Review Article

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Affecting of Hypervirulent Multidrug Resistant *Klebsiella pneumoniae* on Public Health

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Abstract

Hypervirulent *Klebsiella pneumoniae* is an evolved pathogenic strain that is more resistant and more virulent than *classical pneumoniae* (cKp). *Klebsiella pneumoniae* is a Gram-negative bacillus of the Enterobacteriaceae family that is usually grouped with non-motile, lactose-fermenting. *hv-K. pneumoniae* is a fascinating bacterium that can be a natural inhabitant of human and animals, a very efficient pathogen capable of causing several community or hospital-acquired infections or an opportunistic multidrug-resistant strain. *hv-K. pneumoniae* has worldwide dissemination and is usually found in the environment and commensal flora of humans and other animal species. It includes several strains such as ST23\K1, ST86\K2 and ST29\K54, the most important of which are widespread around the world, especially in Asian countries. *hv-K. pneumoniae* is responsible for pneumonia, septicemia, and urinary tract and soft-tissue infections, but it is most famous for its role in community-acquired liver abscesses in Asia. In addition to its clinical relevance, *hv-K. pneumoniae* is also intensively studied in the course of basic and applied research, being of interest to a vast range of scientists from microbiologists. This interest is mostly due to its capability to acquire drug resistance and express hypervirulence. h*v-K. pneumoniae* is a very efficient biofilm producer and is involved in nosocomial tuberculosis outbreaks as a clinical co-pathogen. Furthermore, it is now one of the most important antimicrobial resistance threats. However, for the most part, the ability to infect almost all types of immunocompromised hosts and to acquire extreme antimicrobial resistance is the most fascinating characteristic. We conclusion prevalence of multidrug-resistant *hv-K. pneumoniae* in hospitals is quite high and its emergence is rapid according to studies and research. According to this study, it was shown that there are some strains such as 23 that are resistant to multiple drugs, which were the most prevalent compared to others, especially in some countries of the world, such as Taiwan, China, India, and others. The studies also showed that there is a strain such as ST11 that is resistant to most antibiotics KPC, SHV, and ESBL compared to others in

some countries, especially in China and Iran. This means that there is a high affinity for beta-lactam antibiotics compared to other antibiotics.

Key words: hypervirulent-*Klebsiella pneumonia,* Resistance, Public Health**.**

Introduction

Hypervirulent *Klebsiella pneumoniae* (hvKP)

The increasing prevalence of hypervirulent *Klebsiella pneumoniae* (hvKP) strains, particularly those exhibiting antibiotic resistance, poses a significant challenge to public health. The literature on this topic reveals a complex interplay between virulence factors and resistance mechanisms that have evolved over recent years. (1) highlight the urgent concern of carbapenem-resistant Enterobacteriaceae (CRE), particularly focusing on hvKP strains that have emerged as formidable pathogens, capable of causing severe infections in both immunocompromised and healthy individuals. Their review emphasizes the overlap between multidrug-resistant and hypervirulent pathotypes (2, 3). Building on the understanding of *K. pneumoniae's* pathogenicity, delve into the interactions between this bacterium and the human immune system. Their comprehensive analysis reveals how *K. pneumoniae* manipulates immune responses to establish infections, including strategies such as biofilm formation and immune modulation (4). The authors underscore the public health crisis presented by multidrug-resistant strains and advocate for innovative approaches such as immunotherapeutics and phage therapy, given the limited effectiveness of existing antimicrobials. This review provides a valuable perspective on the mechanisms of resistance and the need for new preventive strategies against infections caused by *K. pneumoniae.* (5). by investigating the resistance profiles *of hvKP* compared to classical *Klebsiella pneumoniae* (cKP) strains, specifically in the context of respiratory infections. Their study reveals distinct resistance patterns, emphasizing the role of chromosomal mutations and plasmid-mediated gene transfer in the development of antibiotic resistance (6). The findings indicate that *hvKP* strains are particularly adept at producing extended-spectrum β-lactamases and carbapenemases, which complicates treatment options. This work highlights the necessity for ongoing surveillance and targeted therapeutic strategies to address the evolving resistance landscape of K. pneumonia (7*). Klebsiella spp*. has also been diagnosed in some livestock, causing diseases and thus negatively impacting animal products (8). Overall, pressing need for a multifaceted approach to combat the dual threats of hypervirulence and antibiotic resistance in *Klebsiellaz pneumoniae,* underscoring the importance of continued research and collaboration in this field. (9). The isolated Klebsiella pneumoniae from some animals is also producing toxins in the teleological materials, which poses a risk to public health (10). The Aim of this study is to conduct a comprehensive review of hypervirulent *Klebsiella pneumoniae* infections that have been studied, especially in Asian countries, and to determine the epidemiology, prevalence, and clinical

characteristics of the infection in order to increase health awareness regarding this genus of bacteria.

Epidemiology

Numerous *Klebsiella* species can be found in soil, water, and other surfaces abundantly in nature. *Klebsiella* colonization is more common in Asia (18.8–87.7%) and more common in Western countries (5–35%), according to recent studies the range of the *Klebsiella* carrier rate in hospitalized patients, colonization rates in the nasopharynx rise to 19% while the nasopharynx in non-hospital settings is 1 to 6%. (11). Human *K. pneumoniae* frequently colonizes the upper respiratory tract and the gut, two mucosal surfaces where colonization rates differ greatly between individuals depending on their environment and exposures (12). Many gram-negative bacteria also contribute to environmental pollution and thus the occurrence of diseases in society through their ease of transmission between people (13) . Hypervirulent *K. pneumoniae* (HVKP) infection has become a global public health problem in recent years, with reports of cases in numerous countries. Capsular polysaccharides, siderophores, and other virulence factors are linked to HVKP's pathogenicity (14). China is seeing an increase in the isolation rate of carbapenem-resistant *K. pneumoniae* with children experiencing a greater incidence than adults (15). By direct contact with infected animals or contaminated droplets from sneezing, human can become infected with the multidrug-resistant (MDR) bacteria Klebsiella pneumoniae. Comparatively speaking, MDR infections are more common than CRKP infections (16). Many gram-negative bacteria can be easily transmitted between people, especially on the skin and upper respiratory tract (17). Pneumonia can manifest in three different forms: subacute, acute, and chronic. Subacute or chronic pneumonia accounts for the majority of deaths in humans and animals, including sheep, and because it affects sheep so much economically, most research has concentrated on its causes (18).

Clinical significance *K. pneumoniae*:

Reported on the systemic implications of *Klebsiella* infections, noting that while traditionally viewed as hospital-acquired pathogens, community-acquired systemic infections are becoming increasingly recognized. Their findings indicated that underlying health conditions significantly predispose individuals to multi-system infections, further complicating treatment approaches (19). *Klebsiella,* particularly its clinical significance, has evolved significantly over the years, highlighting the complexities of this pathogen and its implications for public health. Provided critical insights into the prevalence of Extended Spectrum Beta-Lactamase (ESBL) producing *Klebsiella* species in clinical settings, emphasizing the need for effective treatment plans for patients harboring resistant strains. Clinical challenges posed by *Klebsiella spp,* which are among the most common pathogens responsible for hospital-acquired infections, including urinary tract infections, pneumonia, and sepsis. (20, 21). colonization to dissemination of *K. pneumoniae,* highlighting its role as a Gram-negative, encapsulated bacterium that can

lead to severe infections such as pneumonia and bacteremia. The authors emphasize the pathogen's ability to form biofilms on medical devices, which is a major contributor to healthcare-associated infections (22). . Moreover, the distinction between classical (cKp) and *hypervirulent (hvKp)* strains is critical, as *hvKp* strains are particularly concerning due to their capacity to cause serious infections even in immunocompetent individuals (23, 24). The authors note that *K. pneumoniae* is increasingly responsible for community-acquired infections, affecting vulnerable populations such as newborns and the elderly (25). The ability of *K. pneumoniae* to colonize mucosal surfaces and subsequently invade deeper tissues is a key factor in its pathogenicity, reinforcing the need for further investigation into its virulence mechanisms. (26).

The Impact of Hypervirulent *Klebsiella pneumoniae* in Animals:

Phylogenetic analysis of these animal hypervirulent *K. pneumoniae* strains revealed that they were closely related to a large clonal type of hypervirulent K. pneumoniae that is mainly disseminating within human populations. (27) Most of the characterized animal hypervirulent *K. pneumoniae* strains shared the same virulence gene repertoire as that of human hypervirulent *K. pneumoniae*. Poultry-derived hypervirulent *K. pneumoniae* could contain strain-specific virulence genes and carry the blaNDM gene, which encodes metallo-β-lactamases that can hydrolyze almost all known β-lactam antimicrobials and are associated with strain-specific virulence plasmids (28). This suggests that the emergence of hypervirulent *K. pneumoniae* in animals may have occurred due to recent exposure to human practices or that the animal strains serve as a potential reservoir for a human epidemic. However, little is known about the transmission, virulence, pathogenesis, and control of these newly emerged hypervirulent *K. pneumoniae* strains in animals, especially in sheep (29) . This review thus focuses on the recent characterization of hypervirulent *K. pneumoniae* strains found in companion animals, livestock, and poultry and mainly summarizes their epidemiology, transmission, pathogenesis, and potential control strategies. (24).

Hypervirulent *K. pneumoniae's* virulence factors

The relationship between *K. pneumoniae's* virulence factors and the host immune system, highlights the urgent need for innovative strategies to address the public health threat posed by this pathogen. The ongoing research emphasizes the importance of understanding the molecular mechanisms underlying *K. pneumoniae's* virulence in order to inform future therapeutic and preventive measures (4, 30). There are many virulence factors present that contribute to the occurrence of the disease. These factors include capsular polysaccharides, plasmids, and fimbriae lipopolysaccharides (LPS) among the most important virulence factors are siderophore (31). *Klebsiella* has some mechanisms that cause multiple diseases in humans and animals, as it expresses on its surface a soft lipopolysaccharide (LPS with O antigen) and a capsular polysaccharide (K

antigen) (32). All virulence factors in both classical and Hypervirulent *Klebsiella* strains bind the microorganism to the host through two types of fimbriae, also on inanimate surfaces, and this helps in colonization as well as the formation of living membranes. There is also an outer layer in the bacteria called the polysaccharide capsule that interacts with the host. There is also lipopolysaccharide (LPS), an effective protector against many immune and phagocytic proteins in the blood serum (33). There are also several other virulence factors for *Klebsiella* bacteria, including: (1) adhesives (hairs, fimbriae), (2) iron carriers, (3) biofilm formation, and (4) urease production (34).

Convergence of hypervirulence and multidrug resistance in *k. pneumonia:*

Bacteria, including species of the genus *Klebsiella*, are widely available in various environments, including soil, water, and human and animal infections, as these are natural habitats for the intestinal organisms of humans and animals. *K. pneumoniae* is considered a pathogenic bacterium that causes many diseases in humans and animals because it is a common infection in hospitals (35). South and Southeast Asia are considered a major source of antibiotic-resistant *K. pneumoniae* bacteria, as well as highly virulent bacteria, as antibiotic-susceptible strains are community-acquired, leading to the emergence of highly virulent antimicrobial-resistant strains. Some studies have indicated that *Klebsiella pneumoniae* has the ability to break down chemical compounds, including antibiotics, because it possesses genetic traits that enable it to do so (38). Data also indicate that exopolysaccharide diversity poses a problem and challenge for *Klebsiella* control (39). Sometimes *K. pneumoniae* bacteria produce four times more siderophore, as there are genes for the biosynthesis of aerobactin (ent) present in all *Klebsiella*, but the *hvK. pneumoniae* bacteria contain the biosynthesis of aerobactin (iuc) and salmucillin (iro), and some of them contain yersiniabactin (ybt). Some resistance isolates also contain genes for the synthesis of yersiniabactin (ybt). All of this is considered integral factors for both strains, as genes are transferred horizontally between them, and the habit of recombination and horizontal gene transfer explains the restricted range of Siderophore sequence types (40). According to the reports and studies recorded, multidrug resistance and *hvK. pneumoniae* in different countries is shown in Table 1 .

Table 1: Antibiotic resistance ranked by hypervirulant *K. pneumoniae* by country and strain

Country	**Iran**	**Qatar**	**India**	**Italy**	**France**	**China**
Strain	ST11\ ST15	ST383	ST383	ST395	ST86	ST11, ST65, ST268, ST595, ST692
Antibiotics resistance	TEM, SHV, CTX-M15 , OXA-48	NDM	NDM-1, ESBL	VIM, NDM, OXA-505	ESBL	KPC, SHV, ESBL
References	41	42	43	44	45	46,47

Global Distribution of Hypervirulent *Klebsiella Pneumoniae*:

In recent years, hypervirulent, hyperepidemic pathotypes of *Klebsiella pneumoniae* have emerged and spread worldwide, becoming serious public health threats. These hypervirulent pathotypes possess enhanced virulence over classical *K. pneumoniae* strains and occur most frequently as capsular serotypes K1, K2, K5, and K57 (35). Hypervirulent, hyperepidemic *K. pneumoniae* infections are predominantly associated with pyogenic liver abscesses and other serious invasive diseases, such as necrotizing fasciitis and endophthalmitis, most commonly in aged, diabetic, and immunocompromised individuals. Methods to accurately design prevention strategies are currently not available, primarily because the molecular basis for *K. pneumoniae's* increasing virulence is poorly understood. (36) In addition, exacerbating the situation is that hypervirulent pathotypes have a hyperepidemic nature; therefore, they can be easily transmitted and spread globally due to human activities of travel and migration. (37) In fact, hypervirulent *K. pneumoniae* has already caused severe outbreaks on a global scale, in countries including Taiwan, China, Singapore, Japan, India, South Korea, Malaysia, Canada, Australia, the United States, and the European Union. Globally, *K. pneumoniae* is considered one of the top urgent antibiotic-resistant pathogens (6). This review therefore summarizes the epidemiology and global distribution of hypervirulent *K. pneumoniae* strains. These data were collected from a total of 22 countries in five continents, including 134 cities and provinces. In this study, we specifically focused on the discriminatory marker of hv *K. pneumoniae* and characterized the hv *K. pneumoniae* strains by using both phenotypic and genotypic methods. Data from this review identified three predominant and globally distributed highly clonal *K. pneumoniae* sequence-type strains: ST23 phylogenetic group K1 isolates, ST65 phylogenetic group K2, and ST86 phylogenetic group K2. These data offer significant insights into hypervirulent *K. pneumoniae* infections and can inform government policy on disease prevention in different countries Figure 1

Conclusion

The prevalence of multidrug-resistant *hv-K. pneumoniae* in hospitals is quite high and its emergence is rapid according to studies and research. According to this study, it was shown that there are some strains such as 23 that are resistant to multiple drugs, which were the most prevalent compared to others, especially in some countries of the world, such as Taiwan, China, India, and others. The studies also showed that there is a strain such as ST11 that is resistant to most antibiotics KPC, SHV, and ESBL compared to others in some countries, especially in China and Iran. This means that there is a high affinity for beta-lactam antibiotics compared to other antibiotics and it is likely that genes encoding beta-lactams have contributed to the increased resistance of the pathogen. To ensure the success of the health care program, a protocol must be found to prevent the spread of multidrug-resistant bacteria, especially in hospitals.

Conflict of Interest

The authors revealed that there is no conflict of interest.

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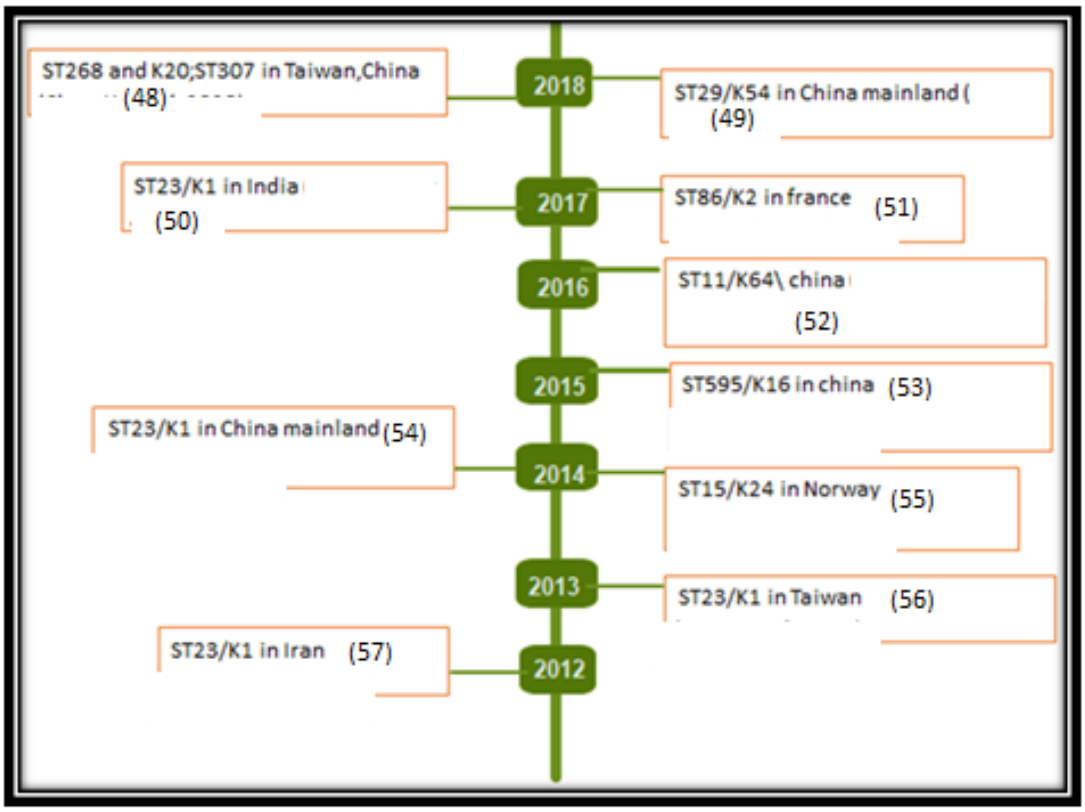

Figure1 : Prevalence of resistance in some hv-*Klebsiella pneumoniae* strains according to origin and years

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تأثير بكتيريا الكلبسيلا الرئوية شديدة العدوى والمقاومة للأدوية المتعددة على الصحة العامة

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الخلاصة

الكلبسيلة الرئوية شديدة الضراوة هي سلالة مُمْرِضة متطورة، أكثر مقاومةً وضراوةً من الكلبسيلا الكلاسك. الكلبسيلا الرئوية عصية سالبة كرام من العائلة المعوية، وعادةً ما تُصنَّف ضمن البكتيريا غير المتحركة المُخَمِّرة للاكتوز. أما الكلبسيلا فهي بكتيريا مميزة، يُمكن أن تكون موطنًها الطبيعيً الإنسان والحيوان، وهي مُمْرِضٌ فعّالٌ للغاية قادرٌ على التسبب في العديد من العدوى المكتسبة من المجتمع أو المستشفيات، كذلك سلالةٌ انتهازيةٌ مقاومةٌ للأدوية المتعددة. تنتشر هذه البكتيريا عالميًا، وعادةً ما توجد في البيئة وفي ST23\K1 وST86\K2 النباتات المُتعايشة مع البشر وأنواعٍ حيوانيةٍ أخرى. وتشمل سلالاتٍ عديدةً مثل أهمها منتشرٌ على نطاقٍ واسعٍ حول العالم، وخاصةً في الدول الآسيوية. ST29\K54 تُعتبر البكتيريا الكلبسيلا الرئوية شديدة الضراوة مسؤولةً عن الالتهاب الرئوي، وتسمم الدم، والتهابات المسالك البولية والأنسجة الرخوة، إلا أنها تُعرف بشكل خاص بدورها في خراجات الكبد المكتسبة من المجتمع في آسيا. بالإضافة إلى أهميتها السريرية، تُدرس البكتيريا الرئوية شديدة الضراوة بشكل مكثف في سياق البحوث الأساسية والتطبيقية، مما يجعلها موضع اهتمام مجموعة واسعة من العلماء، بما في ذلك علماء الأحياء الدقيقة. ويعود هذا الاهتمام في الغالب إلى قدرتها على اكتساب مقاومة للأدوية والتعبيرعن فرط الضراوة. تُنتجه البكتيريا الرئوية شديدة الضراوة ألاغشية الحيوية عالية الكفاءة، وتشارك في تفشي مرض السل التي علاوة على ذلك، تُعتبر الآن واحدة من أهم تهديدات مقاومة مضادات الميكروبات. ومع ذلك، فإن قدرتها على إصابة جميع أنواع العوائل ضعيفة المناعة تقريبًا واكتساب مقاومة شديدة لمضادات الميكروبات هي السمة الأكثر إثارة للاهتمام. نستنتج أن معدل انتشار البكتيريا الرئوية شديدة الضراوة المقاومة للأدوية فيالمستشفيات مرتفع للغاية، وأن ظهورها سريع وفقًا للدراسات والأبحاث. وفقًا لهذه الدراسة، تبيّن وجود سلالات، مثل السلالة 23، مقاومة لأدوية متعددة، وهي الأكثر انتشارًا مقارنةً بغيرها، وخاصةً في بعض KPO, SHV and ESBL مقاومة لمعظم المضادات مثل ST11دول العالم، مثل تايوان والصين والهند وغيرها. كما أظهرت KPC مقارنة بالاخرى في بعض البلدان خاصة في الصين وايران وهذا يعني هناك الفة عالية مع مضادات البيتالاكتام .

الكلمات المفتاحية : الكلبسيلا الرئوية شديد الضراوة، المقاومة، الصحة العامة.