RAPID RISK ASSESSMENT

Emergence of hypervirulent *Klebsiella pneumoniae* ST23 carrying carbapenemase genes in EU/EEA countries, first update

14 February 2024

Summary

Since the last ECDC rapid risk assessment in 2021, the number of European Union/European Economic Area (EU/EEA) countries reporting cases of hypervirulent *Klebsiella pneumoniae* (hvKp) sequence type (ST) 23 has increased from four to 10 countries, and the number of isolates submitted for analysis by these countries has increased from 12 to 143 isolates. Furthermore, there is now evidence of sustained spread of the globally dominant hvKp ST23-K1 lineage carrying carbapenemase genes between healthcare facilities in Ireland over a period of five years, despite enhanced control efforts. Clusters of hvKp ST23-K1 isolates signifying potential within-country transmission were also detected in France, Latvia, and Lithuania; however, these have so far not been confirmed as being most likely due to within-country transmission with epidemiological data. Similar spread in and between healthcare facilities may already occur in other EU/EEA countries with less established surveillance.

The emergence of *K. pneumoniae* isolates with combined hypervirulence and resistance to last-line antibiotics such as carbapenems is of concern as, in contrast to 'classic' *K. pneumoniae* strains, hvKp strains can cause severe infections in healthy individuals, often complicated by dissemination to various body sites. Previously, hvKp strains were primarily found in Asia, were mainly community-acquired, and were only rarely resistant to antibiotics. However, recent reports point to increasing geographic distribution, healthcare association and multidrug resistance. With the convergence of virulence and antimicrobial resistance in hvKp strains, there is a possibility of potentially untreatable infections in previously healthy adults. An even higher morbidity and mortality must be expected if carbapenem-resistant hvKp strains spread in healthcare settings and affect a vulnerable patient population. Sustained transmission of hvKp ST23 carrying carbapenemase genes between healthcare facilities in an EU/EEA country has been confirmed. The probability of further spread and establishment of hvKp carrying carbapenemase genes in healthcare settings in EU/EEA countries with consequent significant impact on morbidity and mortality is therefore currently considered to be high.

It is important to detect hvKp early and prevent further dissemination in healthcare settings in EU/EEA countries to avoid further establishment of hvKp carrying carbapenemase genes as a healthcare-associated pathogen. Options for response include alerts to clinicians and clinical microbiology laboratories, the establishment of sufficient laboratory capacity to detect hvKp isolates including whole-genome sequencing, the submission of all suspected hvKp isolates with or without additional antimicrobial resistance to national reference laboratories, and enhanced infection prevention and control measures in healthcare facilities. Prospective data collection on hvKp isolates, including epidemiological and clinical data on cases of infection, carriage and associated risk factors, would improve the understanding of national spread and transmission routes and determine the need for further surveillance and control measures. For further details, please refer to the 'Options for response' section below.

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Event background

Whole-genome sequencing and epidemiological analysis

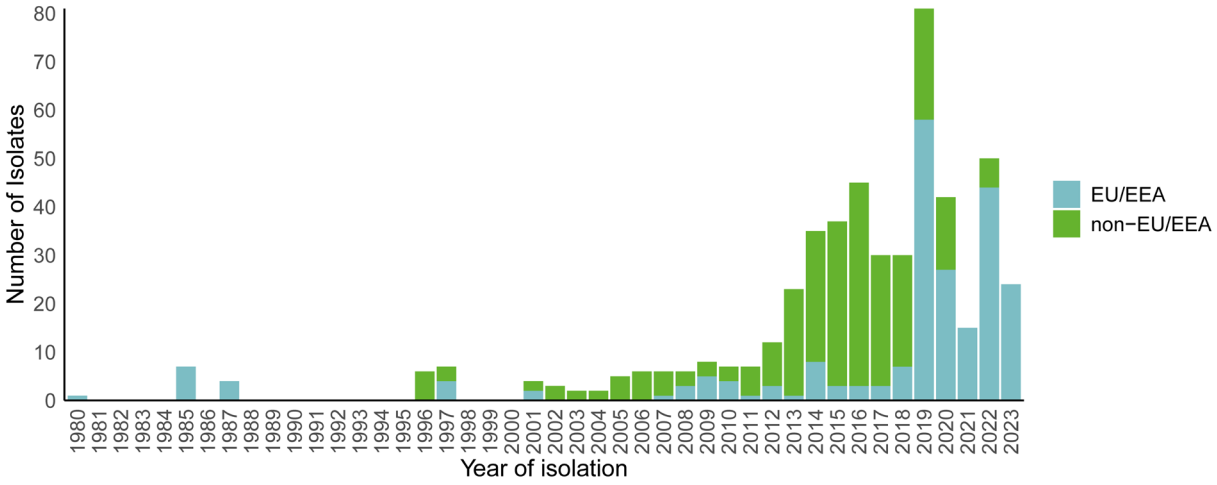
Following EpiPulse posts reporting the cases in European Union (EU) / European Economic Area (EEA) countries of hypervirulent *Klebsiella pneumoniae* (hvKp) sequence type (ST) 23-K1 lineage carrying *bla*$_{NDM-1}$ (26 October 2022) or *bla*$_{KPC-2}$ (21 September 2023), whole-genome sequencing (WGS) and epidemiological data from 131 *K. pneumoniae* ST23 isolates associated with infection or carriage were submitted to ECDC by the national reference laboratories (NRLs) of 10 countries covering the period of 2018-2023: Denmark (n=4 isolates), Finland (n=1), France (n=13), Hungary (n=1), Ireland (n=87), Italy (n=2), Latvia (n=9), Lithuania (n=8), the Netherlands (n=4), and Norway (n=2).

The genomes (raw reads) (n=131) received by ECDC were assembled using SPAdes and subjected for analysis in Pathogenwatch. Of the submitted genomes, 126 passed quality control, with more than 95% of core genes detected. Three isolates from Ireland were included in the analysis due to their relevance for the epidemiological investigation despite the detection of only more than 90% of core genes. The names of the assembled genomes were pseudonymised using the country code and consecutive numbers.

In total, 551 non-duplicate *K. pneumoniae* ST23 genomes were considered for further analysis, including the 129 genomes submitted by the NRLs, and 422 genomes from other data sources: 386 from public databases, 24 from the survey of carbapenem- and/or colistin-resistant Enterobacterales (CCRE survey) and 12 from the previous rapid risk assessment conducted in 2021. A phylogenetic tree was constructed using Pathogenwatch core genome single nucleotide polymorphisms (cgSNPs) [1]. Antimicrobial resistance genes, virulence genes (as well as the derived virulence score), and capsule type genes were identified using Kleborate [2] and visualised using Microreact [3].

The 422 genomes from other sources were from *K. pneumoniae* ST23 isolates from Asia (n=189), EU/EEA countries (n=105), non-EU/EEA European countries (n=57), Americas (n=41), Oceania (n=20), and Africa (n=7). For three genomes, information on the country of origin of the isolate was not available. The 105 genomes from EU/EEA from other data sources were reported from Austria (n=1), Belgium (n=10), Bulgaria (n=1), Croatia (n=3), Czechia (n=3), Denmark (n=1), Estonia (n=1), Finland (n=1), France (n=27), Germany (n=8), Greece (n=2), Ireland (n=5), Italy (n=4), Malta (n=1), the Netherlands (n=4), Norway (n=11), Poland (n=8), Portugal (n=1), Romania (n=4), Slovenia (n=1), Spain (n=6), and Sweden (n=2). Figure 1 shows the timeline for the *K. pneumoniae* ST23 isolates for which genomes were provided by the NRLs for this analysis or obtained from other data sources, by year of isolation. In this figure, only 505 isolates with information on the year of isolation could be included. For the remaining isolates (n=46), the year of isolation was not available.

Figure 1. *Klebsiella pneumoniae* ST23 isolates included in this analysis, by region and year of isolation (n=505)*†



** Only isolates with available year of isolation are shown; † The time distribution illustrated above should not be interpreted as an epidemic curve as the year-to-year variation may be affected by bias in detection and reporting and not represent a reflection of true temporal trends in incidence. The low number of isolates from countries not in the EU/EEA in the period 2020 to 2023 is likely due to a delay in data upload to public databases.*

The earliest isolates included in this analysis were detected in 1980 in France. There were also three human invasive isolates from 1997 detected in Belgium, the Netherlands, and Spain, respectively, which were sequenced for an analysis of the population genomics of the hvKp ST23-K1 lineage. However, the time distribution of isolates illustrated above should be interpreted with caution as the data might be biased by increased access to WGS from 2001 onwards. In particular, the numbers of isolates in recent years may be artificially low due to a delay until WGS data are made available in the public domain, and may substantially increase in the future when more recent data

are uploaded to public databases. Most of the EU/EEA isolates with a year of isolation of 2018 and onwards are the isolates for which the non-public genomes were submitted to ECDC by the NRLs for this assessment. Further analysis showed that the included 551 isolates belonged to two separate lineages, including the dominant globally distributed hvKp ST23-K1 lineage (n=511 isolates) and the smaller, more recent *K. pneumoniae* ST23-K57 lineage (n=40 isolates) [4], which are described in further detail below.

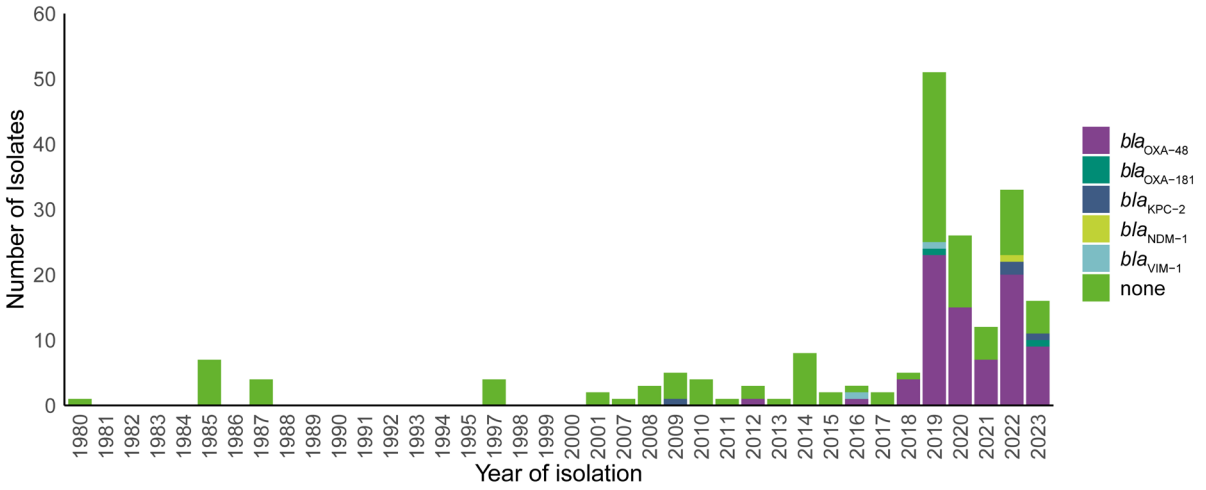
Klebsiella pneumoniae ST23-K1 lineage

Most of the hvKp ST23 isolates in this analysis belonged to the worldwide hvKp ST23-K1 lineage mostly identified as capsule serotype K1 and known as the dominant lineage associated with community-acquired invasive infections (such as liver abscess with metastatic spread) that can occur in healthy individuals [4]. In this analysis, 511 (92.7%) genomes were part of the ST23-K1 lineage, of which 200 (39.1%) genomes were submitted by EU/EEA countries: 107 genomes obtained from NRLs and 93 genomes obtained from other data sources (65 from public databases, 20 from the CCRE survey and eight from the previous rapid risk assessment). The remaining 311 (60.9%) genomes were from outside of EU/EEA and were obtained from either the public domain or the CCRE survey. Of the 511 isolates, 463 (90.6%) had the highest virulence score of 5 based on the presence of the virulence genes encoding for yersiniabactin (*ybt*), colibactin (*clb*) and aerobactin (*iuc*) as determined by Kleborate [2].

Carbapenemase genes

HvKp ST23-K1 isolates have previously been largely susceptible to antibiotics [5]. In this analysis, carbapenemase genes were found in 89 (45.9%) of 194 hvKp ST23 isolates detected in the EU/EEA with available year of isolation. The first hvKp ST23-K1 isolate with a carbapenemase gene (*bla*$_{\text{KPC-2}}$) was detected in 2009 in Poland [6,7]. Only isolates carrying *bla*$_{\text{OXA-48}}$ and *bla*$_{\text{VIM-1}}$ had been described in EU/EEA countries at the time of the ECDC rapid risk assessment in 2021. In 2022, the Netherlands reported, via the EpiPulse platform, the detection of a hvKp ST23-K1 isolate carrying *bla*$_{\text{NDM-1}}$ in a patient with a history of travel to Morocco. In 2023, Lithuania reported, also via the EpiPulse platform, three ST23-K1 isolates carrying *bla*$_{\text{KPC-2}}$. France and Ireland submitted one hvKp ST23-K1 isolate each that was carrying *bla*$_{\text{OXA-181}}$ from 2019 and 2023, respectively (Figure 2). Despite the observed diversification of carbapenemase genes in the analysed isolates, *bla*$_{\text{OXA-48}}$ remains the most frequently detected carbapenemase gene in the EU/EEA (Table 1).

Figure 2. Hypervirulent *Klebsiella pneumoniae* (hvKp) ST23-K1 lineage isolates, by presence or absence of a carbapenemase gene and year of isolation, EU/EEA (n=194)*†



** Only isolates with available year of isolation are shown; † The time distribution illustrated above should not be interpreted as an epidemic curve as it is more likely that year-to-year variation is related to bias in detection and reporting than a reflection of true temporal trends in incidence. As hvKp isolates are mainly detected and subjected to WGS with screening targeted to carbapenem resistance, carbapenem-susceptible isolates may be considerably underdetected.*

Table 1. Carbapenemase gene detections in the hypervirulent *Klebsiella pneumoniae* (hvKp) ST23-K1 lineage isolates in the EU/EEA, by country and year(s) of isolation (n=89)*

Carbapenemase gene	Country	Year(s) of isolation	No. of detections
bla$_{OXA-48}$	Ireland	2019–2023	64
	France	2018–2019, 2021–2023	11
	Croatia	2019	2
	Germany	2012	1
	Latvia	2022	1
	Spain	2016	1
bla$_{KPC-2}$	Lithuania	2022–2023	3
	Poland	2009	1
bla$_{VIM-1}$	Italy	2016	1
	Poland	2019	1
bla$_{OXA-181}$	France	2019	1
	Ireland	2023	1
bla$_{NDM-1}$	The Netherlands	2022	1

** Only isolates with available year of isolation are shown.*

Clusters

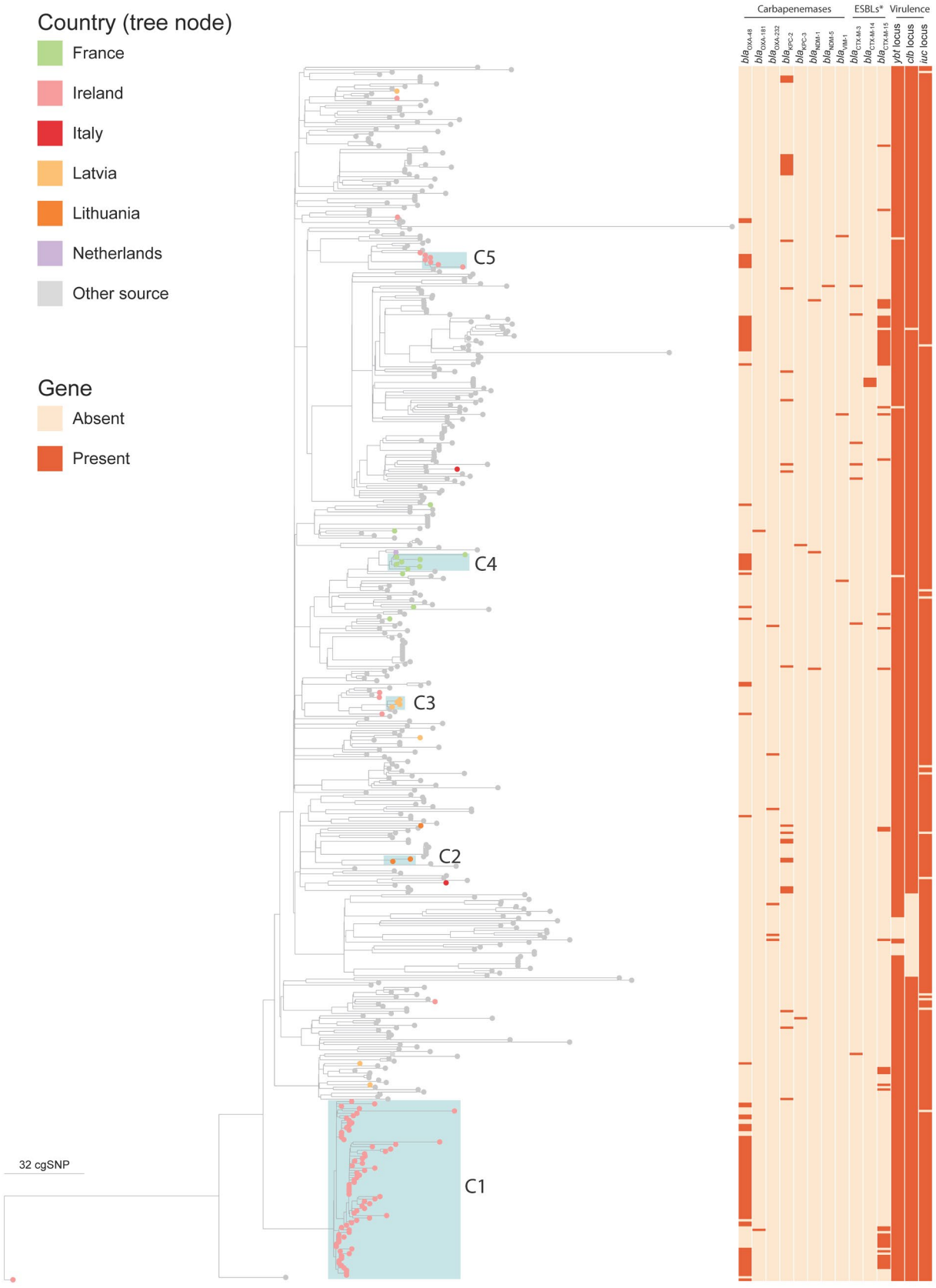
Five clusters with a difference of up to 38 SNPs were detected among isolates submitted to ECDC for analysis with a size ranging from 2–74 isolates and spanning one to five years. Cluster C1 is the best characterised cluster with epidemiological information. The results of the detailed investigation of 28 cases in this cluster confirmed spread within a network of acute care and residential facilities in Ireland [8]. Based on genomic relatedness, one cluster was also detected in each of France, Latvia and Lithuania; however, these have not been confirmed as being most likely due to within-country transmission by epidemiological information (Table 2, Figure 3).

Table 2. Description of clusters including two or more hypervirulent *Klebsiella pneumoniae* (hvKp) ST23-K1 lineage isolates submitted by NRLs in EU/EEA countries for this assessment (n=5 clusters)

Cluster	No. of isolates	No. of SNPs	Country	Year of isolation	Carbapenemase gene(s)	Epidemiological information
C1	74	0-38*	Ireland	2019–2023	None or *bla*$_{OXA-48}$ or *bla*$_{OXA-181}$	Investigation confirmed transmission in a network of healthcare facilities including acute care hospitals and residential facilities in the south-east of Ireland with sporadic related cases in other regions likely related to patient transfer.
C2	2	7	Lithuania	2022	*bla*$_{KPC-2}$	Cases in two different hospitals ~5 months apart.
C3	4	1-10	Latvia	2022	None	Cases in the same hospital over a period of ~4 months.
C4	7	2-38	France	2018–2021	*bla*$_{OXA-48}$	Cases in four different hospitals in the same region of France over a period of three years, considered to represent travel-related introductions.
C5	6	0-17	Ireland	2020–2022	*bla*$_{OXA-48}$	Cases in at least two different hospitals of the same region in Ireland over a period of two years.

** Sequence type single or double locus variants were excluded from the cluster distance estimation; SNP – single nucleotide polymorphism.*

Figure 3. Hypervirulent *Klebsiella pneumoniae* (hvKp) ST23-K1 lineage 23 with neighbouring relationships of isolates submitted by NRLs in EU/EEA countries for this assessment (tree nodes coloured by country) and from other data sources (grey) (n=511)



** Extended spectrum β-lactamase (ESBL) genes were only displayed if found in >2 isolates; ybt: yersiniabactin, clb: colibactin, iuc: aerobactin; cgSNP: core genome single nucleotide polymorphism; C1-5: clusters 1 to 5.*

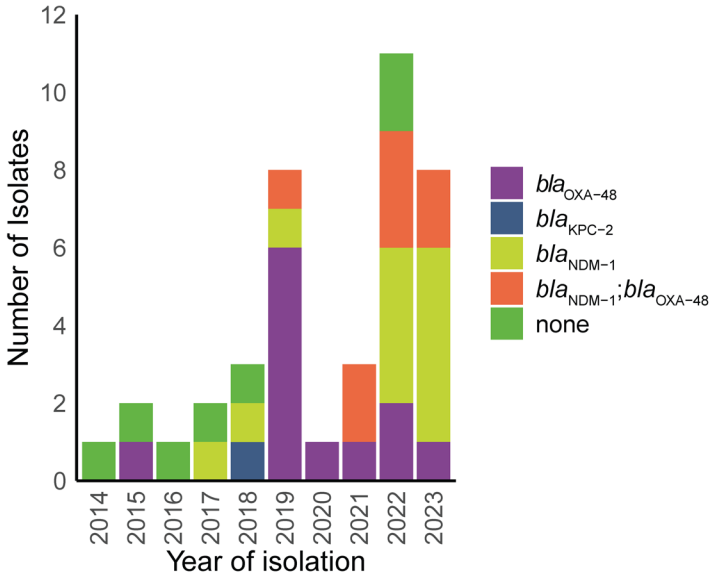
Klebsiella pneumoniae ST23-K57 lineage

In this analysis, 40 *K. pneumoniae* ST23 isolates belonged to a separate ST23-K57 lineage with distinct characteristics in comparison to the hvKp ST23-K1 lineage described above. Despite sharing the same sequence type by 7-locus MLST, this lineage is otherwise highly distant from the main hvKp ST23-K1 lineage for which hypervirulence, clinical presentation, and outcomes have been described in detail [4,7,9]. It is therefore not possible to assume that this lineage has the same clinical relevance as *K. pneumoniae* ST23-K1 [4]. However, *K. pneumoniae* ST23-K57 is also carrying a virulence plasmid, making it potentially hypervirulent and 'high-risk' due to the frequent combination with carbapenemase genes [4]. While hvKp ST23-K1 lineage is normally associated with the serum-resistant K1 capsule [10] and this is the capsule type of most isolates described in the previous section, the isolates in the ST23-K57 lineage have different capsule synthesis loci (KL57 or KL107). KL57 has previously been described as associated with hypervirulence [10]. In addition, these ST23-K57 isolates have a virulence score of 4, i.e. presence of the genes encoding for aerobactin (*iuc*) and yersiniabactin (*ybt*), but absence of the genes encoding for colibactin (*clb*). There are various further differences in the genetic characteristics between the ST23-K1 and ST23-K57 lineages, and it is therefore important to reliably differentiate them. In addition, further studies to better describe epidemiological and clinical characteristics are warranted.

Carbapenemase genes

The first isolate of the *K. pneumoniae* ST23-K57 lineage in this dataset was detected in 2014 in Moscow, Russia. Nine isolates detected from 2014 to 2018 were reported either from Poland (n=4) or Russia (n=5). None of the five isolates from Russia carried carbapenemase genes; however, isolate SRR7181964 (local code: KP254) was described as phenotypically resistant to carbapenems in a related publication [11]. The four isolates from Poland isolated between 2015 and 2018 already carried various carbapenemase genes, including $bla_{\text{OXA-48}}$, $bla_{\text{NDM-1}}$ or $bla_{\text{KPC-2}}$. The majority of ST23-K57 isolates detected from 2019 onwards carry at least one carbapenemase gene (Table 3, Figure 4).

Figure 4. *Klebsiella pneumoniae* ST23-K57 lineage isolates by presence or absence of a carbapenemase gene and by year of isolation (n=40)*†



** Only isolates with available year of isolation are shown; † The time distribution illustrated above should not be interpreted as an epidemic curve as the year-to-year variation may be affected by bias in detection and reporting and not represent a reflection of true temporal trends in incidence. The absence of reported isolates from non-EU/EEA countries in the period 2020-2023 is likely caused by a delay in data upload to public databases.*

Table 3. Carbapenemase gene detections in the *Klebsiella pneumoniae* ST23-K57 lineage isolates in the EU/EEA, by country and year(s) of isolation (n=32)*

Carbapenemase gene	Country	Year(s) of isolation	No. of detections
bla$_{OXA-48}$	France	2019-2020, 2022-2023	4
	Poland	2015, 2019	3
	Finland	2019, 2021	2
	Spain	2019	2
	Norway	2022	1
bla$_{NDM-1}$	Lithuania	2022-2023	5
	The Netherlands	2022	2
	Poland	2017-2018	2
	France	2019	1
	Ireland	2023	1
	Norway	2022	1
bla$_{NDM-1}$; *bla*$_{OXA-48}$	Denmark	2021-2022	3
	France	2022	1
	Hungary	2023	1
	Latvia	2023	1
	The Netherlands	2022	1
bla$_{KPC-2}$	Poland	2018	1

** Only isolates with available year of isolation are shown.*

Clusters

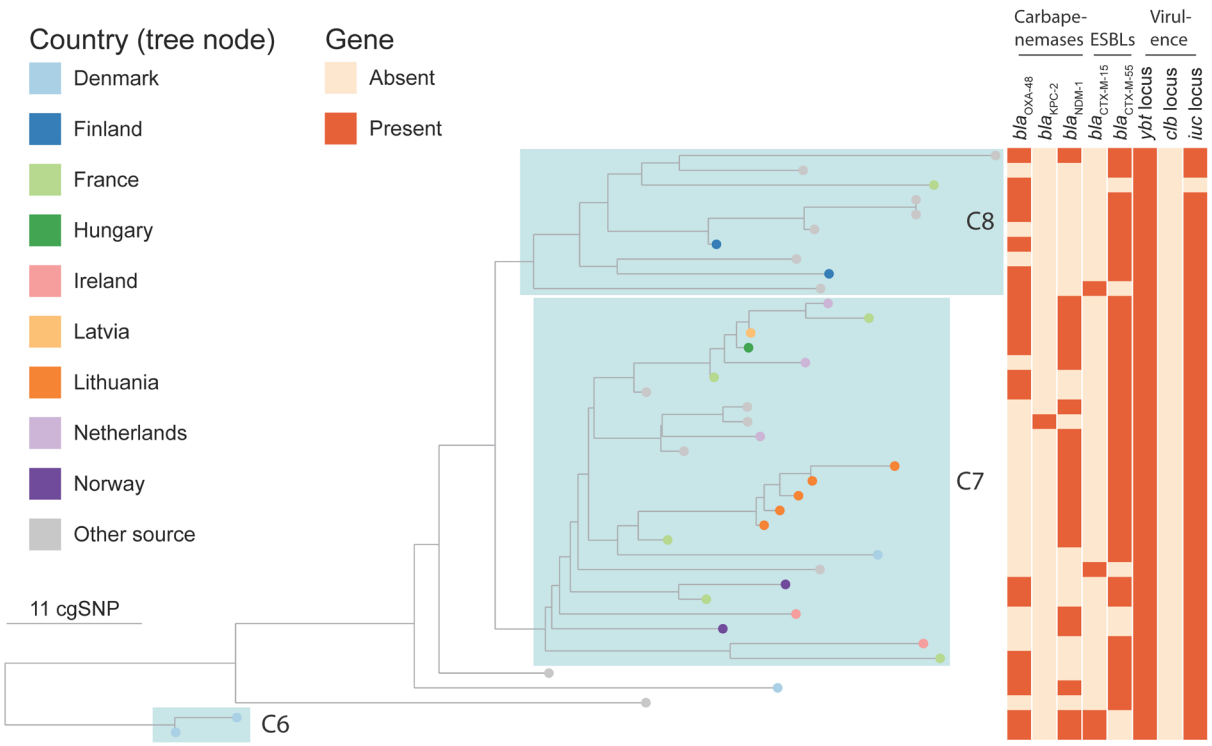
Three clusters were detected among *K. pneumoniae* ST23-K57 isolates ranging from a small cluster of two isolates in a single country to a multi-country cluster of 25 isolates detected in 10 countries. In line with the first detection of *K. pneumoniae* ST23-K57 in 2014 in Russia, 11 isolates detected in EU/EEA countries in the following years had an epidemiological link to Belarus, Russia, or Ukraine (Table 4). Six of these 11 isolates were collected in recent years (2022–2023) and were all epidemiologically linked to Ukraine. For many of the isolates from EU/EEA countries in these clusters, the nearest neighbouring isolate is from another country, suggesting independent introductions with the eastern European region as the likely origin; however, there are also several closely related isolates within the same EU/EEA country, i.e. Lithuania, indicating potential onward spread within the EU/EEA after initial introduction (Figure 5).

Table 4. Description of clusters including two or more *Klebsiella pneumoniae* ST23-K57 isolates submitted by NRLs in EU/EEA countries for this assessment (n=3 clusters)

Cluster	No. of isolates	No. of SNPs	Country	Year of isolation	Carbapenemase gene(s)	Epidemiological information
C6	2	5	Denmark	2021	*bla*$_{NDM-1}$/ *bla*$_{OXA-48}$	One isolate with history of travel to Belarus.
C7	25	0-61†	Multi-country (DK, FR, HU, IE, LT, LV, NL, NO, PL, RU)	2015–2023	*bla*$_{OXA-48}$ or *bla*$_{KPC-2}$ or *bla*$_{NDM-1}$ or *bla*$_{NDM-1}$/ *bla*$_{OXA-48}$	Eight isolates with history of travel (n=1) or hospitalisation (n=4) or both (n=3) in Ukraine and one isolate with history of travel and hospitalisation in Russia.
C8	10	0-60†	Multi-country (ES, FI, FR, PL, RU)	2015–2023	*bla*$_{OXA-48}$ or *bla*$_{NDM-1}$/ *bla*$_{OXA-48}$	One isolate with history of hospitalisation in Russia.

† large cluster SNP distance is due to inclusion of epidemiologically relevant isolates collected in a span of several years; SNP – single nucleotide polymorphism; DK, Denmark; ES, Spain; FI, Finland; FR, France; HU, Hungary; IE, Ireland; LT, Lithuania; LV, Latvia; NL, the Netherlands; NO, Norway; PL, Poland; RU, Russia.

Figure 5. *Klebsiella pneumoniae* ST23-K57 lineage isolates with neighbouring relationships of isolates submitted by NRLs in EU/EEA countries for this assessment (tree nodes coloured by country) and from other data sources (grey) (n=40)



ESBL, extended-spectrum β-lactamase, ybt – yersiniabactin, clb – colibactin, iuc – aerobactin; cgSNP – core genome single nucleotide polymorphism; C6-8 – clusters 6 to 8.

Disease background

Hypervirulent *Klebsiella pneumoniae* (hvKp)

HvKp is a clinically significant pathogen causing invasive infections such as pneumonia or lung abscess, but is primarily associated with hepatic abscesses in both healthy and immunocompromised individuals [12]. HvKp from these severe pyogenic liver abscesses often spread to distant sites, leading to meningitis, necrotising fasciitis, and endophthalmitis [13]. In addition, a case report from Australia described multi-focal osteomyelitis in a previously healthy 20-year-old man, which is a rare complication of hvKp [14]. Notably, life-threatening hvKp infections may occur in young and healthy individuals and are associated with high morbidity and mortality, mainly due to the high invasiveness of hvKp and rapid progression of the infection. A significant number of hvKp infections are community-acquired, suggesting that hvKp strains circulate among healthy individuals. The first reports of hvKp were from Taiwan and Southeast Asia in the mid-1980s and 1990s. HvKp is considered as the main cause of liver abscesses in Hong Kong (China), Singapore, South Korea, and Taiwan. In 10 Chinese cities, an average 37.8% of *K. pneumoniae* isolates causing healthcare-associated infections were found to be hvKp, with the highest percentage (73.9%) in Wuhan [15].

Reports from other geographic regions indicate global distribution [13,16]. Sporadic cases of liver abscess due to hvKp have been reported from Europe as well as Canada and the United States (US), often connected with travel or migration [17-22]. In a Canadian study of *K. pneumoniae* isolates causing community-acquired bacteraemia in the Calgary area, 10 (8.2%) of 134 isolates had a hypermucoviscous phenotype [23]. In a US study of *K. pneumoniae* bloodstream isolates from two hospitals in Houston, Texas, four (6.3%) of 64 isolates carried at least one of the virulence genes *rmpA* and *magA* [24]. Screening of patients in a hospital in New York detected multiple strains of hvKp acquired within the community, leading the authors to conclude that several clones of the hvKp are established in New York [25]. Data on the prevalence of hvKp infections in the EU/EEA are scarce. In a study of bacteraemia caused by hvKp in a teaching hospital in Barcelona, Spain, for the period 2007 to 2013, 1.8% of the blood isolates were hvKp ST23 [26].

Emergence of hvKP carrying carbapenemase genes

Carbapenem resistance has previously been rare in hvKp ST23 isolates. However, Figure 2 shows that, since 2012, the hvKp ST23-K1 lineage has acquired diverse carbapenemase genes with increasing frequency. In addition to the

increasing frequency of carbapenemase genes in the worldwide dominant lineage of hvKp, the combination of virulence and carbapenem resistance genes on the same plasmid is also of concern, as this allows for the simultaneous acquisition of virulence and resistance genes. In 2013, a Chinese study detected hvKp ST23 carrying a KPC-2-encoding element integrated into a virulence plasmid [27]. Researchers from the UK also described virulence plasmids in healthcare-associated isolates of various 'high-risk' *K. pneumoniae* sequence types (e.g. ST15, ST101, and ST147) that carried carbapenemase genes [28]. More specifically, an NDM-producing hypervirulent *K. pneumoniae* ST23 was isolated in a patient of Bangladeshi origin hospitalised in London (UK) [29]. Carbapenemase-producing hvKp ST23 strains have been also described in Argentina [30]. In a recent report from India, a neonate was infected with an OXA-232-producing hvKp ST23-K1 strain causing neonatal sepsis [31].

Risk assessment questions

What is the risk associated with the dissemination of hvKp ST23 carrying carbapenemase genes in the EU/EEA?

ECDC risk assessment for the EU/EEA

Extended disease spectrum and mortality

Due to its increased virulence, hvKp causes a different spectrum of disease than the 'classic' (non-hypervirulent) *K. pneumoniae* infections known to clinicians in EU/EEA countries. While 'classic' *K. pneumoniae* is an opportunistic pathogen typically affecting vulnerable patients with comorbidities in healthcare facilities, hvKp has the ability to cause infections in previously healthy individuals [10]. In the Asian countries where it is endemic, hvKp has emerged as a frequent cause of pyogenic liver abscess, community-acquired pneumonia (CAP), and community-acquired meningitis, while these types of infection are non-existent or rare with 'classic' *K. pneumoniae* [10]. In endemic countries, hvKp is not only a major cause of the above-mentioned infections but is also driving an increasing incidence of pyogenic liver abscesses [10].

There is also some evidence that, in areas where hvKp is endemic, *K. pneumoniae* partially replaces other pathogens such as *Streptococcus pneumoniae* as a frequent cause of CAP [32,33]. Another difference from 'classic' *K. pneumoniae* infection is that hvKp infection often presents at multiples sites and with metastatic spread [10]. Although EU/EEA-specific data on the outcome of hvKp infections are not available apart from anecdotal reports, it is expected that an increased frequency of hvKp infections, particularly those carrying a carbapenemase, in the EU/EEA would result in increased morbidity. Four of 28 hvKp ST23-K1 cases in Ireland had an infection at the time of detection (three bloodstream infections and one urinary tract infection); however, there was no systematic follow-up of asymptomatic carriers for subsequent hvKp infection [8].

Hospital outbreaks of carbapenem-resistant hvKp have been associated with very high mortality [34-36]. In an outbreak of ventilator-associated pneumonia (VAP) caused by KPC-2-producing hvKp ST11 in a Chinese hospital, all five affected patients died of severe lung infection, multi-organ failure or septic shock [34]. In an outbreak of VIM-2 producing hvKp ST23 among mechanically ventilated patients in an Iranian ICU, four of five patients with hvKp ST23 died compared to none of 48 patients with VAP with 'classic' *K. pneumoniae* [36]. In a study from Eastern China, KPC-2 producing hvKp meningitis resulted in the death of all 15 affected patients, a majority of whom had prior neurosurgical conditions [35]. In the US, mortality of hvKp infection has been shown to be higher than that of 'classic' *K. pneumoniae* infections and of multidrug-resistant 'classic' *K. pneumoniae* infections [25]. While mortality of severe infections of carbapenemase-producing 'classic' *K. pneumoniae* is already high, with reported mortality rates between 30 and 75% [37], mortality seems to be, based on the above, even higher in healthcare-associated hvKp infections, although only limited data are currently available.

Resistance pattern

According to the literature, as well as shown in our analysis, various carbapenemase genes have in recent years been detected in hvKp isolates, including *bla*$_{\text{OXA-48}}$-like, *bla*$_{\text{KPC}}$, *bla*$_{\text{NDM}}$, and *bla*$_{\text{VIM}}$ carbapenemases genes. The spectrum of carbapenemase genes detected in hvKp ST23-K1 isolates in the EU/EEA has increased, with the detection of isolates carrying the *bla*$_{\text{NDM-1}}$, *bla*$_{\text{KPC-2}}$ and *bla*$_{\text{OXA-181}}$ carbapenemase genes in addition to isolates carrying *bla*$_{\text{OXA-48}}$ and *bla*$_{\text{VIM-1}}$ already described in the previous ECDC rapid risk assessment.
Isolates with and without carbapenemase genes are widely distributed throughout the phylogenetic tree (Figure 3), indicating that carbapenemase gene acquisition has most likely occurred independently, on various occasions, and probably by acquisition of resistance plasmids. The hvKp ST23-K1 isolates from the EU/EEA had mainly acquired *bla*$_{\text{OXA-48}}$-like carbapenemase genes that often result in low-level carbapenem resistance. Nevertheless, carbapenem treatment failures when treating infections with OXA-48-producing bacteria have been described, as well as, in animal models, a lack of activity of carbapenems against OXA-48-producing Enterobacterales despite *in vitro* susceptibility to carbapenems [38]. In addition, 24 of 105 hvKp ST23-K1 isolates carrying *bla*$_{\text{OXA-48}}$-like genes also carried *bla*$_{\text{CTX-M-15}}$ thus ruling out third-generation cephalosporins as a treatment option. In addition, hvKp ST23 isolates resistant to last-resort antibiotics such as colistin or ceftazidime-avibactam have been described in the

literature [39,40]. An extensively drug-resistant (XDR) hvKp ST23 isolate was reported from Spain [41]. Twenty of the investigated 28 isolates from Ireland were classified as multidrug-resistant and 20 of these as XDR [8]. These reports indicate that hvKp ST23 infections may become increasingly difficult to treat.

Frequency of detection in the EU/EEA

The number of EU/EEA countries detecting hvKp ST23 isolates increased considerably, from 4 to 10 countries, since the previous ECDC rapid risk assessment in 2021, and the number of isolates submitted for analysis by these countries from 12 to 143 isolates. However, the increasing frequency of detection could also partially be explained by increased laboratory capacity for molecular testing and an increased likelihood for detecting hvKp carrying carbapenemase genes with screening of patients for carriage of carbapenem-resistant Enterobacterales (CRE).

There is still a high likelihood that hvKp isolates and infections are currently underdetected in the EU/EEA. Since the detection of hypervirulence is not part of routine diagnostic microbiology, hvKp may go unnoticed, unless suspected by clinicians aware of the clinical picture from descriptions in the scientific literature and the isolates are then referred for further characterisation. The clinical presentation and extended disease spectrum of hvKp has not yet been encountered by many clinicians in EU/EEA countries. In addition, a presumptive clinical diagnosis would depend on the presentation of the typical clinical features of a community-onset infection. This clinical picture may, however, differ in vulnerable patients in healthcare settings, likely making the clinical diagnosis of healthcare-associated hvKp difficult. Phenotypic tests such as the string test for hypermucoviscosity have a low sensitivity [25], and molecular testing would be needed for the identification of virulence genes. While many laboratories have the capacity for molecular identification of the most frequent carbapenem resistance genes with in-house or commercial molecular tests, the identification of virulence genes is currently not part of standard diagnostics. Increased carbapenem resistance in hvKp might lead to the more frequent identification of hvKp isolates detected with patient screening procedures focused on the detection of CRE carriage. However, hypervirulence would still only be detected if PCR-screening for virulence genes, such as those encoding for yersiniabactin, colibactin and aerobactin, is followed by WGS of positive isolates [42] or if there is high national WGS coverage of carbapenem-resistant *K. pneumoniae* with systematic analysis of virulence genes or further investigation of STs associated with hypervirulence, such as ST23.

Potential routes of spread

Transmission in community

While the transmission of 'classic' (non-hypervirulent) carbapenem-resistant *K. pneumoniae* strains is largely driven by spread in healthcare settings [43], hvKp ST23 was initially described mainly as the causative agent of community-associated infections. Based on the routes of spread of Enterobacterales in general, hvKp acquisition could potentially occur via contaminated food or water, person-to-person transmission in close contacts such as family members, as well as zoonotic transmission [10]. In general, hvKp colonises the gut of healthy individuals, and can spread further via the faecal-oral route [44]. Contamination of a food sample (cucumber) with hvKp ST23 carrying bla_{KPC-2} has been described in China [45]. In some areas in Asia, there is a high prevalence of hvKp carriage in the population, with a high probability of transmission if adequate hygiene and sanitation standards are not available. However, it is unlikely that the probability of transmission in the community in the EU/EEA can be inferred from examples from other geographical areas with different climatic, environmental, and living conditions.

As hvKp can also be found in the environment, this might affect prevalence in the overall population and therefore the subsequent risk of further transmission in the community; however, the exact role of environmental factors is currently unknown [46]. In most cases, the immediate source for human infection with hvKp is likely the patient's own gut flora, reflecting prior carriage [44]. In the community, transmission and acquisition of Enterobacterales, including multidrug-resistant and hypervirulent *K. pneumoniae*, likely result, in most cases, in silent transient or persistent gut colonisation with only a minority of acquisitions resulting in clinical presentation of infection. The frequency with which infection develops is currently unclear. In a study assessing carriage of *K. pneumoniae* of 2 975 people in Norway in 2015–2016, only one person was found to carry hvKp ST23 [47]. In the absence of further studies investigating hvKp carriage also in other EU/EEA countries and in more recent years, it is not possible to assess the extent to which hvKp is present in the EU/EEA population. Detection of hvKp in the community is challenging and will ultimately require molecular testing for reliable identification. In practice, detection of cases in the community mostly depends on the recognition of clinical features of a typical community-onset hvKp infection when a patient seeks healthcare.

Transmission in healthcare settings

A shift from community-acquired infections to healthcare-associated infections seems to have already occurred in areas where hvKp is endemic, e.g. in Asia. A report from China indicates that hvKp strains may have started to replace other non-hypervirulent *K. pneumoniae* strains in healthcare settings [48]. This, as well as various outbreaks reported from China, Iran, and Russia [34-36,49], indicates that carbapenemase-producing hvKp has the capacity to establish itself as a healthcare-associated pathogen in a similar way as 'classic' (non-hypervirulent) carbapenem-resistant *K. pneumoniae* clones that are already spreading in healthcare settings in many EU/EEA

countries [37]. While the common risk factors for 'classic' multidrug-resistant (including carbapenem-resistant) *K. pneumoniae* infections include intensive care, critical illness, and invasive devices [50,51], the patient population at risk for hvKp infections will be much larger than these well-known high-risk groups. In addition, virulence genes are now also being acquired by 'classic' high-risk clones of *K. pneumoniae*, which are known to transmit efficiently in healthcare settings.

The strongest evidence of healthcare-associated transmission in the EU/EEA comes from Ireland where a cluster of 74 isolates, the majority of which carried a carbapenamase, with sampling dates spanning a period of five years has been detected (Table 1). Further investigation of 28 of these isolates confirmed transmission of hvKp ST23-K1 in a network of healthcare facilities in Ireland with all cases having a history of recent hospitalisation or residence in a long-term care facility [8]. Clusters of hvKp ST23-K1 isolates were also detected in France, Latvia and Lithuania although these were not confirmed by epidemiological information. A hvKp ST23-K1 isolate was described as part of a cluster of seven isolates in Germany [52].

Risk of further spread

Since the last ECDC rapid risk assessment in 2021, the number of EU/EEA countries reporting hvKp ST23 cases has increased from four to 10 countries and the number of isolates submitted for analysis by these countries has increased from 12 to 143 isolates even though detailed information about carriage/infection status is not available. The spectrum of carbapenemase genes detected in hvKp ST23-K1 isolates in the EU/EEA has also increased, with the detection of isolates carrying the *bla*$_{\text{NDM-1}}$, *bla*$_{\text{KPC-2}}$ and *bla*$_{\text{OXA-181}}$ carbapenemase genes in addition to isolates carrying *bla*$_{\text{OXA-48}}$ and *bla*$_{\textit{VIM-1}}$ already described in the previous ECDC rapid risk assessment. Furthermore, there is now evidence of sustained spread of the dominant hvKp ST23-K1 lineage between healthcare facilities in Ireland over a period of five years, despite enhanced control efforts. Clusters of hvKp ST23 isolates indicating potential within-country transmission were also detected in France, Latvia and Lithuania; however, these have so far not been confirmed as being most likely due to within-country transmission with epidemiological data. Similar spread of hvKp may already occur in and between healthcare settings in other EU/EEA countries with less well-established surveillance.

There is a high probability that hvKp can spread further in healthcare settings in EU/EEA countries, in analogy to the dissemination of 'classic' (non-hypervirulent) carbapenemase-producing *K. pneumoniae* and other carbapenem-resistant Enterobacterales that rapidly disseminated within and between healthcare settings in the EU/EEA in recent years [43,53]. In addition, the 'classic' *K. pneumoniae* have also been shown to acquire hypervirulence. As described above, a high health impact (morbidity, mortality) on the EU/EEA patient population of the spread of hvKp could be expected. **The probability for further dissemination and establishment of hvKp carrying carbapenemase genes in healthcare settings in EU/EEA countries with consequent significant impact on morbidity and mortality is therefore considered to be high, based on the evidence for sustained transmission of the hvKp ST23-K1 lineage carrying carbapenemase genes in healthcare settings within the EU/EEA.**

The difficulties with laboratory detection and confirmation of hvKp may result in its transmission in the community and in healthcare settings being unnoticed. To date, there is no evidence of sustained community transmission of hvKp ST23-K1 in the EU/EEA; however, this may only be due to lack of awareness and underdetection. The CCRE survey detected 19 isolates of hvKp ST23 in 11 countries, of which 16 were part of the carbapenem-susceptible comparator group, thus indicating that carbapenem-susceptible hvKp ST23 also has a wider distribution and is more frequent than previously reported. While the risk for spread of hvKp in the community is currently considered moderate, there remains a possibility for further introductions which may result in sustained community spread.

Options for response

Clinical awareness

The implementation of control measures depends on early and reliable identification of hvKp in clinical settings and by national surveillance. There is therefore a need for increased clinical and public health awareness as well as increased laboratory capacity for the detection of hvKp throughout the EU/EEA. As the extended disease spectrum of hvKp infections has to date rarely been encountered in EU/EEA countries, it is also advisable to raise awareness among clinicians and diagnostic laboratory services to suspect hvKp infections based on (a) the typical picture of community-acquired hvKp infections, (b) unusual metastatic spread of *K. pneumoniae* infections, or (c) clusters of healthcare-associated *K. pneumoniae* infections with increased severity and mortality. Early communication of clinicians with the laboratory staff to request testing for virulence genes in *K. pneumoniae* infections with signs of increased virulence and antimicrobial resistance is vital. However, there would also be a need to include, in diagnostics and clinical decision-making pathways and in addition to antimicrobial resistance, other potentially equally dangerous characteristics of bacteria such as enhanced virulence.

Laboratory capacity and surveillance

Reliable identification of hvKp currently requires molecular testing of the isolates. NRLs therefore require the capacity to detect and analyse relevant virulence genes in addition to resistance genes. PCR-based testing of *K. pneumoniae* isolates for virulence genes and the systematic collection of hvKp isolates at the NRLs would improve the understanding of the extent of national spread, as well as provide data for assessment at the EU/EEA level. NRLs need the capacity and resources for routine WGS of selected *K. pneumoniae* isolates for outbreak detection and monitoring of resistance genes and virulence genes, and the capacity to support national outbreak investigations.

The experience from Ireland shows that waiting for an increasing number of severe *K. pneumoniae* infections may result in missing the timepoint for effective early control of hvKp spread. Although, in Ireland further molecular and epidemiological investigations were implemented following a signal of two blood culture isolates, hvKp ST23 had at that point in time already spread throughout a network of healthcare facilities. As other *K. pneumoniae* high-risk clones in healthcare settings, hvKp ST23 mainly spreads via non-symptomatic carriers. EU/EEA countries are therefore encouraged to regularly test *K. pneumoniae* isolates, especially those from bloodstream infections, for the presence of virulence genes and implement WGS-based surveillance for *K. pneumoniae* for the early identification of the introduction of hvKp ST23 into their healthcare system.

Carbapenem AST for Enterobacterales is routine in most clinical laboratories in the EU/EEA, frequently complemented by testing for resistance genes. Depending on the frequency with which hvKp isolates are detected at national level, there may also be the need for building capacity in clinical microbiology laboratories for the detection of virulence genes associated with hypervirulence. This might provide valuable information for the clinical management of patients with hvKp infections. For this purpose, effective methods and strategies to screen for virulence genes in the routine diagnostic laboratory would need to be developed. If there is evidence of dissemination of hvKp within countries, surveillance systems may need to include options for tracking virulence genes in addition to resistance genes.

Infection prevention and control measures

Enhanced infection prevention and control (IPC) measures for hvKp ST23 carrying carbapenemase genes should be applied in acute care facilities in analogy to enhanced control measures for carbapenem-resistant non-hypervirulent *K. pneumoniae*. Effective infection control measures to prevent the spread of CRE, including carbapenemase-producing *K. pneumoniae*, include:

- implementation of active surveillance through rectal screening for CRE of patients at risk for CRE carriage on hospital admission, or admission to specific wards/units, and during outbreaks (of note, there is currently no established screening method specifically for hvKp);
- pre-emptive implementation of contact precautions, including isolation on admission during outbreaks and/or based on risk factors for carriage;
- hand hygiene;
- patient isolation in a single room (preferably with their own toilet facilities) when available;
- when single-patient rooms are in short supply, patients should be cohorted in the same room(s) or ward, and dedicated staff and medical equipment should be ensured;
- environmental cleaning of the immediate surrounding area (that is, the 'patient zone') of patients;
- IPC training of staff;
- case notification/flagging;
- contact tracing; and
- antibiotic stewardship.

Note: the application of the above measures should be implemented according to the epidemiological situation, as described in more detail in ECDC's Rapid Risk Assessment on 'Carbapenem-Resistant *Enterobacteriaceae* – second update' [37]. In residential care settings, all practical IPC measures to reduce the risk of spread should be implemented taking account of the total care needs of residents and the harm to residents associated with extended periods of single room isolation.

For details on control measures for CRE in general, please refer to:

- ECDC's guidance on IPC measures and tools for the prevention of the entry of carbapenem-resistant *Enterobacteriaceae* into healthcare systems [54];
- ECDC's Rapid Risk Assessment on Carbapenem-resistant *Enterobacteriaceae* – second update, 26 September 2019 [37];
- WHO's guidelines for the prevention and control of carbapenem-resistant Enterobacteriaceae, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in healthcare facilities [55]; and
- WHO's implementation manual to prevent and control the spread of carbapenem-resistant organisms at the national and healthcare facility level: interim practical manual supporting implementation of the guidelines for the prevention and control of carbapenem-resistant *Enterobacteriaceae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in healthcare facilities [56].

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All experts have submitted declarations of interest, and a review of these did not reveal any conflict of interest.

Disclaimer

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