Emerging Antimicrobial-Resistant High-Risk Klebsiella pneumoniae Clones ST307 and ST147

Gisele Peirano[a,b], Liang Chen[c,d], Barry N. Kreiswirth [c,d] and Johann D. D. Pitout[a,b,e,*]

[a]Alberta Precision Laboratories, Calgary, Alberta, Canada

[b]University of Calgary, Calgary, Alberta, Canada

[c]Hackensack Meridian Health Center for Discovery and Innovation, Nutley, New Jersey, USA

[d]Hackensack Meridian School of Medicine at Seton Hall University, Nutley, New Jersey, USA

[e]University of Pretoria, Pretoria, Gauteng, South Africa

*Address correspondence to Johann D. D. Pitout, jpitout@ucalgary.ca.

ABSTRACT

There is an enormous global public health burden due to antimicrobial-resistant (AMR) Klebsiella pneumoniae high-risk clones. K. pneumoniae ST307 and ST147 are recent additions to the family of successful clones in the species. Both clones likely emerged in Europe during the early to mid-1990s and, in a relatively short time, became prominent global pathogens, spreading to all continents (with the exception of Antarctica). ST307 and ST147 consist of multiple clades/clusters and are associated with various carbapenemases (i.e., KPCs, NDMs, OXA-48-like, and VIMs). ST307 is endemic in Italy, Colombia, the United States (Texas), and South Africa, while ST147 is endemic in India, Italy, Greece, and certain North African countries. Both clones have been introduced into regions of nonendemicity, leading to worldwide nosocomial outbreaks. Genomic studies showed ST307 and ST147 contain identical *gyrA* and *parC* mutations and likely obtained plasmids with *bla*$_{\text{CTX-M-15}}$ during the early to mid-2000s, which aided in their global distribution. ST307 and ST147 then acquired plasmids with various carbapenemases during the late 2000s, establishing themselves as important AMR pathogens in certain regions. Both clones are likely underreported due to restricted detection methodologies. ST307 and ST147 have the ability to become major threats to public health due to their worldwide distribution, ability to cause serious infections, and association with AMR, including panresistance. The medical community at large, especially those concerned with antimicrobial resistance, should be aware of the looming threat posed by emerging AMR high-risk clones such as K. pneumoniae ST307 and ST147.

KEYWORDS: antimicrobial resistance, high-risk clones

Antimicrobial resistance (AMR) is recognized by the scientific community, society at large, and policymakers as one of the greatest threats to human health. Several fields of modern medicine will not be able to function properly without the availability of effective antibiotics.

Biological evolution is defined as "descent with modification within a defined population" with the sole purpose of adaptation to environmental changes (1). Evolution provides the means for members of a population to adapt, survive, and reproduce in an effective manner. For evolution to progress in an orderly fashion, a process selecting for desirable traits is required. Natural selection is due to the interaction of a population with the environment, while artificial selection mostly occurs due to human intervention. The use of antimicrobial agents, with the subsequent selection of beneficial AMR mutations within bacteria, is one of the most efficient artificial selection pressures introduced by humans. Thus, it should not be surprising that the use of antibiotics has selected for certain successful bacterial clones with the ability to adapt and survive in challenging environments that contain antibiotics.

The major burden of AMR is due to the global spread of certain successful AMR clones (referred to as high-risk, epidemic, eminent, or problem clones) and/or the movement of AMR genes between diverse clones (2). In this article, we refer to these successful clones as high-risk clones. The term "clone" in this context refers to any bacteria propagated from a single colony and isolated at a specific time and place that show common phylogenetic origins (3). Such isolates/strains have similar phenotypic and genotypic traits, indicating they belong to the same lineage originating from a common ancestor. The terms "clone" and "clonal relatedness" are useful in the field of molecular epidemiology, particularly when studying the possible relationships between isolates or strains obtained from different geographical areas over various time periods.

For a clone to qualify as a global AMR high-risk clone, isolates must have similar or identical phenotypic and genotypic characteristics and share the following characteristics (3): (i) they must have been obtained from different geographical locations across the world, (ii) they must possess various AMR determinants, (iii) they must be able to colonize and persist in hosts for long time intervals (at least 6 months), (iv) they must be transferred effectively between different hosts, (v) they must show enhanced pathogenicity and/or fitness, and (vi) they must have the ability to cause severe and/or recurrent infections. It is important to remember that standard definitions of "global" (i.e., how many countries across how many continents), "various AMR determinants" (i.e., the number representing different antibiotic classes), "effective transmission," "enhanced virulence/pathogenicity/fitness," and "severe and/or recurrent infections" (i.e., how many over what time periods) are currently lacking.

High-risk clones likely possess certain beneficial biological factors that lead to increased "fitness," providing the strains with Darwinian survival skills and edging out other isolates of the same species (1). Such skills provide them with the ability to outcompete other bacteria and to become the principal part of the bacterial population, initially as colonizers that subsequently lead to infections.

AMR high-risk clones outcompete other, non-AMR clones in an environment containing antibiotics (1). These clones provide formidable platforms for the dissemination of AMR genetic components (2, 3). AMR determinants are provided to the offspring of high-risk clones in a vertical fashion. High-risk clones can also transfer these determinants to other bacteria in a horizontal fashion. AMR high-risk clones have been instrumental in the recent global emergence of AMR among several bacterial species, especially within the *Enterobacterales*. Examples of established global AMR high-risk clones among the *Enterobacterales* are Escherichia coli ST131 and Klebsiella pneumoniae clonal group 258 (CG258) (i.e., ST258, ST11, and ST512) and CG14 (i.e., ST14 and ST15) (4, 5). Recent

reports have indicated that certain clones (e.g., K. pneumoniae ST307 and ST147; E. coli ST410 and ST1193) are emerging globally as important vehicles for the dissemination of AMR determinants (1, 6, 7).

K. pneumoniae is the most clinically relevant *Klebsiella* species and is responsible for the majority of human infections due to members of the genus. During the 1960s and 1970s, K. pneumoniae established itself as one of the most important causes of global AMR nosocomial infections, especially urinary tract infections (UTIs), respiratory tract infections (RTIs), and bloodstream-associated infections (BSIs), and today, these bacteria often rank among the top five most common global nosocomial pathogens (5). The World Health Organization has recently identified extended-spectrum β-lactamase (ESBL)- and carbapenem-resistant K. pneumoniae isolates as critical public health threats (8). Since reports describing K. pneumoniae ST307 and ST147 are increasing globally and both clones are associated with ESBLs and carbapenemases (the most important causes of carbapenem resistance), the aim of this article is to review the published literature pertaining to ST307 and ST147 and to determine if they qualify as AMR high-risk clones.

KLEBSIELLA PNEUMONIAE ST307

K. pneumoniae ST307 appeared during 2008 in the multilocus sequence typing (MLST) database submitted from the Netherlands (https://bigsdb.pasteur.fr/klebsiella/klebsiella.html). The first published reports occurred in 2013 from the United States (9) and Pakistan (10); the U.S. isolates contained *bla*$_{\text{KPC-2}}$ and were obtained in 2010 from different hospitals in Texas, while the Pakistani isolates contained *bla*$_{\text{CTX-M-15}}$ and were obtained during 2009. This was followed by publications during 2014 and 2015 from Italy (11, 12) and Colombia (13) of isolates with *bla*$_{\text{KPCs}}$ and from South Korea (14) and Tunisia (15) of isolates with *bla*$_{\text{CTX-M-15}}$ and *qnrB*. During 2016, the worldwide appearance of the clone became more apparent, with reports from Spain (16) of isolates with *bla*$_{\text{OXA-48}}$ and from Russia (17), Brazil (18), and Japan (19) of isolates with *bla*$_{\text{CTX-M-15}}$.

ST307 isolates shared the same K and O loci (i.e., KL102, associated with *wzi* allele 173, and O2v2) and contained the second capsule 2 cluster (similar to the capsular cluster of Klebsiella quasipneumoniae and *Enterobacter* spp.), π-fimbrial cluster (similar to that of uropathogenic E. coli), and type VI secretion system (T6SS) (20).

Molecular epidemiology

Wyres and colleagues performed whole-genome sequencing on a collection of ST307 isolates ($n = 95$) with *bla*$_{\text{CTX-M-15}}$ and *bla*$_{\text{KPCs}}$ obtained from 11 countries (21). Their results indicated that ST307 emerged around 1994 and consisted of two deep-branching lineages; one lineage contained the *gyrA* S83I and *parC* S80I mutations in the quinolone resistance determinant regions (QRDR) and showed global distribution (i.e., Australia, Cambodia, Nepal, Thailand, Iran, Italy, Norway, Netherlands, United Kingdom, United States, and Colombia); the other lineage (which contained an additional *gyrA* D87N mutation) was present only in the United States (Texas). There was genomic evidence of intercountry movement of patients infected or colonized with ST307 isolates that belonged to the "global" lineage. The *bla*$_{\text{CTX-M-15}}$ gene was present among 99% of ST307 isolates and was situated adjacent to IS*Ecp1*, harbored within FIB-like plasmids, which were highly similar within the different isolates irrespective of the time period and the geographical location. A closely related FIB-like plasmid, named pKPN3-307_type A, with *bla*$_{\text{CTX-M-15}}$ was previously reported from ST307 isolates obtained in Italy, Colombia, and the United Kingdom (20).

A recent study investigated large country-wide nosocomial outbreaks of ST307 with *bla*$_{\text{CTX-M-15}}$ and *bla*$_{\text{OXA-181}}$ within several South African provinces (22). Sequences obtained from that study and GenBank (n = 708) divided ST307 isolates into six clades: clades I, II, III, and IV were limited to Texas and contained the *gyrA* S83I, *gyrA* D87N, and *parC* S80I QRDR mutations; clade V showed a global distribution; and clade VI was restricted to South Africa (22). Clades V and VI contained the *gyrA* S83I and *parC* S80I QRDR mutations. The Wyres "global" lineage correlated with clade V, and the Wyres "Texas" lineage correlated with clades I to IV (21). ST307 clade VI emerged around March 2013 and then evolved during 2014 into two distinct lineages, which spread over a 15-month period across 23 cities and towns within six South African provinces (22).

Global distribution and prevalence

K. pneumoniae ST307 has true global distribution and has been reported from all continents except Antarctica (Fig. 1). The clone has been responsible for several global nosocomial (23–26) and long-term care center (27, 28) outbreaks. ST307 isolates have been obtained from a variety of human clinical specimens, including urine, blood, respiratory secretions, fluids, and pus (22, 26), as well as from other sources, e.g., human rectal samples (11, 16), companion animals (19), domestic animals (29), wildlife (30), and environmental and sewage water samples (18). Infection was associated with recent travel when a patient returning from Puerto Rico imported ST307 into a hospital in the Dominican Republic (31).

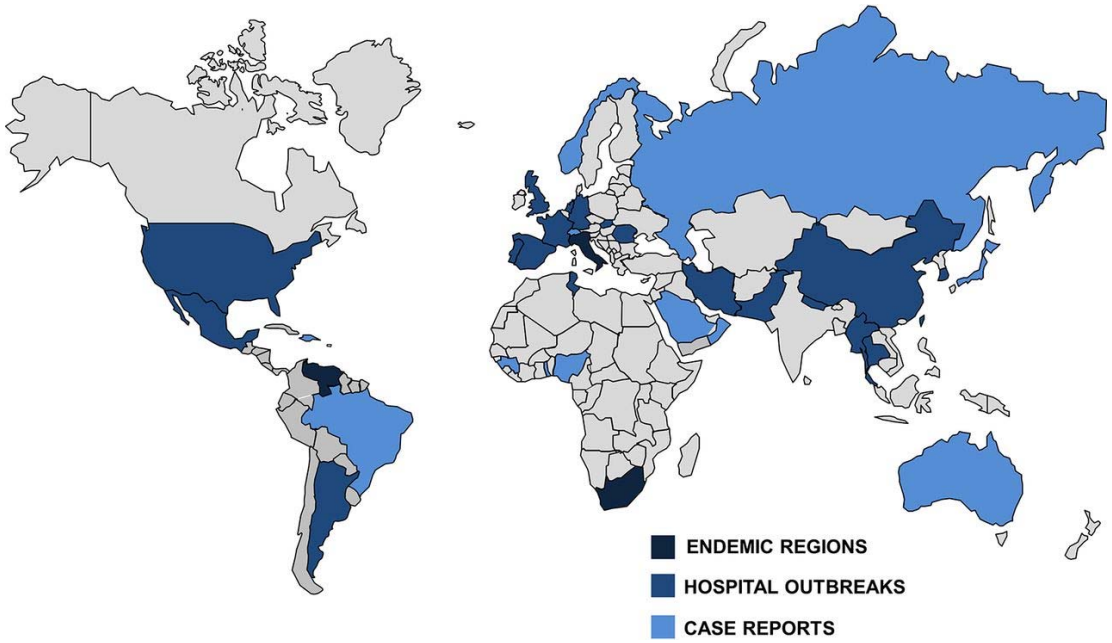

FIG 1 Global distribution of K. pneumoniae ST307.

Reports from the United States (Texas) (32), Colombia (13) Italy (11), and Argentina (33) have shown that the overall prevalence of ST307 is increasing over time among AMR carbapenemase-producing K. pneumoniae isolates, even replacing other AMR high-risk clones, like ST258, in certain regions, such as Italy and Colombia. A South African study showed that ST307 was present among 350/574 (61%) carbapenemase-producing K. pneumoniae isolates obtained from several hospitals from 2014 to 2016, illustrating that the

clone can dominate the population structure of carbapenemase-producing K. pneumoniae during outbreak situations (22).

Association with antimicrobial resistance determinants

K. pneumoniae ST307 is associated with various AMR determinants, including the following ESBLs and carbapenemases: CTX-M-15 (21, 22), KPC-2 and -3 (20, 21), OXA-48 (34), NDM-1 (35), OXA-181 (22), and VIM-1 (36). Carbapenemase genes in ST307 had been found on various plasmid backbone types, e.g., KPCs on pKpQIL and IncN (20), OXA-48 on IncL (22), NDMs on various Inc replicon types, OXA-181 on IncX3 (22), and VIMs on IncFII (26).

The majority of global ST307 isolates reported in the literature contained *bla*$_{\text{CTX-M-15}}$ harbored on highly similar FIB-like plasmids (20–22). These plasmids carried two replicons (FIIK7 and FIB) and contained several additional AMR determinants responsible for resistance to the aminoglycosides [*strA*, *strB*, *aac(3)-IIa*, and *aac(6')Ib-cr*], quinolones (*qnrB1* and *oqxAB*), and other agents (*sul2*, *dfrA14*, *catB3*, and *fosA*) (20–22). Resistance to colistin (due to *mcr-1*) (37) and ceftazidime-avibactam (due to a point mutation in *bla*$_{\text{KPC-2}}$) (38) have also been described among ST307 isolates.

Ability to colonize human hosts

Gut-colonizing isolates are the most common source for K. pneumoniae infections (39). Several studies have shown that symptomatic and asymptomatic patients in the health care setting are colonized with ST307 (11, 16, 26). Prevalence studies of human rectal colonization are currently lacking, and it is unknown whether the prevalence or duration of ST307 intestinal colonization in humans is different from that of other K. pneumoniae clones or isolates.

Effective transmission among hosts

Two South African studies have used genomics to document the transmission of ST307 between patients in the same hospital and between patients who were admitted to various hospitals in different cities and provinces. Genomics combined with admission, discharge, and transfer data showed evidence of intrahospital, interhospital, and interprovincial spread of ST307 due to the movement of patients across 42 hospitals within Gauteng, Mpumalanga, North West, Limpopo, Free State, and Eastern Cape Provinces (22).

ST307 was introduced into a South African public health tertiary-care institution after a patient with ST307 was transferred from a different hospital (26). The clone then spread rapidly to different wards and units despite infection prevention and control measures. The initial ST307 isolate contained an OXA-181 IncX3-harboring plasmid that was subsequently transferred to non-ST307 K. pneumoniae sequence types (STs) (i.e., ST17 and ST29), E. coli, and *Enterobacter* spp. The study highlighted the dual threat associated with high-risk clones containing promiscuous plasmids: ST307 initially spread rapidly to different wards and units and then donated the OXA-181 plasmid to E. coli, *Enterobacter* spp., and other K. pneumoniae clones that were subsequently responsible for separate nosocomial outbreaks (26).

Enhanced pathogenicity and fitness

ST307 isolates are negative for the K. pneumoniae virulence plasmid that encodes salmochelin, aerobactin siderophores, and RmpA/RmpA2. Some isolates are positive for the yersiniabactin siderophore locus and the following virulence factor genes: *fhuA* to *-D*, *fimA-I*, *mrkA* to *-J*, *sitA* to *-D*, and *wabG* (21).

Villa and colleagues postulated that the pKPN-307 IncF plasmids (there are four types, namely, A, B, C, and D) were likely crucial for the evolution of ST307 (20). The largest version of the plasmid, pKPN-307_type A, carried five putative virulence clusters, namely, the *lacZYI* operon, the Fec-like iron(III) dicitrate, the glutathione ABC transport systems, the urea transport system, and the cluster for glycogen synthesis. They suggested that certain characteristics of ST307 present on pKPN-307 IncF plasmids may lead to increased fitness, persistence, and adaptation to the hospital environment and the human host.

Evidence for increased virulence and fitness of ST307 compared to other K. pneumoniae clones or isolates is currently lacking.

Cause of severe or recurrent infections

Information about clinical infections due to ST307 are mostly limited to case reports of nosocomially acquired UTIs, RTIs, and BSIs, often in patients with underlying comorbid conditions. Strydom and colleagues reviewed the clinical data of 59 patients infected or colonized with ST307 (26). In 23 (39%) patients, the isolation of ST307 was considered to represent colonization (as opposed to infection). The most common clinical feature was primary bloodstream infection (54%), followed by urinary tract infection (23%) and pneumonia (23%). The overall crude mortality rate for patients infected with ST307 was 19%. This was a description of cases, and controls were not included.

Summary

K. pneumoniae ST307 is emerging as an important AMR clone and clearly possesses most of the essential characteristics that define a global AMR high-risk clone. Studies regarding pathogenicity, virulence, fitness of ST307 isolates, and the clinical features of patients infected with ST307 are currently limited. The global prevalence of ST307 among AMR and non-AMR K. pneumoniae isolates, as well as rates of human rectal colonization among the hospital and community populations, are absent or scarce in the literature.

KLEBSIELLA PNEUMONIAE ST147

The first published records of K. pneumoniae ST147 appeared in 2008 and 2009, when investigators from Hungary (40) and Spain (41) characterized CTX-M-15-producing isolates and identified a novel clone named ST147. The Hungarian isolates ($n = 46$) were submitted to the local ESBL reference laboratory during 2005 and appeared in the MLST database during 2007 (https://bigsdb.pasteur.fr/klebsiella/klebsiella.html). The ST147 isolates were resistant to the fluoroquinolones due to *gyrA* S83I and *parC* S80I QRDR mutations, and *bla*$_{\text{CTX-M-15}}$ was associated with IS*Ecp1* (40). This was followed by publications from 2011 to 2013 of isolates with *bla*$_{\text{VIMs}}$ and *bla*$_{\text{KPC-2}}$ from Greece (42, 43) and Italy (44, 45); of isolates with *bla*$_{\text{VIMs}}$ from Sweden and Denmark (46); of isolates with *bla*$_{\text{NDM-1}}$ from Canada (47), the United Kingdom (48), and Finland (49); of isolates with *bla*$_{\text{OXA-181}}$ and *bla*$_{\text{NDM-1}}$ from India (44); and of isolates with *bla*$_{\text{OXA-48}}$ from Libya (50). The patients from Finland and Canada had recently traveled to India (51), and those from Sweden and Denmark had recently visited

Greece (46). During 2014, the worldwide appearance of this clone escalated, with reports from China (52), Australia (53), Yemen (54), the United States (55) (of isolates with *bla*$_{\text{NDMs}}$), andFrance (of isolates with *bla*$_{\text{OXA-48}}$) (56), as well as Cuba (57), Portugal (58), and Brazil (59) (of isolates with *bla*$_{\text{CTX-M-15}}$).

ST147 isolates have K loci associated with different *wzi* alleles, namely, 64 (the most common, K14 and K64), 12, 14, 23, 56, 99, 420, and 448, and contain conservative arrays in CRISPR region 1 common to all members of ST147 (60).

Molecular epidemiology

Limited information is currently available about the molecular epidemiology of K. pneumoniae ST147. Chen and colleagues performed the largest genomic study to date (61). They defined the evolution and global epidemiology of ST147 isolates ($n = 61$) obtained from 23 countries (United Kingdom, Norway, China, Philippines, Canada, Germany, Italy, Turkey, Argentina, Greece, France, Israel, Romania, Russia, Belgium, India, Switzerland, Iraq, Kenya, United States, United Arab Emirates, Singapore, and Australia) across five continents collected from 2002 to 2015. All ST147 isolates contained the *gyrA* S83I and *parC* S80I QRDR mutations, and phylogenetic analysis separated them into six different clades, which correlated strongly with geographic locations and types of carbapenemase genes (i.e., ST147 isolates with *bla*$_{\text{NDMs}}$, *bla*$_{\text{KPCs}}$, *bla*$_{\text{OXA-48}}$, *bla*$_{\text{OXA-181}}$, and *bla*$_{\text{VIMs}}$ formed separate clusters). The study also showed intercountry movement of patients (e.g., isolates with *bla*$_{\text{NDMs}}$ obtained from India, Canada, the United States, and the United Kingdom were highly similar).

ST147 emerged around the early 1990s, and its global dispersion occurred during the late 1990s and early 2000s, primarily driven by QRDR mutations and the acquisition of *bla*$_{\text{CTX-M-15}}$ located on IncF or IncR plasmids (61). Further global spread of ST147 then occurred in the mid- to late 2000s and was associated with the acquisition of various carbapenemase genes at different geographic locations, e.g., *bla*$_{\text{VIM}}$ and *bla*$_{\text{KPC}}$ were likely acquired in Greece and then spread to Italy, Sweden, and Denmark (46); *bla*$_{\text{OXA-48}}$ was likely acquired in Libya and Tunisia and then spread to various countries in Europe, while *bla*$_{\text{NDM}}$ and *bla*$_{\text{OXA-181}}$ were likely acquired in India and then spread to the United Arab Emirates, Canada, and the United States (61–64).

Global distribution and prevalence

K. pneumoniae ST147 has true global distribution and has been reported from all the continents except Antarctica (Fig. 2). The clone has been responsible for several global nosocomial outbreaks (65–68), including endoscopy-associated transmission (69)] and long-term care center outbreaks (70). ST147 isolates have been obtained from a variety of human clinical specimens, including urine, blood, respiratory secretions, fluids, and pus (65–68), as well as from other sources, e.g., human rectal samples (71), companion animals (72, 73), domestic animals (74), and environmental samples (75). Infections have also been associated with recent travel to certain regions of endemicity. For example, patients returning from Tunisia imported ST147 to hospitals in Poland (76), and patients with recent travel to India and Greece introduced ST147 to Canada (51), the United States (63), Sweden, and Denmark (46).

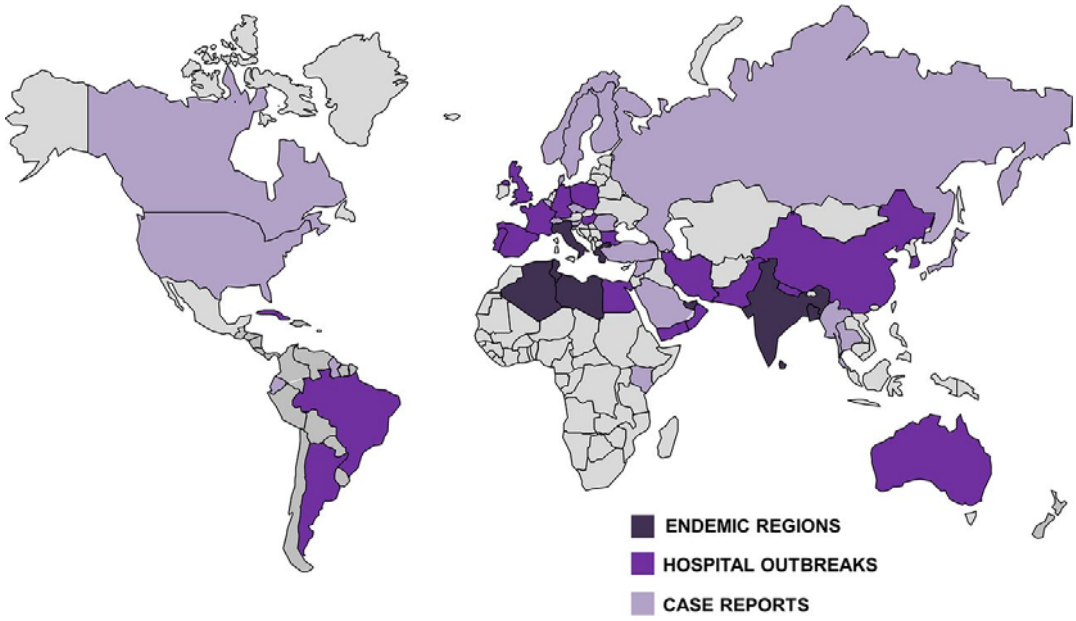

FIG 2 Global distribution of K. pneumoniae ST147.

Studies addressing the prevalence of ST147 among K. pneumoniae isolates are relatively rare. Studies from Hungary have shown that over 20% of ESBL-producing K. pneumoniae isolates belong to ST147 (40). A Canadian longitudinal study investigating bloodstream infections due to ESBL-producing K. pneumoniae over a 10-year period (2000 to 2009) found ST147 to be rare in that collection (77). Global molecular surveillance data showed that ST147 in general is the most common clone among VIM-producing K. pneumoniae (78) and the second most common clone among KPC-producing K. pneumoniae isolates (behind CG258) (42, 62).

Association with antimicrobial resistance determinants

K. pneumoniae ST147 is especially successful in acquiring various types of AMR determinants, including the following ESBLs and carbapenemases: SHV-2 (79), SHV-5 (78), SHV-36 (64), CTX-M-15 (40), KPCs (62), NDMs (47), VIMs (46), OXA-48 (56), OXA-181 (44), and OXA-204 (69). Carbapenemase genes in ST147 have been found on various plasmid incompatibility types, including the following: *bla*$_{\text{KPCs}}$ on pKpQIL (42) and IncN (70); *bla*$_{\text{VIMs}}$ on IncN and IncFII$_{\text{K}}$; (46), *bla*$_{\text{NDMs}}$ on various platforms, including IncFIIA (47), IncA/C (48), and IncX3 (52); *bla*$_{\text{OXA-48}}$ on IncL (56); and *bla*$_{\text{OXA-204}}$ on IncA/C (69). Studies have shown integration of *bla*$_{\text{OXA-181}}$ into the chromosome of ST147 (63, 64).

Similar to ST307, the majority of ST147 isolates reported in the literature contained *bla*$_{\text{CTX-M-15}}$. However, limited information is currently available on the plasmid structure harboring *bla*$_{\text{CTX-M-15}}$ in ST147; a study from Germany using long-read sequencing characterized a 61-kb IncR plasmid containing *bla*$_{\text{CTX-M-15}}$ with several additional AMR determinants responsible for resistance to the aminoglycosides (*strA* and *strB*), quinolones (*qnrS1*), and other agents [*tet*(A) and *dfrA1*] (80).

Various AMR determinants have been identified in ST147, including *aph(3")-Ib*, *aph(6)-Id*, *aadA1*, *aac(3)-II*, *aac(6')-Ib-cr*, *aacA4*, *aacA7*, *aadA1*, *armA rmtF*, *rmtC qnrA1*, *qnrB1-2*, *oqxAB rmtB*, *rmtF*, *qac*Δ*E*, *cepA*, *arr-2*, *dfrA14*, *sul1*, *sul2*, *fosA6*, and heavy metal resistance genes, namely, *ars* and *sil*.

Of special concern are panresistant isolates (including resistance to colistin and tigecycline) that have been described in the United Arab Emirates (64) and Greece (81).

Ability to colonize human hosts

Studies have shown that symptomatic and asymptomatic patients in the health care setting are rectally colonized with ST147, especially during outbreak situations (71, 82). Prevalence studies of human rectal colonization are currently lacking, and it is unknown whether the prevalence or duration of intestinal colonization in humans is different for ST147 than for other K. pneumoniae clones or isolates.

Effective transmission among hosts

Several studies have described the efficient transmission of K. pneumoniae ST147 between patients in the hospital setting. Studies from Greece (67), China (82), and Slovenia (83) described the successful spread of ST147 throughout different health care institutions after the introduction of an index patient colonized or infected with ST147. The clone quickly spread within the same intensive care unit (ICU) or ward and then to different ICUs/wards within the same hospital. The greatest interhospital spread occurred in Singapore (84).

Enhanced pathogenicity and fitness

As noted for ST307, most ST147 isolates are negative for the *Kp* virulence plasmid (encoding the salmochelin and aerobactin siderophores plus RmpA/RmpA2). Some isolates are positive for the yersiniabactin siderophore locus and the plasmid-mediated virulence gene *rmpA*. Overall, ST147 isolates are often positive for the following virulence factor genes: *iutABCD-iucABCD*, *mrkABCDF*, *fimH*, *wabG*, *uge*, *fyuA*, *ybtS*, *kfuB*, *ureA*, and *alls* (44, 64, 85).

Toth and colleagues investigated the fitness of high-risk clones (i.e., ST11, ST15, and ST147) using a propagation assay and showed significantly less fitness cost associated with fluoroquinolone-resistant ST11, ST15, and ST147 due to *gyrA* and *parC* QRDR mutations than with fluoroquinolone-resistant non-high-risk K. pneumoniae clones (86).

A French study showed similar biofilm production and environmental survival of ST147 and the non-high-risk clone ST395 (87).

Cause of severe or recurrent infections

Information about clinical infections due to ST147 is mostly limited to case reports of nosocomially acquired UTIs, RTIs, and BSIs, and often in patients with underlying comorbid conditions. A study from Northern Greece reviewed the clinical characteristics of patients infected with ST147 admitted to different ICUs (67). Of the 25 patients with positive cultures for ST147, 17 (68%) developed BSIs, with a crude mortality rate of 59% among the patients. The overall mortality of the patients during the outbreak with ST147 was 48% (67). Another Greek study, from Piraeus, described BSIs involving 4 patients with panresistant ST147 isolates who had undergone surgery prior to their transfer to the ICU (60). One of the 4 patients died due to the BSI.

Summary

K. pneumoniae ST147 is emerging as an important AMR clone and clearly possesses most of the essential characteristics that define a global AMR high-risk clone. Studies regarding the molecular epidemiology, pathogenicity, virulence, and fitness of ST147 isolates and the clinical features of patients infected with ST147 are currently limited. Reports of the

global prevalences of ST147 among AMR and non-AMR K. pneumoniae isolates, as well as rates of human rectal colonization among the hospital and community population, are absent or rare in the literature.

CONCLUSIONS

The presence of AMR isolates among "classic/nonhypervirulent" K. pneumoniae isolates is relatively common, but only limited clones (especially those that belong to CG258 and CG14) have the necessary attributes to qualify as high-risk clones (88). However, sparse information is available about which specific features of high-risk clones have enabled them to become such successful global pathogens in relatively short times (3). There is an enormous public health burden due to K. pneumoniae AMR high-risk clones, and they have played pivotal roles in the global spread of AMR (5). The basic biological mechanisms responsible for the overall success of high-risk clones remain poorly understood. This lack of information has limited the ability of the medical community to develop strategies for curbing the dissemination of such clones (3).

Genomic studies have suggested that certain AMR determinants, virulence factors, and fitness might be important factors for the success of AMR high-risk clones (2). It is also likely that mobile genetic elements, such as plasmids, contributed to the diversification and "clonalization" of the K. pneumoniae population in general (88).

The roles of virulence factors in the global dominance of certain high-risk AMR clones among classic/nonhypervirulent K. pneumoniae infections are murky at best. It is plausible that fitness is pivotal for the continued success of AMR high-risk clones, even in antibiotic-free environments. Fuzi and colleagues recently proposed that the roles of multiple stepwise mutations in *gyrA* and *parC* were central to favorable fitness (defined as "greater speed of replication") for successful clones among Staphylococcus aureus, K. pneumoniae (i.e., CC15), E. coli, and Clostridioides difficile (89). Low levels of fluoroquinolones, likely in the environment, played an important role in the initial selection of certain stepwise QRDR mutations with subsequent minimal effects on the burden and fitness normally associated with AMR (89).

Global surveillance data regarding the prevalence of high-risk clones among K. pneumoniae populations are biased toward certain regions and countries with the financial capacity and the necessary expertise to perform large-scale genomic surveillance studies that are able to identify AMR high-risk clones. Low- and middle-income countries (LMICs), in general, lack the necessary funds and capability to perform such genomic surveillance studies. This has hampered the medical community's understanding of the true prevalence and global distribution of such clones.

K. pneumoniae ST307 and ST147 are recent additions to the family of successful clones in the species (Table 1). Both clones appeared in the K. pneumoniae MLST database in the late 2000s and in a relatively short time became prominent global pathogens, spreading to all the continents (with the exception of Antarctica) (Fig. 1 and 2). ST307 and ST147 are associated with various carbapenemases (KPCs, NDMs, OXA-48-like, and VIMs). ST307 is endemic in Italy, Colombia, Texas, and South Africa, while ST147 is endemic in India, Italy, Greece, and certain North African countries. Both clones have been introduced into regions of nonendemicity, leading to various worldwide nosocomial outbreaks.

TABLE 1 Characteristics of K. pneumoniae ST307 and ST147

Characteristic	Description[a]	
	ST307	**ST147**
Country of isolation	Netherlands	Hungary
Yr of isolation	2008	2005
Regions of endemicity	Italy, Colombia, South Africa	Italy, Greece, Algeria, Tunisia, Libya, India, United Arab Emirates
Countries with hospital outbreaks	USA (Texas), Argentina, Portugal, Spain, France, UK, Germany Netherlands, Slovenia, Iran, Romania, Pakistan, China, Nepal, Thailand, Taiwan, South Korea, Mexico, Cambodia	Brazil, Argentina, Portugal, Spain, France, UK, Germany, Poland, Bulgaria, Hungary, Iran, Oman, Yemen, Pakistan, Nepal, China, Australia, South Korea
Countries with case reports	Brazil, Guinea, Austria, Saudi Arabia, Oman, Yemen, Japan, Australia	Canada, USA, Ecuador, Venezuela, Denmark, Sweden, Norway, Finland, Switzerland, Czech Republic, Saudi Arabia, Lebanon, Japan, Thailand, Cambodia
AMR determinants		
β-Lactamases	Various; most prominent are CTX-M-15, KPCs, NDMs, OXA-48, OXA-181, VIMs	Various; most prominent are SHVs ESBLs, CTX-M-15, KPCs, NDMs, OXA-48, OXA-181, OXA-204, VIMs
Others	*gyrA* 83I, *parC* 80I, multiple others	*gyrA* S83I, *parC* S80I, multiple others
Molecular epidemiology	Emerged in early 1990s; associated with $bla_{\text{CTX-M-15}}$	Emerged in early 1990; associated with $bla_{\text{CTX-M-15}}$
	Six clades: I–IV (USA [Texas]), V (global), VI (South Africa)	Limited information about clades; six identified that correlated with location
	Various genetic environments and plasmid platforms	Various genetic environments and plasmid platforms
Acquisition	Nosocomial with intra- and interhospital spread between cities and provinces, LTCFs	Nosocomial with intra and inter hospital spread, LTCFs
Types of infection	Colonization, BSIs, UTIs, RTIs	BSIs, UTIs, RTIs, Colonization
Mortality	Limited information; 19%	Limited information; 48–59%
AMR high-risk clone	Yes	Yes

[a]LTCFs; long-term care facilities.

ST307 and ST147 share strikingly similar features (Table 1). Both clones likely emerged in Europe during the early to mid-1990s, following the introduction of ciprofloxacin into clinical medicine. Genomic studies have shown that they contained identical *gyrA* and *parC* mutations and likely obtained IncF or IncR plasmids with $bla_{\text{CTX-M-15}}$ in the early to mid-2000s, which aided in the global spread of both clones (Fig. 3). In certain regions, they also acquired plasmids with various carbapenemases, likely during the late 2000s and early 2010s (e.g., bla_{NDM} and $bla_{\text{OXA-181}}$ were likely acquired in India; bla_{KPCs} was likely acquired in Greece, Italy, Texas, and Colombia, while $bla_{\text{OXA-48}}$ was likely acquired in North Africa [Fig. 3]). These additional carbapenem resistance determinants enabled ST307 and ST147 to establish themselves as important endemic pathogens in certain regions of Greece, Italy, Colombia, India, and South Africa.

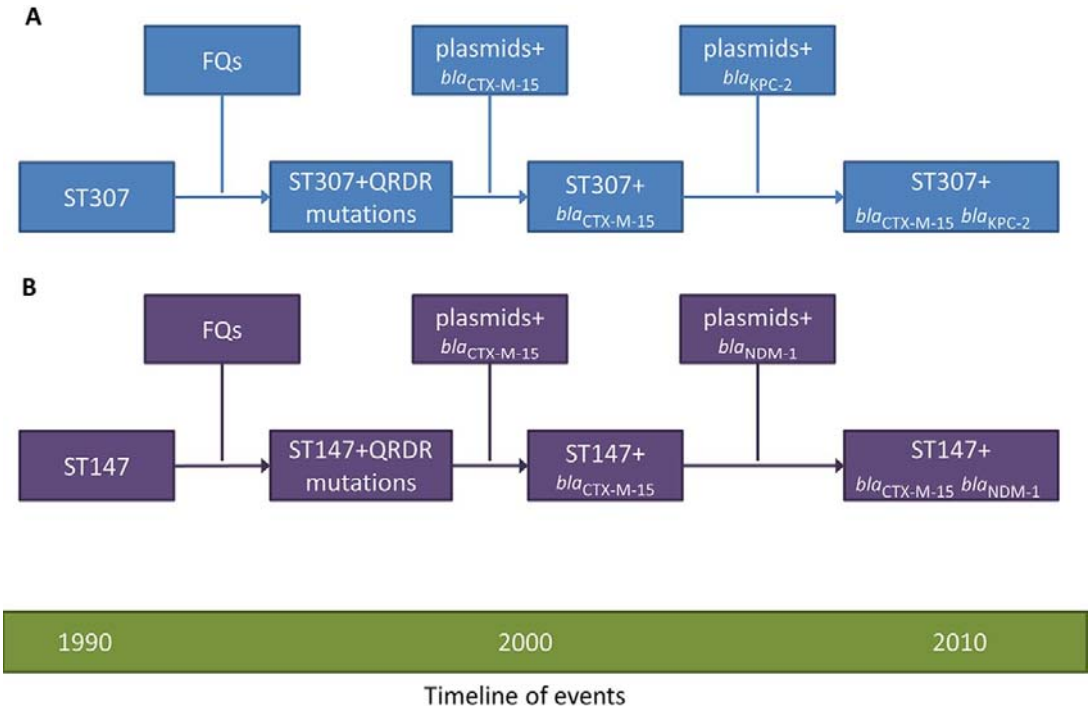

FIG 3 Stepwise progression of K. pneumoniae ST307 and ST147 toward carbapenem resistance. (A) K. pneumoniae ST307 likely emerged during the mid-1990s, and its global dispersion occurred during the early 2000s, driven primarily by the acquisition of $bla_{CTX-M-15}$ located on highly similar FIB-like plasmids, which aided in the global spread. In certain regions, ST307 also acquired plasmids with various carbapenemases (especially KPCs) during the late 2000s and early 2010s (e.g., bla_{KPC-2} was likely acquired in Greece, Italy, Texas, and Colombia). (B) K. pneumoniae ST147 likely emerged around the early 1990s, and its global dispersion occurred during the late 1990s and early 2000s, primarily driven by the acquisition of $bla_{CTX-M-15}$ located on IncF or IncR plasmids. Further global spread of ST147 then occurred in the mid- to late 2000s and was associated with the acquisition of various carbapenemases at different geographic locations (e.g., bla_{NDM-1} was likely acquired in India).

This brings up some intriguing issues regarding the stepwise progression of high-risk clones toward carbapenem resistance. Previous studies have shown that fluoroquinolone resistance due to QRDR mutations, combined with the acquisition of IncF plasmids containing $bla_{CTX-M-15}$, was pivotal in the global dominance of E. coli ST131 clade C (1). It seems that a similar scenario unfolded with K. pneumoniae ST307 and ST147, namely, the initial selection of fluoroquinolone resistance due to stepwise QRDR mutations followed by acquisition of plasmids containing $bla_{CTX-M-15}$ (Fig. 3). Carbapenemases are currently relatively rare among E. coli ST131 isolates (90). K. pneumoniae ST307 and ST147, though, took the additional step toward panresistance and established themselves as important vectors and reservoirs of AMR determinants in certain regions of Greece, Italy, Colombia, and South Africa (Fig. 1 to 3).

Basic mechanistic, evolutionary, surveillance, and clinical studies are urgently required to investigate the reasons for the success and high transmission rates of these high-risk clones. K. pneumoniae ST307 clade VI spread rapidly and seemingly effortlessly between various hospitals across South Africa, despite infection and prevention measures (22). A PCR for the detection of ST307 clade VI has been published and was used to track the clade throughout northeastern South Africa (22, 26). The medical community needs similar approaches for the rapid and cost-effective detection of K. pneumoniae high-risk clones, including all ST307 clades and ST147. Such approaches will provide essential

information on the global prevalence and distribution of K. pneumoniae high-risk clones, including LMICs.

The use of antimicrobial agents will continue to create selection pressure that enhances the risk for the selection of AMR high-risk clones and provides opportunities for them to cause infections, especially in immunocompromised patients. Research projects addressing which features are important for the success of such clones are currently lacking and need to be funded. Such projects will serve as models to predict what can possibly happen in the future with the continuing emergence of successful clones among clinically relevant bacteria.

ACKNOWLEDGMENTS

This work was supported by a research grant from the JPIAMR/Canadian Institute Health Research program (10016015 to J.D.D.P.) and National Institutes of Health grants R01AI090155 (B.N.K.) and R21AI117338 (L.C.).

We have no conflicts of interest pertaining to the manuscript.

REFERENCES

1. Pitout JDD, Finn TJ. 2020. The evolutionary puzzle of *Escherichia coli* ST131. *Infect Genet Evol* 81:104265.

2. Baker S, Thomson N, Weill FX, Holt KE. 2018. Genomic insights into the emergence and spread of antimicrobial-resistant bacterial pathogens. *Science* 360:733–738.

3. Mathers AJ, Peirano G, Pitout JD. 2015. The role of epidemic resistance plasmids and international high-risk clones in the spread of multidrug-resistant Enterobacteriaceae. *Clin Microbiol Rev* 28:565–591.

4. Pitout JD, DeVinney R. 2017. *Escherichia coli* ST131: a multidrug-resistant clone primed for global domination. *F1000Res* 6:195.

5. Wyres KL, Lam MMC, Holt KE. 2020. Population genomics of *Klebsiella pneumoniae*. *Nat Rev Microbiol* 18:344–359.

6. Manges AR, Geum HM, Guo A, Edens TJ, Fibke CD, Pitout JDD. 2019. Global extraintestinal pathogenic *Escherichia coli* (ExPEC) Lineages. *Clin Microbiol Rev* 32:e00135-18.

7. Pitout JDD, Peirano G, Kock MM, Strydom KA, Matsumura Y. 2019. The global ascendency of OXA-48-type carbapenemases. *Clin Microbiol Rev* 33:e00102-19.

8. World Health Organization. 2017. Global priority list of antibiotic-resistant bacteria to guide research, discovery and development of new antibiotics. https://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/.

9. Castanheira M, Farrell SE, Wanger A, Rolston KV, Jones RN, Mendes RE. 2013. Rapid expansion of KPC-2-producing *Klebsiella pneumoniae* isolates in two Texas hospitals due to clonal spread of ST258 and ST307 lineages. *Microb Drug Resist* 19:295–297.

10. Habeeb MA, Haque A, Nematzadeh S, Iversen A, Giske CG. 2013. High prevalence of 16S rRNA methylase RmtB among CTX-M extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* from Islamabad, Pakistan. *Int J Antimicrob Agents* 41:524–526.

11. Bonura C, Giuffre M, Aleo A, Fasciana T, Di Bernardo F, Stampone T, Giammanco A, Palma DM, Mammina C, MDR-GN Working Group. 2015. An update of the evolving epidemic of blaKPC carrying *Klebsiella pneumoniae* in Sicily, Italy, 2014: emergence of multiple non-ST258 clones. *PLoS One* 10:e0132936.

12. Gona F, Barbera F, Pasquariello AC, Grossi P, Gridelli B, Mezzatesta ML, Caio C, Stefani S, Conaldi PG. 2014. In vivo multiclonal transfer of bla(KPC-3) from K*lebsiella pneumoniae* to *Escherichia coli* in surgery patients. *Clin Microbiol Infect* 20:O633–O635.

13. Ocampo AM, Chen L, Cienfuegos AV, Roncancio G, Chavda KD, Kreiswirth BN, Jimenez JN. 2016. A two-year surveillance in five Colombian tertiary care hospitals reveals high frequency of non-CG258 clones of carbapenem-resistant *Klebsiella pneumoniae* with distinct clinical characteristics. *Antimicrob Agents Chemother* 60:332–342.

14. Park DJ, Yu JK, Park KG, Park YJ. 2015. Genotypes of ciprofloxacin-resistant *Klebsiella pneumoniae* in Korea and their characteristics according to the genetic lineages. *Microb Drug Resist* 21:622–630.

15. Mansour W, Grami R, Ben Haj Khalifa A, Dahmen S, Chatre P, Haenni M, Aouni M, Madec JY. 2015. Dissemination of multidrug-resistant blaCTX-M-15/IncFIIk plasmids in *Klebsiella pneumoniae* isolates from hospital- and community-acquired human infections in Tunisia. *Diagn Microbiol Infect Dis* 83:298–304.

16. Ruiz-Garbajosa P, Hernández-García M, Beatobe L, Tato M, Méndez MI, Grandal M, Aranzábal L, Alonso S, López MÁ, Astray J, Cantón R. 2016. A single-day point-prevalence study of faecal carriers in long-term care hospitals in Madrid (Spain) depicts a complex clonal and polyclonal dissemination of carbapenemase-producing Enterobacteriaceae. *J Antimicrob Chemother* 71:348–352.

17. Lazareva IV, Ageevets VA, Ershova TA, Zueva LP, Goncharov AE, Darina MG, Svetlichnaya YS, Uskov AN, Sidorenko SV. 2016. Prevalence and antibiotic resistance of carbapenemase-producing Gram-negative bacteria in Saint Petersburg and some other regions of the Russian federation. *Antibiot Khimioter* 61:28–38.

18. Dropa M, Lincopan N, Balsalobre LC, Oliveira DE, Moura RA, Fernandes MR, da Silva QM, Matté GR, Sato MIZ, Matté MH. 2016. Genetic background of novel sequence types of CTX-M-8- and CTX-M-15-producing *Escherichia coli* and *Klebsiella pneumoniae* from public wastewater treatment plants in Sao Paulo, Brazil. *Environ Sci Pollut Res Int* 23:4953–4958.

19. Harada K, Shimizu T, Mukai Y, Kuwajima K, Sato T, Usui M, Tamura Y, Kimura Y, Miyamoto T, Tsuyuki Y, Ohki A, Kataoka Y. 2016. Phenotypic and molecular characterization of antimicrobial resistance in *Klebsiella* spp. isolates from companion animals in Japan: clonal dissemination of multidrug-resistant extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*. *Front Microbiol* 7:1021.

20. Villa L, Feudi C, Fortini D, Brisse S, Passet V, Bonura C, Endimiani A, Mammina C, Ocampo AM, Jimenez JN, Doumith M, Woodford N, Hopkins K, Carattoli A. 2017. Diversity, virulence, and antimicrobial resistance of the KPC-producing *Klebsiella pneumoniae* ST307 clone. *Microb Genom* 3:e000110.

21. Wyres KL, Hawkey J, Hetland MAK, Fostervold A, Wick RR, Judd LM, Hamidian M, Howden BP, Lohr IH, Holt KE. 2019. Emergence and rapid global dissemination of CTX-M-15-associated *Klebsiella pneumoniae* strain ST307. *J Antimicrob Chemother* 74:577–581.

22. Lowe M, Kock MM, Coetzee J, Hoosien E, Peirano G, Strydom KA, Ehlers MM, Mbelle NM, Shashkina E, Haslam DB, Dhawan P, Donnelly RJ, Chen L, Kreiswirth BN, Pitout JDD. 2019. *Klebsiella pneumoniae* ST307 with blaOXA-181, South Africa, 2014–2016. *Emerg Infect Dis* 25:739–747.

23. Baek EH, Kim SE, Kim S, Lee S, Cho OH, In Hong S, Shin JH, Hwang I. 2020. Successful control of an extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* ST307 outbreak in a neonatal intensive care unit. *BMC Infect Dis* 20:166.

24. Haller S, Kramer R, Becker K, Bohnert JA, Eckmanns T, Hans JB, Hecht J, Heidecke CD, Hubner NO, Kramer A, Klaper K, Littmann M, Marlinghaus L, Neumann B, Pfeifer Y, Pfennigwerth N, Rogge S, Schaufler K, Thurmer A, Werner G, Gatermann S. 2019. Extensively drug-resistant Klebsiella pneumoniae ST307 outbreak, north-eastern Germany, June to October 2019. *Euro Surveill* 24:1900734.

25. Perdigao J, Modesto A, Pereira AL, Neto O, Matos V, Godinho A, Phelan J, Charleston J, Spadar A, de Sessions PF, Hibberd M, Campino S, Costa A, Fernandes F, Ferreira F, Correia AB, Goncalves L, Clark TG, Duarte A. 2020. Whole-genome sequencing resolves a polyclonal outbreak by extended-spectrum beta-lactam and carbapenem-resistant *Klebsiella pneumoniae* in a Portuguese tertiary-care hospital. *Microb Genom* doi:

26. Strydom KA, Chen L, Kock MM, Stoltz AC, Peirano G, Nobrega DB, Lowe M, Ehlers MM, Mbelle NM, Kreiswirth BN, Pitout JDD. 2020. *Klebsiella pneumoniae* ST307 with OXA-181: threat of a high-risk clone and promiscuous plasmid in a resource-constrained healthcare setting. *J Antimicrob Chemother* 75:896–902.

27. Boonstra MB, Spijkerman DCM, Voor In 't Holt AF, van der Laan RJ, Bode LGM, van Vianen W, Klaassen CHW, Vos MC, Severin JA. 2020. An outbreak of ST307 extended-spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumoniae* in a rehabilitation center: An unusual source and route of transmission. *Infect Control Hosp Epidemiol* 41:31–36.

28. Giufre M, Accogli M, Ricchizzi E, Barbanti F, Farina C, Fazii P, Mattei R, Sarti M, Barozzi A, Buttazzi R, Cosentino M, Nardone M, Savini V, Spigaglia P, Moro ML, Cerquetti M. 2018. Multidrug-resistant infections in long-term care facilities: extended-spectrum beta-lactamase-producing Enterobacteriaceae and hypervirulent antibiotic resistant *Clostridium difficile*. *Diagn Microbiol Infect Dis* 91:275–281.

29. Loncaric I, Cabal Rosel A, Szostak MP, Licka T, Allerberger F, Ruppitsch W, Spergser J. 2020. Broad-spectrum cephalosporin-resistant *Klebsiella* spp. isolated from diseased horses in Austria. *Animals* 10:332.

30. Schaufler K, Nowak K, Dux A, Semmler T, Villa L, Kourouma L, Bangoura K, Wieler LH, Leendertz FH, Guenther S. 2018. Clinically relevant ESBL-producing *K. pneumoniae* ST307 and *E. coli* ST38 in an urban West African rat population. *Front Microbiol* 9:150.

31. Rojas R, Macesic N, Tolari G, Guzman A, Uhlemann AC. 2019. Multidrug-resistant *Klebsiella pneumoniae* ST307 in traveler returning from Puerto Rico to Dominican Republic. *Emerg Infect Dis* 25:1583–1585.

32. Long SW, Olsen RJ, Eagar TN, Beres SB, Zhao P, Davis JJ, Brettin T, Xia F, Musser JM. 2017. Population genomic analysis of 1,777 extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* isolates, Houston, Texas: unexpected abundance of clonal group 307. *mBio* 8:e00489-17.

33. Cejas D, Elena A, Guevara Nuñez D, Sevillano Platero P, De Paulis A, Magariños F, Alfonso C, Berger MA, Fernández-Canigia L, Gutkind G, Radice M. 2019. Changing epidemiology of KPC-producing *Klebsiella pneumoniae* in Argentina: emergence of hypermucoviscous ST25 and high-risk clone ST307. *J Glob Antimicrob Resist* 18:238–242.

34. Novovic K, Trudic A, Brkic S, Vasiljevic Z, Kojic M, Medic D, Cirkovic I, Jovcic B. 2017. Molecular epidemiology of colistin-resistant, carbapenemase-producing Klebsiella pneumoniae in Serbia from 2013 to 2016. *Antimicrob Agents Chemother* 61:e02550-16.

35. Bocanegra-Ibarias P, Garza-González E, Morfín-Otero R, Barrios H, Villarreal-Treviño L, Rodríguez-Noriega E, Garza-Ramos U, Petersen-Morfin S, Silva-Sanchez J. 2017. Molecular and microbiological report of a hospital outbreak of NDM-1-carrying Enterobacteriaceae in Mexico. *PLoS One* 12:e0179651.

36. Piazza A, Comandatore F, Romeri F, Brilli M, Dichirico B, Ridolfo A, Antona C, Bandi C, Gismondo MR, Rimoldi SG. 2019. Identification of blaVIM-1 gene in ST307 and ST661 *Klebsiella pneumoniae* clones in Italy: old acquaintances for new combinations. *Microb Drug Resist* 25:787–790.

37. Saavedra SY, Diaz L, Wiesner M, Correa A, Arévalo SA, Reyes J, Hidalgo AM, de la Cadena E, Perenguez M, Montaño LA, Ardila J, Ríos R, Ovalle MV, Díaz P, Porras P, Villegas MV, Arias CA, Beltrán M, Duarte C. 2017. Genomic and molecular characterization of clinical isolates of Enterobacteriaceae harboring mcr-1 in Colombia, 2002 to 2016. *Antimicrob Agents Chemother* 61:e00841-17.

38. Giddins MJ, Macesic N, Annavajhala MK, Stump S, Khan S, McConville TH, Mehta M, Gomez-Simmonds A, Uhlemann AC. 2017. Successive emergence of ceftazidime-avibactam resistance through distinct genomic adaptations in blaKPC-2-harboring *Klebsiella pneumoniae* sequence type 307 isolates. *Antimicrob Agents Chemother* 62:e02101-17.

39. Gorrie CL, Mirceta M, Wick RR, Edwards DJ, Thomson NR, Strugnell RA, Pratt NF, Garlick JS, Watson KM, Pilcher DV, McGloughlin SA, Spelman DW, Jenney AWJ, Holt KE. 2017. Gastrointestinal carriage is a major reservoir of *Klebsiella pneumoniae* infection in intensive care patients. *Clin Infect Dis* 65:208–215.

40. Damjanova I, Tóth A, Pászti J, Hajbel-Vékony G, Jakab M, Berta J, Milch H, Füzi M. 2008. Expansion and countrywide dissemination of ST11, ST15 and ST147 ciprofloxacin-resistant CTX-M-15-type beta-lactamase-producing *Klebsiella pneumoniae* epidemic clones in Hungary in 2005—the new 'MRSAs'? *J Antimicrob Chemother* 62:978–985.

41. Coelho A, Mirelis B, Alonso-Tarrés C, Nieves Larrosa M, Miró E, Clivillé Abad R, Bartolomé RM, Castañer M, Prats G, Johnson JR, Navarro F, González-López JJ. 2009. Detection of three stable genetic clones of CTX-M-15-producing *Klebsiella pneumoniae* in the Barcelona metropolitan area, Spain. *J Antimicrob Chemother* 64:862–864.

42. Giakkoupi P, Papagiannitsis CC, Miriagou V, Pappa O, Polemis M, Tryfinopoulou K, Tzouvelekis LS, Vatopoulos AC. 2011. An update of the evolving epidemic of blaKPC-2-carrying *Klebsiella pneumoniae* in Greece (2009-10). *J Antimicrob Chemother* 66:1510–1513.

43. Papagiannitsis CC, Kotsakis SD, Petinaki E, Vatopoulos AC, Tzelepi E, Miriagou V, Tzouvelekis LS. 2011. Characterization of metallo-beta-lactamase VIM-27, an A57S mutant of VIM-1 associated with *Klebsiella pneumoniae* ST147. *Antimicrob Agents Chemother* 55:3570–3572.

44. Lascols C, Peirano G, Hackel M, Laupland KB, Pitout JD. 2013. Surveillance and molecular epidemiology of *Klebsiella pneumoniae* isolates that produce carbapenemases: first report of OXA-48-like enzymes in North America. *Antimicrob Agents Chemother* 57:130–136.

45. Richter SN, Frasson I, Franchin E, Bergo C, Lavezzo E, Barzon L, Cavallaro A, Palu G. 2012. KPC-mediated resistance in *Klebsiella pneumoniae* in two hospitals in Padua, Italy, June 2009-December 2011: massive spreading of a KPC-3-encoding plasmid and involvement of non-intensive care units. *Gut Pathog* 4:7.

46. Samuelsen O, Toleman MA, Hasseltvedt V, Fuursted K, Leegaard TM, Walsh TR, Sundsfjord A, Giske CG. 2011. Molecular characterization of VIM-producing *Klebsiella pneumoniae* from Scandinavia reveals genetic relatedness with international clonal complexes encoding transferable multidrug resistance. *Clin Microbiol Infect* 17:1811–1816.

47. Peirano G, Pillai DR, Pitondo-Silva A, Richardson D, Pitout JD. 2011. The characteristics of NDM-producing *Klebsiella pneumoniae* from Canada. *Diagn Microbiol Infect Dis* 71:106–109.

48. Giske CG, Froding I, Hasan CM, Turlej-Rogacka A, Toleman M, Livermore D, Woodford N, Walsh TR. 2012. Diverse sequence types of *Klebsiella pneumoniae* contribute to the dissemination of blaNDM-1 in India, Sweden, and the United Kingdom. *Antimicrob Agents Chemother* 56:2735–2738.

49. Osterblad M, Kirveskari J, Hakanen AJ, Tissari P, Vaara M, Jalava J. 2012. Carbapenemase-producing Enterobacteriaceae in Finland: the first years (2008-11). *J Antimicrob Chemother* 67:2860–2864.

50. Lafeuille E, Decre D, Mahjoub-Messai F, Bidet P, Arlet G, Bingen E. 2013. OXA-48 carbapenemase-producing *Klebsiella pneumoniae* isolated from Libyan patients. *Microb Drug Resist* 19:491–497.

51. Peirano G, Ahmed-Bentley J, Fuller J, Rubin JE, Pitout JD. 2014. Travel-related carbapenemase-producing Gram-negative bacteria in Alberta, Canada: the first 3 years. *J Clin Microbiol* 52:1575–1581.

52. Wang X, Xu X, Li Z, Chen H, Wang Q, Yang P, Zhao C, Ni M, Wang H. 2014. An outbreak of a nosocomial NDM-1-producing *Klebsiella pneumoniae* ST147 at a teaching hospital in mainland China. *Microb Drug Resist* 20:144–149.

53. Shoma S, Kamruzzaman M, Ginn AN, Iredell JR, Partridge SR. 2014. Characterization of multidrug-resistant *Klebsiella pneumoniae* from Australia carrying blaNDM-1. *Diagn Microbiol Infect Dis* 78:93–97.

54. Gharout-Sait A, Alsharapy SA, Brasme L, Touati A, Kermas R, Bakour S, Guillard T, de Champs C. 2014. Enterobacteriaceae isolates carrying the New Delhi metallo-beta-lactamase gene in Yemen. *J Med Microbiol* 63:1316–1323.

55. Lee C-S, Vasoo S, Hu F, Patel R, Doi Y. 2014. *Klebsiella pneumoniae* ST147 coproducing NDM-7 carbapenemase and RmtF 16S rRNA methyltransferase in Minnesota. *J Clin Microbiol* 52:4109–4110.

56. Liapis E, Pantel A, Robert J, Nicolas-Chanoine M-H, Cavalié L, van der Mee-Marquet N, de Champs C, Aissa N, Eloy C, Blanc V, Guyeux C, Hocquet D, Lavigne J-P, Bertrand X, ONERBA. 2014. Molecular epidemiology of OXA-48-producing *Klebsiella pneumoniae* in France. *Clin Microbiol Infect* 20:O1121–O1123.

57. Quiñones D, Valverde A, Rodríguez-Baños M, Kobayashi N, Zayaz A, Abreu M, Cantón R, del Campo R. 2014. High clonal diversity in a non-outbreak situation of clinical ESBL-producing *Klebsiella pneumoniae* isolates in the first national surveillance program in Cuba. *Microb Drug Resist* 20:45–51.

58. Rodrigues C, Machado E, Ramos H, Peixe L, Novais A. 2014. Expansion of ESBL-producing *Klebsiella pneumoniae* in hospitalized patients: a successful story of international clones (ST15, ST147, ST336) and epidemic plasmids (IncR, IncFIIK). *Int J Med Microbiol* 304:1100–1108.

59. Rocha LKL, dos Santos Neto RL, da Costa Guimarães AC, Almeida ACS, Vilela MA, de Morais MMC. 2014. Plasmid-mediated qnrA1 in *Klebsiella pneumoniae* ST147 in Recife, Brazil. *Int J Infect Dis* 26:49–50.

60. Avgoulea K, Di Pilato V, Zarkotou O, Sennati S, Politi L, Cannatelli A, Themeli-Digalaki K, Giani T, Tsakris A, Rossolini GM, Pournaras S. 2018. Characterization of extensively drug-resistant or pandrug-resistant sequence type 147 and 101 OXA-48-producing *Klebsiella pneumoniae* causing bloodstream infections in patients in an intensive care unit. *Antimicrob Agents Chemother* 62:e02457-17.

61. Chen LPG, Bradford P, Motyl M, Kreiswirth B, Pitout JD. 2017. Genomic diversity and global epidemiology of carbapenem-resistant K. pneumoniae (CRKp) clonal group 147 (CG147), abstr 25. ASM Microbe, New Orleans, LA, USA.

62. Peirano G, Bradford PA, Kazmierczak KM, Chen L, Kreiswirth BN, Pitout JD. 2017. Importance of clonal complex 258 and IncFK2-like plasmids among a global collection of *Klebsiella pneumoniae* with blaKPC. *Antimicrob Agents Chemother* 61:e02610-16.

63. Rojas LJ, Hujer AM, Rudin SD, Wright MS, Domitrovic TN, Marshall SH, Hujer KM, Richter SS, Cober E, Perez F, Adams MD, van Duin D, Bonomo RA. 2017. NDM-5 and OXA-181 beta-lactamases, a significant threat continues to spread in the Americas. *Antimicrob Agents Chemother* 61:e00454-17.

64. Sonnevend A, Ghazawi A, Hashmey R, Haidermota A, Girgis S, Alfaresi M, Omar M, Paterson DL, Zowawi HM, pal T. 2017. Multihospital occurrence of pan-resistant *klebsiella pneumoniae* Sequence Type 147 with an ISEcp1-directed blaOXA-181 insertion in the mgrB gene in the United Arab Emirates. *Antimicrob Agents Chemother* 61:e00418-17.

65. Hamzaoui Z, Ocampo-Sosa A, Maamar E, Fernandez Martinez M, Ferjani S, Hammami S, Harbaoui S, Genel N, Arlet G, Saidani M, Slim A, Boutiba-Ben Boubaker I, Martinez-Martinez L. 2018. An outbreak of NDM-1-producing *Klebsiella pneumoniae*, associated with OmpK35 and OmpK36 porin loss in Tunisia. *Microb Drug Resist* 24:1137–1147.

66. Naha S, Sands K, Mukherjee S, Roy C, Rameez MJ, Saha B, Dutta S, Walsh TR, Basu S. 2020. KPC-2-producing *Klebsiella pneumoniae* ST147 in a neonatal unit: clonal isolates with differences in colistin susceptibility attributed to AcrAB-TolC pump. *Int J Antimicrob Agents* 55:105903.

67. Protonotariou E, Poulou A, Politi L, Sgouropoulos I, Metallidis S, Kachrimanidou M, Pournaras S, Tsakris A, Skoura L. 2018. Hospital outbreak due to a *Klebsiella pneumoniae* ST147 clonal strain co-producing KPC-2 and VIM-1 carbapenemases in a tertiary teaching hospital in northern Greece. *Int J Antimicrob Agents* 52:331–337.

68. Tavoschi L, Forni S, Porretta A, Righi L, Pieralli F, Menichetti F, Falcone M, Gemignani G, Sani S, Vivani P, Bellandi T, Tacconi D, Turini L, Toccafondi G, Privitera G, Lopalco P, Baggiani A, Gemmi F, Luchini G, Petrillo M, Roti L, Pezzotti P, Pantosti A, Iannazzo S, Mechi MT, Rossolini GM, on behalf of the Tuscan Clinical Microbiology Laboratory Network. 2020. Prolonged outbreak of New Delhi metallo-beta-lactamase-producing carbapenem-resistant Enterobacterales (NDM-CRE), Tuscany, Italy, 2018 to 2019. *Euro Surveill* 25:2000085.

69. Potron A, Bernabeu S, Cuzon G, Ponties V, Blanchard H, Seringe E, Naas T, Nordmann P, Dortet L. 2017. Analysis of OXA-204 carbapenemase-producing Enterobacteriaceae reveals possible endoscopy-associated transmission, France, 2012 to 2014. *Euro Surveill* 22:17-00048.

70. Rodrigues C, Bavlovic J, Machado E, Amorim J, Peixe L, Novais A. 2016. KPC-3-producing *Klebsiella pneumoniae* in Portugal linked to previously circulating non-CG258 lineages and uncommon genetic platforms (Tn4401d-IncFIA and Tn4401d-IncN). *Front Microbiol* 7:1000.

71. Maamar E, Ferjani S, Jendoubi A, Hammami S, Hamzaoui Z, Mayonnove-Coulange L, Saidani M, Kammoun A, Rehaiem A, Ghedira S, Houissa M, Boutiba-Ben Boubaker I, Slim A, Dubois V. 2016. High prevalence of gut microbiota colonization with broad-spectrum cephalosporin resistant Enterobacteriaceae in a Tunisian Intensive care unit. *Front Microbiol* 7:1859.

72. Ovejero CM, Escudero JA, Thomas-Lopez D, Hoefer A, Moyano G, Montero N, Martin-Espada C, Gonzalez-Zorn B. 2017. Highly tigecycline-resistant *Klebsiella pneumoniae* Sequence type 11 (ST11) and ST147 isolates from companion animals. *Antimicrob Agents Chemother* 61:e02640-16.

73. Zogg AL, Simmen S, Zurfluh K, Stephan R, Schmitt SN, Nuesch-Inderbinen M. 2018. High prevalence of extended-spectrum beta-lactamase producing Enterobacteriaceae among clinical isolates from cats and dogs admitted to a veterinary hospital in Switzerland. *Front Vet Sci* 5:62.

74. Zhang R, Li J, Wang Y, Shen J, Shen Z, Wang S. 2019. Presence of NDM in non-*E. coli* Enterobacteriaceae in the poultry production environment. *J Antimicrob Chemother* 74:2209–2213.

75. Suzuki Y, Nazareno PJ, Nakano R, Mondoy M, Nakano A, Bugayong MP, Bilar J, Perez M, Medina EJ, Saito-Obata M, Saito M, Nakashima K, Oshitani H, Yano H. 2019. Environmental presence and genetic characteristics of carbapenemase-producing Enterobacteriaceae from hospital sewage and river water in the Philippines. *Appl Environ Microbiol* 86:e01906-19.

76. Izdebski R, Bojarska K, Baraniak A, Literacka E, Herda M, Zabicka D, Guzek A, Polgrabia M, Hryniewicz W, Gniadkowski M. 2015. NDM-1- or OXA-48-producing Enterobacteriaceae colonising Polish tourists following a terrorist attack in Tunis, March 2015. *Euro Surveill* 20:21150.

77. Peirano G, Sang JH, Pitondo-Silva A, Laupland KB, Pitout JD. 2012. Molecular epidemiology of extended-spectrum-beta-lactamase-producing *Klebsiella pneumoniae* over a 10 year period in Calgary, Canada. *J Antimicrob Chemother* 67:1114–1120.

78. Peirano G, Lascols C, Hackel M, Hoban DJ, Pitout JD. 2014. Molecular epidemiology of Enterobacteriaceae that produce VIMs and IMPs from the SMART surveillance program. *Diagn Microbiol Infect Dis* 78:277–281.

79. Zurfluh K, Nüesch-Inderbinen M, Morach M, Zihler Berner A, Hächler H, Stephan R. 2015. Extended-spectrum-beta-lactamase-producing Enterobacteriaceae isolated from vegetables imported from the Dominican Republic, India, Thailand, and Vietnam. *Appl Environ Microbiol* 81:3115–3120.

80. Zautner AE, Bunk B, Pfeifer Y, Spröer C, Reichard U, Eiffert H, Scheithauer S, Groß U, Overmann J, Bohne W. 2017. Monitoring microevolution of OXA-48-producing *Klebsiella pneumoniae* ST147 in a hospital setting by SMRT sequencing. *J Antimicrob Chemother* 72:2737–2744.

81. Bathoorn E, Tsioutis C, da Silva Voorham JM, Scoulica EV, Ioannidou E, Zhou K, Rossen JW, Gikas A, Friedrich AW, Grundmann H. 2016. Emergence of pan-resistance in KPC-2 carbapenemase-producing *Klebsiella pneumoniae* in Crete, Greece: a close call. *J Antimicrob Chemother* 71:1207–1212.

82. Guo L, An J, Ma Y, Ye L, Luo Y, Tao C, Yang J. 2016. Nosocomial outbreak of OXA-48-producing *Klebsiella pneumoniae* in a Chinese hospital: clonal transmission of ST147 and ST383. *PLoS One* 11:e0160754.

83. Pirš M, Cerar Kišek T, Križan Hergouth V, Seme K, Mueller Premru M, Jeverica S, Logar M, Mrvič T, Žnidaršič B, Jordan Markočič O, Lejko Zupanc T. 2019. Successful control of the first OXA-48 and/or NDM carbapenemase-producing K*lebsiella pneumoniae* outbreak in Slovenia 2014–2016. *J Hosp Infect* 101:142–149.

84. Khong WX, Marimuthu K, Teo J, Ding Y, Xia E, Lee JJ, Ong RT, Venkatachalam I, Cherng B, Pada SK, Choong WL, Smitasin N, Ooi ST, Deepak RN, Kurup A, Fong R, Van La M, Tan TY, Koh TH, Lin RT, Tan EL, Krishnan PU, Singh S, Pitout JD, Teo YY, Yang L, Ng OT, Carbapenemase-Producing Enterobacteriaceae in Singapore (CaPES) Study Group. 2016. Tracking inter-institutional spread of NDM and identification of a novel NDM-positive plasmid, pSg1-NDM, using next-generation sequencing approaches. *J Antimicrob Chemother* 71:3081–3089.

85. Turton JF, Payne Z, Coward A, Hopkins KL, Turton JA, Doumith M, Woodford N. 2018. Virulence genes in isolates of *Klebsiella pneumoniae* from the UK during 2016, including among carbapenemase gene-positive hypervirulent K1-ST23 and 'non-hypervirulent' types ST147, ST15 and ST383. *J Med Microbiol* 67:118–128.

86. Toth A, Kocsis B, Damjanova I, Kristof K, Janvari L, Paszti J, Csercsik R, Topf J, Szabo D, Hamar P, Nagy K, Fuzi M. 2014. Fitness cost associated with resistance to fluoroquinolones is diverse across clones of *Klebsiella pneumoniae* and may select for CTX-M-15 type extended-spectrum beta-lactamase. *Eur J Clin Microbiol Infect Dis* 33:837–843.

87. Muggeo A, Guillard T, Klein F, Reffuveille F, Francois C, Babosan A, Bajolet O, Bertrand X, de Champs C, CarbaFrEst Group. 2018. Spread of *Klebsiella pneumoniae* ST395 non-susceptible to carbapenems and resistant to fluoroquinolones in north-eastern France. *J Glob Antimicrob Resist* 13:98–103.

88. Pitout JD, Nordmann P, Poirel L. 2015. Carbapenemase-producing *Klebsiella pneumoniae*, a key pathogen set for global nosocomial dominance. *Antimicrob Agents Chemother* 59:5873–5884.

89. Fuzi M, Rodriguez Bano J, Toth A. 2020. Global evolution of pathogenic bacteria with extensive use of fluoroquinolone agents. *Front Microbiol* 11:271.

90. Peirano G, Pitout JDD. 2019. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: update on molecular epidemiology and treatment options. *Drugs* 79:1529–1541.