RAPID RISK ASSESSMENT

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

17 March 2021

Summary

In an urgent inquiry in ECDC's Epidemic Intelligence Information System (EPIS) Antimicrobial Resistance and Healthcare-Associated Infections (AMR-HAI) platform, Ireland reported the isolation of hypervirulent *Klebsiella pneumoniae* (hvKp) ST23, from diagnostic samples and from rectal or faecal samples collected for the surveillance of carriage of carbapenemase-producing Enterobacterales (CPE) since March 2019 with two distinct geographical clusters as well as sporadic cases. Information on further hvKp ST23 isolates detected in the European Union/European Economic Area (EU/EEA) were either found in public databases (n=26) or submitted by National Reference Laboratories (NRLs) in reply to a data request to the European Antimicrobial Resistance Genes Surveillance Network (EURGen-Net) (n=12). The analysis showed that several of the isolates detected in EU/EEA countries after 2012 carried carbapenemase genes, most frequently $bla_{\text{OXA-48}}$.

This emergence of *K. pneumoniae* isolates with combined hypervirulence and resistance to reserve antibiotics such as carbapenems is of concern as, in contrast to 'classic' *K. pneumoniae* strains, hvKp strains are capable of causing 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 antimicrobial resistance and virulence in hvKp strains, there is a possibility of potentially untreatable (difficult-to-treat) infections in previously healthy adults. An even higher morbidity and mortality is to be expected if carbapenem-resistant hvKp strains spread in healthcare settings and affect a vulnerable patient population. Although only few cases and clusters have been reported in the EU/EEA to date, it is important to detect hvKp early and prevent further dissemination in healthcare settings in EU/EEA countries to avoid the establishment of carbapenemase-producing hvKp as a healthcare-associated pathogen similar to 'classic' carbapenemase-producing *K. pneumoniae*. The risk associated with the further dissemination of carbapenemase-producing hvKp for the patient population in the EU/EEA is currently considered to be moderate, but might become high in the future if hvKp ST23 is established in healthcare settings. Further studies are needed to determine the prevalence of hvKp ST23 in the EU/EEA.

Options for response include alerts to clinicians and clinical microbiology laboratories, the establishment of sufficient laboratory capacity to detect hvKp isolates, and the submission of all suspected hvKp isolates (for example, based on hypermucoviscosity and a positive string test) with or without additional antimicrobial resistance to National Reference Laboratories (NRLs) for further analysis. Prospective data collection on hvKp, including epidemiological data on cases 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.

Suggested citation: European Centre for Disease Prevention and Control. Emergence of hypervirulent *Klebsiella pneumoniae* ST23 carrying carbapenemase genes in EU/EEA countries. 17 March 2021. ECDC: Stockholm; 2021.

Event background

Urgent inquiry and data request to EURGen-Net

On 17 November 2020, Ireland posted an urgent inquiry (UI) on the EPIS AMR-HAI platform reporting the detection of hypervirulent *Klebsiella pneumoniae* (hvKp) ST23 isolates in Ireland since March 2019. These hvKp ST23 isolates included isolates from clinical samples, e.g. blood cultures (n=2), liver abscess (n=2), urine (n=4), wound swabs (n=1) as well as $bla_{\text{OXA-48}}$-positive hvKp isolates from rectal or faecal samples collected for surveillance of carriage of carbapenemase-producing Enterobacterales (CPE) (n=23). The isolates were initially reported in EPIS AMR-HAI as carrying the following genes that are associated with hypervirulence: *iroB*, *iroC*, *iroD*, *iroN* (salmochelin), *iutA*, *iucB*, *iucC*, *iucD* (aerobactin), and *rmpA2* (hypermucoviscosity). Two geographically distinct clusters were identified, as well as two additional sporadic cases. One of these sporadic cases was associated with travel from North Africa. Prior to March 2019, *K. pneumoniae* ST23 isolates had not been reported in the database of the relevant Irish National Reference Laboratory Service.

To gain more information on the potential spread of hvKp ST23 in the EU/EEA, ECDC requested the 37 National Reference Laboratories (NRLs) participating in the European Antimicrobial Resistance Genes Surveillance Network (EURGen-Net) to submit whole-genome sequencing (WGS) data from their collection on isolates of *K. pneumoniae* ST23. WGS data and basic epidemiological data from *K. pneumoniae* ST23 isolates were submitted by Finland (n=1), France (n=5), and Sweden (n=1), as well as for a subset of five representative isolates from Ireland.

Whole-genome sequencing analysis

Methodology

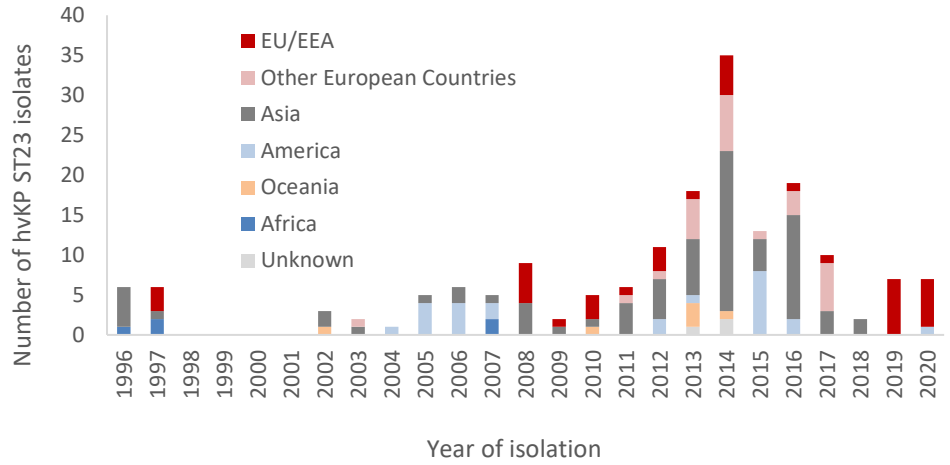
Raw reads were assembled using SPAdes and uploaded to Pathogenwatch for analysis. All genomes passed quality control, with more than 95% of core genes detected. The file names of the assembled genomes were pseudonymised using the country code and consecutive numbers. The submitted genomes were compared against 120 genomes of *K. pneumoniae* ST23 isolates available in Pathogenwatch after the removal of 20 isolates of non-human origin (a group of isolates isolated from horses in France in the 1980s and a group of environmental isolates from a hospital outbreak in the United Kingdom (UK) in 2015) and complemented with 57 genomes of isolates listed in the supplemental material of a recent study on the population genomics of the hvKp clonal group 23 [1]. A search with the National Centre for Biotechnology (NCBI) pathogen detection database [2] for closely related isolates of human origin to the isolates submitted by the countries identified two additional isolates with genomes already assembled in the public domain. A search for additional isolates included in scientific articles on hvKp ST23 in European countries yielded another four genomes from three studies [3-5]. From the four aforementioned genomes, one genome reported from a Russian study as being of ST23 was included although the locus variant for *rpoB* was not found after genome assembly of the raw reads. HvKp isolates described in eight other studies [6-13] were either already included, not subjected to WGS, or did not have a link to WGS data available in the public domain.

All additional genomes were uploaded to Pathogenwatch. In total, 195 non-duplicate genomes were considered for further analysis, including 183 from public databases and 12 submitted by the NRLs. A phylogenetic tree was constructed using Pathogenwatch core genome SNPs [14]. Antimicrobial resistance genes, virulence genes (as well as the derived virulence score), and capsule type genes were identified using Kleborate [15] and visualised using Microreact [16]. Phenotypic information on hypermucoviscosity was not reported to ECDC for the submitted genomes. In addition, carbapenem antimicrobial susceptibility testing (AST) results were not available to a sufficient extent to conclude on phenotypic carbapenem resistance at the time of writing this assessment.

Results

The 183 genomes of *K. pneumoniae* ST23 isolates from the public databases originated from Asia (n=92), EU/EEA countries (n=26), non-EU/EEA European countries (n=25), America (n=25), Oceania (n= 7), and Africa (n=5). For three genomes, no information on the country of origin of the isolate was available. The 26 genomes from EU/EEA isolates in the public domain were reported from Austria (n=1), Belgium (n=1), Czechia (n=3), Denmark (n=2), Estonia (n=1), France (n=9), Germany (n=1), Italy (n=2), the Netherlands (n=1), Norway (n=4), and Spain (n=1). Figure 1 shows the timeline for the *K. pneumoniae* ST23 isolates provided by countries for this analysis and the data gathered from public domain, by year of isolation. Only 178 of 195 isolates with information on the year of isolation could be included. For the remaining isolates, the year of isolation was not available (n=3) or only a range of years was specified (n=14).

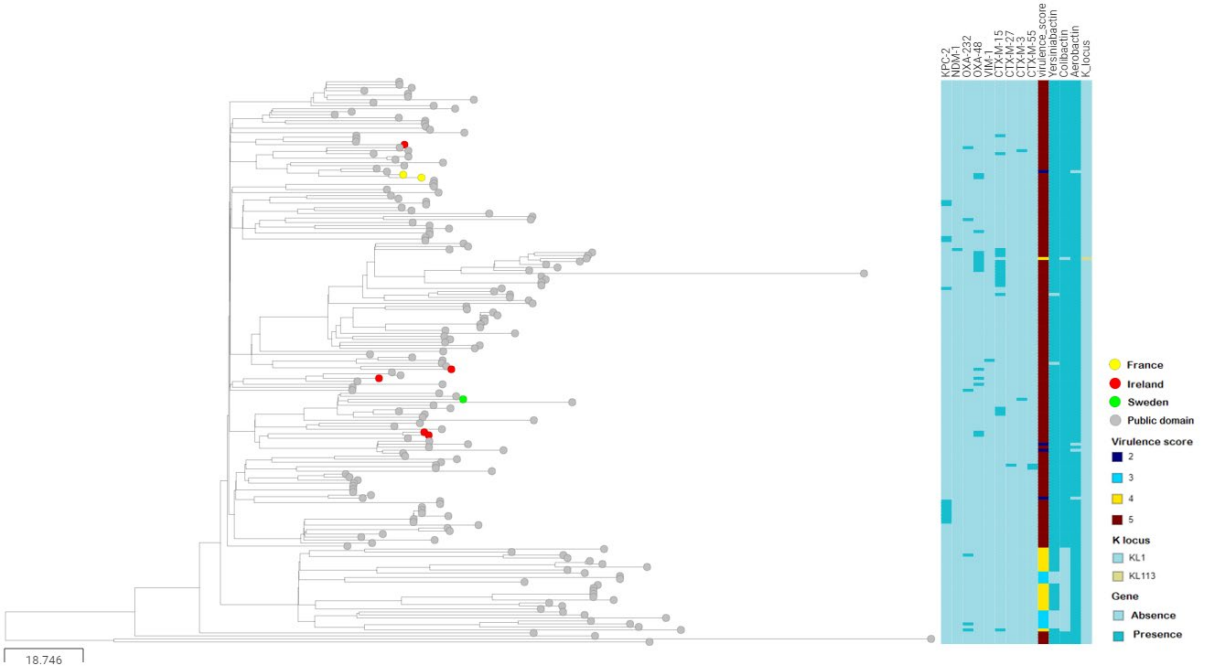
Figure 1. Time distribution of hypervirulent *Klebsiella pneumoniae* (hvKp) ST23 isolates included in this analysis, by continent and year (n=178)*†



** Only isolates with available year of isolation are shown; † The time distribution illustrated above should not be interpreted as an epidemic curve as it more likely that year-to-year variation is related to bias in detection and reporting than a reflection of true temporal trends in incidence.*

The earliest isolates included in this analysis were detected in 1996 in Asia (n=5) and Africa (n=1). The earliest isolates from the EU/EEA were three human invasive isolates from 1997 detected in Belgium, the Netherlands, and Spain, which were sequenced for an analysis of the population genomics of the hvKp clonal group 23 [1]. 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 2002 onward. The time distribution should also not be interpreted as an epidemic curve as it more likely that year-to-year variation is related to bias in detection and reporting than a reflection of true temporal trends in incidence. For example, the lower numbers described above after 2016 might reflect a delay until WGS data are made available in the public domain. Most of the EU/EEA isolates with the year of isolation after 2018 are the isolates with the non-public data submitted by EU/EEA countries for this assessment. Further analysis showed that the included 195 isolates belonged to two separate clades with a global main clade (188 isolates) and a smaller more recent clade (seven isolates), which are shown in Figures 2 and 5, and described in further detail below.

Figure 2. Main K1 ST23 clade with neighbouring relationships of hypervirulent *Klebsiella pneumoniae* (hvKp) ST23 isolates submitted for this study (coloured by country) and from open-access databases (grey) (n=188)



Main K1 ST23 clade

Most of the hvKp ST23 isolates in this analysis belonged to one worldwide clade with capsule type 1 that included isolates from five continents over a period of 24 years. This clade was composed of 188 isolates (99.4% of the isolates in this analysis), of which 180 genomes were from the public domain. From these 188 isolates, 155 (82.4%) had a virulence score of 5 based on the presence of the genes encoding for yersiniabactin (*ybt*), colibactin (*clb*) and aerobactin (*iuc*) as determined by Kleborate [15]. Eight of the genomes provided by France, Ireland, and Sweden belonged to this main clade and were located in six distant positions throughout the phylogenetic tree (Figure 2) and were not closely clustered (within 30 core genome SNPs) with any of the other included isolates. Table 1 shows that, according to the nearest related isolates, hvKp ST23 isolates detected in the EU/EEA are linked to diverse geographic regions, including North America, the Middle East, Asia, Russia, and Africa, as well as other EU/EEA countries.

Table 1. Main clade of hypervirulent *Klebsiella pneumoniae* (hvKp) ST23: description of isolates submitted for this analysis and nearest related isolates from the public domain

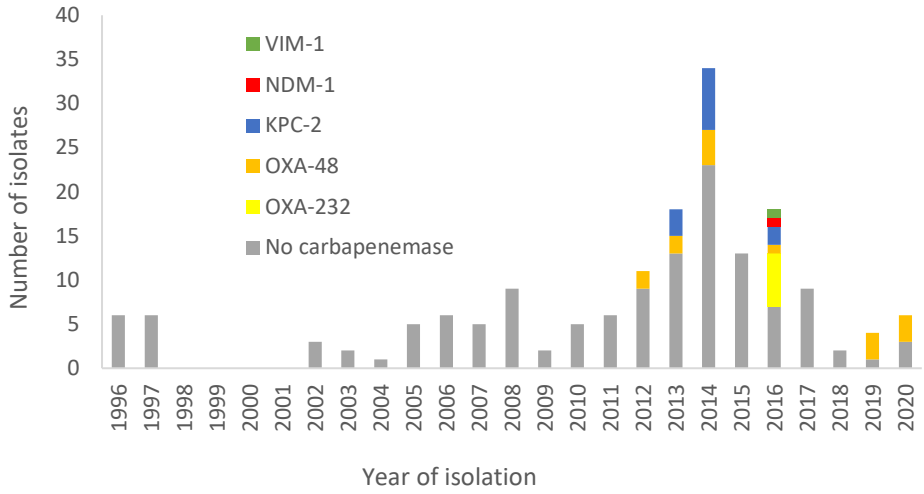
Isolates submitted for this study				Nearest related isolates from the public domain				
Isolate no.	**Origin, year of isolation**	**CP gene**	**Virulence score**	**Isolate no.**	**Origin, year of isolation**	**CP gene**	**Virulence score**	**SNP distance**
hvKP23_IR004*	Ireland, 2020	None	5	ERR560523 ERR560521 ERR562357	Madagascar, 2007 Madagascar, 2007 France, 2011	None None None	5 5 5	61
hvKP23_FR001 hvKP23_FR004	France, 2019 France, 2019	bla_{OXA-48} bla_{OXA-48}	5 5	SRR5713912 SRR5713916	Spain, 1997 Belgium, 1997	None None	5 2	35-41
hvKP23_IR003	Ireland, 2020	bla_{OXA-48}	5	EuSCAPE_IT149 ERR3164635 SRR5082371 SRR4036807	Italy, 2014 Italy, 2016 Singapore, UNK United States, 2012	None bla_{VIM-1} None None	5 5 5 5	40-81
hvKP23_IR001	Ireland, 2020	bla_{OXA-48}	5	ERR3891219 ERR3891099 SRR5082357	Saudi Arabia, 2018 Saudi Arabia, 2018 Singapore, UNK	None None None	5 5 5	29-31
hvKP23_SW001	Sweden, 2019	None	5	SRR9208897 SRR9208904 SRR5432530 SRR12102923	Russia, 2013 Russia, 2015 Russia, 2003 Russia, 2017	None None None None	5 5 5 5	53-82
hvKP23_IR002 hvKP23_IR005	Ireland, 2020 Ireland, 2020	bla_{OXA-48} bla_{OXA-48}	5 5	ERR2586422	Vietnam, 2012	None	5	70-71

CP, carbapenamase; UNK, unknown. patient with a travel history to Morocco in the previous year*

Carbapenemase genes

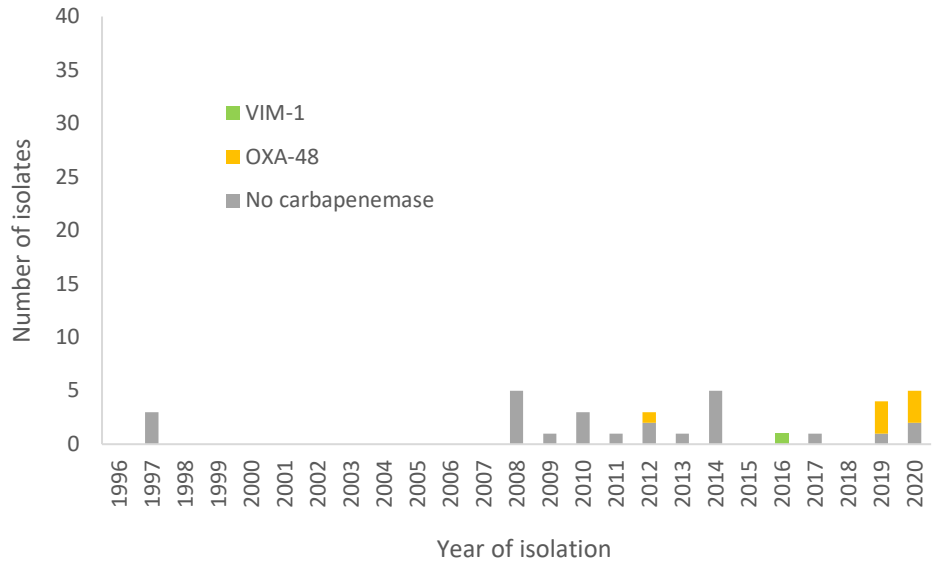
HvKp ST23 isolates have previously been largely susceptible to antibiotics [1]. In this analysis, carbapenemase genes were found in 35 (20.5%) of 171 hvKp ST23 isolates with available date of isolation from the main clade (Figure 3). The first carbapenemase-producing hvKp ST23 isolate in the main clade was isolated in 2012 in Russia (SRR9208900, isolated from sputum). In the following years, hvKp ST23 isolates carrying carbapenemase genes were observed in the main K1 ST23 clade, including isolates carrying KPC-2, NDM-1, OXA-48, OXA-232 and VIM-1. In the EU/EEA, the first hvKp ST23 isolate with a carbapenemase gene (bla_{OXA-48}) in this dataset was detected in 2012 in an isolate from Germany that was described as being part of an outbreak [8]. Only OXA-48 and VIM-1 were detected in EU/EEA isolates in the main clade (Figure 4).

Figure 3. Number of hypervirulent *K. pneumoniae* (hvKp) ST23 isolates with and without carbapenemase genes in the main clade, worldwide, n=171*†



** Only isolates with available year of isolation are shown; † The time distribution illustrated above should not be interpreted as an epidemic curve as it more likely that year-to-year variation is related to bias in detection and reporting than a reflection of true temporal trends in incidence.*

Figure 4. Number of hypervirulent *K. pneumoniae* (hvKp) ST23 isolates with and without carbapenemase genes in the main clade, EU/EEA, n=33*†



** one isolate with missing year of isolation was excluded; † The time distribution illustrated above should not be interpreted as an epidemic curve as it more likely that year-to-year variation is related to bias in detection and reporting than a reflection of true temporal trends in incidence.*

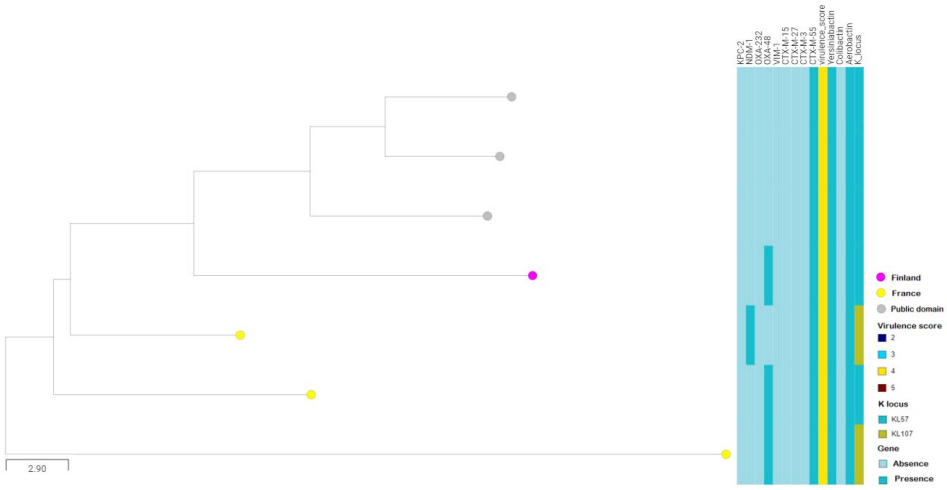
Separate K57 ST23 clade

Four isolates submitted by EU/EEA countries for this analysis belonged to a separate clade with distinct characteristics in comparison to the main K1 ST23 clade described above. Despite sharing with ST23 the same sequence type by 7-locus MLST, this clade is otherwise highly distant from the main K1 ST23 lineage for which hypervirulence, clinical presentation, and outcomes have been described in detail. It is therefore not possible to assume that this clade has the same clinical relevance as K1 ST23. However, it is also carrying a virulence plasmid, making it potentially hypervirulent and 'high-risk' due to the frequent combination with carbapenemase genes. While hvKp clonal group 23 is normally associated with the serum-resistant K1 capsule [1] and this is the capsule type of all isolates except one in the main clade in this dataset, the isolates in this separate clade have different capsule synthesis loci (KL57 or KL107). KL57 has previously been described as associated with hypervirulence [17]. In addition, these isolates have a virulence score of 4, i.e. presence of the genes encoding for aerobactin (*iuc*) and yersiniabactin (*ybt*), but absence of the gene encoding for colibactin (*clb*). There are multiple further differences in the genetic characteristics between the K1 ST23 and the distant K57 ST23 clade, and it would therefore be important to reliably differentiate these two clades. So far, these clades can be differentiated by clustering by

WGS, but assignment of a core genome ST for the new clade is pending. In addition, further studies to better describe this clade may be are warranted.

While isolates of the main K1 ST23 clade in this dataset were detected as early as 1996, the isolates of this separate clade only appear from 2014 onwards in Russia and from 2019 onwards in the EU/EEA (Figures 5 and 6).

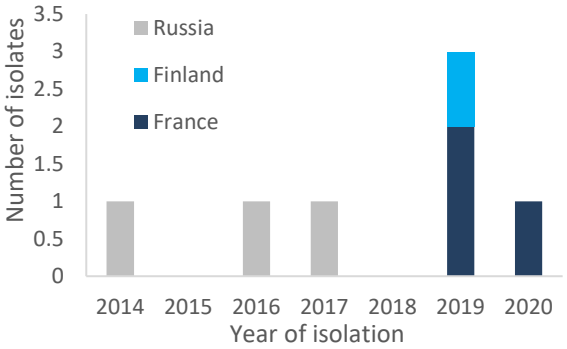
Figure 5. Separate clade with neighbouring relationships of hypervirulent *Klebsiella pneumoniae* (hvKp) ST23 isolates submitted for this study (coloured by country) and from open-access databases (grey) (n=7)



The isolate from Finland in 2019 and three isolates from France from 2019 (n=2) and 2020 (n=1) were related (28-56 SNPs) to an isolate from Russia (SRR7181964, local code KP254) in February 2016 submitted from the I.N. Blokhina Research Institute of Epidemiology and Microbiology in Nizhny Novgorod (400 km east of Moscow) and described as isolated from the site of inflammation in an adult male patient in the related entry in the European Nucleotide Archive. Two additional clinical isolates from Russia in 2014 and 2017 were identified via NCBI Pathogen Detection as closely related (18-19 SNPs) to isolate KP254 from Russia (Table 2). The three isolates from Russia predate the detection of the isolates from this clade in the EU/EEA from 2019 onwards (Figure 6A, Table 2). HvKp ST23 isolates of this separate clade, co-carrying *bla*$_{\text{NDM-1}}$ and *bla*$_{\text{KPC-2}}$ were also isolated in Poland in 2018 in a single hospital and are currently studied in more detail (data not shown).

Figure 6. Number of cases of hypervirulent *K. pneumoniae* (hvKp) ST23 isolates in the separate clade, (A) by country and (B) presence of carbapenemase (n=7)

A



B

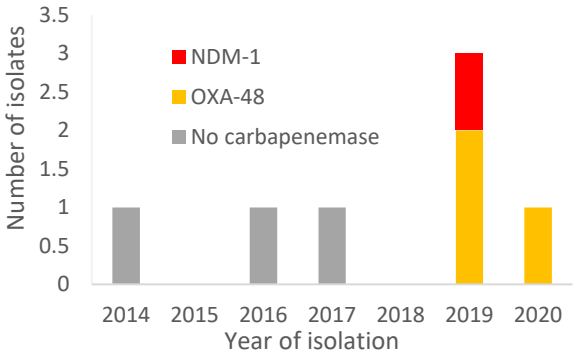


Table 2. Separate clade of hypervirulent *Klebsiella pneumoniae* (hvKp) ST23: description of isolates submitted for this analysis and nearest related isolates from the public domain

Isolates submitted for this study				Nearest related isolates from the public domain				
Isolate no.	**Origin, year of isolation**	**CP genes**	**Virulence score**	**Isolate no.**	**Origin, year of isolation**	**CP genes**	**Virulence score**	**SNP distance**
hvKP23_FI001	Finland, 2019	*bla*$_{OXA-48}$	4	SRS7484649	Russia, 2014	None	4	10-66
hvKP23_FR002	France, 2019	*bla*$_{NDM-1}$	4	SRR7181964*	Russia, 2016	None	4	
hvKP23_FR003	France, 2019	*bla*$_{OXA-48}$	4	CriePir108	Russia, 2017	None	4	
hvKP23_FR005	France, 2020	*bla*$_{OXA-48}$	4					

*CP, carbapenemase. *local code KP254*

Carbapenemase genes

Isolate SRR7181964 (local code: KP254) did not carry any carbapenemase gene, but was described as phenotypically resistant to carbapenems in a related publication [18]. In contrast to the three isolates from Russia, all isolates from the EU/EEA in this separate clade carried carbapenemase genes, either *bla*$_{OXA-48}$ for isolates hvKP23_FI001, hvKP23_FR003 and hvKP23_FR005, or *bla*$_{NDM-1}$ for isolate hvKP23_FR002 (Table 2, Figure 6B). Co-carriage of NDM and KPC was detected in additional hvKp isolates in this clade detected in Poland in 2018 (not included in the table). All isolates in this cluster were also positive for the extended-spectrum beta-lactamase gene *bla*$_{CTX-M-55}$, including the three isolates from Russia.

Disease background

Hypervirulent *K. pneumoniae*

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 [19]. HvKp from these severe pyogenic liver abscesses often spread to distant sites, leading to meningitis, necrotising fasciitis, and endophthalmitis [20]. 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. Notably, hvKp life-threatening infections frequently occur in young and healthy individuals and are associated with high morbidity and mortality, mainly due to high invasiveness of hvKp and rapid progression of disease. 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 to be the main cause of liver abscesses in Hong Kong (China), Singapore, South Korea, and Taiwan. In 10 Chinese cities, an average of 37.8% of *K. pneumoniae* isolates causing healthcare-associated infections were found to be hvKp, with the highest rate (73.9%) in Wuhan [21].

Reports from other geographic regions indicate worldwide spread, even though the prevalence is still relatively low [20,22]. 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 [7,23-27]. In a Canadian study of *K. pneumoniae* isolates causing community-acquired bacteraemia in the Calgary area, 10 (8.2%) of 134 isolates showed a hypermucoviscous phenotype [28]. 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* [29]. Screening of patients in a New York City hospital 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 City [30]. Data on the prevalence of hvKp infections in the EU/EEA is scarce. In a study of bacteraemia caused by hvKp in a teaching hospital in Barcelona (Spain) for the period 2007-2013, 1.8% of cases were found to be hvKp ST23 [10].

Emergence of hvKP carrying carbapenemase genes

Carbapenem resistance has previously been rare in hvKp ST23 isolates. However, Figure 3 shows that, since 2012, the combination of virulence and resistance genes has occurred with increasing frequency in hvKp ST23. The combination of virulence and carbapenem resistance genes on the same plasmid as described in the literature is especially of concern, as this allows for the simultaneous acquisition of virulence and resistance genes. In 2013, a Chinese study detected *K. pneumoniae* ST23 carrying a *bla*$_{KPC-2}$-encoding element integrated into a virulence plasmid [31]. Researchers from the UK also described virulence plasmids in healthcare-associated isolates of various 'high-risk' sequence types (e.g. ST15, ST101, and ST147) that carried carbapenemase genes [32]. More specifically, a New-Delhi-Metallo-beta-lactamase (NDM)-producing hypervirulent *K. pneumoniae* ST23 was isolated in a patient of Bangladeshi origin hospitalised in London (UK) [33]. Hypervirulent strains of carbapenemase-producing *K. pneumoniae* ST23 have been also described in Argentina [34]. In a recent report from India, a neonate was infected with an OXA-232-producing hvKp ST23 K1 strain causing neonatal sepsis [35].

Risk assessment questions

What is the risk associated with the dissemination of carbapenemase-producing hvKp of sequence type (ST) 23 and other STs in the EU/EEA?

ECDC risk assessment for the EU/EEA

Extended disease spectrum

Due to its increased virulence, hvKp causes a different spectrum of disease than the 'classic' *K. pneumoniae* infections known to clinicians in EU/EEA countries. While 'classic' K. *pneumoniae* is an opportunistic pathogen typically affecting vulnerable patients with comorbid conditions in healthcare facilities, hvKp has the ability to cause infections in previously healthy individuals in the community [17]. 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 infections are non-existent or rare with 'classic' *K. pneumoniae* [17]. In endemic countries, hvKp is not only a major cause of the above-mentioned infections, it is also driving an increasing incidence of pyogenic liver abscesses. There is also some evidence that, in areas where hvKp is endemic, *K. pneumoniae* partially replaces other frequently associated pathogens such as *Streptococcus pneumoniae* as a cause of community-acquired pneumonia [36,37]. Other than 'classic' *K. pneumoniae* infection, hvKp infection often presents at multiples sites and with metastatic spread [17]. It is therefore expected that an increased frequency of hvKp infections in the EU/EEA would result in increased morbidity.

Mortality of healthcare-associated hvKp

Hospital outbreaks of carbapenem-resistant hvKp have been associated with very high mortality [38-40]. 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 [38]. Similarly, in an outbreak of KPC-2 producing hvKp ST11 in an intensive care unit (ICU) in Wenzhou, China, all eight affected patients, with an age range of 13 to 69 years, died of respiratory and multi-organ failure and septic shock. In an outbreak of VIM-2 producing hvKp ST23 among mechanically ventilated patients in an Iranian ICU, four out of five patients with hvKp ST23 died compared to none out of 48 patients with VAP with 'classic' *K. pneumoniae* [40]. 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 [39]. In the US, mortality of hvKp has been shown to be higher than that of 'classic' *K. pneumoniae* infections and of multidrug-resistant 'classic' *K. pneumoniae* infections [30]. While mortality of severe infections of 'classic' carbapenemase-producing *K. pneumoniae* is already high, with reported mortality rates between 30 and 75% [41], mortality seems to be even higher in healthcare-associated hvKp infections, although only limited data are currently available in this respect.

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 OXA-48-like carbapenemases, KPC, NDM, and VIM. Tables 1 and 2 show that the nearest related isolates to EU/EEA isolates analysed for this rapid risk assessment are mainly isolates without carbapenemase genes, indicating that carbapenemase acquisition has most likely occurred independently, on various occasions, and probably by acquisition of resistance plasmids. The isolates from the EU/EEA in the main K1 ST23 clade had mainly acquired the OXA-48 carbapenemase that often results 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 [42].

In addition, colistin-resistant hvKp ST23 strains and ceftazidime-avibactam-resistant hvKp ST23 strains have been described in the literature [43,44]. An extensively drug-resistant hvKp ST23 isolate was very recently reported from Spain [45]. These reports indicate that hvKp ST23 infections may become increasingly difficult to treat.

Frequency of detection in the EU/EEA

Reports of hypervirulent and carbapenemase-producing *K. pneumoniae* ST23 detected in the EU/EEA have so far been rare. The first carbapenemase-producing hvKp isolate with genomic data in the public domain was a OXA-48-producing hvKp ST23 isolate from Germany in 2012, with no further information on the clinical or patient history [8]. An NDM-producing hvKp ST23 was detected in a women of Bangladeshi origin in the UK in 2015 [33]. Thirty-eight genomes from hvKp ST23 isolates detected in the EU/EEA were analysed for this rapid risk assessment. Many of the isolates detected in EU/EEA countries in the last two years carried carbapenemase genes, mainly $bla_{\text{OXA-48}}$. However, the increasing frequency of detection could also be explained by increased laboratory capacity for molecular testing and an increased likelihood for detecting hvKp carrying carbapenemase genes with screening of patients targeted towards carbapenem-resistant Enterobacterales.

There is a high likelihood that hvKp are currently underdetected in the EU/EEA. As detection of hypervirulence genes is not part of diagnostic microbiology routines, 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 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 typical clinical features of a community-onset infection. This clinical picture might differ in vulnerable patients in healthcare settings, likely making the clinical diagnosis of healthcare-associated hvKp impossible. Phenotypic tests such as the string test for hypermucoviscosity have a low sensitivity [30], and whole genome sequencing would be needed for the reliable identification of hypervirulence genes. While many laboratories have the capacity for molecular identification of frequent carbapenem resistance genes with in-house or commercial molecular tests, the identification of virulence genes is not part of standard diagnostics in these laboratories. Increased carbapenem resistance in hvKp might lead to the more frequent identification of hvKp isolates detected with patient screening procedures focused on carbapenem-resistant Enterobacterales. However, hypervirulence would still only be detected if there is high national WGS coverage of carbapenem-resistant *K. pneumoniae* with systematic analysis of virulence genes, or further investigation of sequences types associated with hypervirulence, such as ST23.

Potential routes of spread

Transmission in community

While the transmission of carbapenem-resistant 'classic' *K. pneumoniae* strains is driven largely by spread in healthcare settings [46], hvKp ST23 was initially described mainly as the causative agent of community-associated infections. Based on 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 [17]. In general, hvKp colonises the gut flora of healthy individuals, and can spread further via the faecal-oral route [47]. Contamination of a food sample (cucumber) with hvKp ST23 carrying bla_{KPC-2} has been described in China [48]. In some areas in Asia, there is a high prevalence of hvKp carriage in the population, with a high probability of transmission if hygiene and prevention measures are not consistently applied. 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 [49]. The main reservoir for human infection with hvKp remains the patient's own gut flora [47]. In the community, transmission of Enterobacterales, including multidrug-resistant and hypervirulent *K. pneumoniae*, likely results in silent transient or persistent gut colonisation in most cases, with only a minority of acquisitions resulting in clinical presentation of infection. The frequency with which infection develops is currently unclear. In the absence of studies of to assess for carriage, it is not possible assess the extent to which hvKp is present in the EU/EEA population. Similarly to healthcare settings, clinical diagnosis and 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 will in most cases depend on the recognition of clinical features of a typical community-onset hvKp infection when patients seek healthcare.

Transmission in healthcare settings

A shift from community-acquired infections to also healthcare-associated infections seems to have already occurred in areas where hvKp is endemic, e.g. in Asia. A recent report from China indicates that hvKp may have started to replace the 'classic' non-hypervirulent *K. pneumoniae* strains in healthcare settings [50]. This, as well as various outbreaks reported from China, Iran, and Russia [38-40,51], indicates that carbapenemase-producing hvKp has the capacity to establish itself as a healthcare-associated pathogen in a similar way as the carbapenem-resistant 'classic' *K. pneumoniae* clones that are already spreading in healthcare settings in many EU/EEA countries [41]. While the common risk factors for 'classic' multidrug-resistant *K .pneumoniae* infections include intensive care, critical illness, and invasive devices [52,53], the patient population at risk for hvKp infections will be much larger than these well-known high-risk groups. In addition, hypervirulence genes are now also being acquired by 'classic' MDR high-risk clones of *K. pneumoniae*, which are known to transmit efficiently in healthcare settings.

Some of the isolates submitted from the countries for this analysis were closely related, indicating recent transmission. Healthcare-associated clusters were reported by Ireland in EPIS AMR-HAI and by Germany in a published article [8]. Poland reported that hvKp ST23 isolates of the separate clade co-producing NDM- and KPC carbapenemases were isolated in 2018 in one single hospital (personal communication). There is thus evidence, albeit currently very limited, that cross-border transmission of hvKp ST23 as well as transmission within countries is already occurring in the EU/EEA. In addition, an outbreak of carbapenemase-producing hvKp ST23 has been reported from an immediately adjacent country such as Russia [51].

Risk of further spread

There is currently a lack of data on the prevalence of hvKp ST23 in the community and healthcare settings in the EU/EEA, thus limiting the confidence with which the risk can be assessed. The prevalence of hvKp in the EU/EEA is likely still low; however, the difficulties with detection of hvKp might allow transmission in healthcare settings to go unnoticed. This is especially relevant in healthcare settings where infection prevention and control guidelines are not strictly followed and may result in spread within and between facilities. While the probability of sustained community transmission in the EU/EEA is considered to be currently low, there does remain a possibility for further introductions of hvKp from the community into healthcare settings with subsequent spread within healthcare settings if the capability for early detection is not in place. There is a high probability that hvKp can spread further in healthcare settings in EU/EEA countries, in analogy to the dissemination of carbapenemase-producing 'classic' *K. pneumoniae* and other carbapenem-resistant Enterobacterales that rapidly disseminated within and between healthcare settings in the EU/EEA in recent years [46,54]. In addition, the 'classic' *K. pneumoniae* have also been shown to acquire hypervirulence genes. As described above, a high impact on the patient population in terms of morbidity and mortality could be expected. **The risk associated with the further dissemination of carbapenemase-producing hvKp for the patient population in the EU/EEA is therefore currently considered to be moderate, but might become high in the future if hvKp ST23 is established in healthcare settings.** Further studies to determine the prevalence of hvKp ST23 in the EU/EEA are needed.

Options for response

Awareness and laboratory capacity to identify hvKP

The institution of control measures will depend on early and reliable identification of hvKp in clinical settings and for national surveillance. There is therefore a need for clinical and public health awareness and laboratory capacity for the detection of hvKp throughout the EU/EEA. Reliable identification of hvKp currently requires molecular testing. NRLs will therefore need the capacity to detect and analyse relevant virulence genes in addition to resistance genes. Depending on the frequency with which hvKp is detected at national level, there may also be the need for capacity for detection of virulence markers in clinical laboratories as identification of hypervirulence might provide valuable information for clinical management of patients with hvKp infections. Effective methods and strategies to screen for hypervirulence in the routine diagnostic laboratory would then need to be developed.

As the extended disease spectrum of hvKp 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 the typical picture of community-acquired hvKp infections, unusual metastatic spread of *K. pneumoniae* infections, or clusters of healthcare-associated *K. pneumoniae* infections with increased severity and mortality. Early communication of clinicians with the laboratory staff to request testing for hypervirulence in *K. pneumoniae* infections with signs of increased virulence and antimicrobial resistance is vital. However, there would also be the need to change from the currently nearly exclusive focus on antimicrobial resistance to include other, potentially equally dangerous, characteristics of bacteria, such as enhanced virulence into diagnostics and clinical decision-making.

Prospective data collection and surveillance

Testing of *K. pneumoniae* isolates for hypervirulence 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 on EU/EEA level. If capacity for large-scale WGS coverage at the national level is not available, smaller studies of virulence genes in subsets of invasive isolates might provide an opportunity to gather data on the prevalence of hvKp infections. If there is evidence of dissemination of hvKp, surveillance systems may need to include options for tracking virulence in addition to resistance markers.

Infection prevention and control measures

There is a lack of data on the effectiveness on infection prevention and control (IPC) measures specifically for hvKp. Enhanced IPC control measures for carbapenem-resistant hvKp should therefore be applied in both acute care and long-term care facilities, in analogy to enhanced control measures for carbapenem-resistant 'classic' *K. pneumoniae*. Effective infection control measures to prevent the spread of carbapenemase-producing Enterobacteriaceae, the application of which may be implemented according to the epidemiological situation, as described in more detail in ECDC's Rapid Risk Assessment on 'Carbapenem-Resistant Enterobacteriaceae – second update', include:

- early implementation of active patient surveillance through rectal screening for carbapenem-resistant Enterobacterales (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;
- 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 restriction.

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 [55], ECDC's Rapid Risk Assessment on Carbapenem-resistant Enterobacteriaceae – second update, 26 September 2019 [41], WHO's guidelines for the prevention and control of carbapenem-resistant Enterobacteriaceae, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in healthcare facilities [56] 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 [57].

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

Disclaimer

ECDC issues this risk assessment document based on an internal decision and in accordance with Article 10 of Decision No 1082/13/EC and Article 7(1) of Regulation (EC) No 851/2004 establishing a European centre for disease prevention and control (ECDC). In the framework of ECDC's mandate, the specific purpose of an ECDC risk assessment is to present different options on a certain matter. The responsibility on the choice of which option to pursue and which actions to take, including the adoption of mandatory rules or guidelines, lies exclusively with the EU/EEA Member States. In its activities, ECDC strives to ensure its independence, high scientific quality, transparency and efficiency.

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