Clinical outcomes and bacterial characteristics of carbapenem-resistant *Klebsiella pneumoniae* complex among patients from different global regions (CRACKLE-2): a prospective, multicentre, cohort study

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Summary

Background Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is a global threat. We therefore analysed the bacterial characteristics of CRKP infections and the clinical outcomes of patients with CRKP infections across different countries.

Methods In this prospective, multicentre, cohort study (CRACKLE-2), hospitalised patients with cultures positive for CRKP were recruited from 71 hospitals in Argentina, Australia, Chile, China, Colombia, Lebanon, Singapore, and the USA. The first culture positive for CRKP was included for each unique patient. Clinical data on post-hospitalisation death and readmission were collected from health records, and whole genome sequencing was done on all isolates. The primary outcome was a desirability of outcome ranking at 30 days after the index culture, and, along with bacterial characteristics and 30-day all-cause mortality (a key secondary outcome), was compared between patients from China, South America, and the USA. The desirability of outcome ranking was adjusted for location before admission, Charlson comorbidity index, age at culture, Pitt bacteremia score, and anatomical culture source through inverse probability weighting; mortality was adjusted for the same confounders, plus region where relevant, through multivariable logistic regression. This study is registered at ClinicalTrials.gov, NCT03646227, and is complete.

Findings Between June 13, 2017, and Nov 30, 2018, 991 patients were enrolled, of whom 502 (51%) met the criteria for CRKP infection and 489 (49%) had positive cultures that were considered colonisation. We observed little intra-country genetic variation in CRKP. Infected patients from the USA were more acutely ill than were patients from China or South America (median Pitt bacteremia score 3 [IQR 2–6] *vs* 2 [0–4] *vs* 2 [0–4]) and had more comorbidities (median Charlson comorbidity index 3 [IQR 2–5] *vs* 1 [0–3] *vs* 1 [0–2]). Adjusted desirability of outcome ranking outcomes were similar in infected patients from China (n=246), South America (n=109), and the USA (n=130); the estimates were 53% (95% CI 42–65) for China versus South America, 50% (41–61) for the USA versus China, and 53% (41–66) for the USA versus South America. In patients with CRKP infections, unadjusted 30-day mortality was lower in China (12%, 95% CI 8–16; 29 of 246) than in the USA (23%, 16–30; 30 of 130) and South America (28%, 20–37; 31 of 109). Adjusted 30-day all-cause mortality was higher in South America than in China (adjusted odds ratio [aOR] 4·82, 95% CI 2·22–10·50) and the USA (aOR 3·34, 1·50–7·47), with the mortality difference between the USA and China no longer being significant (aOR 1·44, 0·70–2·96).

Interpretation Global CRKP epidemics have important regional differences in patients' baseline characteristics and clinical outcomes, and in bacterial characteristics. Research findings from one region might not be generalisable to other regions.

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Introduction

Antimicrobial resistance is a global catastrophe that threatens progress in various medical fields. Among multidrug-resistant organisms, carbapenem-resistant Enterobacterales are of specific concern given their scarce treatment options and potential for community spread. WHO recognises carbapenem-resistant Enterobacterales as being among the highest priority pathogens.[1] Within carbapenem-resistant Enterobacterales, carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is the most common bacterial species.[2] In previous studies, the pooled mortality associated with CRKP infections was

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Research in context

Evidence before this study

We searched PubMed and Google Scholar without language restrictions for articles published between database inception and Feb 1, 2021, using the terms "carbapenem resistant *Klebsiella pneumoniae*", "carbapenemase", "multi-locus sequence type" and "mortality". The results of these searches mostly included observational studies on epidemiology, risk factors, and outcomes associated with carbapenem-resistant *Klebsiella pneumoniae* (CRKP). Multi-locus sequence types belonging to clonal group 258 are the most commonly globally distributed type in CRKP. In two meta-analyses, the pooled mortality associated with CRKP infections was estimated to be between 33% (95% CI 28–38) and 42% (37–47). Reported risk factors for mortality included host factors, such as comorbid conditions, and treatment-related variables, such as delayed time to effective antibiotics and the use of polymyxin-based treatments compared with novel β-lactam antibiotics. Four pathogen-directed, randomised trials, which enrolled patients with a range of infections caused by various carbapenem-resistant Gram-negative bacteria, evaluated the activity of novel antibiotics against CRKP. In three of the four trials, a numerical mortality benefit was associated with novel agents compared with the best available therapy.

Added value of this study

In this study, we used a prospective, standardised, contemporary approach to evaluate an all-inclusive cohort of hospitalised patients with CRKP in eight countries around the world. We showed that the genetic epidemiology of CRKP was unique within each specific region. Adjusted desirability of outcome ranking outcomes were similar in infected patients from China (n=246), South America (n=109), and the USA (n=130). In patients with CRKP infections, unadjusted 30-day all-cause mortality was lower in China (12%, 95% CI 8–16; 29 of 246) than in the USA (23%, 16–30; 30 of 130) and South America (28%, 20–37; 31 of 109). After adjustment for culture source, Pitt bacteremia score, Charlson comorbidity index, location before admission, and age at culture, mortality was higher in South America than in China (adjusted odds ratio [aOR] 4·82, 95% CI 2·22–10·50) and the USA (aOR 3·34, 1·50–7·47), with the mortality difference between the USA and China no longer being significant (aOR 1·44, 0·70–2·96).

Implications of all the available evidence

Together with previous evidence, these results support the notion that the characteristics of the CRKP epidemics in various parts of the world are different. Strain types, plasmid replicons, and carbapenemase genes are strongly associated with regions. Clinical outcomes in patients with CRKP infections are probably driven by acute and chronic levels of illness and vary according to region. These findings raise questions about the external generalisability of clinical studies on CRKP done in any specific global region.

estimated to be between 33% (95% CI 28–38) and 42% (37–47).[3,4]

In most regions of the world, *Klebsiella pneumoniae* carbapenemases (KPCs) are the most common cause of carbapenem resistance in CRKP.[2,5,6] In China, carbapenem resistance in *K pneumoniae* increased from 3% in 2005 to 21% in 2017, primarily mediated through KPCs.[6] By contrast, the number of hospitalised patients with carbapenem-resistant Enterobacterales in the USA remained relatively stable from 2012 to 2017.[3]

We recently reported data from the CRACKLE-2 study on the molecular and clinical epidemiology of carbapenem-resistant Enterobacterales in US hospitals between April 30, 2016, and Aug 31, 2017.[2] Enrolment in CRACKLE-2 continued within and beyond the USA. Here, we compare the clinical characteristics and outcomes of this new international cohort of patients with CRKP infection. We also analyse the differences between bacterial isolates from eight countries around the world.

Methods

Study design and participants

CRACKLE-2 was a prospective, multicentre, cohort study that has been previously described.[2] Briefly, patients with carbapenem-resistant Enterobacterales (defined by the Centers for Disease Control and Prevention) isolated in a clinical culture from any anatomic site during hospitalisation were consecutively enrolled; patients with cultures obtained for surveillance purposes only were excluded. Patients were excluded from the study if their isolate did not harbour a carbapenemase gene and was susceptible or intermediately susceptible to meropenem and ertapenem upon testing. Here, 71 hospitals in Argentina, Australia, Chile, China, Colombia, Lebanon, Singapore, and the USA contributed patients. The first culture positive for CRKP was included for each unique patient enrolled during the study period with an available CRKP isolate (appendix p 1). The study was approved by the institutional review boards of all the health systems involved and the requirement to obtain informed consent was waived.

Procedures

Clinical data, including demographics, clinical characteristics, and outcomes, were obtained from health records by on-site investigators after index hospitalisation. Infections were defined by previously described standard criteria, otherwise positive cultures were considered colonisation (appendix p 1).[2] The Pitt bacteremia score[7] and the Charlson comorbidity index[8] were used as measures for acute and chronic severity of illness, respectively. The Charlson comorbidity index ranges from 0 to 37, with higher scores indicating more comorbidities. A patient with a score of 3 could have

three level 1 comorbidities (eg, dementia, chronic pulmonary disease, and congestive heart failure), or one level 1 (eg, dementia) and one level 2 comorbidity (eg, leukaemia), or one level 3 condition (eg, moderate or severe liver disease). For the Pitt bacteremia score, higher scores indicate more severe acute illness. For instance, a patient with a score of 3 could have one level 1 marker of acute illness (eg, disoriented mental status) and one level 2 marker (eg, hypotension). At 90 days after discharge, data on post-hospitalisation death and readmission were collected from health records by on-site investigators.

Determination of initial eligibility of the CRKP isolates was done in local microbiology laboratories (appendix pp 1–2). Carbapenemase genes were identified through whole genome sequencing of all included isolates. Meropenem and ertapenem susceptibility testing was later done in the Antibacterial Resistance Leadership Group (ARLG) Laboratory Center (Rochester, MN, USA) by use of broth microdilution on all isolates that did not carry a carbapenemase gene.

Whole genome sequencing was done on all isolates at UTHealth, Houston, TX, USA (HiSeq 4000, NextSeq 2000, and MiSeq; Illumina; San Diego, CA, USA), the Molecular Resource Facility, Rutgers, New Brunswick, NJ, USA (NextSeq 500; Illumina; San Diego, CA, USA), the University of El Bosque, Bogotá, Colombia (MiSeq, HiSeq 4000, and NextSeq 2000; Illumina; San Diego, CA, USA), and BGI Genomics, BGI-Shenzhen, Shenzhen, China (HiSeq X; Illumina; San Diego, CA, USA), as previously described.[2] Draft genomes were assembled by use of SPAdes, version 3.13.0.[9] *K pneumoniae* complex subspecies, multi-locus sequence types, *wzi* allele, capsule (K locus), O locus, and acquired virulence loci were analysed by Kleborate, version 2.0.1, and Kaptive, version 0.7.3.[10–13] Resistance genes were called by AMRFinderPlus, version 3.9.8, and ARIBA, version 2.14.6.[14,15] Core genome alignment was generated by Snippy, version 4.6.0 and a maximum likelihood phylogenetic tree was constructed in RAxML, version 8.2.4.[16] The genomes sequenced in this study were deposited in GenBank (accession number PRJNA658369; appendix pp 1–2).

Outcomes

The primary outcome was a desirability of outcome ranking, as previously described,[2] at 30 days after the index culture (appendix pp 2–4). Briefly, the desirability of outcome ranking analysis assessed three deleterious events (absence of clinical response, prolonged hospitalisation [hospitalisation for ≥30 days after the first positive culture or readmission within 30 days]), and adverse events [new renal failure, *Clostridioides difficile* infection, or both]), in addition to survival at 30 days after the index culture (appendix pp 2–4).[2] The best outcome was defined as being alive without deleterious events. The worst outcome was death. The three categories in between these two extremes were: alive with one, two, and three deleterious events, respectively. As only two of 502 patients with CRKP infections were categorised into the alive with three deleterious events category, this category was grouped post-hoc with the alive with two deleterious events category for our analysis, totalling four different categories of outcomes. We also considered 30-day all-cause mortality and 90-day all-cause mortality as secondary outcomes, separate from the desirability of outcome ranking.

Statistical analysis

From our international cohort, we defined three regions: South America (Argentina, Chile, and Colombia), the USA, and China. Patients from Australia, Lebanon, and Singapore were described but not included in our comparative outcome analyses because of the countries' small sample sizes. We compared regions using pairwise desirability of outcome ranking analyses and multivariable logistic regression. Outcome analyses were limited to patients with infections.[17] The following variables were used in inverse probability weighting: location before admission (home *vs* other), Charlson comorbidity index (>3 *vs* ≤3), age at culture, Pitt bacteremia score, and anatomical culture source (blood *vs* respiratory *vs* urine *vs* grouped other sources).[18,19] The Pitt bacteremia score has previously been validated for non-bacteraemic infections.[7] Post-hoc, bacterial risk factors (multi-locus sequence types, yersiniabactin, colibactin, OmpK35, OmpK36, K locus, and O locus) for all-cause mortality were evaluated by use of multivariable logistic regression models and adjusted odds ratios (aORs) were calculated. The same clinically relevant confounders used in the inverse probability weighting model to calculate weights, plus region, were included in all adjusted logistic regression models. To visualise all-cause mortality within 30 days of the initial culture, Kaplan–Meier curves with log-rank tests of unadjusted survival probability without censoring were created. Censoring was absent as, unless known to have died, patients were assumed to be alive at 30 days from the initial culture (appendix pp 2–4). A p value of 0·05 or less was considered statistically significant. The analysis used SAS, version 9.4. This study is registered with ClinicalTrials.gov, NCT03646227.

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.

Results

Between June 13, 2017, and Nov 30, 2018, 991 unique patients from 71 hospitals in eight countries were enrolled (table 1), of whom 502 (51%, 95% CI 48–54) met the criteria for CRKP infection and the remaining 489 (49%, 46–53) had positive cultures that were considered colonisation (appendix pp 5–6). A higher proportion of patients in South America (64%, 95% CI 57–71; 109 of 170)

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See Online for appendix

For more on **snippy** see https://github.com/tseemann/snippy

than in China (51%, 46–55; 246 of 485) or the USA (46%, 40–52; 130 of 284) were infected (p=0·0007). Patients in the USA had more comorbidities than those in China and South America (table 1). Compared with China and South America, notable specific comorbidities that were more common in the USA included diabetes (absolute difference *vs* China 24%, 95% CI 18–31; absolute difference *vs* South America 16%, 7–25), chronic kidney disease (21%, 16–27; 15%, 8–22), and dementia (9%, 5–13; 8%, 4–13; appendix p 12). Infected patients from the USA were more acutely ill than were patients from China or South America (median Pitt bacteremia score 3 [IQR 2–6] *vs* 2 [0–4] *vs* 2 [0–4]) and had more comorbid conditions (median Charlson comorbidity index 3 [IQR 2–5] *vs* 1 [0–3] *vs* 1 [0–2]). In China, CRKP was most frequently isolated from respiratory cultures (62%, 95% CI 58–67; 302 of 485), whereas urine was the most common single source in South America (44%, 36–51; 74 of 170) and the USA (40%, 35–46; 115 of 284). Patients were hospitalised for a shorter duration before their first positive CRKP culture in the USA than in China or South America (table 1). In 334 (34%, 95% CI 31–37) of 991 patients, another pathogen was isolated from the same source within 7 days of the index culture. Antibiotic treatment for patients with CRKP infections is summarised in the appendix (p 7).

Based on whole genome sequence data, 97% (95% CI 96–98; 963 of 991) of bacterial isolates were *K pneumoniae* sensu stricto. Other *K pneumoniae* complex subspecies were *K variicola* subsp *variicola* (n=12), *K quasipneumoniae*

	China (n=485 [49%])	South America (n=170 [17%])	USA (n=284 [29%])	Australia, Lebanon, and Singapore (n=52 [5%])	All infected patients (n=502 [51%])	Total (n=991)	p value*
Age, years	60 (46–69)	63 (42–73)	63 (50–73)	67 (55–76)	62 (47–71)	62 (47–72)	0·029
Sex							
Female	162 (33%)	68 (40%)	140 (49%)	23 (44%)	205 (41%)	393 (40%)	<0·0001
Male	323 (67%)	102 (60%)	144 (51%)	29 (56%)	297 (59%)	598 (60%)	..
Charlson comorbidity index†	1 (0–2)	1 (0–3)	3 (1–5)	2 (1–4)	2 (0–4)	1 (0–3)	<0·0001
Pitt bacteremia score‡	2 (0–4)	2 (0–4)	2 (1–5)	1 (0–3)	2 (0–4)	2 (0–4)	0·0002
Intensive care unit location on the day of first positive culture	263 (54%)	44 (26%)	101 (36%)	25 (48%)	202 (40%)	433 (44%)	<0·0001
Time to positive culture, days§	8 (2–18)	8 (1–22)	2 (0–17)	15 (3–34)	8 (1–22)	7 (1–19)	<0·0001
Admitted from¶							
Home	171 (35%)	125 (74%)	127 (45%)	43 (83%)	250 (50%)	466 (47%)	<0·0001
Hospital transfer	310 (64%)	43 (25%)	50 (18%)	4 (8%)	194 (39%)	407 (41%)	..
Long-term chronic care	3 (1%)	0	80 (28%)	2 (4%)	44 (9%)	85 (9%)	..
Long-term acute care	0	0	26 (9%)	2 (4%)	11 (2%)	28 (3%)	..
Transferred from foreign country	0	0	1 (<1%)	1 (2%)	2 (<1%)	2 (<1%)	..
Hospice	1 (<1%)	1 (1%)	0	0	0	2 (<1%)	..
Culture							
Blood: infection	41 (8%)	34 (20%)	49 (17%)	6 (12%)	130 (26%)	130 (13%)	<0·0001
Urine: infection	30 (6%)	38 (22%)	41 (14%)	4 (8%)	113 (23%)	113 (11%)	..
Urine: colonisation	32 (7%)	36 (21%)	74 (26%)	10 (19%)	..	152 (15%)	..
Respiratory: infection	118 (24%)	5 (3%)	14 (5%)	1 (2%)	138 (27%)	138 (14%)	..
Respiratory: colonisation	184 (38%)	11 (6%)	50 (18%)	2 (4%)	..	247 (25%)	..
Wound: infection‖	11 (2%)	13 (8%)	13 (5%)	0	37 (7%)	37 (4%)	..
Wound: colonisation	5 (1%)	10 (6%)	23 (8%)	3 (6%)	..	41 (4%)	..
Intra-abdominal: infection‖	46 (9%)	18 (11%)	13 (5%)	5 (10%)	82 (16%)	82 (8%)	..
Other: infection‖	0	1 (1%)	0	1 (2%)	2 (<1%)	2 (<1%)	..
Other: colonisation	18 (4%)	4 (2%)	7 (2%)	20 (38%)	..	49 (5%)	..

Data are n (%) or median (IQR). *p value comparing China, South America, and the USA, and distributions, where applicable. †A chronic comorbidity score ranging from 0 to 37, with higher scores indicating the presence of more comorbidities. A patient with a score of 3 could have three level 1 comorbid conditions, one level 1 and one level 2 comorbid condition, or one level 3 comorbid condition.[8] ‡An acute severity of illness score, with higher scores indicating more severe illness. A patient with a score of 3 would have one level 1 marker and one level 2 marker of acute illness.[7] §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. ¶For analysis purposes in this table, these categories were grouped as home plus transferred from foreign country, long-term acute care plus hospital transfer, and long-term chronic care plus hospice. One person from South America had missing data for their location before admission. ‖This table shows wound and intra-abdominal infection seperately. For the outcome analyses, these categories were grouped into the other sources category.

Table 1: **Patient characteristics**

subsp *quasipneumoniae* (n=8), and *K quasipneumoniae* subsp *similipneumoniae* (n=8). Carbapenemase genes were present in 888 (90%) of 991 isolates (table 2; appendix pp 8–9), of which bla_{KPC} was the most common (807 [81%] of 991). In China, bla_{KPC-2} was the predominant carbapenemase gene (table 2). In South America and the USA, most CRKP carried bla_{KPC-2} or bla_{KPC-3} (table 2). $bla_{OXA-48-like}$ or bla_{OXA-48} genes were the most common family of carbapenemases in Lebanon (15 [75%] of 20) and Singapore (15 [94%] of 16). In Lebanon, six isolates carried both bla_{OXA-48} and bla_{NDM-5}. Extended-spectrum β-lactamase genes were more common in isolates from China than in isolates from South America or the USA (table 2). bla_{CTX-M} genes were found in 60% of isolates and were more common in China than in South America or the USA (table 2). $bla_{CTX-M-65}$ accounted for most bla_{CTX-M} genes in isolates from China (table 2); $bla_{CTX-M-65}$ was only found in one isolate outside of China. In South America and the USA, $bla_{CTX-M-15}$ was the predominant bla_{CTX-M} gene. Extended-spectrum β-lactamase bla_{SHV} genes were also more common in China than in South America and the USA (table 2).

We observed little intra-country genetic variation (figure 1). Multi-locus sequence types were strongly associated with region. Strain type ST11 was predominantly found in in China and South America (table 2). The ST11 strains in China mainly harboured KL64 and KL47, and the ST11 strains in South America mainly carried KL105 and KL39 (table 2). South American ST11 isolates were located at different phylogenetic clades to the Chinese ST11-KL64 and KL47 strains (figure 1). The mean difference in core single nucleotide polymorphisms (SNPs) between ST11-KL64 strains from China and ST11-KL47 strains from China was 22 (range 1–53; SD 8). The mean difference between grouped ST11 strains carrying either KL64 or KL47 from China and South American ST11-KL39 strains was 67 SNPs (range 54–93; SD 8), and the difference between grouped Chinese ST11-KL64 and ST11-KL47 strains and ST11-KL105 strains from South America was 52 SNPs (range 31–81; SD 9). In the USA, 57% of CRKP isolates were ST258 strain types, mainly harbouring KL107 and KL106 (table 2). ST11 isolates from China were associated with four specific plasmid replicons (figure 1).

Specific putative virulence genes more common in Chinese isolates than in South American or US isolates included *rmpA2*, *rmpADC*, yersiniabactin, and aerobactin (table 2). By contrast, colibactin was less common in isolates from China than in isolates from South America or the USA (table 2).

The distribution of outcomes from the unadjusted desirability of outcome ranking analysis is shown in figure 2. Inverse probability weighting-adjusted outcomes were similar in infected patients from China (n=246), South America (n=109), and the USA (n=130); the estimates were 53% (95% CI 42–65) for China versus South America, 50% (41–61) for the USA versus China, and 53% (41–66) for the USA versus South America. The proportion of patients with infections who were alive at 30 days after the first positive culture without deleterious events was lowest in China (31%, 95% CI 26–37; 77 of 246), compared with South America (45%, 36–54; 49 of 109) and the USA (41%, 32–49; 53 of 130). Among patients with infections who were alive at 30 days, an absence of clinical response was observed in 135 (62%, 95% CI 55–68) of 217 patients from China, 22 (28%, 18–38) of 78 patients from South America, and 24 (24%, 16–32) of 100 patients from the USA. For infected patients, the length of stay was shorter in the USA (median 19 days, IQR 8–46) than in China (28 days, 17–47) and South America (25 days, 14–49; p=0·0055). Readmissions within 30 day for patients with infections who were discharged alive were more common in the USA (29%, 95% CI 20–38; 29 of 100) than in China (4%, 1–6; eight of 213) and South America (14%, 6–21; ten of 74). Readmissions within 90 days for patients with infections who were discharged alive were more common in the USA (50%, 40–60; 50 of 100) than in China (7%, 3–10; 14 of 213) and South America (23%, 13–33; 17 of 74; p<0·0001).

In patients with CRKP infections, unadjusted all-cause 30-day mortality was 19% (95% CI 15–22; 93 of 502) and unadjusted all-cause 90-day mortality was 22% (19–26; 111 of 501; figure 3A). Unadjusted all-cause 30-day and 90-day mortality were lower in China (12%, 8–16; 29 of 246; and 13%, 9–17; 32 of 246) compared with South America (28%, 20–37; 31 of 109; and 35%, 26–44; 38 of 109) or the USA (23%, 16–30; 30 of 130; and 28%, 20–36; 36 of 129; p=0·0003 and p<0·0001, respectively; figure 3A). After adjusting for age at culture, location before admission, Charlson comorbidity index, Pitt bacteremia score, and culture source, all-cause 30-day mortality was higher in South America than in China (aOR 4·82, 95% CI 2·22–10·50) and the USA (aOR 3·34, 1·50–7·47), with the mortality difference between the USA and China no longer being significant (aOR 1·44, 0·70–2·96).

In patients with CRKP infections (appendix p 10), a Charlson comorbidity index of more than 3 (aOR 2·93, 95% CI 1·53–5·61) and the Pitt bacteremia score (aOR per point increase 1·45, 1·31–1·60) were independently associated with increased 30-day mortality, whereas urinary infection was associated with lower 30-day mortality (*vs* bacteraemia aOR 0·13, 0·05–0·34; *vs* respiratory infection aOR 0·26, 0·09–0·78). In all patients with CRKP bacteraemia, unadjusted 30-day mortality was 34% (95% CI 26–42; 44 of 130) overall, 24% (11–38; ten of 41) in China, 56% (39–73; 19 of 34) in South America, and 31% (18–44; 15 of 49) in the USA.

No independent associations were found between 30-day mortality and multi-locus sequence type, K locus, yersinibactin, colibactin, or the *OmpK35* and *OmpK36* porin genes in post-hoc analyses (data not shown). There was insufficient diversity in the distribution of aerobactin,

	China (n=485)	South America (n=170)	USA (n=284)	Australia, Lebanon, and Singapore (n=52)	All infected patients (n=502)	Total (n=991)	p value*
Carbapenemases†							
Carbapenemase(s) present	473 (98%)	127 (75%)	249 (88%)	39 (75%)	443 (88%)	888 (90%)	<0·0001
bla$_{KPC-2}$	454 (94%)	66 (39%)	124 (44%)	2 (4%)	324 (65%)	646 (65%)	<0·0001
bla$_{KPC-3}$	0	51 (30%)	105 (37%)	0	78 (16%)	156 (16%)	<0·0001
Other *bla*$_{KPC}$‡	2 (<1%)	0	3 (1%)	0	3 (1%)	5 (1%)	0·28
bla$_{NDM-1}$	8 (2%)	14 (8%)	6 (2%)	3 (6%)	16 (3%)	31 (3%)	<0·0001
Other *bla*$_{NDM}$§	4 (1%)	0	0	9 (17%)	7 (1%)	13 (1%)	0·15
bla$_{OXA-48}$	0	0	7 (2%)	25 (48%)	10 (2%)	32 (3%)	0·0003
Other *bla*$_{OXA-48-like}$¶	3 (1%)	1 (1%)	7 (2%)	5 (10%)	8 (2%)	16 (2%)	0·053
Other‖	4 (1%)	3 (2%)	0	1 (2%)	4 (1%)	8 (1%)	0·10
No carbapenemase detected	12 (2%)	43 (25%)	35 (12%)	13 (25%)	59 (12%)	103 (10%)	..
Extended-spectrum β-lactamase							
bla$_{CTX-M}$	395 (81%)	95 (56%)	77 (27%)	31 (60%)	302 (60%)	598 (60%)	<0·0001
bla$_{CTX-M-15}$	81 (17%)	77 (45%)	75 (26%)	26 (50%)	121 (24%)	259 (26%)	<0·0001
bla$_{CTX-M-65}$	300 (62%)	0	1 (<1%)	0	151 (30%)	301 (30%)	<0·0001
bla$_{SHV}$**	218 (45%)	18 (11%)	93 (33%)	4 (8%)	155 (31%)	333 (34%)	<0·0001
bla$_{TEM}$**	0	3 (2%)	0	0	1 (<1%)	3 (<1%)	0·0011
bla$_{AmpC}$	51 (11%)	2 (1%)	5 (2%)	6 (12%)	31 (6%)	64 (6%)	<0·0001
Multi-locus sequence type							
ST11	379 (78%)	76 (45%)	16 (6%)	2 (4%)	250 (50%)	473 (48%)	<0·0001
ST258	0	13 (8%)	163 (57%)	1 (2%)	78 (16%)	177 (18%)	..
ST15	78 (16%)	1 (1%)	15 (5%)	2 (4%)	44 (9%)	96 (10%)	..
ST147	3 (1%)	2 (1%)	5 (2%)	15 (29%)	14 (3%)	25 (3%)	..
Other	25 (5%)	78 (46%)	85 (30%)	32 (62%)	116 (23%)	220 (22%)	..
K locus							
KL64	298 (61%)	3 (2%)	6 (2%)	1 (2%)	165 (33%)	308 (31%)	<0·0001
KL107	0	12 (7%)	96 (34%)	0	46 (9%)	108 (11%)	..
KL19	69 (14%)	0	2 (1%)	0	31 (6%)	71 (7%)	..
KL106	0	1 (1%)	57 (20%)	2 (4%)	29 (6%)	60 (6%)	..
KL47	58 (12%)	0	1 (<1%)	0	29 (6%)	59 (6%)	..
KL105	2 (<1%)	45 (26%)	3 (1%)	1 (2%)	34 (7%)	51 (5%)	..
KL39	0	29 (17%)	0	0	18 (4%)	29 (3%)	..
Other	58 (12%)	80 (47%)	119 (42%)	48 (92%)	150 (30%)	305 (31%)	..
O locus							
O2v1	307 (63%)	5 (3%)	14 (5%)	7 (13%)	175 (35%)	333 (34%)	<0·0001
O2v2	6 (1%)	66 (39%)	171 (60%)	6 (12%)	119 (24%)	249 (25%)	..
Other	172 (35%)	99 (58%)	99 (35%)	39 (75%)	208 (41%)	409 (41%)	..
Porin genes							
OmpK35 mutation	441 (91%)	72 (42%)	200 (70%)	13 (25%)	358 (71%)	726 (73%)	<0·0001
OmpK36 mutation	433 (89%)	80 (47%)	89 (31%)	19 (37%)	316 (63%)	621 (63%)	<0·0001
Putative virulence genes							
Aerobactin	299 (62%)	0	4 (1%)	8 (15%)	156 (31%)	311 (31%)	<0·0001
Colibactin	3 (1%)	13 (8%)	61 (21%)	3 (6%)	33 (7%)	80 (8%)	<0·0001
rmpA2	284 (59%)	0	1 (<1%)	6 (12%)	148 (29%)	291 (29%)	<0·0001
rmpADC	185 (38%)	0	1 (<1%)	2 (4%)	97 (19%)	188 (19%)	<0·0001
Yersiniabactin	460 (95%)	104 (61%)	119 (42%)	23 (44%)	357 (71%)	706 (71%)	<0·0001

Data are n (%), unless otherwise specified. *Comparisons between China, South America, and the USA. †Totals exceed 100% as 17 isolates carried more than one carbapenemase gene. ‡Other *bla*$_{KPC}$ were *bla*$_{KPC-12}$ (n=2), *bla*$_{KPC-28}$ (n=1), *bla*$_{KPC-31}$ (n=1), and *bla*$_{KPC-34}$ (n=1). §Other *bla*$_{NDM}$ were *bla*$_{NDM-4}$ (n=2), *bla*$_{NDM-5}$ (n=10), and *bla*$_{NDM-7}$ (n=1). ¶Other *bla*$_{oxa-48-like}$ were *bla*$_{oxa-163}$ (n=1), *bla*$_{oxa-181}$ (n=5), and *bla*$_{oxa-232}$ (n=10). ‖Other carbapenemases were *bla*$_{VIM-2}$ (n=1), *bla*$_{VIM-24}$ (n=2), *bla*$_{IMP-1}$ (n=1), and *bla*$_{IMP-4}$ (n=4). **Limited to *bla*$_{SHV}$ and *bla*$_{TEM}$ genes that are considered extended-spectrum β-lactamase genes: *bla*$_{SHV-12}$ (n=279), *bla*$_{SHV-2A}$ (n=32), *bla*$_{SHV-110}$ (n=8), *bla*$_{SHV-27}$ (n=3), *bla*$_{SHV-2}$ (n=3), *bla*$_{SHV-30}$ (n=2), *bla*$_{SHV-32}$ (n=2), *bla*$_{SHV-5}$ (n=2), *bla*$_{SHV-100}$ (n=1), *bla*$_{SHV-42}$ (n=1), and *bla*$_{TEM-26}$ (n=3).

Table 2: **Bacterial characteristics**

For an **interactive Figure 1** see
http://arlg.med.unc.edu/crackle/

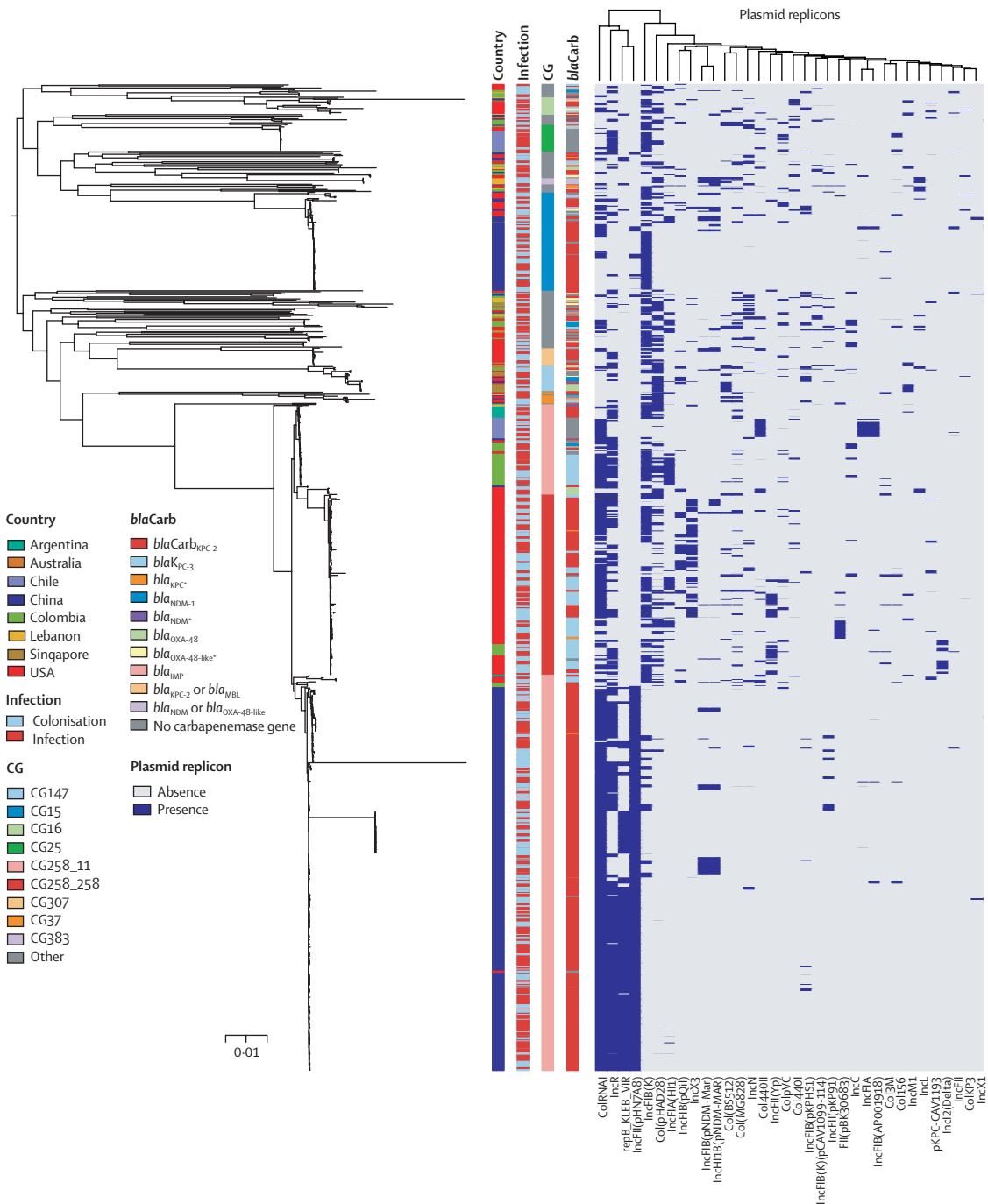

Figure 1: **Bacterial population structure**
Maximum likelihood phylogenetic tree limited to *Klebsiella pneumoniae* sensu stricto is shown with corresponding metadata indicating country, CG, carbapenemase genes, and plasmid replicons present in each strain. CG=clonal group.

rmpA2, and *rmpADC* to allow for inclusion in adjusted models. The association between the O locus and 30-day mortality was evaluated post-hoc in US and South American patients, excluding the five patients from China whose isolates had the O2v2 locus and who all survived to 30 days. In patients from South America and the USA, the O2v2 O locus was associated with lower 30-day mortality (figure 3B) when compared with other O loci (aOR 0·34, 95% CI 0·15–0·78). Our results for our post-hoc analysis of the association between

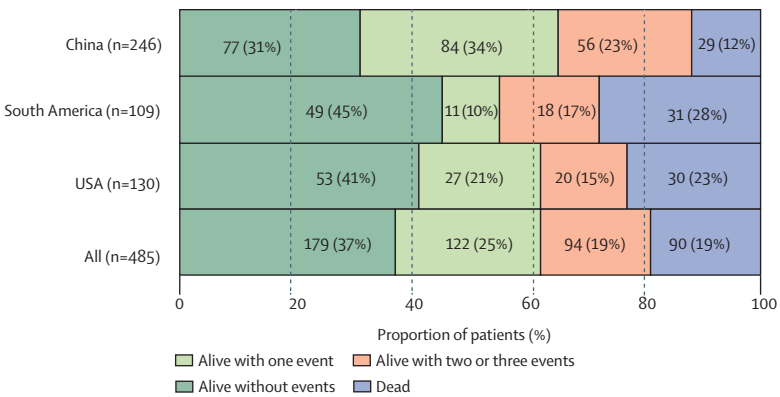

Figure 2: **Unadjusted distribution of desirability of outcome ranking outcomes**
Outcomes at 30 days after the index culture are shown. The best outcome was defined as being alive without deleterious events. The worst outcome was death. The three deleterious events were: the absence of a clinical response, prolonged hospitalisation, and adverse events (appendix pp 3–4).

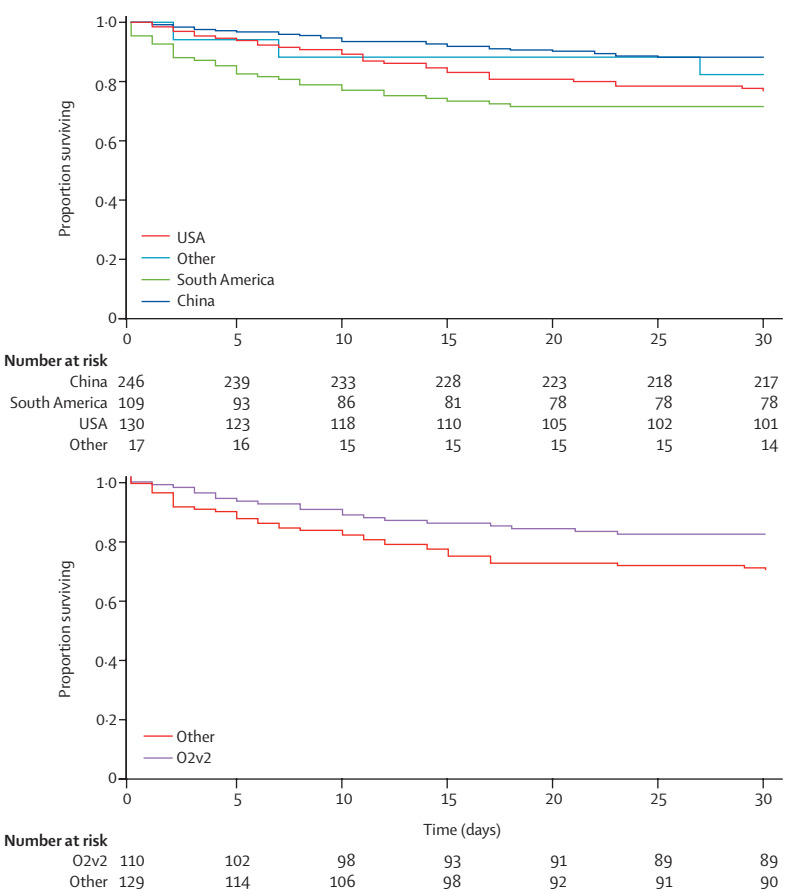

Figure 3: **Kaplan–Meier curves for all-cause 30-day mortality**
(A) Survival for 502 patients with carbapenem-resistant *Klebsiella pneumoniae* infection by region. (B) Survival for 239 patients with carbapenem-resistant *K pneumoniae* infection from South America and the USA by O locus.

multi-locus sequence types and 30-day mortality in South American and US participants are reported in the appendix (p 11).

Discussion

In this large, multinational, prospective cohort study, unadjusted all-cause 30-day and 90-day mortality in patients with CRKP infections was lower in China than in South America or the USA. A high prevalence of chronic comorbidities and a high acuity of illness (as measured by the Pitt bacteremia score) in US patients probably accounted for the observed mortality difference between China and the USA. After adjusting for chronic and acute illness, the odds of dying within 30 days for patients with CRKP infections were about three to five times higher in South America than in China and the USA, and the mortality difference between the USA and China was no longer significant. Increased mortality in South America compared with the USA could be related to the limited availability of novel anti-carbapenem-resistant Enterobacterales antibiotics, such as ceftazidime–avibactam, during the study period.[20,21] In addition, factors that we did not evaluate in this study, such as health-care system characteristics and resulting differences in health care-seeking behaviours, might play a role in the observed increased mortality in South America. For example, inequality in access to care has been shown to be an important factor in mortality associated with COVID-19 in Chile.[22]

Another possible explanation for the variance in mortality is bacterial virulence. The genetically homogeneous CRKP from China might represent bacteria that are less likely to cause severe disease or detrimental host responses. However, most putative virulence genes we evaluated were more common in isolates from China than in those from South America and the USA. Among the other bacterial factors that we investigated, only the O2v2 O locus, which was uncommon in China, was associated with survival for patients in South America and the USA. Genes encoded in the O locus are involved in the composition of bacterial lipopolysaccharide. Lipopolysaccharide interacts with innate immune receptors, including Toll-like receptor 4, to drive the host response to Gram-negative bacterial infection.[23] Therefore, the observed association between the O locus and mortality has biological plausibility. This finding should be considered hypothesis generating and requires confirmation in independent cohorts and animal studies.

30-day all-cause mortality in patients with CRKP infections was 19%. Previous estimates of mortality after CRKP infections are mostly based on retrospective studies. The prospective, European cohort study EURECA has finished enrolment, with no data yet available.[24] A meta-analysis of 62 studies published between 1999 and 2015 estimated pooled mortality after CRKP infections to be 42% (95% CI 37–47).[4] The pooled mortality was 33% (28–38) in KPC-producing CRKP infections in a meta-analysis of 21 studies done in the USA, Greece, Italy, Brazil, China, Spain, and Israel, and published during 2007–18.[3] The lower mortality in our

study could reflect the type of infections included and advances in the treatment of CRKP infections with time.

Overall, unadjusted 30-day mortality in patients with CRKP bacteraemia in our cohort was 34%, lower than that reported previously. In the INCREMENT study,[25] 30-day mortality was 43% in a retrospective cohort of patients with carbapenemase-producing Enterobacterales bacteraemia predominantly from hospitals in Europe in 2004–13. Similarly, 30-day mortality was 45% in patients with KPC-producing CRKP bacteraemia in two Italian intensive care units during 2015–18.[26] In South Africa in 2015–18, in-hospital mortality associated with carbapenem-resistant Enterobacterales bacteraemia was 38%.[27]

In our desirability of outcome ranking analyses, no differences in the overall likelihood of a better outcome between infected patients in China, South America, and the USA were seen. Desirability of outcome ranking estimates are equally impacted by shifts between any of the ordinal outcomes. Although mortality was lower in China, the proportion of patients without a clinical response was higher. These findings illustrate that evaluating multiple outcomes as part of the desirability of outcome ranking provides more granular data as compared with only evaluating mortality outcomes. The underlying reasons for the observed discrepancy between clinical response rates and overall mortality remain to be determined.

Although CRKP infections are a global threat, characteristics of the CRKP epidemics vary by region. For instance, in China, we found that CRKP was more frequently isolated from respiratory cultures than in blood or urine or other cultures. This result probably reflects the microbiological testing pattern in China. In the China Antimicrobial Surveillance Network, 97 203 (39·7%) of 244 843 bacterial isolates were cultured from the respiratory tract, as compared with 46 030 (18·8%) from urine and 36 236 (14·8%) from blood.[28] Whole genome sequencing data revealed that CRKP epidemics are also genetically different in different parts of the world. In China, a genetically homogeneous set of isolates was responsible for most CRKP infections. These isolates were characterised by the ST11 strain type, the KL64 capsule type, and the harbouring of $bla_{\text{KPC-2}}$, $bla_{\text{CTX-M-65}}$, and four common plasmid replicons uncommon in other regions. The emergence of a ST11 plus KL64 plus $bla_{\text{KPC-2}}$ strain around 2016 was reported in a Chinese single centre retrospective study.[29] Of note, that strain was not reported to carry $bla_{\text{CTX-M-65}}$.[29] These markers could be used to monitor the clonal spread of other CRKP strains into China or, conversely, of ST11 strains out of China. The predilection of specific CRKP strain types for certain regions was also observed in Europe in the EuSCAPE study.[5] In this study, CRKP spread in Europe was identified to be primarily nosocomial in 2013–14.[5] These regional differences might have implications on whether studies evaluating diagnostics, treatments, and prognosis can be extrapolated from one region of the world to another.

Our study has several important limitations. First, few patients were contributed from Lebanon, Singapore, and Australia, which prohibited the inclusion of these countries in our comparative analyses. Similarly, although this study had a broad geographical reach, it did not represent some important areas of the world. Data from Europe will be forthcoming through the EURECA study.[24] Several other regions (eg, Europe and Africa) with known high incidences of antimicrobial resistance were similarly not included in our study. Our results should not be interpreted as being representative of CRKP epidemiology for all types of hospitalised patients in the participating countries. Nonetheless, a strength of our study is that we used a standardised, contemporary approach to include hospitalised patients with CRKP within a broad geographical area, combined with detailed clinical and bacterial genetic analyses. Second, we could only use data collected as part of routine clinical practice, which might vary between regions, because the requirement to obtain informed consent was waived. Nonetheless, this method allowed for consecutive enrolment without selection bias. Finally, we compared a large number of variables across three regions, which could raise issues with multiple comparisons. However, we only evaluated two outcome variables: the desirability of outcome ranking, which was adjusted through inverse probability weighting, and all-cause mortality, for which we used multivariable logistic regression.

In summary, this evaluation of the CRKP epidemics in different parts of the world revealed more differences than similarities. Strain types, carbapenemase genes, and plasmid replicons were strongly associated with region. Hospitalised patients with CRKP in China had a lower unadjusted mortality rate, prevalence of comorbidities, and illness severity, than did other regions. CRKP infections in China were also genetically homogeneous. After adjusting for contributing factors, CRKP-associated mortality was highest in South America. These findings raise questions about the external generalisability of clinical studies on CRKP done in any specific global region.

Contributors

DvD led the protocol from which the study data are derived. DvD and MW were responsible for overall analysis development, supervision of the project, and review of the final manuscript. VGF and HFC acquired funding for the study. DvD, ME, LK, CH, and KB accessed the data in the study and take responsibility for the verification and integrity of the data and the accuracy of the data analysis. DvD, MW, CAA, and DLP served as regional leads. LK and ME performed the validation, developed the methods, and generated the tables and figures. LC created the genomic visualisations. BMH, CAA, MW, JR oversaw sequencing activities and LC, BMH, and CH did the bioinformatic analysis on the sequence results. All authors were involved with the scientific review and editing of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Declaration of interests

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Data sharing

Individual deidentified participant data (and supporting documentation, data dictionaries, and protocol) that underlie the results in this Article can be made available to investigators following submission of a plan for data use, approval by the ARLG or designated entity, and execution of required institutional agreements. Provision might be contingent upon the availability of funding for data preparation and deidentification. More information can be found at https://arlg.org/how-to-apply/request-data/. Sequences are publicly available through the National Center for Biotechnology Information (accession number PRJNA658369; https://www.ncbi.nlm.nih.gov/bioproject/658369).

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