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Global spread and evolutionary convergence of multidrug-resistant and hypervirulent *Klebsiella pneumoniae* high-risk clones

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ABSTRACT

For people living in developed countries life span is growing at a faster pace than ever. One of the main reasons for such success is attributable to the introduction and extensive use in the clinical practice of antibiotics over the course of the last seven decades. In hospital settings, *Klebsiella pneumoniae* represents a well-known and commonly described opportunistic pathogen, typically characterized by resistance to several antibiotic classes. On the other hand, the broad wedge of population living in Low and/or Middle Income Countries is increasing rapidly, allowing the spread of several commensal bacteria which are transmitted via human contact. Community transmission has been the original milieu of *K. pneumoniae* isolates characterized by an outstanding virulence (hypervirulent). These two characteristics, also defined as "pathotypes", originally emerged as different pathways in the evolutionary history of *K. pneumoniae*. For a long time, the Sequence Type (ST), which is defined by the combination of alleles of the 7 housekeeping genes of the Multi-Locus Sequence Typing, has been a reliable marker of the pathotype: multidrug-resistant clones (e.g. ST258, ST147, ST101) in the Western world and hypervirulent clones (e.g. ST23, ST65, ST86) in the Eastern. Currently, the boundaries separating the two pathotypes are fading away due to several factors, and we are witnessing a worrisome convergence in certain high-risk clones. Here we review the evidence available on confluence of multidrug-resistance and hypervirulence in specific *K. pneumoniae* clones.

KEYWORDS

Klebsiella pneumoniae; global pathogen; multidrug-resistance; carbapenem; hypervirulence; convergence

Introduction

Klebsiella pneumoniae stands up among other members of the Enterobacterales order, both for the speed and for the tenacity of its spread. These fermentative, non-motile, gram-negative bacteria can be considered ubiquitous microorganisms: members of the genus *Klebsiella* are widely represented in soil, water, and vegetation [1]. They are also natural inhabitants of the gut microbiota of healthy humans and animals [1–3]. Within the genus, *K. pneumoniae* represents an emerging worldwide public health issue, being one of the most frequent bacterial species associated with nosocomial infections [4,5].

While it can be a silent bowel colonizer for long periods of time [6,7], the pooled mortality rate for *K. pneumoniae* infections is high even nowadays, ranging from 21% to 42% based on its susceptibility to antimicrobial agents [8].

As a matter of fact, *K. pneumoniae 'sensu stricto'* (not to be mistaken with other members of the related species complex, which seem to be more often linked with the environment) [5] emerged as an epidemically successful bacterium via two different evolutionary pathways, often defined as pathotypes: Multidrug-Resistant *K. pneumoniae* (MDR-*Kp*) and hypervirulent *K. pneumoniae* (hv*Kp*) [9].

In both cases, infections often start from colonization of the gut microbiota [10], yet the pathophysiology of the host–microorganism interaction is fundamentally different [4].

In Western countries MDR-*Kp* is a leading cause of hospital acquired infections [11,12] and it is the subject of frequent risk assessments by health authorities [13–15]. On the other hand, in Asia, and more specifically in the Asian Pacific Rim, several cases of severe and invasive infections caused by hv*Kp* in otherwise healthy individuals were reported since the mid-late 1980s [16].

Notwithstanding a 30-year history, hv*Kp* in the scientific literature is way less represented than MDR-*Kp*, and its characteristics are less defined; yet, its spread is highly worrisome due to its ability to cause disease in healthy subjects [17].

In this review, we focus on specific Clonal Groups (CGs) [18], and on their associated Sequence Types (STs) [19], which are considered the leading causes of the spread of MDR- and of hv*Kp*, respectively. In particular, GC258, CG147, and CG101 were considered as representatives of the MDR-*Kp* type, and CG23, CG65, and CG86 as those of the hv*Kp*. These lineages spread globally from different geographical areas over various time periods, and they are for this reason referred to as high-risk clones. Isolates/strains belonging to the same

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high-risk clone have similar phenotypic and genotypic traits and phylogenetic relatedness. By comparing common and discriminating genetic features, this review aims to summarize these characteristics in a selection of relevant CGs.

Multidrug-Resistance

The infections caused by MDR-*Kp*, often described as the 'Classical *K. pneumoniae*', represent a huge threat to medical care of the growing number of critically ill patients [20]. This pathotype is of great concern because of i) its fast and vast dissemination, especially in critical settings such as Intensive Care Units (ICUs), ii) its ability to acquire multiple antimicrobial resistance (AMR) genes, and iii) the scarcity of effective antibiotics for extensively drug resistant *K. pneumoniae*. In fact, MDR-*Kp* has been listed as a priority bacterial pathogen for which new antibiotics are urgently needed by the World Health Organization [21].

Even though in *K. pneumoniae* a proportion of AMR (e.g. toward colistin [22] or tigecycline [23]) emerges occasionally through chromosomal mutations [24], the vast majority of AMR in this pathogen results from Horizontal Gene Transfer (HGT) of large, conjugative plasmids [4]. In this scene, the acquisition of β-lactamases set the pace for the expansion of antimicrobial resistance in *K. pneumoniae*.

The bla_{SHV-1} gene is a chromosomally encoded β-lactamase gene which is found across members of the species and which provides resistance to ampicillin; the relationship between this specific AMR gene and *K. pneumoniae* is so tight that this bacterium has been proposed as the original source of the SHV β-lactamase family [25].

The detection of Extended Spectrum β-lactamases (ESBLs) genes in *K. pneumoniae* began shortly after the introduction of third-generation cephalosporins in the clinical practice during the first half of the 1980s [26,27] While originating from *Kluyvera* spp., an environmental bacterium [28,29], β-lactamases of the CTX-M family are the most prevalent ESBLs in the Enterobacterales order; in addition, these ESBLs were at the basis of the success of some *K. pneumoniae* STs [30].

Nevertheless, the *K. pneumoniae* trump card has been the acquisition of carbapenemases [31]. These specific β-lactamase enzymes, which can hydrolyze a last-resort class of drugs named carbapenems, are often associated with Mobile Genetic Elements (MGEs), which mediate their horizontal diffusion within and between bacterial species. Since 1996, the *Klebsiella Pneumoniae* Carbapenemase (KPC) became the most prevalent carbapenemase in *K. pneumoniae* [32].

More than 100 different acquired AMR genes have been identified in *K. pneumoniae* [33], and they are mostly carried by AMR plasmids [34,35]. The *K. pneumoniae* plasmids pKpQIL and pKPN were initially identified in the genomes of the earliest carbapenemase-resistant isolates belonging to the ST258 clone from Israel and the U.S.A [31,36]. Both plasmids have FII-related replicons, subcategorized as FIIk [37], and highly different FIB-replicons, named as FIB-pKpQIL and FIB-pKPN, respectively. pKpQIL and pKPN plasmids are compatible with each other, being co-resident in most of the ST258 bacterial cells. They can recombine, and, in some cases, they can create plasmid fusions [38]. Besides the IncFIIk, many different plasmid families encoding for AMR genes have been described in *K. pneumoniae*, with IncA, IncC, IncHI1, IncX3, and IncN being the most prevalent ones [5,31]. These have been associated with the acquisition and spread of other carbapenemase genes, such as bla_{OXA-48} and bla_{NDM}.

Hypervirulence

The first description of hv*Kp* dates back in the 1980s, when this pathotype became endemic in the Pacific Rim region [16].

While the phenotype needed to define a MDR strain is clear and well described [39], the same cannot be said for the hypervirulent one [40]. The string test, in which a colony cultured in standard conditions can be stretched into a string of at least 5 mm, was initially believed to be pathomognomonic of hv*Kp* [41]. However, a positive result to this test only states a hypermucoviscous phenotype. Furthermore, given the semi-qualitative nature of this test, sedimentation tests are currently preferred over the string-test due to their higher robustness as hypermucoviscosity detection methods [42,43].

The presence of a hyper-expressed capsule mediated by upregulators of gene expression (regulator of the mucoid phenotype *rmpA/rmpA2-rmpD* [44,45]) is a trait correlated with higher virulence, both *in vivo* [46] and in clinical studies [47,48]. However, this characteristic alone does not define a strain as hypervirulent: not all hv*Kp* strains are hypermucoviscous and, viceversa, some hypermucoviscous isolates do not carry virulence genes [49,50]. This misconception led to uncertainty in the scientific literature, especially when this phenotypic trait is used alone to categorize a strain as belonging to the hv*Kp* pathotype [51].

Similarly, the presence of genes encoding for the siderophores-salmochelin (*iro*), aerobactin (*iuc*), yersiniabactin (*ybt*) – the iron-foraging molecules which are associated with systemic infections, is not enough to define an isolate as hv*Kp* [33,52–55]. This is also true for the presence of the K1 or K2 capsule types: though being generally associated with hypervirulence and particularly resistant to phagocytosis and serum [56–58] they cannot be considered as discerning traits. In addition to siderophores, colibactin (*clb*), a genotoxin first described in E*scherichia coli* [59] which causes

cross-links in the DNA and induces double-strand DNA breaks [60,61] is diffused in K. *pneumoniae* too. Its prevalence ranges from 3.5% to 4% in the general population [62] to 17–25% in the endemic East Asia region [63]

As a matter of fact, hypervirulence should be considered as a multifactorial phenotype conferred by the presence of multiple virulence genes carried on large virulence plasmids (e.g. pK2044 [64] and pLVPK [65]) and within chromosomally inserted Integrative Conjugative Elements (ICEs).

Taken into consideration the limits associated with the prediction of a phenotype based on the genotype, a valid approach to the evaluation of virulence in a specific strain has been implemented by the creators of Kleborate [66]. This tool does not return a dichotomic answer 'virulent', 'not virulent', rather it gives a 'virulence score', ranging from 0 to 5 . Specifically, the virulence score is calculated as follows: 0 if the isolate is negative for all of *ybt*, *clb,* and *iuc*, 1 if the isolate carries *ybt* only, 2 if the isolate carries *ybt* and *clb* or *clb* only, 3 if the isolate carries *iuc* (typically associated with the *rmpADC* and *iro* loci) only, 4 if the isolate carries *ybt* and *iuc* but not *clb* and 5 if the isolate carries *clb*, *ybt* and *iuc*. A similar *modus operandi* is applied to antimicrobial resistance, each isolate is given a score ranging from 0 to 3. Specifically, the score is 0 if no ESBLs nor carbapenemases are detected, 1 if there is one ESBL alone, 2 if there is a carbapenemase and 3 if the carbapenemase is associated with colistin resistance. On top of that, Kleborate also quantifies how many drug classes have at least one resistance gene detected. These approaches, despite the above-mentioned limits, are a valid starting point not only for considering hypervirulence and multidrug-resistance as nuances, but also for the detection and analysis of strains displaying simultaneously both hypervirulence and multidrug-resistance.

Convergence

Compared to the vast literature of MDR- and hv*Kp*, there are not many reports describing isolates characterized by both pathotypes. Owing to the danger of clones possessing both these characteristics, surveillance systems are being implemented [67–69].

Most cases of *K. pneumoniae* isolates carrying both MDR and virulence traits have been described in Asian countries (China leading this chart, with more than 2/3 of the reports), and this is coherent with the prevalence of isolates displaying these characteristics alone [70]. Yet, this kind of phenomenon is being reported more and more frequently worldwide.

Under an evolutionary light, it is possible to identify three main patterns which can lead to a convergence of the two pathotypes [9,71]: i) hv*Kp* isolates acquire MDR genes [72,73], ii) MDR-*Kp* isolates acquire hypervirulence plasmids [74–76], and iii) acquisition of hybrid plasmids carrying both virulence and resistance genes [30,77,78].

Research methodology

In January 2022, we searched the literature on PubMed for the keywords '*Klebsiella pneumoniae*' and one of the selected CGs (GC258, CG147, CG101, CG23, CG65 or CG86), and 'either associated with MDR or hv'. The STs comprised within each CG were searched on the BIGSdb database hosting the public *Klebsiella pneumoniae* database (https://bigsdb.web.pasteur.fr/klebsiella/) by using the 'Search by locus combination' option to retrieve every isolate belonging to a specific ST. Albeit being a biased search method, since not every isolate reported in literature is sequenced and not all sequenced isolates are uploaded on that database, this methodology allows for standardized and reproducible results (Figures 1 and 2).

In the interest of simplification and intelligibility, we chose to only illustrate well-documented cases for each CG where strong evidence demonstrated the convergence of virulence and resistance genotypes, reporting about their evolution, spread, and genetic characteristics.

Clonal group 258 (ST11, 258, and ST512)

Three of the globally epidemic STs, namely ST11, ST258 and ST512, belong to the CG258, making this CG the most diffused MDR-*Kp* group [79,80] in the BIGSdb database, 965 isolates belonged to this CG (n = 476, ST11; n = 363, ST258; n = 126, ST512) (Figure 1).

CG258 is a frequent carrier of the bla_{KPC} carbapenemase gene, which can be found in most cases on plasmids with a pKpQIL backbone; even if this association is very high, it is neither absolute nor mutual, since this backbone can be found in other clonal groups [81–83]. Furthermore, members of the CG258 can also carry numerous other acquired AMR genes [84,85].

ST11 is by far the dominant clone of KPC-producing *K. pneumoniae* in China, with the bla_{KPC-2} gene usually found on plasmids of the IncF type [86–88]. Its endemicity in this country is so high that more than one clone belonging to this ST can cause simultaneous outbreaks in the same hospital [89]. In 2015, two reports describing carbapenem-resistant *K. pneumoniae* belonging to ST11 with a hypervirulent phenotype were issued from the Beijing region [90,91], alerting the nation for a threat bigger than just carbapenem-resistance. The isolates carried the bla_{KPC-2} carbapenemase and the capsular type was defined as 'non typeable' by the capsular polysaccharide synthesis PCR method [89,90]. A retrospective study demonstrated how, up until 2016, the main carbapenem-resistant *K. pneumoniae* ST11 lineage of a hospital in the Zhejiang region harbored a K47 capsule which, over time, was replaced by the ST11-K64 sub-clone [92]. In this specific case, the edge of the ST11-K64 was the co-occurrence of a pLVPK-like virulence plasmid interplaying with several other plasmids. Other studies describing

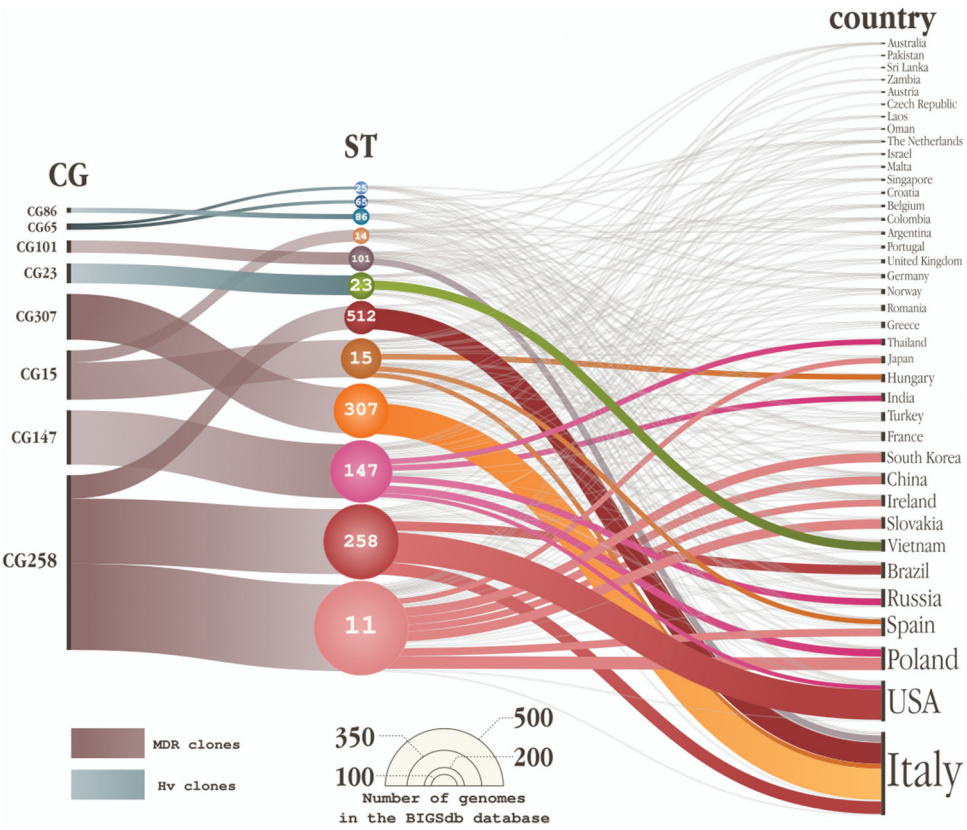

Figure 1. Alluvial diagram depicting the distribution of the various clonal groups (CGs) (left) in the sequence types (STs) that compose them (center), sorted by country (right). Connections between CGs and STs are color-coded according to the original pathotype, while connections between STs and Countries counting more than 10 isolates are color-coded according to the ST. Nodes (i.e. CGs, STs, or countries) counting less than 7 isolates are not shown for the sake of clarity.

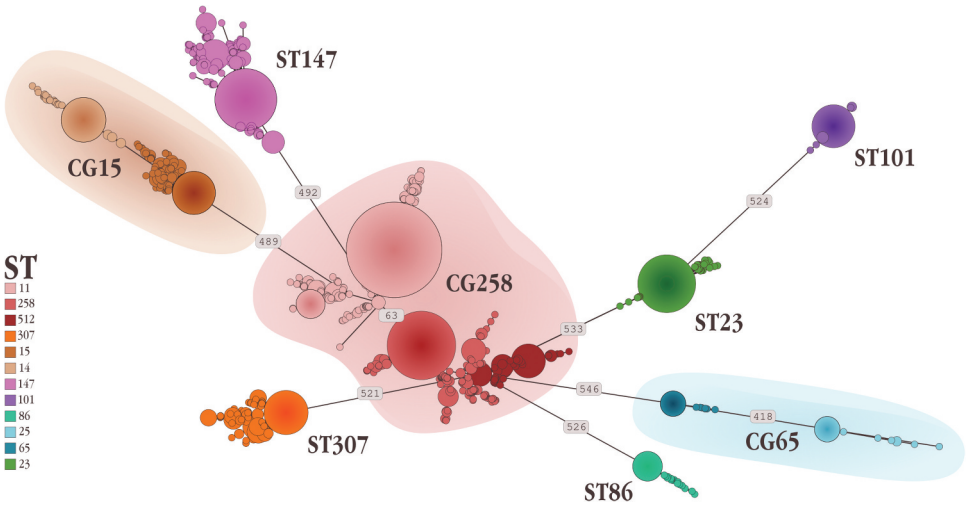

Figure 2. Minimum spanning tree representing one of the potentially many relationship which link the isolates belonging to the different high-risk clones. Numbers on the branches indicate the Single Nucleotide Polymorphisms differentiating the connected Sequence Types.

outbreaks of carbapenem-resistant and hypervirulent ST11 in China detected K64 as the most common capsular type (up to 25% of the infections caused by carbapenem-resistant *K. pneumoniae* in certain regions) [93], and highlighted how the fecal carriage of these isolates played a key role in their spread [94].

Other reports describe how ST11-K47 has also been able to acquire hypervirulence traits. In several cases, the acquisition of a non-conjugative pLVPK-like plasmid has been held responsible for this evolutionary convergence [95]. This type of HGT might have happened with the help of the conjugative IncF plasmid

harboring *bla*$_{KPC-2}$, which has an 11 kb region homologous to that of pLVPK [96]. Interestingly, in another case, the co-existence of the two pathotypes in a ST11 isolate was possible thanks to the acquisition of a 141 kb IncFII plasmid (pR16-Hv-CRKp1, which does not show high homology with the known virulent plasmids), which harbored both resistance (*bla*$_{KPC-2}$, *bla*$_{CTX-M-65}$ and *rmtB* among the others) and putative virulence genes (such as R16_5486) [73].

The acquisition of a virulence plasmid plays a key role in the spread of ST11 carbapenem-resistant hv*Kp* strains [21], and points to a worrisome evolutionary trajectory. This should elicit increased surveillance of the dissemination of these strains not only in nosocomial but also in community settings [97]. Hypervirulent isolates can spread at a faster pace, given the limited fitness costs of virulence plasmids [98], and their longer environment survival [92].

With regard to the treatment, even if the carbapenem-resistant hypervirulent ST11-KL64 sub-clone has been capable of evolving resistance toward tigecycline and colistin during therapy [99], for now ceftazidime-avibactam seems to be a valid therapeutic option against infections caused by KPC-2-producing hv*Kp* [100].

ST11 is also the ancestor of ST258, a hybrid clone composed by a replacement event between ST11, which supplied about 80% of the genetic material, and a single locus variant of ST258 called ST442 [101]. Though there is a tight association between with the *bla*$_{KPC}$ carbapenemase gene, ST258 and its most common derivative ST512, no description about these two STs being hypervirulent has been outlined.

Clonal group 147 (ST147, ST273 and ST392)

Between 2008 and 2014, outbreaks caused by ST147 were reported in Germany and Hungary, with isolates producing OXA-48, KPC-2 and NDM-1 carbapenemases [102,103]. In 2016–17, three strains carrying the *bla*$_{OXA-181}$ located on a 6 kb small ColKP3 plasmid were identified. These strains also carried a 110 kb IncFIB-like plasmid, that encoded tellurite/colicin resistance determinant, and phage-related genes (CP084394.1, CP074089.1) [104]. In 2017, *K. pneumoniae* ST147 was described in the Middle East and India [103,104]. These isolates produced chromosomally encoded OXA-181, and the majority also produced the NDM-5 carbapenemase. The *bla*$_{NDM-5}$ gene was located within an IncFII plasmid [105,106]. In Algeria in 2017, ST147 carried the *bla*$_{NDM-1}$ gene located on an IncR plasmid [107]. The evolutionary origin of ST147 and the two closely related ST273 and ST392 (grouped into CG147) was recently investigated. A time-scaled phylogeny reconstructed from this CG was structured into three main branches, each corresponding to ST147, ST273, and ST392, respectively. Within ST147, two main clades were observed, each characterized by distinct KL type and liposaccharide O antigen loci: clade KL64-O2 from Europe, and clade KL10-O3a from Asia, which emerged in 1994 and 2002, respectively. ST147 represents the paradigm of a clone in which antimicrobial resistance and virulence determinants converged thanks to the acquisition and exchange of mosaic plasmids. Different y*bt*/ICE*Kp* subtypes (*ybt*16/ICE*Kp*12, *ybt*10/ICE*Kp*4) were observed within the ST147-KL64 clade, further discerning it in subclades 1 and 2 [108]. Differently, virulence genes were rare among genomes of ST392 and ST273.

In 2018–2019, a large outbreak of NDM-1 producing ST147 *K. pneumoniae* occurred in Tuscany, Italy, with a total of 1,645 cases [109]. The outbreak clone was resistant to all beta-lactam antibiotics, including carbapenems, and aminoglycosides, but susceptible to colistin, tigecycline, cefiderocol, and the aztreonam – avibactam combination. Reports of ST147 strains in Tuscany continued in 2020 and through 2021 [110,111].

Genomic studies performed on NDM-producing ST147 from Italy revealed that they belonged to the KL64 clade and that they were related with clinical isolates from the Middle East, the USA, Thailand, Myanmar, Egypt, Lebanon, the UK, Denmark, Germany, and Hungary [111]. In Italian ST147, virulence genes encoding aerobactin (*iutA-iucABCD*), regulators of the mucoid phenotype (*rmpADC* and *rmpA2*, the latter often carrying a frameshift mutation), proteins involved in iron metabolism (*cobW*), and hemin and lysine transport system (*shiF*) were located on a large hybrid virulence/resistance plasmid carrying the HIB-FIB (Mar) replicons. This also carried *bla*$_{CTX-M-15}$ and the 16S methyltransferase *armA* genes. The origin of the hybrid virulence/resistance plasmid can be traced back to the pNDM-Mar plasmid, carrying the same IncFIB/IncHI1 replicons (IncHI1B_pNDM-Mar; IncFIB_pNDM-Mar JN420336), identified in 2011 in *K. pneumoniae* ST15 from Morocco. pNDM-Mar was positive for the *bla*$_{NDM-1}$, *bla*$_{CTX-M-15}$ and *qnrB1* genes, but negative for virulence genes [112]. The virulence content probably originates from the pK2044 and pLVpK virulence plasmids of hv*Kp* that are characterized by the replicon IncHI1B_pNDM-Mar but carry a different FIB-like replicon (repB_KLEB_VIR_AP006726).

The *bla*$_{NDM-1}$ gene has been located mostly on plasmids of the FIB(pKpQIL)-type, showing 99% identity and 51% coverage with the backbone of plasmid pKpQIL (NC_014016), which massively contributed to the dissemination of KPC-type carbapenemases in CG258 [110]

Virulence/resistance genes were also identified in the chromosome of ST147-KL64, with the most relevant being the yersiniabactin-encoding genes (*ybtSXQPA, irp1, irp2, ybtUTE*, and *fyuA*) associated with an ICEKp3, the *mrkA-H* genes encoding a type 3

fimbriae, as well as two additional bla_{CTX-15} genes located in the chromosome [110,111,113]

ST147 strains from Italy did not exhibit a maximal hypervirulent phenotype compared with canonical hypervirulent isolate hv-Kp2. This was demonstrated using both a subcutaneous model of infection in immunocompetent CD1 mice but also in the *Galleria mellonella* infection model [110,111]

Despite the *G. mellonella* model was shown to not accurately differentiate hypervirulent from less virulent *K. pneumoniae* strains some strains in the model showed an overall enhanced virulence potential compared with a representative of the ST258 high-risk clone, with LD50 comparable or lower than those of reference hvKp strain NTUH-K2044. Furthermore, in serum bactericidal assays, the Italian ST147 isolates exhibited different grades of serum resistance associated with a different status of *pal*, *csrD*, and *ramR* chromosomal genes. In particular, the inactivation of CsrD has been associated with increased serum fitness by promoting capsule production and thickness, suggesting that ST147 virulence grade could be dependent by the status or function of bacterial surface components that can be variable during the clonal expansion [110].

In May 2020, a new variant of the Italian ST147 was reported in a hospital in Tuscany. A shift in the NDM variant from NDM-1 to NDM-9 was observed, and this strain evolved to extreme-drug resistance by acquisition of resistance to colistin, tigecycline, and fosfomycin. The new clone emerged from highly related strains identified in 2019, showing mutations in RamR and MgrB proteins, implicated in tigecycline and colistin resistance, respectively. The fosfomycin resistance was associated with a defect in the glycerol-3-phosphate transporter [114].

Clonal group 101 (ST101, ST1685, ST2016, ST2017, and ST2502)

The emergence of CG101 is estimated at the beginning of the 1990s [115], yet it only needed a few years to become one of the most well-represented carbapenemase-producing *K. pneumoniae* in Europe [116,117]. Albeit strongly associated with the yersiniabactin locus [5], there is only one report describing CG101 strains as having acquired hypervirulence trait [78]. These isolates were sampled in 2018 in the United Kingdom and carried the bla_{OXA-48} carbapenemase (on the IncL/M plasmid CP031374.2), the 16S rRNA-methyltransferase *armA* and the macrolide resistance genes *msr(E)* and *mph(E)* (on the FIB/HI1B pNDM-Mar plasmid CP031372.2) and the quinolone resistance gene *qnrS1* (on the IncX3 plasmid CP031373.2). A IncFII(K)/IncFIB(K) virulence plasmid (CP031369.2), carrying *rmpA*, *rmpA2*, *iutA*, *iucABD*, (with a truncation in both *iucB* and *iucD*), was retrieved alongside the resistance ones.

Nonetheless, several studies highlight the resistance of this clone not only to first-class antibiotics, such as carbapenems [118], but also to colistin [119–121], which is associated with a higher in-hospital mortality [119], and tigecycline [122]. Furthermore, in high-endemic settings for KPC-producing isolates, such as Italy, ST101 is developing several variants of this specific carbapenemase in order to resist to ceftazidime-avibactam (e.g. bla_{KPC-39} and bla_{KPC-68} [38] bla_{KPC-46} [123] or bla_{KPC-31} [124].

Meanwhile, this ST is giving rise to its own CG by generating single locus variants (e.g. ST2502 [124,125], ST1685 [115] or ST2016 and 2017 [126]).

Clonal group 23 (ST23, ST26, ST57, and ST163)

Strictly associated with K1 capsular type [49,58], CG23 is highly diffused in the East Asia area [127] (Figure 1) and it has been described as a hv*Kp* with 'moderate virulence' in the *G. mellonella* model [128]. The spread of the main clade of this lineage (CG23-I [17]) is rapidly and steadily involving Western countries through multiple independent transmissions, embedding AMR genes along its way. Since 2018 there have been several reports of isolates belonging to ST23, which developed resistance toward carbapenems, mainly due to the acquisition of the IncL plasmid harboring bla_{OXA-48} [129,130].

Historically, the first traces of the encounter of this hv*Kp* lineage with a plasmid conferring carbapenem resistance can be dated back to 2012. The strains were isolated from Russia [131] and Germany [103].

Following the report of several hv*Kp* belonging to the ST23 in Ireland in March 2019, the European Center for Disease Prevention and Control (ECDC) performed a Rapid Risk Assessment (RRA), published in March 2021 [67]. The ECDC asked 37 National Reference Laboratories to submit WGS data from ST23, receiving 5 representative isolates from Ireland, 5 from France and 1 from both Finland and Sweden. The isolates were split into two clades, a main one characterized by the K1 capsule loci, and one unrelated one with a K57 capsule. Despite all the Irish ST23 isolates belonged to the K1 clade, and most of them harbored the bla_{OXA-48} carbapenemase gene, a SNPs analysis on the core genome revealed that they were not related between each other. Differently, 2 out of 5 of the France isolates had a K1 capsule cluster and harbored bla_{OXA-48}, while the other three had a K57 capsule, two of which carried bla_{OXA-48} and one bla_{NDM-1}. The Swedish isolate had a K1 capsule and did not carry any carbapenemase gene, while the Finnish one had a K57 capsule and carried bla_{OXA-48}. This peculiar spread and the comparison of the European isolates with

the most related ones from the public domain show how the acquisition of bla_{OXA-48} from ST23 is rather recent and happened several times independently across the continent [67].

The spread of ST23 isolates that acquired carbapenemase genes in Europe is not limited to the cases reported by the RRA [132].

An eXtensively Drug Resistant (XDR [39]) *K. pneumoniae* isolate harboring bla_{OXA-48} and the 16S rRNA methyltransferase *armA* on a plasmid has been described in Spain [133]. The more relevant, and worrisome, difference with the RRA isolates is the fact that the virulence plasmid was fused within a large hybrid virulence/resistance plasmid carrying a copy of the $bla_{CTX-M-15}$, while another copy of $bla_{CTX-M-15}$, was in the chromosome [133].

Despite more and more studies about hv*Kp* in Europe are being published [134–136], the scattered diffusion of ST23 in this region is a sign of the unnoticed spread of hv*Kp* in the continent. An additional issue is that the convergence of the hypervirulent ST23 with carbapenem resistance in Europe seems to be strictly associated with the bla_{OXA-48} gene, for which there is a lack of guidelines for treatment [137].

Clonal group 65 (ST25 and ST65)

CG65 is characterized by a K2 capsular serotype [18,138], and it is considered to be hypervirulent [71] due to the carriage of pLVPK-like virulence plasmids and of the *pks* gene cluster (which is necessary for the synthesis of colibactin) [63]. It comprises two STs, which differ in their epidemiology.

ST65 is spread worldwide, and it has the ability to acquire several plasmids harboring various carbapenemase genes. The epicenter of reports of carbapenem-resistant ST65 is China where, starting from 2015, several isolates manifesting both characteristics have been described. Two isolates have been reported carrying bla_{KPC-2} in the 2010–2014 period [91], suggesting that this convergence happened prior to 2010, and one isolate in 2017–2018 period causing a bloodstream infection (BSI) [95]. Furthermore, a case bla_{NDM-5} on a 'canonical' IncX3 plasmid [139] was described [140].

With regard to less diffused carbapenemases, two isolates belonging to ST65 carrying bla_{IMP-4} on IncU and IncN plasmids, in the latter case also coupled with tigecycline resistance [141] were described.

While epidemiological studies in China report a high level of genetic diversity and an absence of MDR in hv*Kp* [142,143], they only provide us with a glimpse of the tip of the iceberg (i.e. strains with peculiar phenotypes): the high plasticity of the ST65 genome, which can accept different resistance plasmids maintaining hypervirulence traits, poses a great danger.

There have been several reports of carbapenem resistance in ST65 also in other countries, such as Japan, where a study reported that out of 104 IMP-producing *K. pneumoniae* 12 were ST65-K2 [144], or in Argentina, where bla_{KPC-2} has been described carried by IncM plasmid [145].

ST25, instead, is the second most common carbapenemase-producing *K. pneumoniae* in Argentina, where in recent years there has been a shift from primarily ST258 [146,147] to a number of STs [148,149]. A study undertaken to characterize the isolates showing both MDR and hypervirulent phenotype collected during a 6-month period reported how, out of 35 isolates, 13 were bla_{KPC-2} harboring-ST25-K2 [150]. Furthermore, this clone is spreading in the South American continent, particularly in Colombia [151] and in Ecuador [152].

Clonal group 86 (ST86 and ST3994)

Most of the isolates belonging to ST86 are characterized by a K2 capsular serotype and by the presence of a pLVPK-like plasmid backbone, which confer the hypervirulent phenotype [58]. This ST is an international clone with global distribution, and a cause of community acquired infections in most continents, with a slight predisposition for animal infection.

In Australia, it is the cause of well-documented community-acquired infections since 1977, demonstrating a high PFGE similarity level throughout the years [153]. Starting from the 2001–2003 breeding seasons, ST86 caused several outbreaks in New Zealand sea lion pups, eventually becoming endemic in the population in this country [154].

The American continent has been affected from north to south by ST86. In North America, a carbapenemase-producing (KPC-2) ST86 isolate has been described as the cause of urine infections in Canada [155], while in the Caribbean, a case of meningitis sustained by an hv*Kp* has been reported [156]. In South America, specifically in Brazil in 2013 [157], an isolate belonging to the ST3994-K2 (a single locus variant of ST86, belonging to the same CG) was reported as the cause of a bloodstream infection [157], while in the same nation in 2019, a ST86 clone was the cause of sudden death in 11 captive marmosets [158].

Several reports have been provided by Asian countries, mainly from China, where the first report of ST86 can be traced back to two fatal infections caused by a susceptible isolate [159], and it is considered an important cause of asymptomatic bacteriuria, which may lead to a BSI [160].

Over time, ST86 has been described as associated with the bla_{KPC-2} carbapenemase gene. Alone, on an atypical IncX6 plasmid [161], or in association with bla_{NDM-1} [162]. In Japan, it has been held up as cause of severe infections, from community-acquired

pneumonia [163,164] to infections in the veterinary field, particularly in captive-bred ruffed lemurs [165].

In Europe, ST86 has been described as a cause of BSIs in a teaching hospital in Spain [166] and there have been multiple descriptions of this ST in France [167]. In this country, the first reports date back to 2011, when two cases of fatal infection in patients who recently returned from international travels were ascribed to this clone [168]. The number of cases grew subsequently and in a 5-year period (2011–2016). Five community acquired infections (mainly pneumonia) that required ICU hospitalization were attributed to this ST [167].

Despite all the previously mentioned strains were susceptible, this is not always the case: in the same nation two isolates belonging to this ST, both harboring several virulence genes, have been detected as MDR, the first one because of the presence of the $bla_{\text{OXA-48}}$ on a IncL plasmid, the latter because of $bla_{\text{CTX-}M\text{-}15}$ on an IncN plasmid coupled with deletions in the *ompK36* and *ramR* genes [169].

Though mostly being caused by susceptible isolates, the impact of outbreaks happening in veterinary settings should not be underestimated. The presence of hv*Kp* in reservoirs close to human is of concern, and the application of a One Health approach is mandatory to control and contrast it [170].

Conclusions

The identification of carbapenem resistance genes is nowadays routine in most clinical microbiology laboratories, but the detection of virulence genes is not. Phenotypic methods, such as the string test, cannot be considered reliable, since they lack sensitivity [49]. Apart from the vast symptoms range to which clinicians may not be used to, as of today it is mainly the simultaneous presence of carbapenem resistance and hypervirulence that leads to the identification of the latter.

To tackle these issues and to be prepared to face the spread of hv*Kp*, there are two strategies, which are not mutually exclusive: worthwhile tests to identify virulence genes/lineages (e.g. MLST screening of clinical isolates of *K. pneumoniae* [171] or multiplex PCR assay for identification of clones with capsular serotype K2 [172)], and a wider worldwide Whole Genome Sequencing and analysis coverage.

This identification is of the uttermost importance due to the fact that for a long time, the two *K. pneumoniae* MDR-*Kp* and hvKp pathotypes have been considered as two distinct, non-intersecting phenotypes, the first mostly associated with infections in immunocompromised patients, the second causing infections in healthy patients. As of today, oversimplified line we drew to keep MDR-*Kp* and hv*Kp* apart is fading away since the two pathotypes are converging. We are not also allowed to conceive the risk of acquisition of hv*Kp* and MDR-*Kp* strains restricted to patients linked to Asia or to patients from western countries with weakened immune systems, respectively.

Currently, the boundaries dividing the two pathotypes are less and less marked. Yet, since the intersection of the two pathotypes is something completely new, their description is moving on different tracks, and genomic epidemiology is needed as part of the diagnostic routine. On the one hand, case reports of single isolates and/or outbreaks are published with higher frequency, making a sufficient noise to depict a threat more and more tangible as time passes by, but from a quantitative point of view they are just scratching the surface. On the other hand, epidemiological studies portrait a dire summary of what the situation actually is, and the direction toward which we are heading: the spread of strains with converging pathotypes is rising, and it is just a matter of time before these strains are going to have the upper hand against the single pathotypes.

While focusing on the similarities and the distinctive traits of the global spread of MDR-*Kp* and of hv*Kp* STs, this review highlights that, in the future years, the definition of these two pathotypes as dichotomous *K. pneumoniae* manifestations is going to be much harder. Rather, it is clear that, to tackle the diffusion of this global pathogen, the best approach will be to assess spectra of resistance and virulence.

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