Antimicrobial Resistance, Hypervirulent Klebsiella pneumoniae Global situation

World Health Organization

SITUATION AT A GLANCE

In early 2024, the Global Antimicrobial Resistance and Surveillance System on Emerging Antimicrobial Resistance Reporting (GLASS-EAR) issued a request for information to assess the current global situation given the increased identification of isolates of hypervirulent Klebsiella pneumoniae (hvKp) sequence type (ST) 23 carrying resistant genes to the carbapenem antibiotics – carbapenemase genes. K. pneumoniae strains that can cause severe infections in healthy individuals and have been identified with increasing frequency in recent years are considered hypervirulent compared to classical strains because of their ability to infect both healthy and immunocompromised individuals and because of their increased tendency to produce invasive infections.The presence of hvKp ST23 was reported in at least one country in all six WHO Regions. The emergence of these isolates with resistance to last-line antibiotics like carbapenems necessitates the administration of alternative antimicrobial treatment, which may not be available in many contexts. WHO recommends that Member States progressively increase their laboratory diagnostic capacity to allow for the early and reliable identification of hvKp, as well as reinforce laboratory capacities in molecular testing and detection and analyses of relevant virulence genes in addition to resistance genes. The assessment of risk at the global level is moderate given the challenges with surveillance, lack of information on laboratory testing rates, track and scale of community transmission, the gap in the available data on infections, hospitalization, and the overall burden of the disease.

DESCRIPTION OF THE SITUATION

In early 2024, the Global Antimicrobial Resistance and Surveillance System on Emerging Antimicrobial Resistance Reporting (GLASS-EAR) issued a request for information to the Global Antimicrobial Resistance and Surveillance System (GLASS) Antimicrobial Resistance (AMR) National Focal points enrolled in GLASS-AMR (n=124). The aim was to rapidly assess the current global situation given the increased identification of isolates of hypervirulent Klebsiella pneumoniae (hvKp) sequence type (ST) 23 carrying resistant genes to the carbapenem antibiotics – carbapenemase genes – reported in several countries. The documented sustained transmission of this lineage has been observed over several years and the genes associated with the antimicrobial resistance were detected in hvKp strains in recent years in multiple countries.

A total of 43 out of 124 countries, territories, and areas across the six WHO Regions provided responses: Africa (10); Europe (10); East Mediterranean (10); Western Pacific (6); America (4); South-East Asia (3). From these, a total of 16 countries and territories (Algeria, Argentina, Australia, Canada, Cambodia, Hong Kong Special Administrative Region (China), India, Iran, Japan, Oman, Papua New Guinea, Philippines, Switzerland, Thailand, the United Kingdom of Great Britain and Northern Ireland (the United Kingdom), and the United States of America) reported the presence of hvKp and 12 reported specifically the presence of the strain ST23-K1 (Algeria, Argentina, Australia, Canada, India, Iran, Japan, Oman, Philippines, Switzerland, Thailand and the United Kingdom).

The information and knowledge on the mechanisms that enhance the ability of the bacteria to cause the disease are still incomplete. 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. There is a need to discover new therapeutic alternatives aimed not only at the treatment of multi-resistant infections, but also at infections caused by hypervirulent variants.

WHO African Region

In the WHO African region, cases of hvKp might be present but the extent of the problem is not yet known. Detection of hvKp ST23 carrying carbapenem resistance genes or any other virulence or resistance marker requires the use of molecular methods which may not be routinely monitored in many microbiology laboratories across the region.

Although data on resistance of K. pneumoniae to carbapenems cannot be applied to the entire region due to the limited number of countries that reported this resistance profile and the limited testing coverage, the resistance of K. pneumoniae to carbapenems may already be a serious problem in the WHO African region that merits further investigation and calls for strengthening diagnostic capacity, infection prevention and control interventions, and access to novel therapeutic agents.

WHO Region of the Americas

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

Health systems and health-care services in some countries in the Region may encounter challenges in implementing infection control measures, as well as in identifying and adequately responding to cases of hvKp infection carrying carbapenem resistance genes. 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 people who are colonized by the bacteria, are some of the challenges to be considered in the face of an increased risk of spread of carbapenemase-carrying hvKp strains in hospital and community settings.

WHO Eastern Mediterranean Region

The available data on the prevalence of hvKp is scarce in the WHO Eastern Mediterranean region and is documented only through laboratory surveillance for AMR within healthcare facilities or retrospective epidemiological studies in a few countries.

Although two countries in the region (Iran and Oman) have reported the presence of hvKp since 2018, little is known about the extent of its dissemination or the situation in most of the countries in the region.

With limited microbiology laboratory infrastructure and capacity to detect hvKp in most of the countries and with protracted or active conflicts or other fragile or vulnerable contexts in at least nine countries, improved surveillance requires increased investment in building laboratory networks, ensuring uninterrupted supplies, and appropriate training for laboratory personal. Increased engagement with non-state actors may be required in fragile, conflict-affected and vulnerable settings. The probability of hvKp going undetected is high in many of these settings and with substantial movements between countries in the region, the clinical and public health implications remain high.

WHO European Region

Resistance to the third-generation cephalosporin antibiotics in Kp has become widespread in the WHO European Region. While many European laboratories regularly perform tests to characterize the bacteria and have the capacity for molecular identification of the most frequent carbapenem resistance genes, the identification of genes that enhance the ability of the bacteria to cause a disease (virulence) is currently not part of standard diagnostics. Since the detection of hypervirulence is not part of routine diagnostic microbiology, hvKp may go unnoticed, unless suspected by clinicians with awareness of the clinical picture and requesting the isolates to be referred for further characterization or sequencing. The clinical presentation and extended disease spectrum of hvKp has not yet been encountered by many clinicians in countries of the European region. 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 health-care settings, likely making the clinical diagnosis of healthcare-associated hvKp difficult.

WHO South-East Asia Region

The WHO South-East Asia Region has documented the convergence of genes related to both hypervirulence and carbapenem resistance, a critical factor that exacerbates the challenge of managing infections caused by hvKp.

In India, efforts have been made to characterize Kp isolates since 2015. The carbapenem-resistant hvKp was identified in India in 2016, and subsequently, its clinical profile, antibiogram, molecular epidemiology, evolutionary trajectory, and the prevalence of hvKp variants were reported. The convergence of mechanisms that enhance the ability of the bacteria to cause a disease (virulence) and antimicrobial resistance in K. pneumoniae has been detected in various occasions. The roles of resistance and this virulence genes in different types of K. pneumoniae have also been studied.

However, systematic surveillance is not yet developed in most countries in the Region, making it difficult to monitor the circulation levels of these strains effectively. Despite the establishment of national AMR surveillance systems in several countries, there are significant gaps in diagnostic and epidemiological capacities, which are still evolving. The detection and identification of hvKp strains are highly reliant on laboratory capacity, which varies widely across the region. Many laboratories lack the necessary resources to perform genomic sequencing or to analyze specific markers indicating hypervirulence. Consequently, hvKp-associated infections are likely under-detected and under-reported, obscuring the true extent of the threat they pose.

The traditional clinical diagnosis delineation of hvKp from classical Kp has become more challenging in the region because of the changing epidemiology of hvKp, which is now more commonly acquired in hospitals from patients with co-morbidities than in the community. The risk of having high prevalence of the disease may also be increased by rising co-morbidities, especially diabetes, as well as contributory variables such as high-density populations and inadequate access to high-quality health care in the region.

WHO Western Pacific Region

In the WHO Western Pacific region, due to widespread antibiotic resistance and insufficient measures to prevent infection in various areas, it is possible that instances of hvKp have occurred but have not been fully recognized. Identifying hvKp strains such as ST23 that possess carbapenem resistant genes or other significant virulence or resistance traits necessitates enhanced diagnostic tests, which are not commonly employed in standard microbiology laboratories. Several Member States in this region have the capacity to conduct antimicrobial susceptibility testing and detect Kp strains with carbapenem resistance.

EPIDEMIOLOGY

Klebsiella pneumoniae (K. pneumoniae) is a Gram-negative, bacteria 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 upper part of the throat (nasopharynx) and gastrointestinal tract. K. pneumoniae 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.[1] It is estimated that K. pneumoniae is the etiologic agent of 20-30% of nosocomial pneumonias in the Region of the Americas and is among the top three isolated in in-hospital Gram-negative bacteremia. K. pneumoniae has natural resistance to ampicillin, due to the presence of a gene encoding a specific enzyme (β-lactamase). Classic K. pneumoniae strains (cKp) can cause serious infections including pneumonia, urinary tract infections, and bloodstream infection (bacteremia) or meningitis, especially when they infect immunocompromised individuals.2

In recent decades, there has been an increase in the acquisition of resistance to a wide range of antibiotics by strains derived from the classical K. pneumoniae. Two main types of antibiotic resistance have been commonly identified: one mechanism involves the expression of enzymes known as extended spectrum β-lactamases (ESBL), which render bacteria resistant to the following antibiotic groups: penicillins, cephalosporins, and monobactams. The other mechanism of resis-

[1] 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.

tance is the expression of another type of enzymes known as carbapenemases, which renders bacteria resistant to all available β-lactams, another classification of antibiotics which includes penicillins, cephalosporins, monobactams and carbapenems.[2] K. pneumoniae strains that can cause severe infections in healthy individuals and have been identified with increasing frequency in recent years are considered hypervirulent compared to classical strains because of their ability to infect both healthy and immunocompromised individuals and because of their increased tendency to produce invasive infections.

PUBLIC HEALTH RESPONSE

WHO recommends that Member States progressively increase their laboratory diagnostic capacity to allow for the early and reliable identification of hvKp, as well as reinforcing laboratory capacities in molecular testing and detection and analyses of relevant virulence genes in addition to resistance genes. WHO will promote the strengthening of clinical and public health awareness for the detection of hvKp strains and will support the development of a consensus definition of hvKp as well as required detection and confirmation algorithms. WHO will continue to closely monitor reported cases and events.

WHO RISK ASSESSMENT

Globally, there is no systematic surveillance that allows for the routine identification and information collection of hvKp strains. Identification of hvKp is 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.

Assessing the current risk of hvKp at the global level aims to incorporate several risk components including 1) the emergence and sustained transmission of hvKp carrying carbapenem resistance genes, considering the public health impact of the identified resistance for the AMR related events; 2) the risk of geographical spread; 3) the risk of insufficient control capacities with available resources; and 4) the risk of resistance spread to other bacterial species via mobile genetic elements.

The risk at the global level is assessed as moderate considering that:

1. Infections caused by hvKp traditionally have occurred within communities in certain geographical regions (Asia) and are associated with high morbidity and mortality as well as high pathogenicity and limited antibiotic choices. However, recent reports from the WHO European region and the European Centre for Disease Prevention and Control (ECDC) have shown transmission in health-care settings, and several studies from China have reported clusters of health care-associated infections of hvKp; hence highlighting the importance of strict infection prevention and control (IPC) measures when managing these cases in health-care 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.
2. As with other resistance mechanisms, the risk of spread could increase due to high movements of people (within and between countries and regions).
3. There are very limited antimicrobial treatment options for the carbapenem-resistant hvKp isolates and these strains have the capacity to generate outbreaks.
4. The high conjugation capacity of the carbapenem-resistant hvKp (CR-hvKp) and the potential for further dissemination in clinical settings; hvKp ST23 particularly out-competes other gut bacteria facilitating colonization and spread.
5. Detection of the emergence of multi-resistant or extensively resistant pathogens requires established resistance laboratory surveillance systems as well as effective infection prevention and control programs in health-care facilities.
6. Lack of laboratory capacity contributes to the restriction of laboratory diagnosis, and this affects the sensitivity of the surveillance. Most affected countries do not have the capacity for diagnosis in the clinical setting as the laboratory diagnosis of hvKp infections depends on the availability of molecular tests.

[2] 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

7. There is global heterogeneity in laboratory surveillance capacity for this pathogen; because of this, there is no systematic surveillance (detection, monitoring, and reporting) of hvKp infections in most countries or regions. Outbreaks and cases are documented in a non-systematic way through laboratory surveillance for antimicrobial resistance, or retrospective epidemiological studies, making data on the prevalence of hvKp infections scarce.
8. The prevention and control of carbapenem-resistant hvKp poses significant challenges because it has not been possible to establish the extent of its dissemination in the countries of the different regions and information on this subject is currently limited.

The level of confidence in the available information and risk assessment at the global level is moderate given the challenges with surveillance, lack of information on laboratory testing rates, ability to track and determine scale of community transmission, the gap in the available data on infections, hospitalization and from the overall burden of the disease.

WHO ADVICE

A. Awareness and laboratory capacity to identify carbapenem resistance hvKp

- Countries should strengthen clinical and public health awareness for the detection of carbapenem resistance (CR)-hvKp. The isolation of invasive isolates of K.pneumoniae with associated carbapenem resistance should prompt consideration of further testing (where available). The ability to differentiate hvKp from classical Klebsiella pneumoniae is needed for optimal clinical management. Furthermore, the sites of infection due to hvKp could dictate modifications of the antimicrobial regimen to optimize tissue concentrations [e.g., prostate, central nervous system] and may affect the duration of therapy. This is even more important for antimicrobial resistant hvKp (e.g., CR-hvKp) due to more limited treatment options. There is a need to raise awareness among clinicians and diagnostic laboratory services to detect suspected hvKp infections based on the typical clinical picture of community-acquired hvKp infections, unusual spread of K. pneumoniae infections within the body, or clusters of healthcare-associated K. pneumoniae infections related to increased severity and mortality.
- WHO in liaison with Member States should implement a consensus definition of hvKp as there is no current agreement on the definition, partly due to the diversity of genetic backgrounds and the complexity of virulence mechanisms, which results in a lack of understanding of the prevalence, identification, and diagnosis of hvKp infections. To date, multiple virulence factors and phenotypes have been well characterized and some of these features serve as a marker for hvKp. Until such a consensus definition is agreed upon, countries should continue to use with caution current available schemes to detect hvKp such as the detection of biomarkers, Kleborate virulence scores or other available methods.
- Countries should reinforce the central role of the national reference laboratories in molecular testing and in detection and analyses of relevant virulence genes in addition to resistance genes. Develop effective methods and strategies to screen for hypervirulence in the routine diagnostic laboratory, as well as clinical case definitions that would aid the detection of samples for higher characterization.

B. Prospective data collection and surveillance

- Countries should develop a surveillance system (if not already in place) for the systematic collection of microbiological and clinical data that includes invasive infections and monitors the number of cases at the national level, accounting for body sites where CR-hvKp may be present, such as the eyes (endophthalmitis), lungs, and central nervous system.
- Develop algorithms for the detection, confirmation, and characterization of hypervirulence from the clinical presentation of infections to the genetic characterization of virulence markers and the interpretation of the results, as well as a need for a menu of methodologies that allow Member States to detect these isolates regardless of the available resources.
- Evaluate clinical outcomes as well as creating a surveillance system to monitor antibiotic treatment when CR- hvKp infections are suspected or confirmed.
- Countries should continue to report new cases of CR-hvKp to WHO via GLASS-EAR and other available global and regional channels.

C. Infection prevention and control (IPC) measures

- Health-care facilities should be familiar with the general IPC measures (standard and transmission-based precautions) required when managing all patients in both acute care and long-term care facilities
- Enhanced IPC measures should be in place for the prompt management of suspected and/or confirmed cases and contacts of carbapenem-resistant hvKp in both acute care and long-term care facilities as per WHO Guideline and Implementation manual to prevent and control the spread of carbapenem-resistant organisms at the national and health care facility level.
- Enhanced IPC control measures for CR-hvKp in both acute care and long-term care facilities are analogous to the enhanced control measures for carbapenem-resistant 'classic' K. pneumoniae, hence the infection control requirements described in the guidelines are still valid.

FURTHER INFORMATION

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