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Global distribution of *Klebsiella pneumoniae* producing extended-spectrum β-lactamases in neonates

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Dear Editor,

Klebsiella pneumoniae, a member of the *Enterobacterales*, is a common resident of the gastrointestinal tract of humans and animals and is also ubiquitous in the environment. *Klebsiella pneumoniae* is also a common pathogen recovered from clinical samples and is able to cause a wide range of infections including life-threatening bacteremia, meningitis, and pneumonia [1]. β-Lactams, especially third-generation cephalosporins and carbapenems, are mainstay antimicrobial options for infections caused by the *Enterobacterales* such as *K. pneumoniae*. Worryingly, *K. pneumoniae* has emerged as a major carrier of antimicrobial resistance determinants including those encoding extended-spectrum β-lactamases (ESBL) and carbapenem-hydrolyzing β-lactamases (carbapenemases). ESBL—or carbapenemase-producing *K. pneumoniae*—is difficult to treat, is associated with high mortalities and morbidities [2], and is therefore recognized by the World Health Organization as one of the global priority pathogens in critical need of next-generation antimicrobials and new control strategies [3]. The situation is particularly concerning for the neonatal population [4]. Neonatal sepsis caused by ESBL-producing *K. pneumoniae* is not uncommon and typically leads to increased mortality, particularly in low- and middle-income countries (LMICs) [5]. Limited antimicrobial options against ESBL-producing *K. pneumoniae* highlight the importance of surveillance to guide countermeasures.

Notably, *K. pneumoniae* is a complex comprising six closely-related species, *K. pneumoniae* (sensu stricto), *Klebsiella quasipneumoniae*, *Klebsiella variicola*, *Klebsiella quasivariicola*, *Klebsiella africana*, and an unnamed species (genomospecies 5) [6]. Previously, we have demonstrated the clonal diversity of neonatal carbapenem-resistant strains of *K. pneumoniae* species complex (KpSC) [7]. However, many ESBL-producing KpSC strains were not resistant to carbapenems. Particularly, the global distribution of ESBL-producing KpSC in neonates remains unclear. Therefore, we mined publicly available genomes to unveil the clonal diversity of ESBL-producing KpSC, which may provide information for precise prevention and control of multi-drug resistant organisms in the newborn population.

Here, we examined all publicly accessible KpSC genomes from neonates (accessed by 30 June 2022) for determining the clonal diversity of neonatal strains carrying $bla_{\text{CTX-M}}$, the most common ESBL gene in the *Enterobacterales* [8]. The search, retrieval, assembly, and quality control for these genomes and the subsequent precise species identification, strain typing, and antimicrobial resistance gene detection were performed as described previously [7]. Each genome was subjected to identifying the precise species using FastANI v1.33 (https://github.com/ParBLiSS/FastANI) with type strains of each *Klebsiella* species, determining sequence types (ST) and capsule types using Kleborate v2.2.0 (https://bactopia.github.io/latest/bactopia-tools/kleborate/), and detecting antimicrobial resistance genes using AMRFinderPlus v3.10.23 (https://github.com/ncbi/amr).

A total of 1992 neonatal KpSC genomes were analyzed (Supplementary Dataset S1). The vast majority ($n = 1782$, 89.46%) of these KpSC genomes belonged to *K. pneumoniae* (*sensu stricto*), followed by genomospecies 5 ($n = 169$, 8.48%), *K. variicola* ($n = 30$, 1.51%), *K. quasipneumoniae* ($n = 9$, 0.45%), and *K. quasivariicola* ($n = 2$, 0.10%), while *K. africana* is not present (supplementary Table S1, see online supplementary material). Of the 1992 KpSC genomes, 82.18% ($n = 1637$) had $bla_{\text{CTX-M}}$, a type of ESBL gene (supplementary Table S1), indicating a high prevalence. Of note, most (1227, 75.0%) of the 1637 CTX-M-encoding strains had no known carbapenemase genes (Dataset S1). $bla_{\text{CTX-M}}$ genes encoding 20 CTX-M variants (CTX-M-1, -3, -8, -9, -14, -15, -25, -27, -36, -55, -63, -65, and 8 new unnamed ones) were found, among which CTX-M-15 was seen in the vast majority ($n = 1521$, 92.9%) followed by CTX-M-14 ($n = 64$, 3.9%) (supplementary Table S2, see online supplementary material). These CTX-M-encoding strains could be assigned to 184 STs including 17 new types, suggesting a remarkable clonal diversity. ST307 ($n = 230$) was the most common CTX-M-encoding type in neonates seen in Africa (Kenya, Nigeria, Rwanda, and Zambia) and Asia (Bangladesh, Cambodia, and China) (Table 1). ST15 ($n = 120$) was the second most common ESBL-producing type in neonates, seen in Cambodia, China, Vietnam, the Indian subcontinent, and Nigeria (Table 1). Other common types (comprising ≥50 genomes) are ST17 ($n = 95$), ST14 ($n = 77$), ST35 ($n = 58$), and ST39 ($n = 50$), all of which were found in multiple countries (Table 1).

Although publicly accessible genomes could be largely biased, they are still precious sources able to provide crucial information for understanding the clonal background of multi-drug resistant organisms to complement epidemiological studies and help in the precise design and implementation of countermeasures. First, it appears that most KpSC neonatal strains have genes encoding ESBLs, which confer resistance to

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Table 1. Sequence types of CTX-M-encoding *K. pneumoniae* complex comprising ≥50 genomes in publicly accessible genomes[a].

ST[b]	No. of genomes	CTX-M variant[c]	Country[d]	KL[e]
307	230	3, 15, N3	Bangladesh, Cambodia, China, Kenya, Nigeria, Rwanda, Zambia, NA	102, NT
15	120	3, 14, 14 + 15, 15, 27	Bangladesh, Cambodia, China, India, Nepal, Nigeria, Pakistan, Vietnam, NA	10, 102, 112, 24, 28, 38, 48, NT
17	95	14, 15	Bangladesh, Cambodia, Colombia, Ethiopia, Ghana, Kenya, Nigeria, Pakistan, Rwanda, South Africa, Tanzania, Vietnam, NA	112, 122, 127, 155, 23, 25, NT
14	77	3, 14 + 15, 15	Bangladesh, China, India, Kenya, Malawi, Nepal, Rwanda, Tanzania, Vietnam, Zambia, NA	16, 2, 64, NT
35	58	14, 15, 27	Bangladesh, Ethiopia, Israel, Kenya, Rwanda, Tanzania, Vietnam, NA	108, 110, 16, 22, NT
39	50	15	Bangladesh, Ethiopia, Gambia, Ghana, Kenya, Nigeria, Rwanda, South Africa, UK, Vietnam	116, 2, 23, 62, NT

[a]The complete list of all sequence types of CTX-M-encoding *K. pneumoniae* regardless of the number of genomes is shown in supplementary Table S3, see online supplementary material.
[b]All of the STs belong to *K. pneumoniae* (*sensu stricto*).
[c]Some strains have two CTX-M variants, which is indicated by "+". N3 is a new unnamed CTX-M variant, a single amino acid variant of CTX-M-15.
[d]NA, not available for some strains.
[e]NT, not typable for some strains.

cephalosporins. This needs to be considered when choosing antimicrobial agents as an empiric treatment for neonatal sepsis, for which KpSC is a common pathogen, using precision medicine approaches. As ESBLs cannot hydrolyze carbapenems and most ESBL-producing KpSC do not encode carbapenemases, carbapenems appear to be a reasonable choice for treating severe infections due to KpSC. However, alarmingly, still about a quarter of ESBL-producing KpSC with genome sequences being deposited in GenBank have carbapenem-encoding genes. This highlights that rigorous surveillance on carbapenem resistance in KpSC is required to guide empiric treatment for its infection. Second, $bla_{\text{CTX-M}}$ is the most common type of ESBL-producing gene in KpSC, but a variety of $bla_{\text{CTX-M}}$ variants are identified in KpSC. $bla_{\text{CTX-M}}$ genes are typically carried by plasmids in KpSC [9], while CTX-M-encoding KpSC exhibits quite a diverse clonal background. This indicates that the dissemination of $bla_{\text{CTX-M}}$ genes in KpSC is largely driven by plasmids. As such, the curb of further spread of CTX-M-encoding KpSC requires measures to address the transmission of plasmids, which may be achieved by inhibiting conjugation or plasmid curing. Nevertheless, more studies are urgently needed to develop anti-plasmid tools and strategies to combat antimicrobial resistance, which may employ tailored approaches to counter the various mechanisms of plasmid replication. Third, certain types of ESBL-producing KpSC such as ST307 and ST15 are relatively common and widely distributed. Notably, $bla_{\text{CTX-M-15}}$-carrying ST307 has been reported to have caused an outbreak in a neonatal intensive care unit [10]. These outstanding lineages are likely to represent high-risk clones, which warrant further studies to investigate their emergence and monitor their spread. Fourth, we found the ESBL-producing KpSC mainly from LMICs. The World Health Organization proposed that the burden of antimicrobial resistance was disproportionately high in LMICs and urged early addressing with more surveillance data [3]. To achieve this, surveillance in LMICs needs to be improved to address problems such as insufficiency, inconsistency, and lack of quality [5].

In summary, our analysis uncovers the circulation of a wide range of ESBL-producing *K. pneumoniae* strains in neonates, with several STs being common and widely spread, which warrants precise monitoring and further studies. In particular, global prospective epidemiological investigations are required to prompt precise therapy and control of infections due to ESBL-producing KpSC such as neonatal sepsis.

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Author contributions

Ya Hu (Conceptualization, Data curation, Funding acquisition, Investigation, Writing—original draft), Yu Feng (Data curation, Formal analysis, Funding acquisition, Validation), and Zhiyong Zong (Conceptualization, Funding acquisition, Supervision, Writing—review & editing).

Supplementary data

Supplementary data is available at *PCMEDI Journal* online.

Conflict of Interest

None declared.

References

1. Podschun R, Ullmann U. *Klebsiella* spp. as nosocomial pathogens: epidemiology, taxonomy, typing methods, and pathogenicity factors. *Clin Microbiol Rev* 1998;**11**:589–603. https://doi.org/10.1128/CMR.11.4.589.
2. Murray CJL, Ikuta KS, Sharara F *et al.* Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet North Am Ed* 2022;**399**:629–55. https://doi.org/10.1016/S0140-6736(21)02724-0.

3. *WHO Bacterial Priority Pathogens List, 2024: bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance*. Geneva: World Health Organization, 2024.
4. Laxminarayan R, Bhutta ZA. Antimicrobial resistance-a threat to neonate survival. *Lancet Glob Health* 2016;**4**:e676–7. https://doi.org/10.1016/S2214-109X(16)30221-2.
5. Russell NJ, Stöhr W, Plakkal N *et al.* Patterns of antibiotic use, pathogens, and prediction of mortality in hospitalized neonates and young infants with sepsis: A global neonatal sepsis observational cohort study (NeoOBS). *PLoS Med* 2023;**20**:e1004179. https://doi.org/10.1371/journal.pmed.1004179.
6. Long H, Hu Y, Feng Y *et al.* Genome analysis of *Klebsiella oxytoca* complex for antimicrobial resistance and virulence genes. *Antimicrob Agents Chemother* 2022;**66**:e0218321. https://doi.org/10.1128/aac.02183-21.
7. Hu Y, Yang Y, Feng Y *et al.* Prevalence and clonal diversity of carbapenem-resistant *Klebsiella pneumoniae* causing neonatal infections: A systematic review of 128 articles across 30 countries. *PLoS Med* 2023;**20**: e1004233. https://doi.org/10.1371/journal.pmed.1004233.
8. Rossolini GM, D'Andrea MM, Mugnaioli C. The spread of CTX-M-type extended-spectrum β-lactamases. *Clin Microbiol Infect* 2008;**14**:33–41. https://doi.org/10.1111/j.1469-0691.2007.01867.x.
9. Castanheira M, Simner PJ, Bradford PA. Extended-spectrum β-lactamases: an update on their characteristics, epidemiology and detection. *JAC Antimicrob Resist* 2021;**3**:dlab092. https://doi.org/10.1093/jacamr/dlab092.
10. Baek EH, Kim SE, Kim S *et al.* Successful control of an extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* ST307 outbreak in a neonatal intensive care unit. *BMC Infect Dis* 2020;**20**:166. https://doi.org/10.1186/s12879-020-4889-z.

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