..	..	7 (1%)	..
bla_{OXA-48}	6 (1%)	..	..	6 (1%)	..
Other $bla_{OXA-48-like}$§	15 (2%)	..	..	15 (1%)	..
Other¶	10 (2%)	..	..	10 (1%)	..
Extended spectrum β-lactamase					
bla_{CTX-M}	121 (20%)	59 (30%)	45 (20%)	225 (22%)	0·0044
bla_{SHV}‖	217 (35%)	19 (10%)	14 (6%)	250 (24%)	<0·0001
bla_{TEM}**	0	0	1 (<1%)	1 (<1%)	0·41
bla_{AmpC}	116 (19%)	112 (58%)	141 (62%)	369 (35%)	<0·0001

Data are n (%). *Totals exceed 100%, because eight isolates carried more than one carbapenemase gene. †Other bla_{KPC} included bla_{KPC-4} (three), bla_{KPC-6} (one), bla_{KPC-8} (one), and bla_{KPC-18} (two). ‡Other bla_{NDM} included bla_{NDM-5} (six) and bla_{NDM-7} (one). §Other $bla_{oxa-48-like}$ included $bla_{oxa-181}$ (two) and $bla_{oxa-232}$ (13). ¶Other carbapenemases included bla_{VIM} (four), bla_{IMI} (two), bla_{SME} (three), and bla_{NMC-A} (one). ‖bla_{SHV} that are considered extended spectrum β-lactamase genes, including bla_{SHV-12} (217), bla_{SHV-7} (12), bla_{SHV-30} (11), bla_{SHV-2} (five), bla_{SHV-5} (four), and $bla_{SHV-105}$ (one). **bla_{TEM-10}.

Table 2: **Bacterial characteristics including distribution of common β-lactamase genes**

(200 [55%]) and bla_{KPC-3} (161 [44%]). Among carbapenemase producing CG258 *K pneumoniae* isolates, ST258 encompassed 334 [92%] of 364 isolates. After CG258, the most frequent clonal group was CG307 (44 [7%] of 593), concentrated in the participating hospitals of Houston, TX, USA. Similar to CG258, 37 (84%) of 44 CG307 isolates were carbapenemase-producing, with bla_{KPC-2} detected in 35 (95%) of them. All CG307 harboured bla_{CTX-M}, a common group of extended-spectrum β-lactamases. The geographical distribution of ST307 *K pneumoniae* is shown in the appendix (p 13).

Enterobacter spp isolates were the second most frequent group of CDC-defined CRE (figure 2B). Due to the observed genetic heterogeneity of the *Enterobacter cloacae* complex, genetic clades were used to show the population structure of *Enterobacter* spp isolates.[16] In 146 (76%) of 192 *Enterobacter* species, no carbapenemase genes were present. In the remaining 46 (24%), bla_{KPC-2} (n=16), bla_{KPC-3} (n=19), and typical carbapenemase genes previously described in *Enterobacter* species were found (bla_{IMI-1}, bla_{IMI-2}, and bla_{NMC-A}; one of each). Additionally, various metallo-β-lactamases genes were identified, including bla_{NDM-1}, bla_{NDM-7}, bla_{VIM-1}, and bla_{VIM-4} (one of each).

In *E coli*, diverse genetic lineages were observed (figure 2C). In 84 (69%) of 122 *E coli*, no carbapenemase genes were present. ST131 accounted for 37 (30%) and was present in hospitals belonging to all geographical areas studied. The most common carbapenemases in *E coli* were bla_{KPC-2} (n=15) and bla_{KPC-3} (n=14), with sporadic isolates containing bla_{NDM-5} (n=4), $bla_{OXA-232}$ (n=2), and bla_{OXA-48} (n=3).

Phylogenetic reconstructions of *K pneumoniae*, *E coli*, and *Enterobacter* spp comparing infecting and colonising isolates (appendix p 14) show that both groups of isolates are highly related, suggesting that infecting isolates are likely originating from initial colonisation events.

Of the 1040 included patients, 449 (43%) met criteria for CDC-defined CRE infection. Using DOOR outcomes at 30 days after index culture, 183 (41%) patients with infection were alive without events, 97 (22%) alive with one event, 62 (14%) alive with two or three events, and 107 (24%) were dead (table 3). Outcomes were not significantly different between groups after adjusting

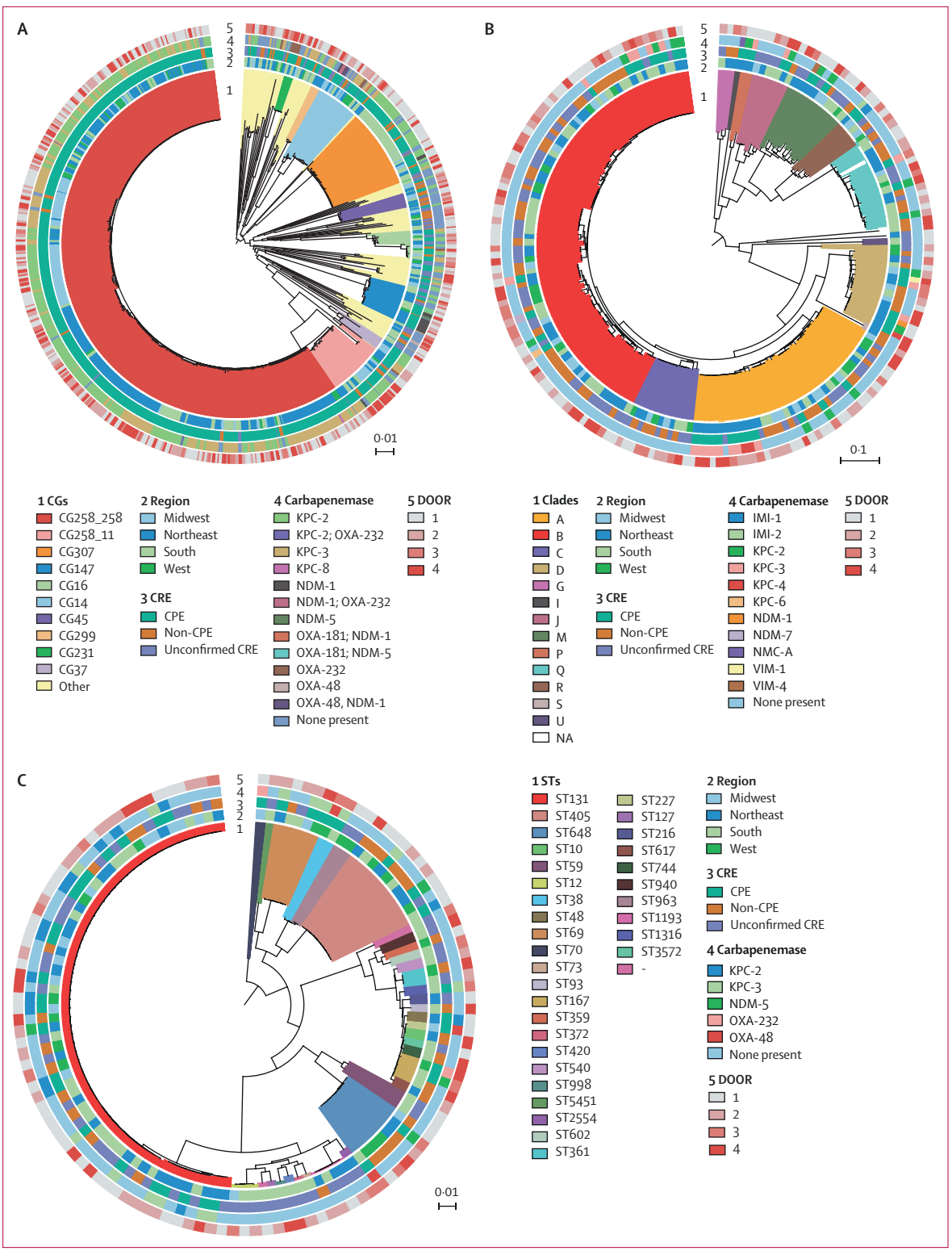

Figure 2: **Phylogenetic population structures**
(A) *Klebsiella pneumoniae*. (B) *Enterobacter* spp. (C) *Escherichia coli*. An interactive version of this figure is available online. CG=clonal group. CPE=carbapenemase-producing Enterobacterales. CRE=carbapenem-resistant Enterobacterales. DOOR=desirability of outcome ranking. Non-CPE=non-carbapenemase-producing Enterobacterales.

For **interactive figure 2** see http://arlg.med.unc.edu/crackle/

	CPE (n=253)	Non-CPE (n=102)	Unconfirmed CRE (n=94)	All (n=449)	p value
DOOR at 30 days	..	..	..	..	N/A*
Alive without events	106 (42%)	37 (36%)	40 (43%)	183 (41%)	..
Alive with one event	53 (21%)	26 (25%)	18 (19%)	97 (22%)	..
Alive with two or three events	31 (12%)	17 (17%)	14 (15%)	62 (14%)	..
Dead	63 (25%)	22 (22%)	22 (23%)	107 (24%)	..
DOOR components at 30 days†					
Not discharged	103 (41%)	45 (44%)	36 (38%)	184 (41%)	0·70
Readmitted	32 (13%)	12 (12%)	14 (15%)	58 (13%)	0·79
Lack of clinical response	86 (34%)	35 (34%)	32 (34%)	153 (34%)	>0·99
Lack of symptomatic response	74 (29%%)	29 (28%)	28 (30%)	131 (29%)	0·98
Relapse	12 (5%)	3 (3%)	3 (3%)	18 (4%)	0·66
Remains on anti-CRE antibiotic	8 (3%)	9 (9%)	7 (7%)	24 (5%)	0·060
Renal failure	13 (5%)	5 (5%)	5 (5%)	23 (5%)	0·99
Clostridium difficile infection	3 (1%)	2 (2%)	0 (0%)	5 (1%)	0·42
Length of hospital stay, days	19 (9–38)	29 (12–60)	15 (6–35)	20 (8–45)	0·0018
Post-culture length of hospital stay, days	11 (5–22)	16 (6–26)	10 (4–19)	12 (5–23)	0·023
30-day mortality	63 (25%)	22 (22%)	22 (23%)	107 (24%)	0·80
90-day mortality	79 (31%)	33 (32%)	25 (27%)	137 (31%)	0·64
90-day readmissions‡	81/183 (44%)	37/69 (54%)	32/73 (44%)	150/325 (46%)	0·37
Clinical response	167 (66%)	67 (66%)	62 (66%)	296 (66%)	>0·99
Disposition§	..	..	..	..	0·034
Death	63 (25%)	27 (26%)	19 (20%)	109 (24%)	..
Home	72 (28%)	38 (37%)	40 (43%)	150 (33%)	..
Hospice	7 (3%)	6 (6%)	2 (2%)	15 (3%)	..
Long-term acute care	29 (11%)	7 (7%)	2 (2%)	38 (8%)	..
Long-term care	71 (28%)	21 (21%)	24 (26%)	116 (26%)	..
Transfer other hospital	11 (4%)	3 (3%)	6 (6%)	20 (4%)	..
Transferred to a foreign country	0	0	1 (1%)	1 (<1%)	..

Data are n (%) n/N (%), or median (IQR). CPE=carbapenemase-producing Enterobacterales. CRE=carbapenem-resistant Enterobacterales. DOOR=desirability of outcome ranking. N/A=not applicable. Non-CPE=non-carbapenemase-producing Enterobacterales. *Inverse probability weighted DOOR analyses indicated no significant differences between groups. The inverse probability weighted-adjusted probability of a patient with CPE versus non-CPE having a better outcome is 52% (95% CI 45–58), with CPE versus unconfirmed CRE 52% (44–61), and non-CPE versus unconfirmed CRE 51% (95% CI 41–60). †DOOR analysis components as defined in the appendix (pp 2, 3). ‡In patients discharged alive. §Grouped for analysis purposes as death or hospice, home or transferred to a foreign country, long-term acute care or transfer to other hospital and long-term care.

Table 3: **Outcomes in patients with CRE infections**

for possible confounding factors. Inverse probability weighted DOOR analyses indicated no significant differences between groups. In DOOR analysis, 50% likelihood of a better outcome is equal to no difference between groups, whereas a greater than 50% probability, combined with a 95% CI that does not cross 50%, indicates a significantly greater likelihood of a better outcome in one group versus the other. Inverse probability weighted-adjusted probabilities of a patient with CPE versus non-CPE having a better outcome was 52% (95% CI 45–58), CPE versus unconfirmed CRE 52% (95% CI 44–61), and non-CPE versus unconfirmed CRE 51% (95% CI 41–60). In the subset of patients with invasive infections (pneumonia, bacteraemia, or intra-abdominal infection, n=256), there was also no significant difference in DOOR outcome (inverse probability weighted-adjusted probability of a better outcome of 54%, 95% CI 42–66). Similarly, in DOOR analyses stratified on the basis of Pitt bacteraemia score, and when time from admission to first positive culture was included as an additional inverse probability weighted-confounder, differences between CRE groups were not observed (appendix pp 9, 10). Likewise, when limiting inverse probability weighted-adjusted DOOR analysis to 238 patients infected with *K pneumoniae*, no significant difference between groups was observed (data not shown). All-cause 30-day mortality in patients with CDC-defined CRE infections was 107 (24%, 95% CI 20–28) of 449, and 90-day mortality was 137 (31%, 95% CI 26–35) of 449 (table 3). Mortality was not significantly different between patients infected with CPE, non-CPE, and unconfirmed CRE. Of 325 patients discharged alive after CDC-defined CRE infection, 150 (46%, 95% CI 41–52) were readmitted within 90 days, with a median time to readmission of 21 days (IQR 8–44). Antibiotic treatment is outlined in the appendix (p 11). In patients with unconfirmed CRE, 204 (38%) of 449 received a carbapenem as part of their empiric and 155 (37%) of 414 as part of their definitive treatment regimen.

In 591 patients with CDC-defined CRE colonisation, 30-day mortality was 111 of 591 (19%, 95% CI 16–22). The 90-day readmission rate in patients with CDC-defined CRE colonisation who were discharged alive was 186 of 469 (40%, 95% CI 35–44).

Discussion

In this contemporary analysis of CRE in hospitalised US patients, three clinically and molecularly distinct subsets of CRE were identified. CPE are generally considered of the greatest epidemiological interest for their association with poor outcomes and ability to spread rapidly throughout health-care systems. However, in this cohort, 41% of isolates that met CDC guidelines did not carry carbapenemase genes, and 22% were not carbapenem-resistant upon centralised laboratory retesting. Thus, resources dedicated to halting the spread of CPE might therefore be directed at bacteria of lesser public health concern. Correct identification of carbapenemase production at the patient, hospital, regional, and national levels is important for treatment selection, infection control, and prevention of spread.

Clinical outcomes were not significantly different regardless of infection with CPE, non-CPE, or unconfirmed CRE. Because most CPE are KPC-producing ST258 *K pneumoniae*, this comparison is primarily between these strains and a genetically much more diverse group of Enterobacterales of various species. Three non-mutually exclusive explanations for

this finding may be considered. First, CDC criteria might identify patients with infections that, regardless of the underlying mechanism of carbapenem resistance or in-vitro reproducibility of the phenotype, are associated with high risk of mortality and readmissions. Second, improved treatment options for CPE infections that were available during the study period might have decreased the difference in patient outcomes predicted based on earlier studies. Third, the label of CRE might lead to unnecessary treatment with more toxic or less effective antibiotics. A retrospective, single-centre study evaluated 83 patients with CDC-defined CRE bacteraemia diagnosed between 2013 and 2016 and compared infection with CPE with non-CPE. Although limited by a small sample size and inclusion of only bacteraemia cases, infection with CPE was marginally associated with both increased 14-day (adjusted odds ratio 4·92, 95% CI 1·01–24·81, p=0·05) and 30-day mortality (3·19, 0·99–10·25, p=0·05).[17] Ceftazidime-avibactam—superior to polymyxins in the treatment of CRE infections—was not available during that study.[11,17,18] Thus, treatment of high-risk patients with CPE infections with ceftazidime-avibactam could have resulted in improved outcomes.[11] However, only a subset of patients with CPE received ceftazidime-avibactam as empiric (17%) and definitive therapy (23%). Furthermore, 95% of patients with non-CPE received a carbapenem in that single-centre study, as compared with less than 40% in this study. Carbapenems are superior to piperacillin-tazobactam and are considered by many to be the preferred treatment for patients with severe infections with ceftriaxone-resistant, carbapenem-susceptible Enterobacterales.[17,19]

The large proportion of non-CPE amongst CDC-defined CRE appears to be a direct consequence of the change in definition implemented in 2015. When we applied the 2012 definition to this dataset, the percentage of CDC-defined CRE without carbapenemases decreased to 162 (24%) of 682. Based on similar outcomes between patients infected with different subgroups of CDC-defined CRE, this broad definition might well be justified. However, control of infections with bacteria in these various subgroups might not respond to the same infection prevention and control strategies. In a 2017 CDC surveillance study, 68% of CRE were non-carbapenemase producers.[20] Additionally, 22% of CDC-defined CRE were not carbapenem resistant upon central testing. The simplest explanation for these unconfirmed CRE is that they reflect major errors of automated carbapenem susceptibility testing, specifically when using ertapenem. Additionally, unconfirmed CRE might in part represent isolates with ertapenem MICs close to breakpoints, in which a single dilution difference might change the interpretation of susceptibility from resistant to intermediate. However, when tested in the central laboratory, ertapenem MICs ranged widely in these isolates. Another explanation is loss of resistance genes during transport and passage. However, loss of a carbapenemase-containing plasmid would not explain the high rates of meropenem and imipenem susceptibility observed at the contributing local microbiology laboratories. Additionally, because unconfirmed CRE are found in patients who are clinically different from patients with CPE and display a species distribution and non-carbapenem susceptibility pattern distinct from CPE, a stochastic random event is unlikely to explain the observed unconfirmed CRE. Regardless, infection with unconfirmed CRE seems to be an indicator of increased risk of mortality to the same extent as infection with CPE.

Of CPE, CG258 *K pneumoniae* containing bla_{KPC} remains the most common.[21] Additionally, ST307 is now the most common *K pneumoniae* lineage containing bla_{CTX-M} and bla_{KPC} in the Houston area, supporting the introduction of this novel high-risk clone. Previous reports suggest that ST307 is likely to follow a similar pattern of spread to CG258.[22,23] Treatment-emergent resistance to ceftazidime-avibactam has been reported in ST307 *K pneumoniae*, similar to CG258 strains.[24,25] Additional mechanisms of resistance were also seen, such as CRE containing $bla_{OXA-48-like}$ and genes encoding metallo-β-lactamases. Horizontal gene transfer might cause spread of bla_{NDM}, bla_{VIM}, and bla_{OXA} in a comparable manner to bla_{KPC}.

The most common genetic lineage of *E coli* in the CRE isolates was a highly related clade of ST131. Given that ST131 is the most common *E coli* lineage among pathogenic isolates causing extra-intestinal disease worldwide, acquisition of carbapenem resistance among these isolates is concerning.[26,27] Most troubling are those ST131 *E coli* that have acquired a carbapenemase gene, because these clones have great potential for causing severe invasive disease.[28,29]

This study has several limitations. First, hospitals were selected on the basis of the interest of site investigators, rather than randomly. Small hospitals were under-represented in our study hospitals and large teaching hospitals were over-represented. Therefore, these findings should not be extrapolated to hospitals with fewer than 100 beds. However, the study hospitals represented a wide range of sizes, ownership models, community versus tertiary care, and CRE admission rates. Second, this was a consent-waived study, and only electronic health record data were included. This approach allows for unbiased, sequential inclusion, regardless of ability to provide consent. Third, patients and isolates were compared in three groups for several variables, which might introduce problems with multiple comparisons. However, the primary outcome variable—the DOOR analysis—was a-priori defined, and no significant difference was observed between groups. Fourth, our sampling was limited to a single country. The epidemiology of CRE in other parts of the world might be substantially different. Ongoing studies in the Multi-Drug Resistant Organism Network are evaluating the international epidemiology of CRE.

In the USA, KPC-producing CG258 *K pneumoniae* is the most common CPE. Among US patients with CDC-defined CRE in 49 hospitals in 26 sites, there were similar clinical outcomes among three subgroups, including the novel unconfirmed CRE group. These data provide guidance for clinical practice and public health policy; CDC-defined CRE represent a diverse group of bacteria, whose spread might not respond to interventions directed solely to carbapenemase-producing CPE. Regardless of CRE subgroup, CDC-defined CRE infections are associated with poor outcomes.

Contributors

HFC and VGF procured funding for this project. DvD, CAA, LK, MW, DLP, RB, RP, SE, CH, RA, HFC, VGF, BNK, and RAB contributed to its conception. DvD, CAA, GW, EC, OBG, JTJ, MJS, BCF, YD, SD, KSK, and RAB were responsible for epidemiological and clinical data collection. AMH, KMH, TND, RP, CH, and RAB were responsible for generating and analysing microbiological data. ME and SE contributed to the statistical analyses. CAA, LC, BH, WS, AD, CM, CL, and BNK generated and analysed whole genome sequence data. DvD, CAA, BNK, and RAB prepared the manuscript; DvD and CAA contributed equally. BNK and RAB contributed equally. All authors contributed to the interpretation of results and critical review of the manuscript.

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Declaration of interests

DvD is an advisory board member for Allergan, Achaogen, Qpex, Shionogi, Tetraphase, Sanofi-Pasteur, T2 Biosystems, NeuMedicine, Roche, MedImmune, Astellas, and Merck. He also declares travel reimbursement from Infectious Diseases Society of America (IDSA), American Society of Microbiology (ASM), and European Society for Clinical Microbiology and Infectious Diseases. CAA declares grant support from Merck, MeMed Diagnostics, and Entasis Therapeutics, royalties from UptoDate, Harrison's Principles of Internal Medicine, and Mandell's Principles and Practice of Infectious Diseases, and reimbursement for travel from IDSA and ASM. GW declares research support from Allergan. MJS is an advisory board member for Achaogen and Shionogi and declares grant support from Merck and Allergan. YD declares grant support from The Medicines Company, Accelerate Diagnostics, and National Institutes of Health (NIH), and is an advisory board member for Meiji, Tetraphase, Roche, and Geom. KSK has been a consultant and grant investigator for and has received speaker's bureau, consulting fees, grants, and speaker honorarium from Allergan, receives grants from Merck, and is a consultant for Merck, Xellia, and Achaogen. JCG has been a consultant for Achaogen, Tetraphase, and Melinta, received speaker honoraria from Allergan, Melinta, and MerckMerck, and received a grant from Merck. LMA declares speaker honoraria from Pfizer, Merck Sharp & Dohme, and Merck and is a paid advisory board member for Achaogen, Nabriva, and Roche Diagnostics. RP declares research support from CD Diagnostics, bioMerieux, BioFire, Curetis, Merck, Contrafect, Hutchison Biofilm Medical Solutions, Accelerate Diagnostics, Allergan, EnBiotix, Contrafect, and The Medicines Company, is or has been a consultant to Curetis, Specific Technologies, Selux Dx, GenMark Diagnostics, Roche, PathoQuest, Heraeus Medical, and Qvella (monies are paid to Mayo Clinic), has a patent on *Bordetella pertussis* and *Bordetella parapertussis* PCR issued (8507201), a patent on a device and method for sonication (8076117) with royalties paid by Samsung to Mayo Clinic, and a patent on an anti-biofilm substance issued (8802414), and has received travel reimbursement from ASM and IDSA, an editor's stipend from ASM and IDSA, and honoraria from the National Board of Medical Examiners, UptoDate, and the Infectious Diseases Board Review Course. FP receives grants from Accelerate, Merck, and Pfizer. JJL is a consultant for Merck. DLP is a board member for Merck, Pfizer, Shionogi, Achaogen, AstraZeneca, Leo Pharmaceuticals, Bayer, GlaxoSmithKline, Cubist, Venatorx, and Accelerate and receives grants from Shionogi and Merck (MSD) and speakers bureau from Pfizer. SE is a consultant for Takeda-Millennium, Pfizer, Roche, Novartis, Achaogen, ACTTION, Genentech, Amgen, GlaxoSmithKline, AstraZeneca, Teva, Zeiss, Dexcom, Claret Medical, Vir, Arrevus, Five Prime, Shire, Alexion, Gilead, Spark, Nuvelution, Tracon, WAVE, Advantagene, Braeburn, Cardinal Health, Lipocine, Microbiotix, and Stryker. VGF declares grants or research support from MedImmune, Cerexa-Forest-Actavis-Allergan, Pfizer, Advanced Liquid Logics, Theravance, Novartis, Cubist-Merck, Medical Biosurfaces, Locus, Affinergy, Contrafect, Karius, Genentech, Regeneron, and Basilea, educational fees from Green Cross, Cubist, Cerexa, Durata, Theravance; Debiopharm, and royalties from UpToDate. He is also a paid consultant for Pfizer, Novartis, Galderma, Novadigm, Durata, Debiopharm, Genentech, Achaogen, Affinium, The Medicines Company , Cerexa, Tetraphase, Trius, MedImmune, Bayer, Theravance, Cubist, Basilea, Affinergy, Janssen, xBiotech, Contrafect, Regeneron, Basilea, and Destiny and is the co-chair for the Merck V710 Vaccine trial. RAB declares grants or research support from Achaogen, Allecra, Entasis, Merck, Roche, Shionogi, and Wockhardt. All other authors declare no competing interests.

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