Molecular Epidemiology of multidrug-resistant *Klebsiella pneumoniae, Enterobacter cloacae,* and *Escherichia coli* outbreak among neonates in Tembisa Hospital, South Africa

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Running Head: Multidrug-resistant *Enterobacterales* outbreak in neonates.

Abstract

Background. An outbreak of multidrug-resistant *Klebsiella pneumoniae*, *Escherichia coli, and* *Enterobacter cloacae* infections in a neonatal ward within a tertiary hospital in South Africa resulted in the mortality of 10 patients within six months. In this work, the genomic epidemiology of and the molecular factors mediating this outbreak were investigated.

Methods. Bacterial cultures obtained from clinical samples collected from the infected neonates underwent phenotypic and molecular analyses to determine their species, sensitivity to antibiotics, production of carbapenemases, complete resistance genes profile, clonality, epidemiology, and evolutionary relationships. Mobile genetic elements flanking the resistance genes and facilitating their spread were also characterized.

Results. The outbreak was centered in two major wards and affected mainly neonates between September 2019 and March 2020. Most isolates (n = 27 isolates) were *K. pneumoniae* while both *E. coli* and *E. cloacae* had three isolates each. Notably, 33/34 isolates were multidrug resistant (MDR), with 30 being resistant to at least four drug classes. All the isolates were carbapenemase-positive, but four $bla_{\text{OXA-48}}$ isolates were susceptible to carbapenems. $Bla_{\text{NDM-1}}$ (n = 13) and $bla_{\text{OXA-48/181}}$ (n = 15) were respectively found on *IS*91 and *IS*6-like *IS*26 composite transposons in the isolates alongside several other resistance genes. The repertoire of resistance and virulence genes, insertion sequences, and plasmid replicon types in the strains explains their virulence, resistance, and quick dissemination among the neonates.

Conclusions. The outbreak of fatal MDR infections in the neonatal wards were mediated by clonal (vertical) and horizontal (plasmid-mediated) spread of resistant and virulent strains (and genes) that have been also circulating locally and globally.

Keywords: carbapenem; neonates; sepsis; outbreak; infection control; colistin.

Introduction

Escherichia coli, *Enterobacter cloacae* complex, and *Klebsiella pneumoniae* are three of the most challenging Gram-negative bacterial pathogens implicated in numerous nosocomial infections and outbreaks [1–3]. They are mostly associated with multidrug resistance in urinary tract infections, bacteraemia, meningitis, and pneumonia [2,4,5]. Among infants, these two pathogens are mainly associated with blood-stream infections (sepsis) and pneumonia. Outbreaks among neonatal units and these bacteria are usually antibiotic resistant [3].

E. coli, *E. cloacae*, and *K. pneumoniae* have been associated with resistance to carbapenems, colistin, tigecycline, other β-lactams, fluoroquinolones, aminoglycosides, tetracyclines, fosfomycin, and all other antibiotic classes [2,5–7]. It is therefore not uncommon for these species to harbour several resistance determinants and express multidrug resistance phenotypes. Furthermore, highly virulent strains, including hypervirulent *K. pneumoniae*, have emerged and several reports have shown the presence of multidrug resistance and hypervirulence in nosocomial and community *K. pneumoniae* strains [8,9].

From September 2019, physicians at Tembisa hospital, South Africa, began to see a spike in neonatal infections. The paediatrician notified the Department of Medical Microbiology at the University of Pretoria and requested an investigation into the cause of the spike in infection among neonates. Unfortunately, while preparations were ongoing to initiate the investigations, an outbreak occurred between November 2019 and January 2020[10]. Twenty infants were infected with carbapenem-resistant *K. pneumoniae* and *E. coli* during this outbreak and 10 demised. The infections however continued until March 2020[11].

Clinical samples from the hospital's neonatal unit that had been sent for diagnosis at the National Health Laboratory Services (NHLS), Tshwane Academic Division/Department of Medical Microbiology, University of Pretoria, between September 2019 and March 2020, were therefore collected and analysed. A series of phenotypic and molecular analyses of the samples were undertaken to delineate the molecular epidemiology and resistance mechanisms of the strains involved in the outbreak. Using whole-genome sequencing and phylogenomics, the evolutionary relationship between the isolates and other regional and global strains as well as the genetic context of their resistance determinants is characterised herein.

Methods

Study setting and samples. An uptick in carbapenemase-mediated infection outbreak was observed at the Tembisa hospital in September 2019. We thus followed up on this to trace and reign in the infection from further spread. Forty-five neonatal demographic data and 48 clinical samples from the Tembisa hospital were sent to the National Health Laboratory Services (NHLS), Tshwane Academic Division/Department of Medical Microbiology, University of Pretoria, between September 2019 and March 2020. The clinical and demographic data were curated into Microsoft Excel for downstream statistical analysis. The host age, disease, and sample sources were included in the clinical data. Descriptive statistics were used to analyse the demographic data.

Isolate identification and resistance screening. The samples (48 stored isolates) were retrieved from the -70°C freezer, thawed and plated out on blood agar plates (BAP) (Diagnostic Media Products, South Africa) for further testing. However, only 40 isolates could be revived. Hence, all subsequent phenotypic and PCR tests were done on 40 isolates. The species and antibiotic resistance profiles of the forty isolates were identified using Vitek 2 (Biomerieux, Johannesburg,

South Africa). Furthermore, the carbapenem minimum inhibitory concentrations (MIC) for all isolates was determined with ertapenem, imipenem and meropenem Epsilon tests (E-tests) (BioMèrieux, France). Briefly, a 0.5 McFarland inoculum of each isolate was lawned onto a Mueller-Hinton agar plate (Diagnostic Media Products, South Africa) and the E-test was placed at the center of the plate and incubated in ambient air at 35-37^{0}C for 18-24 hours. The MIC was read at the point where the inhibition ellipse intersects with the test strip using the 2023 CLSI M-100 breakpoints [imipenem, meropenem, and doripenem resistance: ≥ 4 µg/mL; ertapenem resistance: ≥ 2 µg/mL][12].

The colistin MIC for the isolates were determined with broth microdilution (BMD). Colistin BMD was performed according to the Clinical and Laboratory Standards Institute (CLSI) document M07-A10 in an untreated 96-well microtiter polystyrene plate [13]. Following subculture of the isolates on BAP's, a 0.5 McFarland was inoculated into microtiter wells with colistin concentration ranging from 0.125 µg/mL to 64 µg/mL. The microtiter plates were incubated in ambient air at 35-37^{O}C for 18-24 hours. The MIC was read at the first well with no macroscopically visible bacterial growth and interpreted using the 2023 CLSI M-100 breakpoints [Colistin resistance: ≥ 4 µg/mL] [12].

The modified carbapenem inactivation method (mCIM) was used to phenotypically screen the isolates for carbapenemase production [14].

DNA extraction and PCR. A second subculture on BAP was done to obtain fresh cultures for DNA extraction and PCR to determine the presence of carbapenemase and colistin mobile resistance (*mcr*) genes. The isolates were further screened molecularly using multiplex PCR for *bla*$_{IMP}$, *bla*$_{KPC}$, *bla*$_{VIM,}$ *bla*$_{OXA}$, and *bla*$_{NDM}$ carbapenemases as well as for *Mcr -1, Mcr -2, Mcr -3, Mcr-4,* and *Mcr-5* colistin resistance genes. The PCR screening included one multiplex PCR

for *bla*$_{VIM}$, *bla*$_{OXA}$ and *bla*$_{NDM}$ primers and two singleplex PCRs for both *bla*$_{KPC}$ and *bla*$_{IMP}$.The primers and the conditions used are shown in Table S1. In-house positive controls for carbapenemases were used while *mcr*-positive controls were provided by the Technical University of Denmark.

Genomic and bioinformatic analyses. Owing to funding restrictions, we could only sequence 34 isolates. Therefore, we used the phenotypic data of the isolates to select the subset of 34 out of 40 isolates for genomic DNA extraction and sequencing; isolates with resistance to more than three antibiotics were prioritized for the whole-genome sequencing. gDNA were extracted from the isolates using the MagnaPure 96 instrument (Roche, South Africa) from 24-hour BAP cultures. The gDNA were sequenced on an Illumina Miseq at the genomic core sequencing facility of the National Institute of Communicable Diseases (NICD) (Johannesburg, South Africa). The generated fastQ and fastA files were submitted to GenBank under bioproject number PRJNA850834.

The genomes were annotated with NCBIs PGAP. The generated .gff files were used to delineate the genetic environment and associated mobile genetic environment of the resistance genes. The species of each of the isolates were confirmed using NCBIs ANI. ResFinder (https://cge.food.dtu.dk/services/ResFinder/) was used to determine the resistance determinants in the genomes. The clonality of the isolates and their multi-locus sequence typing (MLST) numbers were identified using MLST 2.0 (https://cge.food.dtu.dk/services/MLST/)[15]. The plasmid replicon genes or incompatibility groups and associated contigs were determined using PlasmidFinder (https://cge.food.dtu.dk/services/PlasmidFinder/). Mobile Element Finder was used to identify the mobile genetic elements

(https://cge.food.dtu.dk/services/MobileElementFinder/) in the genomes, while the virulence genes were identified using VirulenceFinder (https://cge.food.dtu.dk/services/VirulenceFinder/).

Phylogenomics

The genomes of *K. pneumoniae*, *Enterobacter cloacae*, *Citrobacter portucalensis*, and *E. coli* isolates that are carbapenem- and/or colistin-resistant were curated from NCBI and PATRIC for purposes of determining their evolutionary relationships with this study's isolates. These curated genomes were categorized geographically into South Africa, Africa, and global for the phylogenetic analyses. This study's genomes and those from each of the three categories described above were aligned using Clustalw, which selected and aligned genes and sequences that were common to all aligned isolates. A minimum of 1000 genes from each isolates' genome were thus aligned for the core genome phylogenetic tree construction. The phylogenies were subsequently inferred using RAxML (using a bootstrap reassessment of 1,000 x) and annotated with Figtree.

The ARGs from this study's genomes and those of the genomes curated from NCBI and PATRIC were obtained from NCBI or ResFinder (https://cge.food.dtu.dk/services/ResFinder/). These ARGs were tabulated and arranged according to the host isolates' location on the phylogenetic tree to provide a comparative phylogenomic view of the ARGs per clone or evolutionary distance.

Ethical approval. This research was approved by the Ethical Review Board of the School of Medicine, University of Pretoria, South Africa.

Results

Outbreak settings and demographics. An increase in carbapenem-resistant infections were observed between September 2019 and March 2020 within the neonatal unit 4 at Tembisa hospital, South Africa. This outbreak involved 45 neonates who were born between August 2019 and March 2020 (Table S2). The affected infants were aged between 1 and 70 days (Table S2). Blood cultures (n = 26 specimen), and rectal swabs (n = 23 specimen) formed the most common clinical specimens collected from the infants. Single specimens were taken from tracheal aspirate (n = 1), urine (n = 1) and pus swab (n =1). Some of the specimens were taken from the same patient/infant (duplicates), hence the higher number of specimens than that of infants.

Initial identification and antibiotic sensitivity testing. The isolates from the specimen were initially identified by Vitek 2 as *K. pneumoniae*, with seven specimens having a mixture of both *K. pneumoniae* and *Citrobacter* spp. (n = 2), *Enterobacter* spp. (n = 2), and/or *E. coli* (n = 3). Vitek II susceptibility testing found two isolates to be resistant to colistin with MICs ≥ 64 mg/uL and 19 isolates to be resistant to at least one carbapenem with an MIC of ≥ 2 mg/uL (Table S2).

Carbapenemase production, MICs, and PCRs. The results of mCIM, carbapenems MICs (E-test except for ertapenem for which Vitek 2 was used), colistin BMD, and PCRs are summarized in Table 1. All except four of the isolates were resistant to at least one carbapenem (imipenem and/or ertapenem) from the E-test; yet the four non-resistant isolates harboured a $bla_{\text{OXA-48}}$-like carbapenemase. There were 31 imipenem- or ertapenem-resistant isolates, and 27 meropenem-resistant isolates while 27 isolates were resistant to all three carbapenems. All except seven isolates were colistin-resistant; these seven resistant isolates had no *mcr-1* to *-5* genes (Table 1).

All the isolates were positive for the mCIM and PCR carbapenemase tests, except T21 (JSK_2019-20), which was mCIM-positive, but PCR-negative. There were 15 NDM-positive isolates, 18 OXA-48–like–positive isolates, three NDM + OXA-48–like–positive isolates, and

one VIM + OXA-48–like–positive isolates. None of the isolates was *mcr-1* to -5–positive. Compared with OXA-48–like–positive isolates, all NDM-positive isolates were resistant to all three carbapenems except T33 (meropenem MIC = 4 µg/mL), T23 (imipenem MIC = 24 µg/mL; meropenem MIC = 4 µg/mL), and T8 (OXA-48–like and NDM-positive; meropenem MIC = 4 µg/mL); see Table 1.

Genomic analyses

Identification and resistance profiles. The species of the isolates were confirmed by their average nucleotide identity (ANI) on NCBI. Of the 34 sequenced isolates, 27 were *Klebsiella pneumoniae*, three were *E. coli* (T-5, T-11, and T-48), three were *E. cloacae* (T-13, T-20, and T-46), and one was *Citrobacter portucalensis* (T-22). The inferred resistance profiles of the isolates, from their resistance genes, showed that 33/34 isolates were multidrug resistant. Except *E. cloacae* (T13, T20, and T46) and T48 (*E. coli*), all the other isolates were resistant to at least four antibiotic classes: aminocyclitol, aminoglycosides, amphenicol, βeta-lactam, folate pathway antagonist, fosfomycin, macrolide, peroxide, quaternary ammonium compound, quinolone, rifamycin, and tetracycline (Table S3). Only one isolate had a tetracycline resistance gene.

Resistance determinants. The distribution of the antibiotic resistance genes per isolate is shown in Table S3, with the most frequently identified being *oqxAB* (n = 28 isolates), *fosA* (n = 27 isolates), *sul-1* & *sul-2* (n = 23 isolates), *qacE* (n = 22 isolates), *mphA* (n = 20 isolates), *aac(6')-Ib-cr* (n = 20 isolates), *aph(3")-Ib* (n = 17 isolates), *aph(6)-Id* (n = 17 isolates), *aadA16* (n = 16 isolates), *dfrA27* (n = 16 isolates), *arr-3* (n = 16 isolates), $bla_{\text{CTX-M-15}}$ (n = 16 isolates), $bla_{\text{TEM-1B}}$ (n = 16 isolates), $bla_{\text{OXA-48}}$ (n = 15 isolates), $bla_{\text{SHV-187}}$ (n = 14 isolates), and *rmtC* (n = 12 isolates). $bla_{\text{NDM-1}}$ was present in 13 isolates (Table S3).

Common mutation-based resistance mechanisms were found in *gyrA* (n = 25 isolates), *ompK36* (n = 26 isolates), and *ompK37* (n = 26 isolates). Nineteen *K. pneumoniae* isolates viz., T8, T9, T10, T12, T14, T16, T17, T18, T19, T23, T27, T28, T29, T30, T31, T32, T33, T37, and T39, had between 15 and 22 resistance genes (Table S3).

Discrepancies between the PCR data and the whole-genome sequencing (WGS) data were observed. PCR did not identify $bla_{\text{OXA-181}}$ in strain T21 (JSK-2019-20), albeit WGS identified this gene and mCIM showed the presence of a carbapenemase. Moreover, the WGS data did not confirm the presence of VIM + OXA-48, NDM + OXA-48, and the presence of OXA and NDM in some of the isolates. Indeed, some of the isolates could not be revived for WGS after the PCR screening step. Evidently, some might have lost their plasmids during the subsequent culturing steps to obtain 24-hour genomic DNA for the WGS. However, the presence of both NDM and OXA-48/181 in the isolates were mostly confirmed by both PCR and WGS (Tables 1 and S3).

Virulence factors. Among the 34 sequenced isolates, 24 virulence genes were identified: *air* (n = 1 isolate), *ccl* (n = 12 isolates), *cia* (n = 2 isolates), *chuA* (n = 2 isolates), *cvaC* (n = 1 isolate), *eilA* (n = 2 isolates), *etsC* (n = 1 isolate), *fyuA* (n = 18 isolates), *gad* (n = 2 isolates), *hylF* (n = 1 isolate), *KpsMII_K5* (n = 1 isolate), *KpsE* (n = 1 isolate), *ipfA* (n = 2 isolates), *iroN* (n = 1 isolates), *irp2* (n = 18 isolates), *iss* (n = 2 isolates), *iucC* (n = 1 isolate), *iutA* (n = 28 isolates), *mchF* (n = 1 isolate), *ompT* (n = 2 isolates), *sitA* (n = 1 isolate), *terC* (n = 12 isolates), *traT* (n = 5 isolates), and *yfcV* (n = 1 isolate). *E. coli* isolates T11 and T48 had the highest number of virulence genes (n = 17 and 13, respectively), while the other isolates harboured between one and four genes.

Plasmid replicon/incompatibility types. An average of four plasmid incompatibility groups were found in each isolate, with higher numbers being detected in isolates T1 (n = 7), T2 (n = 9), T11

(n = 5), T18 (n = 8), T20 (n = 5), T22 (n = 6), T39 (n = 6), and T40 (n = 6). The remaining isolates had between one and four incompatibility groups, with four plasmid types per isolate being very dominant. There were 25 plasmid types, of which IncFIA(HI1) (n = 5 plasmid types), Col(pHAD28) (n = 8 plasmid types), ColKP3 (n = 10 plasmid types), ColRNAI (n = 14 plasmid types), IncFIB(K) (n = 15 plasmid types), IncFIB(pNDM-Mar) (n = 7 plasmid types), IncFII(Yp) (n = 16 plasmid types), IncL (n = 16 plasmid types) and IncX3 (n = 10 plasmid types) were most common.

Of the 55 mobile genetic elements (MGEs) identified in the isolates, *IS*Vsa3 (n = 5 isolates), *IS*Ec15 (n = 7 isolates), *IS*Ec36 (n = 10 isolates), *IS*Kpn19 (n = 11 isolates), *IS*Kpn21 (n = 11 isolates), *IS*Kpn26 (n = 11 isolates), *IS*Kpn28 (n = 11 isolates), *IS*Kpn34 (n = 11 isolates), *IS*Kpn43 (n = 11 isolates), *IS*Sen4 (n = 11 isolates), *IS*26 (n = 12 isolates), *IS*Ec33 (n = 13 isolates), *IS*Kox1 (n = 13 isolates), *IS*5075 (n = 19 isolates), *IS*6100 (n = 22 isolates), *IS*Kox3 (n = 24 isolates), and *IS*Kpn1 (n = 20 isolates) were prominent. The number of MGEs per isolate ranged from three to 16, with an average of nine MGEs per isolate.

The MGEs associated with $bla_{\text{NDM-1}}$ and $bla_{\text{OXA-48/-181}}$ are shown in Figure 1. Irrespective of the strain (MLST) or species, the same genetic environment in the same or reversed orientation, or a truncated version of it (in the case of OXA-181), was found within the immediate flanks of $bla_{\text{NDM-1}}$, $bla_{\text{OXA-48}}$, and $bla_{\text{OXA-181}}$ (Fig. 1).

The clonality of the isolates was determined using their MLST (see Tables 1 & S3). All the three *E. coli* strains were not related and three of the *K. pneumoniae* strains (i.e., ST5785, ST25, and ST297) were also singletons with no relation with the other *K. pneumoniae* strains that occurred in multiples: ST17 (n = 2); ST1266 (n = 3); ST307 (n = 9); ST152 (n = 13). Whereas the single *K. pneumoniae, E. coli,* and *C. portucalensis* clones as well as the three *E. cloacae* clones were

isolated in 2020 from rectal swabs, *K. pneumoniae* ST307 and ST152 were identified between 2019 and 2020 from different specimen types: pus, ETA, rectal swab, blood culture, and urine. *K. pneumoniae* ST17 was only isolated in 2019 from blood cultures only.

A uniformity in resistance profiles, ARGs, virulence genes, plasmid types, and MGEs was not observed among isolates of the same clone although some genes and genetic elements were uniformly present in members of the same clone (Table S3).

Phylogenomics.

The evolutionary relationships and antibiotic resistance patterns between this study's isolates and other closely related isolates are depicted in Figures 2-8, Figures S1-S9, and Table S4. With some exceptions, isolates belonging to the same MLST (clones) were found to be closely related (found on the same branch with bootstrap values of more than 50) to each other than those from different MLST clones on the trees. Moreover, the resistance profiles of the clones/isolates found on the same branch (with very close evolutionary distance) were very similar, albeit some differences were also observed. For instance, irrespective of country, source, and date of isolation, *E. coli* ST131 clones had very similar ARG profiles (Fig. 2), suggesting a possible international transmission of that clone with their associated ARGs. Similar trends were also observed in closely related *K. pneumoniae* clones and isolates on the same cluster or branch. Notably, *E. cloacae* isolates that were of very close evolutionary distance in Fig. 7 had very similar resistance profiles, which differed from those that were distant and found on different branches and clusters. These uniform patterns were observed in strains that were isolated from different parts of the world and from different clinical and environmental specimen types.

Discussion

In this study, we describe an outbreak of fatal carbapenem-resistant *K. pneumoniae*, *E. coli*, and *E. cloacae* infections in a tertiary hospital in Gauteng, South Africa, which contributed to the mortality of at least 10 neonates. It is worrying to note that the strains were mostly multidrug-resistant, with all except four of the strains being resistant to at least four antibiotic classes (Figures 2-8 and S1-S9; Tables 1 and S1-S4). More concerning is the presence of carbapenemases in all the strains, which confer resistance to almost all β-lactams. Although no *mcr* genes were identified, seven strains were resistant to colistin, a last-resort antibiotic for carbapenem-resistant Gram-negative bacterial infections [7].

Outbreaks involving *K. pneumoniae* and *E. coli* in hospital settings are common; including fatal outbreaks in neonatal units as reported in this study [3]. Indeed, this is not the first outbreak to occur in South Africa as well. However, this study presents one of the most comprehensive molecular and genomic analyses of infection outbreaks involving these species and *E. cloacae* [5].

Although all the isolates were mCIM-positive and all-but-one was PCR-positive for carbapenemases, they were not all phenotypically resistant to carbapenems; at least four isolates were carbapenem-susceptible (Table 1). This observation is not singular as some isolates with carbapenemases have been reported to be phenotypically susceptible to carbapenems. For such observations, it was concluded that the carbapenemases were not expressed, although they were present [16,17]. For the PCR-negative but mCIM-positive isolate, there could be the presence of either a novel carbapenemase or a known carbapenemase that was not targeted by the PCR. The latter possibility was invalidated by the presence of $bla_{\text{OXA-181}}$, which was identified by the whole-genome data but was not identified by the PCR. Thus, the mCIM agreed with the whole-genome sequencing data.

However, it is worth noting that carbapenem resistance is not only mediated by carbapenemases as other determinants such as hyperexpression of AmpCs, ESBLS, and efflux pumps and hypo-expression of porins also determine carbapenem resistance [18–20]. The presence of a resistance gene with a non-commensurate phenotypic expression of the resistance gene is not limited to carbapenems alone. This is one of the reasons why molecular diagnostic tests for antibiotic resistance genes cannot be used solely as representative or confirmatory of phenotypically resistant pathogens. In this study, we also observed that the colistin-resistant isolates did not have *mcr* genes [7,18].

As recently observed in a molecular study to screen for carbapenemases and *mcr* genes, *mcr* genes are relatively less prevalent than carbapenemases [21]. This phenomenon was also observed in this study as no *mcr* gene was identified, albeit seven isolates were colistin-resistant. This is a positive finding as colistin is currently the last-resort antibiotic for carbapenem-resistant infections [7,22]. Moreover, the rarity of *mcr* genes will help reduce the spread of colistin resistance as *mcr* genes are mainly plasmid-borne and very mobile.

Similar findings with higher prevalence of $bla_{\text{OXA-181/48}}$ and bla_{NDM} carbapenemase genes in Gram-negative bacteria has been reported in South Africa, confirming this observation, and showing that these two carbapenemases are common in South African hospitals [16,23–27]. The phylogenomic analyses of the South African isolates confirm these observations and similar patterns (Table S4). Furthermore, the presence of other clinically important resistance genes such as $bla_{\text{CTX-M-15}}$, bla_{SHV}, bla_{TEM}, *qnrB/S, oqxA/B, dfrA, Sul1/2/3, aac(6')-lb-cr, aadA,* and *mph(A)* explains the multidrug and pan-drug resistance nature of the isolates. This might explain the failure of the clinicians to treat these infections, leading to the mortality of 10 infants.

As shown in Fig. 1, the carbapenemases in the isolates were flanked by other resistance genes and mobile genetic elements such as composite transposons: *IS*91 (bla_{NDM}) and *IS*6-like *IS*26 ($bla_{OXA-181}$). Instructively, irrespective of the strain in which any of the three carbapenemase i.e., bla_{OXA-48}, $bla_{OXA-181}$, and bla_{NDM-1}, was found, their genetic support/environment were all the same. This similarity in synteny and flanks around these resistance genes is further corroborated by the fact that most of these isolates, irrespective of the species or the clone, had the same insertion sequences: *IS*26 (n = 12); *IS*Ec33 (n = 13); *IS*Kpn26 (n = 16); *IS*Sen4 (n = 16); *IS*5075 (n = 19); *IS*Kpn1 (n = 20); *IS*6100 (n = 22); *IS*Kox3 (n = 24) (Table S3: MGEs). Furthermore, each of the isolate had an average of three plasmid replicons/incompatibilities, with the least being one and the highest being nine. The commonest of these plasmid types among all the isolates were IncL (n = 16), IncFII(Yp) (n = 16), IncFIB(K) (n = 15), ColRNAI (n = 14), IncX3 (n = 10), and ColKP3 (n = 10). Owing to the break-up of the genomes into several contigs, it is difficult to associate these plasmid types with each ARG. However, taken together, these show that the ARGs in these MDR isolates are being disseminated through these MGEs (Table S3: Plasmid incompatibility).

These genetic environments and ARG flanks are also commonly observed in other studies involving the same or different species within Enterobacterales from both South Africa and globally, corroborating the role of MGEs in the transmission of carbapenemases and other ARGs within and across clones and species [2,5,7,16,28].

Although there are differences in the ARGs present in the isolates (Table S3: ARGs), there are very close similarities and uniformity in the ARGs present in the isolates. This uniformity in ARGs, MGEs, and plasmid incompatibility/replicon types across the isolates suggest that irrespective of the clones and species, there are plasmid-borne MGEs that are shuttling the ARGs

between and across the species and clones [5,7,16,28,29]. Therefore, there is both clonal and plasmid-mediated transmission of the same ARGs in the hospital, particularly when the outbreak occurred in two major wards: ward 4 and 4a-NICU.

In fact, this observation is also magnified in Figures 2-8, where the same ARGs were seen among isolates of the same clone and isolates with very close evolutionary distance. In particular, the phylogenomic analyses of the isolates show that the same ARGs, possibly hosted on MGEs, and clones are being disseminated across South Africa, Africa, and globally. It is observed from Figures 2-8 that the same clones among the three species cluster together closely in the phylogenetic tree alongside other clones. The presence of other clones clustering alongside the same clones is not surprising given the higher resolution of whole-genome-based typing compared to multi-locus sequence typing (MLST) that only uses seven house-keeping genes. The *E. coli* isolates from this outbreak were of the same clone as *E. coli* clones ST58, ST69, ST87, ST103, ST131, ST457, ST616, and ST648, which were common among other isolates from South Africa, Africa, and globally. The resistance profiles within each of these clones or phylogenetic cluster were mostly uniform with multidrug resistance (Fig. 2-3).

The *K. pneumoniae* clones in this study shared the same clone and phylogenetic cluster as *K. pneumoniae* ST14, ST15, ST17, ST25, ST101, ST152, ST231, and ST307, and the resistance profiles within each of these clonal clusters were very similar with multiple resistance genes (Fig. 4-6). Likewise, the *E. cloacae* isolates clustered with *E. cloacae* ST84 and ST456 with very similar multi-resistance profiles (Fig. 7-8). These observations support the fact that there is clonal and MGE-mediated transmission of these ARGs across the globe, which caused the outbreak in the hospital under study.

In summary, the outbreak that occurred at the Tembisa hospital was clonally and horizontally mediated, spreading multidrug-resistant infections and causing fatalities.

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462

Table 1. Summary of phenotypic, biochemical, and molecular (PCR) results for the carbapenem-resistant strains

No.	Sample_name	Episode number	Study number	Specimen	mCIM	Carbapenemase (KPC, OXA, VIM, NDM, IMP)	Carbapenem MICs	Col BMD mg/L	Mcr 1-5
1	JSK_2019-1	IL02324174	T1	Rectal swab	+[*]	OXA+VIM	I[†]=0.5, M[‡]=0.5, E[§]=>32	0.25	-[**]
2	JSK_2019-2	IL02320320	T2	Rectal swab	+	OXA	I=1, M=2, E=4	0.25	-
3		IL02319935-2	T3	Rectal swab	+				NG[††]
4	JSK_2019-3	IL02312035	T4	Rectal swab	+	OXA	I=1, M=0.5, E=0.5	0.25	
5	JSK_2019-4	IL02284805-2 (*E. coli*)	T5	Rectal swab	+	OXA	I=2, M=0.5, E=0.5	0.125	-
6	JSK_2019-5	IL02284805-3 (*K. pneumo*)	T6	Rectal swab	+	OXA	I=>32, M=>32, E=>32	32	-
7	JSK_2019-6	IL02282080	T7	Rectal swab	+	OXA+NDM	I=>32, M=>32, E=>32	0.125	-
8	JSK_2019-7	IL02277245	T8	Pus swab	+	OXA+NDM	I=32, M=4, E=32	0.5	-
9	JSK_2019-8	IL02273128	T9	Rectal swab	+	OXA	I=>32, M=>32, E=>32	32	-

[*] Positive results
[†] Imipenem MIC
[‡] Meropenem MIC
[§] Ertapenem MIC
[**] Negative PCR results
[††] No growth

10	JSK_2019-9	IL02268788	T10	Blood culture	+	OXA	I=>32, M=>32, E=>32	>64	-
11	JSK_2019-10	IL02267712-1 (*E. coli*)	T11	Rectal swab	+	OXA	I=>32, M=1, E=16	0.25	-
12	JSK_2019-11	IL02267712-2 (*K. pneumo*)	T12	Rectal swab	+	OXA	I=32, M=>32, E=>32	>64	-
13	JSK_2019-12	IL02267712-3 (*E. cloacae*)	T13	Rectal swab	+	OXA	I=>32, M=>32, E=>32	>64	-
14	JSK_2019-13	IL02267312	T14	Blood culture	+	NDM	I=>32, M=>32, E=>32	2	-
15	JSK_2019-14	IL02246685	T15	Urine	+	OXA	I=>32, M=>32, E=>32	0.25	-
16	JSK_2019-15	IL02261808	T16	Rectal swab	+	NDM	I=>32, M=>32, E=>32	0.125	-
17	JSK_2019-16	IL02257486	T17	Blood culture	+	NDM	I=>32, M=>32, E=>32	0.125	-
18	JSK_2019-17	IL02253744	T18	Rectal swab	+	OXA+NDM	I=>32, M=>32, E=>32	0.125	-
19	JSK_2019-18	IL02250251-1 (*K. pneumo*)	T19	Rectal swab	+	OXA	I=>32, M=>32, E=>32	0.125	-
20	JSK_2019-19	IL02250251-2 (*E. cloacae*)	T20	Rectal swab	+	OXA	I=>32, M=>32, E=>32	0.125	-
21	JSK_2019-20	IL02250245-	T21	Rectal	+	No gene detected	I=>32, M=1,	>64	-

		1 (*C. freundii*)		swab			E=>32		
22	JSK_2019-21	IL02250245-2 (*K. pneumo*)	T22	Rectal swab	+	OXA	I=>32, M=>32, E=>32	0.25	-
23	JSK_2019-22	IL02250352	T23	Blood culture	+	NDM	I=2, M=4, E=>32	0.25	-
24	JSK_2019-23	IL02246823	T24	Blood culture	+	NDM	I=>32, M=>32, E=>32	0.5	-
25		IL02246225-1 (*C. freundii*)	T25	Rectal swab	+	NG			NG
26		IL02246225-2 (*K. pneumo*)	T26	Rectal swab	+	NG			NG
27	JSK_2019-24	IL02243704	T27	Rectal swab	+	NDM	I=>32, M=>32, E=>32	0.125	-
28	JSK_2019-25	IL02245959	T28	Blood culture	+	NDM	I=>32, M=>32, E=>32	0.125	-
29	JSK_2019-26	IL02243664	T29	Blood culture	+	NDM	I=>32, M=>32, E=>32	0.125	-
30	JSK_2019-27	IL02241322	T30	ETA	+	NDM	I=>32, M=>32, E=>32	1	-
31	JSK_2019-28	IL02243241	T31	Blood culture	+	NDM	I=>32, M=>32, E=>32	0.25	-
32	JSK_2019-29	IL02241855	T32	Blood culture	+	NDM	I=>32, M=>32,	0.25	-

							E=>32		
33	JSK_2019-30	IL02239816	T33	Blood culture	+	NDM	I=>32, M=4, E=>32	0.125	-
34	JSK_2019-31	IL02239311	T34	Blood culture	+	NDM	I=>32, M=>32, E=>32	0.125	-
35		IL02238220	T35	Rectal swab	+	NG			NG
36		IL02237822	T36	Blood culture	+	NG		0.25	NG
37	JSK_2019-32	IL02217473	T37	Blood culture	+	OXA	I=>32, M=>32, E=>32	0.125	-
38	JSK_2019-33	IL02195267	T38	Rectal swab	+	OXA	I=>32, M=>32, E=>32	0.125	-
39	JSK_2019-34	IL02158904	T39	Blood culture	+	OXA	I=>32, M=>32, E=>32	0.125	-
40	JSK_2019-35	IL02157057	T40	Blood culture	+	OXA	I=1, M=0.25, E=0.5	0.25	-
41	JSK_2019-36	IL02292248-1 (*K. pneumo*)	T41	Rectal swab	+	NDM	I=32, M=16, E=O/S (no Vitek MIC)	0.125	-
42	JSK_2019-37	IL02290036	T42	Rectal swab	+	NDM	I=>32, M=>32, E=O/S (no Vitek MIC)	0.125	-
43		IL02290034	T43	Rectal swab	+	NG			NG
44		IL02296394-3	T44	Rectal swab	+	NG			NG
45	JSK_2019-38	IL02298389	T45	Rectal	+	OXA	I=1, M=0.25,	0.25	-

				swab			E=0.5		
46	JSK_2019-39	IL02292248-2 *(E. cloacae)*	T46	Rectal swab	+	OXA	I=4, M=16, E=O/S (no Vitek MIC)	>64	-
47		IL02296394-1	T47	Rectal swab	+	NG			NG
48	JSK_2019-40	IL02296394-2 (*E. coli)*	T48	Rectal swab	+	OXA	I=16, M=2, E=O/S (no Vitek MIC)	0.25	-

Table S1. Primers, PCR conditions, & PCR Results.

Table S2. De-identified demographic data of the human hosts from which the strains were isolated.

Table S3. Raw sequence and genomic data of the strains

Table S4. Phylogenomic and comparative genomic data of the strains.

Figure S1. Comparative phylogenomics of *Escherichia coli* strains from both this study and other strains from South Africa. The names of the strains from this study are coloured green. The names of closely related strains to this study's strains are shown in blue. Branches holding this study's strain with very high bootstrap values (>50%) are shown in red to depict isolates with very close evolutionary distance.

Figure S2. Comparative phylogenomics of *Escherichia coli* strains from both this study and other strains from Africa. The names of the strains from this study are coloured green. The names of closely related strains to this study's strains are shown in blue. Branches holding this study's strain with very high bootstrap values (>50%) are shown in red to depict isolates with very close evolutionary distance.

Figure S3. Comparative phylogenomics of *Escherichia coli* strains from both this study and other strains from the world. The names of the strains from this study are coloured green. The names of closely related strains to this study's strains are shown in blue. Branches holding this study's strain with very high bootstrap values (>50%) are shown in red to depict isolates with very close evolutionary distance.

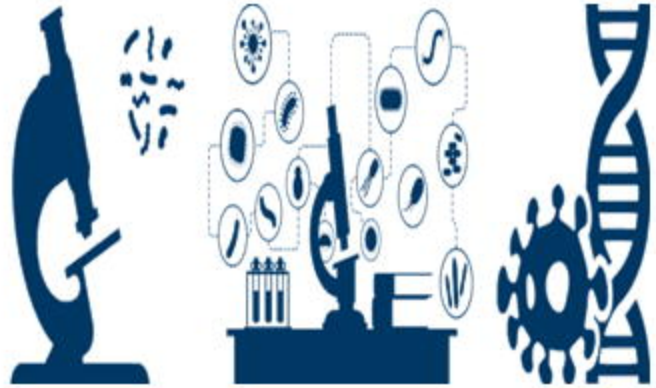
Figure S4. **Comparative phylogenomics of *Klebsiella pneumoniae* strains from both this study and other strains from Africa**. The names of the strains from this study are coloured green. The names of closely related strains to this study's strains are shown in blue. Branches holding this study's strain with very high bootstrap values (>50%) are shown in red to depict isolates with very close evolutionary distance.

Figure S5. Comparative phylogenomics of *Klebsiella pneumoniae* strains from both this study and other strains from the world. The names of the strains from this study are coloured green. The names of closely related strains to this study's strains are shown in blue. Branches holding this study's strain with very high bootstrap values (>50%) are shown in red to depict isolates with very close evolutionary distance. Both S5A and S5B are phylogenetic analyses of global strains.

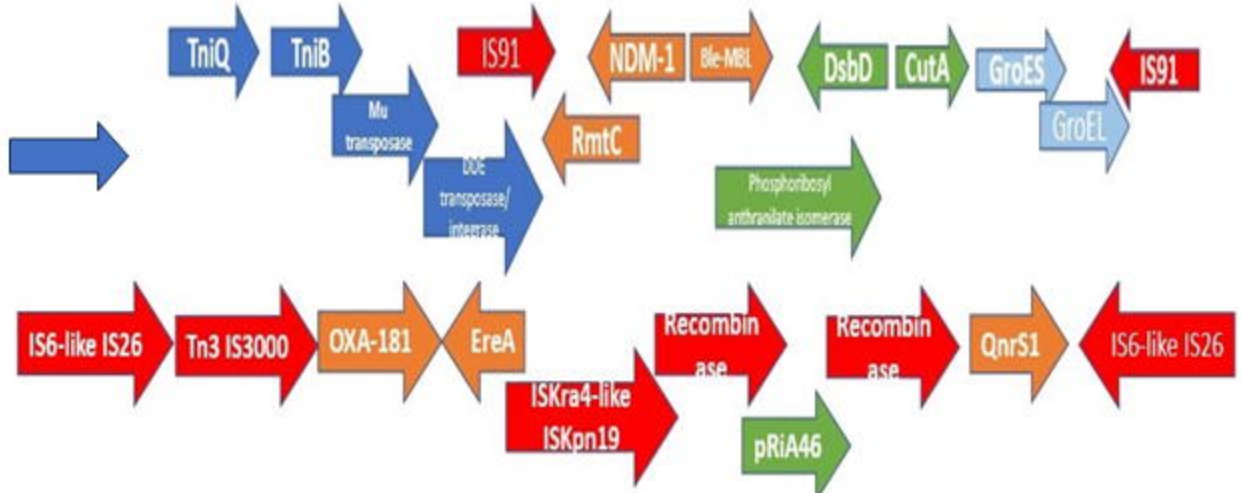
Figure S6. Comparative phylogenomics of *Enterobacter cloacae* strains from both this study and other strains from Africa. The names of the strains from this study are coloured green. The names of closely related strains to this study's strains are shown in blue. Branches holding this study's strain with very high bootstrap values (>50%) are shown in red to depict isolates with very close evolutionary distance.

Figure S7. Comparative phylogenomics of *Citrobacter portucalensis* strains from both this study and other strains from the whole world. The names of the strains from this study are coloured green. The names of closely related strains to this study's strains are shown in blue. Branches holding this study's strain with very high bootstrap values (>50%) are shown in red to depict isolates with very close evolutionary distance.

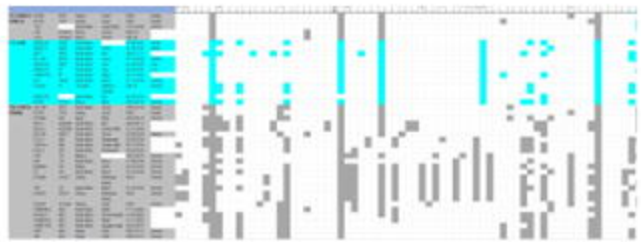
Increased infant infections and fatalities were observed in Tembisa Hospital, 2019.



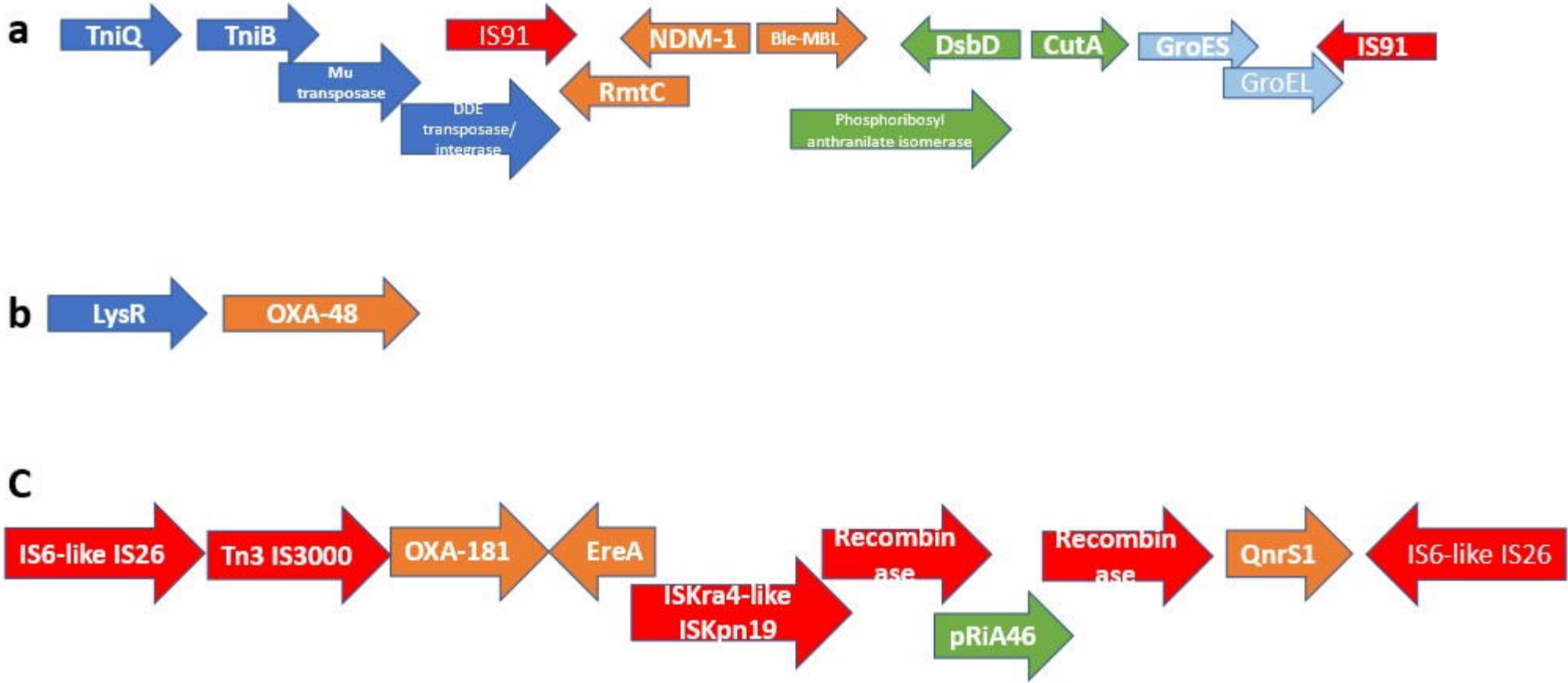
Clinical specimen were collected from the hospital for microbiological analyses



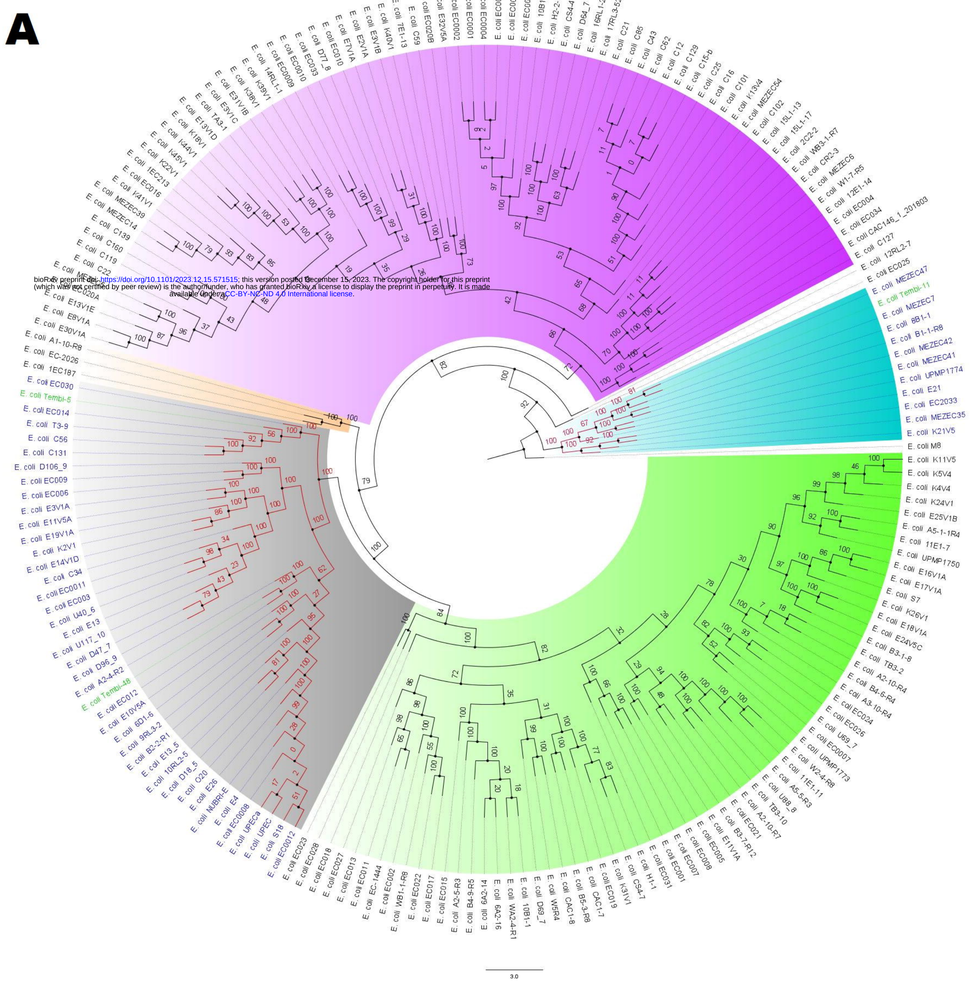
The isolates recovered from the clinical samples had plasmid-borne NDM and OXA-48/181 carbapenemase genes bracketed by Iss and composite transposons that facilitated their dissemination across species and clones in the hospital environment.



A core genome phylogenomics showed that the strains causing the fatal outbreak were both clonal and multiclonal. These strains had been previously found in South Africa, Africa, and globally.


a
TniQ
TniB
Mu transposase
DDE transposase/ integrase
IS91
RmtC
NDM-1
Ble-MBL
Phosphoribosyl anthranilate isomerase
DsbD
CutA
GroES
GroEL
IS91
b
LysR
OXA-48
C
IS6-like IS26
Tn3 IS3000
OXA-181
EreA
ISKra4-like ISKpn19
Recombinase
pRiA46
Recombinase
QnrS1
IS6-like IS26

A

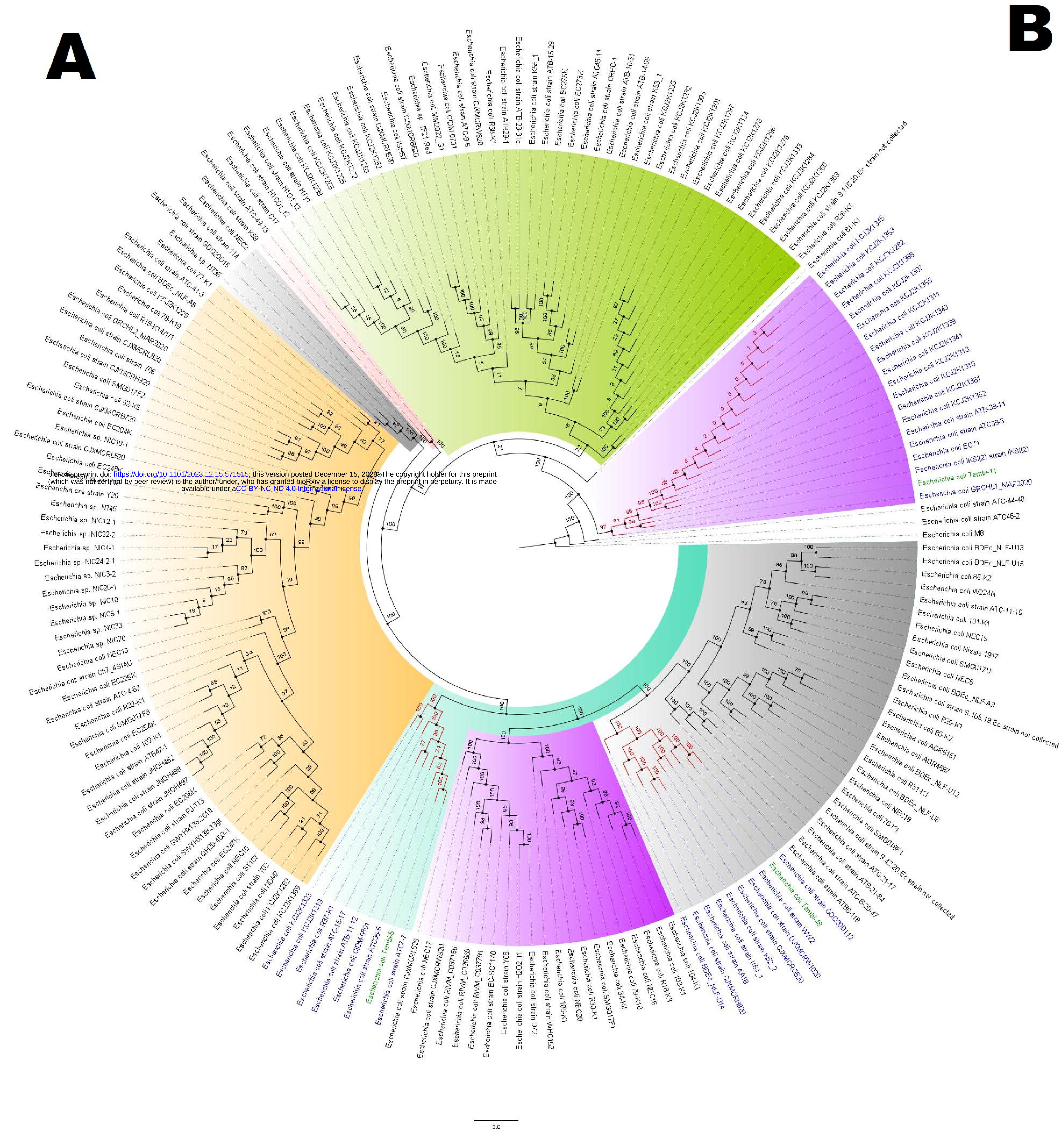


B

Strain: MLST	Related genomes	MLST	country/region	Specimen	Year	Host
	Africa					
T5: ST5907(1)	EC030	3018	Ghana	Cecal	2020	Poultry
ST906 (2)	EC014	1140	Ghana	Cecal	2020	Poultry
	T3-9		South Africa	meat (thigh)	16-01-2019	Animal
	C56	5759/411	Kenya	Camel	May-18	
	C131	5759/411	Kenya	Camel	Sep-18	
T11: ST58	MEZEC47	24/58	South Africa		14-08-2018	Sheep
	MEZEC7	58/24	South Africa	Feces	14-08-2018	Sheep
	8B1-1	58/87	South Africa	Soil	2018-11-11	
	B1-1-R8	87/58	South Africa	Feces	27-12-2018	Animal
	MEZEC42	58/87	South Africa	Oral	24-05-2018	Cow
	MEZEC41	87	South Africa	Oral	24-05-2018	Cow
	UPMP1774	87	South Africa	Water	29-11-2018	
	E21	155/21	South Africa	Blood	21-11-2018	Human
	EC2033	21	Tanzania	patient in hospital	Apr-18	Human
	MEZEC35		South Africa	Soil	24-05-2018	
	K21V5	21/155	Kenya	Stool	2019-09-10	Human
T48: ST457(1)	A2-4-R2	4373	South Africa	Feces	2018-04-10	Animal
ST829(2)	EC012	1722	Ghana	Cecal	2020	Poultry
	E10V5A	435	Egypt	Stool	2019-09-10	Human
	6D1-6	435/2951	South Africa	Soil	2018-08-11	
	9RL3-2	435/2951	South Africa	Chicken litter	15-11-2018	
	B2-2-R1	48/117	South Africa	Feces	20-09-2018	Animal
	E13_5	569	South Africa	Wastewater	22-05-2018	
	10RL2-5	998	South Africa	Chicken litter	22-11-2018	
	D18_5	372	South Africa	Wastewater	22-05-2018	
	O20	131	Nigeria		2019-03-05	Human
	E26	131	South Africa	Blood	13-09-2018	Human
	NUBRI-E	131	Sudan	Urine	25-01-2019	Human
	E4	131	South Africa	Blood	14-10-2018	Human
	EC0008	131/43	Ghana	Soft tissue biopsy	2018	Human
	S18	131	South Africa	Blood	14-10-2018	Human
	EC0012	43/131	Ghana	Soft tissue biopsy	2018	Human
	EC0019	511/449	Ghana	Urine	2018	Human
	UPMP2007	69/3	South Africa	Water	17-11-2020	
	KU10A-3	69/3	South Africa	Environmental	13-02-2020	
	UPMP2010	69/3	South Africa	Water	17-11-2020	
	UPMP1745	69/3	South Africa	Irrigation water	2018-05-07	
	37EC	69/3	Sudan	Urine	2020-01-01	Human
	7EC	69/3	Sudan	Urine	2020-01-01	Human

Resistance genes

aac(3)-Ib'-cr5 | aac(3)-Ib-cr5 | aac(3)-IVa | aac(3)-Via | aadA1 | aadA5 | acrF | aph(3')-Ia | aph(3')-Ia-1b | aph(4)-Ia | aph(6)-Id | ARR-2 | blaB | catA1 | catB3 | cmlA1 | cyaA_S352T | dfrA1 | emrA(2) | emrB(6) | emrD | eptA | erm(A) | fosA | fosR | fthL_N37NYRIN | gyrA_E446K | gyrA_D87NNY | gyrA_S83L | lnuF() | marR_S3N | mcr-1.1 | mdtM | mdt(B) | mphA | mphB | ompA | oqxA | oqxB | parC_E84GV | parC_S57T | parC_S80I | parE_D475E | parE_I355T | parE_L529I | parE_L445H | parE_S458A | pmrB_E123D | pmrB_Y358N | psiI_V25I | qnrB6 | qnrS1 | sdiA | sul1 | sul2 | tet(30) | tet(A) | tet(B) | tet(M) | tet(X4) | blaOXA | blaNDM-1 | blaTEM | blaOXA | blaCMY-2 | blaCTX-M | blaEC | blaIPC-2 | blaLAP-2 | blaNDM-1 | blaOXA | blaTEM



Strain: MLST	Related genomes	MLST	country/region	Specimen	Year	Host
Globally						
T5: ST5907(1)	KCJ2K1323		USA		2020	Deer
ST906 (2)	KCJ2K1319		USA		2020	Deer
	R37-K1		Austria	Intestinal tract	2020-07-09	Human
	ATC-15-17	436/32	Switzerland	Raw meat	2020	
	ATB-11-12	753	Switzerland	Raw meat	2020	
	CIDM-0801	11/628	Australia	Feces	2020-08-03	Human
	ATC7-7	1819	Switzerland	Raw meat	2020	
	L29	2485	Nigeria	Backyard farm	2019	Chicken
	L23	2485	Nigeria	cloacal swab	2019	Chicken
	Kcontrol-03	628/11	South Africa	Laboratory	30-06-2020	
	UPMP1749	753	South Africa	Water	2018-01-07	
	NWU_2C	543	South Africa	Cattle farm	16-05-2018	
	NWU_8C	543	South Africa	Cattle farm	16-05-2018	
	L39	2954	Nigeria	liver	2019	Chicken
	EW827	1775	Brazil	Urban stream	Feb-20	
	Pk8243	2847	Pakistan		2020	Chicken
T11: ST58	KCJ2K1345	616/21	USA		2020	Deer
	KCJ2K1353	21/616	USA		2020	Deer
	KCJ2K1282	616/21	USA		2020	Deer
	KCJ2K1368	616/21	USA		2020	Deer
	KCJ2K1307	616/21	USA		2020	Deer
	KCJ2K1355	616/21	USA		2020	Deer
	KCJ2K1311	616/21	USA		2020	Deer
	KCJ2K1343	616/21	USA		2020	Deer
	KCJ2K1339	616/21	USA		2020	Deer
	KCJ2K1341	616/21	USA		2020	Deer
	KCJ2K1313	616/21	USA		2020	Deer
	KCJ2K1310	616/21	USA		2020	Deer
	KCJ2K1361	616/21	USA		2020	Deer
	KCJ2K1352	616/21	USA		2020	Deer
	ATB-39-11	683/21	Switzerland	Raw meat	2020	
	ATC39-3	683/21	Switzerland	Raw meat	2020	
	EC71	155/21	China	Urine	30-06-2020	Human
	IKSI(2)	87/58	Nigeria	food	2020-10-06	Human
	GRCHL1_MAR 2020	58	New Zealand		2020-11-03	
	UPMP1548	87/58	South Africa	Fresh Produce	2019-05-02	
	UPMP1549	87/58	South Africa	Apple	2019-05-02	
	UPMP2097	87/58	South Africa	Irrigation water	2018-01-10	
	UPMP1547	87/58	South Africa	Cabbage	2019-05-02	
	UPMP1545	87/58	South Africa	Carrots	18-07-2018	
	IKSI(2)	87/58	Nigeria	food	2020-10-06	
	IPK9(1)	87/58	Nigeria	food	2019-10-06	
	EC005	58/414	Ghana	Fecal swab	2020	Pig
	UPMP1716	58	South Africa	cucumber	2018-12-06	
	EC002	58	Ghana	Fecal swab	2020	Pig
	MEZEC8	58/24	South Africa	Sheep	14-08-2018	
	A-1-8-1	155/21	Egypt	Feces	2019	Chicken
	A-1-4-1	21/155	Egypt	Feces	2019	Chicken
	15CS-C-C	155/21	Tanzania	Stool	Jul-18	
	E-T613	533	China	Anal swab	2020	Human
	ASHEST_CHL1_JAN2020	654	New Zealand		2020-01-30	
	Pk8219	24/2099	Pakistan		2020	Chicken
	Pk8230	24/2099	Pakistan		2020	Chicken
T48: ST457(1)	KEC3	648	Kenya		24-06-2019	Human
ST829(2)	EC017	398/1598	Ghana	Cecal	2020	Poultry
	EC016	537	Ghana	Cecal	2020	Poultry
	KAB20	38/8	Kenya		2018-12-06	Human
	24EC	8//1938	Sudan	Urine	2020-01-01	Human
	EC0021	38/8	Ghana	Urine	2018	Human
	EC0019	511/449	Ghana	Urine	2018	Human
	UPMP2007	3//1969	South Africa	Water	17-11-2020	
	KU1OA-3	69/3	South Africa	Environmental	13-02-2020	
	UPMP2010	69/3	South Africa	Water	17-11-2020	
	UPMP1745	69/3	South Africa	Irrigation water	2018-05-07	
	37EC	3//1969	Sudan	Urine	2020-01-01	Human
	7EC	69/3	Sudan	Urine	2020-01-01	Human
	GDQ20D112	457	China	Liver sample	2020-02-08	Duck
	WW2	594/457	China	Sludge	2020-04-10	
	DJXMCRW1020	39/354	China	Duck gizzard	Jul-20	Duck
	CJXMCRO520	39/354	China	Chicken wing	Jul-20	Chicken
	K62_2		China	Feces	2020-01-03	Human
	K64_1	648	China	Feces	2020-01-03	Human
	AA18	648	Brazil	Fecal swab	2020-04-01	
	CJXMCRH820	648	China	Chicken wing	Jul-20	Chicken
	BDEc_NLF_U14		Bangladesh	Urine	2020	Human
	SMG017F3	59/34	Brazil	Rectal swab	2020	Human
	E-T123	39/354	China	Anal swab	2020	Human
	Z30	1485	China		Jun-20	Human
	BECR3	648	USA		2020-02-15	Human
	CK5_MAY2020	1722	New Zealand		20-05-2020	
	BECR6	457	USA		14-02-2020	Human
	BECR9	457	USA		21-03-2020	Human
	E-T953	457	China	Anal swab	2020	Human
	WW2	457/594	China	Sludge	2020-04-10	
	CSCIP1_MAR2020	457	New Zealand		2020-11-03	

Strain	Related genomes	MLST	country	Px's	Specimen	Year	Host
South Africa							
T2	E28	25	South Africa		Blood	2019-01-09	Human
	ST_25:K161	25	South Africa	29	Urine	2013-10-02	Human
	UPMP1134	25	South Africa		Hand Swab	2018-11-01	
	E24	25	South Africa		Blood	2018-11-15	Human
	K8	25	South Africa		Blood	2018-10-07	Human
	EDO1502268	432	South Africa		Rectum	2017	Human
T39 & T40	ED010500733	983	South Africa		Rectum	2017	Human
	A105R1B5	983	South Africa		Rectum	2017	Human
	UPMP2094	20	South Africa		Water	2018-10-01	
	UPMP2096	20	South Africa		Fresh produce	2018-10-01	
	UPMP2037	20	South Africa		Irrigation water	2017	
	H2737	17	South Africa		rectal swab	2019-02-19	Human
	H8844R	17	South Africa		rectal swab	2019-02-19	Human
	Kp29	17	South Africa	50	swab	2018	Human
	UPMP2078	17	South Africa		Fresh produce	2018-03-01	
	A111R1B2	17	South Africa		Rectum	2017	Human
	UPMP2071	17	South Africa		Water	2017-10-01	
	UPMP2070	17	South Africa		Irrigation water	2017-10-01	
	H8773R	17	South Africa		rectal swab	2019-02-19	Human
	H8770	17	South Africa		rectal swab	2019-02-19	Human
	K35	17	South Africa		blood	2018-08-06	Human
T1	ST152:K021	152	South Africa	65	Urine	2013-04-25	Human
	UPMP1782	13	South Africa		water	2018-11-29	
	UPMP1783	13	South Africa		Irrigation water	2018-11-01	
	UPMP2021	252	South Africa		Fresh produce	2018-03-01	
T7	UPMP1724	14	South Africa		Irrigation water	2018-06-01	
	ST-14:K118	14	South Africa	7	urine	2013-07-20	Human
	ST14:944535499	14	South Africa				Human
	ST15:E041	15	South Africa	56	urine	2013-08-24	Human
	UPMP2091	15	South Africa		Water	2018-11-01	
	UPMP1161	15	South Africa		Fresh produce	2018-11-01	
	UPMP2118	15	South Africa		Irrigation Water	2017-11-30	
	UPMP2089	15	South Africa		Fresh produce	2018-11-01	
	UPMP1160		South Africa		Hand Swab	2018-11-01	
	UPMP2046	15	South Africa		Water	2018-11-01	
T12, T15, T21, T37, T10, T19, T9, T38, T6	Kpn01733	307	South Africa		clinical material	2016	Human
	Kp_4:MM	307	South Africa	35	urine	2019-01-27	Human
	Kpn01732	307	South Africa		clinical material	2016	Human
	Kp_180	307	South Africa		pus	2015-11-24	Human
	ECO3638959	307	South Africa		rectal swab	2020-03-14	Human
	ECO3623002	307	South Africa		rectal swab	2020-03-03	Human
	Kp_C6	307	South Africa		urine	2013-05-21	Human
	ECO3632007	307	South Africa		rectal swab	2020-03-10	Human
	ECO3607707	307	South Africa		rectal swab	2020-02-19	Human
	Kp_L28	307	South Africa		pus	2016-07-15	Human
	Kp_24MM	307	South Africa	35	tracheal aspirate	2019-09-26	Human
	Kp8	307	South Africa	42	Pus swab	2018	Human
	ECO3605938	307	South Africa		Rectal swab	2020-01-18	Human
T28, T27, T18, T31, T14, T16, T8, T29, T17, T32, T30, T23, T33	KZ00369997	152	South Africa		Rectum	2016	Human
	G702R2B5	152	South Africa		Rectum	2017	Human
	KZ00361153	3136	South Africa		Rectum	2017	Human
	ST-152:K031	152	South Africa	30	hospitals	2013-04-29	Human
	AA03535901	152	South Africa		Rectum	2017	Human
	ST-152:K051	152	South Africa	32	urine	2013-05-06	Human
	ST-152:K110	152	South Africa	54	hospitals	2013-07-09	Human
	ST-152:K025	152	South Africa		urine	2013-04-25	Human
	KZ00372150	152	South Africa		Rectum	2016	Human
	ST-152:K181	152	South Africa	89	urine	2013-04-14	Human
	AA03814079	152	South Africa		Rectum	2017	Human
	AA03509400	152	South Africa		Rectum	2017	Human
	ST-152:K071	152	South Africa	29	Blood	2013-05-17	Human
	G702R1B5	152	South Africa		Rectum	2017	Human
	ED01503757	152	South Africa		Rectum	2017	Human
	ST-152:K131	152	South Africa	62	urine	2013-08-09	Human
	AA03064255	152	South Africa		Rectum	2017	Human
	KZ00370220	152	South Africa		Rectum	2016	Human
	KZ00371410	152	South Africa		Rectum	2016	Human
	US2	152	South Africa		wastewater	2019-02-18	Human
	K37	152	South Africa		Blood	2017-11-17	Human

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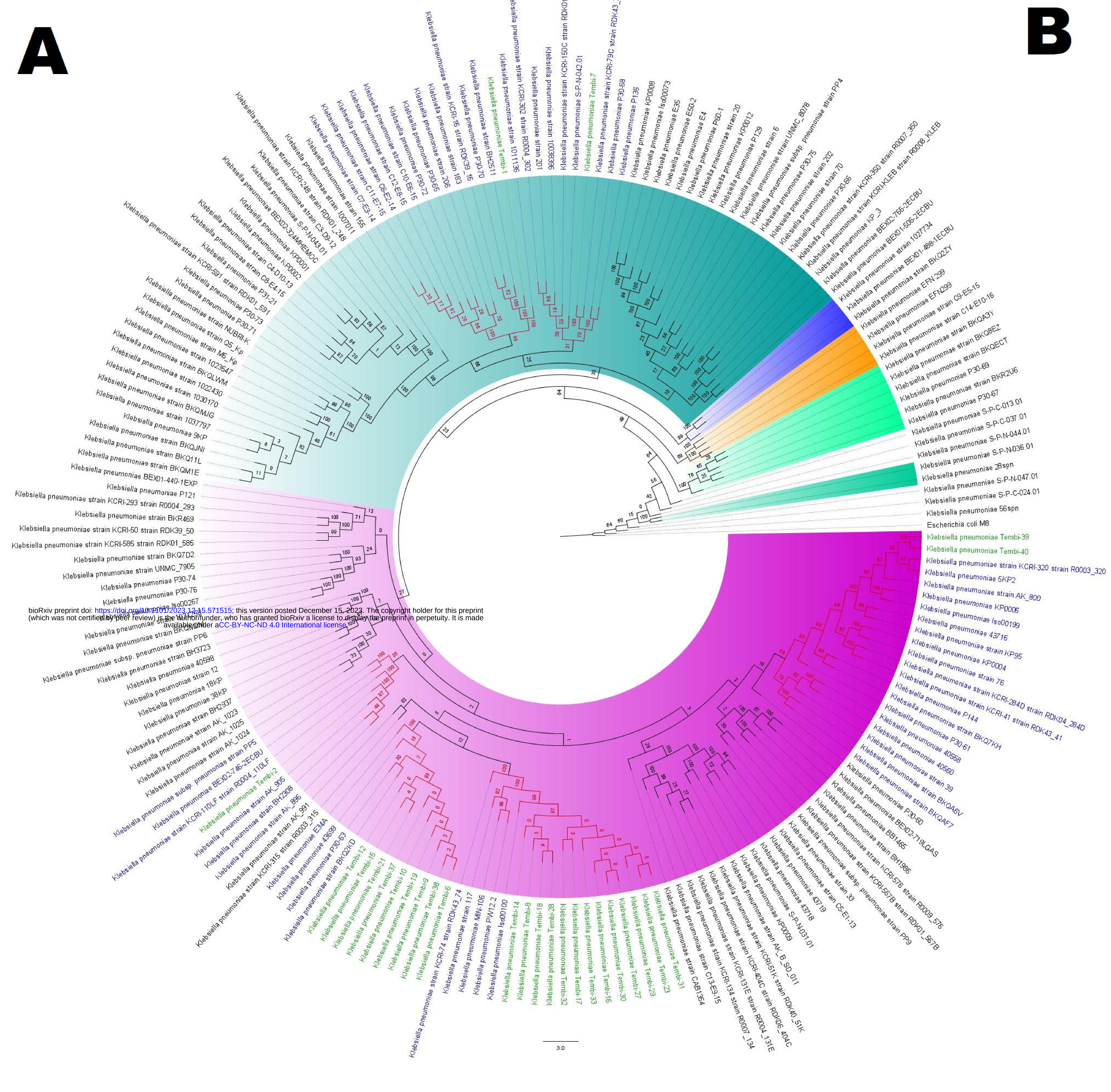

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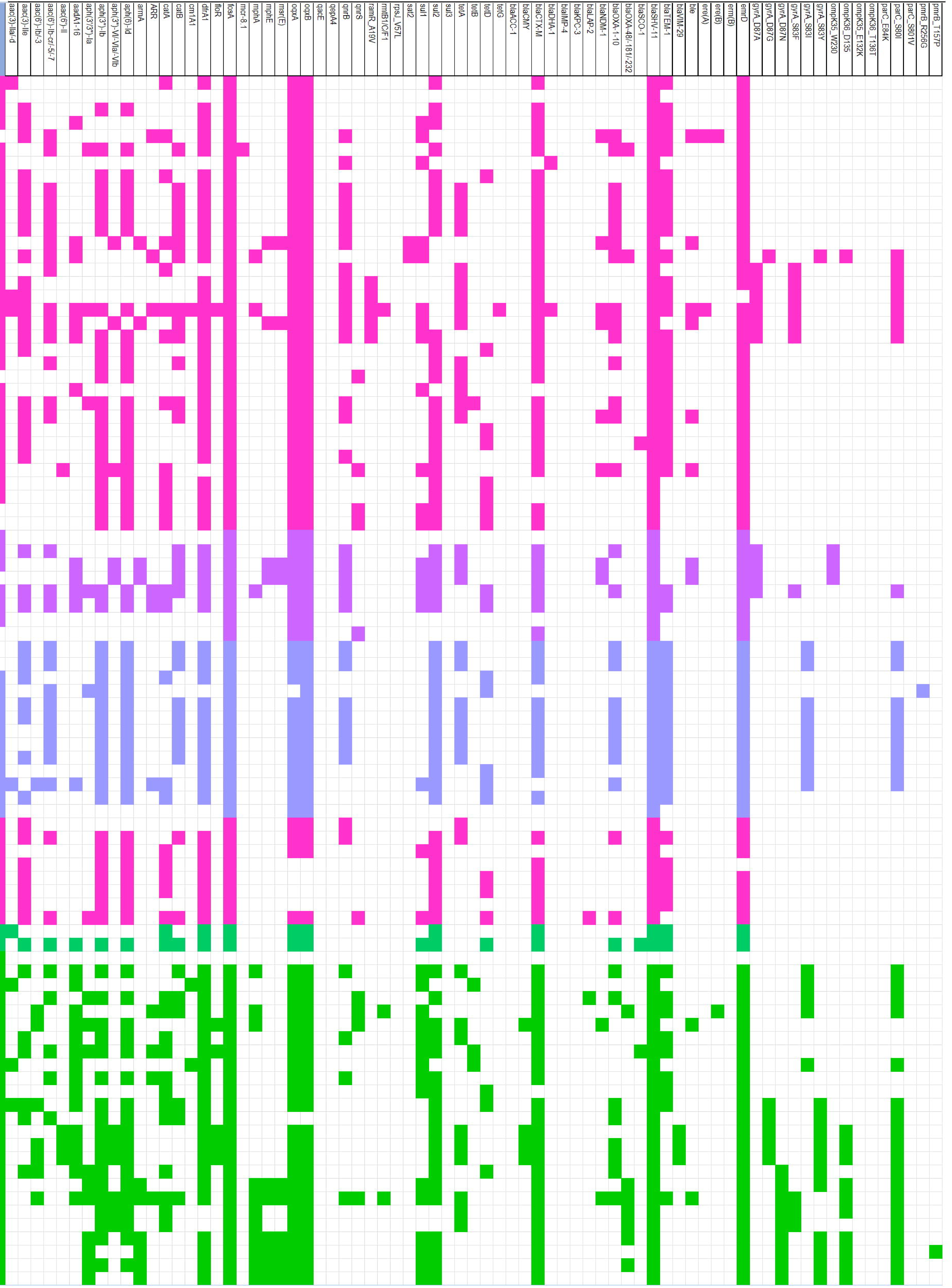
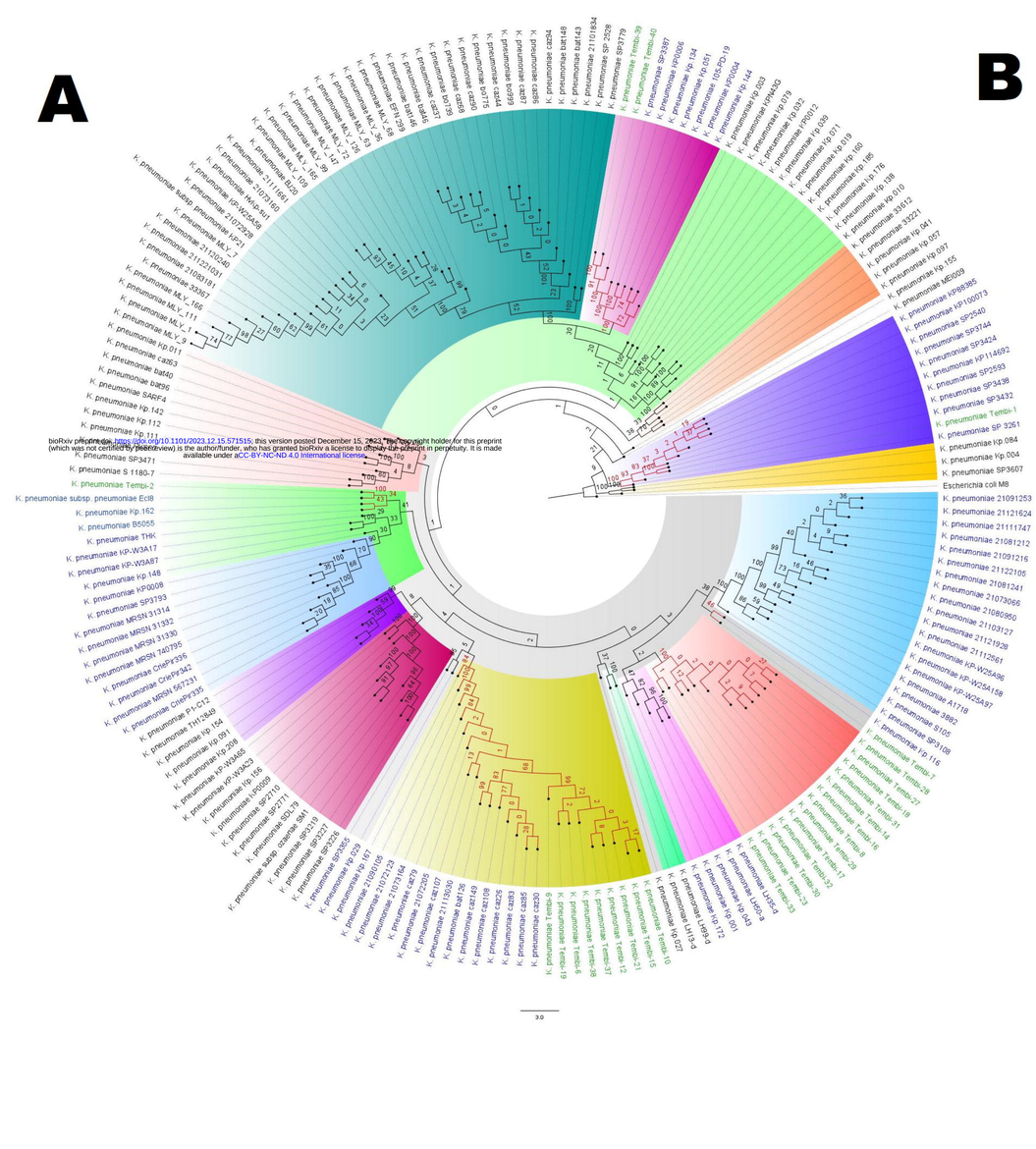


Strain	Related genomes	MLST	country	Px's	Specimen	Year	Host
Africa							
T39 & T40	R0003_320	17	Tanzania		wound swab	2014	Human
	5KP2	17	Sudan		urine	2020-01-01	Human
	AK_800	17	Nigeria		Blood	2015-12-15	Human
	Iso00199	17	Ghana		Chronic wound	2016	Human
	43716	17	Tunisia		seafood	2016	
	KP95	336	Algeria		oral cavity pus	2018-10	Human
	KP0004	17	Ghana		urine	2018	Human
	76	17	Ghana	5	urine	2015	Human
	1337	14	Nigeria		Wound swab	2015	Human
	263	14	Nigeria		Blood	2015	Human
	157	14	Nigeria		Blood	2015	Human
	1628	14	Nigeria		urine	2015	Human
	MRSN368001	14	Kenya		not collected	2015-11-16	Human
	K14	14	Kenya	36	urine	2016-03-16	Human
	2471	15	Nigeria		urine	2015	Human
	C8	15	Nigeria		urine	2015	Human
	C2	15	Nigeria		urine	2015	Human
	MRSN613682	15	Kenya		Enviromental	2018-04-12	Human
	852k	15	Nigeria		urine	2015	Human
	2822	15	Nigeria		Wound swab	2015	Human
	U1	17	Nigeria		urine	2015	Human
	MRSN702261		Kenya		Wound	2019-03-26	Human
	18CMI-B	17	Tanzania		chicken meat	2018-07	
	H39	17	Nigeria		hospital-2, ICU, urine	2019	Human
	P30-61		Malawi		urine	2016-08-10	Human
	2018-MM-ABU-00001	22	Nigeria		Blood	2018	Human
	G4712	17	Nigeria		Blood	2016-07-25	Human
	G3704	17	Nigeria		Blood	2015-03-25	Human
	MM_2436	17	Nigeria		Blood	2015-12-15	Human
	EGKP5	17	Egypt		feces from livestock fa	2015	Cow
	P01563	16	Nigeria		Blood	2010-05-14	Human
	P01805	16	Nigeria		Blood	2010-08-30	Human
	113CSB.N.B	17	Tanzania		stool	2018-07	
	113CSB.F.B	17	Tanzania		stool	2018-07	
T31, T23, T29, T27, T30, T16, T33, T17, T32, T28, T18, T8, T14	RDK43_74	152	Tanzania		wound swab	2013	Human
	117	152	Ghana	33	urine	2015	Human
	MIN-106	152	Ghana			2021-06-10	Human
	PW122	152	Ghana		hospital surface	2021	
	Iso00100	152	Ghana		Chronic wound	2016	Human
	3600	789	Nigeria		urine	2015	Human
	OE54NF	152	Nigeria		stool	2020-02-14	Human
	87CS.F.C	1741	Tanzania		stool	2018-07	
T12, T15, T21, T37, T10, T19, T9, T38, T6	E34A	307	Ghana		dripstand	2021-06-29	
	43699	307	Tunisia		seafood	2016	
	P30-63	307	Malawi		urine	2016-11-01	Human
	MRSN702325	485	Kenya		wound	2019-02-12	Human
	A3	307	Nigeria		Wound swab	2015	Human
	3264	307	Nigeria		urine	2015	Human
	1643k	307	Nigeria		urine	2015	Human
	5854	307	Nigeria		urine	2015	Human
	G3051	307	Nigeria		Blood	2014-06-23	Human
	G3435	307	Nigeria		Blood	2014-10-28	Human
	HH510E21	307	Cameroon		Hand	201(	Human
	P30_63	307	Malawi		urine	2016-11-01	Human
	G1598	587	Nigeria		Blood	2013-08-30	Human
T2	PP5		Madagascar		Sputum	2017	Human
	BEX02-7 46-2ECBU	70	Madagascar			201!	Human
	R0004_II0LF	25	Tanzania		Stool	2014	Human
	AK_905	25	Nigeria		CSF	2016-03-08	Human
	BH2308	25	Nigeria		Blood	2014-09-09	Human
	AK_896	25	Nigeria		Blood	2016-02-29	Human
	P01238	25	Nigeria		Blood	2010-02-12	Human
	G2629	25	Nigeria		Blood	2014-03-17	Human
T7	RDK43_79C	297	Tanzania		wound swab	2013	Human
	P136	1552	Ghana		rectal	2021-07-22	Human
T1	1O11136		Malawi			2011	Human
	BH2511	231	Nigeria		Blood	2014-10-21	Human
	P30-70	231	Malawi		pus	2016-12-14	Human
	RDK39_16	231	Tanzania		wound swab	2013	Human
	CK8	231	Kenya	62	urine	2016-04-01	Human
	KKP2	219	Kenya			2019-02-04	Human
	P30-68	1552	Malawi		urine	2016-10-13	Human
	P30-60	607	Malawi		pus	2016-07-26	Human
	P30-70	231	Malawi		pus	2016-12-14	Human
	R0006_365		Tanzania		wound swab	2014	Human
	G3504	101	Nigeria		Blood	2014-11-12	Human
	P30-72	101	Malawi		pleural fluid	2016-12-09	Human
	P30-65	101	Malawi		Urine	2016-11-22	Human
	SF	101	Egypt			2012	Human
	SK	101	Egypt			2012	Human
	HM	101	Egypt			2012	Human
	PO1407	101	Nigeria		Blood	2010-04-01	Human
	k16 before	101	Egypt			2019-11-25	Human
	k16 after	383	Egypt			2019-12-20	Human
	k14 before	383	Egypt			2018-12-30	Human
	k14 after	383	Egypt			2019-10-30	Human
	k92 before	101	Egypt			2018-10-30	Human
	k92 after	101	Egypt			2018-11-30	Human
	k5 before	101	Egypt			2017-10-30	Human
	k5 after	101	Egypt			2017-11-30	Human



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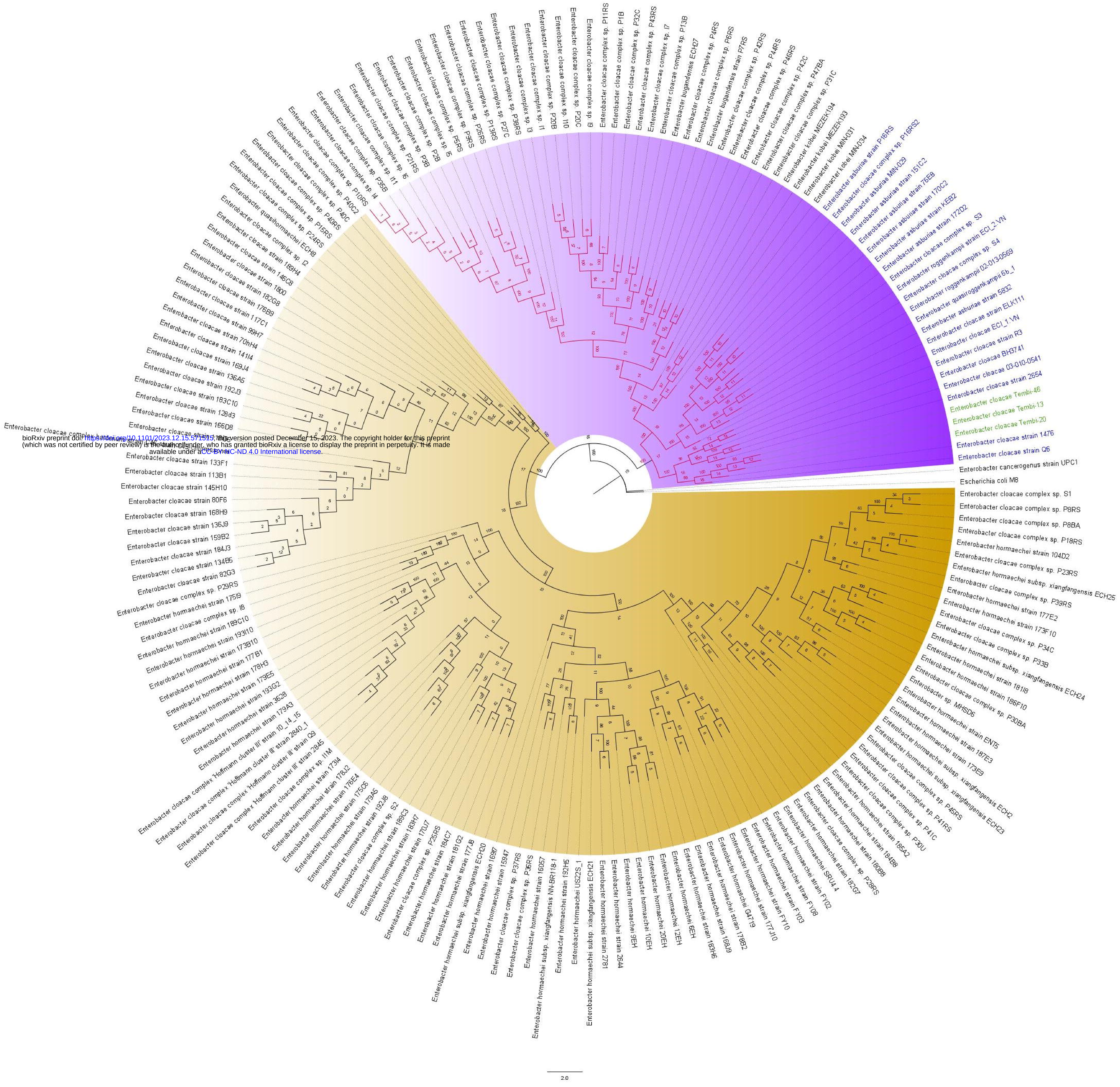
Strain	Related genomes	MLST	country	Px's Specimen	Year	Host	Resistance genes
Global							aac(3)-Ia-d, aac(3)-IIe, aac(6')-Ib-3, aac(6')-Ib-cr-5/-7, aac(6')-II, aadA1-16, aph(3')-Ia, aph(3')-Ib, aph(3')-VI/-VIa/-VIb, aph(6)-Id, armA, ARR, catA, catB, cml1A1, dfrA1, fkpA, floA, mcr-8.1, mphA, mphE, msr(E), oqxA, oqxB, qacE, qnrB, repA4, qnrS, ramR(-A18V, rmtB/-IGF1, rpsJ-V57L, sul1, sul2, sul3, tetA, tetB, tetD, tetG, tetM, tetX-M, tmrB/-HA-1, tmrB/HA-1, tmrB/MP-4, tmrB/PC-3, tmrA/-AP-2, tmrA/-M1, tmrA/OXA-1.10, tmrA/OXA-48/-181/-232, tmrB/SCO-1, tmrB/-EBA-1, tmrA/-EBA-1, tmrA/MIM-29, tmrB, tmrA, tmrB/-1, tmrB/-1, tmrB/-1, tmrB/-1, tmrA/-L667A, tmrA/-L667G, tmrA/-L667N, tmrA/-S83I, tmrA/-S83R, tmrA/-S83Y, tmrA/-W29G, tmrA/K5_D135, tmrA/K5_E132K, tmrA/K6_T136I, tmrC_E54K, tmrC_S80I, tmrC_S80R, tmrC_S80V, tmrE_D29GG, tmrE_T57P
T1	KP88385	231	China	Blood	2018-12-12	Human	
	KP100073	231	China	Blood	2019-06-26	Human	
	SP2540	231	India	Respiratory specimer	2020	Human	
	SP3744	231	India	Respiratory specimer	2020	Human	
	SP3424	231	India	Respiratory specimer	2020	Human	
	KP114692	231	China	Blood	2019-11-23	Human	
	SP2593	231	India	Respiratory specimer	2020	Human	
	SP3438	231	India	Respiratory specimer	2020	Human	
	SP3261	231	India	Respiratory specimer	2020	Human	
	BA32173	231	India	Blood	2020	Human	
	BA29915	231	India	Blood	2020	Human	
	BA37048	231	India	Blood	2019	Human	
	Kp_14 MM	219	South Africa	23 Pus aspirate	2019-11-07	Human	
	SCAID PND1-2022(426	101	Kazakhstan	purulent-necrotic detri	202	Human	
	BL101-1	101	China	Patient17 sputum	2016-06-24	Human	
	BL101-2	101	China	Patient11 sputum	2017-06-08	Human	
	Kp102	43	China	Nasal swab	2018-07-18	Dog	
	Kp145	43	China	Throat swab	2018-11-26	Dog	
T28, T27, T18, T31, T14, T16, T8, T29, T17, T32, T30, T23, T33	SHX180		China	Blood	2018	Human	
	BL105	105	China	Patient2 sputum	2016-01-22	Human	
	Kp37		China	Abscess	2018-06-24	Dog	
T12, T15, T21, T37, T10, T19, T9, T38, T6	batt126	307	Italy	Blood	2021-03-20	Human	
	caz149	307	Italy	Rectal swab	2021-03-25	Human	
	caz108	307	Italy	Bronchial aspirate	2021-01-07	Human	
	K210372	307	China	Stool	2021	Human	
	batt103	307	Italy	Blood	2021-02-05	Human	
	6700160_kpn	307	Israel	Rectal	2022-04-04	Human	
	batt32	307	Italy	Blood	2020-06-27	Human	
	bo438	307	Italy	Blood	2020-04-27	Human	
	Kp_24 MM	307	South Africa	35 tracheal aspirate	2019-09-26	Human	
	Caz89	307	Italy	Rectal swab	2020-11-19	Human	
	batt33	307	Italy	Blood	2020-07-15	Human	
	Caz06	307	Italy	Rectal swab	2020-01-09	Human	
	K210387	307	China	Stool	2021	Human	
	BL307	307	China	Patient5 sputum	2017-11-19	Human	
	KpHUPM-56	307	Spain	urine	202(	Human	
	KpHUPM-86	307	Spain	urine	202(	Human	
	KpHUPM-58	307	Spain	urine	2021-02-04	Human	
	KpHUPM-90	307	Spain	Human rectal swab	2020-07-28	Human	
	Kp_4 MM	307	South Africa	35 urine	2019-01-27		
	Kp118	307	China	Tracheal lavage	2018-06-15	Dog	
	Kp181	307	China	urine	2019-09-19	Dog	
	Kp_15MM	307	South Africa	urine	2019-10-11	Human	
	KW2	766	China	well water	2019-07		
	KW3	766	China	well water	2019-07		
T2	Ecl8	375	USA		1982	Human	
	Kp.162		China	feces	201(	Human	
	B5055	66	Australia		2020	Human	
	KP1138	25	Peru	not collected	2020	Human	
	KP1137	25	Peru	not collected	2020	Human	
	KP4962	25	China	Sputum	202(	Human	
	BL1427	1427	China	Patient6 sputum	2017-09-05	Human	
T39 & T40	SP3387	17	India	Respiratory specimer	2020	Human	
	KP0006	17	Ghana	urine	2018	Human	
	Kp.051	20	China	feces	201(	Human	
	105-PD-19	17	Mexico			Human	
	KP0004	17	Ghana	urine	2018	Human	
	Kp.144	17	China	feces	201(	Human	
	43716	17	Tunisia	Seafood	2016		
	KPA1	16	Thailand		2020-07-18	Dog	
	40558	983	Tunisia	Seafood	2015		
	40560	983	Tunisia	Seafood	2015		
	K210337	1401	China	Sputum	2021	Human	
	19051132	54	China	Sputum		Human	
	KPH1	16	Thailand	microbial	2020	Human	
	KP151	16	China	Urine	2018-08-06	Dog	
	FY25	20	China	Sputum	201(	Human	
	FY20	20	China	Sputum	201(	Human	
	KP68	17	China	Abscess	2018-05-03	Dog	



Strain	Related genomes	MLST	Country/region	Px's age	Specimen	Year	Host
			Africa				
T46, T13, & T20	ELK111	84	Nigeria: Lagos		dry sand	2017-11-05	Dry sand
	ECl_1.VN	84	South Africa: Pretoria	26 yrs	rectal swab	2020-12-10	Human
	R3	156	Nigeria		N/C 4	2015	Human
	BH3741		Nigeria	19 days	blood	2015-09-29	Human
	03-010-0541		Nigeria	58 month	blood	2015-09-28	Human
	2654		Nigeria		urine	2015	Human
	1476	454	Nigeria		urine	2015	
	Q6	187	Nigeria			2015	Human
	SMART_1094	456	Tunisia	76 years		2013	Human
	SMART_1093	456	Tunisia	76 years		2013	Human
	ECLO_716754_SO	456	Togo:Lome	64 years	urine	2016-07-07	Human
	749	456	Togo:Lome	5 years	urine	2016-07-05	Human
	194	456	Ghana: Kumasi	45 years	sputum	2015	Human
	EFN743	456	Ghana		urine	2019	Human
	CC14		Nigeria:Ibadan		water	2015-01	
	CC90		Nigeria:Ibadan		water	2015-01	
	CC80		Nigeria:Ibadan		water	2015-01	
	CC81		Nigeria:Ibadan		water	2015-01	
	898U	156	Togo: Lome	32 years	urine	2016-08-05	
	ECL001	1	Ghana: Accra		urine	2018	Human
	NK-BR1052-1	1	Nigeria		rectal swab	2015/2017	Human
	OE43NF		Nigeria: Osun State		stool	2020-02-13	Human
	HB_Z_2347		Nigeria		Blood	2015-06-11	Human
	Ecl_1.VN	84	South Africa: Pretoria	26 years	rectal swab	2020-12-10	Human
	FACU4	167	Egypt: Borg AlArab city			2019-09	
	ELK111	84	Nigeria: Lagos		dry sand	2017-11-05	
	NK-BR6054-2	84	Nigeria		rectal swab	2015/2017	Human
	UJ_AT_5.1		Nigeria: Sokkoto State		Ant gut	2021	Termites
	170		Ghana: Kumasi	3 years	Scalp abcess aspirate	2015	Human
	UJ_RJK_5.4	475	Nigeria: Sokkoto State		ant gut	2/16/2021	Termites
	R_G5		South Africa: Pretoria	66 years	Intravenous catheter		Human
	40513		France			2015-06-16	Corvus
	40508		France		Pica pica	2015-06-03	
	S20-4		Sudan			2017	fox