Public Health Rapid Risk Assessment related to hypervirulent *Klebsiella pneumoniae* carrying carbapenemase genes in the Region of the Americas.

20 March 2024

Risk assessment elaborated with the data available as of 5 March 2024

Overall risk
Regional
Moderate

Confidence in the information available
Regional
Moderate

General risk statement

In view of the increased identification of isolates of hypervirulent *Klebsiella pneumoniae* (hvKp) ST23 carrying carbapenemase genes in several European countries, especially in Ireland, where a sustained spread of this lineage has been observed over a five-year period *(1)*, and, given that hvKp strains in which genes associated with antimicrobial resistance have been detected in recent years in some countries of the Region of the Americas *(2,3,4)*, a Rapid Risk Assessment (RRA) for public health in the Region is presented below.

This RRA aims to assess the current regional risk related to the presence of hvKp carrying carbapenemase genes, taking into account the potential risk to human health (clinical-epidemiological behavior of the disease, severity indicators, risk factors), the risk of dissemination (limited capacity for timely detection and implementation of infection prevention and control measures) and the risk of insufficient capacity for prevention and control with available resources (including capacities to support the response, surveillance capacities, detection techniques, preparedness of health services and supplies).

Since the first hvKp isolates were identified in Taiwan and Southeast Asia in the mid-1980s and 1990s, hvKp isolates have been identified in several countries in Asia, Europe, and North America over the past two decades. Historically, hvKp has affected countries of the Asian continent in greater proportion, where detailed analysis of identified strains has shown the convergence of genes related to hypervirulence and carbapenemases production *(5)*.

In the countries of the Region of the Americas, there is consolidated surveillance of antimicrobial resistance, which has made it possible to widely document the detection of *Klebsiella pneumoniae* (Kp) strains carrying carbapenemases. However, there is no systematic surveillance that allows the routine identification of hvKp strains and allows the collection of information on these strains.

Identification of hvKp is a challenging given that it is determined by available laboratory capacity to perform genomic sequencing tests or analysis of specific markers that may indicate hypervirulence, so the prevalence of hvKp-associated infections may be underestimated.

The information on infections caused by strains hvKp comes mainly from retrospective studies. Through the analysis of isolates identified during the last two decades it has been possible to establish a characterization of the clinical-epidemiological behavior of associated infections with this pathogen. Strains of hvKp could cause infections in both immunocompromised patients and healthy individuals, so they may be associated with community-acquired infections. HvKp is carried in the gastrointestinal tract, which contributes to its spread in the community and in health care settings. Cause of pyogenic liver abscesses and can metastasize to distant sites, for example in the eyes, lungs, and central nervous system (CNS). HvKp has also been implicated in primary extrahepatic infections, including bacteremia, pneumonia, and soft tissue infections. Symptoms of hvKp are nonspecific and may include fever, chills, abdominal pain, nausea, and vomiting, but also depend on the location of the primary and metastatic infection *(6)*.

The hvKp strains are mainly associated with infections occurring in the community, in contrast to what has been observed in Kp non-hypervirulent infections, where infections occur mainly in the in-hospital setting. Likewise, due to this convergence, an increase in morbidity and mortality in infections caused by these strains is expected.

Health systems and health care services in some countries in the Region of the Americas may face a challenge in implementing infection control measures, as well as in identifying and adequately responding to cases of hvKp infection carrying carbapenemases. The lack of clinical suspicion, detection, and implementation of infection control measures indicated for the cases (standard and contact precautions, including isolation), as well as the detection and management of the colonized, are some of the challenges to be considered in the face of an increased risk of spread of these carbapenemase-carrying hvKp strains in hospital and community settings.

In the Region of the Americas, the monitoring of carbapenem resistance through the Latin American and the Caribbean Network for Antimicrobial Resistance Surveillance (ReLAVRA+ per its acronym in Spanish) has led to an increase in reports on the emergence of carbapenemase-producing Enterobacteriaceae (CPE) and an increase in the number of isolates expressing resistance. The convergence of virulence genes and the increasing antimicrobial resistance in hvKP strains generate a high risk for the emergence of invasive infections that are difficult to treat.

Information and knowledge on virulence mechanisms is still partial, and more research is needed to develop diagnostic tools that are available in countries with limited laboratory capacity. The prevention and control of carbapenemase-carrying hvKp poses significant challenges as it has not been possible to establish the extent of its dissemination in the countries of the region and information on this subject is currently limited.

Based on the criteria defined for this assessment, the overall risk at the Americas Regional level has been classified as **" Moderate "** with a **"Moderate"** level of confidence in the available information**.**

Criteria	Evaluation		Risk	Rationale
	Likelihood	Consequences		
Potential risk to human health	Likely	Moderate	Moderate	– Infections caused by hvKp occur mainly within a community and are associated with high morbidity and mortality, due to high pathogenicity. HvKp often results in cryptogenic pyogenic liver abscesses and unusual septic metastases, such as endophthalmitis or meningitis, in immunocompetent hosts. These clinical conditions increase the complexity of clinical management if antibiotic resistance is also present. – The emergence of hvKp isolates with resistance to carbapenems requires the administration of effective antimicrobial treatment, which sometimes may not be available in health facilities. – Hypervirulence and increased levels of resistance associated with hvKp can potentially lead to increased use of broad-spectrum antimicrobials such as carbapenems, increasing the risks of untreatable infections.

Risk of dissemination	Likely	Moderate	Moderate	– The finding of isolates producing carbapenemases not previously described or double/multiple carbapenemases, especially their identification in hvKp strains, should be considered of high epidemiological risk due to the capacity to generate outbreaks and very limited antimicrobial treatment options. – Retrospective cohort studies in Canada and the United States of America have shown the identification of both sensitive hvkp isolates and those in which carbapenemase-coding genes converge *(2,3,4).* – The first genomic characterization of a carbapenem-resistant hvKp isolate was performed in Chile in 2023 *(7).* – The hvKp strains are mainly associated with infections occurring within a community, in contrast to what has been observed in non-hypervirulent Kp infections, where infections are mainly recorded in hospital settings. With the concurrence of hypervirulence and antibiotic resistance, it is expected that there will be an increased risk of spread of these strains at both the community and hospital levels. – The risk of spread could increase due to high movements of people (within and between countries).
Risk of insufficient capacity for prevention and control with the available resources	Likely	Moderate	Moderate	– Laboratory diagnosis of hvKp infections depends on the availability of molecular tests in the country. Most affected countries do not have the capacity for diagnosis in the clinical setting. Restriction of laboratory diagnosis contributes to less sensitive surveillance. – Data on the prevalence of hvKp infections is scarce because they depend on retrospective studies and analyses, which are not systematically performed. – There is heterogeneity in laboratory surveillance capacity and response to cases and outbreaks within the Region. – There is no systematic surveillance (detection, monitoring, and reporting) of hvKp infections in most countries in the region. Outbreaks and cases are documented through laboratory surveillance for antimicrobial resistance, or retrospective epidemiological studies. – There is lack of participation and mobilization of local communities in activities related to the appropriate use of antimicrobials. – The prevention and control of carbapenemase-carrying hvKp poses significant challenges because it has not been possible to establish the extent of its dissemination in the countries of the region and information on this subject is currently limited. – Detection of the emergence of multiresistant or extensively resistant pathogens requires established resistance laboratory surveillance systems as well as effective infection prevention and control programs in healthcare facilities.

Background information

Hazard assessment

Klebsiella pneumoniae
Klebsiella pneumoniae (Kp) is a gram-negative, facultative anaerobic, nonmotile, usually encapsulated bacterium belonging to the family Enterobacteriaceae. It is found in the environment (including soil, surface water, and medical devices), on mammalian mucous membranes and in humans it colonizes the nasopharynx and gastrointestinal tract. Kp is a leading cause of infections acquired in healthcare institutions globally and has been considered an opportunistic pathogen, as it typically causes infections in hospitalized or immunocompromised individuals *(8,9,10).* It is estimated that Kp is the etiologic agent of 20-30% of nosocomial pneumonias in the Region of the Americas and is among the top three pathogens isolated in in-hospital Gram-negative bacteremia. Kp has natural resistance to ampicillin, due to the presence of a chromosomal gene encoding a specific β-lactamase. Classic Kp strains (cKp) cause serious infections including pneumonia, urinary tract infections, and bloodstream infection bacteremia or meningitis, especially when they infect immunocompromised individuals *(11).* The virulence of Kp depends on several factors that can lead to infection and antibiotic resistance. Among the most important virulence factors that allow the bacterium to evade opsonophagocytosis and serum clearance by the host organism are the polysaccharide capsule, the presence of lipopolysaccharides that coat the external surface of the bacteria, the fimbriae, which allow its adherence to host cells, and the siderophores responsible for causing infection in hosts. Kp possesses a large accessory genome of plasmids and chromosomal gene loci; that divides Kp strains into opportunistic, hypervirulent, and multiresistant groups *(11).* Over the past few decades, there has been an increase in the acquisition of resistance to a wide range of antibiotics by strains derived from "classical" Kp. Two main types of β-lactam antibiotic resistance have been commonly identified: one mechanism involves the expression of extended spectrum β-lactamases (ESBL), which render bacteria resistant to penicillins, cephalosporins, and monobactams. The other mechanism of resistance is the expression of carbapenemases, which renders bacteria resistant to all available β-lactams, including carbapenems *(10).* Kp strains that can cause severe infections in healthy individuals and have been identified with increasing frequency in recent years: these strains are considered hypervirulent (hv) compared to classical strains because of their ability to infect both healthy and immunocompromised populations and because of their increased tendency to produce invasive infections. This additional virulence correlates with the acquisition of a 200- to 220-kb virulence plasmid containing genes that enhance capsule production and encode siderophores *(10, 11).* HvKp is a virulent variant of cKp and can cause invasive infections affecting the eyes (endophthalmitis), lungs, and central nervous system (meningitis) in immunocompetent individuals, causing high morbidity and mortality *(12).* Unlike most infections caused by cKp strains, many hvKp infections originate in the community, suggesting that hvKp strains circulate among healthy individuals *(1).* The hvKp strains are often associated with pyogenic liver abscesses, although they can also cause pneumonias, lung abscesses, and other types of infections. Infections caused by hvKp strains have been identified mainly in Taiwan and Southeast Asia; with more recent reports of international spread in North America and Europe *(10).* As with the cKp, hvKp strains can remain in healthy (colonized) individuals without causing disease. Symptoms of hvKp are not specific and may include fever, chills, abdominal pain, nausea, and vomiting, but also depend on the location of the metastatic infection *(6).*

It has been observed that hvKp strains have mostly retained susceptibility to antimicrobials. However, with increasing pressure for antibiotic selection, there have been increasing reports of hvKp isolates carrying ESBL, carbapenemases and even colistin-resistant plasmids. Cases have been reported of acquisition of a plasmid carrying bla_{KPC-2} by hvKp, with fatal outcome for patients, have been reported. Hospital outbreaks associated with antimicrobial resistant hvKp have been documented, such as the one documented in the ICU of a hospital in China where five fatal cases were recorded *(13).* According to available information, the likelihood of further convergence of multidrug resistance genes with hypervirulent *K. pneumoniae* is increasingly high *(14).*

Exposure assessment

Globally, the first isolates of hvKp were identified in Taiwan and Southeast Asia in the mid-1980s and 1990s**.** HvKp is now considered the leading cause of liver abscesses in Hong Kong (Special Administrative Region of the People's Republic of China), Singapore, the Republic of Korea, and Taiwan *(1,12).* The incidence of hvKp infections has steadily increased over the past three decades mainly in Western Pacific countries; however, hvKp infections are increasingly recognized outside of Asia, particularly in countries in Europe and North America *(15).*

A study carried out in South and Southeast Asian countries, in which about 365 *K. pneumoniae* isolates associated with bloodstream infections from seven large health care facilities showed that the aerobactin synthesis locus (iuc), associated with hypervirulence, was present in 28% of the isolates, while 7% of isolates harbored the iuc gene plus ESBL and/or carbapenemase, indicating genotypic convergence of antimicrobial resistance and virulence, which is generally considered a rare phenomenon, but was particularly common among South Asian bloodstream infections (17%). Additionally, seven novel plasmids carrying both iuc and antimicrobial resistance genes were identified in this study, raising the possibility of cotransfer of resistance and virulence phenotypes among *K. pneumoniae* isolates. Analysis of these isolates identified diverse serotypes, capsular, and lipopolysaccharide (LPS), with a high prevalence of multirresistance, hypervirulence-associated loci, and convergent multirresistant virulent strains *(5).*

Likewise, according to the results of the analysis conducted in the study on the high prevalence of hypervirulent Kp infection in 10 cities in China, in the period of February to July 2013, it was found that 37.8% of 230 Kp isolates from bloodstream infections, hospital-acquired pneumonia and intra-abdominal infections analyzed were hvKp, with the highest rate in Wuhan (73.9%) and the lowest in Zhejiang (8.3%). Notably, 12.6% of hvKp isolates were ESBL producing and most of them carried bla_{CTX-M} genes *(16).*

In November 2020, Ireland reported the detection of hvKp sequence type 23(ST23) isolates which were recorded in March 2019. These hvKp ST23 included isolates from blood cultures (n=2), liver abscess (n=2), urine (n=4), wound swabs (n=1), as well as bla_{OXA-48}-positive hvKp isolates from rectal or fecal specimens collected for carbapenemase-producing Enterobacteriaceae (CPE) carriage surveillance (n=23). Isolates were reported as carrying hypervirulence-associated genes: iroB, iroC, iroD, iroN (salmochelin), iutA, iucB, iucC, iucD (aerobactin) and rmpA2 (hypermucoviscosity). Two geographically distinct, as well as two additional sporadic cases were identified. One of these sporadic cases was associated with travel from North Africa *(17).*

Since 2021, the number of countries in Europe reporting hvKp ST23 cases has increased from four to ten countries, and the number of isolates submitted for analysis by these countries has increased from 12 to 143 isolates *(1).* In the latest risk assessment published by European Centre for Disease Prevention and Control (ECDC), it is noted that national reference laboratories (NRLs) from ten countries in the European Region reported the identification during the period from 2018 to 2023 of 131 hvkp ST23 isolates associated with infection or carriage: 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). Ireland is the country with the highest number of isolates with this identification, where surveillance data have shown evidence of a sustained spread of the globally dominant hvKp ST23-K1 lineage carrying carbapenemase genes in healthcare facilities over a five-year period *(1).*

In a more detailed analysis of the genomes of hvKp ST23, performed as part of the risk assessment conducted by ECDC, which included 200 isolates from countries in the European region (107 submitted by the national reference laboratories and 93 from other data sources), carbapenemase genes were found in 89 (45.9%) of the 194 hvKp ST23 isolates with available information on the year of isolation. It was also identified that the first isolate of hvKp ST23-K1 with a carbapenemase gene (bla_{KPC-2}) was detected in 2009 in Poland. In 2022, the Netherlands reported the detection of an hvKp ST23-K1 isolate carrying blaNDM-1 in a patient with a history of travel to Morocco. In 2023, Lithuania reported three ST23-K1 isolates carrying bla_{KPC-2}. France and Ireland each reported one isolate of hvKp ST23-K1 carrying $bla_{OXA-181}$ in 2019 and 2023, respectively *(1).*

Region of the Americas

In the Region of the Americas**,** retrospective surveillance-based cohort studies from Calgary and Quebec in **Canada** found that 10/134 (7.5%) and 1/110 (0.9%), respectively, of *K. pneumoniae* blood isolates contained virulence factors suggestive of hvKp, in which the presence of a hypermucoviscous phenotype was identified *(3,4).*

In the **United States**, a study conducted on genomic surveillance of hvKp analyzed strains isolated from the bloodstream of 33 institutions between 2007 and 2021 (n=104), identifying that four (3.8%) isolates were hvKp; two of these isolates belonged to the ST23 lineage, and one to the reemerging ST66 lineage. Among the findings of concern was that two of these isolates contained plasmids with *tra* conjugation loci, suggesting the potential for transmission. In addition, they analyzed 963 genomes of Kp bloodstream isolates from different locations within the United States. As a result of this analysis, a total of 32 (3.3%) of these isolates were found to contain aerobactin biosynthesis genes and 26 (2.7%) contained at least two genetic characteristics of hvKp strains, suggesting elevated levels of virulence. Additionally, six (0.6%) isolates were identified that were ST associated with hvKp: ST23 (n=4), ST380 (n=1), and ST65 (n=1) *(2).*

Likewise, a study conducted in two hospitals in Houston, Texas, where Kp isolates from the bloodstream were analyzed, identified that four (6.3%) of the 64 isolates analyzed carried at least one of the virulence genes rmpA and magA *(18)*. Screening of patients in a New York hospital over three years, in which 463 Kp isolates were analyzed, detected multiple, unrelated hvKp strains, which may indicate that they correspond to community-acquired infections; the authors of the study concluded that several of the hvKp clones are established in New York *(19).*

In **Chile**, a study was published in 2023 showing the analysis of the genomic characteristics of an isolate of carbapenem-resistant hvKp, recovered in 2022 from a patient with COVID-19, this being the first genomic characterization of an isolate of K1-ST23 isolate in Chile that harbors a bla_{KPC} plasmid *(7)*.

Context assessment

In the Region of the Americas, carbapenem resistance in gram-negative bacilli has been monitored since 1996 through ReLAVRA+*(20)*. From 2006 to 2010, carbapenem resistance in Kp was a sporadic finding in some countries, and the percentage of *K. pneumonia* resistant to carbapenems has continuously increased. This situation worsened during the COVID-19 pandemic, when the national authorities of several countries in the Region, based on the results of the national reference laboratories members of ReLAVRA+, issued reports on the emergence of previously

undescribed carbapenemase-producing Enterobacteriaceae (CPE), or on the increase in the number of isolates expressing two or more of these enzymes *(21)*.

The situation is currently worrying from a clinical-epidemiological point of view, due to the dispersion of hypervirulent and multiresistant clones that are associated with high mortality rates throughout the world.

The information and knowledge on virulence mechanisms is still partial, so more research is needed to develop diagnostic tools that are available in countries with limited laboratory capacity, allowing rapid identification of infections caused by hvKp strains, as well as to find novel therapeutic alternatives aimed not only at the treatment of multirresistant infections, but also at infections caused by hypervirulent variants.

The prevention and control of carbapenemase-carrying hvKp poses significant challenges because it has not been possible to establish the extent of its dissemination in the countries of the region and information on this subject is currently limited.

Health systems and facilities in some countries of the region may face a great challenge in implementing infection control measures, as well as in identifying and adequately responding to cases of hvKp infection carrying carbapenemases, given that because they face concomitant emergencies related to other events of public health interest such as dengue and respiratory viruses.

Capacities	**Vulnerabilities**
Coordination • PAHO/WHO has established with Member States in Latin America and the Caribbean the Latin American and Caribbean Network for Antimicrobial Resistance Surveillance (ReLAVRA+ per its acronym in Spanish) through which surveillance of antimicrobial resistance is coordinated. • Bimonthly meetings are held among ReLAVRA+ members, most of which are virtual in nature, where priority issues are coordinated and discussed. **Surveillance** • ReLAVRA+ has been monitoring carbapenem resistance in gram-negative bacilli since 1996. • Generation of regional epidemiological alerts and updates along with recommendations for Member States regarding antimicrobial resistance. • ReLAVRA+ holds meetings with all its members on a regular basis to exchange information on resistance surveillance in the countries. • Provision of laboratory reagents for the detection of emerging mechanisms of antimicrobial resistance, technical support in surveillance and response to national authorities.	**Coordination** • Limited coordination between national reference laboratories, epidemiological surveillance departments, and infection prevention and control programs in some countries of the Region. • Variability in the countries of the Region regarding the implementation and monitoring of different strategies for the control of multidrug-resistant and hypervirulent pathogens in health facilities. **Surveillance** • Reference laboratories are overburdened due to numerous large-scale, high-risk parallel outbreaks and other public health emergencies in the region. • Low detection and response systems for multirresistant and hypervirulent pathogens in health facilities.

Laboratory • PAHO/WHO has the support of ReLAVRA+ in charge of maintaining and managing direct communication with laboratories and advising countries on issues such as the usefulness and limitations of phenotypic methods for resistance detection. • In its country-level structure, ReLAVRA+ has 33 national reference laboratories, which, in turn, draw on the work of more than 1,000 sentinel laboratories. • Improving genomic surveillance capacity in national reference laboratories. • RT-PCR and genomic sequencing platforms installed in many countries of the Region.	**Laboratory** • The capacity for detection of hvKp strains, as well as pharmacoresistance, is limited in the clinical laboratories, which may be compounded by the simultaneous response to outbreaks related to other events of public health concern. • Insufficient supplies of laboratory reagents and consumables, particularly reagents for molecular techniques. • Limited number of national reference laboratories capable of performing genomic sequencing and the application of hvKp detection methods.
Case Management • Some countries have national networks of clinical experts under the direction of the Ministries of Health of each country, who are responsible for providing clinical training in case analysis and management. • ReLAVRA+ advises countries on emerging issues, such as the evaluation of new medicaments for the treatment of serious infections.	**Case Management** • Lack of clinical practice guidelines or recommendations for the treatment of suspected or confirmed cases of hvKp. • Inadequate treatment supplies (appropriate antimicrobials for treatment of multidrug-resistant infections, lack of diagnostic tests or point-of-care monitoring, etc.). • No previous clinical experience in the suspicion, detection, and clinical management of hvKp cases.
Risk communication and community participation • The coordination of the partners has been strengthened.	**Risk communication and community participation** • Limited resources. • Lack of specific and effective risk communication on correct use and proper dispensing of antibiotics. • Limited understanding of risk perception in the face of antibiotic use.
Logistics • PAHO's Strategic Fund can facilitate access to appropriate diagnostic tests and antimicrobials for the diagnosis and treatment of severe multidrug-resistant infections.	**Logistics** • Insufficient financial resources to respond in a timely and effective manner at the national level. • In some countries there are insufficient personnel and resources with expertise in infection control and case management of drug-resistant infections.

Reference documents

1. European Centre for Disease Prevention and Control. Emergence of hypervirulent *Klebsiella pneumoniae* ST23 carrying carbapenemase genes in EU/EEA countries, first update, 14 February 2024. Stockholm: ECDC; 2024. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/RRA-20240129-48%20FINAL.pdf
2. Kochan T, Nozick S, Medernach R, Cheung B, Gatesy S, Lebrun-Corbin M, et al. Genomic surveillance of hypervirulent or multidrug-resistant *Klebsiella pneumoniae* among United States bloodstream isolates. BMC Infect Dis. 2022 Jul 7;22(1):603. doi: 10.1186/s12879-022-07558-1. PMID: 35799130; PMCID: PMC9263067. Available from: http://doi.org/10.1186/s12879-022-07558-1
3. Peirano G, Pitout J, Laupland K, Meatherall B, Gregson D. Population-based surveillance of hypermucoviscosity *Klebsiella pneumoniae* causing community-acquired bacteremia in Calgary, Alberta. Can J Infect Dis Med Microbiol 2013;24(3):e61-e64. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3852459/pdf/jidmm24e061.pdf
4. Doshi S, Forbes JD, Mubareka S, Andany N. Disseminated hypervirulent *Klebsiella pneumoniae* causing endophthalmitis, and lung and liver abscesses. CMAJ. 2022 May 9;194(18):E645-E648. doi: 10.1503/cmaj.211413. PMID: 35534028; PMCID: PMC9259407. Available from: http://doi.org/10.1503/cmaj.211413
5. Wyres K, Nguyen T, Lam M, Judd L, van Vinh Chau N, Dance D, et al. Genomic surveillance of hypervirulence and multidrug resistance in invasive *Klebsiella pneumoniae* from South and Southeast Asia. Genome Medicine volume 12, Article number: 11 (2020). Available from: https://doi.org/10.1186/s13073-019-0706-y
6. Choby J, Howard-Anderson J,Weiss D. Hypervirulent *Klebsiella pneumoniae* - clinical and molecular perspectives. J Intern Med. 2020 Mar; 287(3): 283-300. Available from: http://doi.org/10.1111/joim.13007
7. Morales-León F, Matus-Köhler M, Araya-Vega P, Aguilera F, Torres I, Vera R, et al. Molecular characterization of the convergent carbapenem-resistant and hypervirulent *Klebsiella pneumoniae* strain K1-ST23 collected in Chile during the COVID-19 pandemic. Microbiol Spectr. 2023 Jun 15;11(3):e0054023. doi: 10.1128/spectrum.00540-23. Epub 2023 May 16. PMID: 37191539; PMCID: PMC10269581. Available from: http://doi.org/10.1128/spectrum.00540-23
8. Echeverri L, Cataño J. *Klebsiella pneumoniae* as a nosocomial pathogen: epidemiology and drug resistance. Iatreia 23:3 Medellín July/Sept. 2010. Available in Spanish from: http://scielo.org.co/scielo.php?script=sci_arttext&pid=S0121-07932010000300006
9. Ashurst J, Dawson A. *Klebsiella Pneumonia*. [Updated 2023 Jul 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519004/#_ncbi_dlg_citbx_NBK519004
10. Paczosa MK, Mecsas J. *Klebsiella pneumoniae*: Going on the offensive with a strong defense. Microbiol Mol Biol Rev. 2016 Jun 15;80(3):629-61. doi: 10.1128/MMBR.00078-15. PMID: 27307579; PMCID: PMC4981674. Available from: http://doi.org/10.1128/MMBR.00078-15
11. Martin RM, Bachman MA. Colonization, infection, and the accessory genome of *Klebsiella pneumoniae*. Front Cell Infect Microbiol. 2018 Jan 22;8:4. doi: 10.3389/fcimb.2018.00004. PMID: 29404282; PMCID: PMC5786545. Available from: http://doi.org/10.3389/fcimb.2018.00004

12. Du Q, Pan F, Wang C, Yu F, Shi Y, Liu W, Li Z, He P, Han D, Zhang H. Nosocomial dissemination of hypervirulent *Klebsiella pneumoniae* with high-risk clones among children in Shanghai. Front Cell Infect Microbiol. 2022 Aug 29;12:984180. doi: 10.3389/fcimb.2022.984180. PMID: 36105148; PMCID: PMC9464974. Available from: http://doi.org/10.3389/fcimb.2022.984180

13. Danxia G, Ning D, Zhiwei Z, Di L, Man H, Lihua W, et al. A fatal outbreak of ST11 carbapenem-resistant hypervirulent Klebsiella pneumoniae in a Chinese hospital: a molecular epidemiological study. The Lancet Infectious Diseases. 18:1, 37-46,2018. Disponible en ingles en: https://doi.org/10.1016/S1473-3099(17)30489-9

14. Marr C., Russo T. Hypervirulent *Klebsiella pneumoniae*: an emerging public health threat. Expert Review of Anti-infective Therapy, 17:2, 71-73, 2019. Available from: https://doi.org/10.1080/14787210.2019.1555470

15. Russo T, Marr C. Hypervirulent *Klebsiella pneumoniae*. Clin Microbiol Rev 32:10.1128/cmr.00001-19.2019. Available from: https://doi.org/10.1128/cmr.00001-19

16. Zhang Y, Zhao C, Wang Q, Wang X, Chen H, Li H, et al. High prevalence of hypervirulent *Klebsiella pneumoniae* infection in China: geographic distribution, clinical characteristics, and antimicrobial resistance. Antimicrob Agents Chemother 60:6115-6120. doi:10.1128/AAC.01127-16. 2016. Available from: https://doi.org/10.1128/AAC.01127-16

17. European Centre for Disease Prevention and Control. Emergence of hypervirulent *Klebsiella pneumoniae* ST23 carrying carbapenemase genes in EU/EEA countries, 17 March 2021. Stockholm: ECDC; 2021. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/Emergence-of-hypervirulent-Klebsiella-pneumoniae-ST23-carrying-carbapenemase-genes.pdf

18. Chou A, Nuila RE, Franco LM, Stager CE, Atmar RL, Zechiedrich L. Prevalence of hypervirulent *Klebsiella pneumoniae*-associated *rmpA* and *magA* genes in two tertiary hospitals in Houston, TX, USA. J Med Microbiol. 2016 Sep;65(9):1047-1048. doi: 10.1099/jmm.0.000309. Epub 2016 Jul 8. PMID: 27392968; PMCID: PMC5068137. Available from: http://doi.org/10.1099/jmm.0.000309/

19. Parrott A, Shi J, Aaron J, Green D, Whittier S, Wu F. Detection of multiple hypervirulent *Klebsiella pneumoniae* strains in a New York City hospital through screening of virulence genes. Clinical Microbiology and Infection, ESCMID, Volume 27, Issue 4, 2021, Pages 583-589, ISSN 1198- 743X. 2021. Available from: https://doi.org/10.1016/j.cmi.2020.05.012

20. Pan American Health Organization/ World Health Organization. Antimicrobial resistance. Washington, D.C.: PAHO/WHO; 2024. [cited 5 March 2024]. Available from: https://www.paho.org/en/topics/antimicrobial-resistance

21. Pan American Health Organization / World Health Organization. Epidemiological Alert: Emergence and increase of new combinations of carbapenemases in Enterobacteriaceae in Latin America and the Caribbean. 22 October 2021. Washington, DC: PAHO/WHO; 2021. Available from: https://www.paho.org/en/documents/epidemiological-alert-emergence-and-increase-new-combinations-carbapenemases